Cerebellar transcranial direct current stimulation to influence motor learning

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ABSTRACT

Stroke is a widespread health-care problem that causes impairments of neural structure and function, and often limits the ability to move. Despite some spontaneous recovery and rehabilitative efforts, recovery is often incomplete and ongoing disability poses a significant burden both to the person who has experienced a stroke and to their family and caregivers. Recovery relies heavily on neural plasticity mechanisms that are essential for learning lost motor functions. Therefore, interventions that can modulate neural plasticity have potential to promote recovery following stroke; these interventions can be applied as adjuncts to standard rehabilitation to augment the gains achieved.

Cerebellar transcranial direct current stimulation (ctDCS) is a non-invasive brain stimulation technique that alters neural plasticity through weak, continuous, direct currents delivered to the cerebellum. In healthy individuals and people with stroke, the cerebellum has a central role in motor learning; that is, the learning or re-learning of a motor task that results in permanent improvement in performance. The cerebellum is particularly active during error-based motor learning via its inhibitory connections with the cortex. Thus, the cerebellum is an ideal target for stimulation when the goal is to promote motor learning. However, whilst ctDCS can modulate the excitability of the cerebellum, it is not known whether it can enhance motor learning. Therefore, the overall aim of this thesis was to evaluate the effect of ctDCS on motor learning.

Study A, a systematic review, investigated the effects of ctDCS on motor learning in healthy individuals. This review revealed that a single session of ctDCS had no effect on motor performance during or immediately following stimulation but appeared to improve motor learning for up to 48 hours after stimulation. Improvements were seen with anodal stimulation, using a positively charged electrode, but not cathodal stimulation. The findings shed new light on the ability of ctDCS to produce gains that outlast the stimulation period. However, it was not clear whether repeated sessions of ctDCS could produce improvements that last longer than 48 hours.

Study B, a double-blinded, parallel-group, randomised controlled trial (RCT) in healthy individuals, evaluated the effects of repeated sessions of anodal ctDCS on learning a split-belt treadmill task. The study demonstrated that three consecutive sessions of

anodal ctDCS did not affect the ability to adapt to split-belt treadmill walking but significantly prolonged the maintenance of adapted walking patterns at one-week follow-up. For the first time, this study established the ability of repeated anodal ctDCS to influence longer-term motor learning in a complex functional task. This finding provided support for applying anodal ctDCS in combination with split-belt treadmill training (SBTT) to improve walking function following stroke.

Study C, a pilot parallel-group RCT in people with chronic stroke evaluated the feasibility of a research protocol in which repeated sessions of anodal ctDCS combined with SBTT were delivered. The planned RCT was not feasible due to limitations related to the criteria for inclusion and challenges maintaining the fidelity of the SBTT intervention. Future research should focus on either optimising the methods for SBTT delivery or utilising an alternative motor adaptation task to determine the effects of ctDCS on motor learning in people with stroke.

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ATTESTATION OF AUTHORSHIP

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

04.10.2019

Signature Date

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ABBREVIATIONS

3D	3-dimensional
10MWT	10 metre walk test
A/m^2	Ampere per square metre
AFO	Ankle foot orthosis
AUTEC	Auckland University of Technology Ethics Committee
Ca^{2+}	Intracellular calcium ions
CBI	Cerebellar brain inhibition
CC	Cortico-cerebellar
cm	Centimetre
CS	Cortico-striatal
ctDCS	Cerebellar transcranial direct current stimulation
DACA	Detection and correction algorithm
DCN	Deep cerebellar nuclei
df	Degrees of freedom
EA	Early adaptation
ED	Early de-adaptation
EBMR	Evidence based medicine reviews
HDEC	Health and Disability Ethics Committees
Hz	Hertz
fMRI	Functional magnetic resonance imaging
IA	Immediate adaptation
ID	Immediate de-adaptation
K^+	Potassium ion
LA	Late adaptation
LD	Late de-adaptation

LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
mA/cm^2	Milliampere per square centimetre
MDC	Minimal detectable change
MCID	Minimal clinically important difference
MEP	Motor evoked potential
m	Metres
m/s	Metres per second
mA	Milliampere
ms	Millisecond
mV	Millivolts
Na^+	Sodium ion
NZ	New Zealand
NIBS	Non-invasive brain stimulation
NIHSS	National Institute of Health Stroke Scale
NMDA	N-methyl-D-aspartate
NT	Not tested
PAS	Paired associative stimulation
PET	Positron emission tomography
RCT	Randomised controlled trial
RP	Rebound potentiation
SBTT	Split-belt treadmill training
SD	Standard deviation
SE	Standard error
SMA	Supplementary motor area
SMRS	Simplified modified Rankin Scale

SRRT	Serial reaction time tasks
STS	Strides to steady-state motor performance
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TES	Transcranial electric stimulation
TMS	Transcranial magnetic stimulation
TrkB	Tyrosine receptor kinase B
tRNS	Transcranial random noise stimulation

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INTRODUCTION

Stroke is the leading cause of disability and a growing health, social, and economic burden worldwide[1-3]. It is caused by an interruption in the blood supply to the brain, due to a blocked or bleeding blood vessel[4]. This results in loss of motor, sensory, cognitive, and emotional function that lasts more than 24 hours[5]. Despite some spontaneous recovery and improvements associated with rehabilitation, 55-75% of people with stroke continue to experience functional limitations, which can contribute to reduced quality of life for the individual and their family[6,7].

Following stroke, motor learning is an essential component of both spontaneous and rehabilitation-driven recovery that drives improvements at the impairment, activity, and participation level[8-10]. Motor learning is possible due to the ability of the central nervous system to re-wire, modify with experience and/or adapt to changing situations; this is known as neural plasticity[8,11]. Despite motor learning being the fundamental principle guiding rehabilitation after stroke, the functional gains achieved by standard rehabilitation methods are often limited[12]. Whilst numerous animal and human studies have concluded that high repetitions of training are required to drive neural plasticity and motor learning[13-15], in a typical rehabilitation setting, factors such as cost of therapy, staff availability, and patient fatigue, limit the number of repetitions being performed[16-18]. People with stroke spend more than 40% of their inpatient rehabilitation time inactive, while on average only 33 minutes is spent in motor task training[19]. An observational study of 312 post-stroke individuals receiving inpatient and outpatient rehabilitation reported that the average number of upper limb repetitions per session was 32, and walking practice constituted of 357 steps per session[20]. This is in contrast to the hundreds of repetitions of task-specific training recommended to optimise stroke function[21]. These findings suggest that the current dose of rehabilitation is insufficient to induce the neural organisation required for optimal function.

One potential solution to the challenges around optimal dosage for neural re-organisation is to augment the effects of standard rehabilitation with the use of neuromodulatory interventions. Neuromodulation constitutes the alteration of nerve excitability through the targeted delivery of electrical signals, pharmacological agents or other forms of energy by non-invasive or implanted devices[22]. Transcranial direct current stimulation (tDCS) is one such neuromodulatory technique that delivers a weak,

continuous, direct current via non-invasive electrodes, to alter the excitability of the stimulated area[23,24]. To date, studies on animals, healthy individuals, and clinical population have primarily targeted cortical structures with tDCS, and have demonstrated changes at the cellular, system, and behavioural level[25-27]. A subcortical structure that is receiving increased attention as a possible target for neuromodulatory interventions is the cerebellum. The cerebellum has a significant role in controlling motor learning and re-learning[28-30]. Evidence supports the use of tDCS to modulate cerebellar excitability (ctDCS) and produce transient changes in motor performance in healthy individuals following a single application[31]. However, its effect on the long-term learning process is not fully understood. Motor learning encompasses long-lasting persistence of change in motor performance occurring beyond the transient improvements; therefore, this thesis aimed to investigate the effects of ctDCS on motor learning.

"Chapter 1. Background" begins with a narrative review of the literature to provide a scientific context for the application of tDCS over the cerebellum. The review initially provides an overview of motor learning and neural plasticity in healthy individuals. It then describes in detail the neural mechanisms of motor learning highlighting the involvement of distinct cortical and subcortical structures with respect to the time scale of motor learning. Next, a description of the various types of motor learning tasks is given. The cerebellar role and underlying plasticity mechanisms responsible for learning will then be elaborated, followed by motor learning and neural plasticity in post-stroke lesioned brains. Finally, tDCS is presented as a potential non-invasive brain stimulation technique that can be applied over the cerebellum, and its mechanism and safety are discussed.

"Chapter 2. Study A" examines the current evidence for the effect of ctDCS on motor learning through undertaking a systematic review. The systematic review explores the ctDCS effects at various time points of motor learning in healthy individuals. It outlines the gaps in the evidence base and proposes the following research questions which are addressed in Chapters 3 and 4.

1. What are the effects of repeated ctDCS on the learning of a split-belt treadmill walking task in healthy individuals?
2. Is it feasible to conduct an RCT evaluating the effect of repeated ctDCS in conjunction with SBTT in people with chronic stroke?

"Chapter 3. Study B" presents a multi-session, parallel-group RCT that was undertaken to investigate the effects of repeated ctDCS on motor learning in healthy individuals. This study examines the effects of three consecutive sessions of anodal ctDCS on the learning of a split-belt treadmill walking task assessed one week after the intervention. Additionally, changes in motor performance were assessed within and between each of the three intervention sessions, to provide a measure of the within-session, between-session, and cumulative effects.

"Chapter 4. Study C" examines the feasibility of conducting a pilot parallel-group RCT study design. The pilot RCT compared the effects of three consecutive sessions of anodal ctDCS combined with SBTT with three consecutive sessions of sham ctDCS, in people with chronic stroke.

Finally, **"Chapter 5. Integrated discussion and conclusion"** combines the findings from the review of the existing literature and behavioural studies to elaborate on their clinical implications. Recommendations are provided to guide future research into the use of ctDCS to modulate motor learning.

Chapter 1. **Background**

1.1 PROLOGUE

This chapter presents a narrative review of the role of the cerebellum in motor learning to provide a neurophysiological basis for targeting the cerebellum with tDCS. As outlined in the Introduction, neuromodulatory techniques such as tDCS have potential to be used as adjuncts to standard rehabilitation due to their ability to modulate neural plasticity. Therefore, this chapter will first describe motor learning and neural plasticity in the healthy population. It will then discuss the neural activation during various time scales of motor learning and with respect to various types of motor learning tasks. As a key contributor to motor learning, the role of the cerebellum will be discussed, and the neurophysiological basis for targeting the cerebellum with tDCS will be explored. Next, motor learning and neural plasticity in context of stroke recovery and rehabilitation is described. Finally, tDCS and ctDCS intervention will be explained with an emphasis on its mechanism of action and safety.

1.2 MOTOR LEARNING IN HEALTHY INDIVIDUALS

1.2.1 Definition

Motor learning is an internal process characterised by long-lasting changes in skilled motor performance; these changes are acquired through practice or experience[32]. As it cannot be measured directly, motor learning is inferred from the changes in motor performance characteristics[33]. *Performance* is the observed execution of a motor skill at a specific time and in a specific situation[33]. When relatively permanent change in performance occurs even after long delays, it is considered as *motor learning*. There are differences in the neural and behavioural changes that occur during motor performance and motor learning such that improvements in motor performance may be associated with enhanced or impaired motor learning[34,35]. Therefore, it is important to distinguish between transient changes in performance that occur during task practice versus the long-lasting changes that represent motor learning[32,34,35]. Long-lasting changes can be

measured by evaluating the *retention* or *transfer* of motor performance[33]. Retention refers to changes in motor performance that are observed after a delay of at least 24 hours[32]. Transfer refers to the ability to generalise the acquired performance to novel contexts or novel variations of the task[33].

1.2.2 Time scales of motor learning

Motor learning is said to occur over several distinct stages[36] (Refer to Figure 1-1). Initially, there is an *early fast* learning stage, in which improvements in performance are seen rapidly within a single training session[15,37]. This is followed by a *late slow* stage, where further performance gains occur at a slower rate across several sessions of practice[15,38]. Progression from the fast to the slow learning stage depends on appropriate *consolidation* during rest periods and subsequent sleep[39], where spontaneous performance gains can occur without additional practice of the task[38]. With extended practice, the performance of skilled behaviour becomes less attention-demanding and is described as the *automatic* stage[37]. The ability to retain the improved performance after long delays is seen during the final *retention* stage[37,40].

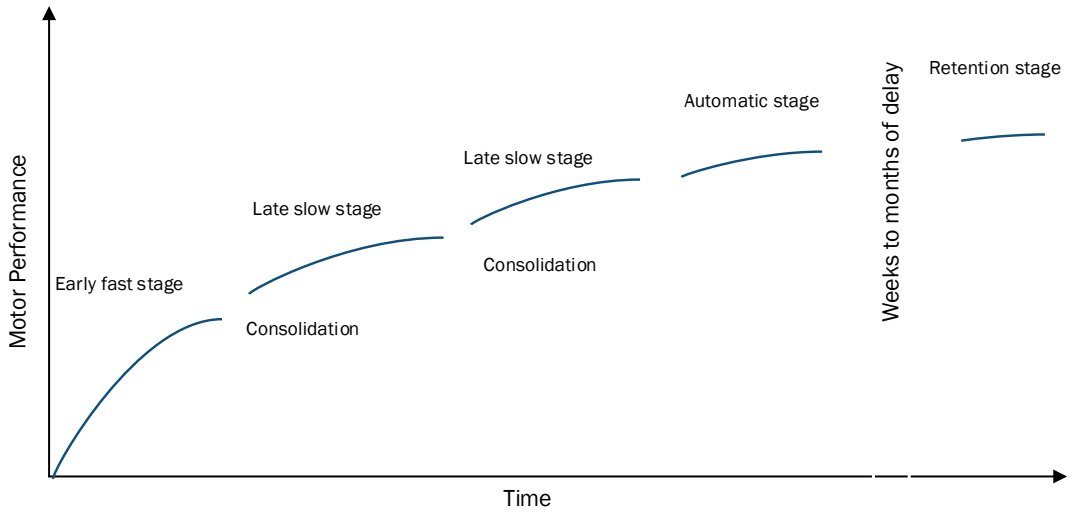

Figure 1-1 Stages of motor learning.
Modified from Wessel et al[41].

1.2.3 Types of motor learning tasks

Motor learning of upper and lower limb tasks can be divided into two paradigms: *motor skill learning* and *motor adaptation*[42].

Motor skill learning constitutes the acquisition of novel movements and improvements in performance that extend beyond baseline levels[42]. The movement may be complex, dexterous or bimanual, such as playing a musical instrument; or a simple, stereotyped or unimanual, such as pressing a button. In the laboratory setting, motor skill learning is commonly investigated using sequential visual isometric pinch tasks[43] or variants of serial reaction time tasks (SRRT) due to their ease of implementation, especially in neuroimaging environments[44]. SRRT variants typically involve responding to visual stimuli by pressing a corresponding button or executing finger-to-thumb opposition. However, some motor skill tasks involve more complex limb movements such as ankle tracking[45] or overhand throwing[46].

Motor adaptation refers to adjustments made to an already-learnt skill in response to perturbations[47]. The adjustment to the perturbation is termed *adaptation*. Perturbations may be induced by changes in the individual, such as those that occur following injury. Perturbations may also occur as a result of changes in the environment, such as windy weather or slippery surfaces, interfering with an individual's ability to execute already-learnt skills, like playing sport or walking. Following removal of the perturbation, the adapted movement pattern is transiently retained for a short period, and this is known as the *after-effect*. The *after-effect* gradually wears off and returns to baseline levels, known as *de-adaptation*[47]. With repeated exposure to the perturbation, the individual experiences faster rates of motor adaptation[48] and learning is observed through a rapid reduction in errors[47]. In the laboratory, motor adaptation can be studied by introducing perturbations to reaching, balancing or walking, over a single session or multiple sessions[49-52]; however, a majority of the motor adaptation literature has measured changes within a single session only, with very few studies assessing repeated adaptation over multiple days[53].

1.2.4 Neural plasticity associated with motor learning

The neurophysiological basis for motor learning is neural plasticity[8,38,54,55]. Neural plasticity is the ability of the nervous system to re-organise its structure, function and connections, in response to an intrinsic or extrinsic stimulus[55]. Intrinsic stimuli constitute development, learning-related processes that take place during rest and sleep, disease, or injury. Extrinsic stimuli include changes in the environment, delivery of rehabilitation, and task practice.

Synaptic mechanisms

During task practice, neural plasticity can be observed at a cellular and molecular level. Animal studies show that a single session of task practice causes short-term changes in the transmission characteristics of synapses, which are either strengthened (potentiation) or weakened (depression)[56,57]. This transiently modulates the excitability of neurons. Repeated practice of the task results in a continuous increase in the excitability of the neurons. This induces further strengthening of synaptic transmission, as well as the formation of new synapses, the synthesis of new proteins, and changes in gene expression leading to the long-term potentiation that underlies motor learning[58]. These changes facilitate the strengthening of existing neural pathways and the development of new pathways[59]. This allows the activation of neural networks between various cortical and subcortical systems; this will be discussed in the next section.

Activation of neural networks

Evidence from neurophysiological, neuroimaging, and behavioural studies in animals and humans illustrate the involvement of cortical and subcortical systems in motor learning[37]. Of particular importance are the cortico-striatal (CS) system, the cortico-cerebellar (CC) system, and the hippocampus[60,61]. Both the CS and CC systems contain active neural networks in the associative premotor and sensorimotor areas[62]. The associative premotor area is comprised of the dorsolateral prefrontal cortex, rostral premotor areas, inferior parietal cortex, rostral basal ganglia, and cerebellar cortex. The sensorimotor area includes the supplementary motor area (SMA), primary motor cortex (M1), caudal basal ganglia, and the dentate nucleus[60,63,64].

The level of activation within the CS and CC systems varies during different stages of motor learning (see Figure 1-1)[14,37,38]. During the *early fast* stage, there is simultaneous activation in the CS and CC systems irrespective of the type of task performed[37,65]. During the *late slow* stage, there is a shift in the activity from associative premotor to sensorimotor areas that occurs over multiple sessions[14,38,62]. During the *automatic* stage, the activation areas vary according to the type of training paradigm; the CC systems are activated during motor adaptation tasks, while the CS systems are activated during the motor skill learning tasks[37,65]. Similar patterns of distributed activation are seen in these systems during the *retention* stage of learning[37].

In addition to the cortical and subcortical systems described above, the activation of networks between the brain and spinal cord alter during the course of motor skill learning[44]. During early stage of motor learning, the connectivity between the spinal cord and sensorimotor cortex gradually reduces; while during the later stages of motor learning, the connectivity between the spinal cord and cerebellum increases[66].

While a number of cortical and subcortical systems are involved in motor learning, the cerebellum is a foundation part of the CC system, with connections to both the associative premotor and sensorimotor areas. Thus, the next section will specifically discuss the role of the cerebellum during motor learning.

1.3 CEREBELLUM

1.3.1 Anatomy

The cerebellum, positioned behind the brainstem, is made up of various lobes and zones[67] (Figure 1-2). Grossly, the primary and the posterolateral fissure divide the cerebellum into the anterior, posterior, and flocculonodular lobes. From medial to lateral, it has three-zones: the vermis, intermediate zone, and lateral hemispheres. The outer area of the cerebellum contains a highly convoluted grey matter called the cerebellar cortex, which encases the inner white matter comprising of four deep cerebellar nuclei (DCN); these are the fastigial nucleus, interposed nuclei, dentate nucleus, and vestibular nuclei[68]. The fastigial, interposed, and dentate are positioned parallel to the inputs they receive from the cerebellar cortex, while the vestibular nuclei are located outside the cerebellum, in the medulla.

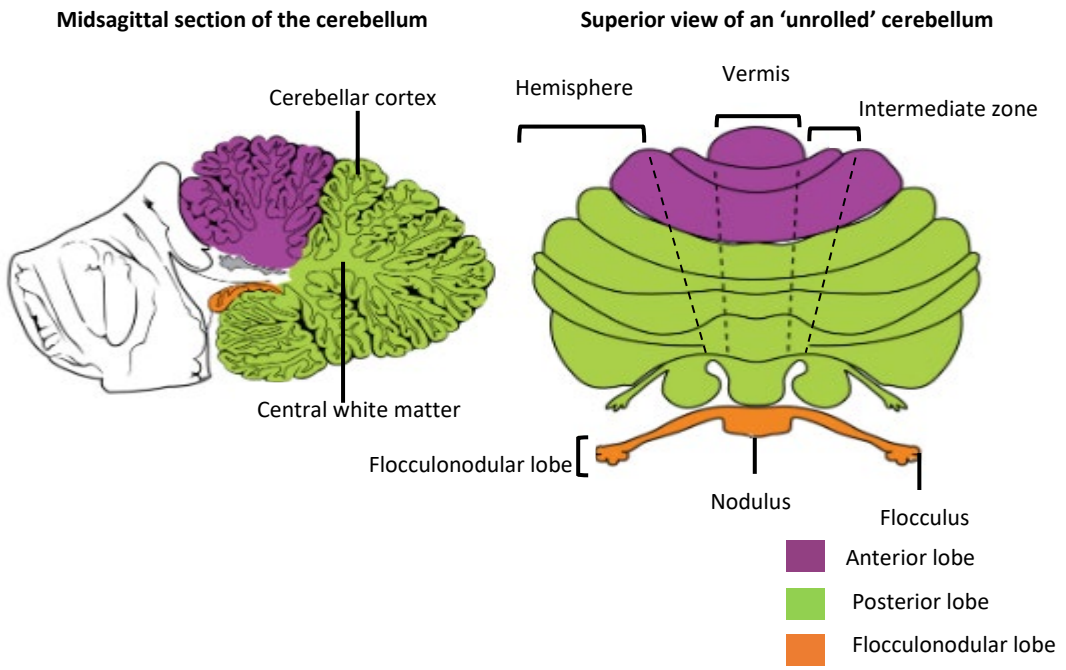

Figure 1-2 Various parts of the cerebellum.
Figure obtained from openstax book Anatomy and Physiology licensed under Creative Commons Attribution 4.0. This book is available at https://openstax.org/.

The cerebellar cortex has three layers, the molecular, Purkinje, and granular layers, each containing different cell types and fibres[69]. The outermost *molecular layer* contains inhibitory interneurons, called stellate and basket cells, and excitatory climbing and parallel fibres. These cells and fibres connect with the Purkinje cells in the *Purkinje cell layer*, the middle layer of the cerebellar cortex. The innermost layer is called the *granular layer* which contains several excitatory and inhibitory cells, particularly the excitatory granule cells and inhibitory Golgi cells. This layer also contains the excitatory mossy fibres that connect with the granule cells.

1.3.2 The circuitry of the cerebellum

The movement-related circuitry of the cerebellum is illustrated in Figure 1-3. Afferent signals associated with movement are carried to the cerebellum via mossy fibres that originate in a variety of structures, including the pontine nuclei, spinal cord, vestibular nuclei, and the reticular formation[70]. Mossy fibres form excitatory synapses with the granule cells and send excitatory collateral projections to the neurons in the DCN. The excitatory input to the granule cells activates the parallel fibres to the Purkinje cells[70]. Purkinje cells also receive movement error signals via the excitatory climbing fibres[71].

Excitation of Purkinje cells exerts *inhibitory* effects on the DCN which reduces the *excitatory* efferent pathways of DCN to the M1 via the thalamus[72,73]. This inhibitory output to the M1 is referred to as cerebellar brain inhibition (CBI)[74]. Therefore, afferent inputs of movement error excite Purkinje cells which result in increased inhibition of the DCN, and less excitation of the M1. The strength of parallel fibre-Purkinje cell synapse correlates with the Purkinje cell outputs to DCN, and the DCN outputs to the M1[75]. The circuitry described allows the cerebellum to modulate movement responses, through its outputs to the M1.

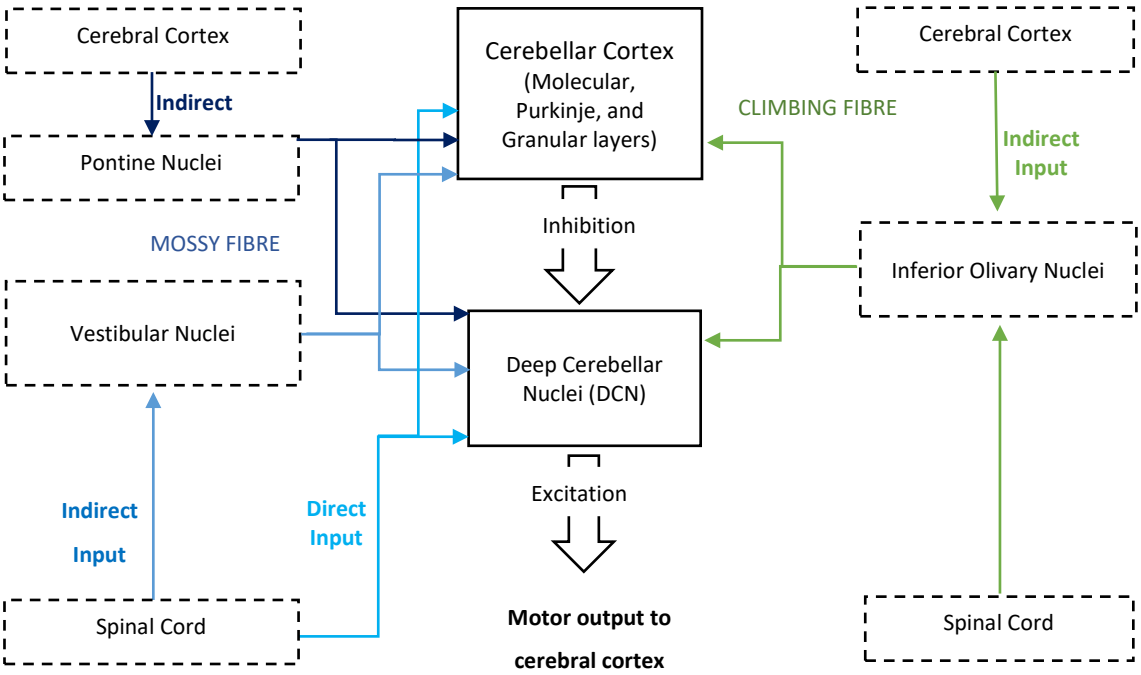

Figure 1-3 Flow of information in the cerebellar system.
Blue arrows represent direct and indirect mossy fibre inputs; green arrows represent climbing fibre inputs.

1.3.3 Role of the cerebellum in motor learning

According to the Marrs-Albus (1965) theory, during learning of a new skill, errors occur, and these trigger sensory signals to the cerebellum via climbing fibres[76,77]. This signal weakens the excitatory parallel fibre-Purkinje cell synapse resulting in long-term depression (LTD). The Marrs-Albus theory considered this LTD at the parallel fibre-Purkinje cell synapse to be foundational to motor learning. Over the years, this theory grew to include the concept that *coupled activation* of both parallel and climbing fibres elicits depression of Purkinje cells[78]. This coupled activation causes a chain of chemical events which increases calcium ions (Ca^{2+}) in the Purkinje cells[79,80]. The high concentration of Ca^{2+} desensitises the glutamate receptors

(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) present on the dendritic spine of the Purkinje cells, and weakens the parallel fibre-Purkinje cell synapse[81].

Recent studies have proposed that cerebellar learning is not limited to Purkinje cell LTD but includes multiple mechanisms and sites, many of which are still unknown[75,78,82-84]. Plasticity is known to occur at multiple synapses in the granular and Purkinje cell layers[75,78,82,83], indicating that neuroplastic responses to motor learning are widely distributed throughout the cerebellum[83]. These widely-distributed mechanisms act synergistically, such that depression (long- or short-term) at excitatory synapses occurs in coordination with potentiation (long- or short-term) at inhibitory interneuronal synapses, and vice versa[83]. One cerebellar plasticity mechanism is called rebound potentiation (RP); this involves LTP at the inhibitory synapses between stellate cell and Purkinje cells. RP is induced by the post-synaptic increase in the Ca^{2+} concentration and is thought to synergistically contribute to parallel fibre-Purkinje cell LTD[85]. Together with Purkinje cells, LTD produced by coupled activation of parallel-climbing fibres, RP also suppresses the activity of Purkinje cells, further inhibiting the activity in the motor cortex and modulating motor output[85]. Therefore, while LTD at the parallel fibre-Purkinje cell synapse has formed the central basis of motor learning for many years, it is now known that plasticity at other sites is involved[86,87]. The cerebellar plasticity mechanisms are illustrated in Figure 1-4.

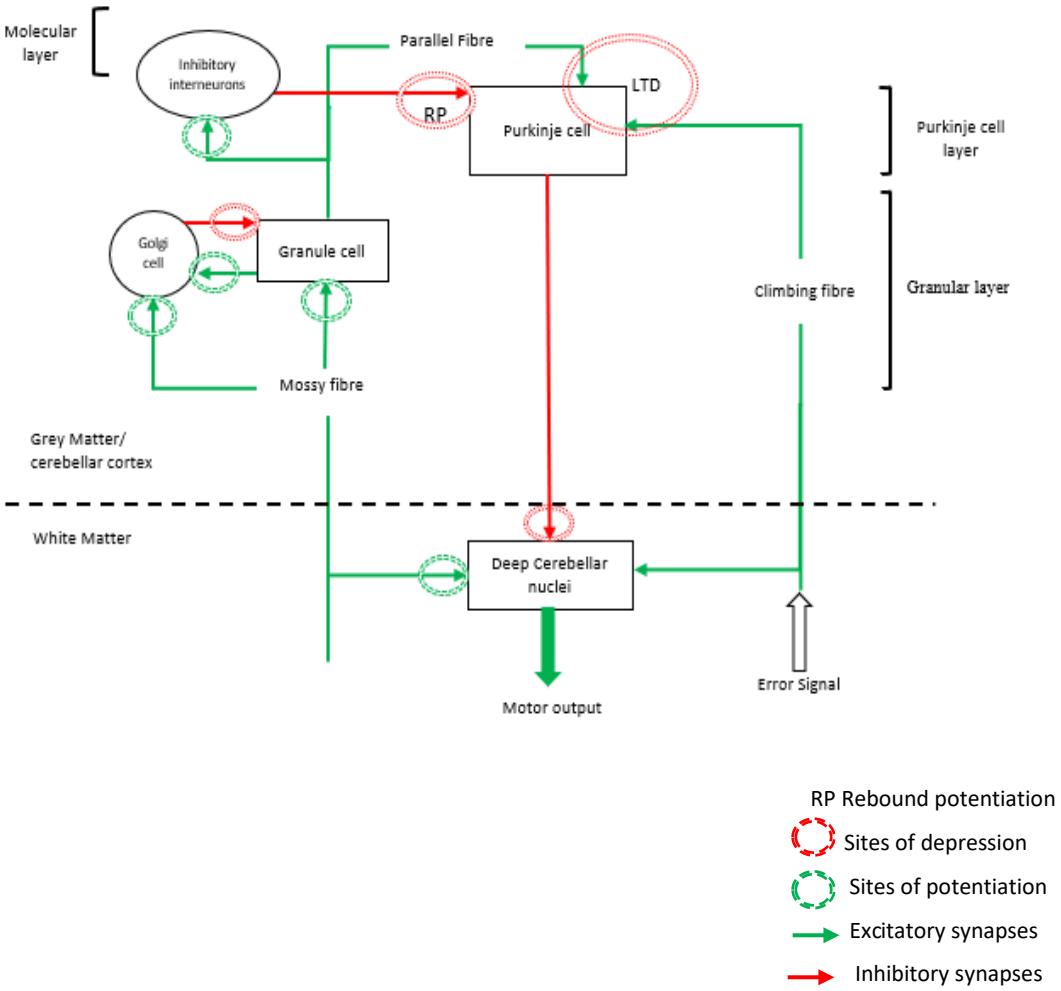

Figure 1-4 Cerebellar plasticity mechanisms at multiple sites in the cerebellum. Modified from Carey[75].

1.3.4 Cerebellar plasticity during different stages of motor learning

Over the different stages of learning, there are neural plasticity changes within the cerebellar circuitry[88]. However, little is known about how these plasticity mechanisms occur at multiple sites. During the *early fast learning* stage, the first trial of movement results in transient depression of the Purkinje cells to correct the movement error. Repetition of movements over several trials results in LTD of Purkinje cells; that is, the depression is long-lasting. With gradual improvement in performance, the Purkinje cell responses undergo potentiation[88]. This potentiation results in a reduction of CBI, which facilitates the successful acquisition and execution of motor skills[74].

1.3.5 Cerebellar plasticity with different types of task

During the practice and acquisition of new motor skills, many errors occur initially[89]; therefore, the cerebellum is particularly active during the *early fast* stage of learning. This is mainly mediated by the activation of the cerebellar cortex. However, the activity in the DCN increases over the course of the *early fast* stage[44]. In the later stages, DCN may be linked with other forms of learning such as reinforcement or use-dependent learning, which may result in the activation of CS system[89]. Therefore, the cerebellum does not play a large role in the later stages of motor skill learning.

During the motor adaptation, or the adaptation of already-learnt skills, the cerebellum is also active during *early fast* stage[37,61,62]. However, in motor adaptation, the cerebellum continues to remain active during the *late slow* stage. This is in contrast to motor skill tasks where the activation shifts to the CS system during the later stages of motor learning[37,90,91]. Adaptation over a single session initially proceeds at a rapid pace, followed by slow adjustments[92,93]. The rapid adjustments are made quickly in response to ongoing afferent feedback and are not stored by the nervous system. In contrast, as the slow adjustments occur with ongoing practice, they are stored for a period after the removal of the perturbation[92,94]. Furthermore, during a single session of motor adaptation, there is regional specificity in the activation of the cerebellum, such that the posterior cerebellum is associated with fast adjustments, while the anterior-medial cerebellum is associated with intermediate and slow adjustments[95].

Overall, LTD at the parallel fibre-Purkinje cell synapse functioning synergistically with multiple plasticity mechanisms at distributed sites within the cerebellum forms the basis of motor learning. The LTD is induced by the coupled activation of the parallel and climbing fibres. This LTD occurs in the *early fast* stage of motor learning, which produces inhibition of the M1 to correct the faulty movement and is followed by potentiation at the later stages. The cerebellum is most active during the *early fast* stage of both motor skill and motor adaptation tasks. At the later stages, cerebellar activation occurs in motor adaptation tasks only.

1.4 MOTOR RE-LEARNING IN PEOPLE WITH STROKE

Motor learning following stroke involves the re-acquisition of lost motor skills, known as motor re-learning[96]. As with healthy motor learning, described in section 1.2.4, neural plasticity underlies motor learning following stroke[97,98,99].

1.4.1 Neural plasticity following stroke

Following stroke, plasticity-induced spontaneous recovery occurs through significant synaptogenesis, dendrite re-modelling, and axonal reorganisation[97]. This is accompanied by an increase in activity in the ipsi- and contra-lesional cerebral cortices[98,99]. In addition, the areas immediately surrounding the lesion may be reorganised to facilitate the development of new neural pathways that bypass the lesion or to allow previously dormant connections to be recruited[4,100-102]. These spontaneous neuroplastic changes appear to be similar to those induced by task practice in healthy individuals[102]. This idea is reinforced by neuroimaging data, which shows that when an individual attempts to move their affected limb early after stroke, there are similar brain activation patterns to those seen during healthy motor learning[103]. This involves widespread recruitment of the bilateral sensorimotor cortex, premotor cortex, SMA, cingulate motor areas, cerebellum, basal ganglia, thalamus, parietal cortex, and prefrontal cortex[103]. Over time, as movement skills are re-learnt, there is a decrease in activation of these areas[30].

1.4.2 Training-induced neural plasticity following stroke

Studies in animals and humans have highlighted the importance of training-induced neural plasticity to augment the spontaneous neural plasticity that occurs following stroke[104-109]. This training needs to be repetitive, high intensity, and task-specific, and must take place in complex, dynamic or enriched environments, in order to best promote neural plasticity[109-112].

Training appears to be particularly important in facilitating activation of the cerebellum; this is because training produces errors between the predicted and actual performance, which are detected and corrected by the cerebellum, similar to healthy individuals learning a new motor skill[113]. For example, a longitudinal functional magnetic resonance imaging (fMRI) study demonstrated that individuals with acute cortical

stroke who received task-specific training had increased activation of the bilateral striatum and contra-lesional cerebellum during attempted movements of the affected hand[103]. At three months post-stroke, there was a decrease in contra-lesional cerebellum activity and increased activation of the ipsi-lesional primary sensorimotor cortex[103], which aligns with the activation patterns seen during execution of an already-learnt task. This pattern of increased contra-lesional cerebellar activation during attempted hemiparetic limb movement early after stroke has been observed in other longitudinal fMRI studies on people with cortical and subcortical non-cerebellar stroke[29,30]. A meta-analysis that used activation-likelihood-estimation evaluated brain activation patterns during attempted movement of the affected upper limb, and demonstrated a decrease in activity of the contra-lesional cerebellum over time following stroke[114]. However, activation of the contra-lesional cerebellum over a longer period of time is associated with better functional recovery[29,30,103,114,115].

This literature supports the important role of the cerebellum in motor re-learning after stroke. In addition, section 1.3 described the cerebellum's potential for neural plasticity and its ability to influence the M1. Together, this provides a strong rationale for targeting the cerebellum with non-invasive brain stimulation techniques for stroke rehabilitation.

1.5 NON-INVASIVE STIMULATION OF THE CEREBELLUM

1.5.1 Non-invasive brain stimulation techniques

Non-invasive brain stimulation (NIBS) techniques generally use electrical or magnetic stimuli to either produce neuronal activity (suprathreshold stimulation) or modulate ongoing neural activity (subthreshold)[116]. Suprathreshold stimulation induces large electric field intensities in the brain to trigger action potentials and includes techniques such as high-intensity short-pulse transcranial electric stimulation (TES), transcranial magnetic stimulation (TMS), electroconvulsive therapy, or paired associative stimulation (PAS)[117]. Subthreshold stimulation induces low-intensity electrical fields and includes techniques such as tDCS, transcranial alternating stimulation (tACS), and transcranial random noise stimulation (tRNS); these techniques modulate the activity of already-active neurons[118]. Subthreshold stimulation techniques have the advantage of being relatively painless in comparison to suprathreshold stimulation, as they do not

activate excitable structures in the skin along with the target area in the brain. tDCS is a subthreshold technique which has further advantages over other suprathreshold techniques, in that it is cost-effective, user-friendly, painless, portable, and can be applied simultaneously with any other forms of rehabilitation[119]. This may allow tDCS to be more rapidly incorporated as an adjunct to rehabilitation[9].

1.5.2 Mechanisms underlying transcranial direction current stimulation

Before describing the mechanism of tDCS, it is necessary to understand the normal mechanisms by which neurons are activated. Normally, to activate a neuron, an incoming stimulus is required to alter the concentration of sodium ions (Na^+) and potassium ions (K^+). This stimulus opens up the ion channels within the membrane which results in the influx of Na^+ inside of the cell and changes the membrane potential from polarised to *depolarised*[120]. When the stimulus is strong enough to cause depolarisation to reach a threshold level of around −50mV, an action potential is generated[120]. This is facilitated by the opening of K^+ channels until maximum depolarisation of +50mV is reached. Following which, Na^+ channels begin to close again which gives rise to the *repolarisation* phase where the membrane starts to return to its resting potential and there is closing of K^+ channels. After eliciting the action potential, the neuron is not receptive to an incoming stimulus until the membrane potential returns to the resting state. This is called the *hyperpolarisation* or refractory period[121].

tDCS induces immediate changes in the neural cell membrane potential by modulating the Na^+ and Ca^{2+} channels[24,122]; this causes either depolarisation or hyperpolarisation. There are two types of stimulation, anodal and cathodal, and the modulatory effects of each depend on the orientation of neurons relative to the electric field[123,124]. When the current flow is parallel to the somatodendritic axis of a neuron, it will hyperpolarise the membrane compartments closest to the current source and depolarise membrane compartments further away from the current source. Anodal tDCS, where the positively charged electrode is applied over the scalp, produces inward current flow at the cortex (refer to the left of Figure 1-5). This induces depolarisation of the soma, due to its proximity to the source of the current flow, and *increases* neural excitability (refer to the left of Figure 1-5)[125]. Cathodal tDCS, where the negatively charged electrode is applied over the scalp, produces outward current flow at the cortex (refer to the right of

Figure 1-5). This elicits hyperpolarisation of the soma, due to its more distant position from the source of current flow, and *decreases* neural excitability[12,123,125].

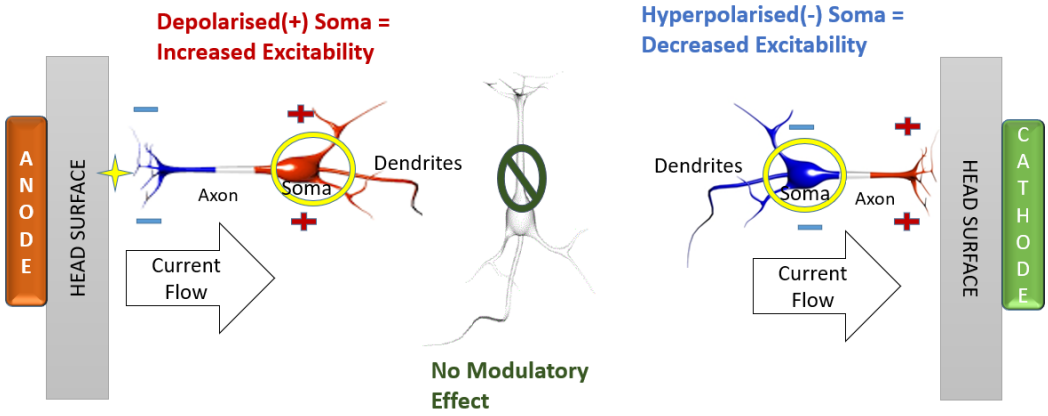

Figure 1-5 Hyperpolarisation (blue) and depolarisation (red) of a neuron based on the direction of current flow.
Modified from Kadosh [125]

The effects of tDCS on neuronal activity encompass the changes that occur *during* stimulation (online) and includes effects that persist *beyond* the stimulation period (offline). The offline effects of tDCS are attributed to alterations in the function of NMDA receptors[24], changes in gamma-aminobutyric acid[126] and glutamatergic synapses[127], altered levels of serotonin, dopamine and acetylcholine neurotransmitters[128], increased brain-derived neurotrophic factor (BDNF), and tyrosine receptor kinase B (TrkB) secretion[129]. These changes result in mechanisms similar to LTP and LTD[124,127]. The duration of offline effects depends on the length of tDCS application and may last as long as three months[43]. For instance, seven minutes of stimulation induces offline effects for a few minutes, while the effects last for over an hour following 13 minutes of anodal stimulation[23].

Due to its online and offline effects, tDCS may be delivered prior to motor training (sequential delivery) or during motor training (concurrent delivery). The evidence for best timing is controversial and may depend on various factors[130]. Due to the assumption that both timings produce the same polarity-specific outcomes[131], the choice of stimulation delivery may be based on pragmatic factors. For instance, concurrent delivery would be preferred over sequential delivery where the duration of the experiment or intervention must be kept to a minimum. However, factors such as initial brain state and task relevancy may influence the stimulation effects irrespective of the timing. An irrelevant activity undertaken prior to, or after, the stimulation may interfere

with the stimulation effects[132]. Similarly, if the initial brain state is at its optimal level due to factors such as caffeine intake or alertness, it may not be further enhanced[133].

1.5.3 Cerebellar transcranial direct current stimulation

The effects of tDCS when applied over M1 have been well investigated; whereas, the mechanisms by which tDCS applied to the cerebellum (ctDCS) modulates neural activity have been less well studied.

TMS studies in healthy individuals have demonstrated that ctDCS modulates the cerebello-cortical pathways and influences the magnitude of CBI[74,134]. This modulates cortical excitability by either increasing or decreasing the inhibition of Purkinje cells in the cerebellar cortex, and subsequently altering their output to the DCN, and then the M1 (refer to Figure 1-6). However, there is limited understanding of the mechanisms involved, due to limitations in the number and size of ctDCS studies, and inconsistencies in TMS and ctDCS methodologies[135].

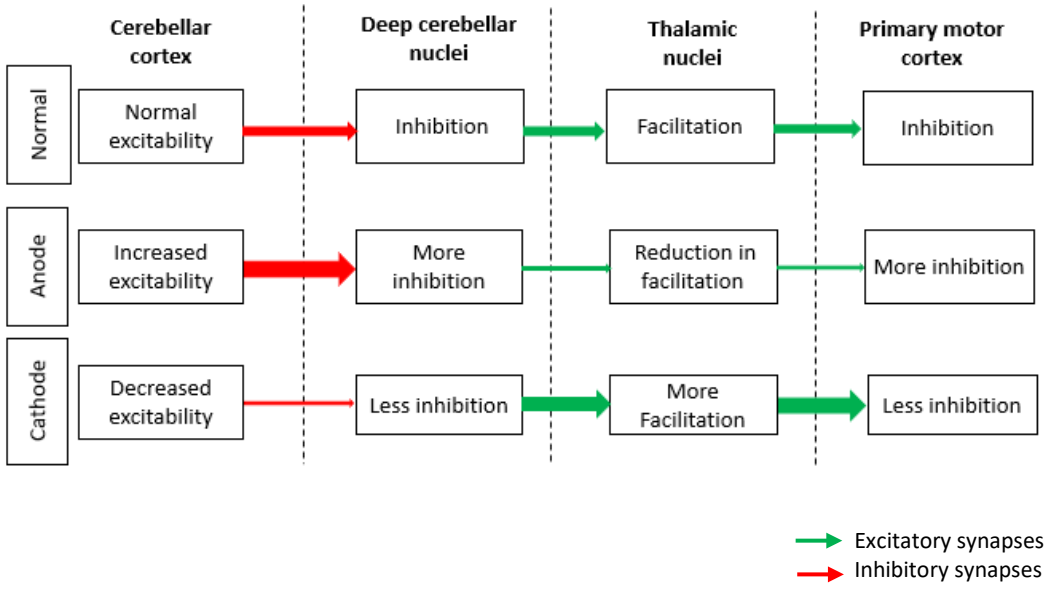

Figure 1-6 Modulation of cerebello-cortical pathways by ctDCS.
Modified from Grimaldi et al[136].

1.5.4 Safety of transcranial direct current stimulation

The safety of tDCS has been inferred from data from animal studies, translational models, computer simulations, and human trials. Upon scaling the results of animal studies to humans, the predicted minimum induced current density for detected damage was between 6.3-17A/m^2 and between minimum intensity of 67-173mA[137,138]. This

suggests that the threshold for brain damage is well above conventional ctDCS protocols, and would require a 100 times higher dose to induce damage[122,137].

In humans, controlled studies involving healthy individuals, children, and individuals with altered neuroanatomy or neurophysiology, support the safety of tDCS[139-141]. No serious adverse effects have been reported across over 33,200 sessions and 1,000 participants with repeated sessions[142]. Other reviews also support the safety of repeated tDCS stimulation[143,144] concluding that the adverse effects of single or multiple sessions of tDCS in healthy individuals or people with neurological conditions are mild and low in frequency[138,143,144]. The spread of electric current to non-stimulated areas has been ruled out by modelling studies that have shown that tDCS to the shoulder does not influence the heart or brainstem[145]. However, one must keep in mind that the reporting, assessing, and publishing of adverse effects related to tDCS is inconsistent across studies which may induce a selective reporting bias[143]. The use of adverse effects questionnaires or rating the severity and relationship of the effects to the stimulation have been recommended to address this issue[143]. Other important considerations for the safe delivery of tDCS are the stimulation parameters and exclusion of participants who have contraindications of tDCS[142].

Tolerability refers to the presence of uncomfortable and unintended symptoms, which are transient and do not induce structural or functional damage[146]. The literature reports that individuals have a high degree of tolerability towards tDCS[140,147]. Commonly reported side effects of cortical tDCS are tingling and itching sensations under the electrodes, erythema under the electrodes, headache, phosphenes, and fatigue; these have been observed following both active and sham tDCS[147,148]. Studies applying tDCS over the cerebellum report similar sensations[149].

Thus, tDCS is considered safe and well-tolerated in humans[138,144] and any adverse effects are assumed mild and low in frequency.

1.6 SUMMARY

Motor learning encompasses long-lasting changes in performance that persist beyond the training period. Neural plasticity forms the basis of motor learning in healthy individuals and during motor re-learning following stroke. Recruitment of brain areas varies during different stages of motor learning, and the cerebellum plays a crucial role

in both motor learning and re-learning. The cerebellum is most active during the *early fast* stage of learning during both motor skill learning and motor adaptation but continues to contribute during the *late slow* stage of motor learning during adaptation tasks. Long-term depression at the parallel fibre-Purkinje cell synapse, along with various other plasticity mechanisms at multiple sites in the cerebellum form the basis of cerebellar learning. At the neural network level, these cerebellar plasticity mechanisms exert an inhibitory effect on M1 via the cerebello-cortical pathway. This pathway can be modulated by the application of ctDCS, which is a safe and easy to use non-invasive neuromodulatory technique capable of producing both online and offline effects. Overall, these findings support the notion that targeting the cerebellum with tDCS has the potential to influence motor learning and motor re-learning in people with stroke.

Chapter 2. **Study A: Systematic Review**

2.1 PROLOGUE

In Chapter 1, it was discussed how the cerebellum, through its error-driven mechanisms, plays a crucial role in motor learning in healthy individuals and motor re-learning after stroke. This chapter presents a systematic review of the effect of ctDCS on motor learning in healthy individuals. The literature was initially reviewed up to the end of September 2016. The literature search was repeated up to the date of July 2019 to update the additional studies published during the period of the thesis. The updated systematic review has been published in a peer-reviewed journal and is presented here as it is with no modification in content and a few minor formatting modifications to facilitate reading[214].

Start of accepted manuscript 1

The effect of cerebellar transcranial direct current stimulation on motor learning: A systematic review of randomised controlled trials

214. Kumari N, Taylor D, Signal N. The effect of cerebellar transcranial direct current stimulation on motor learning: A systematic review of randomised controlled trials. *Frontiers in Human Neuroscience*. 2019;13(328) doi:10.3389/fnhum.2019.00328. 2019.

2.2 ABSTRACT

Background: Cerebellar transcranial direct current stimulation (ctDCS) appears to modulate motor performance in both adaptation and motor skill tasks; however, whether the gains are long-lasting is unclear.

Objectives: This systematic review aims to evaluate the effect of ctDCS with respect to different time scales of motor learning.

Methods: Ten electronic databases (CINAHL, MEDLINE, SPORT Discus, Scopus, Web of Science, Cochrane via OVID, Evidence-Based Reviews (EBM) via OVID, AMED: Allied and Complementary Medicine, PsycINFO, and PEDro) were

systematically searched. Studies evaluating the effect of ctDCS compared to sham ctDCS on motor learning in healthy individuals were selected and reviewed. Two authors independently reviewed the quality of the included studies using the revised Cochrane's risk-of-bias tool. The results were extracted with respect to the time scale in which changes in motor performance were evaluated.

Results: Seventeen randomised controlled trials met the eligibility criteria of which 65% of the studies had a "high" risk-of-bias, and 35% had "some concerns". These studies included data from 629 healthy participants. Of the studies that evaluated the effect of anodal ctDCS during and immediately after the stimulation, four found enhanced, three found impaired, and ten found no effect on gains in motor performance. Of the studies that evaluated the effect of anodal ctDCS after a break of 24 hours or more, seven found enhanced, two found impaired, and one found no effect on gains in motor performance. Of the studies that evaluated the effect of cathodal ctDCS across a range of time scales, five found impaired, one found enhanced, and five found no effect on gains in motor performance.

Conclusions: In healthy individuals, anodal ctDCS appears to improve short to longer-term motor skill learning, whereas it appears to have no effect on gains in motor performance during and immediately after the stimulation. ctDCS may have potential to improve motor performance beyond the training period. The challenge of the motor task and its characteristics, and the stimulation parameters are likely to influence the effect of ctDCS on motor learning.

2.3 INTRODUCTION

Motor learning is the set of processes associated with practice or experience, which lead to a relatively permanent change in skilled motor performance[32]. This is fundamental for acquiring new motor skills, responding to dynamic environmental conditions and for re-learning lost motor skills after injury[150]. Repeated training or practice is required to acquire complex motor skills and achieve peak performance. Therefore, strategies which maximise performance and enhance the acquisition of motor skills have received considerable attention in motor learning and rehabilitation literature[151].

Recently the modulation of cortical and subcortical excitability through external means such as non-invasive brain stimulation has received increasing attention as a means to

enhance performance during training[152-154]. One such application is transcranial direct current stimulation (tDCS). tDCS involves the delivery of continuous, weak electric currents to the brain to alter the resting membrane potentials of neurons to influence excitability[155]. There is growing consumer interest in the ability of tDCS to modulate brain activity. Halo Sport[156] and Caputron[157] are two examples of commercially available tDCS devices being marketed to sporting populations. The manufacturers make reference to research evidence which illustrates the efficacy of tDCS to enhance motor performance[158,159], including in sporting populations[160]. Much of the tDCS research has focused on the primary motor cortex and pre-motor areas[161]; however, researchers are increasingly considering the cerebellum as a target[136,162-164]. The cerebellum contributes to the control of both motor and non-motor behaviours, including learning, posture and balance, coordination, cognition, emotion, and language[165-171]. The cerebellum has a particular role in error-based learning[172-174]. In error-based learning, sensory prediction errors; the difference between predicted sensory consequences of a movement command and the resultant sensory feedback, are used to adjust the subsequent motor output[172,175,176]. Furthermore, evidence from neurophysiological, neuroimaging and behavioural studies in animals and humans suggest that cerebellar activation varies with the type of motor task performed and the stage of motor learning[14,37,38]. Given the importance of the cerebellum in error-based motor learning[28,177] and re-learning of motor skills after central nervous system injury[29,30,178], transcranial direct current stimulation over the cerebellum (ctDCS) has been advocated as an alternative tDCS stimulation site to promote motor learning[179-181].

In a laboratory setting, motor learning is often evaluated using two paradigms: motor adaptation or skill learning. Motor adaptation consists of a perturbation applied during the performance of a well-learnt motor skill, for example, perturbing limb trajectories during reaching. The learner adapts to the error induced by the perturbation rapidly over minutes to hours (adaptation). When the perturbation is removed, the adaptation is retained for a period of time (after-effects) and gradually wanes over time (de-adaptation)[47]. However, with repeated exposure to the perturbation, learning is observed through rapid reductions in errors[47] and faster rates of adaptation on subsequent exposures[182]. In motor skill learning paradigms, learning is evaluated through exposure to a novel motor task. Motor learning is observed through the reduction of errors and performance improvement beyond baseline levels[43].

Motor learning occurs over distinct phases. There is the *early fast* learning in which improvements in performance are seen rapidly within a single training session[37]. In the later *slow* stage, further performance gains are seen across several sessions of practice[38]. Progression from fast to slow learning depends on appropriate rest periods and subsequent sleep[39], where gains in performance can be observed without the additional practice of the task[38]. Changes in performance are initially transient in nature, but with extended practice, the performance of skilled behaviour becomes less attention-demanding and skilled performance is possible even after long breaks[37]. For the purposes of this paper, the time scales of learning are represented as 1) long-term changes in performance measured after a break of 24 hours or more; 2) short-term change in performance after a break of less than 24 hours; 3) change in performance measured immediately after training and 4) change in performance during training.

There is ample evidence indicating that ctDCS can modulate cerebellar activity at a neurophysiological level[74], less is known about its effect on behavioural outcomes[183]. To date, the evidence for the efficacy of ctDCS has been limited to its ability to modulate motor performance[181]. A recent meta-analysis reported the effectiveness of anodal and cathodal ctDCS in modulating motor performance in healthy individuals in both motor adaptation and motor skills tasks[181], however, a systematic understanding of how ctDCS contributes to different time scales of motor learning is still lacking[31,179]. Therefore, the present systematic review aims to elucidate the effects of ctDCS on motor learning across different time scales in healthy individuals to determine if the documented gains in performance persist for a substantial period after training. This understanding will be useful in ascertaining the prospects of using ctDCS as a neuromodulatory tool to augment motor learning in both elite performance in healthy individuals and following brain lesions in clinical populations.

2.4 METHODS

2.4.1 Study design

A systematic search and review of the literature were undertaken based on an *a priori* plan.

2.4.2 Inclusion and exclusion criteria

Studies were included if they met all the following criteria: involved healthy individuals above the age of 18 years, delivered real or sham tDCS over the cerebellum, random assignment to groups, measured behavioural outcomes of change in motor performance, and appeared in peer-reviewed English-language journals. Studies that compared different stimulation areas in the brain were included if data from cerebellar stimulation could be extracted and viewed separately.

Studies were excluded if they were reviews, books, theses, conference papers, commentaries, letters; if the sample consisted of animals; if the motor skill learning task did not involve the use of upper and lower limb; or if ctDCS was applied in combination with another intervention.

2.4.3 Information sources

A search (July 2019) of the following databases was undertaken: CINAHL, MEDLINE, SPORT Discus, Scopus, Web of Science, Cochrane via OVID, Evidence-Based Reviews (EBM) via OVID, AMED: Allied and Complementary Medicine, PsycINFO, and PEDro. No limit was placed on the publication date. The search strategy (Appendix A) included following key search terms: acquisition, motor performance, motor control, learning, adapt*, ctDCS, cerebellar stimulation, tDCS, transcranial direct current stimulation, non-invasive brain stimulation, noninvasive brain stimulation, direct current stimulation, cerebell*. The reference list of included studies, recent systematic reviews, and meta-analyses were also searched.

2.4.4 Study selection

Following duplicate removal, the first author (N.K.) reviewed the titles and abstracts of all remaining studies. If a decision to include an article could not be made based on the title and abstract review, the full text was reviewed. A second reviewer (N.S.) was consulted if eligibility was unclear and a consensus reached.

2.4.5 Data extraction

Data was extracted using a form developed from the Cochrane data extraction and assessment template[184]. Extracted information included the study characteristics, ctDCS

stimulation parameters, motor learning task description, outcome measures, and key findings.

2.4.6 Assessment of study quality

The quality of the included studies was critically appraised using the revised Cochrane's risk-of-bias tool for randomised trials (RoB 2)[185]. Two reviewers (N.K. and N.S.) independently rated the studies with any disagreements being discussed until consensus was reached. The revised Cochrane's risk-of-bias tool evaluates the methodological quality of the studies in relation to trial design, conduct, and reporting. Based on the answers to a series of signalling questions within five domains (randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results), the studies were considered to have "low" or "high" risk-of-bias or "some concerns". For randomised crossover trials signalling questions on carryover effect were additionally assessed. The overall risk-of-bias judgement for each study was categorized according to the revised Cochrane's risk-of-bias guidelines[185].

2.5 RESULTS

2.5.1 Search results

The electronic search retrieved 633 studies, which was reduced to 281 following duplicate removal. Title and abstract review excluded 237 studies which did not meet the eligibility criteria. On full-text review, a further 27 studies were excluded for reasons outlined in Figure 2-1.

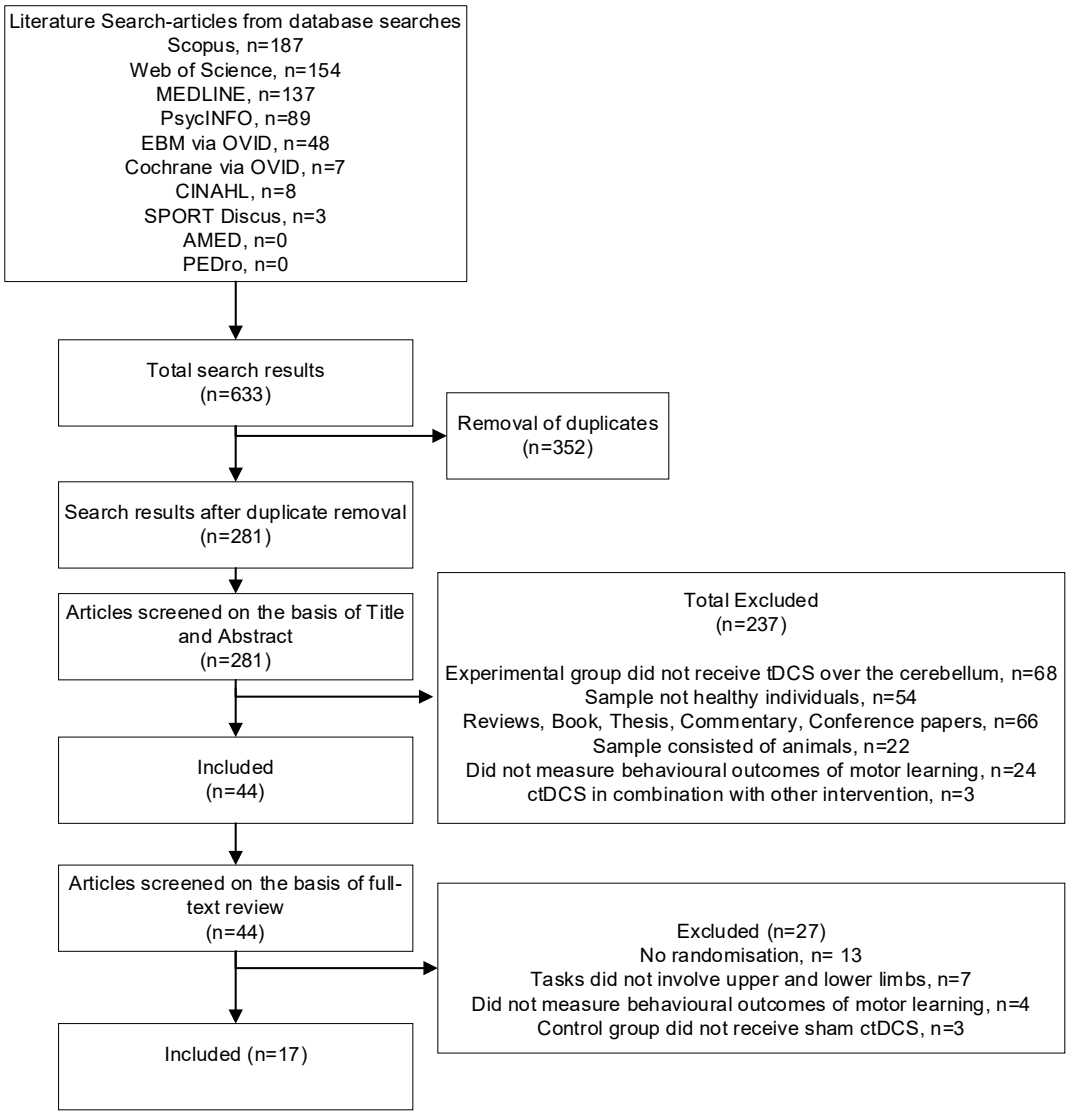

Figure 2-1 Flow chart showing the study selection process and results.

Seventeen RCTs met the criteria for inclusion in this systematic review. No additional studies met the inclusion criteria upon searching the reference list of the included studies. The included studies constituted a total of 629 participants with a mean age between 18 and 69 years (Table 2-1). Only two studies had participants above the age of 40 years[186,187]. Random allocation of participants was in either a parallel (n=14)[46,49,50,52,186-195] or crossover design (n=3)[45,196,197], with 349 participants receiving real ctDCS.

Table 2-1 Characteristics of included studies.

Author, Year	Sample Size; Mean Age (years) ± SD	ctDCS stimulation Type	Task	Training sessions	Outcome measure	Results			
						≥24 Hrs	<24 Hrs	IA	D
Jayaram, 2012[52]	40 (A= 8, C= 8, A= 8, C= 8, S= 8); 27, 20-33	A, C & S	Adaptation: Split-belt treadmill walking task	Single	Step length symmetry: rate, amount	NT	NT	A: X C: X	A: + C: –
Shah, 2013[45]	8 (A= 8, C= 8, S= 8); 18-26	A, C & S	Skill: Ankle tracking task	Single for each condition	Normalised accuracy index	NT	A: + C: +	NT	NT
Dutta, 2014[188]	8 (A= 4, S= 4); 24-36	A & S	Skill: Myoelectric visual pursuit task	Single	Normalised response latency; Tracking accuracy: mean absolute error	NT	NT	NT	–
Panouilleres, 2015[186]	53 (A= 26, S= 27); Old: 63.2 ± 7.5 Young: 22.5 ± 3.1	A & S	Adaptation: Visuomotor rotation task	Single	Angular error	NT	X	NT	X
Yavari, 2016[191]	29 (A= 10, C= 10, S= 9); 24 ± 5	A, C & S	Adaptation: Visuomotor adaptation task	Single	Reach angles; perception of hand position; mean reach direction	NT	NT	NT	A: + C: –
Ehsani, 2016[189]	39 (A= 20, S=19); 22.77 ± 1.32	A & S	Skill: Serial response time task	Single	Response time (RT); number of errors (ER)	RT: + ER: +	RT: X ER: +	NT	RT: X ER: +
Taubert, 2016[50]	41 (A= 14, C= 12, S= 15); 27 ± 3	A, C & S	Adaptation: Force field adaptation task	Single	Reaching error; set-break forgetting	A: – C: X	NT	NT	A: – C: X

I: experiment 1, II: experiment 2, IA: immediately after, D: during the intervention, A: anodal ctDCS, C: cathodal ctDCS, S: sham ctDCS, NT: not tested, +: enhanced, –: impaired, X: no effect, SD: standard deviation, NG: not given.

Table continued…

Author, Year	Sample Size; Mean Age (years) ± SD	ctDCS stimulation Type	Task	Training sessions	Outcome measure	Results			
						≥24 Hrs	<24 Hrs	IA	D
Panico, 2016[190]	26 (C=13, S= 13); 21.57 ± 2.33	C & S	Adaptation: Visuomotor rotation task	Single	Error; error rate; time course of stimulation effect on error	NT	NT	NT	–
Fernandez, 2017[196]	14 (C= 14, S= 14); 28.93 ± 4.59	C & S	Adaptation: Spatio-temporal gait task	Single for each condition	SD of stride length and step time	NT	NT	–	NT
Samaei, 2017[187]	30 (A=15, S= 15); 68.70 ± 5.28	A & S	Skill: Serial Reaction time task	Single	Response time (RT); number of errors (ER)	RT: + ER: X	RT: + ER: X	NT	RT: X ER: X
Foerster, 2017[197]	15 (A= 15, C= 15, S= 15); 21-24	A, C & S	Adaptation: Balance control	Single for each condition	Overall stability index (OSI)	NT	NT	A: X C: –	NT
Poortvliet, 2018[49]	28 (A= 14, S= 14); 25.64 ± 3.82	A & S	Adaptation: Postural adaptation	Single	Postural steadiness: centre of pressure (COP) displacement; SD; total path length	NT	NT	+	NT
Summers, 2018[192]	14 (A=7, S=7); 28.8 ± 10.5	A & S	Skill: Finger tracking task	Single	Tracking accuracy index	NT	NT	X	X

I: experiment 1, II: experiment 2, IA: immediately after, D: during the intervention, A: anodal ctDCS, C: cathodal ctDCS, S: sham ctDCS, NT: not tested, +: enhanced, –: impaired, X: no effect, SD: standard deviation, NG: not given.

Table continued…

Author, Year	Sample Size; Mean Age (years) ± SD	ctDCS stimulation Type	Task	Training sessions	Outcome measure	Results			
						≥24 Hrs	<24 Hrs	IA	D
Liew, 2018 [194]	31 (A:16, S: 15), NG	A & S	Adaptation: Visuomotor adaptation task	Single	Hand endpoint angle: target error (E); reaction time (RcT)	NT	NT	E: X RcT: X	E: X, RT:X
	19 (A:10, S:9), NG	A & S	Adaptation: Visuomotor adaptation task	Single	Hand endpoint angle: target error	NT	NT	X	X
Jongkees, 2019 [193]	72 (A=24, C=24, S=24); A: 19.8 ± 1.6, C: 19.5 ± 1.5, S: 19.3 ± 1.8	A, C & S	Skill: Serial reaction time task	Single	Percentage accuracy (ACC); reaction time (RcT)	A: ACC-X, RT—; C: ACC-X, RT: X	NT	NT	A: ACC-X, RT- –; C: ACC-X, RT: X
Jackson, 2019 [46]	42 (A=21, S=21); 25 ± 3.9	A & S	Skill: Overhand throwing task	Single	Endpoint error: total (T); online (On) and offline (Of) learning	T: +, Of: X	On: +	NT	NT

I: experiment 1, II: experiment 2, IA: immediately after, D: during the intervention, A: anodal ctDCS, C: cathodal ctDCS, S: sham ctDCS, NT: not tested, +: enhanced, –: impaired, X: no effect, SD: standard deviation, NG: not given.

Table continued…

Author, Year		Sample Size; Mean Age (years) ± SD	ctDCS stimulation Type	Task	Training sessions	Outcome measure	Results			
							≥24 Hrs	<24 Hrs	IA	D
Mamlins, 2019[195]	I	30 (A=10, C=10, S=10); 24.1 ± 2.3	A, C & S	Adaptation: Force field adaptation task	Single	Maximum error (extent & rate of learning); perpendicular velocity	NT	NT	A:X, C:X	A:X, C:X
		30 (A=10, C=10, S=10); 24.1 ± 2.3							A:X, C:X	A:X, C:X
	II	30 (A=10, C=10, S=10); 22.3 ± 3.1	A, C & S	Adaptation: Visuomotor adaptation task	Single	Angular end point error (extent & rate of learning)	NT	NT	A:X, C:X	A:X, C:X
		30 (A=10, C=10, S=10); 22.3 ± 3.1							A:X, C:X	A:X, C:X
Summary Total		n=629	A= 15 C= 9	Adaptation=10 Skill=7			A=5 C=2	A=5 C=1	A=6 C=3	A=11 C=5

I: experiment 1, II: experiment 2, IA: immediately after, D: during the intervention, A: anodal ctDCS, C: cathodal ctDCS, S: sham ctDCS, NT: not tested, +: enhanced, –: impaired, X: no effect, SD: standard deviation, NG: not given.

Of the seventeen studies, six had "some concerns"[45,46,49,187,189,196], and eleven had "high" risk-of-bias[50,52,186,188,190,191,193-195,197]. Studies having "some concerns" were due to failure to explicitly report on the randomisation process and trial registration or pre-specified statistical analysis plan. Studies having a "high" risk-of-bias was due to differences in baseline characteristics between the intervention groups suggesting issues with the randomisation process, lack of information on blinding of the outcome assessor, the bias in the selection of reported results, and insufficient time for washout of carry-over effects. Refer to Figure 2-2 and Appendix B.

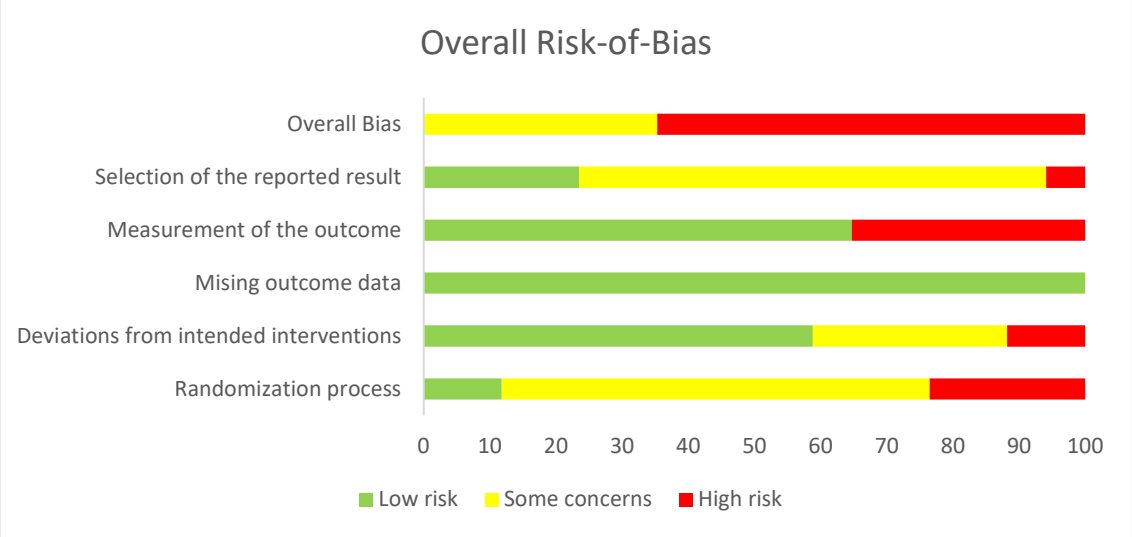

Figure 2-2 Overall risk-of-bias judgements for each domain.

2.5.2 ctDCS intervention

The type of ctDCS stimulation varied across the studies. Eight studies applied anodal ctDCS[46,49,186-189,192,194], two cathodal ctDCS[190,196], and the remaining seven applied both anodal and cathodal stimulation[45,50,52,191,193,195,197].

All studies investigated the effects of a single session of ctDCS. In the majority of studies (n=9) stimulation was delivered *during* the training of a motor task[45,50,52,187-189,191-193]. In three studies stimulation was delivered *prior* to the training of the task[49,196,197] and in the remaining five studies ctDCS was delivered just *prior to and in conjunction with task training*[46,186,190,194,195]. The stimulation duration ranged between 8-30 minutes.

In tasks involving the upper limb, the stimulation was predominantly applied to the lateral cerebellum (n=11) with respect to the training limb, ipsilaterally

(n=10)[45,46,50,186,187,189-191,194,195], or contralaterally (n=1)[188]. Two studies applied the stimulation to the bilateral cerebellar hemispheres[192,193]. Four studies investigated the effect of ctDCS on a bilateral task by placing the target electrode centrally[49] or with respect to the dominant limb[52,196,197]. The return electrode was placed on the forehead[49,188], buccinator muscle[45,50,52,191,192,196], or upper limb[186,187,189,190,197].

ctDCS was delivered at a current density of 0.13mA/cm^2 (n=1)[45], 0.08mA/cm^2 (n=10)[46,50,52,187,189-191,194,195,197], 0.06mA/cm^2 (n=2)[186,196], or 0.03mA/cm^2 (n=4)[49,188,192,193]. Full details of the stimulation parameters are shown in Table 2-2.

Table 2-2 Stimulation parameters.

Author, Year	ctDCS Delivery	Electrode Location		Electrode Size (cm^2)		Intensity (mA)	Density (mA/cm^2)	ctDCS Duration	
		Target	Return	Target	Return			Real (min.)	Sham (min.)
Jayaram, 2012[52]	During the task	Lateral cerebellar hemisphere, I/L & C/L to DL	Buccinator, I/L & C/L to DL	25	25	2	0.08	15	0.5
Shah, 2013[45]	During the task	Left cerebellar hemisphere, I/L to TL	Left buccinator, I/L to TL	8	35	1	0.13	15	0
Dutta, 2014[188]	During the task	Left cerebellar hemisphere, C/L to TL	Forehead above the right supraorbital ridge, I/L to TL	35	35	1	0.03	15	0.17
Panouilleres, 2015[186]	Prior + during the task	Right cerebellar hemisphere, I/L to TL	Left trapezius, C/L to TL	35	35	2	0.06	17	0.5

A: anodal ctDCS, C: cathodal ctDCS, I/L: ipsilateral, C/L: contralateral, TL: training limb, DL: dominant limb, BL: bilateral.

Table continued…

Author, Year	ctDCS Delivery	Electrode Location		Electrode Size (cm^2)		Intensity (mA)	Density (mA/cm^2)	ctDCS Duration	
		Target	Return	Target	Return			Real (min.)	Sham (min.)
Yavari, 2015[191]	During the task	Right cerebellar hemisphere, I/L to TL	Right buccinator I/L, to TL	25	25	2	0.08	15	0.5
Ehsani, 2016[189]	During the task	Right cerebellar hemisphere, I/L to TL	Right deltoid, I/L to TL	25	25	2	0.08	20	1
Taubert, 2016[50]	During the task	Right cerebellar hemisphere, I/L to TL	Right buccinator, I/L to TL	25	25	2	0.08	20	0.5
Panico, 2016[190]	Prior + during the task	Right cerebellar hemisphere, I/L to TL	Right deltoid, I/L to TL	25	25	2	0.08	21	0.5

A: anodal ctDCS, C: cathodal ctDCS, I/L: ipsilateral, C/L: contralateral, TL: training limb, DL: dominant limb, BL: bilateral.

Table continued…

Author, Year	ctDCS Delivery	Electrode Location		Electrode Size (cm^2)		Intensity (mA)	Density (mA/cm^2)	ctDCS Duration	
		Target	Return	Target	Return			Real (min.)	Sham (min.)
Fernandez, 2017[196]	Prior to the task	Right cerebellar hemisphere, I/L to DL	Right buccinator, I/L to DL	35	35	2	0.06	20	0
Samaei, 2017[187]	During the task	Right cerebellar hemisphere, I/L to TL	Right deltoid, I/L to TL	25	25	2	0.08	20	0.5
Foerster, 2017[197]	Prior to the task	Right cerebellar hemisphere, I/L to TL	Right deltoid, I/L to TL	25	25	2	0.08	A:13 C: 9	0.5
Poortvliet, 2018[49]	Prior to the task	Ventral, dorsolateral aspects of the cerebellum and the cerebellar vermis	Centrally on the forehead	35	100	1	0.03	20	0.67

A: anodal ctDCS, C: cathodal ctDCS, I/L: ipsilateral, C/L: contralateral, TL: training limb, DL: dominant limb, BL: bilateral.

Table continued…

Author, Year	ctDCS Delivery	Electrode Location		Electrode Size (cm^2)		Intensity (mA)	Density (mA/cm^2)	ctDCS Duration	
		Target	Return	Target	Return			Real (min.)	Sham (min.)
Summers, 2018[192]	During the task	BL cerebellar hemisphere	Buccinator IL to TL	70	35	2	0.03	30	0.5
Liew, 2018 [194]	Prior + during the task	Right cerebellar hemisphere, I/L to TL	Buccinator IL to TL	25	25	2	0.08	>25	0.5
Jongkees, 2019 [193]	During the task	BL cerebellar hemisphere	BL mastoid	35	35	1	0.03	20	0.25
Jackson, 2019[46]	Prior + during the task	Right cerebellar hemisphere, I/L to TL	Buccinator IL to TL	25	25	2	0.08	25	0.5
Mamlins, 2019[195]	I: During, Prior + during	I: Right cerebellar hemisphere, I/L to TL	I: Buccinator IL to TL	I: 25	I: 25	I: 2	I: 0.08	I: 10.36 (0.12), 13.81 (0.19)	I: 1
	II: During, Prior + during	II: Right cerebellar hemisphere, I/L to TL	II: Buccinator IL to TL	II: 25	II: 25	II: 2	II: 0.08	II: 7.61 [0.17], 10.20 [0.16]	II: 1

A: anodal ctDCS, C: cathodal ctDCS, I/L: ipsilateral, C/L: contralateral, TL: training limb, DL: dominant limb, BL: bilateral.

2.5.3 Motor learning tasks

Ten studies evaluated a motor adaptation task, and seven studies evaluated a motor skill task. The motor adaptation tasks included perturbation during visuomotor[186,190,191,194,195], locomotor[52,196], reaching[50], or postural control[49,197] tasks. Skill learning paradigms used serial reaction time task[187,189,193], tracking[45,188,192], or a throwing task[46].

2.5.4 Outcomes

Motor performance outcomes were measured based on error (n=16)[45,46,49,50,52,186-195,197], response latency (n=1)[188], response time (n=2)[187,189], reaction time (n=2)[193,194], or movement variability (n=2)[49,196]. Studies measured outcomes over a range of time scales including; after a break of 24 hours or more post intervention (n=5)[46,50,187,189,193], after a break of less than 24 hours post intervention (n=5)[45,46,186,187,189], immediately after the intervention (n=7)[49,52,192,194-197], or during the intervention (n=12)[50,52,186-195].

Long-term motor learning- Motor performance after a break of 24 hours or more:

Of the five studies which evaluated the effect of ctDCS after a break of 24 hours or more, three reported enhanced[46,187,189], while two reported impaired[50,193] gains in motor performance with anodal ctDCS. Compared to sham ctDCS, anodal ctDCS enhanced the gains in the performance of a motor skill tasks evaluated after a break of 24[46] and 48 hours[187,189]. This was reflected by a greater reduction in the number of errors and/or faster response time in those aged less than 40 years[46,189] and a greater reduction in response time, but not the number of errors, in individuals over 40 years[187]. Of the two studies that reported impaired gains in motor performance, one found impaired reaction time, but not the number of errors in a motor skill task after 24 hours[193], and the other reported impaired early adaptation in a motor adaptation task when evaluated after 24 hours[50]. Two studies evaluated the effect of cathodal ctDCS and found no difference in motor performance 24 hours after the intervention[50,193]. These studies applied anodal and cathodal ctDCS centred over the inion[193] or ipsilateral to the training limb during task training or prior to and in conjunction with task training[46]. The stimulation was delivered at a current density of 0.03mA/cm^2 [193] or 0.08mA/cm^2 for 20-25 minutes[46,50,187,189,193].

Short-term motor learning- Motor performance after a break of less than 24 hours:

Of the studies that evaluated the effect of anodal ctDCS after a break of less than 24 hours, four found enhanced[45,46,187,189] and one found no effect[186] on gains in motor performance compared to sham ctDCS. Anodal ctDCS enhanced the performance of a motor skill task by reducing the number of errors but not response time in healthy young individuals[189] and reduced the response time but not the number of errors in healthy older individuals tested after a break of 35 minutes[187]. Anodal ctDCS also improved performance of motor skill task 5[46], 10, 30, and 60 minutes after intervention. All four studies stimulated the lateral cerebellum ipsilateral to the training limb for 15[45], 20[187,189], or 25[46] minutes at a current density of 0.13mA/cm^2 [45] or 0.08mA/cm^2 [46,187,189]. Whereas anodal ctDCS did not affect the number of errors in a motor adaptation task performed after a gap of 50 minutes when the stimulation was delivered ipsilateral to the training limb at a current density of 0.06mA/cm^2 for 17 minutes[186].

One study evaluated the effect of cathodal ctDCS on motor performance after a break of less than 24 hours and reported improvement in ankle tracking accuracy tested after 10, 30, and 60 minutes[45].

Immediate motor learning- Motor performance immediately after the intervention:

Of the studies that evaluated the effect of anodal ctDCS immediately after the intervention, one study reported enhanced[49], and five found no effect on gains in motor performance as compared to a sham ctDCS group[52,192,194,195,197]. Anodal ctDCS at a current density of 0.03mA/cm^2 for 20 minutes improved the performance by reducing the postural variability and increasing steadiness when the target electrode was placed centrally over the cerebellum[49]. While the same site of stimulation and current density delivered for 30 minutes had no effect on finger tracking accuracy[192]. Anodal ctDCS delivered ipsilateral to the dominant limb at a current density of 0.08mA/cm^2 for around 15 minutes had no effect on static and dynamic balance[197], visuomotor adaptation[194,195], forcefield adaptation[195], or locomotor adaptation[52].

Application of cathodal ctDCS had no effect[195] or impaired[196,197] gains in motor performance evaluated immediately after stimulation. As compared to sham ctDCS, cathodal ctDCS increased variability in a walking adaptation task[196] and impaired static

but not dynamic balance in adaptation task[197]. These effects were seen when ctDCS was delivered ipsilateral to the dominant limb prior to motor task training at a current density of 0.06mA/cm^2 [196] or 0.08mA/cm^2 [197] for 20[196] or 9[197] minutes.

Simultaneous motor learning- Motor performance during the intervention:

Application of ctDCS had a varied impact on motor performance during task training. Anodal ctDCS enhanced (n=3)[52,189,191], impaired (n=3)[50,188,193], or had no effect on gains in motor performance during task training (n=5)[186,187,192,194,195]. Compared to sham ctDCS, anodal ctDCS enhanced motor performance by improving the rate of adaptation[52,191] and reduced the number of errors but not response time in a serial reaction time task[189]. These effects were primarily observed when anodal ctDCS was delivered ipsilateral to the dominant limb[52] or training limb[189,191] for 15 minutes[52,191] or more[189] at a current density of 0.08mA/cm^2. Anodal ctDCS impaired gains in motor performance during a perturbed reaching task[50], visual pursuit task[188], and serial reaction time task[193]. In the serial reaction task, the impaired gains in motor performance occurred in reaction time but not in the number of errors. In the perturbed reaching task, ctDCS was delivered ipsilateral to the training limb for 20 minutes at a current density of 0.08mA/cm^2 [50]. Whereas, impaired gains in performance of the serial reaction time task or visual pursuit task were seen when the current was delivered centrally[193] or on the lateral cerebellum contralateral to the training limb[188] for up to 20 minutes at a current density of 0.03mA/cm^2 [188,193]. Anodal ctDCS had no effect on response time in skill task[187] and the number of errors in adaptation[186,194,195] or skill task[192] when the current density was 0.08mA/cm^2, 0.06mA/cm^2, and 0.03mA/cm^2, respectively. The target electrode was placed either centrally over the cerebellum[192] or on the lateral cerebellum ipsilateral to the training limb[186,187,192,194,195] which delivered the stimulation for up to 30 minutes.

Of the five studies that evaluated the effect of cathodal ctDCS during task training, three reported impaired[52,190,191] and two reported no effects[193,195] on gains in motor performance. As compared to sham ctDCS, cathodal ctDCS resulted in impaired adaptation[52,190,191] and impaired rate of de-adaptation[190]. These effects were seen when cathodal ctDCS was delivered ipsilateral to training limb[52,190,191] for 15 minutes[52,191] or more[190] at a current density of 0.08mA/cm^2. Two studies found no effect of cathodal ctDCS on skill or adaptation task[193,195]. These studies applied cathodal ctDCS centrally[193] or ipsilateral to the training limb[195] during task training alone[193] or prior to

and in conjunction with task training[195] for up to 20 minutes at a current density of 0.03mA/cm^2 [193] or 0.08mA/cm^2 [195].

2.6 DISCUSSION

This review aimed to determine the effects of cerebellar transcranial direct current stimulation on motor learning. For the first time, this study provides a systematic review of RCTs to quantify the effects of ctDCS based on the time scale of motor learning. There is a modest body of research, with 17 studies including 629 participants. The body of evidence is subject to considerable risk-of-bias. The main findings of this systematic review are that anodal ctDCS appears to be effective at enhancing motor skill learning in the short (< 24 hours) and longer-term (≥ 24 hours). Whereas it appears to have no effect on motor learning immediately after or during stimulation. This review suggests that the type of motor task, the tDCS stimulation parameters and the interaction between task and stimulation parameters are likely to influence the efficacy of ctDCS.

When compared to sham ctDCS, anodal ctDCS appears to be effective at improving short and longer-term motor learning in healthy individuals when applied primarily during motor skill learning[45,46,187,189] but not motor adaptation paradigms[50,186]. Task characteristics and their interaction with the time scale of learning may explain this. Motor skill training paradigms use novel or complex motor skills, which may take weeks or months to master[32]. In contrast, motor adaptation tasks involve modifying a well-learnt skill in response to error feedback. Often participants adapt to induced errors within minutes to hours in motor adaptation tasks[53]. It is possible that motor adaptation paradigms are subject to a ceiling effect in healthy individuals. Repeated exposure to the same adaptation task may not provide sufficient stimulus to induce learning[53,198]. In addition, an interference task was undertaken between the intervention and testing sessions of one of the motor adaptation tasks, making interpretation of their results challenging[50].

The reported gains in the performance of a motor skill task in response to anodal ctDCS may also depend on the measure of motor performance used and the age of the participants. In studies investigating healthy young individuals undertaking a unimanual serial reaction time task, ctDCS enhances accuracy but not response time after a break of less than 24 hours and enhanced accuracy and response time after a break of 24 hours

or more[189]. A previous non-randomised experimental study has also reported that ctDCS may have a greater effect on accuracy than response time within and after 24 hours[199]. In contrast, in a study investigating healthy older individuals undertaking the same task, a greater reduction in response time but not the number of errors was observed in response to ctDCS irrespective of the time scale of measurement[187]. These findings suggest that ctDCS may differentially influence short and longer-term motor learning of different parameters of movement performance. However, it is unclear whether the difference between older and younger individuals reflects differences in the mechanism of action of ctDCS or that older individuals have slower response time but not greater inaccuracy in these types of task[200].

In studies which investigated the effects of ctDCS using serial reaction time tasks, conflicting results were observed. Improved response times were seen in a unimanual task[187,189], whereas impaired reaction time was seen in a bimanual task[193]. The performance measure used to reflect motor learning in the two tasks may evaluate different aspects of motor performance. Reaction time reflects the time between stimulus appearance and movement initiation. Whereas, response time is comprised of both reaction time and movement time[201]. However, it is notable that the studies also differed in the stimulation parameters used, where a current density of 0.03mA/cm^2 centred over bilateral cerebellar hemisphere impaired gains, while a current density of 0.08mA/cm^2 targeting the lateral cerebellum ipsilateral to the training limb enhanced gains in motor performance. The challenge of unpacking these conflicting results illustrates the importance of taking a systematic approach to investigating ctDCS; where the influence of motor task, performance metric, and stimulation parameters should be considered.

Anodal ctDCS appears to have no effect on gains in motor performance measured during and immediately after the intervention, where most of the studies demonstrated no effect[52,186,187,192,194,195,197] and some enhanced[49,52,189,191] or impaired[50,188,193] gains in motor performance. These results were observed irrespective of the type of task being studied (adaptation or skill) as has been noted in previous narrative reviews[31,149]. It is therefore unclear whether ctDCS has any effect on motor learning during or immediately after task training. Motor learning research highlights the paradoxical relationship between learning and performance. That is, motor learning, as defined as a permanent change in motor performance, can occur without immediate changes in motor performance. In fact, immediate changes in motor performance in response to an

intervention are often not sustained after a break[202]. This suggests that changes in motor performance during and immediately after anodal ctDCS are less relevant in determining the effectiveness of anodal ctDCS than changes observed after 24 hours or more.

This systematic review highlights that the site of anodal ctDCS stimulation and current density are the critical stimulation parameters which appear to impact the effect produced, irrespective of time scale. Greater gains in motor performance were seen with the target electrode placed centrally on the cerebellum in a bilateral postural control task[49] and ipsilateral to the training limb in unilateral tasks[45,187,189]. In addition, motor performance is enhanced during a bilateral task involving greater perturbation to one of the limbs with the placement of target electrode ipsilateral to that limb[52]. This suggests that the parameters of the motor task may be an important consideration in determining an appropriate site for stimulation. Therefore, researchers should explicitly consider where in the cerebellum motor control and learning is occurring for a given task and select electrode configuration with this in mind[203], acknowledging that current density and specificity is dependent on electrode size and position[204]. Positive effects were more likely to be observed when anodal ctDCS was delivered with a current density of 0.08mA/cm^2 or more. This current density is greater than that recommended for cerebral ctDCS[205]; however, modelling studies illustrate the need for higher current density to stimulate the cerebellum to overcome large shunting of current at the base of the skull[206]. Other stimulation parameters such as stimulation duration and timing of stimulation delivery (at rest or during task training) had an equivocal effect. The total duration of stimulation was not hugely variable and ranged from 15 to 20 minutes. Contrary to previous literature[207], no relationship between stimulation duration and time scale of effect was observed. Further research is required to unpack the effect of stimulation duration on the permanence of ctDCS effects across time scales.

When compared to sham ctDCS, cathodal ctDCS has an equivocal effect on short and longer-term motor learning in healthy individuals. However, most of the studies found impaired gains in motor performance of adaptation tasks during and immediately after cathodal ctDCS[52,190,191,196,197] with few reporting no effect on gains in motor performance[193,195]. Overall, there is insufficient evidence to infer the effect of cathodal ctDCS on motor learning.

Although most of the included studies employed randomised, blinded, sham-controlled designs, their methodological quality was globally considered to have "high" risk-of-bias. Potential sources of bias included failure to report the method of randomisation used, allocation concealment and failure to explicitly state who was blinded: the participant, the person administering the intervention, and/or the outcome assessor. The majority of studies did not report trial registration details or a pre-specified statistical analysis plan. Further, some studies had baseline differences between intervention groups that suggested a problem with the randomisation process. Whilst these judgements of research quality may not reflect what the researchers actually did during the protocol but rather a lack of explicit documentation; it is essential that adherence to, and reporting of, these standards of practice become commonplace in this body of literature. The potential for bias may contribute to the reporting of contradictory results and suggests that the interpretation of the research findings to date must be approached with some caution[203,208,209].

2.6.1 Limitations, Implications and Future Research:

The included studies had considerable variability in both measurement and data processing methods. Some studies measured the time course of change in error throughout the task training[186], some in specific epochs (early or late epochs)[50,190], some fitted an exponential curve[52,191], while other measured change scores[45,46,187,189]. Furthermore, the method for calculating changes in motor performance was inconsistent across studies. For instance, the error was calculated as mean error[52], mean absolute error[188], or normalised accuracy index using root mean square error[45] while others failed to describe how the error was calculated[189]. The method by which error is calculated affects its accuracy; for example, a simple mean of errors may not reflect individual variability while a mean absolute error encompasses bias due to individual variability[32]. This makes comparing results across studies challenging.

Despite these limitations, the review adds to our understanding of the potential of ctDCS to impact motor learning, with particular reference to the time scale of learning. It highlights the importance of task characteristics, movement parameter outcome measurement techniques, participant age, and stimulation parameters when interpreting the research body and designing future studies. Further research, which explores the time scales of greater than 24 hours are required. There are also many unanswered questions regarding the cumulative effects of ctDCS over multiple sessions and the

long-term retention of performance after a delay of weeks and months. More studies evaluating the effect of ctDCS on motor adaptation tasks over longer time scales are needed to elucidate its effect on adaptive learning.

2.7 CONCLUSIONS

In conclusion, anodal ctDCS appears to be effective at improving short and long-term motor skill learning. However, these results are predicated upon just four modest-quality studies. While these findings illustrate the potential of targeting the cerebellum with tDCS to enhance learning in healthy and clinical populations, researchers need to take a methodologically robust and systematic approach to future research. Factors including the challenge of the motor task and its characteristics, the ctDCS stimulation parameters, method of measuring motor performance, and participant age are likely to influence whether ctDCS will enhance or have no effect on motor learning.

2.8 AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualization and designing of the study. N.K. was involved with the literature search and data extraction. N.K. and N.S. were involved with manuscript preparation. N.S and D.T. were involved in supervision. All authors were involved in reviewing and editing the manuscript.

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2.10 SUMMARY

This systematic review draws attention to the importance of dissociating the ctDCS effects based on the time scales of motor learning when interpreting its effect on motor learning. This chapter highlights that a single session of anodal ctDCS appears to be effective at enhancing short term (<24 hours) and long-term (≥24 hours) changes in motor performance depending on the type of motor learning paradigm investigated. The enhancing effect is seen when anodal ctDCS is delivered ipsilateral to the training limb for 15-20 minutes at a current density of 0.08mA/cm^2 or more. Evidence for the

permanence of the anodal ctDCS effects strengthens its potential to be used as a neuromodulatory tool capable of impacting motor learning in healthy or injured populations. In contrast, the effect of cathodal ctDCS on time scales of motor learning is equivocal, irrespective of the type of task performed. The methodological quality of included RCTs lack explicit reporting of the randomisation process and blinding of personnel administering the tDCS. Lack of trial registry or pre-specified statistical analysis plan was another limitation. The main gaps in the literature identified by this systematic review are that the effect of anodal ctDCS on motor adaptation tasks in short and longer time scale is limited. The effect of repeated application of ctDCS over multiple sessions is also limited in both motor skill and motor adaptation tasks.

Chapter 3. **Study B: RCT in Healthy Individuals**

3.1 PROLOGUE

The results of the systematic review reported in Chapter 2 highlighted the lack of evidence for the effect of repeated anodal ctDCS on motor adaptation tasks over longer timeframes. This chapter describes an RCT which investigates whether three consecutive days of anodal ctDCS can modulate learning of a motor adaptation task in healthy individuals. This study is currently under review with a peer-reviewed journal and is presented here as it was submitted with no modification in content and a few minor formatting modifications to facilitate reading.

Start of submitted manuscript 2

Cerebellar transcranial direct current stimulation for learning a novel split-belt treadmill task: A randomised controlled trial

Kumari N, Taylor D, Rashid U, Vandal AC, Smith PF, Signal N. Cerebellar transcranial direct current stimulation for learning a novel split-belt treadmill task: A randomised controlled trial. Manuscript submitted for publication. 2019.

3.2 ABSTRACT

This study aimed to examine the effect of repeated anodal cerebellar transcranial direct current stimulation (ctDCS) on learning of a split-belt treadmill task. Thirty healthy individuals randomly received three consecutive sessions of active or sham anodal ctDCS during split-belt treadmill training. Motor performance and strides to steady-state performance were evaluated before (baseline), during (adaptation), and after (de-adaptation) the intervention. The outcomes were measured one week later to assess absolute learning and during the intervention to evaluate cumulative, between, and within-session effects. Data were analysed using linear mixed-effects regression models. During adaptation, there was no significant difference in absolute learning

between the groups ($p > 0.05$). During de-adaptation, a significant difference in absolute learning between the groups ($p = 0.03$) indicated slower de-adaptation with anodal ctDCS. Pre-planned secondary analysis revealed that anodal ctDCS significantly reduced the cumulative ($p = 0.01$) and between-session effect ($p = 0.01$) on immediate adaptation. There were significant cumulative ($p = 0.02$) and within-session effects ($p = 0.03$) on immediate de-adaptation. Repeated anodal ctDCS does not enhance motor learning measured during adaptation to a split-belt treadmill task. However, it influences the retention of learning effects, suggesting that it may be beneficial in maintaining therapeutic effects.

3.3 INTRODUCTION

Cerebellar transcranial direct current stimulation (ctDCS), a non-invasive brain stimulation technique, has the potential to become a neurorehabilitation tool to facilitate therapy-induced recovery in people with brain lesions[164,179]. Various neuro-physiological studies[74,210,211] have demonstrated that ctDCS is capable of altering the excitability of the cerebellum, a critical structure in error-based motor learning[28,177,212]. There is evidence of improved gains in motor performance up to 48 hours after a single application of anodal ctDCS[187,189]. However, evidence of its ability to induce long-lasting changes in motor performance with multiple sessions of stimulation is limited[31,149]. This study aimed to elucidate the effect of three consecutive sessions of anodal ctDCS on motor learning of a novel treadmill walking task in healthy individuals.

Motor learning is an internal process associated with practice or experience, which results in the long-lasting acquisition of skilled motor performance[32]. To examine the effect of an intervention on motor learning, evaluation of motor performance more than 24 hours after the intervention is required[32]. This is because the transient effects of the intervention dissipate, but the relatively permanent effects remain at the follow-up evaluation reflecting learning. Such learning is fundamental for acquiring new motor skills and adapting to changing environments in our daily lives. Motor learning is commonly investigated in the laboratory through motor skill and motor adaptation paradigms. Motor skill training paradigms often use novel or complex motor skills, which may take weeks or months to master. In contrast, motor adaptation paradigms involve modifying a well-learnt movement in response to error signals (adaptation) and are characterised by the persistence of adapted patterns upon removal of the error

(after-effects) that gradually returns to its baseline pattern over time (de-adaptation)[53]. Often a person adapts to the induced error within minutes to hours[213]. However, with repeated exposure to errors, immediate reductions in errors[47], faster adaptation on subsequent exposures[182], and a decrease in after-effects are observed[47].

There is a growing body of evidence investigating the effect of ctDCS delivered via a positively charged electrode (anode) or a negatively charged electrode (cathode) on modulating motor performance in healthy individuals. While the majority of the studies have investigated motor skill paradigms, there are limited studies that have evaluated the effect of anodal ctDCS on learning of motor adaptation tasks, particularly functional tasks such as walking (locomotor adaptation)[214]. In addition, research investigating the effect of ctDCS on learning motor adaptation tasks has failed to evaluate its effect on motor learning measured more than 24 hours after the intervention[51,52,215,216]. Only one study has evaluated the effect of anodal ctDCS on locomotor adaptation tasks involving walking on a split-belt treadmill in healthy individuals[52]. The authors demonstrated that a single session of anodal ctDCS enhanced the rate of adaptation during a split-belt treadmill task compared to cathodal and sham stimulation. As this was investigated within a single session, it is still unknown whether the effects of ctDCS accumulate over multiple sessions, or whether ctDCS can modulate long-lasting acquisition of a locomotor adaptation task measured after a delay of days or weeks. The primary goal of this study was to investigate the effects of three consecutive sessions of anodal ctDCS on learning a split-belt treadmill walking task in healthy individuals after a delay of one week. Additionally, we investigated if the effects were cumulative over the three sessions of the intervention, between, and within sessions.

3.4 METHODS

3.4.1 Trial design

This study was a single-centre, double-blinded, parallel, randomised, sham-controlled design. Data were collected in a movement analysis laboratory based at Auckland University of Technology's Millennium Institute in Auckland, New Zealand. Participants were randomised with a 1:1 ratio to either the active or the sham ctDCS group using a pseudo-random number generator in MATLAB 2015a (MathWorks Inc.). All participants and the principal investigator, who administered the ctDCS application and measured the outcomes, were blinded to group allocation. To ensure blinding, two

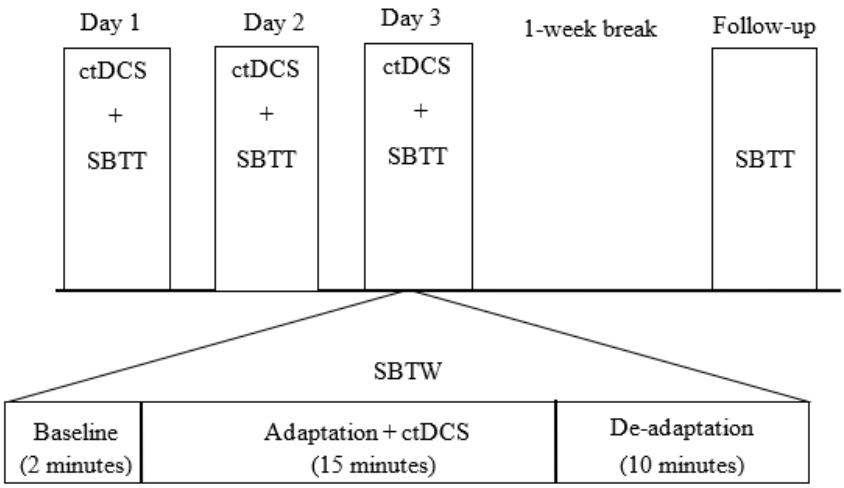
separate battery-operated stimulators were pre-programmed as either active or sham and labelled with separate codes by another researcher. This researcher was also involved with the generation of the random allocation sequence, enrolment, and allocation of participants to interventions. Blinding was maintained until the completion of the data analysis. The study was registered retrospectively on 5th August 2019 with the Australian New Zealand Clinical Trials Registry (Registration Number ACTRN12619001074189).

3.4.2 Study participants

The sample size for this study was estimated based on a previous research[199]. This was due to a lack of data describing the effects of ctDCS on motor learning after a delay of one week in motor adaptation tasks, and insufficient reporting in studies investigating the effects of ctDCS on motor learning in motor skill tasks to calculate a sample size. The sample size was elevated to 30 participants to allow for sampling error and drop-outs. This sample size is larger than all the previous studies that have reported enhanced gains in motor adaptation tasks with a single session of ctDCS[49,52,191]. Participants were recruited through posters on university notice boards and word-of-mouth. Participants were included if they were healthy individuals aged 18 years or above. Exclusion criteria consisted of a history of orthopaedic, cardiac, or neurological conditions that could interfere with walking, and any contraindications to the application of ctDCS[130]. Eligible participants volunteered to participate in the study by giving informed written consent, which conformed to the Declaration of Helsinki. The study was approved by the Ethics Committee of the Auckland University of Technology (16/338).

3.4.3 Study procedure

Each participant attended four sessions; three intervention sessions held on consecutive days and a follow-up session one week later (see Figure 3-1 for an illustration of the study protocol). During the intervention sessions, participants received either active ctDCS or sham ctDCS during split-belt treadmill walking according to the randomisation schedule. At follow-up, split-belt treadmill walking was undertaken without ctDCS.



SBTT: Split-belt treadmill training.

Figure 3-1 An illustration of the study protocol.

3.4.4 Intervention

Cerebellar tDCS (HDCstim part of HDC kit, Magstim) was delivered via two electrodes (25cm^2) embedded in 0.9% saline-soaked sponges. The anodal electrode was placed 3cm lateral to the inion to position it over the cerebellar hemisphere ipsilateral to the dominant leg which was placed on the fast belt of the split-belt treadmill[52]. The cathode was placed over the ipsilateral buccinator muscle (see Figure 3-2 for an overview of the experimental setup on one of the participants who consented for publishing his photograph). The active ctDCS stimulator delivered 2mA of current for 15 minutes with a 30-second ramp-up and ramp-down duration to slowly attenuate skin sensation[217,218]. The sham ctDCS stimulator ramped up the current to 2mA over 30 seconds and then immediately ramped down to 0mA over 30 seconds to ensure effective blinding. Participants in both the groups were familiarised with the ctDCS sensation by turning on the stimulator for a few seconds before the start of the treadmill walking task. To monitor any adverse event after ctDCS application, each participant was asked to give their feedback regarding the sensation of the ctDCS.

(a)  (b) 

Figure 3-2 Overview of the experimental setup.
(a) Participant performing the split-belt walking task, (b) ctDCS electrode positioning.

3.4.5 Split-belt treadmill walking task

The split-belt treadmill task involved walking on a split-belt treadmill (Bertec Corporation, USA) in three phases: baseline, adaptation, and de-adaptation. Each phase was defined by belt speed (slower, faster) and belt symmetry (belts moving together) or asymmetry (belts moving at different speeds). Participants were instructed to stand in the middle of the treadmill with one foot on each belt holding onto a front rail, looking straight ahead whilst walking. The participant's fastest comfortable walking speed was assessed by slowly increasing treadmill speed until the participant reported an inability to comfortably tolerate any further increase. This was undertaken three times and averaged to determine the speed of the faster treadmill belt. The speed of the slower belt was set to half that of the fast belt[219]. During *baseline,* participants walked with symmetrical belts at the slow walking speed. After 2 minutes of walking, the treadmill was stopped, and the ctDCS unit was turned on. During the *adaptation* phase, the treadmill was restarted at the slow speed, and then the belt speed of the fast belt was increased until the fast walking speed was attained. This asymmetrical speed ratio of 2:1 was then maintained for 15 minutes. Finally, in the *de-adaptation* phase, the ctDCS was turned off, and the participant walked for 10 minutes with both belts symmetrical at the slow speed (see Figure 3-1 for an illustration of the study protocol showing split-belt treadmill walking task).

3.4.6 Data collection

A Vicon motion capture system (Vicon Nexus 2.4, Vicon Motion System Inc.) was used to record force and position data from treadmill force plates and reflective markers, respectively. The position of 33 reflective markers, placed according to the Cleveland clinic model[220], was captured via nine-cameras at a frame rate of 200Hz. The data were recorded during the last minute of the baseline phase and throughout the adaptation and the de-adaptation phase.

3.4.7 Outcome measures

Motor performance was measured based on step length symmetry. Step length symmetry is a kinematic variable under predictive control which demonstrates robust adaptation during split-belt treadmill walking[213]. It is calculated as:

$$Step\ length\ symmetry = \frac{fast\ leg\ step\ length - slow\ leg\ step\ length}{fast\ leg\ step\ length + slow\ leg\ step\ length}$$

A symmetry value of zero represents perfect symmetry, whereas a positive value indicates a longer fast leg step length and a negative value indicates a longer slow leg step length[52].

Motor performance was determined by measuring mean step length symmetry during specified time periods during the adaptation and de-adaptation phases:

Immediate adaptation and immediate de-adaptation were determined from the mean step length symmetry of the first three strides of the adaptation and de-adaptation phases, respectively.

Early adaptation and early de-adaptation were determined from the mean step length symmetry of the fourth stride to the point where steady-state performance was achieved for individual participants during the adaptation and de-adaptation phases.

Late adaptation and late de-adaptation were determined from the mean step length symmetry of the last 100 strides of the adaptation and de-adaptation phase, respectively.

The strides to steady-state motor performance were calculated by determining the number of strides taken to achieve a steady-state where the respective stride remained

within the mean ± 2 standard deviations of the last 100 strides for 30 strides[221]. Refer to Figure 3-3 for an illustration of outcome measures.

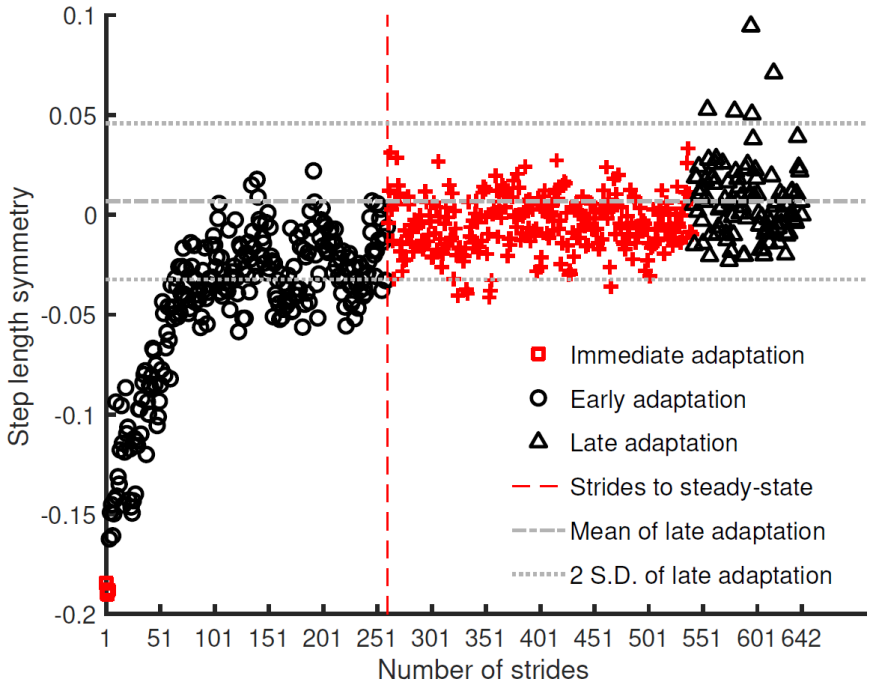


Figure 3-3 Illustration of outcome measures for a single participant during the adaptation phase.

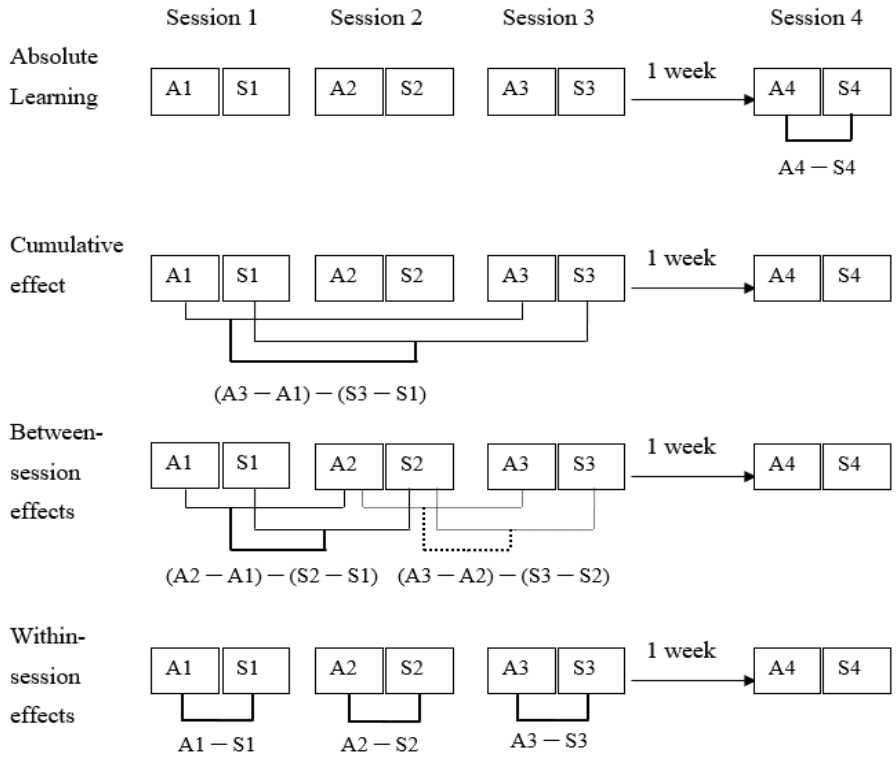
3.4.8 Data processing

A MATLAB-based implementation of the Detection and Correction Algorithm (DACA)[222] was utilised for determining the gait events: heel strikes and toe-offs for each foot. Once the gait events were detected, fast step length and slow step length were calculated[52].

3.4.9 Statistical analysis

The statistical analysis aimed at answering the following questions: 1) What are the absolute learning, cumulative, between-session, and within-session effects of multi-session anodal ctDCS on the adaptation phase of split-belt treadmill walking? 2) What are the absolute learning, cumulative, between-session, and within-session effects of multi-session anodal ctDCS on the de-adaptation phase of split-belt treadmill walking? These questions were addressed with respect to motor performance and strides to steady-state motor performance. Motor performance was analysed with respect to a) immediate; b) early; and c) late adaptation and de-adaptation, respectively (see Figure 3-4 for an illustration of statistical analysis performed). Linear mixed regression

analyses in R (R Foundation for Statistical Computing version 3.5.0) were used to answer these questions. The lme4 package version 1.1-17 was used for fitting all models[223]. Linear mixed regression method yields higher statistical power compared to repeated measures ANOVAs and reduces the risk of type-I error[224]. A blinded *a priori* co-variate selection was undertaken to identify co-variates explaining 5% or more of the variance in the data. These covariates were added to the models to control for their effect. As testing group differences at baseline is considered invalid[225], we entered mean baseline symmetry from session 1 as a covariate to the models where it explained more than 5% or more of the variance in the data. This also catered to any difference in mean baseline symmetry of individual groups from perfect symmetry. Model selection was based on least AICc values (corrected version of Akaike Information Criterion)[226]. Hypothesis testing was undertaken by entering participant and group as categorical variables and session, mean step length symmetry and strides to symmetry as continuous variables. A Gaussian distribution and Gamma distribution with log link were used to model the data pertaining to motor performance and strides to steady-state motor performance, respectively.



A: anodal ctDCS group, S: sham ctDCS

Figure 3-4 Statistical analysis for absolute learning, cumulative effect, between-session effects, and within-session effect measurement time points.

3.5 RESULTS

Thirty participants were recruited to the study between November 2016 and January 2017 (See study flow in Appendix H and baseline demographic characteristics in Appendix I). All participants completed the research protocol and intervention without any adverse events or protocol deviations. The stride-by-stride plots of step length symmetry averaged over all participants in each group are represented in Figure 3-5 and Figure 3-6 along with the mean estimates and standard error of strides to steady-state, immediate, early and late adaptation and de-adaptation, respectively.

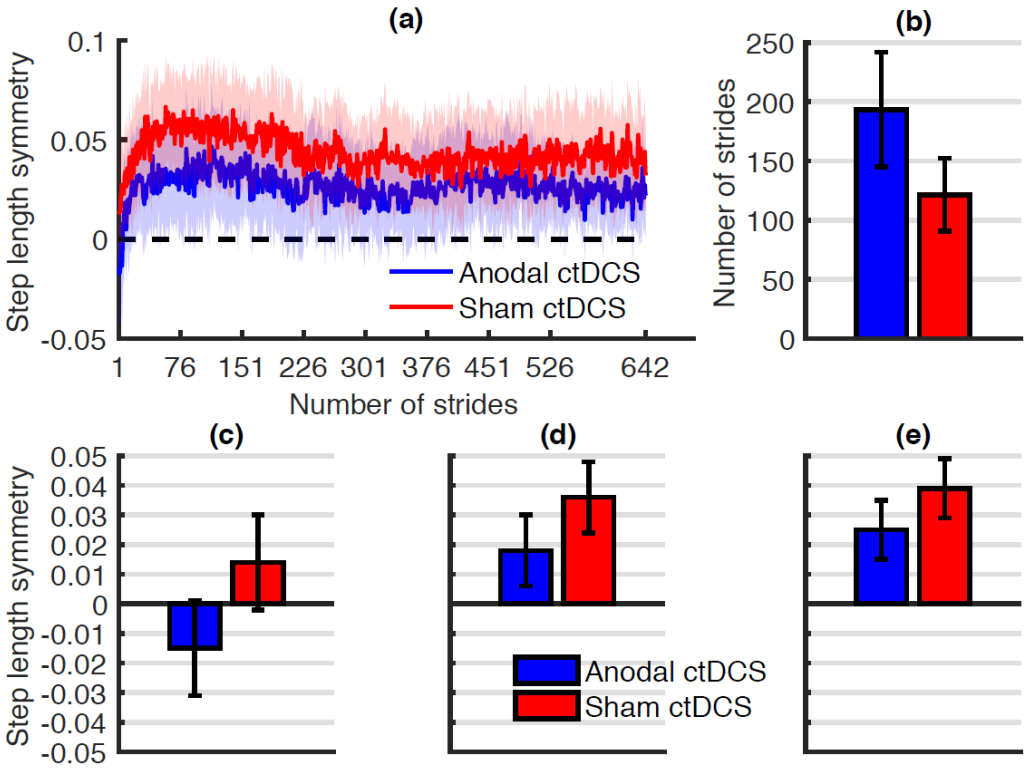


Figure 3-5 Graphs illustrating the results of the adaptation phase at the follow-up session.
(a) Stride-by-stride mean step length symmetry plot. Lightly shaded areas indicate 95% confidence interval. The inset bar graphs indicate mean estimates and standard error from the statistical models for (b) the number of strides to steady-state, (c) immediate adaptation, (d) early adaptation, (e) late adaptation.

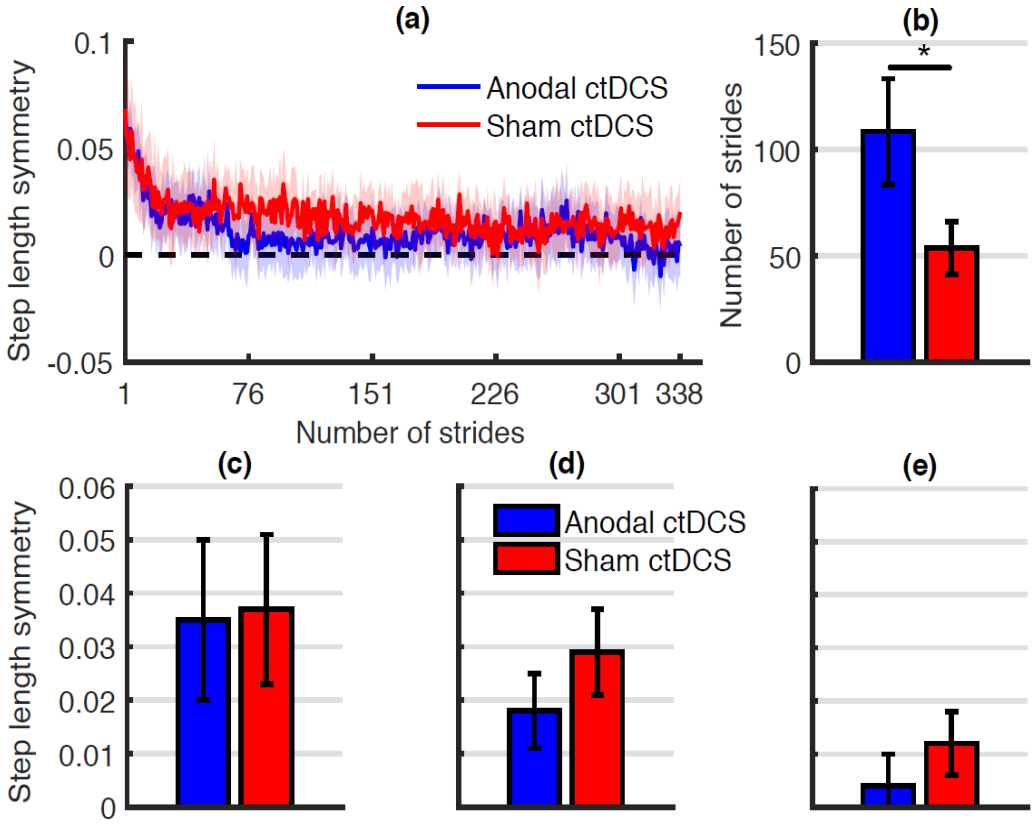


Figure 3-6 Graphs illustrating the results of the de-adaptation phase at the follow-up session.
(a) Stride-by-stride mean step length symmetry plot. Lightly shaded areas indicate 95% confidence interval. The inset bar graphs indicate mean estimates and standard error from the statistical models for (b) the number of strides to steady-state, (c) immediate de-adaptation, (d) early de-adaptation, (e) late de-adaptation.

The comparison of absolute learning, cumulative effect, between-session effects, and within-session effects between the anodal ctDCS and sham ctDCS groups during the adaptation and de-adaptation phases is elaborated in Table 3-1 (p. 60,61). It should be noted that larger estimates in the adaptation phase imply *more* adaptation and *less time taken* to adapt, whereas larger estimates in the de-adaptation phase mean *less* de-adaptation and *more time taken* to de-adapt.

3.5.1 Adaptation

Absolute learning

The linear mixed model analysis revealed that compared to sham ctDCS, anodal ctDCS had no statistically significant effect on the absolute learning of a split-belt treadmill walking task during the adaptation phase, as illustrated by findings for immediate ($p = 0.18$), early ($p = 0.30$) and late adaptation ($p = 0.29$), and strides to steady-state ($p = 0.19$). Absolute learning results are presented in Figure 3-5 (b), (c), (d), (e).

Cumulative effect

There was a statistically significant cumulative effect on immediate adaptation such that anodal ctDCS caused a smaller change in immediate adaptation across the three intervention sessions ($p = 0.01$, ─0.039, S.E. = 0.015) (see Figure 3-7 (a) for immediate adaptation results). However, anodal ctDCS had no statistically significant cumulative effect on early adaptation ($p = 0.37$), late adaptation ($p = 0.09$), or strides to steady-state ($p = 0.71$).

Between-session effects

There was a statistically significant between-session effect on immediate adaptation such that anodal ctDCS caused smaller change in immediate adaptation between sessions 1 and 2 ($p = 0.01$, ─0.039, S.E. = 0.015) but had no effect between sessions 2 and 3 ($p = 0.99$) (see Figure 3-7 (a) for immediate adaptation results). However, anodal ctDCS had no statistically significant between-session effect, between sessions 1 and 2 or sessions 2 and 3, on early adaptation ($p = 0.38$, $p = 0.99$), late adaptation ($p = 0.26$, $p = 0.55$), or strides to steady-state ($p = 0.75$, $p = 0.96$).

Within-session effects

As compared to sham ctDCS, anodal ctDCS had no statistically significant within-session effect on immediate, early, or late adaptation or the strides to steady-state in any of the three intervention sessions (see Table 3-1 for contrast estimates for treatment effects).

3.5.2 De-adaptation

Absolute learning

As compared to sham ctDCS, anodal ctDCS had no statistically significant effect on the immediate ($p = 0.86$), early ($p = 0.15$), or late de-adaptation ($p = 0.18$). However, there was a statistically significant effect on absolute learning during de-adaptation phase for strides to steady-state such that anodal ctDCS slowed de-adaptation at the follow-up session ($p = 0.03$, 2.024, S.E. = 0.659). Absolute learning results are presented in Figure 3-6 (b), (c), (d), (e).

Cumulative effect

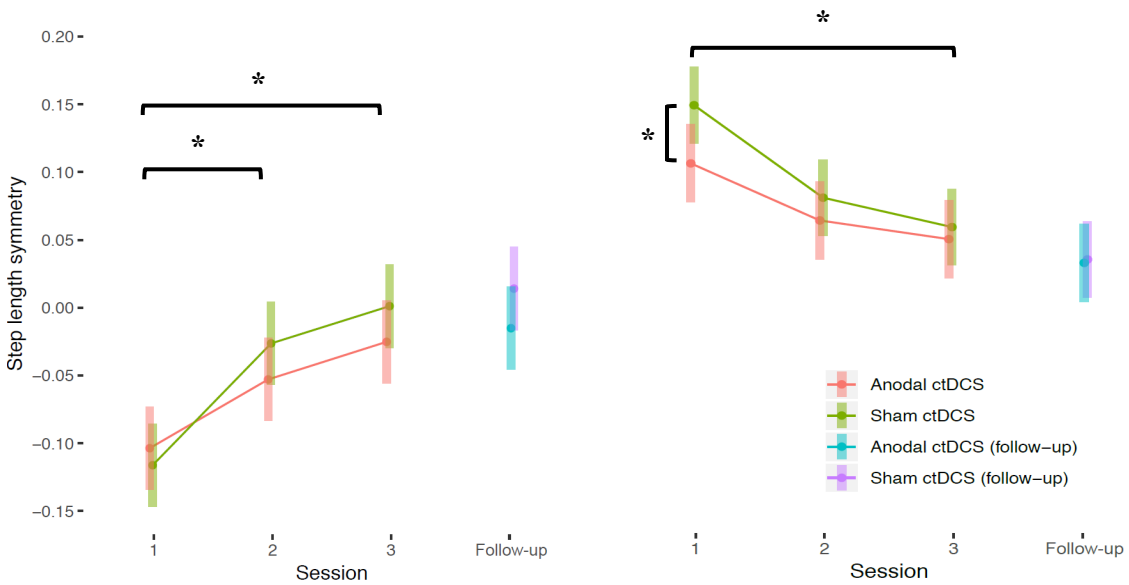
There was a statistically significant cumulative effect on the immediate de-adaptation (p = 0.02, 0.035, S.E. = 0.014) such that anodal ctDCS caused a larger change in immediate de-adaptation across the three intervention sessions (see Figure 3-7 (b) for immediate de-adaptation results). However, anodal ctDCS had no statistically significant cumulative effect on early de-adaptation (p = 0.52), late de-adaptation (p = 0.74) or strides to steady-state (p = 0.48).

Between-session effects

As compared to sham ctDCS, anodal ctDCS had no statistically significant between-session effect, either between sessions 1 and 2 or sessions 2 and 3, on the immediate de-adaptation (p = 0.07, p = 0.58), early de-adaptation (p = 0.50, p = 0.98), late de-adaptation (p = 0.78, p = 0.96), or strides to steady-state (p = 0.57, p = 0.88).

Within-session effects

There was a statistically significant within-session effect on immediate de-adaptation in sessions such that anodal ctDCS caused a greater within-session immediate de-adaptation in session 1 (p = 0.03, −0.044, S.E. = 0.014) but had no effect on subsequent sessions (see Figure 3-7 (b) for immediate de-adaptation results). However, anodal ctDCS had no within-session effect on the early or late de-adaptation or the strides to steady-state in any of the three intervention sessions.



(a) Immediate adaptation **(b) Immediate de-adaptation**

Figure 3-7 Comparison of mean estimates and 95% confidence intervals between groups over the four sessions.

Table 3-1 Contrast estimates for treatment effects with the standard errors estimated from the statistical models.

Type of effect (Session)	Outcome measure	Adaptation		De-Adaptation	
		T_X ± S.E.	t[df], *p* or z, *p*	T_X ± S.E.	t[df], *p* or z, *p*
Learning (4)	Immediate	-0.029 ± 0.022	-1.353[52.1], 0.182	-0.003 ± 0.014	-0.177[84], 0.860
	Early	-0.020 ± 0.018	-1.050[51.5], 0.299	-0.012 ± 0.008	-1.455[92.4], 0.149
	Late	-0.015 ± 0.014	-1.081[49.1], 0.285	-0.008 ± 0.006	-1.365[86.4], 0.176
	STS	1.592 ± 0.569	1.299, 0.194	2.024 ± 0.659	2.166, *0.030
Cumulative effect (1,3)	Immediate	-0.039 ± 0.015	-2.586[96.4], *0.011	0.035 ± 0.014	2.427[96.4], *0.017
	Early	-0.012 ± 0.013	-0.908[91.8], 0.366	0.006 ± 0.009	0.645[92.7], 0.521
	Late	0.015 ± 0.009	1.729[96.4], 0.087	-0.002 ± 0.006	-0.331[96.4], 0.742
	STS	0.830 ± 0.417	-0.371, 0.711	1.287 ± 0.461	0.705, 0.481
Between-session effect (1,2)	Immediate	-0.039 ± 0.015	-2.604[96.4], *0.011	0.027 ± 0.014	1.864[96.4], 0.065
	Early	-0.012 ± 0.013	-0.887[91.8], 0.377	0.006 ± 0.009	0.671[92.8], 0.504
	Late	0.010 ± 0.009	1.126[96.4], 0.263	-0.002 ± 0.006	-0.277[96.4], 0.782
	STS	0.854 ± 0.428	-0.316, 0.752	1.220 ± 0.423	0.571, 0.568
Between-session effect (2,3)	Immediate	0.0002 ± 0.015	0.017[96.4], 0.986	0.008 ± 0.014	0.563[96.4], 0.575
	Early	-0.0003 ±0.0135	-0.019[91.7], 0.985	0.0002 ± 0.009	-0.026[93.1], 0.980
	Late	0.005 ± 0.009	0.603[96.4], 0.548	-0.0003±0.006	-0.054[96.4], 0.957
	STS	0.972 ± 0.489	-0.056, 0.956	1.056 ± 0.377	0.152, 0.879
Within-session effect (1)	Immediate	0.013 ± 0.022	0.581[52.1], 0.564	-0.044 ± 0.014	-3.015[84], *0.003
	Early	-0.015 ± 0.018	-0.821[50.3], 0.415	-0.009 ± 0.008	-1.112[87.6], 0.269
	Late	-0.023 ± 0.014	-1.694[49.1], 0.097	-0.006 ± 0.006	-1.079[86.4], 0.284
	STS	1.204 ± 0.428	0.522, 0.602	0.756 ± 0.243	-0.872, 0.383

STS: strides to steady-state, TX: treatment Effect (in actual units for immediate, early and late outcome measures; in ratio for STS), S.E.: standard error, t: t-statistics, df: degrees of freedom, z: z-statistics, p: p-value

Table continued…

Type of effect (Session)	Outcome measure	Adaptation		De-Adaptation	
		T_X ± S.E.	t[df], *p* or z, *p*	T_x ± S.E.	t[df], *p* or z, *p*
Within-session effect (2)	Immediate	-0.027 ± 0.022	-1.231[52.1], 0.224	-0.017 ± 0.014	-1.179[84], 0.242
	Early	-0.027 ± 0.018	-1.457[52.7], 0.151	-0.003 ± 0.083	-0.371[89.8], 0.711
	Late	-0.013 ± 0.014	-0.968[49.1], 0.338	-0.008 ± 0.006	-1.374[86.4], 0.173
	STS	1.028 ± 0.366	0.076, 0.939	0.922 ± 0.297	-0.253, 0.800
Within-session effect (3)	Immediate	-0.026 ± 0.022	-1.219[52.1], 0.228	-0.009 ± 0.014	-0.625[84], 0.534
	Early	-0.027 ± 0.018	-1.472[52.5], 0.147	-0.003 ± 0.008	-0.399[90], 0.691
	Late	-0.008 ± 0.014	-0.579[49.1], 0.565	-0.009 ± 0.006	-1.431[86.4], 0.156
	STS	0.999 ± 0.354	-0.003, 0.998	0.973 ± 0.321	-0.083, 0.934

STS: strides to steady-state, TX: treatment Effect (in actual units for immediate, early and late outcome measures; in ratio for STS), S.E.: standard error, t: t-statistics, df: degrees of freedom, z: z-statistics, p: p-value

3.6 DISCUSSION

This study investigated the effects of multiple sessions of anodal ctDCS on learning a split-belt treadmill walking task. Successful rehabilitation outcomes depend on improvements in motor performance which persist beyond the intervention period[10]. Elucidating the effects of anodal ctDCS on motor learning is critical if it is to be used as a rehabilitation tool. It was found that three sessions of anodal ctDCS did not influence motor learning measured during the adaptation phase of a split-belt treadmill task. In contrast to the hypotheses, anodal ctDCS reduced the cumulative and between-session effects on immediate adaptation across three sessions and between the first two sessions of the intervention, respectively. This suggests that anodal ctDCS impairs immediate changes in motor performance during the intervention but does not influence motor learning measured after a delay of one week. Interestingly, during the de-adaptation phase, anodal ctDCS significantly prolonged the training effect without impacting immediate, early or late de-adaptation. This indicates that anodal ctDCS affects the length of time that healthy individuals maintain an adapted walking pattern during the de-adaptation phase. Furthermore, anodal ctDCS induced cumulative immediate de-adaptation across the three sessions of intervention and greater immediate de-adaptation in session 1. These findings suggest that ctDCS may extend the benefits of motor training by prolonging the retention of motor learning.

To our knowledge, this is the first study to demonstrate that three sessions of anodal ctDCS does not affect the adaptation phase motor learning after a delay of one week as compared to sham ctDCS. One study has investigated the effects of three sessions of anodal ctDCS using a motor skill learning paradigm. In contrast to the findings of our study, the authors reported improved speed-accuracy trade-off in an upper limb skill task after a delay of one week[199]. Our contrasting findings may be explained by the differences in task characteristics. A motor skill task may take weeks and months to master, whereas optimal performance may be achieved within a single day's practice of a motor adaptation task[227]. This may render motor adaptation tasks subject to ceiling effects in healthy individuals. Differential anodal ctDCS effects with respect to task characteristics have also been noted following a single session of anodal ctDCS where stimulation enhanced gains in motor performance measured up to 48 hours after the intervention in motor skill learning[187,189] but not motor adaptation paradigms[50,186]. The cerebellum's contribution to motor learning is to a large extent dependent on

error-based learning; repeated exposure to the same adaptation task may provide an insufficient stimulus to evoke a cerebellar contribution to motor learning[198]. The importance of the size of the stimulus for error-driven recruitment of the cerebellum is reflected in our results for cumulative and between-session effects of anodal ctDCS, which illustrate that anodal ctDCS modulates immediate adaptation but not early or late adaptation. It is likely that there is an insufficient error stimulus in the early or late phases for the effects of ctDCS to be observable[228]. This is also supported by neurophysiological studies which report that activation of the cerebellum depends on the time scale of adaptation[229] where cerebellar activation decreases over time[211].

Furthermore, anodal ctDCS modulated immediate adaptation by reducing the cumulative and between-session effect across three sessions and between the first two sessions of the intervention, respectively. The reason for the impaired gains could be related to homeostatic plasticity, where the repetition of tDCS after a break may reverse the expected facilitatory or inhibitory effects resulting in interference with performance[230]. Induction of homeostatic plasticity is dependent on the repetition interval where the second intervention session must be administered during the after-effects of the first session[231]. In a study involving cathodal tDCS over the motor cortex, the authors reported reduced inhibition of cortical excitability when tDCS was delivered 3-24 hours after the first intervention session[207]. However, such homeostatic plasticity-induced changes are relatively unexplored in tDCS over the cerebellum. Therefore, investigating cerebellar tDCS-induced cortical excitability and motor performance changes with respect to repetition interval is an important issue for future research.

Anodal ctDCS had no absolute, cumulative, or between-session effect on strides to steady-state performance. This may relate to the role of the cerebellum in the multi-day adaptation process. A recent fMRI study identified neural predictors of adaptability by evaluating the time course of activation over four sessions of a visuomotor adaptation task. Faster adaptation in later sessions was associated with activation of non-cerebellar regions, while slower adaptation was associated with greater activation in the M1-cerebellar motor loop[229]. Therefore, increasing the excitability of the cerebellum with anodal ctDCS may cause slower adaptation as reflected by the cumulative and between-session estimates in this study. Although there was no statistically significant cumulative effect and between-session effect on the strides to steady-state performance,

the estimates for anodal ctDCS were larger than sham ctDCS, indicating slower adaptation.

There was no within-session effect of anodal ctDCS on motor performance or strides to steady-state during the three intervention sessions. In session 1, anodal ctDCS had no effect on immediate adaptation or late adaptation, which is consistent with previous observations[52,186]. However, the results for early adaptation and strides to steady-state are in contrast to those of Jayaram, Tang, Pallegadda, Vasudevan, Celnik, Bastian [52] who found an enhanced early adaptation and adaptation rate with a single session of anodal ctDCS. Possible reasons for the inconsistent result could be due to differences in split-belt protocols and the method of calculating outcomes between the two studies. In our split-belt treadmill protocol, the slow and fast belt speed was set to the individual's fastest comfortable treadmill walking speed at a ratio of 2:1. In contrast, Jayaram et al used a fixed speed at the ratio of 3:1 for all participants[52]. We individualised the calculation of early adaptation and rate of adaptation, whereas Jayaram et al used a fixed number of strides to estimate early adaptation (150 strides) and calculated rate by fitting an exponential function to the group data rather than analysing individual data[52].

An important finding was that anodal ctDCS slowed the strides to steady-state during the de-adaptation phase after a delay of one week. Prolonging the retention of the adapted pattern after training is important in rehabilitation[10]. The mechanism of locomotor learning may explain this retention of learning. In a single session of a motor adaptation task, walking pattern adapts to the induced perturbation which when removed results in persistence of adapted walking patterns for several strides as an after-effect. This is represented by immediate de-adaptation in our study. However, with repeated adaptation and de-adaptation, the persistence of the adapted walking pattern decreases and ultimately disappears when newly learned locomotor programs become stored separately from the baseline program, and one can automatically switch between two motor patterns without relying on the trial and error-based learning[53,213]. This was reflected in our study results where we found that anodal ctDCS had a cumulative effect between session 1 and session 3, and enhanced the immediate de-adaptation in session 1. Cumulative effects across three sessions and greater immediate de-adaptation in session 1 reflect decreased reliance on central command calibrations suggesting improvement in the ability of the central nervous system to predict the optimal locomotor pattern[227]. These results highlight the strength of the study design, which

enabled the illustration of the effect of the multiple-day intervention protocol on both adaptation and de-adaptation.

3.6.1 Strengths, Limitations and Future Directions

This study had a strong research design, consisting of a multi-session, randomised, double-blinded sham-controlled design evaluating a range of outcome measures using robust methods to elucidate the effect of an intervention program on long-term learning. However, some limitations should be considered. We set the slow and fast belt speed based on an individual's fastest comfortable walking speed on the treadmill[219]. This may not have provided enough challenge to healthy individuals. The two belts moved at a speed ratio of 2:1 which may have caused them to reach their asymptote level faster due to the fact that a smaller speed ratio induces a smaller initial error[232]. Considering that our participants were healthy individuals, both of these factors may have caused a ceiling effect. Future studies may wish to examine how anodal ctDCS effects vary with task difficulty in healthy individuals.

3.7 CONCLUSIONS

Three sessions of anodal ctDCS had no effect on motor learning measured during locomotor adaptation in healthy individuals; in fact, it reduced the cumulative and between-session effect on immediate adaptation. Importantly, three sessions of anodal ctDCS prolonged the de-adaptation along with having an immediate and cumulative effect on immediate de-adaptation. Extending the time taken to de-adapt following motor training with anodal ctDCS has potential therapeutic benefits which warrant further investigation.

3.8 ACKNOWLEDGEMENTS

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3.9 AUTHOR CONTRIBUTIONS

N.K., N.S., and D.T. were involved in the conceptualisation and designing of the study. N.K. and U.R. were involved with data collection. N.K., U.R., A.C.V., and P.F.S. were involved in the data analysis. N.K., U.R., N.S., and D.T. were involved with interpretation of the results. N.K. and N.S. were involved in manuscript preparation. All the authors were involved in reviewing and editing the manuscript.

3.10 FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

3.11 ADDITIONAL INFORMATION

Competing interests

The authors declare no competing interest.

3.12 ADDITIONAL WORK

An additional work constituting the validation of a detection and correction algorithm (DACA) was undertaken as a part of Study B[222]. The DACA was developed by the research officer involved with the study in response to invalid force plate data identified while processing the 3D motion analysis data. The force data were found to be corrupted at instances where the participants placed both their feet on the same belt of the split-belt treadmill. The DACA automatically identified and replaced the invalid force data with 3D marker position data. This allowed utilisation of complete kinematic measures collected by the 3D motion analysis system and prevented the loss of data. The performance of DACA was evaluated by comparing its performance against visual examination. Using the receiver operator characteristics, area under the curve, and Youden Index a good to excellent performance was concluded. The published paper is included in Appendix K.

3.13 SUMMARY

This RCT illustrated the effect of repeated ctDCS on motor adaptation in healthy individuals. The study demonstrated that although the repeated anodal ctDCS did not

influence how much and how fast healthy individuals adapted to split-belt treadmill walking, it supported the maintenance of adapted pattern for longer following the intervention by extending the de-adaptation phase. This effect may be useful for extending the benefits of motor training beyond the intervention period. Thus, for the first time, this study provides evidence for anodal ctDCS effects on adaptive locomotor learning to support its potential as rehabilitation tool in people with stroke.

Chapter 4. **Study C: Pilot RCT in People with Chronic Stroke**

4.1 PROLOGUE

The previous chapter demonstrated that repeated sessions of anodal ctDCS can prolong the retention of learnt walking patterns in healthy individuals. This chapter presents a pilot RCT that aimed to evaluate the feasibility of an RCT study design in which repeated sessions of ctDCS were delivered during SBTT in people with chronic stroke. This study is currently under review with a peer-reviewed journal; its content is presented below with some minor formatting modifications to facilitate reading.

Start of submitted manuscript 3

Cerebellar transcranial direct current stimulation for motor learning in people with chronic stroke: A pilot randomised controlled trial

Kumari N, Taylor D, Olsen S, Rashid U, Signal N. Cerebellar transcranial direct current stimulation for motor learning in people with chronic stroke: A pilot randomised controlled trial. Manuscript submitted for publication. 2019.

4.2 ABSTRACT

Background: To date, studies of cerebellar transcranial direct current stimulation (ctDCS) have primarily evaluated the effect of a single intervention session. The feasibility of evaluating the effect of repeated ctDCS on motor learning in people with stroke has not been investigated. This study aims to evaluate the feasibility of conducting a randomised controlled trial (RCT) delivering three consecutive days of ctDCS in conjunction with split-belt treadmill training (SBTT) in people with chronic stroke.

Methods: Using a double-blinded, parallel-group RCT study design, eligible participants were randomly allocated to receive either active anodal ctDCS or sham ctDCS combined with SBTT, on three consecutive days. Outcomes were assessed at

one-week follow-up, using step length symmetry as a measure of motor learning, and comfortable over-ground walking speed as a measure of walking capacity. Feasibility of the RCT protocol was evaluated based on recruitment, retention, protocol deviations, and data completeness. Feasibility of the intervention was assessed based on safety, adherence, and intervention fidelity.

Results: Of the 26 potential participants identified over four months, only four were enrolled in the study (active anodal ctDCS n=1, sham ctDCS n=3). Both the inclusion criteria and the fidelity of the SBTT relied upon accurate estimation of step length asymmetry. The method used to determine the side of the step length asymmetry was unreliable and led to deviations in the protocol. The ctDCS intervention was well adhered to, safe, and delivered as per the planned protocol. Motor learning outcomes for individual participants revealed that treadmill step length symmetry remained unchanged for three participants but improved for one participant (sham ctDCS). Comfortable over-ground walking speed improved for two participants (sham ctDCS).

Conclusion: The feasibility of the planned protocol and intervention was limited by intra-individual variability in the magnitude and side of the step length asymmetry. This limited the sample and compromised the fidelity of the SBTT intervention. To feasibly conduct a full RCT investigating the effect of ctDCS on locomotor adaptation, a reliable method of identifying and defining step length asymmetry in people with stroke is required. Future ctDCS research should either optimise the methods for SBTT delivery or utilise an alternative motor adaptation task.

Trial Registration: Australian New Zealand Clinical Trials Registry, ACTRN 12618000094279.

4.3 BACKGROUND

Globally, stroke is the second largest cause of disability in developing countries and the third largest cause of disability in developed countries[1]. Whilst there is some spontaneous recovery after stroke[101], and standard rehabilitation can produce additional improvements[59,233,234], over 50% of individuals are left with functional limitations at six months post-stroke[235]. One of the common limitations that persist after stroke is the inability to walk[236], with as many as 45% unable to ambulate independently in the

community one year post-stroke[237]. This restricts community integration and lowers quality of life[238].

Motor re-learning is the term used to describe the internal process by which people regain functional motor skills after stroke[10]. The underlying mechanism by which motor re-learning occurs is neural plasticity; a process in which the brain alters its structure and neural connections[239]. While motor learning often refers to the acquisition of new motor skills, a process which can take weeks, months, or even years of practice[32], this paper focuses on a type of motor learning that occurs within a shorter time-frame, known as 'motor adaptation'. Motor adaptation is seen when perturbations are applied during an already-learnt motor task and a number of trial-and-error adjustments are made to improve task performance[47]. The adjustments occur over minutes to hours and then revert to baseline levels upon removal of the perturbation. With repeated exposure to the perturbation, learning is observed through a rapid reduction in errors[53]. Motor adaptation is particularly important during walking, where individuals may need to adjust their movements to the perturbations induced by constantly changing demands, for instance walking on a slippery surface or uneven ground[53,232].

One rehabilitation intervention which has gained attention for its ability to promote motor adaptation is SBTT[232]. Through promoting adaptive walking patterns, SBTT is able to reduce spatio-temporal walking asymmetries which accompany stroke[240]. This improved symmetry may improve walking efficiency[241], balance control[242,243], or walking speed[244], and may prevent secondary impairments such as musculoskeletal pain and joint degeneration[245,246]. Improving walking symmetry is considered an important determinant of stroke recovery[247,248]. Yet, unlike other features of walking, such as balance and speed, which commonly improve with rehabilitation interventions[249-251], only a small proportion of people experience improvements in spatial asymmetry (step length symmetry) during standard walking rehabilitation[252]. This is in contrast to temporal asymmetries, such as stance time, swing time and double-limb support time, which are more responsive to standard walking rehabilitation[252] and improve with traditional treadmill interventions[253-255].

During SBTT, motor adaptation, also called locomotor adaptation, is seen when one leg is placed on a faster treadmill belt and the other leg is placed on a slower belt. The intent is to induce perturbations to normal walking patterns. In response to the perturbation, initially fast reactive feedback adjustments are made to the intra-limb

spatio-temporal parameters such as stride length or stance time[213]. Within a few minutes, slow predictive feedforward adjustments are made to the inter-limb parameters such as step length, double-limb support time[213]. When healthy individuals are exposed to the perturbation, their step lengths initially become more asymmetrical. As they adapt to the uneven belt speeds, their step lengths restore to near baseline levels. When the belts are moved at equal speeds again, after-effects in the form of opposite asymmetry are seen which is de-adapted over time[213].

When SBTT is applied to people with stroke, the leg taking the shorter step length is placed on the faster belt[256]. Step length is defined by the distance between the two feet at heel strike of the leading leg[52]. According to literature, most people with stroke have a shorter step-length on the less affected leg[244,257-259]. Placing the leg with the shorter step length on the faster belt augments the error associated with the asymmetrical walking pattern[256,260]. This is thought to make the person aware of the asymmetry, which was previously perceived as normal, so that it can be corrected. Exposure to SBTT initially worsens asymmetry, but individuals with some capacity in the cerebello-cortical pathways will start making adjustments to increase the step length of both legs, particularly of the leg on the faster belt[261]. This adaptation occurs within 10-15 minutes[213]. When the belt speeds are returned to normal, the adapted walking pattern is maintained, which results in an after-effect of more symmetrical step lengths, indicating storage of the adapted pattern[53]. While most people with stroke demonstrate the ability to adapt to SBTT[262], the adaptation occurs more slowly than in healthy individuals[263,264]. Nevertheless, just a single session of SBTT in people with chronic stroke can result in short-term improvements in step length symmetry[262,265]. These single session effects are partially carried over to over-ground walking[261] but, with repeated sessions, there are sustained improvements in step length symmetry during over-ground walking[240,266]. This is particularly significant for the stroke population, who often show immediate improvements in performance with training, but fail to retain improvements[10].

A large body of research has been devoted to investigating methods to harness neural plasticity after stroke, and this has included the exploration of non-invasive brain stimulation techniques as adjuncts to standard rehabilitation interventions[267,268]. One such intervention is tDCS, a non-invasive brain stimulation technique that modulates neural plasticity via a continuous weak electric current delivered to the scalp through positively or negatively charged electrodes[23]. tDCS is known to influence neural cell

membrane potential and alter the synaptic function of various receptors, synapses, and neurotransmitters[23,269]. In people with stroke, the lesioned or non-lesioned primary motor cortices are commonly targeted with tDCS[270], but recently the cerebellum has been targeted due to its involvement in error-based motor adaptation[180,211]. In people with cortical lesions, where the cerebellar networks are intact but their influence on the primary motor cortex is impaired, tDCS can be applied over the cerebellum (ctDCS) to modulate its excitability and influence its control over the cortex[164]. When ctDCS is applied during SBTT or other motor adaptation task, it can potentially facilitate the motor adaptation process as the individual adjusts their movement patterns to the perturbation[52].

Previous research investigating ctDCS has primarily investigated the efficacy of single session applications during motor skill and motor adaptation tasks in healthy individuals (see review by van Dun et al[31]). A 15-20 minute session of anodal ctDCS (current density of 0.08mA/cm^2) delivered ipsilateral to the training limb in healthy individuals appears to enhance the acquisition of a new motor skill, but does not promote motor adaptation during already-learnt tasks[214]. Similarly, repeated application of anodal ctDCS over three consecutive days can enhance motor skill learning[199] but not locomotor adaptation in healthy individuals[271]. There is limited research concerning the effects of ctDCS in people with stroke[272,273]. One study demonstrated that a single session of contra-lesional anodal ctDCS enhanced performance of a balance adaptation task as measured by a post-intervention improvement in tandem standing balance[273]. Another unpublished study demonstrated that a single session of ipsi-lesional anodal ctDCS during SBTT prolonged the after-effects of training; that is, the improvements in step length symmetry were maintained for longer[272]. While the few studies that have looked at the effects of single session ctDCS are promising, there have been no studies investigating the efficacy of repeated application of ctDCS in people with stroke. As rehabilitation interventions are commonly given over multiple sessions, it is important to evaluate the effect of repeated sessions of ctDCS combined with SBTT on measures of walking symmetry. Prior to conducting a fully-powered RCT, a pilot RCT was conducted to establish feasibility of the study protocol and the ctDCS intervention delivered in conjunction with SBTT. The feasibility of the RCT protocol was investigated in terms of recruitment, retention, protocol deviations, and data completeness. The feasibility of anodal ctDCS + SBTT intervention was assessed in relation to adherence, intervention fidelity and safety.

4.4 METHODS

4.4.1 Study design and setting

This was a double-blinded, parallel-group, sham-controlled, pilot RCT. Participants were randomly allocated to one of two intervention groups: active anodal ctDCS or sham ctDCS. Participants were blinded to group allocation but were aware that they would be randomised to one of the two conditions where the stimulation intensity differed. The principal investigator, who applied the ctDCS and performed outcome measurements, was blinded to group allocation. Blinding to group allocation was ensured by using two separate battery-operated constant current stimulators (HDCstim part of HDC kit, Magstim) which were labelled with two separate codes; these had been labelled and pre-programmed as either active or sham by another researcher. Blinding was maintained until data processing and analysis were complete. Study outcomes were collected immediately before the intervention, immediately after the intervention, and at follow-up one week later.

The study was undertaken at a movement analysis laboratory at Auckland University of Technology (Auckland, New Zealand). The study was approved by the New Zealand Health and Disability Ethics Committees (17/STH/147) and Auckland University of Technology Ethics Committee (18/7). The experimental protocol was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000094279).

4.4.2 Participants

Participants were included if they were aged 18 years or over, had sustained a single, unilateral stroke more than six months ago, and had some difficulty in walking. Exclusion criteria included the inability to continuously walk for five minutes, radiological or clinical evidence of a cerebellar lesion, the affected leg having a shorter step length, history of orthopaedic, cardiac, or neurological conditions that could interfere with walking, and any contraindications to the application of ctDCS[130].

Participants were recruited through local private rehabilitation providers, local hospitals, stroke advocacy networks, and professional networks. All individuals who expressed an interest in the study were provided with a participant information sheet (Appendix N). Potential participants were initially screened over the telephone by a trained researcher. Potential participants were then offered a face-to-face appointment at the laboratory to

confirm which leg had the shorter and longer step length. This was carried out using video observation of the participant as they walked with their usual walking aid on a 20-metre walking track (refer to video-screening in Figure 4-1). Visual analysis of step length symmetry has been used in previous research[261] and was chosen over other measurement methods, such as an electronic pressure sensitive walkway[266,274,275] and 3D motion analysis[265], to reduce the time-burden for participants[265,276,277] and increase feasibility within a clinical setting. A decision to include only individuals who had a longer step length on their affected leg allowed us to compare our results with those of Jayaram, Tang, Pallegadda, Vasudevan, Celnik, Bastian[52].

4.4.3 Randomisation

Following consent, participants were allocated via pseudo-randomisation to either the active ctDCS or sham ctDCS group using the Minim program[278]. Minimisation with *a priori* prognostic factors for response to treatment intervention (age and comfortable walking speed) was used. This method lowers the risk of unmatched groups when the sample size is small[279] and is considered methodologically equivalent to true randomisation[280].

4.4.4 Study procedures

Each participant attended four sessions; three intervention sessions held on consecutive days and a follow-up assessment session one week later (Figure 4-1). Following screening and consent, a clinical assessment was performed to collect demographic and medical information, and assess stroke severity using the National Institute of Health Stroke Scale (NIHSS)[281] and global disability using the simplified modified Rankin Scale (SMRS)[282]. Next, tests of over-ground walking speed and over-ground step length symmetry during the timed 10-metre walk test (10MWT) (represented by blue in Figure 4-1) were performed as pre-intervention measures. These measures were repeated at the end of session 3 (post-intervention), and at session 4 (follow-up).

During the three intervention sessions (sessions 1-3), participants walked on a split-belt treadmill for 20 minutes; this included two-minutes of walking with equal belt speeds (baseline phase), 15 minutes of SBTT during which the belt speeds were unequal and participants received either active ctDCS or sham ctDCS (adaptation phase), and a further three-minutes of walking with equal belt speeds (de-adaptation phase) (refer to

Figure 4-1). Measures of treadmill step length symmetry were collected during the intervention sessions, in the baseline phase of session 1 (pre-intervention) and the first five strides of the de-adaptation phase of session 3 (post-intervention). Treadmill step length symmetry was reassessed one week later in session 4 (follow up), during two-minutes of treadmill walking at equal belt speeds (without ctDCS). Sessions were held at the same time of day and lasted approximately two hours.

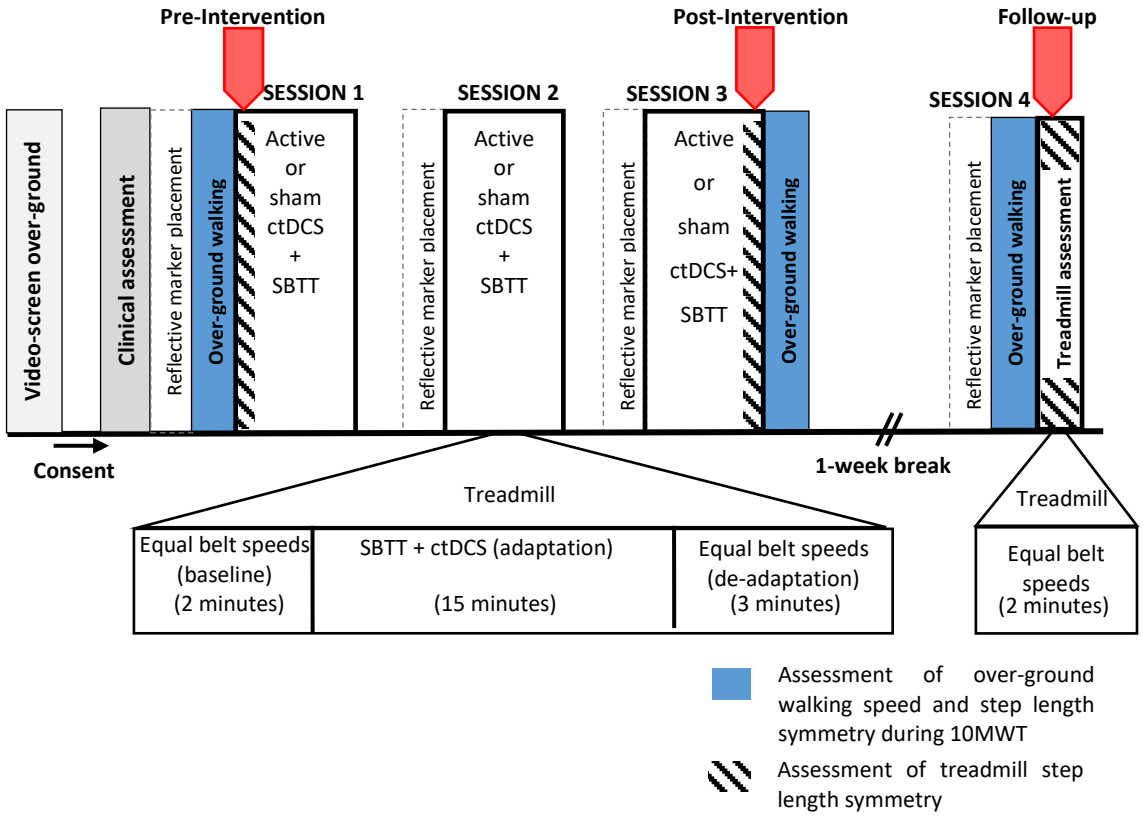


Figure 4-1 An illustration of the study protocol.

4.4.5 Data collection and data processing

At each of the four data collection sessions, 33 reflective markers were attached to the participant with double-sided tape, according to the Cleveland clinic model[220]. Participants performed over-ground walking while the marker position data were collected using an eight-camera 3D motion capture system (Vicon Nexus 2.4, Vicon Motion System Inc.). During treadmill walking, along with marker position data, force data were collected from the force plates embedded in split-belt treadmill belts. Kinematic data was sampled at 200Hz and kinetic data at 1000Hz. Participants initially walked over-ground for 10-metres (10MWT). Three trials were performed with their usual walking aids. Participants then completed the treadmill training task. Participants

wore a safety harness and were positioned in the middle of the treadmill. They were instructed to look straight ahead while walking on the treadmill and hold onto a front handrail adjusted to elbow-height. Data were collected during the last minute of the baseline phase, and throughout the adaptation and de-adaptation phases, excluding rest periods.

The raw over-ground and treadmill kinematic and force data were processed and gap-filled in Vicon software. The data were further processed with custom-made MATLAB software[222], which low-pass filtered the force data at 10Hz and identified heel strike and toe-off events. Heel strike and toe-off events were visually checked for accuracy. A modified version of step length was calculated as the anteroposterior distance between the lateral malleoli reflective markers of each leg at heel strike of the leading leg[52]. Step length data were used to calculate step length symmetry values (see the section on Outcome measures).

4.4.6 Interventions

Split-belt treadmill training

Both active and sham groups walked on a split-belt treadmill (Bertec Corporation, USA) which comprised two separate belts capable of moving together or at different speeds. The speed of the belts during each of the three phases (baseline, adaptation, de-adaptation) was determined based on the participant's comfortable over-ground walking speed. The individual's comfortable walking speed was chosen to set the belt speeds as it has been found to be associated with larger after-effects in healthy individuals[283]. The slow belt speed was set to 80% and the fast belt speed to 160% of comfortable walking speed. When both belts were set to the same speed, the speed was set to 80% of the comfortable walking speed as people with stroke walk slower on the treadmill[284]. During the *baseline phase*, the participant walked on the treadmill with both belts moving together at the slow speed for two-minutes. During the *adaptation phase,* the speed of the belt under the leg with the shorter step length was increased to the fast speed[262,266,272] while the belt under the leg with the longer step length was kept at the slow speed. This exaggerates the individual's step length asymmetry[260]. Mandatory sitting or standing breaks were given every three-minutes to prevent fatigue. ctDCS was delivered only during the *adaptation phase* and was switched off during rest periods. After five bouts of adaptation, both belts were returned the slow speed and the

participant walked for a further three-minutes. This is referred as the *de-adaptation phase*. Figure 4-2 illustrates the split-belt treadmill protocol.

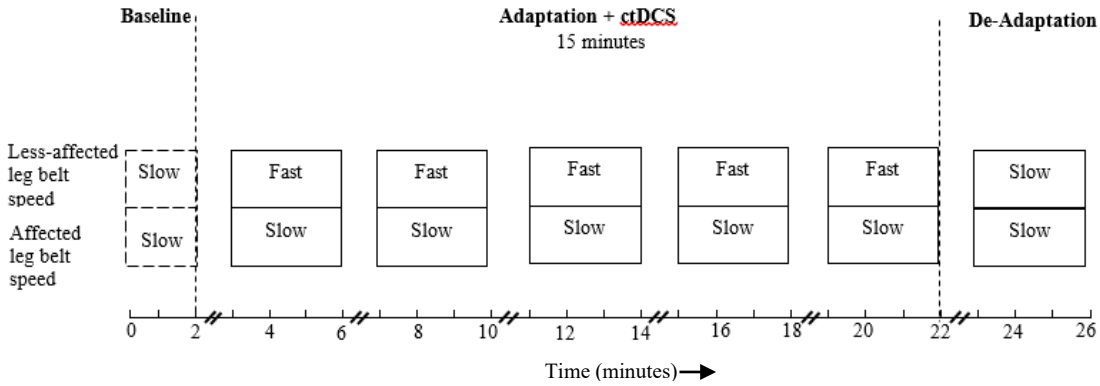


Figure 4-2 Split-belt treadmill training protocol.

ctDCS

Active anodal or sham ctDCS was delivered via a pair of rubber electrodes (5cm X 5cm) encased in saline (0.9%) soaked sponges. The anode was positioned 3cm lateral to the inion towards the affected side to target the lateral cerebellar hemisphere contralateral to the lesioned side (contra-lesional stimulation). The contra-lesional cerebellum was stimulated because this has crossed connections with the ipsi-lesional primary motor cortex, so enhancing its function might strengthen the cerebello-cortical pathways to the affected hemisphere[285]. The cathode was placed over the ipsilateral buccinator muscle. In the active anodal ctDCS group, a constant current of 2mA was delivered during the 15 minutes of SBTT. In the sham ctDCS group, the current was ramped up to 2mA over 30 seconds and then immediately ramped down to 0mA over 30 seconds during each of the five bouts of SBTT[52].

4.4.7 Outcome measures

Primary measure:

The primary outcome of the study was motor learning which was evaluated based on pre-intervention to follow-up change in step length symmetry during both over-ground and treadmill walking. Step length symmetry is an inter-limb kinematic variable that undergoes robust adaptation in response to split-belt treadmill walking[213]. Step length symmetry was calculated separately for treadmill and over-ground walking. Pre-intervention and follow-up assessment utilised the average of all the strides of

treadmill (baseline phase) or over-ground walking at session 1 and follow-up, respectively.

- **Treadmill step length symmetry**

Treadmill step length symmetry was calculated using the symmetry index, as per the following equation:

$$Symmetry\ index = \frac{Affected\ leg\ step\ length\ (A)}{Affected\ leg\ step\ length\ (A) + less\ affected\ leg\ step\ length\ (LA)}$$

A symmetry index of 0.50 indicates perfect step length symmetry[241,286]. Values > 0.5 indicate the affected leg took the longer step. Values < 0.5 indicate the less-affected leg took the longer step leg[241].

- **Over-ground step length symmetry**

Over-ground step length symmetry was calculated using the symmetry ratio, as per the following equation[287,288]:

$$Symmetry\ ratio = \frac{Longer\ step\ length\ (L)}{Shorter\ step\ length\ (S)}$$

This equation produces symmetry ratios of 1 and over, with a value of 1 indicating perfect step length symmetry.

Secondary measures:

- **Pre- to post-intervention change in step length symmetry**

Pre-intervention to post-intervention change in step length symmetry during treadmill and over-ground walking represented the magnitude of after-effects and magnitude of carry-over, respectively. The post-intervention assessment constituted the average of first five strides of the session 3 treadmill de-adaptation phase[262] and first over-ground walking trial[261].

- **Comfortable over-ground walking speed**

Comfortable over-ground walking speed was recorded as a measure of walking capacity. This was evaluated with the timed 10MWT based on the average of three trials[289]. The 10MWT is a reliable and valid measure of walking performance in people

with stroke[289,290]. This was measured pre-intervention (session 1), after the three intervention sessions (post-intervention session 3) and one week later (session 4).

4.4.8 Feasibility measures

The feasibility of the RCT protocol and the intervention (anodal ctDCS in conjunction with SBTT) were evaluated in relation to pre-determined criteria outlined in Table 4-1. The data related to these criteria were recorded on data collection sheets.

Table 4-1 Feasibility criteria and assessment.

Feasibility criteria	Questions asked	Records of
Recruitment	Can 30 participants be recruited to the study within four months?	-Number of participants considered, screened, and included -Reasons for exclusion
Retention	Is the drop-out rate of participants not more than 20%?	-Number of participants who dropped out of the trial -Reason for dropping out
Protocol Deviation	Can the deviations in the protocol be addressed with minor alterations to the protocol and its implementation?	-Any deviations from the described protocol
Data Completeness	Does data completion exceed 95%?	-Missing data -Reasons for missing
Intervention Adherence	Does the participant's adherence to the intervention exceed 80%?	-Session attendance
Intervention Fidelity	Can the anodal ctDCS be delivered as per the planned protocol such that the fidelity exceeds 80%?	-Stimulation location -Stimulation intensity -Stimulation duration
	Can the SBTT be delivered as per the planned protocol such that the fidelity exceeds 70%?	-Setup of fast and slow belt speed -Allocation of limbs to split-belt condition -Duration of each phase and rest break
Intervention Safety	Is the three consecutive days of anodal ctDCS safe?	-Medical or physical changes at the beginning of each session and during the session -Any adverse events reported - Description and rating of participant's experience with the ctDCS stimulation
	Is the three consecutive days of SBTT safe?	-Medical or physical changes at the beginning of each session and during the session -Any adverse events reported

4.4.9 Data analysis

Change-scores for both treadmill and over-ground step length symmetry were calculated as pre- minus post-intervention values such that a positive value would indicate improvement. Motor learning and walking ability measures were analysed

using descriptive statistics (means and mean differences). The feasibility issues were evaluated through percentage where applicable.

4.5 RESULTS

4.5.1 Feasibility of the research protocol

Recruitment

Recruitment was undertaken from February 2018 until May 2018. Over the four-month recruitment period, 26 individuals expressed interest in participating in the study. At telephone screening, seven declined to go ahead with further screening and 11 were deemed ineligible as they did not meet the inclusion criteria (Figure 4-3). The remaining eight individuals were offered an appointment for lab-based screening, of which four individuals were excluded as their step length was shorter on the affected side. Four participants were recruited into the study. Refer to Figure 4-3 for an outline of the study flow.

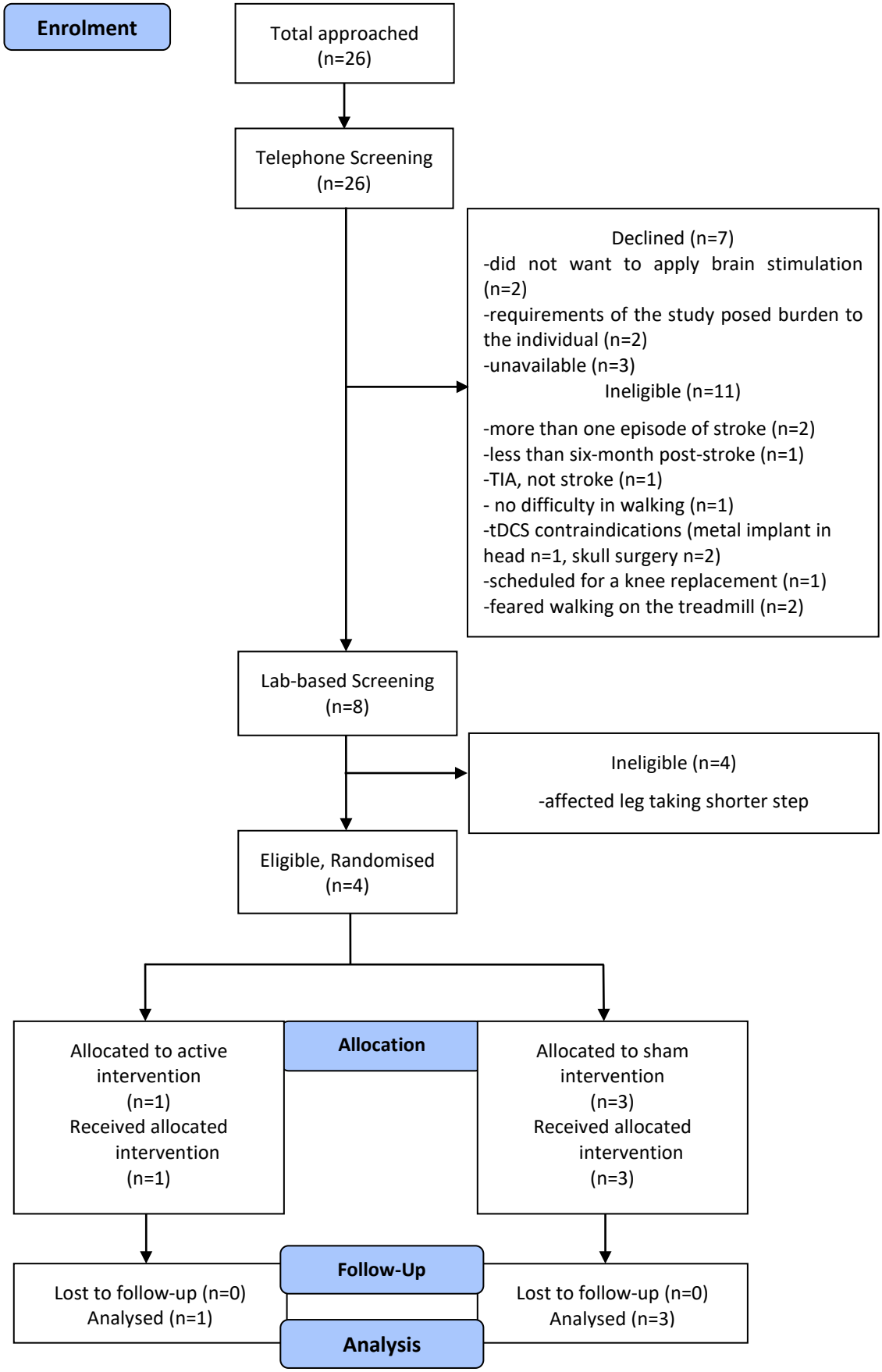


Figure 4-3 CONSORT study flow diagram.

Characteristics of the sample

Participants' demographics and stroke characteristics are presented in Table 4-2. The participants had a mean age of 67 years (SD=12.69 years), and a mean over-ground walking speed 0.66m/s (SD=0.27m/s) indicating moderate walking disability[291]. Stroke severity was mild according to NIHSS and SMRS scores[281,282].

Table 4-2 Demographics and stroke characteristics.

P. N.	Sex	Age (yrs)	Ethnicity	Affected side	Time since stroke (months)	OG walking speed (m/s)	TM walking speed (m/s)	NIHSS score	SMRS score	Gait aid
1	F	64	NZ European	L	240	0.25	0.20	2	2	cane
2	F	74	NZ European	R	12	0.75	0.60	0	2	nil
3	M	51	Maori Chinese	L	171	0.81	0.65	0	1	nil
4	M	80	NZ	R	62	0.81	0.65	1	1	cane

P.N: participant number, F: female, M: male, OG: over-ground, TM: treadmill, NIHSS: National Institute of Health Stroke Scale, SMRS: simplified modified Rankin Scale

Retention

All four participants completed the full study protocol.

Protocol deviations

During the lab-based screening, high intra-individual variability in step length symmetry posed a challenge in determining the side of asymmetry during over-ground walking. To supplement the video assessment of over-ground walking, additional video assessment of treadmill walking was undertaken.

Data completeness

Data completeness of 100% was achieved.

4.5.2 Feasibility of the intervention

Adherence

Participants completed all three intervention sessions.

Intervention fidelity

- **ctDCS**

All participants received their allocated ctDCS intervention according to the planned location and intensity. The ctDCS interventions lasted an average of 26 minutes (range 19 to 38 minutes); this included 15 minutes of stimulation delivery (five 3-minute bouts) and the remaining minutes were spent resting. Overall, 96.7% of the stimulation bouts were delivered correctly, with only two occasions where ctDCS was delivered during rest periods due to a technical fault.

- **Split-belt treadmill training**

The speed of the fast and slow belts was set at the desired ratio for all sessions. The protocol dictated that the leg with the shorter step-length be placed on the fast belt. Due to difficulty in determining which side had the shorter step-length using video observation of *over-ground* walking, this was assessed using video observation of *treadmill* walking. However, on retrospective comparison of the baseline video recording of treadmill walking with the baseline 3D motion analysis of treadmill walking, there was a discrepancy in three of the four participants. Based on the video observation of treadmill walking, the less-affected leg was deemed to have the shorter step length and, therefore, it was allocated to the fast belt. However, according to the pattern of walking observed on the treadmill via 3D motion analysis, the affected leg should have been placed on the fast belt as it had the shorter step length. This discrepancy occurred for three out of four participants (75%). Refer to Table 4-3 for the comparison of step length asymmetry direction determined during video observation (over-ground walking) and 3D motion analysis data (treadmill walking) with symmetry threshold determined by the step length difference. The duration of SBTT at each phase was as per the planned protocol.

Table 4-3 Comparison of step length asymmetry direction and step length difference.

		Over-ground step length symmetry				Treadmill step length symmetry			
	Participants>	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Video observation		V	V	V	V	A>L	A>L	A>L	A>L
3D motion data	-Mean step length	L>A	L>A	L>A	L>A	A>L	L>A	L>A	L>A
	-Difference in step lengths, cm (mean ± SD)	9.30 ± 3.70	1.30 ± 2.75	1.99 ± 3.58	2.2 ± 6.09	6.21 ± 2.45	5.71 ± 4.55	8.36 ± 3.55	8.01 ± 3.00
	-Exceeds asymmetry threshold	✓*	X*	X*	X*	✓^	✓^	✓^	✓^
	-Leg with shorter step length placed on fast belt (fidelity)	✓	✓	✓	✓	✓	X	X	X

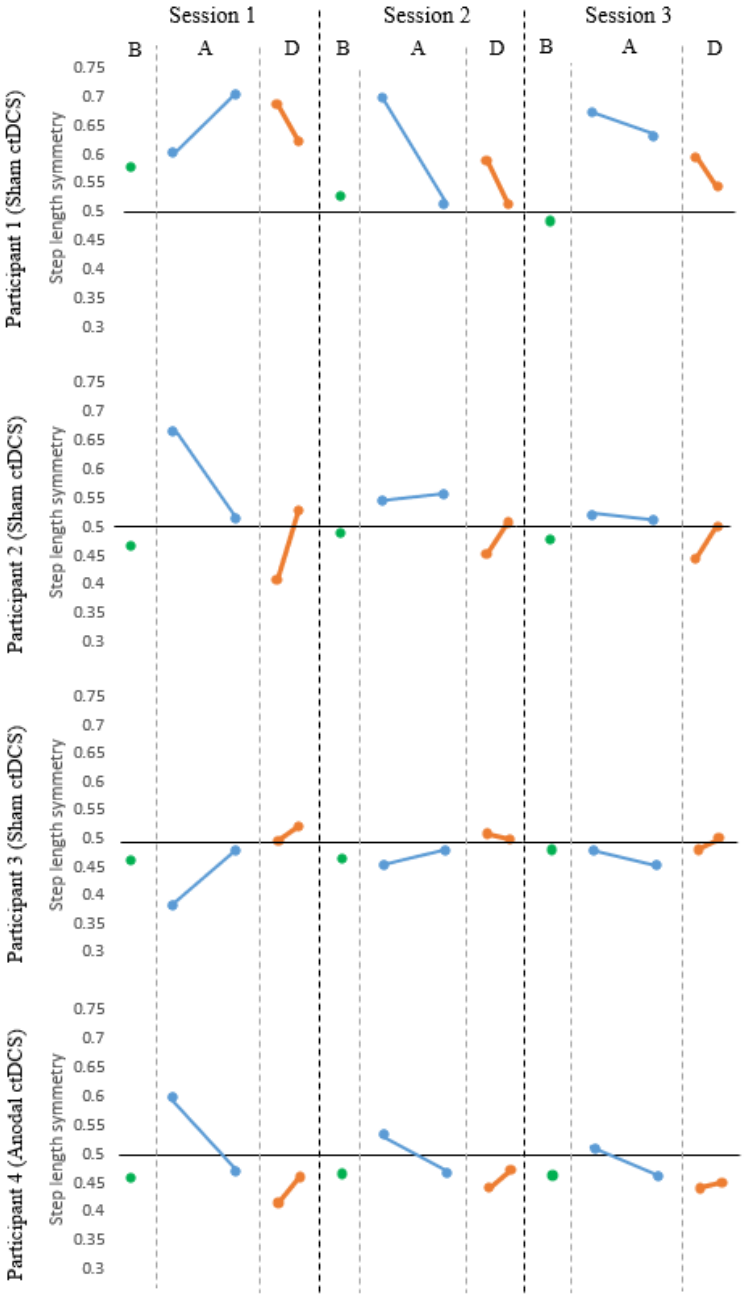
V: variability in the side with shorter step length, A: affected leg, L: less-affected leg, *: asymmetry threshold 5cm determined from Reisman et al[266], ^: asymmetry threshold 2cm determined from Reisman et al[262].

Intervention safety

There were no adverse events. The participants who received sham ctDCS reported no sensation in 66.6% of sessions, twitching of the cheek in 33.3% of sessions, and a metallic taste in 22.2% of sessions. The participant who received active anodal ctDCS reported tingling on the cheek in all sessions. The participants perceived all the sensations as mild and related to ctDCS.

4.5.3 Outcome measures

As only four participants completed the experimental protocol, individual data are presented rather than group data. Individual changes in symmetry were interpreted based on minimal detectable change (MDC) reported in the literature. All the participants demonstrated variable patterns of treadmill step length symmetry during the three consecutive intervention sessions. For participant 1 (sham ctDCS) and participant 3 (sham ctDCS), their treadmill step lengths became more asymmetrical at the end of the adaptation phase in sessions 1 and 3, indicating they did not adapt to the split-belt treadmill walking. Their de-adaptation phase step length symmetry was variable. The trends for baseline, adaptation, and de-adaptation phase for participant 2 (sham ctDCS) and participant 4 (anodal ctDCS) resembled the expected pattern except that their initial symmetry at the start of the adaptation phase was exaggerated in the opposite direction to the baseline symmetry (Figure 4-4).



The black horizontal line represents perfect symmetry. B: mean step length symmetry at the baseline phase, A: mean step length symmetry of first five and last five strides of the adaptation phase, D: mean step length symmetry of first five and last five strides of the de-adaptation phase.

Figure 4-4 Treadmill step length symmetry over three consecutive sessions.

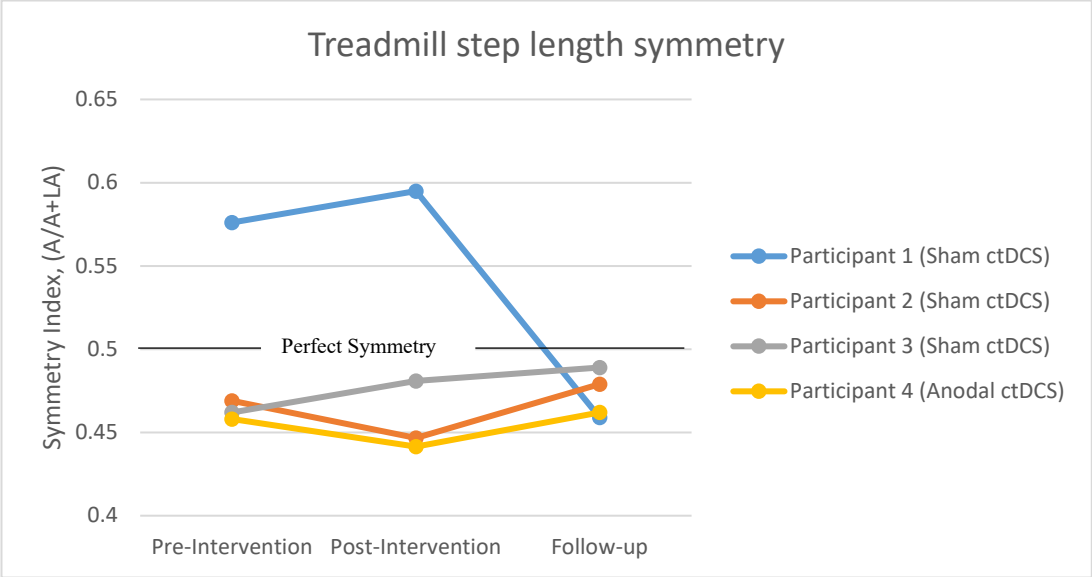
Treadmill step length symmetry

- **Pre- to post-intervention assessment**

Refer to Figure 4-5 for illustration of results. The change in mean treadmill step length symmetry from pre-intervention to post-intervention remained unchanged for participants 1 (sham ctDCS: −0.02), 2 (sham ctDCS: 0.02), 3 (sham ctDCS: −0.02), and 4 (anodal ctDCS: 0.02).

- **Pre-intervention to follow-up assessment**

The change in mean treadmill step length symmetry from pre-intervention to follow-up remained unchanged for participants 2 (sham ctDCS: ─0.01), 3 (sham ctDCS: ─0.03), and 4 (anodal ctDCS: ─0.004) (Figure 4-5). However, for participant 1 (sham ctDCS: 0.12), step length symmetry moved closer to the perfect symmetry value of 0.5; this change exceeded the minimal detectable change (MDC) (0.068).



The black horizontal line represents perfect symmetry. A: affected step length, LA: less-affected step length.

Figure 4-5 Mean treadmill step length symmetry at pre-intervention, post-intervention, and follow-up assessment.

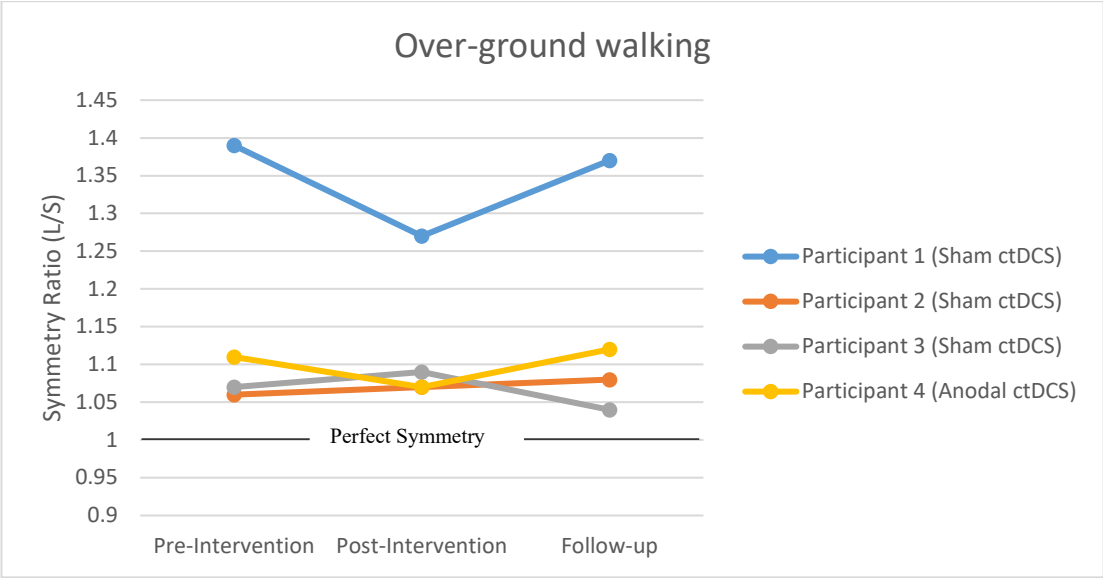
Over-ground step length symmetry

- **Pre- to post-intervention assessment**

The change in mean over-ground step length symmetry from pre-intervention to post-intervention remained unchanged for participants 2 (sham ctDCS: ─0.01), 3 (sham ctDCS: ─0.02) and 4 (anodal ctDCS: 0.04) (Figure 4-6). For participant 1 (sham ctDCS: 0.12), the over-ground step length symmetry moved towards perfect symmetry value of 1 but did not exceed the MDC (0.15).

- **Pre-to follow-up assessment**

The change in mean over-ground step length symmetry from pre-intervention to follow-up remained unchanged for participants 1 (sham ctDCS: 0.02), 2 (sham ctDCS: ─0.02), 3 (sham ctDCS: 0.03), and 4 (anodal ctDCS: ─0.01) (Figure 4-6).



The black horizontal line represents perfect symmetry. L: longer step length, S: shorter step length.

Figure 4-6 Mean over-ground step length at pre-intervention, post-intervention, and follow-up assessment session.

Comfortable over-ground walking speed

Comfortable over-ground walking speed increased from pre-intervention to post-intervention for participants 2 (0.20m/s change) and 3 (0.22m/s change). This improvement in walking speed was maintained at follow-up and exceeded the minimally clinical important difference (MCID) (participant 2 sham: 0.25m/s, participant 3 sham: 0.23m/s). Comfortable over-ground walking speed remained largely unchanged for participants 1 and 4. Refer to Figure 4-7.

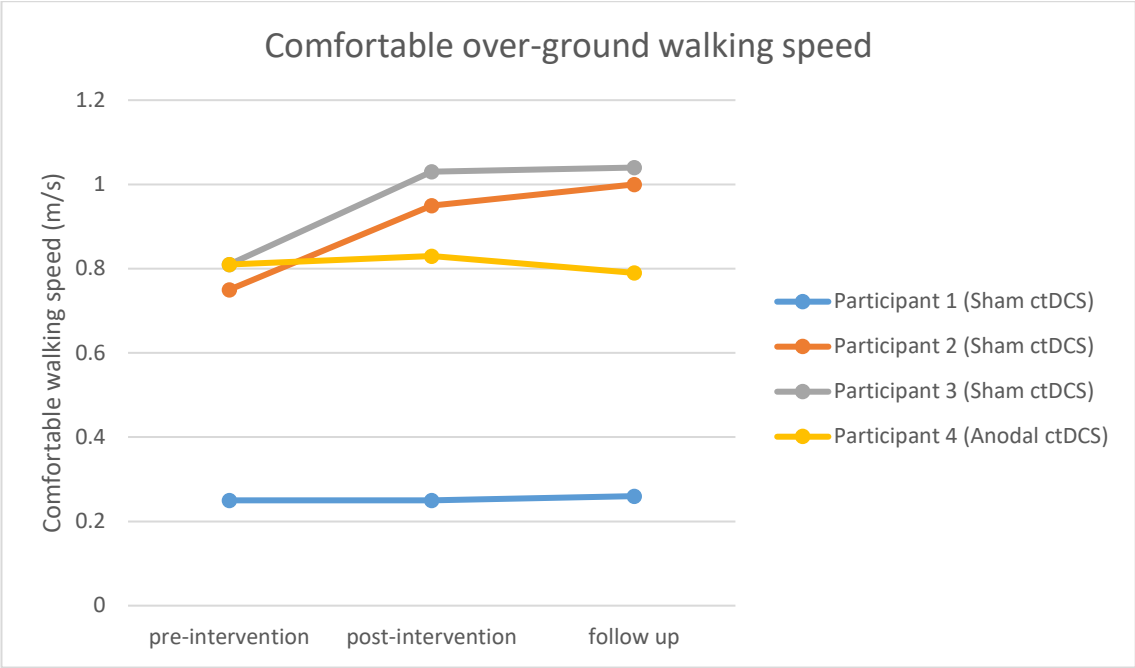


Figure 4-7 Comfortable walking speed at pre-intervention, post-intervention, and follow-up assessment session.

4.6 DISCUSSION

This is the first study to examine the feasibility of a research protocol investigating three consecutive sessions of anodal ctDCS in people with chronic stroke. Determining feasibility is an important prerequisite to evaluating intervention efficacy; this allows the research protocol to be refined and increases the likelihood of implementing a successful level one RCT[292,293]. The intent of the full RCT was to evaluate the effect of repeated anodal ctDCS on motor learning in people with chronic stroke by measuring changes in motor performance in response to locomotor adaptation training. This training paradigm is commonly used in motor learning research[232], and is advocated as a treatment intervention to correct walking asymmetry in people with stroke[240,266]. The findings of this study revealed that the planned RCT protocol and ctDCS-SBTT intervention are not feasible. The main feasibility issue related to the assumptions that a) the majority of people with stroke have a walking asymmetry in which the less affected leg has the shorter step length[244,257-259] and b) that this asymmetry can be assessed with video observation[261]. Our data challenged these assumptions. Of the eight people who underwent the lab-based screening, four were excluded as their affected leg had the shorter step length. This illustrates the heterogeneity in step length asymmetry that exists in the stroke population[294] which can be attributed to the diversity in clinical presentation[258]. It suggests that SBTT protocols should not require that the less affected

side have the shorter step length; rather, that the leg with the shorter step length, whichever side, be placed on the fast belt. This would improve the recruitment feasibility, enhance the external validity of the research findings and translation to clinical practice.

In relation to the assumption that walking asymmetry can be assessed with video observation[295,296,297], our study raised several factors that contest this idea. Of the four included participants, there was intra-individual variability in the side with the shorter step length both *within* the over-ground walking condition, and *between* the over-ground and treadmill walking conditions. This meant that determining which leg to place on the fast treadmill belt was challenging (refer to Table 4-3). Variability in walking patterns between over-ground and treadmill conditions has been observed in other studies of people with chronic stroke. It has been noted that treadmill walking is associated with shorter stride lengths, faster cadence, and greater step time, stance time, and stance-swing time ratios than over-ground walking[284,298]. For one participant in our study, the 3D motion data showed a complete reversal of the side with the shorter step length between over-ground and treadmill walking. Although the exact reason for this is unclear, the use of handrails during treadmill walking may contribute to these differences[299-302]. Given these feasibility issues, future research should determine the validity and reliability of step length asymmetry measurement methods and their relevance to both over-ground and treadmill walking in people with stroke.

In addition to the variability between over-ground and treadmill walking conditions, there were also discrepancies between the video observation and 3D measurements. Post-hoc analysis revealed inconsistencies in step length asymmetry measured using video observation and the 3D motion analysis during treadmill walking in three out of four participants. Whilst, video observation of walking has moderate reliability and validity in people with stroke[295,296], and is time-efficient and cost effective[303-305], it is considered inferior to 3D motion analysis. The reliability of video analysis for determining step length asymmetry is reduced in the absence of marked asymmetry[297]; this may have contributed to the inconsistencies between video and 3D analysis in this study, as most participants had over-ground asymmetry values that did not exceed the asymmetry threshold of a 5cm difference between affected and less-affected legs[266]. Thus, in our study, it appears that the use of video observation contributed to an inaccurate assessment of step length asymmetry, and this meant that for three of the four participants, the leg with the longer step length was placed on the fast belt. This is a

deviation from the SBTT intervention recommended in the literature, which states that the initial asymmetry must be exaggerated by placing the leg with the shorter step length on the fast belt[256]. However, there is also evidence for placing the less-affected leg on the fast belt in case the magnitude of baseline step length asymmetry is within the normal symmetry threshold[261]. The assessment of step length asymmetry proved challenging and comprised the fidelity of the SBTT intervention. This is a significant issue for further research, as although 3D analysis may be preferred for its accuracy, it is time-consuming and generally not available in a clinical setting. Therefore, further work is needed to identify a quick and reliable method for determining step length asymmetry if SBTT is to translate into clinical practice.

In addition to intra-individual variability in the *side* of the shorter step length, there were also differences in the *magnitude* of step length asymmetry between the over-ground and treadmill walking conditions. An asymmetry threshold represents the cut-off value for the presence or absence of walking asymmetry. Several criteria to determine the asymmetry threshold have been reported in the literature, including use of an arbitrary value of 10% deviation from perfect symmetry[306], 95% confidence intervals[244,246], or 2 SD[262] of gait symmetry obtained in healthy control participants. The majority of participants, whose asymmetry did not exceed 5cm asymmetry threshold during over-ground walking[266], did exceed the 2cm threshold during treadmill walking[266]. Future studies should consider screening potential participants on the basis of *magnitude* of baseline asymmetry, such that only those with marked asymmetry are included. It is also important to consider whether the aim of the intervention is to improve asymmetry during over-ground or treadmill walking when interpreting asymmetry values.

The criterion for recruitment feasibility was that 30 participants would be recruited in four months. This criterion was not met, as only four out of the 26 potential participants were enrolled in the study. The recruitment period was not extended as it would have been unethical to recruit more participants and continue collecting data with a compromised SBTT intervention. In addition to the exclusion of people with a shorter step length on the affected side, other factors that limited recruitment were presence of contraindications to the use of ctDCS and fear of walking on the split-belt treadmill. With regard to the other criteria for feasibility, retention and data completeness were satisfactory, as well as adherence and safety of the SBTT intervention. The fidelity,

adherence, and safety of anodal ctDCS were sufficient; however, this finding must be approached with some caution as it is inferred from only one participant.

All participants' motor learning outcomes remained unchanged, except for one participant in the sham ctDCS group who had marked baseline asymmetry and received SBTT with the leg with the shorter step length on the fast belt (as per protocol). This participant had more symmetrical step lengths at follow-up, indicating that SBTT alone had resulted in retention of this improved walking pattern (i.e., motor learning had occurred). This change exceeded that threshold for MDC. A clinically-meaningful improvement being evident in one participant and not others likely highlights the importance of correctly determining the magnitude and side of baseline step length asymmetry, as this participant's asymmetry exceeded the 5cm threshold and the leg with the shorter step length was correctly allocated to the fast belt during SBTT. Therefore, to maximise the efficacy of the intervention, it is necessary to ensure people with stroke have a magnitude of asymmetry which will respond to SBTT and that the appropriate belt speeds are used during SBTT.

It is also noteworthy that improvements in treadmill walking for this participant did not transfer to over-ground walking. This finding is contrary to previous studies which have found improvement in over-ground step length symmetry following repeated SBTT alone[240,266]. However, these improvements have been reported following higher doses of SBTT and using over-ground step length symmetry to allocate belt speeds during SBTT. Another explanation could be related to the way the errors were introduced. In both healthy and people with chronic stroke, greater transfer to over-ground walking is noted when the belt speed is changed slowly but not abruptly[307,308]. The slow change in belt speeds induces smaller errors which may fall within the individual's baseline variability such that one adapts to natural over-ground walking patterns. In contrast, an abrupt change in belt speed produces large errors beyond the normal range resulting in an adapted pattern that does not transfer, regardless of the gains in motor learning over the treadmill[307]. Therefore, in our study, the use of abrupt change in the belt speed may have resulted in the lack of transfer to over-ground walking. Overall, factors such as SBTT dose, type, and size of error may influence transfer to over-ground walking. Therefore, these factors need to be considered when designing future studies.

In all the participants, improvements in comfortable over-ground walking speed had no relation to whether the symmetry improved or remained unchanged. In participants

receiving sham ctDCS, over-ground comfortable walking speed did not change for the participant who displayed improved symmetry. Two sham participants, who did not have improved step symmetry, experienced improvements in walking speed that exceeded the minimal clinically important difference at both post-intervention and follow-up assessment. Step length symmetry and walking speed are only weakly correlated in people with stroke[306], suggesting that these improvements in speed may be entirely unrelated to any changes in symmetry, despite improved symmetry being the goal of SBTT. Improved walking speed may be related to other compensatory mechanisms adopted by the participants during the intervention[306], although data from more participants is required to determine the effect of SBTT on walking speed.

4.6.1 Limitations, implications and future research

One of the main limitations of this study was the lack of qualitative data to determine the acceptability of the intervention. Considering the findings of other feasibility measures, it is unlikely that this would have altered the main findings of the study. Inferring the feasibility of anodal ctDCS from a single participant who received the intervention was another limitation. Despite these limitations, the study identified a number of unanticipated issues that highlight the importance of evaluating the feasibility of an intervention and research protocol prior to a larger trial. These issues, primarily relating to the variability in step length asymmetry, can be overcome by: recruiting stroke participants with shorter step length on either side, including stroke participants who have baseline asymmetry above the normal symmetry threshold, and setting up SBTT with respect to the individual's step length asymmetry. Given the lack of clarity in the SBTT research in regard to whom and how SBTT is best delivered for people with stroke, alternative methods of evaluating motor learning during adaptation in people with stroke should be considered. The efficacy of repeated ctDCS in people with stroke may be more appropriately investigated using motor adaptation tasks such as force-field tasks applying robot-induced forces to upper limb reaching movements[309], or locomotor tasks involving unilateral leg weighting during treadmill walking[310,311] or spatio-temporal cues during over-ground walking[196].

4.7 CONCLUSIONS

The planned RCT research protocol constituting three consecutive sessions of intervention is not feasible in its current form. The study revealed substantial variability

in the direction of step length asymmetry influencing the recruitment and delivery of SBTT. This highlights the challenges of delivering an intervention which relies on the assessment of highly variable baseline measures to assure successful error augmentation. The efficacy of ctDCS to influence motor re-learning during motor adaptation in people with stroke is still not known. Future studies need to either resolve feasibility issues around the identification of step length asymmetry and the assignment of it during SBTT or utilise an alternative motor adaptation paradigm to determine the effects of repeated ctDCS on motor learning in people with stroke.

4.8 COMPETING INTERESTS

None.

4.9 FUNDING

None.

4.10 AUTHOR CONTRIBUTIONS

N.K., D.T., and N.S. were involved in the conceptualisation and designing of the study. N.K. was involved with data collection and analysis of the results. U.R. was involved with the processing of outcome measures. N.K., N.S., D.T., S.O., and U.R. were involved in the interpretation of the results. N.K. wrote the manuscript, which was revised by N.S. and S.O. All authors were involved in reviewing and editing the manuscript.

4.11 ACKNOWLEDGEMENTS

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4.12 SUMMARY

This pilot RCT study revealed several unanticipated issues related to step length asymmetry that limited the recruitment and fidelity of SBTT intervention. The variability in the determination of step length asymmetry necessitates optimising the SBTT intervention as a method for evaluating ctDCS effects. Inclusion of stroke individuals irrespective of their side of asymmetry is essential for successful recruitment. The magnitude of baseline asymmetry must be above the normal symmetry threshold values for improving the detection of the side of step length symmetry. However, there is a need to identify a fast and reliable method for detecting step length symmetry. Finally, the anodal ctDCS intervention on its own was found to be feasible. Future studies need to address the issues with SBTT intervention and explore whether ctDCS combined with SBTT has any promise in people with stroke. Alternatively, other motor adaptation tasks must also be explored to determine the effects of repeated sessions of ctDCS.

Chapter 5. **Integrated Discussion and Conclusion**

5.1 PROLOGUE

This thesis has explored the effects of ctDCS on motor learning and contributes to establishing its potential as a neuromodulatory tool to augment motor learning in healthy individuals and motor re-learning following stroke. The thesis was comprised of a narrative review of the neuroscience literature, a systematic review of the ctDCS and motor learning research evidence, a parallel-group RCT investigating the effects of ctDCS in healthy individuals, and a parallel-group pilot RCT in people with chronic stroke investigating the feasibility of the research protocol and the ctDCS intervention combined with SBTT.

5.2 REVIEW OF THE EXISTING LITERATURE

A key strength of this thesis is that it was predicated upon a narrative review of the neuroscience literature and a systematic review of the ctDCS evidence base, that provided strong underpinnings for the application of ctDCS to influence motor learning. The narrative review highlighted that acquisition of new motor skills or re-acquisition of lost motor skills after a stroke relies on neural plasticity dependent motor learning and re-learning[38,239]. This occurs through error-driven adjustments made by the cerebellum, which are evident at the neural network level[172-174]. Notably, research describing the role of the cerebellum in motor learning indicated a dynamic interaction between various networks which changes over the course of learning[37,14]. Behavioural indicators of learning, such as performance improvement, retention, and transfer, also vary across different time scales during the learning of a task[32,34], reinforcing the importance of differentiating the effects of motor learning interventions at different time scales: within a session, between-sessions, and after a period of delay. Whilst there was evidence that ctDCS can alter the activity of the cerebellum, it was unclear whether it induces long-lasting gains at the behavioural level. Therefore, these insights from the narrative review guided the design of the systematic review in study A, such that the

effects of ctDCS on motor learning were differentiated based on the time scale of motor learning in healthy individuals. This allowed for the distinction between temporary (motor performance) and long-lasting (motor learning) changes occurring due to the application of ctDCS.

A previous meta-analysis of randomised and non-randomised studies concluded that both anodal and cathodal ctDCS were effective in altering the motor performance in healthy individuals[181]. For the first time, study A synthesised the findings of RCT's to reveal that a single session of anodal ctDCS appeared to enhance the short and long-term motor skill learning for up to 48 hours after the intervention, while cathodal ctDCS had an equivocal effect irrespective of the time scale[214]. This extended the body of knowledge by indicating that anodal ctDCS may have the potential to induce long-lasting changes in motor performance in healthy individuals. The review also provided recommendations to improve the methodological quality of future studies and insights into the parameters for stimulation. However, it was not clear whether the application of ctDCS over multiple sessions would enhance motor learning over longer time scales. It was also not clear whether similar improvements in performance might occur if ctDCS was applied during motor adaptation tasks.

5.3 BEHAVIOURAL STUDIES

5.3.1 Study B: RCT in healthy individuals

Study B was the first study to investigate the effects of repeated anodal ctDCS on the motor learning of an adaptation task in healthy individuals. By utilising an RCT design, the study compared the effects of three consecutive sessions of anodal ctDCS with sham ctDCS during a split-belt treadmill walking task. The research protocol was designed to investigate both long-term changes in motor performance that occurred at one-week follow-up (motor learning) and the transient changes that occurred within and between intervention sessions. This gave a full picture of how repeated sessions of ctDCS may affect different time scales of motor learning. Furthermore, the outcome measures reflected the magnitude and speed of learning in both the adaptation and de-adaptation phases. This provided a comprehensive understanding of how ctDCS influences different components of motor learning as well as one's ability to respond to repeated adaptation and de-adaptation. Utilisation of a linear mixed models for data analysis

further strengthened the research protocol by reducing the risk of type-I error and increasing the statistical power[224].

It was found that repeated anodal ctDCS applied over the lateral cerebellar hemisphere prolonged the length of time that the healthy individuals maintained the adapted walking pattern at one-week follow-up. This demonstrated the ability of repeated ctDCS to modulate the cerebellar function and to influence motor learning of a motor adaptation task. The effect was only noted during the de-adaptation phase as the results for the adaptation phase did not achieve statistical significance. The magnitude of the treatment effect suggested that anodal ctDCS prolonged the time taken to adapt to the change in belt speed during the adaptation phase. This is in contrast to a previous study in the literature that reported enhanced motor learning of a motor skill task after repeated anodal ctDCS stimulation[199]. Enhanced learning of a motor skill task and not motor adaptation task after a single session of anodal ctdCS was also noted in study A[214]. Differences in task characteristics may explain the findings where contrary to a motor skill task, achieving optimal performance in a short period of time during a motor adaptation task may induce ceiling effects in healthy individuals[53]. Furthermore, repeated task training may be another contributing factor to the ceiling effects. Repeated exposure to the same motor adaptation task may induce insufficient error to evoke cerebellar contribution to motor learning. The importance of the size of error is also reflected in our results, where anodal ctDCS influenced only the immediate and not the early or late epochs of adaptation or de-adaptation phases. Therefore, the size of error stimulus induced by the split-belt treadmill may have implications on the potential impact of ctDCS in a motor adaptation task.

Overall, the findings of study B furthered the results of study A, which provided evidence for long-lasting effects of single session of ctDCS on motor learning of skill tasks, by providing evidence for influencing motor learning of adaptation task with repeated sessions of ctDCS. This reinforced the concept that ctDCS may have the potential to augment the rehabilitative benefits of SBTT in people with stroke. The findings of study B formed the rationale for planning an RCT investigating the effects of repeated sessions of ctDCS combined with SBTT in people with chronic stroke. Prior to executing the full RCT, the feasibility of the planned research protocol and the intervention in people with chronic stroke was investigated in Study C. Furthermore, a technical issue identified and corrected over the course of Study B streamlined the method used for data processing during Study C. This constituted the development and

use of an automatic detection and correction algorithm (DACA) which allowed the utilisation of complete kinematic measures collected by the 3D motion analysis system and prevented loss of data[222].

5.3.2 Study C: Pilot RCT in people with chronic stroke

Study C was the first study that evaluated the feasibility of conducting a pilot parallel-group RCT constituting three consecutive sessions of anodal ctDCS combined with SBTT in people with chronic stroke. Although the delivery of repeated ctDCS intervention was feasible, challenges pertaining to recruitment, assessment of step length asymmetry, and SBTT fidelity were identified as barriers to the execution of the full RCT and the intervention. These challenges were mainly related to the presence of high intra-individual variability in step length asymmetry and concerns about the reliability of video analysis to assess this. Further research is required to address these feasibility issues, which have a direct impact on the fidelity of the SBTT intervention. To improve recruitment, it was recommended that future protocols should include participants irrespective of whether the affected or less affected side has the shorter step. It was also recommended that researchers should consider baseline step length asymmetry of greater than normal symmetry threshold as an inclusion criterion; this will ensure the SBTT intervention is given to those individuals who are most likely to benefit from it. The feasibility of repeated ctDCS intervention provides promise for it being a safe neuromodulatory tool which is well adhered to by people with stroke and can be delivered as per the planned research protocol. This necessitates the importance of resolving challenges around SBTT fidelity so that it can be used as a method for evaluating the effects of ctDCS. If this proves too difficult, future work may need to utilise an alternative motor adaptation training paradigm that allows efficient measurement of motor learning improvements to assess the effects of ctDCS on motor learning. Overall, the findings of this study highlight the importance of utilising a pilot RCT design to determine the feasibility of an intervention prior to the execution of full RCT. The design exposed several barriers to successful implementation so that recommendations can be made to refine future research and reduce wastage of resources[292,293].

5.4 CLINICAL IMPLICATIONS

The neuroscience evidence for the role of the cerebellum in motor learning presented in the narrative review opens up research avenues for modulating cerebellar activity and gives insights into the error-driven cerebellar activity that may be promoted during rehabilitation sessions[172]. For example, error-driven activity can be promoted by introducing novelty to a task training rehabilitation program. The current evidence, from study A and B, that anodal ctDCS has longer-term effects on motor learning has promising implications for prolonging the gains achieved by rehabilitation in a clinical setting. The potential for the application of ctDCS may be early in the rehabilitation when patients make more errors, and it is hard to maintain the improvements between sessions and after a delay. As long-lasting changes in motor performance normally require a high number of repetitions and practice[13-15], the influence of ctDCS on motor learning may reduce the amount of rehabilitation required to achieve the long-lasting changes. The findings of Study C indicated some potential of ctDCS intervention to be successfully translated into clinical practice, due to it being safe, user-friendly, and well-adhered-to.

5.5 LIMITATIONS

Study A undertook a rigorous approach to systematically review the ctDCS evidence base; however, substantial heterogeneity in the studies limited the evaluation of the magnitude of effect size through a meta-analysis. This information would have been useful in planning for Study B.

In Study B, setting the speed ratio of the slow and fast belt of the treadmill to 2:1 may have caused participants to reach their asymptote level more quickly. Thus, the influence of ceiling effects could not be ruled out when interpreting the ctDCS effects on motor adaptation during SBTT. Future studies may wish to explore the relationship between task difficulty and ctDCS effects by progressively increasing the speed in a 2:1 ratio with each intervention session or using a greater speed ratio such as 3:1[52].

In Study C, despite employing an extensive recruitment process to include potential stroke participants, the small sample size limited the ability to provide preliminary estimates of the difference in outcomes. Taking into account that the study was not designed to establish the effectiveness of the ctDCS intervention, the study has

contributed towards identifying potential barriers to conducting full-scale ctDCS research employing an RCT design in people with stroke. Inference on anodal ctDCS intervention feasibility was limited by the fact that only one participant received the intervention. Future larger trials may wish to expand their inclusion criteria in relation to the side of asymmetry while setting a threshold for baseline step length asymmetry for inclusion.

5.6 FUTURE RESEARCH DIRECTIONS

This thesis has described the efficacy of repeated anodal ctDCS for motor learning in healthy individuals. However, ceiling effects related to task characteristics and the size of error stimulus may have limited the full understanding of repeated ctDCS effects in Study B. A natural progression of this study is to explore the effects of ctDCS with increasing task difficulty to overcome the ceiling effects. The difficulty of the task can be varied by increasing the split-belt treadmill ratio such that the belts move at a ratio of 3:1 or 4:1. Furthermore, the addition of neurophysiological measurements to multi-session anodal ctDCS protocols would give insights into the changes in cerebellar excitability associated with motor learning.

This thesis also revealed challenges related to the feasibility of anodal ctDCS + SBTT intervention and research protocol in people with chronic stroke. By considering the recommendations provided by study C, the next phase is to streamline the process for the assessment of step length asymmetry and the allocation of each leg to the appropriate belt speed. This will require further feasibility work. Following optimisation, another pilot study should be undertaken to determine the estimated effects of the intervention in order to inform the sample size for a fully powered RCT. A further study could also examine any association between demographic or clinical characteristics of people with stroke and the magnitude of effects induced by the ctDCS + SBTT intervention. This information may be useful to optimise the intervention to best suit people with stroke. Alternatively, other motor adaptation tasks inducing perturbations through robot-induced forces[309], unilateral leg weighting[310,311], or spatio-temporal cues[196] could be explored to determine the effects of repeated sessions of ctDCS on motor learning.

5.7 CONCLUSION

The findings of this thesis provided the first comprehensive evidence for the effect of ctDCS on motor learning by considering the distinction between performance and motor learning. Some of the highlights of this thesis were that it revealed the nuances of ctDCS effects on motor learning through a comprehensive systematic review that dissociated its effects based on different time scales of motor learning. It was found that a single session of anodal ctDCS appears to enhance the learning of motor skill tasks up to 48 hours after the intervention.

An RCT research design with robust analysis methods was used to compare the effects of repeated anodal ctDCS with sham ctDCS while healthy individuals learnt a complex walking task. The RCT revealed that repeated sessions of anodal ctDCS prolong the maintenance of learnt patterns at one-week follow-up in a motor adaptation task. These findings provide evidence for the potential use of anodal ctDCS as a rehabilitation adjunct to extend the benefits of motor training beyond the intervention period.

Furthermore, this thesis revealed the hurdles in extending the multi-session ctDCS research protocol to people with stroke and provided recommendations for improving the feasibility of delivering the ctDCS combined with SBTT in people with stroke. Although the evaluation of the repeated effects of ctDCS in combination with SBTT in people with stroke requires further optimisation, this thesis has advanced the current ctDCS evidence base regarding the efficacy of single and repeated sessions of anodal ctDCS on long-lasting motor learning.

PUBLICATIONS AND CONFERENCE PRESENTATIONS

- **Kumari N**, Taylor D, Signal N. The effect of cerebellar transcranial direct current stimulation on motor learning: A systematic review of randomised controlled trials. *Frontiers in Human Neuroscience*. 2019;13(328)
- **Kumari N**, Taylor D, Rashid U, Vandal AC, Smith PF, Signal N. Cerebellar transcranial direct current stimulation for learning a novel split-belt treadmill task: A randomised controlled trial. Manuscript submitted for publication. 2019
- **Kumari N**, Taylor D, Olsen S, Rashid U, Signal N. Cerebellar transcranial direct current stimulation for motor learning in people with chronic stroke: A pilot randomised controlled trial. Manuscript submitted for publication. 2019
- Rashid U, **Kumari N**, Taylor D, David T, Signal, N. Gait event anomaly detection and correction during a split-belt treadmill task. *IEEE Access*. 2019;7(1).
- **Kumari N**, Taylor D, Rashid U, Vandal AC, Smith, PF, Signal N. Stimulating the cerebellum with transcranial direct current stimulation to influence motor learning in healthy individuals. Podium presentation, Health and Rehabilitation Research Institute Symposium, Auckland University of Technology, New Zealand. 2019
- **Kumari N**, Taylor D, Rashid U, Vandal AC, Smith, PF, Signal N. Can cerebellar transcranial direct current stimulation influence motor learning in healthy individuals? Podium presentation, Australasian Winter Conference on Brain Research, Queenstown, New Zealand. 2019
- **Kumari N**, Taylor D, Rashid U, Signal N. The effect of cerebellar transcranial direct current stimulation on motor learning in healthy individuals: Early results of an RCT. Poster presentation at the International Neuromodulation Society's 14th world congress, Sydney, Australia. 2019
- **Kumari N**, Taylor D, Signal N. The role of the cerebellum in motor learning. Podium presentation at the Physiotherapy New Zealand Conference, Auckland, New Zealand. 2016

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APPENDICES

Appendix A. Study A: Search terms, search strategy and database search results

AND	Search Terms
Motor learning	acquisition "motor performance" "motor control" learning adapt*
Cerebellar tDCS	ctDCS "cerebellar stimulation" tDCS "transcranial direct current stimulation" "non-invasive brain stimulation" "noninvasive brain stimulation" "direct current stimulation" cerebell*

OR (Motor learning terms)

OR (ctDCS, "cerebellar stimulation")

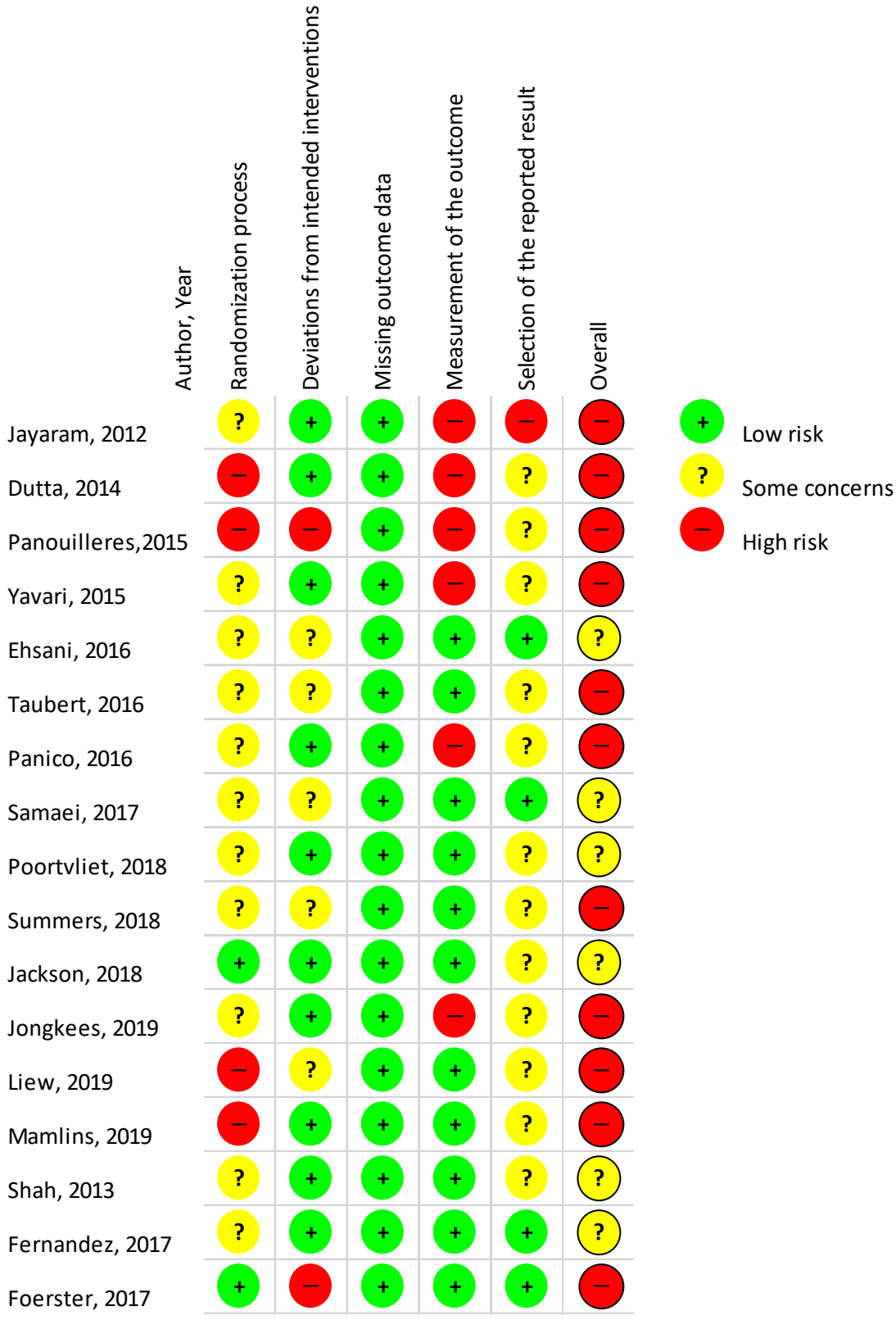
OR (tDCS, "transcranial direct current stimulation", "non-invasive brain stimulation", "noninvasive brain stimulation", "direct current stimulation")

AND (cerebell*)

OR (Cerebellar tDCS terms)

* truncation format used in the specific database

Appendix B. Study A: Quality of included studies



Appendix C. Study B: tDCS screening sheet

Participant Safety Checklist for using Transcranial Direct Current Stimulation

Volunteer Name:_____

Volunteer D.O.B.:_____ Date:_____

Have you ever been diagnosed with epilepsy or suffered from epileptic seizures?	Y / N
Do you wear a pacemaker?	Y / N
Do you have metal implants in any part of your body including your head (except tooth fillings)?	Y / N
Have you ever had a skull fracture?	Y / N
Do you have any known skull defects?	Y / N
Do you suffer from recurring headaches?	Y / N
Have you suffered a head injury or concussion within the last 6 months?	Y / N
Do you suffer from anxiety associated with medical procedures, needles etc.	Y / N
Are you currently, or could you be, pregnant?	Y / N
Are you currently taking any medications?	Y / N

Please list the names of medicines:

Checklist completed by: _____

Signature: _____

Date: _____

Appendix D. Study B: Ethical approval

AUTEC Secretariat

Auckland University of Technology
D-88, WU406 Level 4 WU Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

10 October 2016

Nada Signal
Faculty of Health and Environmental Sciences

Dear Nada

Re Ethics Application: **16/338 The effect of anodal cerebellar transcranial direct current stimulation on learning a novel walking task in health individual**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 10 October 2019.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 10 October 2019;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 10 October 2019 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz. All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Nitika Kumari, nitika.kumari@aut.ac.nz14859882; Denise Taylor

Appendix E. Study B: Participant information sheet

Participant Information Sheet
Date Information Sheet Produced:
02/09/2016

Project Title

The effect of anodal cerebellar transcranial direct current stimulation on learning a novel walking task in healthy individuals.

An Invitation

Kia ora, talofa lava and hello, my name is Nitika Kumari and I am a PhD student at AUT. You are invited to take part in a study that aims to explore the effectiveness of stimulating the cerebellum with constant low electric currents to speed up your learning a novel walking task.

Please remember that:

Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study.

If you do agree to take part you are free to withdraw at any time, without having to give a reason.

This information sheet will explain the research study. Please feel free to discuss with others and ask about anything that you do not understand.

What is the purpose of this research?

This project aims to find out if passing weak electric currents to the cerebellum, a part of the brain at the back of the head, can speed up the learning of novel walking task in healthy individuals. The stimulator we will be using (Transcranial Direct Current Stimulation-tDCS), is a painless and safe device that delivers a constant, low intensity current through two electrodes placed over the head to change the excitability of the brain. There is strong evidence that this can increase the rate and amount of learning in healthy individuals, however, we do not know how long effects are retained. The findings of this study will help better understand how this technique might be used to promote recovery after stroke. The results of the current study will be written up as part of a PhD project and will be published through scientific conferences and research journals.

How was I identified and why am I being invited to participate in this research?

You are being invited to participate in this study as you are a healthy individual with no pain or functional limitations of your legs or back.

You may be eligible for this study if you meet the following entry criteria:

Aged over 18 years

Do not have any history of orthopaedic, cardiac or neurological conditions that could interfere with your walking

Do not have any medical condition such as epilepsy, unexplained recurring headaches and cardiac arrhythmias which may influence the results

Do not have a history of epilepsy, head injury or concussion in the last 6 months

Do not have a skull fracture or other known skull defects

Do not have any metal implants or pacemakers

Are not taking any medications that alters brain activity

We will be recruiting 30 people to participate in the study.

How do I agree to participate in this research?

You should contact Nitika Kumari, 0273707917, nitika.kumari*@aut.ac.nz*. Before participating, you will be given a consent form to read and sign. Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data may not be possible.

What will happen in this research?

Your participation will involve four data collection sessions at the AUT Millennium Running and Cycling Clinic. You will need to wear shorts or short running tights during the session. The first three sessions will be held on consecutive days and the last session will be conducted after 1 week.

Each day, following set up of the stimulator (Figure 1) and the placement of reflective markers on your legs with double sided tape (Figure 2), you will be asked to walk on a treadmill with a separate belt under each foot. The belts will first move at slow speed for two minutes, then the stimulator will be turned on and the speed of the treadmill belts will be split; one belt moves faster than the other for 15 minutes. The stimulator will then be turned off and the treadmill belt speeds will be returned to slow speed for another 10 minutes. As you walk on the treadmill, your movement will be recorded by a number of cameras capturing the position and movement of the reflective markers.

Each session will last approximately 80 minutes, four sessions in total (approximately five and a half hours).

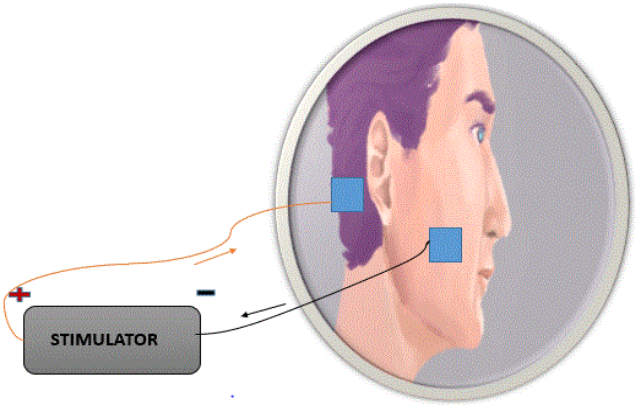


Figure 1: tDCS device setup

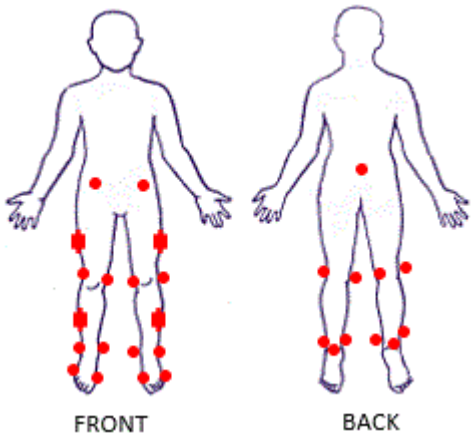


Figure 2: Reflective markers on legs

What are the discomforts and risks?

To date, no adverse effects have been reported by participants taking part in studies involving this type of brain stimulation. There is a small chance of experiencing a tingling/prickling sensation over the area that is in contact with the electrodes. If present, this sensation can only be felt during the first few seconds of stimulation. Some people may also perceive a metallic taste during stimulation.

How will these discomforts and risks be alleviated?

We will use electrical stimulation parameters that are well within safety guidelines for stimulation of the brain. Saline-soaked sponge will be used on the electrodes which will deliver the electric currents at a very low intensity at the start so that you get used to any tingling sensations. To further minimise any risk of skin irritation, scalp/skin area will be cleaned with alcohol before the electrodes are applied on it. We will monitor how you are feeling throughout each procedure and you are able to stop the session at any stage.

What are the benefits?

You will receive no direct benefit from participation in the study. However, the findings from this study will be used to better understand how this technique might be used to promote recovery after stroke. It is hoped that a subsequent study will help to investigate use of this stimulation to improve walking in people with stroke. The combined results of both the studies will be submitted in the form of a thesis to obtain my PhD degree.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, providing the incident details satisfy the requirements of the law and the Corporation's regulations.

How will my privacy be protected?

Your privacy will be maintained throughout the research process as you will always be identified by a code number. Researchers will only have access to coded data, which will prevent them from knowing your identity. The collected data and the consent forms will be stored in separate locked cabinets. This will ensure that no association can be made between the results and the consent forms.

Images of you walking on the treadmill will only show the position and movement of reflective markers, your face and any other identifying characteristics cannot be seen.

When results are reported, no names or any material that could identify you will be published or presented. After ten years, this data will be destroyed.

What are the costs of participating in this research?

There are no monetary costs associated with participating in this research. Each data collection session is expected to take approximately 80 minutes. This would be a total of nearly 5.5 hours over four separate sessions. A $20 voucher will be provided on each visit as a token of appreciation.

What opportunity do I have to consider this invitation?

To consider your participation in the study, you are provided with an opportunity to take time and discuss it with your family/whanau. Therefore, you can take up to two weeks to consider this invitation. We would appreciate it if you could respond back even if you would not be able to take part in the study. Please feel free to contact one of the researcher if you have any doubts or concerns regarding your participation.

Will I receive feedback on the results of this research?

Yes, you are given an opportunity on the consent form to indicate if you would like feedback on the research project. If you answer “yes” to this, a copy of your results and a short summary of the overall findings will be sent to you on completion of the study. This will be sent to the contact details that you provide on the consent form.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Dr Nada Signal, nsignal@aut.ac.nz, 09 9219999 ext 7062

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, Kate O’Connor, *ethics@aut.ac.nz* , 921 9999 ext 6038.

Whom do I contact for further information about this research?

Please keep this Information Sheet and a copy of the Consent Form for your future reference. You are also able to contact the research team as follows:

Researcher Contact Details:

Nitika Kumari
Health and Rehabilitation Research Institute
AUT University
Private Bag 92006
Auckland 1142
nitika.kumari@aut.ac.nz

Project Supervisor Contact Details:

Dr Nada Signal
Health and Rehabilitation Research Institute
AUT University
Private Bag 92006
Auckland 1142
nsignal@aut.ac.nz

Approved by the Auckland University of Technology Ethics Committee on 10/10/2016, AUTEC Reference number *16/338*.

Appendix F. Study B: Written consent form

Consent Form

Project title: *The effect of anodal cerebellar transcranial direct current stimulation on learning a novel walking task in healthy individuals*
Project Supervisor: *Dr Nada Signal, Prof. Denise Taylor*
Researcher: *Nitika Kumari*

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 02/09/2016.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.
- ○ I understand that if I withdraw from the study then I will be offered the choice between having any data or tissue that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.
- ○ I do not have any history of orthopaedic, cardiac or neurological conditions that impairs my physical performance.
- ○ I do not have any medical condition such as epilepsy, unexplained recurring headaches and cardiac arrhythmias
- ○ I do not have a history of epilepsy, head injury or concussion in the last 6 months
- ○ I do not have a pacemaker, artificial heart valve, any metal implants in my head, or skull defects
- ○ I am not taking any medications that alters my brain activity
- ○ I agree to take part in this research.
- ○ I wish to receive a summary of the research findings (please tick one):
  Yes○ No○

Participant's Signatures .....

Participant's name: .....
Participant's Contact Details (if appropriate):
.....
.....
.....
.....
Date:

***Approved by the Auckland University of Technology Ethics Committee on 10/10/2016*, AUTEC Reference number *16/338*.**

Appendix G. Study B: Advertisement

VOLUNTEERS REQUIRED FOR A PhD RESEARCH PROJECT

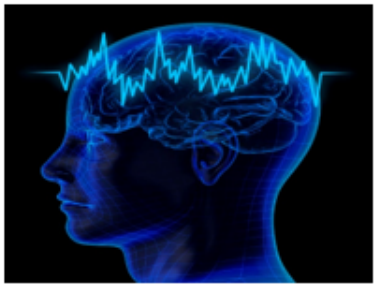
"Can stimulating the brain boost learning?"

We are looking for **healthy participants over 18 years of age** with

- no pain or difficulty in walking
- no history of head injury, epilepsy or recurring headaches
- no pacemakers

to participate in a study aiming to improve learning of movement.

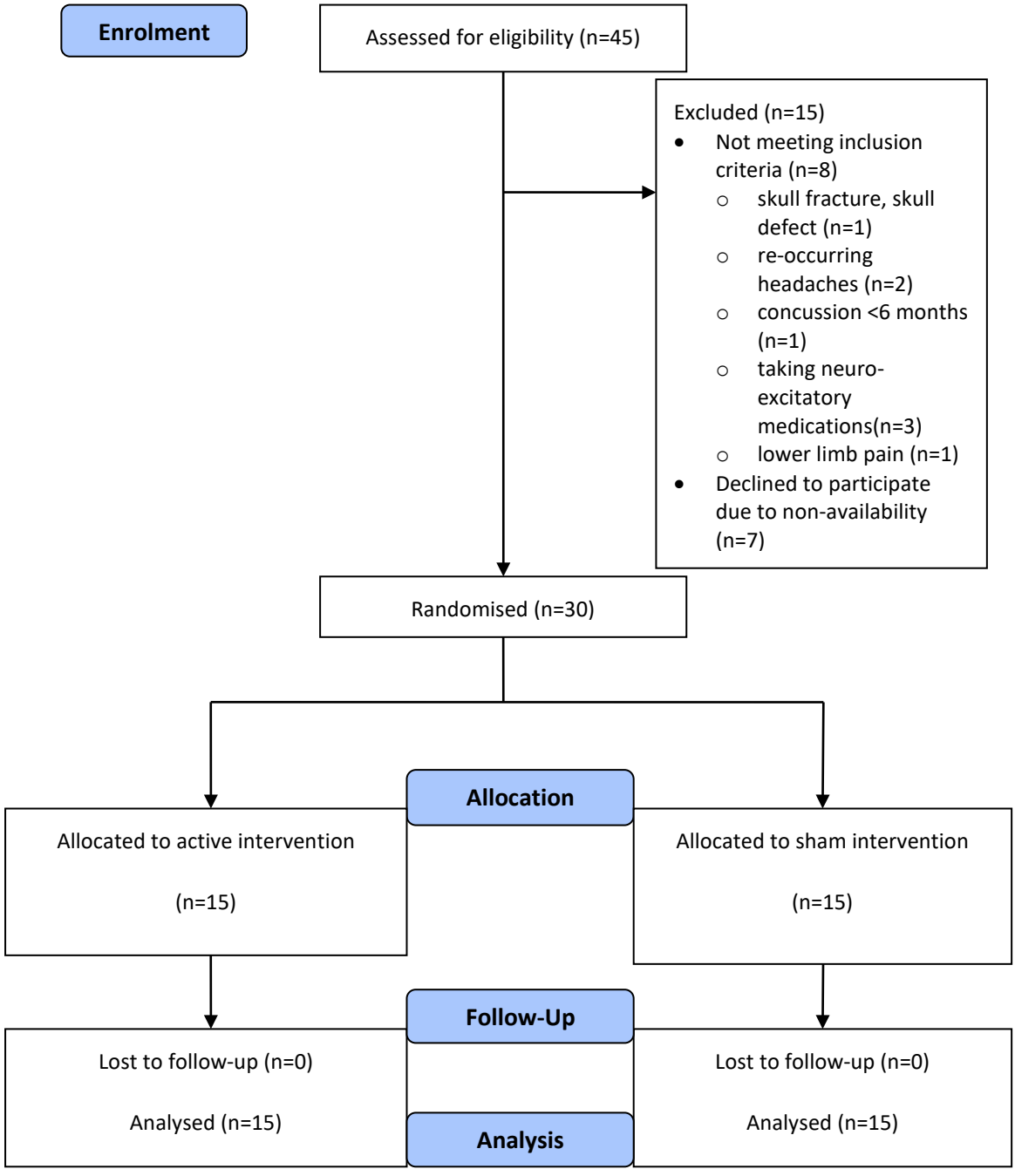
Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique of passing extremely low-intensity currents to the brain using two small electrodes. Single session of tDCS applied to the cerebellum has found to enhance learning of various simple tasks. The purpose of this study is find out whether application of tDCS to the cerebellum can speed up the learning of a more complex and functional task of walking on a split-belt treadmill.



The experiment will take approximately **5.5 hours** of your time spread over **4 separate visits** at the **AUT University Millennium Campus (Running and Cycling clinic)**. A $20 voucher will be provided on each visit as a token of appreciation.

If you are interested in taking part in this study, or would like further information, please contact Nitika Kumari, nitika.kumari@aut.ac.nz

Appendix H. Study B: CONSORT study flow diagram



Appendix I. Study B: Baseline demographic characteristics

		Active ctDCS	Sham ctDCS
N		15	15
Age (years)	Mean (SD)	31.4 (4.14)	29.8 (8.07)
	Range	23-39	21-53
Sex	Male	9	9
	Female	6	6
Height (cm)	Mean (SD)	172.66 (6.71)	174.65 (8.74)
	Range	158.8-181.7	162.6-193.5
Weight (Kg)	Mean (SD)	73.81 (11.88)	76.81 (19.21)
	Range	57.3-92.5	53.8-124.5
Leg Dominance	Right	14	14
	Left	1	1
Fastest comfortable walking speed/ Fast belt speed (m/s)	Mean (SD)	1.60 (0.29)	1.61 (0.26)
	Range	1.10-2.10	1.10-2.10

Appendix J. Study B: Amendment to Study A ethical approval

AUTEC Secretariat

Auckland University of Technology
D-88, WU406 Level 4 WU Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

22 May 2018
Nada Signal
Faculty of Health and Environmental Sciences
Dear Nada

Re: Ethics Application: **16/338 The effect of anodal cerebellar transcranial direct current stimulation on learning a novel walking task in health individual**

Thank you for your request for approval of amendments to your ethics application.
The amendment to research methodology to allow testing of algorithm to detect invalid force data is approved.

I remind you of the Standard Conditions of Approval.

1. A progress report is due annually on the anniversary of the approval date, using form EA2, which is available online through http://www.aut.ac.nz/researchethics.
2. A final report is due at the expiration of the approval period, or, upon completion of project, using form EA3, which is available online through http://www.aut.ac.nz/researchethics.
3. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form: http://www.aut.ac.nz/researchethics.
4. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
5. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.

Please quote the application number and title on all future correspondence related to this project.
AUTEC grants ethical approval only. If you require management approval for access for your research from another institution or organisation then you are responsible for obtaining it. If the research is undertaken outside New Zealand, you need to meet all locality legal and ethical obligations and requirements.
For any enquiries please contact ethics@aut.ac.nz
Yours sincerely,

Kate O'Connor
Executive Manager
Auckland University of Technology Ethics Committee
Cc: nitika.kumari@aut.ac.nz14859882; Denise Taylor; Gwyn Lewis

Appendix K. Study B: Additional work

Link to access article:

http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=8721121&isnumber=8600701

IEEE Access

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Digital Object Identifier 10.1109/ACCESS.2019.2918559

Gait Event Anomaly Detection and Correction During a Split-Belt Treadmill Task

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[1]Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland 0627, New Zealand

[2]Department of Mechanical Engineering, University of Canterbury, Christchurch 8041, New Zealand

Corresponding author: Usman Rashid (urashid@aut.ac.nz)

ABSTRACT During instrumented split-belt treadmill tasks, it is challenging to avoid partially stepping on the contralateral belt. If this occurs, accurate detection of gait events from force sensors becomes impossible, as the force data are invalidated. In this paper, we present an algorithm, which automatically detects these invalid force data using an acceleration derivative-based measure. We used this algorithm in combination with the coordinate-based treadmill algorithm to replace the invalidated gait events detected from force sensors with those detected from 3-D markers. The performance of the proposed algorithm was evaluated against the visual examination of data collected from healthy participants in both the same speed and differential speed configurations, using the receiver operator characteristics, the area under the curve, and the Youden index. We found that the area under the curve (AUC) score was above 0.8 in both the same speed and differential speed configurations. Moreover, there was not enough evidence ($p > 0.05$) to suggest a correlation between walking speed and the performance of the algorithm. We conclude that the algorithm has good to excellent detection and correction performance, which can be useful for research involving analysis of gait with instrumented split-belt treadmills. A MATLAB (MathWorks, Inc., Natick, MA, USA) based implementation of the proposed algorithm and example data files are also presented.

INDEX TERMS Gait analysis, split-belt treadmill, anomaly detection, force plates, 3-D kinematics, accelerometers.

I. INTRODUCTION

A split-belt treadmill is a special type of treadmill which has a separate belt for each leg [1]. As both the belts are separate and individually actuated, the split-belt can be used in two speed configurations. (i) Same speed configuration (SS) in which both the belts move at the same speed. (ii) Differential speed configuration (DS) in which the two belts move at different speeds [2]. Split-belt walking, where one leg is forced to move at a faster speed, is a well studied task in humans, animals and using robots [3]–[14]. It is used in the study of locomotor learning in healthy and pathological populations as it provides a novel and perturbing locomotor environment [15]–[18]. Using split-belt treadmill researchers have also proposed a variety of gait rehabilitation paradigms for patients with motor impairments [19]–[21].

Force plates embedded in the belts, 3-D motion capture camera system, accelerometers, and gyroscopes are generally used to record different aspects of the gait during split-belt treadmill tasks [22]–[28]. Detection of heel-strike (HS) and toe-off (TO) at correct time points from the data recorded with these sensors play an importance role in gait analysis. These events determine the stance and swing phases of gait. Although gait events can be determined from a range of different sensors [29], the detection of gait events by setting a threshold for data obtained from force plates is generally considered the gold standard method [24], [30], [31]. For example, using a threshold of 20 Newtons, a HS is registered at the time when the increasing value of force crosses this threshold. Similarly a TO is registered at the time when the decreasing force crosses this threshold.

A. PROBLEM STATEMENT

Walking on the split-belt treadmill requires a wider base of gait [32] to ensure that the feet remain on the right and left belts respectively [33]. Failure to do so invalidates the force sensor data [34]. This becomes more evident when one has to

The associate editor coordinating the review of this manuscript and approving it for publication was Bora Onat.

walk for a longer duration such as 10–15 minutes. Placing a separator between the two belts is often recommended to avoid the crossing over of the feet [33], however this compromises the natural walking pattern. When thresholding method is used to detect gait events from the force data, it can lead to invalid events. One solution for this problem is to not use the force data and instead rely on secondary sensors such as 3-D kinematic data or accelerometers, however, this is known to be less accurate [35]. Another solution is to manually identify time intervals where force data is invalidated and switch back and forth between events from force plate and the secondary sensor. However, this solution becomes impracticable when analyzing a large dataset, such as a large number of participants, long session duration or multiple data collection sessions. Thus there is a need for a method which can automate the process of gait event detection from force plate data, identify invalidated force data due to placement of both feet on the same belt and correct for these invalidated force data.

B. PROPOSED SOLUTION

In this study we propose a detection and correction algorithm (DACA) which automatically marks time instances where the force data has been invalidated and replaces gait events in these instances with events derived from 3D markers. The proposed method uses an acceleration derivative based measure to transform force plate data into noise levels. It then uses adaptive statistical profiling to detect time intervals where force data has been invalidated due to placement of both feet on the same belt. Combined with existing methods of gait event detection from force plate data and 3-D motion capture system, the proposed method is capable of fully automated gait event detection and correction. The performance of the proposed algorithm was evaluated by comparing its performance against visual examination in both the same speed and differential speed configurations. To the best of our knowledge, this is the first solution for gait event detection and correction from force plates embedded in a split-belt treadmill.

II. METHODS

A. EXPERIMENTAL DATASET

The dataset used for evaluation of the proposed algorithm was taken from a randomized controlled trial involving walking on an instrumented split-belt treadmill (Bertec Corporation, Columbus, OH, USA). The sampling rate of the force platform was 1000 Hz. A nine-camera motion capture system (Vicon Vantage, Nexus 2.4, Vicon Motion Systems Ltd, Oxford, UK) was used to record position data at a frame rate of 200 Hz from 33 reflective markers placed according to the Cleveland clinic model [36]. An illustration of the split-belt treadmill used in this study is shown in Figure 1.

The trial investigated the effect of cerebellar transcranial direct current stimulation (ctDCS) on motor adaptation in a healthy population. Thirty participants (Average age: 30 ± SD 6 years, 12 female) were recruited through professional networks and local advertising. Participants were excluded if they had a history of orthopaedic, cardiac or neurological conditions that could interfere with walking, or any contra-indications to application of ctDCS. All the participants provided written consent before data collection. Ethics approval (16/338) for the study was obtained from Auckland University of Technology Ethics Committee. Data was collected over four $1\frac{1}{2}$ hour sessions at the Running and Cycling Clinic, AUT Millennium Institute, New Zealand.

FIGURE 1. An illustration of the split-belt treadmill used in this study.

Whilst walking on the treadmill, participants were instructed to look straight ahead and stay in the middle of the treadmill with one foot on each belt, and holding a front rail adjusted to their elbow height. The participant's fastest comfortable walking speed on the treadmill was determined. During data collection the participants walked for a total of 25 minutes where 15 minutes were undertaken with the belts moving at different speeds followed by 10 minutes with both belts moving at same speeds. In the differential speed configuration the fast belt speed was set to the participant's fastest comfortable waking speed and the slow belt to half of this speed. The treadmill was configured such that the fast belt was under the participant's dominant leg. In the same speed configuration both belts were set to half of the participant's fastest comfortable walking speed.

To evaluate the proposed algorithm, the six data files with the highest prevalence of invalid force data were selected from each speed configuration. These files included data from 6 different participants over four different sessions. The fastest comfortable walking speed for these participants ranged from 1.1 to 2.1 meters/second (m/s).

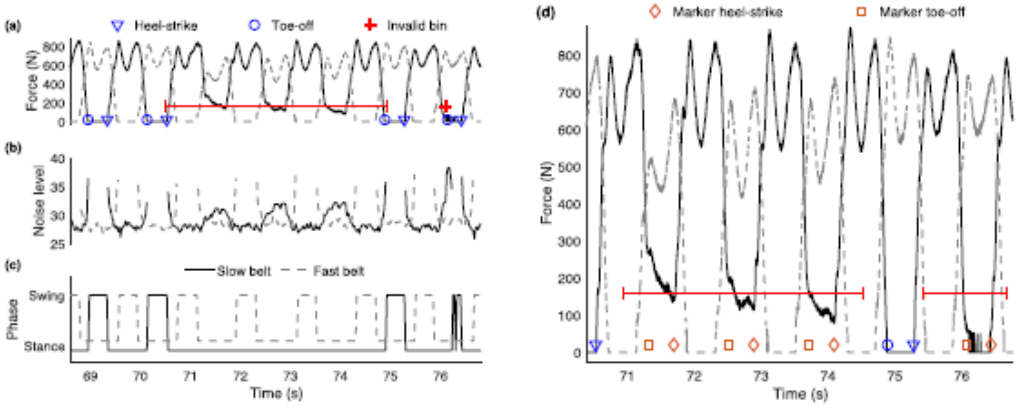

FIGURE 2. Detection and correction of gait events where the force data is invalid. '⊢-⊣' represents intervals of invalid force.

B. EVENT DETECTION FROM FORCE PLATES

To determine heel-strikes and toe-offs for each foot, the data from force plates was first filtered with a 2^{nd} order zero-phase low-pass Butterworth filter with cut-off at 10 Hz. The filtered force was used to obtain the heel-strikes and toe-offs with a threshold at 20 Newtons. A HS was registered at the time when the increasing value of force crossed this threshold. Similarly a TO was registered at the time when the decreasing force crossed this threshold. These events are shown in Figure 2 (a). Mathematically, it was achieved by applying the first order difference operation to the threshold data. The time of positive differences were marked as heel-strikes and time of negative differences as toe-offs.

C. DETECTION AND CORRECTION ALGORITHM (DACA)

The time points and intervals where the force plate data was invalidated by placement of both feet on the same plate were detected by transforming the raw force values to noise levels. This was done by binning raw force data into bins of length 25 milliseconds and finding noise level in each bin. The bin length was chosen to strike a balance between computation time required for data processing and capturing faster dynamics of force data. The noise level was defined as the natural log of the integral of the square of the acceleration derivative as given below.

$$n_i(x) = \ln\left|\frac{1}{(x_i^{peak})^2}\int_{t_i}^{t_{i+1}}\left(\frac{d^3}{dt^3}x(t)\right)^2 dt\right| \tag{1}$$

where $x(t)$ is the raw force plate data, and x_i^{peak}, $n_i(x)$ define the peak raw force value and the measure of noise for the i^{th} bin respectively. This noise measure is similar to the log dimensionless acceleration derivative used to quantify movement smoothness [37]. The noise levels for the bins are shown in Figure 2 (b). Assuming that the raw force data was divided into k bins, the mean and standard deviation of the noise levels from these bins were defined as follows.

$$\bar{n} = \frac{\sum_{i=1}^{k} n_i}{k}$$
$$\sigma_n = \sqrt{\frac{\sum_{i=1}^{k}(n_i - \bar{n})^2}{k-1}} \tag{2}$$

If k_b number of consecutive bins had a noise level above the mean ($\bar{n}$) plus one standard deviation (σ_n), the first bin was marked invalid as shown by '+' in Figure 2 (a). The number of bins (k_b) was used to select the sensitivity of the detector to invalid force.

In reference to the slow belt force data in Figure 2 (a), as the foot was lifted completely off the belt at toe-off, the force became zero. The force remained zero during a normal swing phase and started increasing again at the heel-strike. However in case of the third, fourth and the fifth swing phase, the force did not become zero as the contralateral foot was partially placed on the slow belt. This non-zero force during a swing phase signified the crossing over of feet across belts. When the force was zero, the noise level in corresponding bins was *undefined* as x_i^{peak} was zero. This can be observed in Figure 2 (b), where the plotted noise levels have gaps. These periods of *undefined* noise level correspond to swing phase and the periods of *defined* noise level correspond to the stance phase, as shown in Figure 2 (c). This definition of swing and stance phase gives poor estimates of the actual phases because the accuracy of the estimates is dependent on bin size. However the advantage is that the obtained values do not depend on detected force events. The mode statistic of the time duration of these stance phases was defined as the mode stance time and it was used to identify invalid force intervals. Thus a stance phase which was longer than twice the mode stance time was identified as an invalid force interval, under the assumption that such a stance phase is not

naturally possible. The resulting intervals of invalid force are represented by '⊢⊣' in Figure 2 (a, d).

These intervals and bins of the detected invalid force were then used to remove gait events detected from force data and were replaced by events detected from 3-D marker data. This process of detection and replacement of anomalous gait events was done for each belt separately. The results are shown in Figure 2 (d).

The detected bins of invalid force could not be directly used to remove and replace nearby invalid gait events as the bin size (25 milliseconds) was too short. Thus an interval was created at the time of the invalid bin time. The length of these intervals in each direction was set to three quarters of the mode stance time. This length was chosen to ensure that the nearby invalid events were removed and replaced while valid events from adjacent phases were not. The use of mode stance time for this purpose also ensured that this operation was adaptive to speed changes across belts and participants. The lengths of the detected intervals of invalid force were shortened in each direction by half of the mode stance time. This was done to avoid unnecessarily removing valid force events from adjacent phases.

D. EVENT DETECTION FROM 3-D MARKER DATA

To detect gait events from the 3-D marker data, a modified form of the Coordinate-based Treadmill Algorithm was used [38]. First the marker data was low pass filtered using a 2^{nd} order zero-phase Butterworth filter with cut-off at 25 Hz. The zero-phase filter does not introduce a time lag in the signal and, therefore, does not disrupt the time synchronization between the force plate data and 3-D marker data. Second, the heel-strikes for the left and the right foot were detected as the maxima of the left and the right heel marker position in the anterior-posterior direction respectively. Similarly the toe-offs for the left and the right foot were detected as the minima of the left and the right fifth metatarsal marker position in the anterior-posterior direction respectively.

E. VISUAL EXAMINATION OF DATA

The detection and correction performance of the algorithm was validated by comparison with detection and correction done by a trained examiner. A graphical tool was developed in MATLAB (MathWorks, Inc., Natick, MA, USA) 2017b for this purpose. The examiner inspected the raw force data of a single file at a time by scrolling through it in 10 second windows. The examiner marked an interval of invalid force by selecting a start and an end point. The gait events detected from both the force and the marker data in that interval were then revealed. The examiner reviewed each gait event and selected one of the estimates (force or marker event) and deleted the other.

F. STATISTICAL ANALYSIS

The statistical analysis was performed separately for the two speed configurations, the belt sides (the fast or dominant leg (DL) and the slow or non-dominant leg (NDL)), and excluded force, included marker events. This was done to consider the performance of the algorithm under varying conditions. To illustrate the scope of the problem, the prevalence of excluded force events was defined as the percentage of force events excluded by the examiner from the total number of force events detected. The prevalence of included marker events was defined as the percentage of markers events included by the examiner from the total detected marker events.

To evaluate the performance of the proposed algorithm, we compared; (a) whether the algorithm removed the same set of force events as the examiner and (b) whether the algorithm included same marker events as the examiner. These assessments were made using receiver operator characteristic curves (ROC). It is a graphical tool for visualizing the performance of classifiers [39]. It shows the performance of a classifier in terms of the trade-off between its true positive rate (TRP, hit rate, sensitivity) and its false positive rate (FPR, fall-out). For comparison with the random performance, an identity line (TPR = FPR) is also plotted. The farther is the ROC curve of a classifier above the random performance line, the better is its classification ability. In order to assess the ability of the proposed method to both exclude invalidated force events and include valid marker events, we plotted separate ROC curves. Also separate ROC curves were plotted for the slow belt and the fast belt in the two speed configurations. Thus a total of 8 ROC curves were plotted. All the 6 data files of each speed configuration were used in plotting a curve. To plot a curve we computed TRP and FPR as a function of the number of bins (k_b) used by the proposed algorithm. Its value was varied from 1 to 10. For each value of k_b we computed TPR and FPR for the six data files and averaged TPR and FPR across these files. This corresponded to the threshold averaging method explained by Fawcett [39]. True positive rate for excluded force events (TPR_f), false positive rate for excluded force events (FPR_f), true positive rate for included marker events (TPR_m) and false positive rate for included marker events (FPR_m) was defined as follows.

$$TPR_f = \frac{TP_f}{P_f} \times 100 \tag{3}$$

$$FPR_f = \frac{FP_f}{N_f} \times 100 \tag{4}$$

$$TPR_m = \frac{TP_m}{P_m} \times 100 \tag{5}$$

$$FPR_m = \frac{FP_m}{N_m} \times 100 \tag{6}$$

- TP_f True positive force events: Force events excluded by both the algorithm and the examiner.
- FP_f False positive force events: Force events excluded by the algorithm and not by the examiner.
- P_f Positive force events: Force events excluded by the examiner.
- N_f Negative force events: Force events not excluded by the examiner.

TABLE 1. Means and standard deviations for prevalence of excluded force events and included marker events. NDL stands for non-dominant leg. DL stands for dominant leg. The differential speed configuration corresponds to both the belts moving at different speed with a ratio of 1:2. The same speed configuration corresponds to both the belt moving at same speed with a ratio of 1:1.

Events	Speed configuration	Slow belt (NDL) (%)	Fast belt (DL) (%)
Excluded force	Differential	3.67 ± 2.67	0.18 ± 0.15
	Same	9.45 ± 5.48	0.39 ± 0.72
Included marker	Differential	3.67 ± 2.444	0.23 ± 0.25
	Same	18.05 ± 8.81	0.53 ± 0.95

TP_m True positive marker events: Marker events included by both the algorithm and the examiner.
FP_m False positive marker events: Marker events included by the algorithm and not by the examiner.
P_m Positive marker events: Marker events included by the examiner.
N_m Negative marker events: Marker events not included by the examiner.

To represent ROC performance as a scalar value, we obtained area under the curve (AUC). The AUC score was interpreted as the probability that the proposed algorithm correctly labeled a randomly chosen positive case against a randomly chosen negative case. Thus an AUC score of 1.0 was considered perfect discriminative ability and 0.5 represented random guessing [39]. To identify optimal number of bins (k_b), we obtained Youden index [40]. It was computed as TPR – FPR at each point of the ROC curve and its maximum value (YI_{max}) corresponded to the optimal number of bins (k_b). YI_{max} was interpreted as informedness of the proposed method with 1.0 considered perfect discriminative ability and 0 as random guessing.

To evaluate the relationship between the walking speed of participants and the performance of the proposed method, the Spearman's rank correlation coefficient (ρ) and p-value for zero correlation null hypothesis (H_0: $\rho = 0$) was obtained. The correlation was performed between speed and true positive rate, speed and false positive rate. Significance level was set at 0.05. True positive rates and false positive rates were obtained for excluded force events and included marker events for each belt in each speed configuration as explained in Equations 3 – 6. To keep the analysis simple, no distinction was made between belts, speed configuration, excluded force events or included marker events while performing the correlation. Nonetheless a different number of bins (k_b) parameter of the algorithm was chosen for each speed configuration as dictated by the ROC analysis. Moreover, for the differential speed configuration, the fastest comfortable walking speed was treated as the walking speed. And for the same speed configuration, half of the fastest comfortable walking speed was treated as the walking speed.

Finally to show the implication of using the proposed algorithm on standard gait analyses, we compared the step lengths measured using the corrected gait events derived from DACA against the uncorrected gait events derived from force plates using the threshold method. The step length for both the DL and the NDL of one of the participants was obtained for this purpose. The step length for the DL was calculated for each step at heel-strike as the distance from the DL heel marker to the NDL heel marker. Similarly the step length for the NDL was calculated for each step at heel-strike as the distance from the NDL heel marker to the DL heel marker.

III. RESULTS

A. PREVALENCE

Table 1 lists the prevalence of excluded force events and included marker events by the examiner. The prevalence of included marker events was higher compared to the prevalence of excluded force events due to the fact that in many cases gait events were not detected at all from invalidated force data. The prevalence rates were higher in same speed configuration compared to the differential speed configuration. The rates were also higher for the slow belt compared to the fast belt. These results are further discussed later in Section IV.

B. RECEIVER OPERATOR CHARACTERISTICS

The receiver operator characteristic curves are given in Figure 3. With a single bin ($k_b = 1$) the true positive and the false positive rates for both the excluded force events and the included marker events were equal to 100%. As the number of bins were increased, the false positive rate decreased more rapidly than the true positive rate. This was also reflected by the area under the curve which was above 0.8 in all cases, refer to Table 2. The algorithm demonstrated good performance (AUC $>$ 0.8) for slow belt (NDL) in the differential speed configuration and excellent performance (AUC $>$ 0.9) in all other cases.

The number of bins corresponding to YI_{max} was 3 for both marker and force events for both the slow and the fast belt in the differential speed configuration. In the same speed configuration the number of bins corresponding to YI_{max} was 5 for both the belts for the force events. For the marker events, the number of bins was 6 for slow belt (NDL) and 5 for the fast belt (DL). These results indicated that the algorithm achieved consistent performance under same parameter value within a speed configuration.

C. RELATIONSHIP BETWEEN SPEED AND PERFORMANCE

True positive rates and false positive rates for excluded force events, included marker events, belts and speed

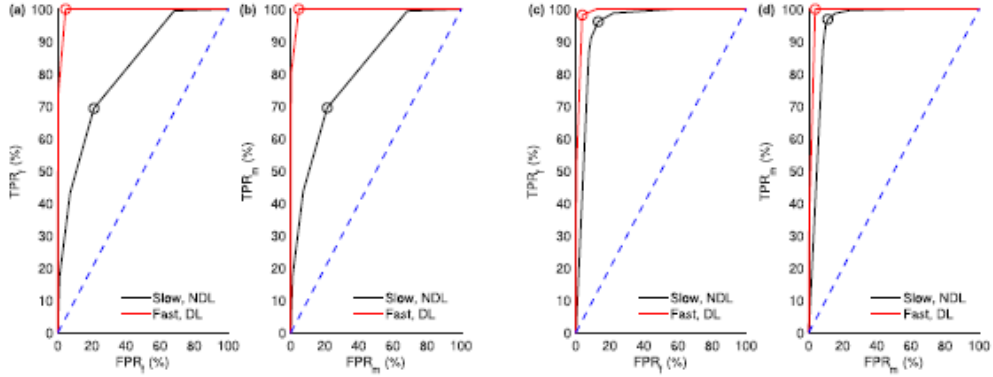

FIGURE 3. Differential speed (a, b) and same speed (c, d) configuration receiver operator characteristics curves for excluded force events and included marker events by the algorithm. 'o' represents the point corresponding to maximum Youden index. NDL stands for non-dominant leg. DL stands for dominant leg. TPR_f and FPR_f are the true positive and the false positive rates for the excluded force events respectively. TPR_m and FPR_m are the true positive and the false positive rates for the included marker events respectively.

TABLE 2. Performance metrics for the proposed algorithm under different conditions. NDL stands for non-dominant leg which was over the slow belt. DL stands for dominant leg which was over the faster belt. k_b represents the number of bins parameter of the algorithm. YI_{max} represents the maximum value of the Youden index.

Speed configuration	Events	Belt	Area under the curve	YI_{max}	k_b at YI_{max}
Differential	Excluded force	NDL	0.81	0.48	3
		DL	0.98	0.96	3
	Included marker	NDL	0.81	0.48	3
		DL	0.99	0.95	3
Same	Excluded force	NDL	0.94	0.83	5
		DL	0.99	0.94	5
	Included marker	NDL	0.95	0.86	6
		DL	0.99	0.96	5

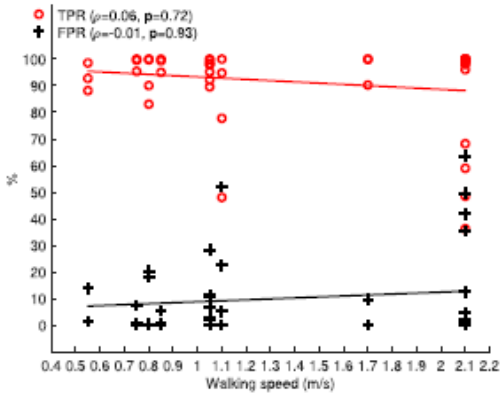

FIGURE 4. True positive rate (TPR) and false positive rate (FPR) plotted against walking speed. ρ, 'p' represent the Spearman's rank correlation coefficient and its corresponding p-value respectively. The solid lines represent the least-squares best fit lines.

configurations are plotted against the walking speed in Figure 4. As dictated by the results of the ROC analysis (Table 2), these TPRs and FPRs were obtained with number of bins (k_b) equal to 3 and 5 for the differential and the same speed configuration, respectively. The correlation between TRP and speed, FPR and speed was 0.06 and 0.01, respectively. There was not enough evidence ($p > 0.05$) to suggest a statistically significant correlation in either case. However there were a few large outliers which are discussed later in Section IV.

D. COMPARISON WITH FORCE THRESHOLD METHOD

Step lengths measured using uncorrected gait events derived with the force threshold method and gait events corrected using DACA are shown in Figure 5 (a) and (b) respectively. The uncorrected gait events resulted in a smaller number of steps (318) with multiple step length outliers. Whereas DACA corrected gait events identified a larger number of steps (352) and normally distributed step lengths.

IV. DISCUSSION

We have developed a novel algorithm which automatically detects invalid force data during a split-belt treadmill task. This rigorous evaluation of the performance of the algorithm indicates that it has good to excellent detection and correction performance in both the same speed and differential speed configurations.

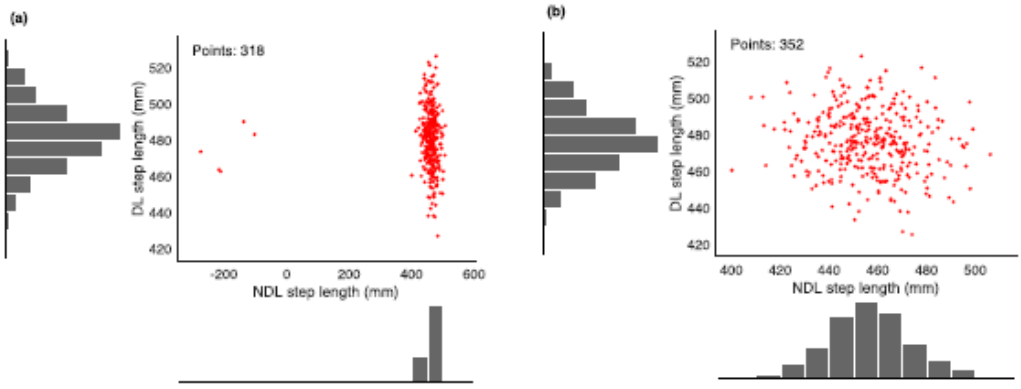

FIGURE 5. Step lengths for the dominant (DL) and the non-dominant leg (NDL) measured using uncorrected gait events derived with the force threshold method (a) and gait events corrected using the proposed method (b). The number of points correspond to the number of steps identified from the gait events.

The prevalence of invalidated and corrected gait events as determined by the examiner varied between 0.18% and 18% dependent upon the speed configuration and duration of the task, illustrating the scope of the problem. This has led researchers to use belt separators which changes the task [33], discard parts of the data or abandon the use of force data in favor of other sensors [34]. Thus the proposed method provides a viable alternative with the benefit of reduced processing time compared to manual examination and correction. Also it results in more robust events for gait analyses as compared to automatic event detection using the force plates alone.

The prevalence of both the excluded force events and included marker events was considerably higher for the slow belt in both differential speed and same speed configurations. The higher prevalence for the slow belt relates to the dominant leg stepping onto the slow belt. This suggests that prevalence of invalid force events is related to leg dominance and not to belt speed. The prevalence of included marker events was also higher compared to the prevalence of excluded force events due to the fact that in many cases, gait events were not detected at all from invalidated force data. Furthermore the prevalence was higher in same speed configuration. This may be due to familiarization to same speed configuration which has been found to narrow the base of gait over time [5], or fatigue resulting from 15 minutes of walking in the differential speed configuration which preceded the same speed configuration in this study.

The parameters of the algorithm are simple, intuitive and can be tuned manually. In future applications, the parameters can be fine tuned to meet the characteristics of the force sensor, the split-belt task and the population. All of the algorithm parameters, except for the length and number of bins, are based on the statistical properties of the recorded data and, thus, adaptive to differences in data. The length of the bin should be chosen based upon the sampling rate of the force sensor, rate of change of force dynamics, and the computational power required to process the data. The number of bins was used to select the sensitivity of the proposed algorithm. Its effect on the performance of the algorithm was studied using the ROC analysis. A larger number of bins reduced the sensitivity and a smaller number of bins increased the sensitivity of the algorithm. The analysis showed that the number of required bins differs across speed configurations, however the same number of bins produce consistent detection performance within the same configuration. This finding is important as only one bin number can be used for processing data for a given configuration. We recommend the use of 3 to 6 bins.

The walking speed of the participant on the split-belt treadmill did not have an effect on the performance of the algorithm in general. The significance of this result is amplified by the fact that same number of bins was used for all the data files for a given speed configuration. Thus, in future application, one can expect generally high detection and correction performance from the proposed algorithm without tuning its parameters for each data file. However as a few large outliers were observed in the speed versus performance analysis, fine tuning of parameters might be inevitable in some instances. A quick diagnostic tool to help this process is the scatter histogram plot of the outcome variable (e.g. step length) as shown in Figure 5. This plot gives a comprehensive overview of the performance of the algorithm and can be used to decide if the algorithm is performing well for the given data file with the selected parameters without the need to scroll through long raw force data. If there are outliers and the distribution of the outcome variable is not as expected, the parameters of the algorithm can be readjusted till desired performance is achieved.

Another important consideration for processing of force sensor data and 3-D marker data is the selection of the cut-off for the low pass filter. In the past, researchers have used varying cut-offs depending on the sensor characteristics, task and the population. For example, for force sensor data, cut-offs at 50 Hz and 20 Hz have been used [24], [38]. Whereas for 3-D marker data, cut-offs at 6 Hz, 7 Hz 10 Hz and 12 Hz were used [24], [25], [31], [41], [42]. In this study we used 10 Hz cut-off for force sensor data and 25 Hz cut-off for 3-D marker data. These cut-offs may compromise the performance of the proposed method in a different population or task. Therefore fine tuning of the cut-offs is suggested for future application in accordance with the sensor characteristics, the task and the population.

We used a 3D marker system to replace invalid gait events from force data or add gait events not detected altogether. Whilst we used the coordinate-based treadmill algorithm to detect gait events from 3D markers, the proposed algorithm can be used with any other algorithm which suits the needs of the researcher. Furthermore it can also be used in combination with an algorithm which detects gait events from other sensors such as accelerometers [26].

The findings of this research should be considered in light of a number of factors. The algorithm uses square of the acceleration derivative to transform the force values into noise levels. Force values with high noise level are labeled as invalid. Mean and standard deviation of the noise levels are used for this purpose. The algorithm also uses these noise levels to estimate swing and stance phases. Those stance phases which are longer than twice the time for most of the stance phases are also labeled as invalid using the mode statistic. Therefore the performance of the algorithm is expected to deteriorate under extremely high prevalence of invalid force where mean, standard deviation and mode can not adequately represent the data characteristics.

A. SOFTWARE AVAILABILITY

The MATLAB (MathWorks, Inc., Natick, MA, USA) based implementation of the proposed algorithm, the graphical user interface tool for visual examination and example data files have been made available online.[1] These tools can be used to import force plate and 3-D marker data from Vicon Nexus, process the data using the proposed algorithm and visualize the invalidated and corrected gait events.

V. CONCLUSION

We have proposed an algorithm which accurately detected invalidated force during an instrumented split-belt treadmill task due to placement of both feet on the same belt. Coupled with a secondary sensor, 3-D markers in this study, the proposed algorithm can automatically replace invalidated gait events in force data with gait events detected from the secondary sensor. ROC curve analysis on data collected from healthy participants in both the same speed and differential speed configurations showed that the proposed algorithm has good to excellent detection and correction capacity. Its performance was also robust to walking speed.

[1] https://github.com/GaitVp/knkTools

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USMAN RASHID received the B.Sc. degree in electrical engineering from the University of Engineering and Technology, Taxila, in 2011, the M.S. degree in robotics and intelligent machines engineering from the National University of Sciences and Technology, Islamabad, in 2015. He is currently pursuing the Ph.D. degree with the Auckland University of Technology, Auckland.

His research interests include control systems, artificial intelligence, brain–computer interfaces, and inferential statistics.

NITIKA KUMARI received the bachelor's degree in physiotherapy, in 2010 and the master's degree in physiotherapy (rehabilitation), in 2013. She is currently pursuing the Ph.D. degree with the Auckland University of Technology (AUT), Auckland.

She has been a full-time Physiotherapist in India for two years, where she has been involved in neurology, community-based rehabilitation, musculoskeletal, and cardio-pulmonary conditions. Her research interests include stroke rehabilitation and the use of neuromodulatory interventions to facilitate motor learning.

DENISE TAYLOR received the Graduate Diploma degree in physiotherapy from Coventry University, Coventry, in 1986, the M.Sc. degree in rehabilitation from Southampton University, Southampton, in 1991, and the Ph.D. degree from the University of Otago, Dunedin, in 2004. Her Ph.D. research was focused on motor control.

She is currently a Professor with the School of Clinical Sciences, Auckland University of Technology, Auckland. Her research interests include neurological rehabilitation and health of older adults. Recently, she has been involved in research and implementation work based on the ideas of population health to improve the health of large populations of people rather than focusing on change at an individual level. This is a different approach in physiotherapy, which mainly focuses on treatment at an individual level. As part of this work, she has become increasingly aware of the importance of economic evaluations alongside clinical trials. In a recently completed multi-site randomized controlled trial of falls prevention in older adults, she was involved in conducting an economic evaluation. Working alongside an economist on this trial sparked her interest and she went on to study health economics, from 2009 to 2010 at the University of Aberdeen and have attended a course on Advanced Methods of Cost-Effectiveness Analysis, in 2011, run by the Health Economics Research Centre, University of Oxford. In 2012, she attended a workshop on Discrete Choice Experiments, run by the Health Economics Research Centre, Aberdeen. This is a relatively new method of health economic evaluation that could be particularly pertinent for rehabilitation research.

TIM DAVID received the B.S. and Ph.D. degrees from the University of Leeds, Leeds.

He is currently a Professor with the Department of Mechanical Engineering, University of Canterbury, Christchurch. His research interests include neurovascular coupling, dynamics of large vascular trees, mathematical and numerical models of cardiovascular blood flow, computational physiology, and dynamics of coupled cells.

Dr. David is a member of many professional organizations, including the Institute of Physics and Engineering in Medicine (IPEM), the Institution of Professional Engineers New Zealand (IPENZ), the Royal Society of New Zealand (RSNZ), and the Institute of Mathematics and its Applications.

NADA SIGNAL'S Ph.D. explored locomotor rehabilitation for people with stroke.

She trained as a Physiotherapist and has extensive clinical and managerial experience in the rehabilitation sector. She was involved in rehabilitation research since embarking on her M.HSc. degree, in 2003. Her research focuses on novel and theoretically sound rehabilitation interventions, including rehabilitation technologies. She is currently a Senior Research Fellow with the Health and Rehabilitation Research Institute, Auckland University of Technology. She is interested how knowledge of the underlying mechanisms associated with impairments, activity limitations, and participatory restrictions may inform the development and implementation of rehabilitation technologies.

Appendix L. Study C HDEC ethical approval

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

04 816 3985
hdecs@moh.govt.nz

12 October 2017

Ms Nitika Kumari
HRRI
AUT University-North Shore Campus
90 Akoranga Drive
Northcote 0627

Dear Ms Kumari

Re:	Ethics ref:	17/STH/147
	Study title:	The effects of anodal cerebellar transcranial direct current stimulation on locomotor re-learning in people with chronic stroke.

I am pleased to advise that this application has been *approved* by the Southern Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Southern Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at *any* locality in New Zealand, it must be registered in a clinical trials registry. This should be a WHO-approved (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au). However https://clinicaltrials.gov/ is acceptable provided registration occurs prior to the study commencing at *any* locality in New Zealand.

3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

- In the Participant Information Sheet please describe randomisation in a general way, such as "you will be randomised into one of three conditions where site of stimulation and intensity may be different, we will tell you which you were in at the completion of the study"
- Please include a debrief for participants, to inform them about which stimulation they received (including 'sham'). When deception or concealment is used in a

study there must be adequate and prompt disclosure and debriefing provided to participants, as soon as appropriate and practicable (Ethical Guidelines for Intervention Studies paragraph 6.31).

Non-standard conditions must be completed before commencing your study. Non-standard conditions do not need to be submitted to or reviewed by HDEC before commencing your study.

If you would like an acknowledgement of completion of your non-standard conditions letter you may submit a post approval form amendment. Please clearly identify in the amendment that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see section 128 and 129 of the Standard Operating Procedures at http://ethics.health.govt.nz/home.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

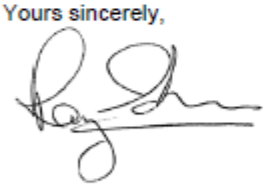
Your next progress report is due by 12 October 2018.

Participant access to ACC

The Southern Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,



Raewyn Idoine
Chairperson
Southern Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	*Version*	*Date*
Protocol: This document elaborates the past literature review and the methodology for the current project	1	21 August 2017
PIS/CF: Amended PIS/CF post full pathway review(document date corrected)	2	11 October 2017
CV for CI	1	21 August 2017
Evidence of scientific review: Feedback from the independent reviewer who approved the study as a part of PGR9 review process of the university.	1	01 August 2016
Evidence of scientific review: Feedback from the independent reviewer who approved the study as a part of PGR9 review process of the university.	1	01 August 2016
Amended Advert post full pathway review	2	11 October 2017
Matauranga Maori Committee Consultation Report	1	05 October 2016
Screening Checklist	1	22 August 2017
Application	1	-
Application: Answer to question a.2.1.3 of Application.pdf	1	-
Response to Committee	1	11 October 2017
Response to Request for Further Information	1	-

Appendix B
Statement of compliance and list of members

Statement of compliance

The Southern Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008713) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Ms Raewyn Idoine	Lay (consumer/community perspectives)	27/10/2015	27/10/2018
Dr Sarah Gunningham	Non-lay (intervention studies)	27/10/2015	27/10/2018
Assc Prof Mira Harrison-Woolrych	Non-lay (intervention studies)	27/10/2015	27/10/2018
Dr Fiona McCrimmon	Lay (the law)	27/10/2015	27/10/2018
Dr Anna Paris	Lay (other)	24/08/2017	24/08/2020
Dr Nicola Swain	Non-lay (observational studies)	27/10/2015	27/10/2018
Dr Devonie Waaka	Non-lay (intervention studies)	13/05/2016	13/05/2019
Dr Mathew Zacharias	Non-lay (health/disability service provision)	27/10/2015	27/10/2018

Unless members resign, vacate or are removed from their office, every member of HDEC shall continue in office until their successor comes into office (HDEC Terms of Reference)

http://www.ethics.health.govt.nz

Appendix M. Study C: AUTEC locality approval

AUTEC Secretariat

Auckland University of Technology
D-88, WU406 Level 4 WU Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

15 August 2019
Nada Signal
Faculty of Health and Environmental Sciences
Dear Nada

Ethics Application: **18/7 The effect of cerebellar transcranial direct current stimulation on locomotor re-learning in people with chronic stroke**

At their meeting of 12 August 2019, the Auckland University of Technology Ethics Committee (AUTEC) received the report on your ethics application. AUTEC noted your report and asked me to thank you.
On behalf of AUTEC, I congratulate the researchers on the successful completion of the project.
When communicating with us about this application, we ask that you use the application number and study title to enable us to provide you with prompt service. Should you have any further enquiries regarding this matter, you are welcome to contact me by email at ethics@aut.ac.nz or by telephone on 921 9999 at extension 6038.

Yours sincerely

Kate O'Connor

Executive Manager

Auckland University of Technology Ethics Committee

Cc: nitika.kumari@aut.ac.nz; Denise Taylor

Appendix N. Study C: Participant information sheet and consent form

Participant Information Sheet

Study Title: **The effect of brain stimulation on learning a treadmill-walking task in people with chronic stroke**

Locality: AUT Millennium Institute, Rosedale, Auckland | Ethics committee ref.: 17/STH/147

Lead Investigator: **Dr Nada Signal** | Contact phone number: 0273707917

AUT University

Kia ora, Talofa lava, and Hello.

You are invited to take part in a study that aims to explore the effect of stimulating the part of the brain at the back of the head, with low electric currents to speed up your learning a walking task. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.
This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether you will participate in this study. Before you decide, you may want to talk about the study with other people, such as family, whanau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is eight pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

This project aims to find out if passing weak electric currents to the cerebellum, a part of the brain at the back of the head, can speed up the learning of treadmill walking task in people who have had a stroke more than 6 months ago. The stimulator we will be using (Transcranial Direct Current Stimulation, tDCS), is a painless and safe brain stimulation that delivers a constant, low intensity current through two electrodes placed over the head. This device is approved for research purposes in conditions like Post-stroke aphasia, Parkinson's disease, Cerebral Palsy, Dementia etc and is currently being used in the treatment of long-standing pain and depression. There is good evidence that tDCS can increase the rate and amount of learning in healthy individuals, however, we do not fully understand its effects in people with stroke. The information gathered through this study will help better understand how this technique might be used to promote recovery after stroke.

This study will also contribute to the qualification of Doctor of Philosophy (PhD) for Nitika Kumari, at AUT University. When the study is completed, the findings will be used in a thesis, conference presentations and an academic journal publication.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You are being invited to participate in this study as you are aged over 18 years, have sustained a single, unilateral stroke more than six months ago and you are able to walk, but still have difficulty with walking since stroke.
You may be eligible for this study if you meet the following entry criteria:

- Do not have any evidence and/or physical examination evidence of cerebellar lesion or cerebellar stroke
- Are able to walk for 5 minutes continuously.
- Do not have any medical conditions such as epilepsy, unexplained recurring headaches and cardiac arrhythmias which may influence the results
- Do not have history of epilepsy, head injury or concussion in the last six months
- Do not have a skull fracture or other known skull defects
- Do not have any metal implants or pacemakers

If you are eligible to participate, and would like to participate in the study, you will be given a consent form to read and sign. We will then inform your GP about your enrolment in the study.

What will happen in this research?
The study involves four sessions held at the AUT Millennium Institute. You will complete three rehabilitation sessions on a treadmill using tDCS and one post-intervention assessment after a gap of one week. At every session we will measure your walking symmetry and speed using 3-dimensional gait analysis. Each session will take approximately two hours (90 minutes-assessment and setting up, 27 minutes-rehabilitation). A total of approximately eight hours will be required from each participant.
The tDCS Intervention:
Following set up of the tDCS device and the placement of reflective markers on your legs, you will be asked to walk on a treadmill (Figure 1) with both the belts moving at same slow speed for two minutes. The tDCS unit will be turned on and the speed of the treadmill belts will be split; one belt moves faster than the other for 15 minutes. The tDCS will then be turned off and the treadmill belt speeds will be returned to slow speed for another 10 minutes.

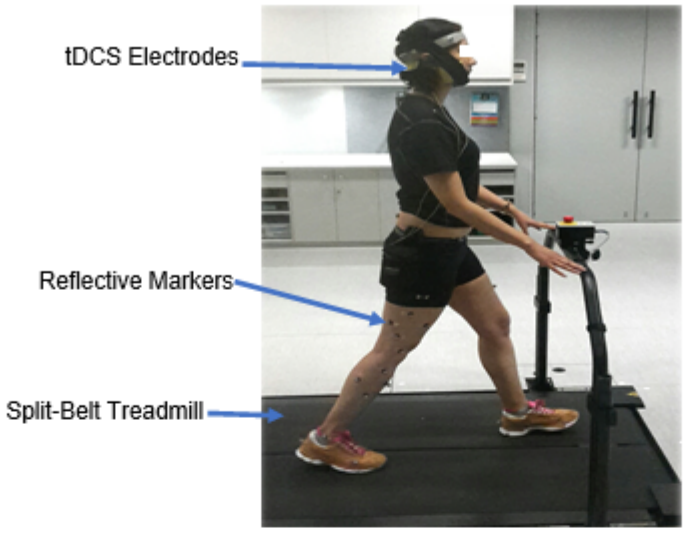


Figure 1: Intervention Setup

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

It is anticipated that some participants may experience improvement in their walking following the treadmill walking procedure over four sessions, although this cannot be guaranteed.

The findings from this study will be used to better understand how this technique might be used to promote recovery after stroke.

There are some risks associated with the study, and these are outlined below:

Fatigue and Tiredness:

This study asks you for a commitment of time and energy. You may feel fatigued due to this commitment. We will monitor how you are feeling throughout each session and you are able to stop the session at any stage.

Transcranial Direct Current Stimulation:

There is a small chance of experiencing a tingling/prickling sensation over the area that is in contact with the electrodes. If present, this sensation can only be felt during the first few seconds of stimulation.

Some people may also perceive a metallic taste during stimulation which lasts for a short duration.

How will these discomforts and risks be alleviated?

We will use electrical stimulation parameters that are well within safety guidelines for stimulation of the brain. Saline-soaked sponge will be used on the electrodes that will deliver the electric currents at a very low intensity at the start so that you get used to any tingling sensations. To further minimise any risk of skin irritation, scalp/skin area will be cleaned with alcohol before the electrodes are applied on it.

WHO PAYS FOR THE STUDY?

There are no monetary costs associated with participating in this research. Either petrol or taxi vouchers will be offered to assist with transport costs to and from AUT Millennium campus.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study will not affect your cover.

WHAT ARE MY RIGHTS?

-Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data may not be possible.

- To consider your participation in the study, you are provided with an opportunity to take time and discuss it with your family/whanau.

-You have the right to privacy and confidentiality. Your privacy will be maintained throughout the research process, as you will always be identified by a code number. Researchers will only have access to coded data, which will prevent them from knowing your identity. The collected data and the consent forms will be stored in separate locked cabinets in Researchers office. When results are reported, no names or any material that could identify you will be published or presented. After ten years, this data will be destroyed.

-You have the right to access information collected about you during the course of the study.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

Following the study, the transcranial direct current stimulation will not be available to you as an intervention. Further research and development will be required before it can be used for rehabilitation. If you are interested in receiving information about other rehabilitation services in your area the researcher can advise you.

-You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data may not be possible.

-The collected data and the consent forms will be stored in separate locked cabinets for ten years. This will ensure that no association can be made between the results and the consent forms. Only members of the research team directly involved in data collection and analysis will have access to raw data. After ten years, all original data collection sheets and questionnaires will be shredded. The files in the external hard drive will be deleted.

-You are given an opportunity on the consent form to indicate if you would like to receive a feedback on your results. If you answer "yes" to this, a copy of your results and a short summary of the overall findings will be sent to you on completion of the study. This will be sent to the contact details that you provide on the consent form.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Doctoral Student

Nitika Kumari
Health and Rehabilitation Research Institute
AUT University
Private Bag 92006
Auckland 1142
0273707917
nitika.kumari@aut.ac.nz

Project Supervisor

Dr Nada Signal
Health and Rehabilitation Research Institute
AUT University
Private Bag 92006
Auckland 1142
Ph. 09 921 9999
nada.signal@aut.ac.nz

For Maori Health support please contact :
He Kamaka Walora
Waitemata District Health Board
09 486 8324 ext 3553
Auckland District Health Board
09 307 4949 ext 29400

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Consent Form

Please tick to indicate you consent to the following

I have read or have had read to me in my first language, and I understand the Participant Information Sheet.		
I have been given sufficient time to consider whether or not to participate in this study.		
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.		
I consent to the research staff collecting and processing my information, including information about my health.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I give permission for the Researcher to inform my GP about my participation in this study. Name of GP:_____ Medical Centre:_____		
I understand the compensation provisions in case of injury during the study.		
I know who to contact if I have any questions about the study in general.		
I understand my responsibilities as a study participant.		
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Participant's Contact Details
Phone:
Email:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

Appendix O. Study C: Advertisement for recruitment of people with stroke

Research Opportunity for People with Stroke

AUT

Are you interested in participating in stroke research?

Do you have one-sided weakness that affects your walking?

This Doctoral Student Research involves investigating whether stimulating the brain could boost re-learning of walking in people with stroke.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique of passing extremely low-intensity currents to the brain using two small electrodes. Single session of tDCS applied to the cerebellum has found to enhance learning of various simple tasks. The purpose of this study is find out whether application of tDCS to the cerebellum can speed up the learning of a more complex and functional task of walking on a treadmill that forces one leg to move faster than the other.

If you are over 18 years old, have had a stroke more than 6 months ago, and have one-sided weakness that affects your walking, we would like to invite you to participate.

What happens during the study?

The study involves attending four sessions at AUT Millennium Campus, Rosedale, Auckland. Participants will be assessed using a number of measures and will receive brain stimulation protocol while walking on a treadmill.

A final decision about your participation can be made after going through the information sheet.

If you would like more information, please contact Nitika Kumari
Email: nitika.kumari@aut.ac.nz

Appendix P. Study C: tDCS safety checklist

Participant Safety Checklist for using Transcranial Direct Current Stimulation

Participant ID:_____

D.O.B.:_____ Date:_____

On visual inspection: Side taking shorter step length (Circle)	Non-Paretic Right Left	Paretic Right Left

	Yes/ No
Do you have metal implants in any part of your body including your head (except tooth fillings)/ Implanted brain devices?	
Have you ever had a skull fracture? / Do you have any known skull defects?	
Have you suffered a head injury or concussion within the last 6 months?	
Have you ever been diagnosed with epilepsy or suffered from epileptic seizures?	
Do you wear a pacemaker?	
Do you suffer from recurring headaches?	
Are you currently taking any medications?	

Please list the names of medicines:

Drug Name	Dosage/time course of medication usage	Drug Type

Checklist completed by: _____Signature: _____Date:

Appendix Q. Study C: Telephone screening checklist

Participant Identifier	

Questions to ask over the phone for finalising the participation

Eligibility criteria	Question	Answer
Time since stroke: chronic stroke	Can I please know the date when you had your stroke	
	Do you know if it was a hemorrhagic or an Ischemic stroke?	
	Do you know where in the brain you had the stroke? the location of the lesion in the brain? (frontal lobe or middle cerebral artery or internal capsule)-unlikely to know	
	Which side of the body is affected? Right or left	
To check if it is a unilateral stroke	Do you have any weakness on the other side of the body as well?	
To check recurrence: Single stroke	Did you have any more episodes of stroke or any episodes of transient ischemic attack (TIA) after the initial one?	
Side taking the shorter step. Non-affected side taking shorter step	When you are walking which side do you think takes the shorter step?	
	Will it be possible for someone to observe your walking now and check which side is taking the shorter step? If not Will it be possible for you to ask someone to record your walking on the phone at a later time point and email it to me? Please make sure the recording is made from the side.	

To check if they will be able to tolerate treadmill walking	Are you able to walk for 3 to 5 minutes continuously? Do you use any walking aid? AFO, walking stick, walking frame	
	Are you engaged in any rehabilitation therapy with a health professional targeting your walking? (write down the name if any) Identify any time point when they will not be engaged in it	
To ensure they are not walking on the treadmill and losing the aftereffects	Do you engage in treadmill walking at the gym?	
Now we will go through some safety checklist for using tDCS stimulation	Go through the tDCS safety checklist	
Checking other medical conditions	-Vascular risk factors (coronary artery disease, Atrial Fibrillation, Diabetes, Hypertension, clinical obesity, smoking and alcohol use, hyperlipidemia)	
	-Any orthopedic condition/or severe pain affecting the back or legs that could restrict your walking?	
Any other comments		

Appendix R. Study C: Adverse events form

Adverse Event Reporting Form

An adverse event is defined as an event that causes the participant to seek attention from a health professional, or limits their activities of daily living for at least two days.

If such an event should occur, please report this by emailing the form below to nada.signal@aut.ac.nz as soon as possible.

Participants Full Name:	
Gender:	Male/Female
DOB:	
GP Name and contact details:	
Name(s) of research staff present:	
Date of adverse event:	
Description of adverse event:	
Was medical care/hospitalisation required?	Yes/No Details:
Outcome:	Fatal/Recovered/Ongoing Details:
Was the event related to the research session?	Related/Unrelated Details:
Name/designation of person reporting:	
Date form completed:	