# REWIRING THE BRAIN AFTER STROKE

A novel neuromodulatory intervention to improve neuromuscular control

Sharon A. Olsen

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# ABSTRACT

A stroke can have devastating consequences for an individual's gait and mobility, and difficulties often continue well after discharge from rehabilitation. Increased knowledge about the role of neural plasticity in stroke recovery has led to the development of neuromodulatory interventions. Neuromodulatory interventions can increase neural activity in the ipsilesional primary motor cortex and have potential to be used as rehabilitation adjuncts to facilitate recovery following stroke. This thesis explores a novel neuromodulatory intervention, thought to have neurophysiological underpinnings similar to that of paired associative stimulation (PAS), and is here called novel paired associative stimulation (novel-PAS).

Novel-PAS pairs the movement-related cortical potential (MRCP), recorded during imagined or voluntary movement, with peripheral electrical stimulation over a nerve supplying the target muscle. Novel-PAS can increase corticomotor excitability in the target muscle in healthy people. In people with stroke, a single study has shown increased corticomotor excitability for up to 30 minutes post-intervention, and improvements in lower limb impairment and function after three sessions targeting the ankle dorsiflexor muscles. Previous research has not considered how novel-PAS could best be implemented in rehabilitation, or assessed its feasibility when applied over several weeks. The aim of this thesis was to address gaps in the novel-PAS knowledge base. Specifically, this research investigates: the efficacy of novel-PAS beyond 30-minutes post-intervention, the immediate effects of novel-PAS in people with stroke, and the feasibility of delivering a four-week intervention.

Study A, a within-subject, repeated-measures experiment in healthy people, explored the immediate effects of novel-PAS, and demonstrated increased corticomotor excitability to the tibialis anterior muscle for 60 minutes post-intervention. The findings provide new understanding about the duration of neuromodulatory effects following novel-PAS, knowledge that can guide decisions about the timing of the intervention within a standard rehabilitation session.

Study B, a pilot randomised controlled trial in people with chronic stroke, evaluated the feasibility of a four-week novel-PAS intervention and research protocol. The protocol was not feasible for further research; the main barriers to its feasibility were the time requirements of the study and the use of transcranial magnetic stimulation (TMS) as an outcome measure.

Recommendations are made to guide the development of future research protocols. New insights into the technical challenges of delivering novel-PAS, and potential limitations to its acceptability in the stroke population, are offered. Important recommendations are made for optimising the novel-PAS intervention to maximise its potential for implementation into rehabilitation practice.

Study C, a repeated-measures, cross-over experiment in people with stroke, arose out of the need to investigate the within-session effects of novel-PAS, without using TMS-induced measures of corticomotor excitability. This study demonstrated that the novel-PAS intervention can significantly increase voluntary activation of the tibialis anterior muscle in people with chronic stroke. This provides important confirmation of the effects of novel-PAS on neural plasticity and supports its potential to be used as a rehabilitation adjunct for people with stroke. Future research should focus on combining novel-PAS with standard rehabilitation techniques, assessing its cumulative effects on stroke recovery, and miniaturising the equipment.

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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.

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# ABBREVIATIONS

| | |
|---|---|
| 3D | 3-dimensional |
| 6-m | six-metre |
| AFO | Ankle foot orthosis |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| AMT | Active motor threshold |
| ANOVA | Analysis of variance |
| AUC | Area under the curve |
| AUTEC | Auckland University of Technology Ethics Committee |
| $Ca2^{+}$ | Intracellular calcium ions |
| BCI | Brain computer interface |
| dCPN | Deep branch of the common peroneal nerve |
| EEG | Electroencephalography |
| EMG | Electromyography |
| HDEC | Health and disability ethics committees |
| ICC | Intraclass correlation coefficient |
| ICF | International classification of functioning, disability and health |
| LTD | Long-term depression |
| LTP | Long-term potentiation |
| M1 | Primary motor cortex |
| Mean PN | Mean of PN phase (-100ms to +100ms of PN of MRCP) |
| MEP | Motor-evoked potential |
| MF | Median frequency |
| MP1 | Motor preparation phase 1 (of the MRCP) |
| MP2 | Motor preparation phase 2 (of the MRCP) |
| MRCP | Movement-related cortical potential |
| m | Metres |

| | |
|---|---|
| m/s | Metres per second |
| MVC | Maximum voluntary contraction |
| MVIC | Maximum voluntary isometric contraction |
| ms | Milliseconds |
| NA | Not applicable |
| N | Newtons |
| NIBS | Non-invasive brain stimulation |
| NMDA | N-methyl-D-aspartate |
| Novel-PAS | Novel paired associative stimulation |
| PAS | Paired associative stimulation |
| PN | Peak negativity (of the MRCP) |
| RCT | Randomised controlled trial |
| ROFD | Rate of force development |
| rTMS | Repetitive transcranial magnetic stimulation |
| RMS | Root mean square |
| RMT | Resting motor threshold |
| S1 | Primary somatosensory cortex |
| s | Second |
| SD | Standard deviation |
| SEM | Standard error of the measurement |
| SRD | Smallest real difference |
| STDP | Spike-timing dependent plasticity |
| TA | Tibialis anterior muscle |
| tDCS | Transcranial direct current stimulation |
| TMS | Transcranial magnetic stimulation |
| UK | United Kingdom |
| VR | Variation ratio |

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# INTRODUCTION

Stroke is a neurological deficit which arises from a disruption to the circulation of the brain and is the most common cause of severe adult disability[1,2]. It can have devastating consequences for quality of life, due to a loss of autonomy and independence, inability to participate in meaningful activities, and social isolation[3]. At 12-months post-stroke, approximately one third of people still have moderate to severe disability[4] and require assistance with activities of daily living[5,6]. In addition, stroke can lead to unemployment, family disruptions, and financial stress[7]. With over 33 million stroke survivors worldwide, and this number steadily increasing, stroke presents a significant health, economic, and societal burden[8,9]. In New Zealand alone, the direct and indirect costs of stroke are estimated at 3-billion dollars annually[10].

Stroke-related disability may arise from impairments related to various body functions, such as movement, sensation, speech, vision, swallowing, or memory[1,11]. Impairments of the lower limb are particularly prominent with 41% of people admitted to hospital with stroke being non-ambulatory and 52% requiring assistance or supervision with gait[12]. Although significant recovery can occur during rehabilitation, at discharge from inpatient care, the majority of people continue to have deficits in gait and mobility[12]. Approximately 12 months after stroke, of those individuals who can walk, 43% are limited to household ambulation, and 45% have limited mobility in the community[13]. This ongoing gait dysfunction can arise from a number of lower limb impairments, of which loss of ankle dorsiflexion strength is known to contribute significantly[14-16].

Current rehabilitation services are not adequately resourced to provide timely access[17,18] to the amount of therapy recommended by stroke guidelines[19]. This challenge has led to the pursuit of new rehabilitation approaches that can promote recovery following stroke without further burdening the already-stretched health system. One approach, which has arisen out of the increased knowledge about neural plasticity as an important mechanism underlying stroke recovery[20], is the use of neuromodulatory interventions. Neuromodulatory interventions are technologies which can alter neural activity via the delivery of a stimulus to a targeted area of the nervous system[21]. In the case of people with stroke, neuromodulatory interventions commonly aim to increase neural activity in the ipsilesional primary motor cortex (M1), which is known to be an active area during motor recovery[22,23].

Neuromodulatory interventions have potential to be used as adjuncts to standard rehabilitation to facilitate recovery from stroke[24].

Paired associative stimulation (PAS) is one neuromodulatory intervention which induces neural plasticity by pairing two stimuli; single pulses of transcranial magnetic stimulation (TMS) over the M1, and single pulses of electrical stimulation over a peripheral nerve[25]. The effectiveness of PAS has been measured with TMS, which enables evaluation of the excitability of neurons in the corticospinal tract, also known as corticomotor excitability. The order and timing of the paired stimuli in PAS determine whether there is an increase or decrease in corticomotor excitability[25-28]. PAS has been shown to alter neural plasticity in people with stroke[29-34] but there is very limited information about its effects on stroke recovery[35]. In addition, there are concerns that PAS might not translate well into practice because it uses TMS, which is contraindicated, cautioned or not tolerated in certain individuals[36], as well as being costly and not readily available in healthcare facilities. These concerns have not been investigated in published literature to date. This thesis explores an innovative PAS intervention which may offer advantages over traditionally-delivered PAS in terms of its cost, safety, and fit with rehabilitation practice. The research in this thesis will be presented in six chapters as follows:

**'Chapter 1: Background'** will present literature describing the effects of stroke, stroke recovery, neural plasticity, limitations of rehabilitation, neuromodulatory interventions, and PAS.

**'Chapter 2: Novel paired associative stimulation'** presents an alternative paired neuromodulatory intervention to PAS, which has been named novel paired associative stimulation (novel-PAS) in this thesis. Novel-PAS can specifically target neural activation of the tibialis anterior, the primary ankle dorsiflexor muscle[37], and therefore has potential to improve gait following stroke. This chapter will explain the delivery method for novel-PAS, review its evidence-base, identify current gaps in the literature, and discuss its potential advantages over other paired neuromodulatory interventions. Finally, this chapter will pose the following research questions which give rise to the three studies in this thesis.

1. *What are the within-session effects of novel-PAS beyond 30 minutes post-intervention?*
2. *What are the within-session effects of novel-PAS in people with stroke?*
3. *Is it feasible to carry out a research protocol involving multiple sessions of novel-PAS to people with stroke?*
4. *What are the cumulative effects of novel-PAS in people with stroke?*

'**Chapter 3: Study A**' addresses the first research question. An understanding of the neuromodulatory effects up to 60-minutes post-intervention would enable researchers and clinicians to understand how novel-PAS might be integrated into a standard rehabilitation session. This chapter will present a single-session, within-subject, repeated-measures study, that was undertaken to assess the duration of the effect of novel-PAS on corticomotor excitability at 0, 30, 45 and 60 minutes post-intervention in healthy people.

'**Chapter 4: Study B**' addresses the second and third research questions. This chapter will present a pilot randomised controlled trial (RCT) that was undertaken to investigate the feasibility of the RCT study design, which compared the effects of a four-week novel-PAS intervention with an attention- and dose-matched sham intervention in people with chronic stroke. The study explores the feasibility of both the research protocol and the intervention and was powered to test the within-session effects of novel-PAS on corticomotor excitability.

'**Chapter 5. Study C**'. The issue of feasibility investigated in Study B proved problematic; therefore, rather than pursuing research question four, the thesis turns back to further explore the within-session effects of novel-PAS. Chapter 5 addresses two supplementary research questions.

- *What alternative outcome measures, other than TMS, could potentially be used to feasibly assess the within-session effects of novel-PAS in people with stroke?*
- *Does novel-PAS produce an immediate effect on measures of muscle strength and neuromuscular fatigue in people with stroke?*

Chapter 5 explores alternative outcome measures in the neuromodulation literature, and then presents a within-subject, repeated-measures, cross-over study, that was undertaken to determine the within-session effects of novel-PAS on ankle dorsiflexor muscle strength and neuromuscular fatigue compared with an attention- and dose-matched sham intervention in people with chronic stroke.

'**Chapter 6. Integrated discussion**' will draw the thesis findings together and make recommendations for future research.

Throughout this thesis, the effects of stroke and measures of recovery will be considered at various levels of the International Classification of Functioning, Disability and Health (ICF) framework[38]. These include:

- *Activity limitations.* This refers to difficulties performing whole-body activities, such as gait, or climbing stairs.

- *Motor impairments* in movement-related body structures and functions. This refers to changes, such as decreased muscle strength, in one or more body parts.
- *Neurophysiological deficiencies*. This refers to the underlying dysfunction of the neuromuscular system, such as decreased motor neuron activation, that causes motor impairments. These underlying neurophysiological changes are not specifically covered by the ICF, but are acknowledged[38].

# Chapter 1.
# Background

## 1.1 PROLOGUE

This chapter highlights the burden of stroke and its effects on motor control. It introduces neural plasticity as an important mechanism underlying motor skill learning in healthy people, with a focus on synaptic plasticity. It then describes the neural plasticity that accompanies stroke recovery and outlines the importance of activity in promoting neural plasticity. The limitations of current stroke rehabilitation are discussed, and neuromodulatory interventions are introduced as potential adjuncts to standard rehabilitation. Finally, neuromodulatory interventions that make use of associative plasticity are described, with a focus on PAS. Associative plasticity provides the neurophysiological basis for the novel PAS intervention which will be introduced in Chapter 2.

## 1.2 EFFECTS OF STROKE

While stroke can cause a range of neurological deficits, this section focuses specifically on the activity limitations, motor impairments, and neurophysiological changes that accompany stroke which are relevant to this thesis.

### 1.2.1 ACTIVITY LIMITATIONS

Stroke can cause significant limitations in daily activities[5,6] such as gait, toileting, dressing, meal preparation, housework, driving, and the use of transportation[39,40]. Of these activity limitations, recovery of gait is a major focus of rehabilitation[41] and remains an important goal for people many years after stroke[42]. In a sample of community-dwelling people with stroke, many continued to require walking aids and were unable to achieve the walking speeds and distances of healthy people[43]. Focus groups with people with stroke, their caregivers and health professionals, have shown that that recovery of gait is a top research priority[44].

### 1.2.2 MOTOR IMPAIRMENTS

Activity limitations following stroke can result from a number of underlying motor impairments. This section will review these motor impairments with a focus on impairments that, a) involve the M1 area or its output via the corticospinal tract, and b) might be improved by an intervention aimed at increasing the neural output from the M1. This focus relates to the target area and underlying mechanism of the novel-PAS intervention, which will be explained in Chapter 2. While spasticity and restricted passive movement may both contribute to motor impairment after stroke, relevant literature[45,46] indicated that these were not appropriate outcomes for measuring the effect of the intervention in this research programme, and therefore these will not be discussed below.

A stroke involving the M1 or corticospinal tract will typically cause a hemiparesis on the contralesional side of the body, due to decussation of the majority of corticospinal fibres[47]. The following components of neuromuscular control are commonly impaired:

- Muscle strength

  Muscle strength is the amount of force exerted in a single maximal effort[48] and is commonly impaired in the hemiparetic limb following stroke[49-52]. Deficits in muscle strength that accompany stroke are significantly correlated with reduced activity levels[53].

- Muscle power

  Muscle power is the ability to exert a movement over a short period of time[48]. Following stroke, muscle power is impaired in the hemiparetic limb, as evidenced by a decrease in the rate of force development (ROFD)[54,55], an increase in the time to reach 90% of peak force[56], and a decrease in peak power[57-59]. Deficits in lower limb muscle power are significantly correlated with reduced activity levels after stroke[57,58].

- Muscle endurance

  Muscle endurance is defined as the ability to repeat or maintain a contraction[48]. During sustained exercise, the reduction in force that occurs as a person loses muscle endurance is called *total neuromuscular fatigue*[60]. Exercise induces total neuromuscular fatigue in both the hemiparetic and non-paretic limbs of people with stroke and in the limbs of healthy people[61]. However, in the hemiparetic limb, the fatigue is related more to changes at a cortical and/or spinal level, whereas in non-paretic or healthy limbs, peripheral changes play a greater role[61]. The central origin of post-stroke

neuromuscular fatigue may contribute to the high levels of subjective fatigue experienced by people with stroke[62].

- Movement control

  Movement control allows a person to effectively carry out a motor task with appropriate accuracy and speed, and is influenced by a number of variables such as movement direction, distance, the precision required, the level of force required, simultaneous and successive movements, visual and kinaesthetic feedback, and the time available[63]. Following stroke, disruptions in movement control such as increased force variability and reduced accuracy have been observed[64-66].

- Movement co-ordination

  Movement co-ordination is the control of two or more muscles, joints or limbs, in order to perform a task[67]. It involves the selection of a particular set of movements within a wide range of possibilities, and is heavily reliant on sensory feedback[67]. Co-ordination after stroke has been studied using 3-dimensional (3D) motion analysis and accelerometers, and shows reduced inter-limb co-ordination during gait[68,69] and reduced inter-joint co-ordination during reaching[70].

- Gait pattern

  Following stroke, gait can be impaired as a consequence of any or all of the impairments described above. People with stroke can have altered kinematic, kinetic and spatiotemporal gait parameters[71,72] as well as altered *gait variability*, which refers to stride-to-stride fluctuations in gait characteristics[73].

- Balance and postural control

  Balance and postural control incorporates the ability to maintain verticality, maintain static and dynamic postural stability, make anticipatory postural adjustments, respond to perturbations, and reweigh sensory information as needed[74]. Following stroke, these postural control mechanisms can be impaired[75], and balance disabilities are common (i.e. the inability to maintain balance while sitting, standing, reaching, taking a step)[76].

Many of these impairments can contribute to limitations in gait following stroke, although studies have shown that the strength of the ankle dorsiflexor muscles is particularly influential. For example, hemiparetic ankle dorsiflexor strength is an independent predictor of gait endurance, accounting for 49% of the variance in distance walked[16]. In addition, hemiparetic ankle dorsiflexion strength is an independent predictor of gait speed[14,15], accounting for 31% of the variance in speed, more than that of 11 other lower limb muscle

groups[15]. Hemiparetic ankle dorsiflexor strength also predicts functional gait mobility[77] and symmetry of single-leg-support time between legs[14]. In addition to this quantitative evidence, people with stroke perceive that their foot and ankle impairments significantly limit community ambulation and exacerbate fears of falling[78]. These studies reinforce the importance of regaining ankle dorsiflexion strength in order to facilitate the recovery of gait following stroke.

### 1.2.3 NEUROPHYSIOLOGICAL MECHANISMS OF ALTERED MOTOR CONTROL

This section will consider the neurophysiological mechanisms which underlie motor impairments following stroke, with a focus on the role of the M1.

In the healthy brain, voluntary motor control relies on complex circuitry between perceptual, motor, and cognitive systems[79]. These systems facilitate the various components of movement control which include the receipt of sensory information, the perception and interpretation of sensory information, the conceptualisation of a movement response, movement planning, the activation of motor outputs, and the monitoring and regulation of movement responses[79]. These processes involve the activation of many cortical and subcortical areas, including the primary sensory cortices, association cortices, frontoparietal attentional networks, M1, secondary motor areas (supplementary, premotor, and cingulate), and subcortical motor areas (basal ganglia, cerebellum, and vestibular system)[79-82]. A stroke can damage any of these areas, their axonal connections, or the descending pathways to the spinal cord[83]. Thus, depending on the lesion size and location, a stroke has potential to disrupt the processing of sensory information about the intended movement, the planning of a movement response, the execution of that response, and/or the processing of sensory feedback, all of which are essential to producing a well-co-ordinated movement[84].

Whilst there are multiple components of motor control, from sensory processing to motor execution, this thesis focuses on a novel intervention which is believed to facilitate just one component of movement control, the activation of motor output from the M1 to the target muscle. Thus, an understanding of some of the key connections to the M1 will assist the reader in understanding the mechanism, target area, and measurement of the novel-PAS intervention.

The M1 has a principal role in motor control[85,86]. It receives direct projections from the premotor, supplementary, and cingulate areas; these areas are involved in the planning, preparation, and selection of movement sequences[87,88]. There are *strong reciprocal* projections between the M1 and the dorsal and ventral premotor areas, which are thought to support the generation and control of movements[87,88]. In addition to these motor connections, the M1 has reciprocal connections with *sensory* processing areas in the parietal cortex, which support the integration of sensory and motor signals[88]. These connections include somatotopically-organised projections from the S1 to the M1[85,89]; these pathways are thought to be utilised in the novel-PAS intervention and their involvement will be described in Chapter 2.

The M1 has direct and indirect outputs through the corticospinal tract to the spinal motor neurons[87,90-92], which control the activation of skeletal muscles[90]. While secondary motor areas also contribute to the corticospinal tract[80,81,93], the M1 makes the largest contribution, comprising 50% of corticospinal tract fibres[87]. Thus, the impairments resulting from a focal lesion in the mouse M1, resemble those of a focal corticospinal tract lesion; both result in severely reduced limb movement with poor accuracy and control[94]. In addition to its main contribution to the corticospinal tract, the M1 has outputs to two other descending pathways, the rubrospinal and reticulospinal tracts, which are involved in postural and limb control[80,81].

The literature above demonstrates that the M1 plays a critical role in movement control, particularly through the corticospinal tract. Both the M1 and corticospinal tract are commonly damaged following stroke, due to the high incidence of anterior circulation infarcts[95,96], resulting in a loss of normal descending input to the spinal cord motor neurons, and impaired activation of motor units. Altered motor unit activation after stroke is evident in electromyography (EMG) recordings from hemiparetic muscles, where there is disruption to the recruitment[97,98] and modulation of motor unit firing[99-101], which impairs the ability to increase and grade muscle contractions. These changes can be influenced not only by the primary damage caused by stroke, but also by the secondary effects of stroke such as degeneration of the corticospinal tract[102], loss of functioning motor units, change in muscle fibre-type[40] and muscle atrophy[103].

## 1.3 MEASURING RECOVERY AFTER STROKE

Recovery after stroke can be assessed according to changes at the *impairment* level, such as improved ankle dorsiflexion movement, or changes at the *activity* level, such as an improved ability to climb stairs[39,104]. The re-acquisition of motor skills can occur through recovery of

the ability to perform the movement in the way it was performed prior to stroke, or through compensation, where new movements or movement sequences are acquired to perform the task using a different technique[105,106]. When a motor skill is practiced repeatedly, and there is a relatively permanent improvement in performance, this is referred to as *motor learning*[107].

## 1.4 NEURAL PLASTICITY

Neural plasticity refers to the brain's ability to alter its structure and function in response to learning and behaviour, and is an important mechanism underlying the recovery of motor skills after stroke[20]. Evidence of neural plasticity can be observed at a number of levels within the nervous system: molecular, synaptic, cellular, neural networks, and behavioural[108,109]. Changes at a network level refer to alterations in pathways of interconnected neurons that have a shared output[80]. Changes in behaviour are the manifestation of altered activity in the underlying neural networks[110].

For the purposes of this thesis, neural plasticity will refer to the underlying neural mechanisms that support the recovery of premorbid movement patterns by way of restoring damaged neural pathways or promoting adaptive rewiring of neural pathways[111]. It is acknowledged that neural plasticity can also promote compensatory movement patterns, where there is activation of brain areas during movement which are not seen in healthy individuals[111]; however this type of plasticity is not the focus of the intervention being investigated in this thesis.

### 1.4.1 MEASURING CORTICOMOTOR EXCITABILITY WITH TRANSCRANIAL MAGNETIC STIMULATION

Prior to discussing categories of neural plasticity, the use of TMS as a method for measuring neural plasticity will be introduced. TMS measurements feature commonly in neural plasticity research and are used in the three studies in this thesis.

TMS is a widely accepted tool for assessing the excitability of the corticospinal tract[112-115]. *Excitability* refers to a property of neurons that enables them to transmit an electrical signal, either a synaptic potential or an action potential[80]. When TMS is applied over the scalp, an electrical current flows through a copper coil producing a perpendicular magnetic field[112]. This activates the axons of cortical interneurons, which then synapse with corticospinal tract neurons in the M1[112,116]. In some cases, the corticospinal tract axons can be activated directly, but only with very high TMS intensities[116]. The activation of corticospinal tract neurons

results in the propagation of one or more descending volleys to the spinal cord; this activates spinal motor neurons which produce a motor-evoked potential (MEP) in the target skeletal muscle[112,116]. The MEP is recorded with EMG and an example is illustrated in Figure 1-1 .

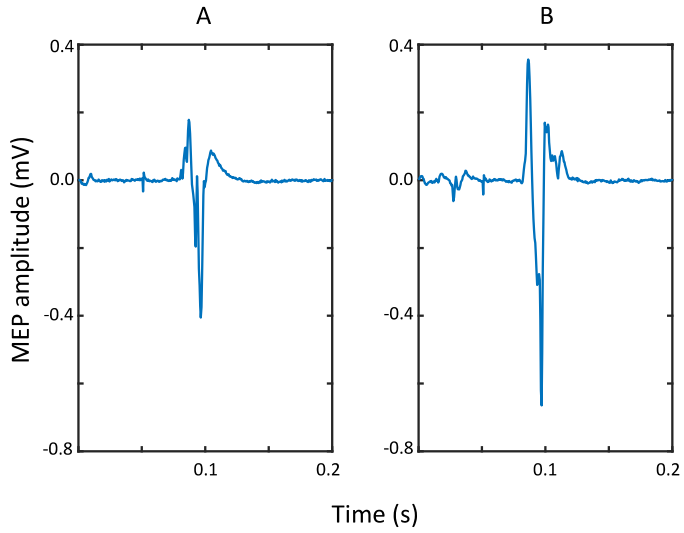



Figure 1-1 TMS-induced MEPs showing increased amplitude from A to B

At higher TMS intensities, more descending volleys are produced with larger amplitudes, resulting in a larger MEP in the target muscle[116]. Performing a voluntary contraction during the application of TMS results in more descending volleys with larger amplitudes, and also increases the excitability of spinal motor neurons, making it possible to produce a MEP with lower TMS intensities[116]. Because an intact corticospinal tract is required to produce a MEP, a MEP cannot be produced in some people with stroke[117].

TMS measurements involve the application of single pulses at a set TMS intensity, while the target muscle is at rest or engaged in a muscle contraction[112]. A number of MEPs need to be recorded to account for the significant variability in MEP size between trials, due to intrinsic fluctuations in cortical and spinal excitability[112]. The motor threshold is the intensity of TMS stimulation required to produce a MEP of specified amplitude in the target muscle, and can be used to gauge changes in the excitability of the corticospinal tract[112]. The motor threshold can be assessed with the muscle at rest or engaged in a voluntary contraction; these are known as resting motor threshold (RMT) and active motor threshold (AMT) respectively. If MEPs can be produced at a lower motor threshold, increased excitability at any point along the corticospinal tract is indicated[112]. This might be due to increased synaptic efficacy between cortical neurons (a mechanism that will be discussed further in 1.4.2), increased intrinsic excitability of cortical neurons[118], or increased excitability at the spinal cord or peripheral

nerve level[112]. These changes in excitability at any point along the corticospinal pathway will be collectively referred to as *corticomotor excitability*.

Other measures of corticomotor excitability involve calculating the size of the MEP under various conditions. This is commonly conducted by applying TMS at a single intensity, usually between 115-125% of motor threshold, and measuring either the peak-to-peak amplitude of the raw MEP signal, or the area under the rectified MEP signal[112]. Figure 1-1 illustrates the increase in MEP amplitude that can occur in response to an intervention. Both MEP amplitude and area will be used as measurement methods in the studies in this thesis. An alternative to measuring MEPs at a single intensity is to use a range of TMS intensities, usually 90-130% of motor threshold, and construct a stimulus-response curve[112]. Changes in corticomotor excitability can cause a sideways shift in the curve or a change in its slope[112]. Yet another measurement method involves applying paired-pulse TMS, where two pulses are delivered in quick succession, at specific time intervals, that elicit either intracortical inhibition or intracortical facilitation[112,116]. The resultant MEP can be used to gauge whether intracortical circuits have been influenced by an intervention[112,116]. A variety of methods for measuring corticomotor and intracortical excitability will feature in the literature reviewed in the remainder of Chapter 1 and in Chapter 2.

### 1.4.2 SYNAPTIC PLASTICITY DURING MOTOR ACTIVITY IN THE HEALTHY BRAIN

Neural plasticity is not only involved in recovery from brain injury but is also considered to be the mechanism by which learning occurs in the healthy human brain[20]. During motor behaviours and motor skill learning, M1 neurons demonstrate the ability to reorganize their connections within the dense horizontal circuitry inside the cortical layers[86]. One important mechanism of such changes within the M1 is a type of synaptic plasticity known as long-term potentiation (LTP)[86,119]. Knowledge about LTP is important to understanding the neural plasticity that occurs in response to the interventions which will be discussed at the end of this chapter (refer to 1.6) and in Chapter 2 (refer to 2.3) It is acknowledged that behaviour and skill learning can induce other changes, such as altered neural structure[82,120,121]; however these will not be discussed further in relation to the healthy brain.

LTP can be observed at a cellular level in animals and involves a persistent increase in synaptic efficacy[119,122]. Various temporal patterns of neuronal stimulation can induce either LTP, or its opposing state, long-term depression (LTD), a decrease in synaptic efficacy[119]. When pairs of stimuli are applied in a specific temporal arrangement to pre- and post-

synaptic neurons in the M1[123] or S1[124,125], LTP or LTD can be induced via a process called spike-timing dependent plasticity (STDP)[126]. The order and timing of paired stimuli determine the amplitude and direction of the change in synaptic efficacy[127]. For example, LTP occurs if a pre-synaptic neuron is stimulated immediately prior to stimulation of the post-synaptic neuron[124]. Whereas, if the order of stimuli is reversed, LTD is produced[124]. This type of plasticity is also termed *associative plasticity* because it relies on associated activity between pairs of stimuli.

The core mechanisms underlying LTP include the activation of N-methyl-D-aspartate (NMDA) receptors, the influx of intracellular calcium ions ($Ca^{2+}$), and the insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at the synapse[122]. These changes cause the post-synaptic cell to become more responsive to the excitatory neurotransmitter glutamate, making it more likely to fire[119,122]. The change in synaptic efficacy is rapid, persistent, topographically specific, and reversible[122]. Although the majority of the knowledge concerning LTP/LTD has come from animal studies, similar processes are presumed to occur during learning-induced plasticity in humans[82]. When human studies record increases in TMS-induced MEP amplitudes as a result of an intervention, LTP is considered to be one possible mechanism for this change[128]. Researchers make assumptions about whether an LTP-like process is occurring by assessing the role of NMDA receptors and $Ca^{2+}$ [25,26].

### 1.4.3 PLASTICITY IN STROKE RECOVERY

Neural plasticity is an important mechanism underlying the recovery of motor skills after stroke[20]. Neural changes are thought to involve the reactivation of existing neural pathways and the establishment of new neural pathways[129]. The following section will describe neural plasticity that has been observed in animals and humans after stroke that may support the formation of neural connections. Changes will be considered in three areas: the area immediately surrounding the lesion, the ipsilesional and contralesional hemispheres, and the connections *between* the hemispheres. Lastly, the role of activity in facilitating neural plasticity will be considered.

#### Cellular plasticity in the area surrounding the lesion

A number of cellular changes have been observed in animal models of stroke. At the core of the lesion there is an area of neuronal death, but immediately surrounding this, is an area called the *penumbra*, where neurons are only partially damaged[130]. If blood flow is restored, these neurons can be partially or fully repaired, a process that begins immediately after

stroke[130]. The non-ischaemic area adjacent to the penumbra is called the *peri-infarct area* and is an active site of neural plasticity[131]. Changes that are seen in the penumbral and peri-infarct areas in the first four weeks after stroke include neuronal hyperexcitability, axonal sprouting, dendritic remodelling, and generation of new synapses[129,131]. There is also an increase in excitatory synaptic activity in the peri-infarct area, which correlates with improved recovery[132]. When brain slices from this peri-infarct area are stimulated, there is increased LTP compared with the same location in control slices[133], indicating a readiness for synaptic plasticity. These structural and functional neuronal changes may contribute to the restoration of existing neural pathways and the promotion of new neural pathways[129].

## Reorganisation of neural networks in the ipsilesional and contralesional hemispheres

Cellular changes occur not only in the area immediately surrounding the lesion, but also in other brain areas. Seven days after an S1 stroke, brain slices from rats show reduced intracortical inhibition of cells in the contralesional hemisphere and unaffected areas of the ipsilesional cortex[134]. The resulting hyperexcitability may assist with reorganisation in these areas after stroke[134]. Human studies which probe the brain at a network level support this idea. For example, early after stroke TMS studies show a decrease in corticomotor excitability from the ipsilesional M1 (i.e. MEP amplitude is reduced and motor threshold is increased)[135,136]. However, within the ipsilesional hemisphere, paired-pulsed TMS studies show a decrease in intracortical inhibition which promotes excitatory activity within this hemisphere[137], and supports the changes observed in brain slices from rats[134]. Over the first four months after stroke, corticomotor excitability in the ipsilesional M1 increases (i.e. MEP amplitude increases and motor threshold decreases)[135,136]. This increase in ipsilesional M1 excitability correlates with improvements in function[135], which might suggest it facilitates the activation of neural networks during motor recovery.

Functional magnetic resonance imaging and positron emission tomography are neuroimaging techniques which have been used to make a number of observations about the level of neural activation in various brain areas when a person with stroke is moving their hemiparetic limb, compared with healthy controls[137-139]. Firstly, overactivation, defined by higher relative cerebral blood flow compared with healthy controls, has been observed in the peri-infarct cortex of an M1 infarct[138,139], which concurs with the increased neural activation seen in this area in animals described above[129,131]. Secondly, there is overactivation of ipsilesional motor and non-motor areas[138,139]. Increased activation in the ipsilesional S1/M1 is associated with better recovery after stroke[22,23]. Thirdly, there is overactivation of the

contralesional S1/M1, and of secondary motor areas and non-motor areas in the contralesional hemisphere[138,139]. Overactivity of the contralesional M1 it is thought to indicate the use of the ipsilateral corticospinal pathways[138], the 10-25% of corticospinal fibres that do not decussate[140]. In subcortical strokes, this overactivity in the contralesional S1/M1 has been shown to decrease by four months post-stroke, as activation of the ipsilesional S1/M1 increases[141]. This combined literature supports the concept that an increase in activity in the ipsilesional S1/M1 may assist with motor recovery.

Animal studies have explored the reorganisation that takes place *within* the ipsilesional S1/M1 after stroke. This involves changes to the somatotopic organisation of the S1/M1[142] which is associated with axonal sprouting[143]. This reorganisation can also be seen in human studies, using TMS to discern which areas of the M1 innervate different body parts[138,144]. For example, the representation of the hand on the ipsilesional M1 is initially smaller after stroke compared with the contralesional side, but an increase in this representation is associated with improved recovery[138,144]. The increase in motor representation is thought to reflect increased synaptic connectivity within the M1[145].

The studies reviewed so far support the idea that functional recovery after stroke relies on the reorganisation of undamaged areas in both hemispheres, and particularly the ipsilesional S1/M1, so that these areas can take over the function of the lesioned area; this is also known as the *vicariation model* for recovery[137]. The following section will introduce an alternative model of recovery.

## Interhemispheric inhibition

Paired-pulse TMS applied over both hemispheres has shown an increase in interhemispheric inhibition from the contralesional hemisphere to the ipsilesional hemisphere at the onset of hemiparetic limb movement[146]. Together with the neuroimaging data previously described, which shows overactivation of the contralesional S1/M1 during hemiparetic limb movement[138,139], these findings have given rise to another model for stroke recovery; the *interhemispheric imbalance model*[137]. This model theorises that a stroke disrupts the balance of inhibition between the two hemispheres, and that lowered excitability in the ipsilesional hemisphere is in part related to excessive interhemispheric inhibition from the contralesional to ipsilesional hemisphere[135,137,147]. This model shifts the focus of recovery from the ipsilesional hemisphere to the contralesional hemisphere[137], and has led to interventions which aim to increase ipsilesional excitability by inhibiting the contralesional hemisphere and reducing interhemispheric inhibition[147]. However, in a recent meta-analysis, this model of stroke recovery has been called into question due to insufficient evidence for imbalanced

interhemispheric inhibition following stroke[148]. Data from subcortical stroke shows that contralesional excitability and interhemispheric inhibition remain stable during subacute recovery, suggesting changes in interhemispheric inhibition are not the source of recovery[135]. One explanation for this is that interhemispheric inhibition is more prominent in individuals with smaller lesions[137] and so grouping data from individuals with a range of lesion severities makes the relationship between interhemispheric inhibition and recovery unclear.

### The importance of activity

Although some spontaneous recovery may occur following stroke, it is well recognised that additional activities are required to drive the neural plasticity that underlies recovery[149]. The plasticity processes discussed above can be modified by a providing an enriched environment, with physical activities, sensory experiences, and social interaction[129]. These purposeful behaviours result in adaptive neural changes (e.g. increased activation of the ipsilesional M1), whereas other behaviours, such as neglecting a hemiparetic limb, can result in maladaptive neural changes (e.g. reduced activation of the ipsilesional M1)[150]. To maximise adaptive plasticity and recovery, physical activity should be specific to the functional goal, repeated frequently, of sufficient intensity, become progressively more difficult, and be meaningful to the individual[20,149,151]. These factors are important components of post-stroke rehabilitation.

## 1.5 LIMITATIONS IN STROKE REHABILITATION

The recovery of motor skills is a major focus of stroke rehabilitation and it is recommended that people with stroke attend as much scheduled physiotherapy and occupational therapy as possible, and continue active task practice outside of rehabilitation sessions[19]. However, this approach to rehabilitation is costly and time-consuming. Consequently, most individuals with stroke receive limited amounts of rehabilitation. In New Zealand, only 50% of stroke patients in hospital receive one-hour of physiotherapy, five times per week[18], which is well short of the recommended two hours of daily active task practice[19]. In addition, rehabilitation after discharge is often delayed or limited[18]. In light of these limitations in stroke rehabilitation services, there is a need to find new rehabilitation approaches that can increase neural plasticity and recovery, without further burdening the limited resources of the health system.

## 1.6 NEUROMODULATORY INTERVENTIONS

### 1.6.1 NEUROMODULATORY INTERVENTIONS FOR STROKE RECOVERY

While traditional stroke rehabilitation involves the delivery of behavioural interventions, an alternative approach involves using neuromodulatory interventions which target neural activity more directly[24]. Neuromodulatory interventions are technologies which can alter neural activity via the delivery of a stimulus, either electrical or chemical, implantable or non-implantable, to a targeted area of the nervous system[21].

*Non-implantable* neuromodulatory interventions have the potential to be used as adjunct interventions to maximise the effects of standard rehabilitation[24]. Commonly these techniques involve the application of electrical or magnetic stimulation over the skull, to activate the underlying neurons of the brain, and are often referred to as non-invasive brain stimulation (NIBS)[112]. Common examples include transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), which have been applied in the acute, subacute, and chronic phases following stroke[152]. There are other non-invasive neuromodulatory approaches which apply stimulation peripherally, for example, electrical stimulation over the peripheral nerve, to indirectly alter cortical activity via afferent input[153,154]. Other approaches, such as PAS, use a combination of stimuli over the brain and periphery to induce changes in cortical activity[25]. This technique will be discussed further in the next section.

In stroke research, non-invasive neuromodulatory techniques are most commonly applied to target the M1, due to its role in motor control[82,86] (refer to 1.2.3), its superficial position, its somatotopic organisation, and the ease of measuring changes in its excitability with TMS (refer to 1.4.1). Different paradigms have been used to apply these techniques in people with stroke. Firstly, neuromodulatory interventions can be applied over the ipsilesional hemisphere using parameters which increase excitability[155,156]. Secondly, they can be applied over the contralesional hemisphere, using parameters which decrease excitability, with the aim of reducing interhemispheric inhibition from the contralesional hemisphere to the ipsilesional hemisphere via the interhemispheric imbalance model[155,156]. A third paradigm involves the successive application of two neuromodulatory interventions, where the delivery of the first intervention influences the effectiveness of the second intervention[157,158]. For example, when excitatory high frequency rTMS is applied just prior to inhibitory low frequency rTMS, greater inhibitory effects are produced in the second session[159]. This is

based on mechanisms of *metaplasticity* where the plasticity response to a second event, is subject to a higher-order form of plasticity that is influenced by a preceding event[160]. The effect can be homeostatic, where the second intervention reverses the effect of the first intervention, or non-homeostatic, where the second intervention promotes the effect of the first intervention[157]. Finally, neuromodulatory interventions, whether excitatory or inhibitory, can be delivered before another motor activity, which is known as *priming*, or concurrently with another motor activity[161-163]. This can attenuate the effects of motor training alone[161-163]. There is a growing body of literature investigating the efficacy of neuromodulatory interventions within each of these delivery paradigms; however, current evidence about their effects on recovery is not yet sufficient to support their routine use in rehabilitation practice following stroke[155,156,164,165].

### 1.6.2 ASSOCIATIVE PLASTICITY-BASED NEUROMODULATORY INTERVENTIONS

#### Paired Associative Stimulation

PAS has been briefly introduced as one type of neuromodulatory intervention. This section will describe the delivery method and mechanism underlying PAS, in order to provide some background about this approach before the novel-PAS intervention is introduced in Chapter 2.

PAS is an intervention which is designed to induce plasticity via the interaction between two associated stimuli (i.e. associative plasticity). Conventionally, it involves the delivery of a single pulse of TMS over the M1 and a single pulse of electrical stimulation over a peripheral nerve[25]. It should be noted that the use of TMS within the PAS intervention, as a method to deliver repeated stimulation to the brain, is distinct from the use of TMS as a measurement tool (described earlier in 1.4.1). Thus, within PAS studies, TMS may be used in two ways: as part of the PAS intervention, and as a tool to measure changes in corticomotor excitability from pre- to post-intervention. Although PAS is commonly used to target the M1, other PAS protocols have targeted other CNS locations, such as the S1[166] or spinal cord[167]. The afferent volley is most often produced with peripheral electrical stimulation, but this can be substituted for a proprioceptive, visual or auditory stimulus[168-170], or a second TMS pulse over another brain area (e.g. contralateral M1)[171].

More often applied in the upper limb, the two PAS stimuli are timed such that the afferent stimulus arrives in the M1 synchronously, or 5 milliseconds (ms) prior to the cortical

stimulus, resulting in an increase in MEP amplitude[25-28]. If the afferent stimulus arrives in the M1 5-13ms after the cortical stimulus, there is a decrease in MEP amplitude[26,28]. The changes in corticomotor excitability induced by PAS are rapid, persistent, reversible, topographically-specific, and dependent on NMDA receptor activation and L-type voltage-gated $Ca^{2+}$ channels[25,26]. In addition, the site of plasticity appears to be cortical, as PAS does not produce changes in brainstem or peripheral nerve excitability[25,26]. Together, these findings suggest that PAS induces a form of plasticity similar to LTP/LTD seen in animals[25]. In addition, because the direction of change following PAS is dependent on the timing and order of the paired stimuli, it has been suggested that the mechanism shares similar rules to that of STDP[172]. However, the mechanism underlying PAS in humans is likely to be much more complex than STDP studied at the single neuron level in animals[157].

Alterations in corticomotor excitability have been observed when PAS is delivered using a variety of approaches. While largely investigated in the upper limb of healthy participants[172], PAS has been shown to alter corticomotor excitability in people with stroke[29-34]. Some studies of people with stroke have delivered PAS in its conventional form by pairing single pulses of peripheral stimulation with single pulses of TMS over the M1[32-34], while others have paired a train of peripheral electrical stimuli with TMS over the M1[29-31,35]. PAS can be applied with the target muscle at rest[29-33], engaged in a low-level voluntary contraction[173,174], or while performing a functional task, such as treadmill walking[175-177]. When PAS was applied to the ipsilesional hemisphere of people with stroke, three out of four studies showed an increase in corticomotor excitability to the hemiparetic limb[29-31,35]. When PAS was applied to the contralesional hemisphere with the aim of reducing inter-hemispheric inhibition, two out of three studies showed an increase in corticomotor excitability to the hemiparetic limb[32-34].

The behavioural effects of PAS have received little attention. There is some evidence in the healthy population that PAS can improve the performance of a thumb flexion task within a session[178] and the learning of a hand control task assessed one-week post-intervention[179]. In a rat model of stroke, PAS has enhanced the early recovery of spontaneous movement, movement symmetry, and climbing ability[180]. In humans with stroke, only one study has measured a PAS-induced improvement in physical function. Uy et al[35] delivered a four-week PAS protocol to nine participants with chronic stroke, and reported participants walked with significantly faster and longer steps post-intervention. However, these effects should be interpreted with caution, as there was potential for bias due to the absence of a control group and failure to blind participants and assessors. In addition, the authors did not report whether follow-up measures two-weeks post-intervention showed that the changes in walking were retained, which would have indicated that motor learning had taken place. Overall, there is

some evidence that PAS can alter corticomotor excitability after stroke, but insufficient evidence about its effects on recovery after stroke. Further research is required before PAS could be translated into rehabilitation practice.

### Paired interventions that utilise endogenous motor activity

There is a small amount of literature that investigates other *paired* neuromodulatory interventions which utilise endogenous M1 activation as one of the two paired components.

Thabit et al[181] modified PAS by removing the peripheral electrical stimulation component and replacing it with a movement task which produced endogenous M1 activation[181]. Thus, the intervention paired *voluntary movement* with *TMS over the M1*. This approach was studied in healthy participants and resulted in time-dependent muscle-specific bidirectional changes in corticomotor excitability[181].

Another approach involved removing the TMS component from the PAS intervention and replacing it with a voluntary or imagined movement task that produces endogenous M1 activation. Two studies by Khaslavskaia et al[182] and Taylor et al[183] paired *voluntary movement* with relatively long phases of *peripheral electrical stimulation* (of 1 and 6 seconds) and produced increased corticomotor excitability in healthy participants. Taylor et al[183] also investigated the intervention in people with stroke but showed no effect[183]. A further study in healthy participants, by Bonassi et al[184], paired *imagined movements* with single pulses of *peripheral electrical stimulation*. However, the effects on corticomotor excitability were no greater than the effects of voluntary movement alone or electrical stimulation alone[184]. These three studies, which combined *voluntary or imagined movement* with *peripheral electrical stimulation,* paired the two components by either triggering the electrical stimulation at the onset of movement[183] or by instructing the participants to synchronise their movements with the onset of electrical stimulation[182,184]. These methods did not allow the researcher to accurately manipulate the timing and order in which the two components activated the M1. The PAS literature, described in the section above, indicates that accurate timing is important in producing associative plasticity, and therefore this factor may have limited the efficacy of these interventions.

## 1.6.3 ACCEPTABILITY AND TRANSLATION TO REHABILITATION PRACTICE

When developing and piloting a complex health intervention, the Medical Research Council recommends that researchers consider the views of end-users, with qualitative research if

possible, as well as considering the context in which the intervention will be implemented and any potential barriers to implementation[185]. While there is a body of work which has investigated neuromodulatory interventions following stroke[155,156], literature devoted to assessing the aforementioned factors is scarce[186]. In relation to PAS, one concern about its future implementation is the use of TMS. TMS is contraindicated, cautioned, or not tolerated in certain individuals[36], as well as being costly and not readily available in healthcare facilities. These factors present possible barriers to the implementation of PAS into rehabilitation practice.

## 1.7 SUMMARY

This chapter has made the following key points:

- Stroke can interrupt motor control and cause a number of impairments which can hinder function. Deficits in ankle dorsiflexion strength are known to limit gait function, and the recovery of gait is an important goal for people with stroke.
- Neural plasticity occurs during motor skill learning and changes at the synaptic level are thought be particularly important. LTP is one type of synaptic plasticity that has been observed at a cellular level in animals and can be induced by applying paired stimuli in a specific temporal order. This process involves STDP or associative plasticity.
- Recovery following stroke involves the recovery of pre-existing movement patterns or the learning of new movement patterns. Neural plasticity underlies this recovery process. Following stroke there are structural and functional changes to neurons in the area surrounding the lesion; these are thought to promote the restoration of pre-existing neural pathways and the development of new pathways. LTP may be involved in the formation of these new connections. In addition, there is widespread reorganisation of undamaged areas in both the ipsilesional and contralesional hemisphere. Increased excitability and activation of the ipsilesional M1 appears to be associated with recovery.
- Current stroke rehabilitation services are limited and neuromodulatory interventions are a promising rehabilitation adjunct. These interventions can increase corticomotor excitability in the ipsilesional M1 and can be applied in conjunction with other interventions to attenuate the effects of standard rehabilitation.
- PAS is one type of neuromodulatory intervention that involves pairing TMS with peripheral electrical stimulation. The order and timing of the two stimuli dictate whether the intervention has an excitatory or inhibitory effect on the M1. There is very limited information about the effects of PAS on stroke recovery.

- Although other paired interventions exist, none of those reviewed involve the finely-controlled timing used in PAS, which is thought to be important for inducing associative plasticity.
- There is a dearth of research in the field of neuromodulation exploring the perspectives of people with stroke and barriers to implementing interventions into rehabilitation practice, yet this is considered essential to the development of complex interventions. The TMS component of PAS may present a barrier to translation into the rehabilitation context.

# Chapter 2.
# Novel paired associative stimulation

## 2.1 PROLOGUE

This chapter introduces an innovative paired intervention, called novel-PAS. Novel-PAS utilises an electroencephalography (EEG) signal called the movement-related cortical potential (MRCP), which will be described in the first part of this chapter. Then the literature related to the development and efficacy of novel-PAS, as well as its advantages over other paired interventions, will be reviewed. Finally, recommendations for further research will be offered.

## 2.2 MOVEMENT-RELATED CORTICAL POTENTIAL

The MRCP is a signal which can provide an indication of the endogenous cortical activity that occurs during imagined or voluntary movement[187,188]. It is an essential component of the novel-PAS intervention which will be introduced in the next section (refer to 2.3).

MRCPs are recorded using EEG which measures voltage differences beween electrodes placed on the scalp, and a reference electrode, often placed on the ear or mastoid process[189]. Decreases in voltage at the scalp indicate excitatory activity in the superficial layers of the cortex[189,190]. The MRCP is a slow EEG signal that can be observed as a person prepares for, and then executes, a movement[187,188]. The movement can be self-paced, cued or imagined[188]. The MRCP gives an indication of the timing and amplitude of neural activity underlying movement planning and execution. It consists of a slow negative shift in EEG 1-2 seconds prior to movement, followed by a larger negative shift approximately 500ms before movement, and then a positive shift after movement onset[187,191] (refer to example in Figure 2-1). When an MRCP is recorded following a warning stimulus and then a cue to move, it is

known as a contingent negative variation[192]. Within this thesis, the contingent negative variation will be referred to under its collective term, the MRCP.

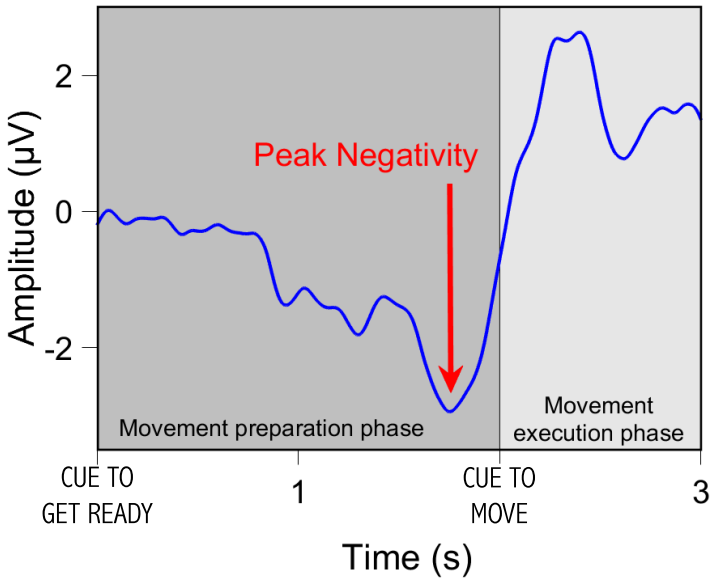



Figure 2-1 Average MRCP recorded during ankle dorsiflexion movements in person with stroke

Using EEG and intracranial recordings, the MRCP can be detected in many cortical and even subcortical areas[193]. However, the primary generators are thought to be the bilateral supplementary motor areas, bilateral pre-supplementary motor areas, bilateral cingulate motor areas, and the contralateral M1, with some evidence also suggesting involvement of the ipsilateral M1[194]. Cued movements are associated with increased activation of the prefrontal, temporal and occipital areas[192]. Scalp EEG recordings, which detect activity in more superficial structures, show similar MRCPs during self-paced voluntary movements, cued voluntary movements, and imagined movements[188]. During ballistic ankle movements, the peak amplitude of the MRCP is largest over the central scalp electrode (Cz or CPz electrode), for both imagined and voluntary movements[195,196]. This point of peak negative amplitude normally occurs just before movement onset, and is known as the *motor potential*, *N-10*, or *peak negativity (PN)*[187]. The PN likely represents activity in both the bilateral supplementary motor areas and the contralateral M1, which generate this part of the MRCP[197]. The M1 is less involved during imagined movements[188].

MRCP features vary with the type of movement, speed of the task, force required, occurrence of a warning signal and a cue to move, the level of uncertainty about the movement, and the presence of neurological conditions[192,193,195,197]. For example, during imagined movements, the MRCP amplitude is lower and the PN is less defined than in voluntary movement[195,198]. In people with stroke, the MRCP amplitude is lower but can increase over time[199].

## 2.3 EVIDENCE FOR NOVEL-PAS

### 2.3.1 EXCITATORY NOVEL-PAS

Novel-PAS is a neuromodulatory intervention that pairs single pulses of peripheral electrical stimulation with the endogenous cortical activity that occurs during imagined or voluntary movements[200-204]. In the intervention, the MRCP described above is utilised as a gauge of endogenous M1 activity, with the PN being indicative of M1 activation[200]. Novel-PAS can specifically target the ankle dorsiflexor muscles, which have been described in Chapter 1 as particularly important in gait recovery following stroke (refer to 1.2.2).

First reported in 2012, Mrachacz-Kersting et al[200] performed a within-subject, repeated-measures study, and paired single pulses of electrical stimulation to the deep branch of the common peroneal nerve (dCPN) with 50 repetitions of visually-cued imagined ankle dorsiflexion in healthy participants (n=9). These two components were paired so that the afferent volley from the electrical stimulation arrived in the M1 at the same time as the PN of the MRCP (Figure 2-1). This specific timing was achieved by pre-recording MRCPs during 50 repetitions of imagined ankle dorsiflexion, and then calculating the PN of the average MRCP with respect to the visual cue. During the intervention, each pulse of electrical stimulation was applied 50ms earlier than the peak PN, to account for the conduction time from the dCPN to the M1[173]. The two components of the intervention are illustrated in Figure 2-2.

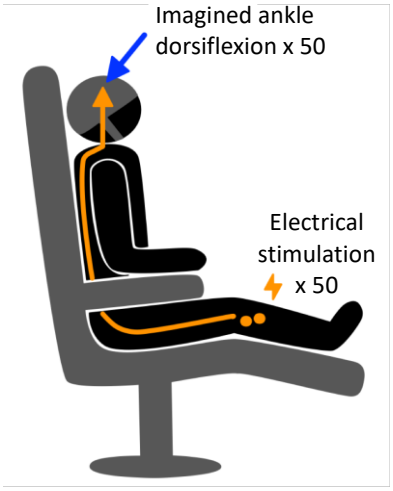



Figure 2-2 The pairing of two components in novel-PAS

The intervention resulted in a significant increase in tibialis anterior muscle (TA) MEP amplitudes[200]. In contrast, when the timing was manipulated so that the afferent volley was

timed to arrive in the M1 before, or after, the PN of the MRCP, there was no change in TA MEP amplitudes[200]. Additional experiments showed that control conditions of *imagination alone* (n=8), *imagined movement with antagonist nerve stimulation* (n=9), and *dCPN stimulation with a visual cue* (n=4), had no effect on corticomotor excitability. These findings indicated that it was the *pairing* of imagined movement with *specifically-timed* afferent volleys from the *agonist* muscle that produced the excitatory effect. The methodological quality of this series of studies could have been improved with blinding of participants and assessors, and sample size calculations. In addition, because the timing of the electrical stimulation was based on a pre-recorded average MRCP, the exact arrival time of each afferent volley is uncertain. Nevertheless, the statistical analysis was of a high quality, and the effects of the intervention, according to the method described, can be viewed with moderate certainty.

The mechanism underlying this novel intervention is thought to be related to the interconnections between the primary somatosensory cortex (S1) and the M1, and the timing of events in the M1. Because animal studies show somatotopically-organised connections between the S1 and the M1[89], it is hypothesised that when the afferent volley is timed to arrive in the M1 at the same time as the PN of the MRCP, an indicator of M1 activation[187], the afferent volley is projected to a group of M1 cells that is already active. This simultaneous M1 activation *may* be the cause of increased corticomotor excitability. An additional study of four participants showed that spinal cord reflexes were not influenced by the intervention[200] which suggests that the underlying mechanisms took place supraspinally, and fits with the hypothesis that M1 was being targeted by the intervention. However, other cortical areas may also be involved, given the widespread connections between the M1 and other motor and sensory areas[87,88], as well as the contribution of other motor areas to the MRCP signal[197]. The intervention born out of this work[200] resembles PAS in several ways including its use of finely-timed pairings that induce a plastic response that is rapid, persistent, and thought to be of supraspinal origin[25,200] (refer to 1.6.2). These similarities indicate that the intervention has similar neurophysiological underpinnings to PAS, possibly through an LTP-like plasticity mechanism, and has therefore been named novel-PAS in this thesis.

In 2012, Niazi et al[201] reported complementary findings with a similar novel-PAS intervention. This time, a brain computer interface (BCI) was used to detect the onset of MRCPs. A BCI is a system that records an individual's brain activity, extracts particular signals that reflect their intent, and then uses this information to control an external device[201]. In Niazi et al's work[201], the timing of the PN in relation to the MRCP onset was calculated from pre-recorded MRCPs. Then during the intervention, the BCI extracted the onset of the MRCP signal while participants imagined dorsiflexing their ankle and timed the delivery of

electrical stimulation to arrive at the PN. This allowed novel-PAS to be delivered during self-paced movements, rather than during cued movements. The efficacy of this intervention was tested in a small controlled experiment with three arms, where the BCI novel-PAS protocol (n=8) was compared with control interventions of *self-paced imagined movements only* (n=4) and *random stimulation of the dCPN only* (n=4). Results showed a significant difference between the intervention and control conditions; this was characterised by a significant increase in corticomotor excitability for the BCI novel-PAS group but not the control groups. The source of plasticity was considered to be supraspinal because stretch reflexes did not increase post-intervention, although only two participants were tested. The quality of results was limited by the lack of randomisation to groups, lack of blinding of assessors and those analysing results, small sample sizes, absence of correction for multiple comparisons, and non-reporting of baseline comparability which may have influenced the size of the relative-changes in MEP amplitude. While these results can only be viewed with low certainty, they provided the first evidence that the peripheral electrical stimulation could be timed to coincide with each repetition of self-paced imagined movement using a BCI. This method may improve the accuracy of matching of afferent volleys with MRCPs.

Two later studies supported the findings above. The first study by Jochumsen et al[203] confirmed that cue-based novel-PAS increases corticomotor excitability to the TA in healthy participants (n=14). This study also applied novel-PAS to the same participants under a range of other conditions, which are described in the next section (refer to 2.3.2). A second study by Mrachacz-Kersting et al[205] compared the cue-based novel-PAS protocol with the BCI novel-PAS protocol in healthy participants (n=10)[205]. This within-subject, repeated-measures study, showed that *both* interventions resulted in increased corticomotor excitability 30 minutes post-intervention, but there were no statistically significant differences between the interventions. While there was some risk of bias in these later studies due to a lack of blinding of assessors and those analysing data, the combined literature from all four studies described[200,201,203,205] supports the excitatory effect of novel-PAS delivered with either cued or self-paced imagined movements in healthy people.

### 2.3.2 INHIBITORY NOVEL-PAS

The above section introduced novel-PAS and its excitatory effects on corticomotor excitability. This section presents an alternative delivery method for novel-PAS, which induces *inhibitory* effects.

The main body of work by Jochumsen et al[203], partially described in the section above, involved testing an inhibitory novel-PAS intervention in a within-subject, repeated-measures study. Single pulses of electrical stimulation were applied to the tibial nerve while healthy participants imagined ankle dorsiflexion in time with a visual cue (n=14). This produced an *antagonist-agonist pairing*, rather than the *agonist-agonist pairing* used in the excitatory novel-PAS intervention (refer to 2.3.1). When each single pulse of tibial nerve stimulation was timed to arrive in the M1 at the PN of the MRCP produced by imagined dorsiflexion, there was a significant *decrease* in TA MEPs. The intervention was not effective when the afferent volley arrived before or after the PN of the MRCP. This echoed earlier work by Mrachacz-Kersting et al[200] which had established effective timing for the *excitatory* novel-PAS intervention. The findings from Jochumsen et al's study[203] contrasted with earlier work by Mrachacz-Kersting et al[200], who had applied antagonist nerve stimulation paired with ankle dorsiflexion as a comparison intervention and found no inhibitory effect (n=9)[200]. These contrasting results may be due to low sample sizes and warrant further investigation.

The combined evidence thus far, while limited in relation to the inhibitory intervention, appears to demonstrate that novel-PAS could produce *bi-directional* effects on corticomotor excitability, depending on the *location* and *timing* of peripheral stimulation. This reinforces the similarities between novel-PAS and PAS, which also produces bi-directional effects[25-28]. However, with PAS, the direction of change in excitability is determined by the interstimulus interval[25-28], rather than the stimulation being applied to the antagonist nerve, as in novel-PAS. This indicates that although PAS and novel-PAS share some neurophysiological underpinnings, their precise mechanisms may be different. However, readers should bear in mind that the evidence for inhibitory novel-PAS is limited and contradictory, and this might be the reason for contrasting findings between PAS and novel-PAS. Further research is required to clarify the neurophysiological processes involved in novel-PAS, since, beyond some limited evidence that novel-PAS acts supraspinally[200,201], the underlying mechanism is not yet understood.

### 2.3.3 MANIPULATION OF INTERVENTION PARAMETERS

This section looks at the manipulation of intervention parameters including the type of movement, the intensity and target area of the electrical stimulation, the source of afferent stimulation, and visual prompts.

## Type of movement and location of electrical stimulation

Mrachacz-Kersting et al[206] referred to an unpublished study comparing five different novel-PAS interventions in healthy participants. Participants performed imagined movements at 20% or 40% of their maximum voluntary contraction (MVC) and received varying intensities of peripheral electrical stimulation (muscle twitch, 20% MVC, 40% MVC). Preliminary results for one participant showed that TA MEP amplitudes were larger if the peripheral electrical stimulation produced a 40% MVC, rather than just a muscle twitch. Full results have not been published and thus this evidence should be viewed with low certainty. However, these single case results suggested that certain features of the novel-PAS intervention could be manipulated to further increase corticomotor excitability.

This hypothesis led to further research by Jochumsen et al[202] who investigated the effect of pairing *muscle* stimulation, rather than *nerve* stimulation, with *voluntary* ankle dorsiflexion movements, rather than *imagined* movements, in a within-subject, repeated-measures study (n=12 healthy participants). Four interventions were compared: i) voluntary ankle dorsiflexion paired with single pulses of electrical stimulation to the dCPN, ii) voluntary ankle dorsiflexion paired with a train of pulses of electrical stimulation to the TA muscle, iii) voluntary ankle dorsiflexion alone, and iv) TA muscle electrical stimulation alone. This study differed from previous work in that the electrical stimulation was timed to coincide with the cue to move, rather than using the PN of each participant's MRCP. The authors' justification for this was based on the perceived ability of healthy participants to consistently time their movements with cue[202], making the cue an approximation of the PN timing. Novel-PAS using TA *muscle* stimulation paired with *voluntary dorsiflexion* resulted in a significant increase in TA MEPs, both immediately after and 30-minutes post-intervention. However, dCPN stimulation paired with voluntary dorsiflexion had no effect. This latter finding contrasted with previous work which had shown an excitatory effect when dCPN stimulation was paired with *imagined* movement[200,201]. These findings may have differed for two reasons. Firstly, Jochumsen et al[202] used voluntary movements, rather than the imagined movements used previously[200,201], and voluntary movements produce MRCPs with higher amplitudes[195]. Thus, one explanation for the findings is that the higher level of cortical activation produced with voluntary movement requires pairing with afferent volleys of higher frequency or amplitude, which could be produced with muscle stimulation. However, more research is required to understand this further. Secondly, Jochumsen et al[202] did not record individual MRCPs, and instead paired the electrical stimulation with the visual cue as an approximation of the PN timing. This approach may have resulted in incorrect timing of some pairings, and might explain why the findings for the *nerve* stimulation intervention contrasted with

previous work[200,201]. Interestingly however, the pairing of *muscle* stimulation with the visual cue, rather than the PN of the MRCP, was effective. This could be related to the train of pulses delivered to the muscle, resulting in a longer duration of afferent input to the M1, which might have increased the likelihood of correct pairings. The quality of evidence was considered moderate, as the only risks of bias were the lack of blinded assessors and those analysing the data. However, given the deviation from the MRCP-based timing used in previous novel-PAS protocols, these findings should be replicated using the timing in the original protocol. Overall, Jochumsen et al's[202] work was the first to demonstrate that the novel-PAS intervention, pairing *muscle* stimulation with *voluntary* movement, might increase corticomotor excitability.

## Different sensory modalities

Three studies have adapted the BCI self-paced novel-PAS protocol by inducing the afferent volley with *passive ankle dorsiflexion* via a robotic device[207-209], rather than using dCPN electrical stimulation as per the original protocol. These three studies, performed on healthy participants (total sample n=33), have shown that imagined movement paired with passive movement can result in increases in corticomotor excitability to the TA for up to 30 minutes post-intervention[207-209]. These effects were equivalent to the increases in excitability produced by i) standard novel-PAS (n=12)[209], ii) imagined movement paired with a combination of dCPN electrical stimulation plus passive movement (n=12)[209], and iii) imagined movement paired with TA muscle stimulation (n=12)[208]. Comparison control interventions of *imagined movement only* and *passive movement only* had no effect on corticomotor excitability (n=9)[207]. This literature demonstrates flexibility in the method used to deliver novel-PAS, which could be advantageous in the rehabilitation environment where interventions need to be tailored to the specific needs of an individual.

## Visual prompts

As part of the cue-based novel-PAS intervention, visual prompts provided on a computer screen guide the participant to prepare, and then imagine, dorsiflexing their ankle. One study explored the effect of adding additional visual prompts after each imagined movement; this told the participants if they had performed the task correctly or incorrectly (n=14 healthy participants)[210]. However, the prompts were random and not based on the participant's performance, and instead the word '*correct'* was displayed randomly 60% or 85% of the time. The study showed that the novel-PAS intervention with random visual prompts enhanced corticomotor excitability more than the standard protocol. This possibly resulted from increased motivation and attention to the task[211,212]. Although it was unclear why the

authors did not assess the effects of genuine feedback about successful performance, which is known to enhance learning [211], the findings demonstrated that a simple modification of the protocol could enhance its excitatory effects.

This section has shown that various parameters of the novel-PAS intervention can be manipulated to produce equivalent or enhanced effects on corticomotor excitability. This flexibility in the delivery method could be advantageous in the rehabilitation environment. Further research is needed to explore the most effective way to deliver novel-PAS.

### 2.3.4 NOVEL-PAS EFFICACY IN PEOPLE WITH STROKE

This section will focus on the effects of novel-PAS in the stroke population. This encompasses just one study which has examined the cue-based novel-PAS protocol.

Mrachacz-Kersting et al[204,213] conducted a two-group controlled trial with repeated-measures to explore the efficacy of three sessions of novel-PAS compared with three sessions of a sham condition in 22 people with chronic stroke. The novel-PAS intervention involved 50 repetitions of cue-based attempted hemiparetic ankle dorsiflexion paired with single pulses of dCPN electrical stimulation, timed to arrive in the M1 at the PN of the MRCP (n=13). The sham condition involved 30-50 repetitions of cue-based attempted hemiparetic ankle dorsiflexion, but this time the single pulses of dCPN stimulation were timed to arrive randomly before or after the PN of the MRCP (n=9). TA MEPs were measured at five intensities (90-130% of RMT), before, immediately after, and 30-minutes post-intervention. Immediately post-intervention there was a significant increase in MEPs recorded at 130% of RMT, but 30-minutes post-intervention there were significant increases in MEPs recorded at 90%, 110% and 130% RMT. Thus, over the 30-minutes following the intervention, corticomotor excitability increased at a range of TMS intensities. Because TMS activates slower-conducting neurons at low intensities and faster-conducting neurons at high intensities[112], the findings suggest that the intervention influenced the excitability of different types of neurons. MEPs at 100% and 120% RMT also increased but not to a statistically significant degree. Given the changes at other TMS intensities, a larger sample may have shown significant effects across the range of TMS intensities. The effects of novel-PAS on corticomotor excitability were not different across each of the three sessions, and there were no significant effects following the sham intervention. Importantly, this study also measured changes in lower limb impairments and function. Following novel-PAS there were statistically significant improvements in the lower limb Fugl-Meyer scale, foot-tapping

frequency, and gait speed, but there were no improvements in these measures following the sham intervention.

There were some quality concerns with this paper, namely the lack of randomisation to groups, the exclusion of MEP data for three participants, and absence of between-group comparisons. In addition, some of the difference between groups could be explained by the fact that the intervention dose was not matched between the intervention and sham conditions. Another limitation was that pre-intervention measures of gait speed were significantly different between groups (the novel-PAS group was 0.4 metres per second (m/s) slower), which suggests groups differed in their functional walking ability at baseline[214]. The change in gait speed following novel-PAS did exceed the standard error of the measure[215]; however it did not reach a clinically meaningful level[13] and retention of this effect was not measured. Thus, it is not clear whether this improvement in gait speed translated into improved function. A final concern relates to the generalisability of the results; data indicated the sample had a mild to moderate lower limb disability[214] and this may limit application of the findings to people with more severe deficits. Overall, Mrachacz-Kersting et al's study[40] provided low to moderate quality evidence that novel-PAS can increase corticomotor excitability for 30-minutes in people with chronic stroke, and that three consecutive sessions can improve lower limb impairment and gait speed.

### 2.3.5 FEASIBILITY OF NOVEL-PAS

As described in Chapter 1 (refer to 1.6.3), the development of complex health interventions should consider the views of the end-user and any potential barriers to implementation[185]. There have been no studies reporting on the feasibility or acceptability of the novel-PAS intervention. In terms of potential for implementation, novel-PAS is thought to offer some advantages over other paired interventions such as PAS, and these will be considered in the next section. Following that, the novel-PAS literature will be synthesised in the final chapter summary.

## 2.4 ADVANTAGES OF NOVEL-PAS

This section will explore the potential advantages of novel-PAS over PAS and other paired interventions.

### 2.4.1 TMS NOT REQUIRED

Unlike traditionally-delivered PAS, novel-PAS does *not* require TMS. This offers major advantages in terms of safety and cost.

TMS is absolutely contraindicated in people with implanted metalware or devices near the discharging coil[36]. This factor alone may reduce the clinical feasibility of PAS, as metalware such as stents and aneurysm clips are used in the prevention and treatment of stroke[216,217]. In addition, due to the risk of inducing seizure, TMS is cautioned in people with brain lesions such as stroke[36]. This risk is confounded in people who also have epilepsy or are taking medications that lower seizure threshold[36], both of which can accompany stroke[218,219]. International studies have shown that approximately 11% of people with acute stroke will develop seizures within five years[220]. In addition, people with stroke are discharged on multiple medications, and antidepressant drugs, which are known to lower seizure threshold[36], are reportedly taken by 25-59% of people early after stroke[221,222]. TMS can also produce side effects such as pain, discomfort or headache[36], factors which may influence whether a person accepts the treatment. These concerns about safety, seizure risk, and potential side effects, limit the feasibility of using TMS in people with stroke. Thus, an intervention that does not use TMS is preferred and could be applied more widely in the stroke population.

A standard TMS machine with suitable chair costs around US $55,000 and requires a trained operator[223]. A single private session of TMS costs US $400-500[224]. These are significant costs that would need to be met publicly or privately; thus, an intervention that does not require TMS would be preferable to both consumers and healthcare funders.

### 2.4.2 FINELY-TIMED PAIRINGS

In Chapter 1 (refer to 1.6.2), some paired interventions were introduced that do not use TMS. Studies by Khaslavskaia et al, Taylor et al, and Bonassi et al, paired *voluntary or imagined movement* with *peripheral electrical stimulation* but did not use finely-timed pairings[182-184]. However, literature previously reviewed supports the importance of timing for driving associative plasticity. Animal studies which have paired electrical stimulation to pre- and post-synaptic neurons, as well as PAS studies in humans, indicate that precisely-timed pairings are required to induce plasticity (refer to 1.4.2 and 1.6.2). The importance of timing has also been demonstrated in novel-PAS literature, which has shown that when the afferent volley is not matched with the PN of the MRCP, there is no effect on corticomotor

excitability[200,203,204] (refer to 2.3.1, 2.3.2, and 2.3.4). Thus, the efficacy of interventions which do not use finely-timed pairings may be limited.

The lack of timed-pairings in other interventions may be less of a concern in healthy people, who can accurately follow a cue, meaning their peak M1 activation is likely to occur close to the cue to move. However, in people with stroke, movement onset may be slower or delayed, making the pattern of M1 activation unpredictable, and potentially affecting the efficacy of the intervention. This is supported by the findings from Taylor et al[183] where peripheral electrical stimulation triggered at the onset of voluntary movement resulted in increased corticomotor excitability in healthy people, but had no effect in people with stroke. Thus, the novel-PAS intervention which is able to individualise the timing of pairings may be more appropriate for people with stroke than other non-TMS paired interventions.

### 2.4.3 POTENTIAL FOR CONCURRENT DELIVERY WITH STANDARD REHABILITATION

Most neuromodulatory interventions are delivered with the participant in a sitting position, which is more feasible when magnetic or electrical stimulation is involved and suits an intervention which is being used for priming prior to other rehabilitation. However, there is a body of research demonstrating that neuromodulatory interventions can be delivered *concurrently* with standard rehabilitation and result in improved motor learning following stroke[163,225-228]. The ability to apply a neuromodulatory intervention concurrently with other motor tasks may be particularly advantageous in the stroke rehabilitation context, where task-oriented training is important for neural plasticity and motor learning[20]. Concurrent delivery may also have benefits in terms of the time saved. Due to its use of equipment that could be miniaturised (EEG cap and electrical stimulator), the novel-PAS intervention has potential to be applied while an individual is performing other motor tasks; this makes it potentially more suited to the stroke rehabilitation environment than other neuromodulatory interventions.

## 2.5 SUMMARY

### 2.5.1 EVIDENCE FOR NOVEL-PAS

The novel-PAS intervention is a neuromodulatory intervention that pairs an afferent volley induced by electrical stimulation to a peripheral nerve, with the PN of the MRCP produced during voluntary or imagined movement. The timing of these pairings is critical; if the

afferent volley arrives before or after the PN there is no change in corticomotor excitability[200,203,204].

Novel-PAS has been delivered with a variety of methods, but the largest body of evidence supports the original protocol where *dCPN electrical stimulation* is paired with *imagined dorsiflexion movements* in healthy people. This intervention can be delivered using cue-based or self-paced movements, and results in increased corticomotor excitability of the TA for up to 30 minutes post-intervention[200,201,203,205,209]. This excitatory effect has also been demonstrated in people with stroke, using a combination of *attempted ankle dorsiflexion* and *dCPN electrical stimulation*[204]. In addition, people with stroke experienced improved lower limb impairment and function after three consecutive sessions[204]. While the stroke findings are promising, they should be viewed with caution as they depend on just a single study, which had potential for bias and did not demonstrate clinically-significant effects.

A number of studies in healthy people have manipulated aspects of the novel-PAS intervention. Applying peripheral electrical stimulation to the antagonist nerve, rather than the agonist, may produce an inhibitory effect[200,203]. Other modifications, such as combining muscle stimulation with voluntary movement[202], replacing the peripheral electrical stimulation with passive movement[207-209], or adding visual prompts[210], can produce excitatory effects similar to, or beyond, those of the original novel-PAS protocol. Thus, there is considerable flexibility in the method used to deliver novel-PAS. This could be advantageous in the stroke rehabilitation environment where certain aspects of such an intervention may be more suited to a patient's needs. For example, a patient with a skin condition may not tolerate electrical stimulation but would tolerate passive movement.

The feasibility of novel-PAS has not been explored. However, due to its advantages in terms of cost, safety, and potential for concurrent delivery with other rehabilitation interventions, it is considered more feasible for implementation into rehabilitation practice than PAS which uses TMS. There are other paired interventions which do not use TMS; however, these do not contain the finely-timed pairings in novel-PAS, which are thought to be important for driving associative plasticity.

The mechanism underlying novel-PAS is hypothesised to involve the simultaneous activation of the M1 by both i) peripheral electrical stimulation and ii) the preparation and/or execution of movement, either voluntary or imagined. The mechanism is thought to be similar to that underlying PAS (refer to 1.6.2) because both interventions produce rapid, persistent and bidirectional changes in corticomotor excitability. Beyond some research indicating the

source of plasticity occurs supraspinally[200,201], further understanding of the mechanism has not been investigated.

At this stage, there is insufficient evidence to determine whether the novel-PAS intervention would contribute to any meaningful improvement in motor recovery after stroke. However, the initial research has been promising, and as novel-PAS has many potential advantages over other paired interventions, further testing of this novel intervention is warranted.

### 2.5.2 RESEARCH QUESTIONS

Continued research is required to address the following research questions:

1. *What are the within-session effects of novel-PAS beyond 30 minutes post-intervention?*

Prior studies have not explored the novel-PAS effect beyond 30-minutes. If novel-PAS is to be integrated into rehabilitation practice, where therapy sessions typically last 60 minutes[229,230], the duration of the excitatory effect may influence how and when therapy is delivered in relation to the timing of the novel-PAS intervention. In addition, prior to further research on people with stroke, where outcome measurement can take considerable time, it is necessary to understand the duration of effect so that the research protocol can be designed with this in mind.

2. *What are the within-session effects of novel-PAS in people with stroke?*

There is a lack of high-quality evidence concerning the within-session effects of novel-PAS in people with stroke, especially those with more severe impairment. Further research is needed to confirm the excitatory effects of novel-PAS in people with stroke with varying severities of lower limb impairment.

3. *Is it feasible to deliver a research protocol involving multiple sessions of novel-PAS to people with stroke?*

Prior studies have not reported on the feasibility of a multi-session programme of novel-PAS. Further research is required to assess the feasibility of a research protocol involving multiple sessions of novel-PAS. This will provide important information about the perspectives of people with stroke, the potential barriers to the implementation of novel-PAS into rehabilitation practice, and the viability of a multi-session research protocol for use in a larger trial.

4. *What are the cumulative effects of novel-PAS in people with stroke?*

There is no evidence investigating the cumulative effects of novel-PAS beyond three sessions in people with stroke. Further high-quality research is required to determine the cumulative

effects of novel-PAS on motor impairment and function in people with stroke. This would be best accomplished with an RCT design that directly compares the effects of multiple sessions of novel-PAS with a sham-intervention.

# Chapter 3.

# Study A.

# Duration of excitatory effects

## 3.1 PROLOGUE

The following chapter presents Study A, which explores the duration of neuromodulatory effects following novel-PAS. This study aims to address the first research gap identified in Chapter 2; *what are the within-session effects of novel-PAS beyond 30 minutes post-intervention?*

## 3.2 INTRODUCTION AND OBJECTIVE

Novel-PAS is a neuromodulatory intervention that has the potential to be used in rehabilitation following stroke. Research has shown that a single session of novel-PAS, applied to the ipsilesional hemisphere of people with stroke, can increase corticomotor excitability to the TA for up to 30 minutes[204]. Here, the within-session effects of novel-PAS beyond 30-minutes post-intervention, will be explored.

An investigation of the duration of neuromodulatory effects is important for two reasons. Firstly, when neuromodulatory interventions are applied in conjunction with standard rehabilitation they have the potential to prime motor networks and enhance the learning response to standard interventions[24]. However, researchers and clinicians need to understand the time-sensitivity of the neuromodulatory effects[20,109] so that they can effectively combine novel-PAS with standard rehabilitation practice. Knowledge about the time-course of neuromodulatory effects would allow researchers and clinicians to consider how they might time other interventions to coincide with the period of increased cortical excitability, which may facilitate motor learning and recovery. Thus, prior to conducting research combining novel-PAS with standard rehabilitation, the duration of neuromodulatory effect must be explored. In stroke rehabilitation, physiotherapy sessions last up to 60 minutes[229,230],

therefore of particular interest to clinicians would be whether neuromodulatory effects last for 60 minutes.

The second reason for investigating the duration of novel-PAS effects is to assist with the planning of future research protocols involving several post-intervention measurements. An understanding of duration of neuromodulatory effects will allow the design of research protocols that measure the effects of the intervention within this window of increased excitability. This is particularly relevant to the second and third studies in this thesis, which will be introduced in Chapter 4 and 5, and which involve multiple post-intervention measurements.

The objective of the following study was to evaluate changes in corticomotor excitability in the 60-minute period following novel-PAS, in healthy participants. The experimental hypothesis was that corticomotor excitability would increase immediately following the intervention, and would remain increased at 30, 45 and 60 minutes post-intervention.

## 3.3 METHOD

### 3.3.1 STUDY SETTING AND DESIGN

Study A was a single-session, within-subject, repeated-measures experiment, and involved pre-intervention TMS measures, delivery of the novel-PAS intervention, and post-intervention TMS measures at 0, 30, 45 and 60 minutes post-intervention. This study was undertaken at the Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand.

### 3.3.2 PARTICIPANTS

#### Sample size

Published data was insufficient to inform a sample size calculation[200], and therefore additional unpublished data from healthy participants was obtained from Aalborg University (Jochumsen, M). According to these data, a sample size of six was needed to detect statistically significant differences between pre- and post-intervention measurements, with 80% power and alpha of 0.05. An elevated sample size of 10 healthy participants was used to account for any dropouts.

### Inclusion criteria

Healthy volunteers were considered for inclusion in the study if they were over 18 years of age.

### Exclusion criteria

Volunteers were excluded if they had medical conditions that could impact the results, or contra-indications or cautions to TMS (refer to Appendix A).

## 3.3.3 ETHICAL CONSIDERATIONS

Ethical approval was received from the Auckland University of Technology Ethics Committee (AUTEC) (14/255). Refer to Appendix B for ethical approval and the main ethical considerations.

## 3.3.4 STUDY PROCEDURES

### Recruitment

Ten healthy participants were recruited by advertising through the University staff and student networks.

### Screening and consent

All potential participants who expressed an interest in the study were provided with the participant information sheet (Appendix C). Potential participants were screened for eligibility over the telephone or in person by a trained research physiotherapist, who sought information about relevant medical conditions, medications and contraindications or cautions to TMS (Appendix A). Potential participants were scheduled to attend a data collection session at the University. At the start of the session participants had the opportunity to ask questions and gave written consent (Appendix D).

### Study flow

The study flow is outlined in Figure 3-1. Following recruitment and screening, participants attended a data collection session in which consent was obtained. Thereafter, each participant performed 50 repetitions of imaginary ankle dorsiflexion while their MRCP was recorded. This recording provided the timing for the subsequent novel-PAS intervention. Then pre-intervention TMS measures of corticomotor excitability were collected, followed by delivery

of the novel-PAS intervention during another 50 repetitions of imagined movement. Post-intervention TMS measures were recorded 0, 30, 45, and 60 minutes after the intervention.

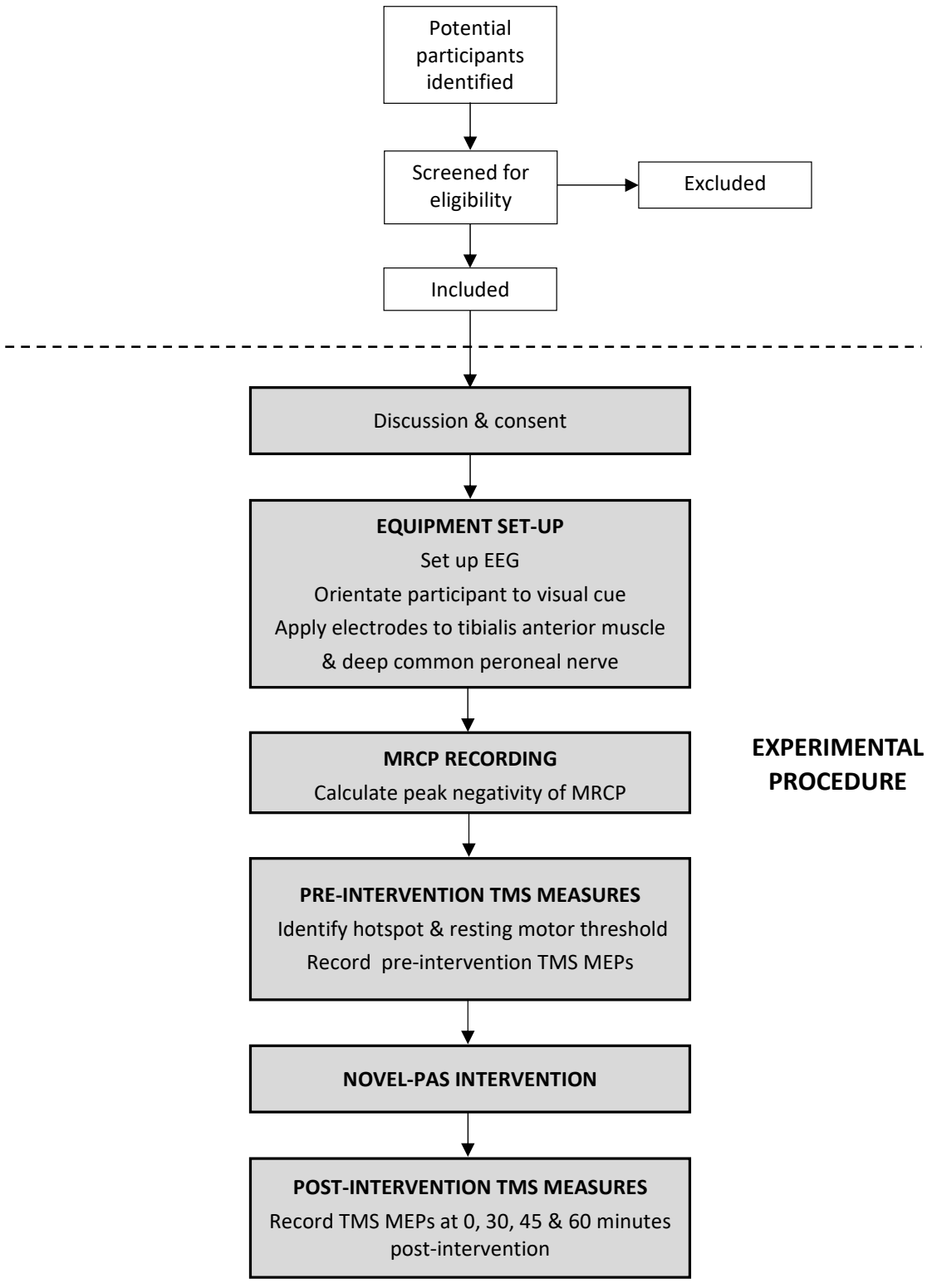



Figure 3-1 Study flow for Study A

## Experimental set-up

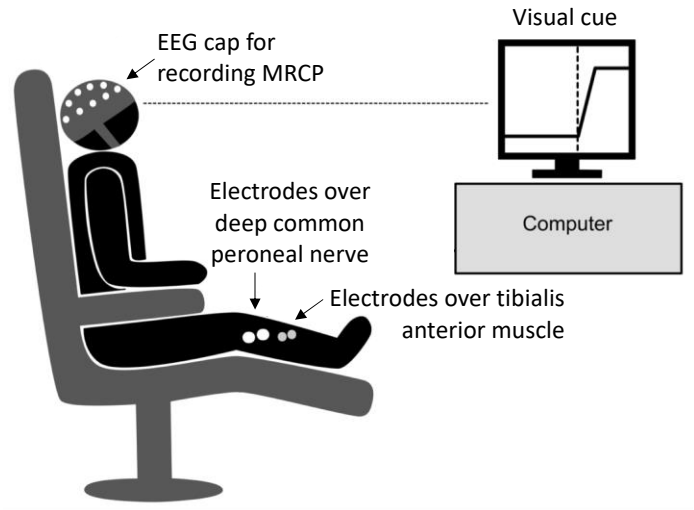



Figure 3-2 Experimental set-up for Study A

The set up for the MRCP recording can be seen in Figure 3-2. Participants were seated with approximate joint angles of hip flexion 90º and knee flexion 20º. Verbal instructions about how to follow the visual cue were provided (refer to Figure 3-3). The visual cue prompted participants to imagine ankle dorsiflexion movement with their right ankle. As illustrated on the right side of Figure 3-3, the cue started with a preparation phase, where a blue line moved horizontally along the screen, cueing participants to prepare for movement. After 3 seconds the blue line intersected a black line, prompting participants to imagine a quick ankle dorsiflexion movement. Each imagined movement was interspersed with a period of *'rest'*, where participants could move or blink, and they were encouraged to actively dorsiflex their ankle as a reminder of how the movement felt. Just prior to the cue appearing, participants were prompted to *'focus'* on the screen.

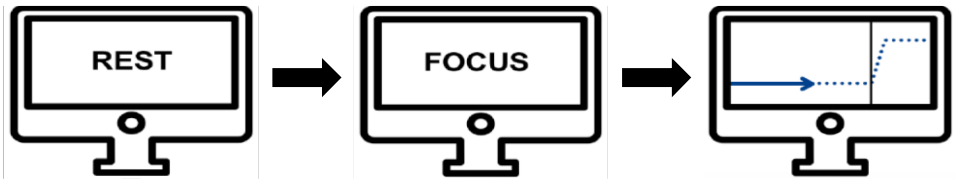



Figure 3-3 Visual cue for MRCP recording and novel-PAS intervention

For the collection of EEG data, an EEG cap (40 channel Quik-cap, Ag/AgCl electrodes, Compumedics Neuroscan, Australia) was applied with the Cz electrode placed midway between the nasion and the inion in the sagittal plane, and midway between each tragus in the coronal plane. A sterile blunt needle was used to abrade skin and apply conductive gel to 10 of the 40 electrodes on the cap until impedance was below 5KΩ. The electrodes were the FP1, F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 electrodes according to the International 10-20

system. A ground electrode was placed to the right of the central forehead, and a reference electrode was placed on the right mastoid process. Continuous EEG data was amplified and recorded with a sampling frequency of 500Hz and 32 bits accuracy (NuAmps 40 channel digital amplifier and SCAN software, Compumedics Neuroscan, Australia).

For the collection of TA EMG data during TMS measures, EMG surface electrodes (Blue sensor N, Ambu, Denmark) were placed over the right TA following skin preparation (shaving, abrasion and cleaning with alcohol). Two electrodes were placed a third of the way along the line between the head of the fibula and the tip of the medial malleolus[231]. A reference electrode was placed on the lower third of the anterior border of the tibia. Impedance was checked with a digital multimeter to ensure a level below 5KΩ. For TMS measures, TA EMG was amplified (AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz using a data acquisition board (Micro 1401, CED, United Kingdom (UK)) and Signal software (CED, UK).

For the delivery of peripheral electrical stimulation during the novel-PAS intervention, a further two surface electrodes (Blue sensor N, Ambu, Denmark) were placed over dCPN, approximately 2-5cm anterior and inferior to the head of the right fibula. Single 1ms pulses of electrical stimulation (DS7A, Digitimer Ltd, UK) were applied at increasing intensity until a twitch contraction was just detectable by the researcher palpating the tendon of the TA muscle. This intensity was used in the subsequent novel-PAS intervention. If the desired muscle activation was not achieved, or concurrent twitches were palpable at the tendons of the peroneal or plantar flexor muscles, the electrodes were moved until the optimal position was located.

## MRCP recording and analysis

Following the visual cue described above, participants completed two sets of 25 repetitions of motor imagery of right ankle dorsiflexion. The MRCP was analysed immediately to inform the timing of the electrical stimulation in the subsequent novel-PAS intervention. The continuous EEG data was filtered with a low pass filter set at 5Hz, to identify the MRCP, and a high pass filter set at 0.05Hz, to remove any direct current drift[232]. The filter was a zero-phase shift infinite impulse response filter and was chosen to obtain a steep transition phase[232]. A large laplacian filter was applied to all channels except FP1, to create a surrogate channel centred around the Cz electrode[233]. This improved the signal to noise ratio of the MRCP originating from the region of the M1 representing the TA. The filtered signal was then divided into 50 epochs, of three seconds duration; a 2-second *movement preparation phase* that ended with the cue to imagine movement, followed by a 1-second *imagined*

*movement phase*. Epochs were time-locked to the cue to imagine movement. Epochs that did not have progressively negative phase prior to the cue were manually rejected. Epochs containing eye movement artefacts were manually rejected following inspection of the epochs extracted from FP1[200]. An average of the remaining MRCPs was computed from the surrogate channel, and the most negative point of the waveform was identified as the PN. An example of one participant's average MRCP, with reference to the visual cue, is shown in Figure 3-4. The timing of the PN of the average MRCP was identified with respect to the visual cue to imagine movement. This timing was used in the subsequent delivery of the intervention.

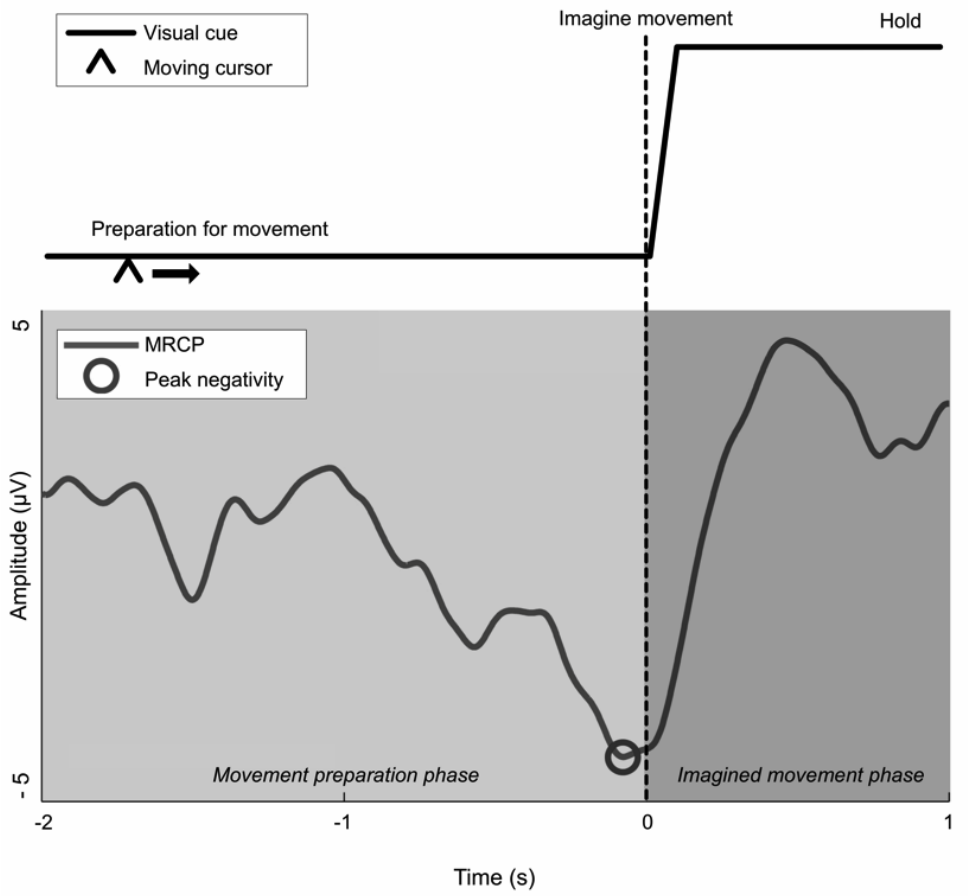



Figure 3-4 Average MRCP for one participant during imagined dorsiflexion (bottom graph), with the corresponding visual cue representing preparation, imagination and hold phases of the task (top graph).

## Outcome measure

The primary outcome of interest was corticomotor excitability as measured by TMS-induced MEPs of the TA muscle. Due to the effects of caffeine and exercise on cortical excitability[212,234], participants were asked to refrain from consuming caffeine or exercising prior to the testing session.

The EEG cap was removed and replaced with a tightly-fitting neoprene cap. TMS was delivered with a Magstim 200 (Magstim Co, Dyfed, UK) using a double-cone coil and monophasic pulses. The juncture of the coil was initially placed approximately 0.5-1cm lateral to the vertex towards the contralateral side[235,236] with a poster-anterior direction of current flow. The TA *hot spot* was found by applying stimulation and moving the coil in 1cm steps around this area until the location eliciting TA MEPs of the largest amplitude was identified. This location was marked on the neoprene cap so that all subsequent stimulation was delivered in the same location. Single pulses were applied to identify the RMT; this was defined as the stimulus intensity required to produce five out of ten MEPs, with a peak-to-peak amplitude of at least 50μV, with the TA muscle at rest. During each pre- or post-intervention measurement, 15 monophasic pulses of TMS were applied at 120% RMT, to produce 15 TA MEPs, which were recorded with EMG of the TA. MEPs were recorded pre-intervention, and at 0, 30, 45 and 60 minutes post-intervention.

## Novel-PAS intervention

Following the MRCP recording and pre-intervention TMS measures, participants completed a further 50 repetitions of imagined ankle dorsiflexion as part of the intervention. Participants performed two sets of 25 repetitions of imagined ankle dorsiflexion, in time with the visual cue, while single pulses of electrical stimulation were delivered to the dCPN (refer to Figure 3-5)[200]. Each pulse of electrical stimulation was timed to arrive in the M1 at the peak PN of the MRCP. The specific timing of electrical stimulation was achieved by calculating the participants PN of the MRCP with respect to the visual cue, and subtracting 50ms, to account for conduction time[173]. The novel-PAS intervention lasted approximately 15 minutes.

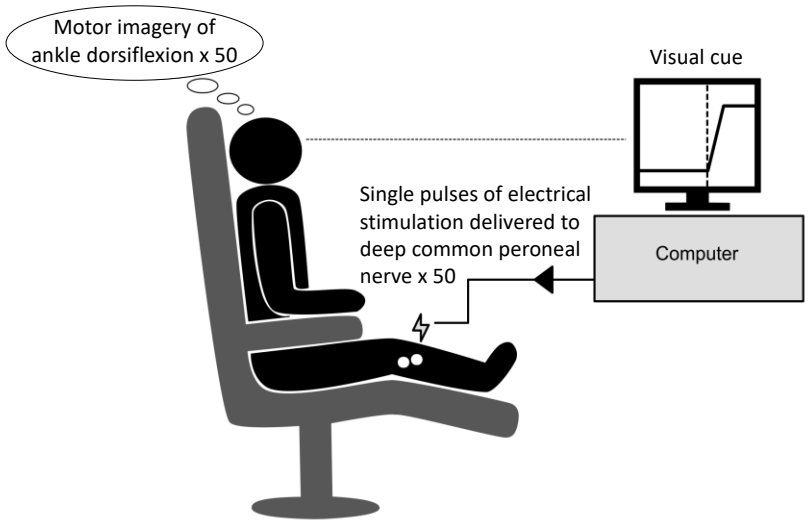



Figure 3-5 Delivery of novel-PAS intervention

### 3.3.1 DATA PROCESSING AND ANALYSIS

TA EMG was processed using Signal software. The background activity was determined by measuring the area of the EMG activity in a 30ms window, between 40ms and 10ms prior to stimulation, and then averaging the 15 MEPs. The TA MEP amplitude was determined by measuring the maximum peak-to-peak amplitude of each MEP, and then averaging to give a mean TA MEP amplitude for each individual at each time interval.

Data was tested for normality using the Shapiro-Wilk test and z-scores for skewness and kurtosis ($z<2.58$ indicates non-normality)[237]. The background TA EMG data was transformed using *logarithmic* and *reflect and logarithmic* transformations, but still failed normality tests. Thus, the raw background TA EMG data was analysed using the non-parametric Friedman test.

All TA MEP amplitude data was log transformed due to a non-normal distribution at the 60-minute time-point (Shapiro-Wilk test $p=0.013$, skewness 2.028 (standard error 0.687), kurtosis 4.985 (standard error 1.334)) and analysed with a one-way repeated-measures analysis of variance (ANOVA) test using a within-subject factor of *'time'* and five levels. Paired t tests were carried out comparing pre-intervention MEP measures with each of the post-intervention MEP measures. The 0.05 alpha level was adjusted for multiple comparisons according to the Holm-Bonferroni method, which maintains statistical power and protects against type I errors[238]. Statistical tests were completed using SPSS Statistics software and are shown in Appendix E.

## 3.4 RESULTS

### 3.4.1 SAMPLE CHARACTERISTICS

Eight participants were excluded at screening due to implanted metalware (n=2) and medications that lower seizure threshold (n=6). Demographics and medical background of the ten included participants are shown in Table 3-1.

### 3.4.2 COMPLETION OF EXPERIMENTAL PROTOCOL

Data collection was completed in March 2015. A single protocol deviation occurred for four participants who had previously had their MRCP recorded in pilot research. For these participants, the PN was determined from an MRCP recorded approximately two weeks prior to the experiment, rather than recording the MRCP on the day of the experiment. All

participants completed the novel-PAS protocol, and pre- and post-intervention measures of corticomotor excitability.

Table 3-1 Participant demographics and medical information

| Participant | Gender | Age (years) | Medical History | Medications |
|---|---|---|---|---|
| 1 | Male | 37 | - | - |
| 2 | Female | 41 | - | - |
| 3 | Female | 22 | Asthma | Budesonide and eformoterol inhaler |
| 4 | Female | 29 | Heart murmur | - |
| 5 | Male | 31 | - | - |
| 6 | Male | 64 | - | Ceased L-carnitine 2 days prior |
| 7 | Male | 27 | - | - |
| 8 | Male | 25 | - | - |
| 9 | Male | 33 | - | - |
| 10 | Male | 28 | - | - |
| | Males n=7<br>Females n=3 | Mean<br>34 years | | |

### 3.4.3 PEAK NEGATIVITY

The PN of the participants' average MRCPs ranged from 100ms before the cue to 290ms after the cue. There was considerable within-subject variability in the timing of the PN across the 50 MRCP trials (mean standard deviation (SD) of PN 277ms).

### 3.4.4 EMG BACKGROUND AREA

Background TA EMG area was not statistically significantly different across time-points ($\chi^2$ (4) = 6.014, p = 0.198), indicating stability of baseline EMG activity. Refer to Table 3-2.

### 3.4.5 TMS-INDUCED MEPS

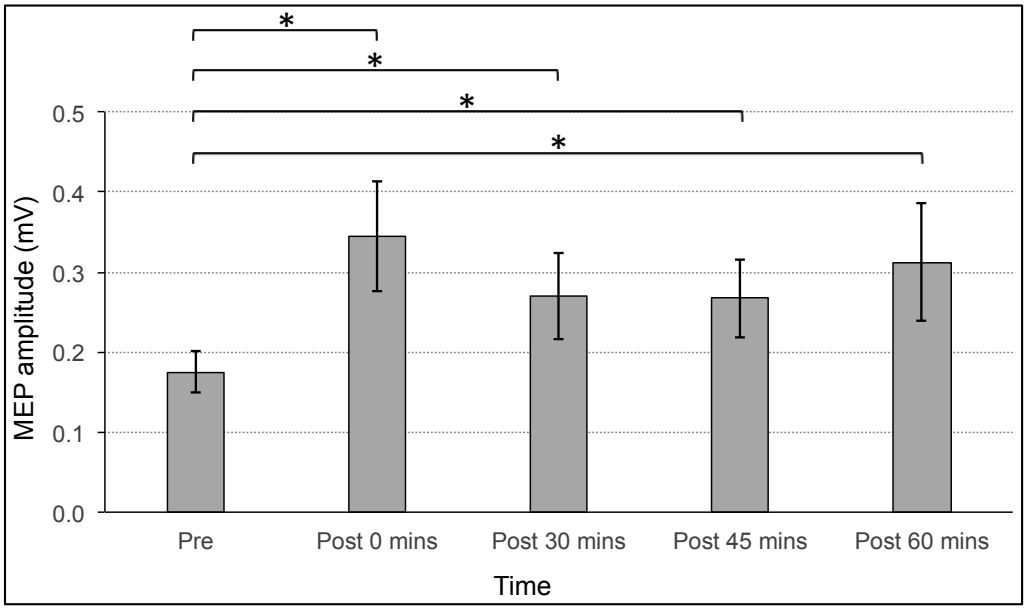
The mean RMT was 55% (SD 9%) of the maximum stimulator output. The absolute and log-transformed TA MEP amplitude data is presented in Table 3-2. The absolute changes in TA MEP amplitude are presented in Figure 3-6.

Table 3-2 Measures of background TA EMG and TA MEPs

| | Pre | Post 0 | Post 30 | Post 45 | Post 60 |
|---|---|---|---|---|---|
| Background TA EMG area (mV.S) | | | | | |
| Mean<br>(SD) | 0.00009<br>(0.000024) | 0.00011<br>(0.000032) | 0.00010<br>(0.000042) | 0.00012<br>(0.000055) | 0.00012<br>(0.000076) |
| TA MEP amplitude (mV) | | | | | |
| Mean<br>(SD) | 0.175<br>(0.083) | 0.345<br>(0.217) | 0.270<br>(0.171) | 0.267<br>(0.154) | 0.312<br>(0.231) |
| $Log_{10}$(TA MEP amplitude) | | | | | |
| Mean<br>(SD)<br>p-value<br>Holm-Bonferroni adjusted alpha level | -0.810<br>(0.240) | 0.561<br>(0.332)<br>p = 0.006 *<br>p < 0.0125 | -0.651<br>(0.294)<br>p = 0.006 *<br>(p < 0.017) | 0.660<br>(0.319)<br>p = 0.027 *<br>(p < 0.05) | -0.596<br>(0.297)<br>p = 0.020 *<br>(p < 0.025) |

Log10(TA MEP amplitude) = log-transformed TA MEP amplitude data used for statistical analysis

* significant difference from pre-intervention measure




Notes: Error bars represent standard error of the mean

* depicts statistically significant differences of log-transformed data

Figure 3-6 Group mean TA MEP amplitudes at each time interval

The one-way repeated-measures ANOVA of log-transformed MEP amplitude data revealed a significant *'time'* effect, indicating that the mean TA MEP amplitudes were statistically significantly different between time intervals ($F(4, 36) = 4.831$, $p = 0.003$). Based on adjusted alpha levels, pairwise comparisons between pre- and post-intervention measures showed that mean MEP amplitudes were statistically significantly greater immediately post-intervention (mean increase of 96%, $p = 0.006$), 30 minutes post-intervention (mean increase of 54%,

p = 0.006), 45 minutes post-intervention (mean increase of 52%, p = 0.027), and 60 minutes post-intervention measures (mean increase of 78%, p = 0.020).

### 3.4.6 INDIVIDUAL RESULTS

An inspection of the individual MEP results showed that all participants had an increase in corticomotor excitability immediately following the novel-PAS intervention (range 4-368%). The response pattern over the 60-minute period was varied, with the maximum increase occurring immediately for some participants, and for others at 30, 45 or 60 minutes. Figure 3-7 demonstrates this in two participants.

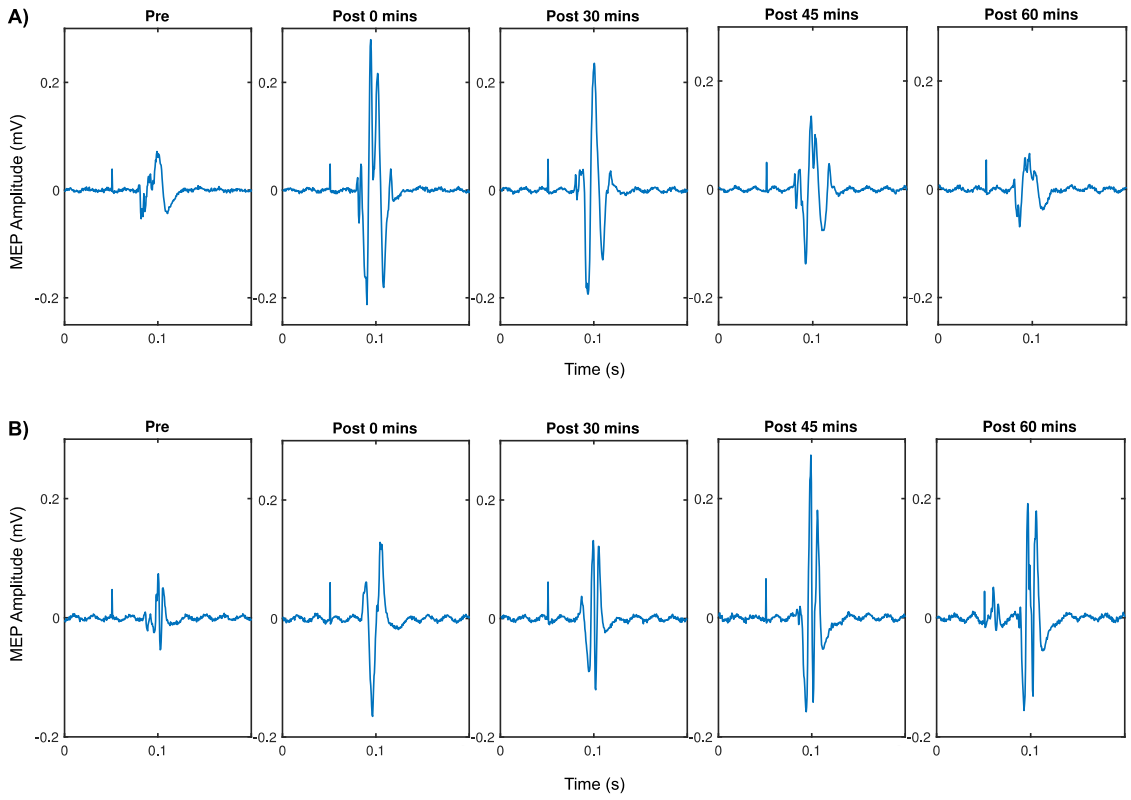



Figure 3-7 Example MEPs for participants A and B showing variability in the response pattern over 60 minutes

## 3.5 DISCUSSION

### 3.5.1 IMPLICATIONS OF FINDINGS

This study increases the body of knowledge about the duration of increased corticomotor excitability following the novel-PAS intervention. A neuromodulatory effect was demonstrated up to 60 minutes post-intervention in healthy participants. This finding has

important implications in relation to the application of novel-PAS within a rehabilitation session, and the planning of future research protocols.

With regard to the combination of novel-PAS with standard rehabilitation, the findings of this study suggest that the neuromodulatory effects of novel-PAS could be harnessed for up to 60 minutes following intervention delivery. Thus, if novel-PAS was applied immediately prior to a standard rehabilitation session to prime the motor cortex, the resulting increase in corticomotor excitability might enhance the motor learning that occurs during the subsequent 60-minutes of therapy[161,239]. This priming effect was described in Chapter 1 (refer to 1.6.1) and has been demonstrated with other neuromodulatory interventions, such as rTMS and tDCS; these have been delivered before or concurrently with motor training, and resulted in improved motor performance[162,163] and motor learning[161]. Further research is needed to establish if a similar effect is possible with the novel-PAS protocol when combined with standard rehabilitation.

In relation to the planning of future novel-PAS research, these findings have important implications for the timing of outcome measurements. Post-intervention measures of neural plasticity could be collected anytime within the 60-minute time-period following novel-PAS. This would allow more flexibility when planning the research protocol, which is particularly important for stroke research, where the set-up and measurement process may require more time.

### 3.5.2 INTER-INDIVIDUAL VARIABILITY

The results of this study showed high inter-individual variability, both in the size of the response (initial increases of 4% to 368%) which for some participants may not have exceeded the error of the measure[240], and the pattern of the response (illustrated in Figure 3-7). High inter-individual variability is also seen following traditionally-delivered PAS[241-243] and other neuromodulatory interventions[212]. This variation in response is not only influenced by the intervention and the measuring technique, but also by factors such as age, gender and genetics[212]. Given this high inter-individual variability[212,241-243], it is promising that in this study, corticomotor excitability was increased in all ten participants, even if the response was variable.

One potential source of variability in response to the intervention was the use of imagined, rather than voluntary movement. Imagined movements were used in this study to enable comparisons with previous novel-PAS studies conducted in healthy people. However, the ability to perform motor imagery varies between individuals[244], a factor which may have

contributed to the variability in the response to the intervention. In addition, there is considerable between-trial variability across an individual's MRCP epochs, and this is greater with imagined movements[245]. This inconsistency may have contributed to an inaccurate estimation of the PN. The substantial within-subject variability in PN reinforces this. However, even with the possibility of participants having difficulty with the imagery task and the potential for mismatched pairings, novel-PAS still resulted in significant increases in corticomotor excitability. That said, future studies might show greater neuromodulatory effects if novel-PAS is applied during voluntary movements. The accuracy of matching pairings could also be improved with the use of a BCI[201] which can detect the onset of each MRCP, as described in Chapter 2 (refer to 2.3.1). This may better accommodate for the between-trial variability in MRCP epochs.

### 3.5.3 STUDY LIMITATIONS

While previous research has demonstrated that control interventions of imagined movement alone, and electrical stimulation alone, do not increase corticomotor excitability[200-202], this study may have been strengthened by the inclusion of control interventions. A further limitation of this study is that the participants were healthy, rather than people with stroke. As noted in Chapter 2, significant increases in TA MEP amplitudes have been measured for 30 minutes following novel-PAS in people with stroke[204]. This supports the generalisability of this study's findings to people with stroke, although this needs to be confirmed with additional research.

This study recorded MEPs at a single TMS intensity of 120% RMT. This intensity had revealed the greatest treatment effects in previous novel-PAS research[200] and reflects other lower limb PAS literature[173,246] and TMS guidelines[112]. It was not considered appropriate to record MEPs at a range of TMS intensities as measures obtained from stimulus-response curves are less reliable than MEP amplitude data[235,236].

This study did not seek to elucidate the mechanism underlying the neuromodulatory effects of novel-PAS, and thus does not add any further understanding to the proposed mechanism discussed in Chapter 2 (refer to 2.3.1).

## 3.6 SUMMARY

This study showed that novel-PAS, delivered by pairing imagined movement with peripheral electrical nerve stimulation, can increase corticomotor excitability for at least 60 minutes in

healthy individuals. These findings will allow clinicians and researchers to make important decisions about the timing of novel-PAS within a standard rehabilitation session and the timing of its outcome measurement in the research context. In relation to this thesis, these findings have implications for the planning of Study B, which involves time-consuming post-intervention measures of corticomotor excitability. These findings indicate that as long as measures are collected within 60-minutes post-intervention, they are likely to capture the neuromodulatory effect.

Further research is needed to confirm if these findings can be replicated in people with stroke. However, given that previous novel-PAS research has shown similar effects in healthy and stroke populations, it is considered likely that a similar response could occur in people with stroke.

# Chapter 4.

# Study B.

# Pilot randomised controlled trial

## 4.1 PROLOGUE

The previous chapter established the duration of corticomotor excitability following novel-PAS in healthy people. This knowledge has been incorporated into the next research protocol, to ensure within-session measures are collected within the period of increased corticomotor excitability. This chapter presents Study B, a four-week pilot RCT in people with chronic stroke. The study aims to address the second and third research questions identified in Chapter 2 concerning the feasibility of delivering multiple sessions of the novel-PAS intervention, and the within-session effects of novel-PAS, in people with stroke.

## 4.2 INTRODUCTION AND OBJECTIVES

Chapter 2 recommended that further high-quality research be carried out to determine the within-session and cumulative effects of novel-PAS on corticomotor excitability and motor recovery in people with stroke. While novel-PAS is viewed as a potential adjunct to standard rehabilitation, initial research has indicated that it may result in improvements in lower limb impairment and function when applied in isolation[204]. Therefore, the following study investigates novel-PAS as a stand-alone intervention, as a preliminary step to testing its efficacy as a rehabilitation adjunct.

It was identified that an investigation of the cumulative effects of novel-PAS would be best accomplished with an RCT comparing the effects of novel-PAS with those of a sham intervention. However, prior to carrying out a fully-powered RCT, the feasibility of both the RCT protocol, and the novel-PAS intervention, needed to be tested to ensure that the future

trial would be achievable and acceptable. This objective was addressed by carrying out a pilot RCT, which utilises an RCT design to evaluate the feasibility of the trial protocol in preparation for a larger study[247]. As previous novel-PAS studies have not reported on the experiences of people with stroke (refer to 2.3.5), a factor considered essential for the development of complex interventions (refer to 1.6.3), this study also sought to understand the perspectives of people with stroke and to identify potential barriers to the implementation of novel-PAS in rehabilitation practice. As well as establishing feasibility, another objective of the study was to provide knowledge about the most appropriate and responsive outcome measures for a future trial. Therefore, a range of outcome measures were selected, to represent activity, impairment, and neurophysiological outcomes of interest[54,204,248-253]. A final objective of the study was to assess the within-session effects of novel-PAS on corticomotor excitability, as previous research in the stroke population was limited to just a single study, which had potential for bias[204] (refer to 2.3.4).

The research questions were:

1. *Is the planned RCT research protocol feasible?*

   This was assessed in relation to the following indicators of feasibility:

   - Recruitment: Twenty participants are recruited to the study within a four-month timeframe.
   - Retention: Drop-outs do not exceed 20%[254,255].
   - Protocol deviations: Any protocol deviations can be addressed with minor modifications to the protocol.
   - Data completeness: At least 90% of planned outcome measurements are recorded.
   - Acceptability: Participants deem the research protocol acceptable.

2. *Is the four-week novel-PAS intervention feasible?*

   This was assessed in relation to the following indicators of feasibility:

   - Adverse events: No adverse events related to the intervention are reported.
   - Adherence: At least 80% of novel-PAS sessions are delivered.
   - Intervention fidelity: At least 80% of the delivered novel-PAS interventions are undertaken according to the intervention protocol.
   - Acceptability: Participants deem the intervention acceptable.

3. *Following a four-week novel-PAS intervention, what are the estimates for the magnitude of the treatment effect and the variance, in a range of activity, impairment and neurophysiological outcomes?*

   This knowledge will enable the selection of appropriate and sensitive measures for a future trial and provide estimates for a sample size calculation.

4. *What are the within-session effects of novel-PAS on corticomotor excitability in people with stroke?*

   This will enable the confirmation of findings from previous novel-PAS research.

## 4.3 METHOD

### 4.3.1 STUDY SETTING AND DESIGN

This study was a double-blind pilot RCT. Participants were randomly assigned to receive either four weeks of a novel-PAS intervention, or an attention- and dose-matched sham intervention. Participants were aware they would be randomised to one of two intervention groups but were advised the groups were moderate-intensity and low-intensity interventions and remained blinded to randomisation. Measures were collected before and after the four-week intervention period to assess the cumulative effects of novel-PAS on activity, impairment, and neurophysiological outcomes. Selected outcomes were also collected at the first intervention session of each week (four time-points) to determine the *between-session* effect on ankle dorsiflexion strength, MRCP parameters, and corticomotor excitability. At these weekly time-points, corticomotor excitability was recorded prior to and immediately following the intervention, to determine the *within-session* effects of novel-PAS. Semi-structured interviews were conducted with participants to explore their experiences of the intervention and research process. The researcher performing outcome measurements, data processing and data analysis remained blinded to randomisation until all data processing and analysis was complete. This study was undertaken at the Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand.

### 4.3.2 PARTICIPANTS

#### Sample size

A sample of 20 participants, with 10 in each arm, was considered sufficient to estimate the variance in activity, impairment, and neurophysiological measures that would be potential outcomes in the future RCT. This sample size was also powered to detect within-session

effects on corticomotor excitability, according to a sample size calculation carried out with unpublished healthy data obtained from Aalborg University (Jochumsen, M.). Unpublished data was required, due to the insufficiency of information available in published data[200]. The sample size calculation indicated that six participants per group would enable the detection of statistically-significant differences in within-session measures of corticomotor excitability (80% power, alpha 0.05).

## Inclusion criteria

Volunteers were considered for inclusion in the study if they met the following criteria:

- Over 18 years of age
- Single stroke more than 6 months previously
- Hemiparesis affecting their ability to walk
- Gait speed between 0.05-1.2 m/s

## Exclusion criteria

Volunteers were excluded if they had any of the following conditions:

- Significant cognitive, perceptual or communication deficits
- Medical conditions that would impact the safety of the participant or the reliability of the results, as determined by the researcher during screening of the medical history
- Cerebellar stroke
- Contra-indications or cautions to TMS
- Inability to tolerate TMS
- No TA MEP in response to TMS

## Ethical and cultural considerations

Ethical approval was granted by AUTEC (Appendix F). The study did not specifically target participants of any particular ethnicity. However, due to the higher rates of stroke in the Maori population, a consultation process was entered with the Matauranga Maori Committee, to ensure the study supported participation of Maori. The study was registered with the Australian New Zealand Trials Registry (Trial ID ACTRN12615001380583).

### 4.3.3 STUDY PROCEDURE

#### Recruitment strategy

Participants were recruited through general practitioner practices, private and public neurological physiotherapists, verbal presentations to health providers and support groups, and collaboration with Laura Fergusson Trust and Akoranga Integrated Health Clinic, involving a mail-out to their databases of current and former clients with stroke.

#### Screening and consent

All potential participants who expressed an interest in the study were provided with the participant information booklet (Appendix G). Potential participants were screened for eligibility over the telephone by a trained research physiotherapist, who sought information about relevant medical conditions, medications, and contraindications or cautions to TMS (Appendix H). On telephone-screening, potential participants who met the study criteria were offered a face-to-face appointment to: screen health information in person, confirm presence of a hemiparesis, confirm gait speed criteria, have any questions answered, and obtain written consent (Appendix I). Potential participants had been made aware that TMS screening was required prior to final entry into the study, and this was performed after consent but prior to randomisation. If there was no TA MEP response to TMS stimulation or the participant could not tolerate the stimulation, they were excluded from the study.

#### Randomisation

After giving consent, and if TMS was tolerated, participants were randomly allocated via a computer-generated randomisation schedule, which was held by a third party. The randomisation sequence was generated using a randomisation website[256]. Participants were randomised to receive either the novel-PAS intervention (n=10) or the sham intervention (n=10).

#### Study flow

The study flow is outlined in Figure 4-1. Following recruitment, screening and randomisation, there was a baseline measurement phase, a four-week intervention phase and a post-intervention measurement phase.

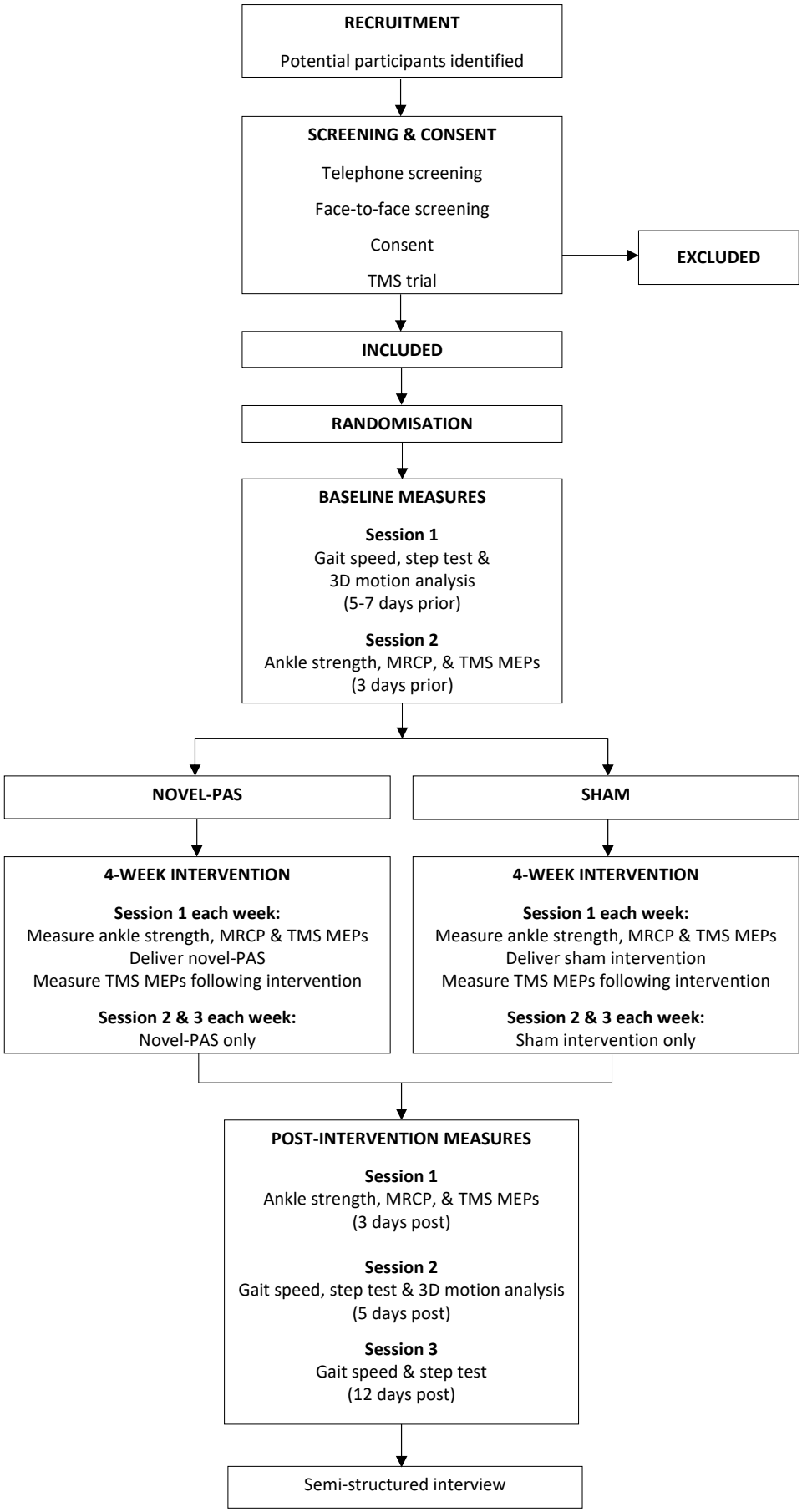



Figure 4-1 Study flow for Study B

### Baseline measures

There were two baseline measurement sessions. The first session took place 5-7 days prior to the start of the intervention phase and involved measuring gait speed, the step test, and 3D motion analysis. The second session took place 3 days prior to the start of the intervention phase and involved ankle strength, MRCP and TMS measures.

### Four-week intervention

The intervention phase involved delivery of either the novel-PAS or sham intervention, three times per week, for four weeks. During the first session of each week, measures of ankle strength, MRCP, and TMS MEPs were collected prior to the intervention. TMS MEPs were also collected immediately following the intervention to measure the within-session effect of novel-PAS on corticomotor excitability. The second and third session of each week involved the delivery of the intervention only.

### Post-intervention measures

There were three post-intervention measurement sessions. The first session took place 3 days post-intervention and involved ankle strength, MRCP and TMS measures. The second session took place 5 days post-intervention and involved measuring gait speed, the step test, and 3D motion analysis. The third session took place 12 days post-intervention and involved measuring gait speed and the step test. A semi-structured interview took place approximately four weeks after the third post-intervention measurement session.

## 4.3.4 OUTCOME MEASURES

### Feasibility measures for research protocol

- **Recruitment**

During the recruitment phase, records were kept of the number of participants screened and included, and reasons for exclusion.

- **Retention**

The number of participants who dropped out of the study was recorded with the reason given.

- **Protocol deviations**

Any deviations from the described protocol were recorded. In addition, at the beginning of each session, participants were asked about any confounding factors which may have influenced the outcome measures, including changes to their medications, new medical issues, pain, therapy or exercise in the previous two days, and caffeine consumption that day.

- **Data completeness**

Missing outcome measures were recorded with the reason for these.

## Feasibility measures for novel-PAS intervention

- **Adverse events and safety**

Safety was monitored by recording any medical or physical changes at the beginning of each session, and any changes during the session. Any adverse events were recorded on an adverse events form (Appendix J).

- **Adherence**

Session attendance and the reason for any missed interventions was recorded in an attendance register.

- **Intervention fidelity**

Intervention fidelity was assessed according to whether the intervention was delivered according to the protocol[257]. This was monitored through written records made during each session; data included the electrical stimulation intensity and pulse width, PN timing, blinded group allocation (novel-PAS or sham), and repetitions completed. To assess the accuracy of the PN timing used in the intervention, the PN calculated during the MRCP recording (in-session analysis) was compared with the PN calculated during the data processing phase (post-hoc analysis).

- **Acceptability - Semi-structured interviews**

A researcher experienced in interviewing, and not involved in any other aspects of data collection or intervention delivery, conducted semi-structured interviews with each participant. The primary aim of the interview was to evaluate the acceptability of the research protocol and the novel-PAS intervention from the perspective of the person with stroke. While the interviews were intended to allow open-ended discussion, the interviewer followed an interview guide to ensure that certain aspects were covered. These included asking the

participants how they felt about the research process and the intervention, their understanding of the intervention, any positive or negative effects of being involved, their opinions about the visual cue, and their ideas for future development of the intervention and research protocol.

## Activity measures

- **Comfortable-paced and fast-paced gait speed**

Comfortable-paced gait speed as described by Lam et al[258] has excellent reliability in people with stroke. The reliability and validity of fast-paced gait speed has also been demonstrated in people with stroke[43].

## Impairment measures

- **Step test**

The step test involves stepping one foot on and off a 7.5cm step as many times as possible in 15 seconds and is a valid and reliable measure of dynamic balance in people with stroke[259,260]. The step test is an impairment-based measure, but is associated with measures of physical function in people with stroke[261]. While the step test is responsive to change, it does have a floor effect due to the difficulty of the task[262].

- **Ankle dorsiflexion strength**

Maximum voluntary isometric contraction (MVIC) is a measure of isometric muscle strength. This measure has moderate reliability for the ankle dorsiflexor muscles in people with stroke[263].

- **Gait pattern**

3D motion analysis is a widely-used method for evaluating changes in an individual's gait pattern that occur in response to a research intervention[264]. The measures of interest were peak dorsiflexion angle during the swing phase of gait and step-ups, gait speed, step length, swing time, and step-up time. 3D motion analysis has shown high between-session reliability for measuring ankle joint dorsiflexion and plantarflexion movements in both healthy and stroke populations[264,265] and can reliably measure a range of spatiotemporal gait parameters[266].

- **Gait variability**

Gait variability refers to the step-to-step fluctuations in gait features, and is a gauge of walking performance which is altered after stroke[73,267]. This is thought to be due to reduced

neuromuscular control[73]. The SD of each of the following gait parameters was used as a measure of gait variability: peak dorsiflexion during the swing phase of gait, peak dorsiflexion during step-ups, and step-up time[73,268,269]. Another measure of gait variability called the variation ratio (VR) was acquired from EMG data, and this will be described in the next section on 'Neurophysiological measures'.

## Neurophysiological measures

- **Visual analysis of tibialis anterior EMG waveforms during gait and step-ups**

Surface EMG provides information about muscle activation patterns[270]. Visual analysis of EMG waveforms is a recognised method for comparing two sets of EMG data (e.g. pre- and post-intervention, or healthy and stroke)[271]. It involves describing the bursts of muscle activity and their temporal pattern[272] and ranking the bursts of activity on an ordinal scale (e.g. absent, inconsistent, present)[271]. This method allows comparison of the entire EMG waveform at an individual level, rather than reducing data to measurable parameters, which may mask important differences in muscle activation patterns within or between individuals[271,272].

- **Variation ratio of tibialis anterior EMG waveforms during gait and step-ups**

The VR represents the variability in EMG waveforms between gait cycles, with values closer to zero indicating more similarity in waveforms, and values closer to one indicating less similarity[250,273]. The VR for the TA muscle in healthy adults is 0.18 to 0.38[273], but in pathological conditions, can be either higher or lower[250] indicating increased or decreased variability.

- **Rate of tibialis anterior EMG rise during step-ups**

The slope of the EMG envelope in the first 100ms of a force production task (the rate of EMG rise) and is an indicator of neuromuscular activation, and is reduced in the hemiparetic limb of people with stroke[54,274].

- **Movement-related cortical potential**

The MRCP was recorded to inform the timing of the novel-PAS intervention but was also an outcome measure. The amplitude of the MRCP is thought to reflect the effort required to perform a motor task[275], as demonstrated by lower amplitudes in expert performers[276,277], increased amplitudes when learning a motor task[251], and decreased amplitudes once a motor

skill is acquired or performance improvements have plateaued[232,251,278]. This has led to the use of the MRCP as a measure of motor recovery following rehabilitation[252].

- **Corticomotor excitability**

TMS-induced MEPs of the TA were used as a measure of corticomotor excitability. As it is not always possible to produce a MEP in the resting muscle of people with stroke[279], TMS was applied during a 10% MVIC of the ankle dorsiflexor muscles to produce an *isometric MEP*. MEPs produced in the lower limb of people with stroke under these conditions have excellent within-session reliability but poor between-session reliability[236,280,281]. Therefore, TMS was also applied during a functional step-up task to produce a *step-up MEP*. This functional technique was proposed to have better between-session reliability, based on previous findings of high between-session reliability of soleus MEPs produced during treadmill walking in people with stroke[280].

### 4.3.5 PROCEDURES AND PROCESSING FOR OUTCOME MEASUREMENTS

## Clinical measures

Six-metre (6-m) walk tests[258] were recorded in a carpeted hallway with ankle foot orthoses (AFOs) removed. Three trials of both comfortable- and fast-paced gait speed were performed, with 2-minutes of rest between each trial. The mean comfortable-paced gait speed and the mean fast-paced gait speed were calculated from the three trials (in m/s).

The step test[259] was completed on both legs. Hand support and AFOs were not used, but a rail was nearby for safety. The number of steps completed for each leg during the step test was used for analysis.

## 3D motion analysis and EMG

The gait lab consisted of a calibrated 8-metre walkway with two force plates, and a nine-camera motion analysis system sampling at 120 Hz (Qualisys AB, Sweden). The cameras were calibrated in preparation for data collection. Participants wore a singlet and loose shorts. Bare feet were preferred, but when this was not possible due to discomfort walking barefoot (n=2), the same shoes were worn on both test occasions. Bipolar surface electrodes (Norotrode 20, Myotronics, Washington) were placed over the bilateral TA and soleus muscles following skin preparation (shaving, abrasion with sandpaper or abrasive gel, and cleaning with alcohol). The TA EMG electrodes were placed a third of the way along the

line between the head of the fibula and the tip of the medial malleolus, and the soleus EMG electrodes were placed two-thirds of the way along the line between the medial femoral condyle and the medial malleolus[231]. For all EMG electrode placements during this study, impedance was checked with a digital multimeter to ensure a level below 5KΩ. If this was not achieved, skin preparation was repeated, electrodes were re-placed, and impedance was rechecked. Wireless EMG sensors (DTS, Noraxon USA Inc., Arizona) were connected to the EMG electrodes and attached to the adjacent skin with double-sided and hypoallergenic tape. Retro-reflective 18mm markers were attached to the participant with double-sided and hypoallergenic tape, according to the modified Helen Hayes model (refer to Figure 4-2). This included 25 markers attached to anatomical landmarks, and two pairs of markers fixed to lightweight rods that were attached to the thigh and lower leg. The 3D position of each marker was captured and saved in Qualisys Track Manager software (Qualisys AB, Sweden). The EMG data was sampled at 1500 Hz using the Clinical DTS system (Noraxon USA Inc., Arizona) and integrated with the 3D motion data in Qualisys Track Manager.

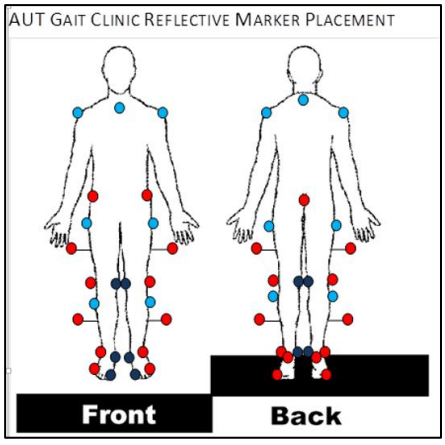



Figure 4-2 Modified Helen Hayes model used for marker placement

Following recording of a static standing posture, which was used as a reference for the biomechanical model, six markers on the medial knees, ankles and feet were removed to avoid these influencing the participant's movement. 3D motion and EMG were captured during two tasks. Firstly, participants walked along the 8-metre gait walkway 4-6 times, with rests in-between, until at least 12 gait cycles of good quality had been collected. Secondly, they stood in front of a 19cm standard-height step and stepped their hemiparetic foot on and off the step 10 times. This measure was designed to replicate the motion required of the hemiparetic foot when climbing steps on a standard flights of stairs, and was collected separately from the step test (referred to above) which measured stepping ability on both legs using a 7.5cm step. Participants did not wear AFOs but were permitted to use their

walking aid for walking trials and to place their non-paretic hand on the back of a chair during step-up trials.

Following data collection, the markers in each trial were manually assigned to the gait model. Gaps were automatically filled using a polynomial algorithm, or, if this was not satisfactory, trials were trimmed to remove the section with gaps. The data was exported to Visual 3D software (C-Motion Inc., Maryland), where gait events were identified using visual analysis and graphs of the kinematic trajectories for the heel markers. The events were heel-strike and toe-off for gait, and heel-off and heel-on, for step-ups. Graphs of kinematic data were produced and visually inspected. Due to the possibility of variation in ankle marker placement between sessions[264], the peak dorsiflexion angle was calculated in *degrees from neutral*. The neutral ankle angle was measured in a period of quiet stance, with a consistent level of force through the hemiparetic leg. A pipeline was created to extract kinematic and spatiotemporal parameters: peak hemiparetic dorsiflexion angle during the swing phase of gait and step-ups (mean and SD), mean gait speed, mean step length, mean swing time, and hemiparetic step-up time (mean and SD). If the number of available parameters differed between pre- and post-measures, the minimum number was used.

TA EMG data was exported to Visual 3D and resampled at 1560Hz, and then exported to MATLAB software (MathWorks, Massachusetts). The data was bandwidth filtered at 10-150Hz[250,271,282-284], full-wave rectified, smoothed using a 10Hz low-pass filter (5$^{th}$ order Butterworth) to create a linear envelope, and time-normalised to 1001 samples for gait cycles[285] and 501 samples for step-up cycles (refer to Appendix K for details). While EMG data is often amplitude-normalised to a reference value, such as the MVIC[286], to account for between-session variability[287], time-demands did not allow for additional MVIC measures and therefore outcomes were chosen that did not require amplitude normalisation. The plotted envelopes were visually inspected for burst characteristics present in healthy gait and step-ups. For gait data, cycles were inspected for two bursts: a high-amplitude burst shortly after heel-strike (heel-strike burst) and a medium-amplitude burst starting at toe-off and peaking around mid-swing (toe-off burst)[288]. These bursts were ranked by the researcher on an ordinal scale as present (in >80% of trials), inconsistent (present in less than 80% of trials) or absent, and other visible changes were described. For step-up data, cycles were inspected for a single burst of activity which starts as the toe lifts off the floor and ends as the heel strikes the step[289] and burst patterns were described. The VR of the TA EMG waveforms was calculated for both gait and step-up trials, for pre- and post-intervention measures[250,267,273]. For the calculation of EMG rise, the data was bandwidth filtered at 10-500Hz[283], full-wave rectified, and smoothed using a moving average technique[290], with a

moving window of 192ms (300 samples). This smoothing technique was chosen over two other smoothing methods (50-100ms moving average and enveloping via a 10Hz low pass filter) because it produced a smooth shape without compromising the pattern of underlying rectified signal. The TA onset was identified using a computerised approach[291] and confirmed by visual inspection. Illustration of the rectified signal, moving average envelope and EMG onset can be seen in Appendix K. The first 100ms of the moving average envelope was plotted for each step-up trial[54], and the mean slope of all trials was used to determine the rate of EMG rise[292,293].

## Strength test

Ankle dorsiflexion strength was established by completing three, 3-5 second MVICs, with two minutes of rest between each contraction. The participants sat in a high-backed arm chair with the hemiparetic leg supported on a rigid force plate, and immobilising straps at the waist, lower leg and foot (approximate joint angles were 100° hip flexion, 25° knee flexion, and 0° dorsiflexion) (Figure 4-3). Loud verbal encouragement and visual feedback via an oscilloscope (TDS2014B, Tektronix, New Zealand) was provided. Force data was collected using a single point load cell (Model PTASP6-E, Precision Transducers Ltd, New Zealand), with a capacity of 300 kilograms and error < 0.02%. Force signals were sampled at 100Hz using a data acquisition board (Micro1401, CED, UK) and Signal software (CED, UK).

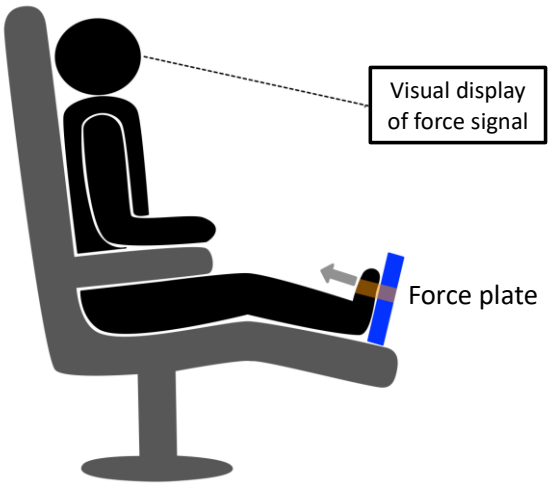



Figure 4-3 Set up for isometric strength test in Study B

The MVIC was calculated by measuring the peak amplitude of the highest trial and subtracting the mean baseline value in a period of rest. This was calculated immediately during the testing session, so that the 10% MVIC value could be used in the TMS

measurements. Processing was performed in Signal Software (CED, UK). Force values were converted from volts to newtons (N) according to a scaling factor determined from calibration data.

## Movement-related cortical potential

Participants remained seated while the force plate was removed (Figure 4-4). Participants then practised at least 25 repetitions of attempted hemiparetic dorsiflexion, in time with the visual cue described in Study A (refer to Figure 3-3), before performing 50 repetitions for the MRCP recording. Instructions were given to reduce blinking and movements of other body parts. The EEG set-up has been previously described in Study A (refer to 3.3.4), with the only variation being that the ground electrode within the cap was used, rather than a disposable electrode applied to the forehead. Continuous EEG data was recorded by an amplifier with a sampling frequency of 500Hz and 32 bits accuracy (NuAmps 40 channel digital EEG and ERP amplifier and SCAN software, Compumedics Neuroscan, Australia).

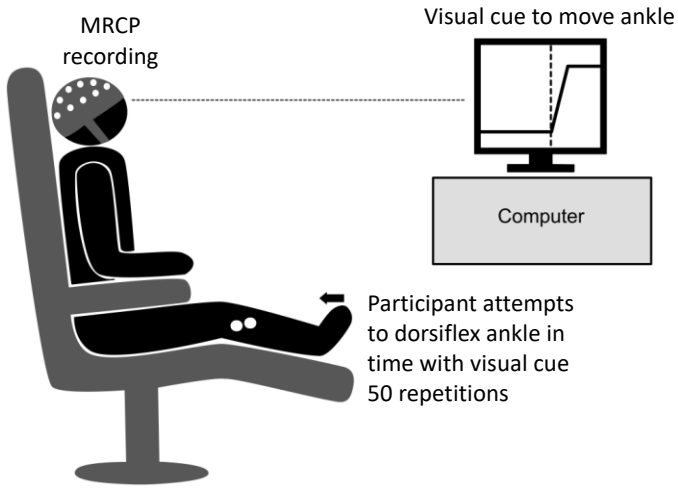



Figure 4-4 Set up for MRCP recording in Study B

During the MRCP recording, surface EMG of the TA was also collected to allow the MRCPs to be referenced to the onset of TA activity. Surface EMG electrodes (Blue sensor N, Ambu, Denmark) were placed over the hemiparetic TA following skin preparation. Two electrodes were placed a third of the way along the line between the head of the fibula and the tip of the medial malleolus[231]. A reference electrode was placed on the lower third of the anterior border of the tibia. The EMG was amplified (AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz using a data acquisition board (Micro 1401, CED, UK) and Signal software (CED, UK).

The MRCP was processed during the testing session (*in-session* analysis) using the method described in Study A to attain the PN timing (refer to 3.3.4). Following data collection, the MRCP data was processed a second time, to enable analysis of the morphology of the MRCP (*post-hoc* analysis). The raw EEG and TA EMG data from 50 repetitions of cue-based dorsiflexion was imported in 4.5-second epochs into a custom-built MATLAB programme, where it was band-pass (128-500Hz) and laplacian filtered around the Cz electrode, and the epochs were visually screened for exclusion. Epochs were excluded if there was no general downward slope for ≈ 2 seconds before the cue, a point of negativity ≈ 500ms either side of the cue (this window could be widened if the PN fell consistently early or late), or if they contained eye movement artefacts near the PN range[200]. The TA EMG data was visualised but due to missing data, poor visibility of the EMG signal due to low levels of EMG in people with stroke[294,295], and difficulty matching the EMG epochs with the EEG epochs, this TA EMG data was not processed further. Following the screening of epochs, the raw EEG data from included epochs was processed in MATLAB; the data was band-pass filtered at 0.05-1Hz, laplacian filtered around the Cz electrode, notch-filtered at 49-51Hz, and divided into 3-second epochs time-locked to the visual cue at the 2-second mark. An average of the MRCP epochs was plotted and the following parameters were calculated based in similar MRCP literature[296]: the mean MRCP amplitude 600-800ms before the PN (motor preparation phase 1 (MP1)), 200-400ms before the PN (motor preparation phase 2 (MP2)), and 100ms either side of the PN (mean PN), and the amplitude and timing of the PN.

## Transcranial magnetic stimulation

To reduce the effect of confounding factors on corticomotor excitability, participants were discouraged from exercising and consuming caffeine before assessment sessions, and were encouraged to maintain a consistent daily routine with sessions kept to the same time of day if possible[212].

For TA MEPs recorded during an isometric contraction (isometric MEPs), participants were seated with their hemiparetic leg secured to the force plate and a neoprene cap with 1x1cm gridlines secured to the head (Figure 4-5). The grid reference of the vertex was recorded to ensure consistent positioning of the cap. Monophasic TMS pulses were delivered as per Study A to identify the TA hot spot (refer to 3.3.4). If MEPs could not be seen, a small dorsiflexion contraction was performed. The hotspot grid reference was recorded and the TMS coil was secured to the hotspot with Velcro. Participants performed a 10% TA MVIC while observing a visual target on the oscilloscope. Single TMS pulses were applied to identify the AMT, defined as the TMS stimulation intensity required to produce 5/10 MEPs, with a

peak-to-peak amplitude of at least 50μV, during a 10% TA MVIC. Single TMS pulses were delivered at 120% AMT, every 7-8 seconds, at 8-12% MVIC, to produce at least 10 isometric TA MEPs.

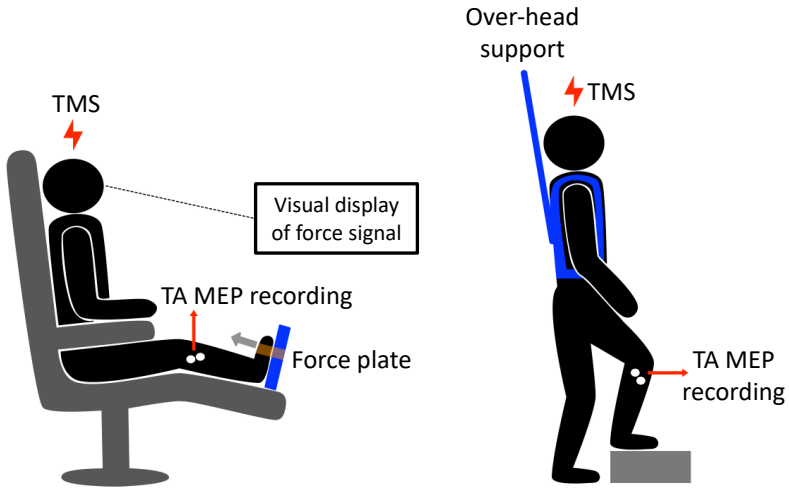



Figure 4-5 Set up for isometric MEPs (left) and stepping-MEPs (right) in Study B

For TA MEPs recorded during step-ups (step-up MEPs), participants were positioned next to a plinth, wearing a safety harness and a heel-switch, and were verbally-cued to step their hemiparetic foot on and off a 19cm step (Figure 4-5). Using the heel-switch as a trigger, the timing of the maximum TA EMG burst during step-ups was calculated during a 2-minute recording, with a custom-made MATLAB programme. The TMS coil was suspended from an over-head gantry and secured to the hotspot. Single TMS pulses were delivered during step-ups at the point of maximum TA burst, at 120% of AMT, until 10 step-up MEPs had been produced (this required 10-15 stimuli). Participants were perturbed by the stimulation, but were able to maintain their balance and complete the step-up task. For all MEP recordings, TA EMG was amplified (AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz using a data acquisition board (Micro 1401, CED, UK) and Signal software (CED, UK).

Following data collection, TA MEP trials were excluded if the participant was distracted, speaking, or moving inappropriately. The data was visually screened, and trials were excluded if the TMS was not triggered, the background activity during the 10% MVIC was too high or too low, or the TMS was improperly timed during the step-up task. A notch filter of 49-51Hz was applied as needed for 50Hz noise. The background EMG activity was determined by measuring the area of each rectified signal in a 45ms window prior to TMS stimulation, and then averaging the 10 measurements. To distinguish MEP onset from background EMG activity, the MEP onset was determined from an average of the 10

rectified EMG signals[297], and defined as the point where the signal exceeded 2 SD of background EMG in a 45ms window prior to stimulation, for more than 3ms. The TA MEP amplitude of each signal was determined by measuring the maximum peak-to-peak amplitude of each MEP, in a 30ms window starting 2ms prior to MEP onset, and then averaging the 10 measurements. The TA MEP area of each signal was determined by measuring the area of each rectified signal, in a 30ms window starting 2ms prior to MEP onset, and then averaging the 10 measurements[281].

### 4.3.6 PROCEDURES FOR INTERVENTIONS

#### Intervention set-up

To maintain consistency between the novel-PAS and sham interventions, the set up was exactly the same in both conditions. Participants were seated in a high-backed arm chair with hips flexed to 100º and legs supported with ankles resting in slight plantarflexion (refer to Figure 4-6). Electrical stimulation was applied over the dCPN according to the method described in Study A (refer to 3.3.4), with the only variation being the use of a movable bar electrode (two 8mm stainless steel disc electrodes, Digitimer Ltd, UK) that was fixed to the leg with tape. The intensity that produced a twitch contraction in the TA muscle was used in the subsequent novel-PAS intervention. Participants were re-oriented to the visual cue. The blinded assessor then left the laboratory and a research assistant controlled the delivery of either the novel-PAS or sham intervention.

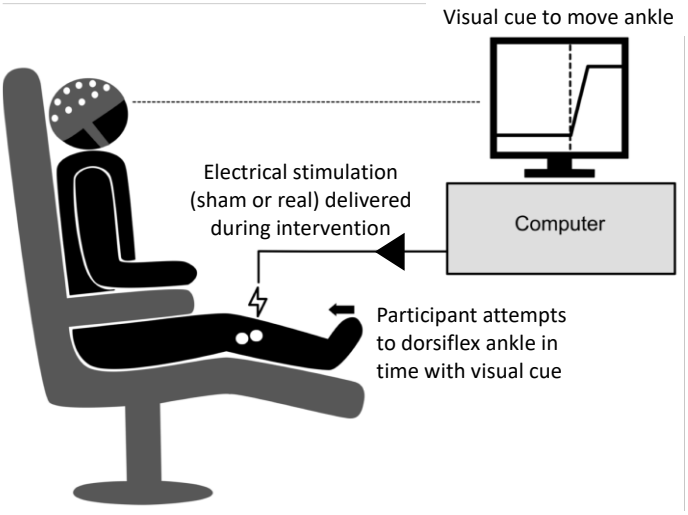



Figure 4-6 Delivery of novel-PAS and sham intervention in Study B

### Novel-PAS intervention

Participants completed 50 repetitions of attempted hemiparetic ankle dorsiflexion, in time with the visual cue, while the computer delivered single pulses of electrical stimulation to the dCPN (refer to Figure 4-6). Using the method described in Study A (refer to 3.3.4) each pulse of electrical stimulation was timed to arrive in the M1 at the PN of the MRCP. The novel-PAS intervention lasted approximately 15 minutes.

### Sham intervention

The electrical stimulation was switched to sham mode, so that a small light continued to flash but no electrical stimulation was delivered. Participants completed 50 repetitions of attempted hemiparetic ankle dorsiflexion, in time with the visual cue, while the computer delivered sham electrical stimulation. The sham intervention lasted approximately 15 minutes.

## 4.3.7 DATA ANALYSIS

### Quantitative data

All feasibility measures were descriptively analysed (mean, percentage). Measures of activity, impairment, and neurophysiology were descriptively analysed (mean, SD, range), except for the descriptive analysis of EMG waveforms which has been described in section 4.3.5.

To estimate the magnitude of any cumulative treatment effects and provide information for a future sample size calculation, an analysis of covariance was planned. To determine the within-session effects of novel-PAS on corticomotor excitability, a two-way repeated-measures ANOVA with factors of *'time'* and *'group'* was planned, with post-hoc t-tests to establish the source of any interaction effects.

### Qualitative data

Interview transcripts were analysed using thematic analysis conducted using a realist framework, which proposes that people's words provide access to their reality[298]. The data was approached inductively, where codes and themes were developed from the raw data, rather than from pre-determined theories[298]. The purpose of the interview material was to answer two questions related to acceptability:

- *Is the RCT protocol acceptable to people with stroke?*
- *Is the novel-PAS intervention acceptable to people with stroke?*

The interview data was transcribed verbatim and then printed. A familiarisation process took place where the material was read, and casual observations, ideas, and questions were noted down. The data was then imported into NVivo software (QSR International Pty Ltd, Australia) for coding. Material that was not related to acceptability was removed. Each sentence, or group of related sentences, was coded *semantically*, so that the code gave a literal understanding of the raw material. The codes were grouped into subgroups in NVivo and then printed on individual pieces of paper and grouped into overall themes. The raw content was checked to ensure it fitted with the overall themes, and themes were adjusted, added or removed as appropriate. The themes and initial codes were presented on four large posters to another researcher to confirm the interpretation of the data into themes. The themes were then discussed with the wider research team and iterated. A single quote was chosen to represent each theme, and the themes were summarised in paragraphs, with additional example quotes.

## 4.4 RESULTS

### 4.4.1 FEASIBILITY OF THE RESEARCH PROTOCOL

Recruitment was initiated in March 2015, and data collection was carried out between April 2015 and March 2016.

#### Recruitment

Twenty-seven people expressed an interest in the study over the 11-month recruitment period and six participants were enrolled. Reasons for exclusion at each phase of the screening process are outlined in Figure 4-7. Six out of 27 people declined to commit due to the time involved and 10 out of 27 people were excluded due to reasons related to TMS.

#### Retention

Two participants dropped out at baseline (refer to Figure 4-7). The reasons reported were an unrelated back injury (n=1) and an unrelated ankle fracture (n=1). Despite the reason for withdrawal being unrelated injuries, these participants did not want to re-join the study at a later date due to other commitments. The other four participants completed the four-week intervention.

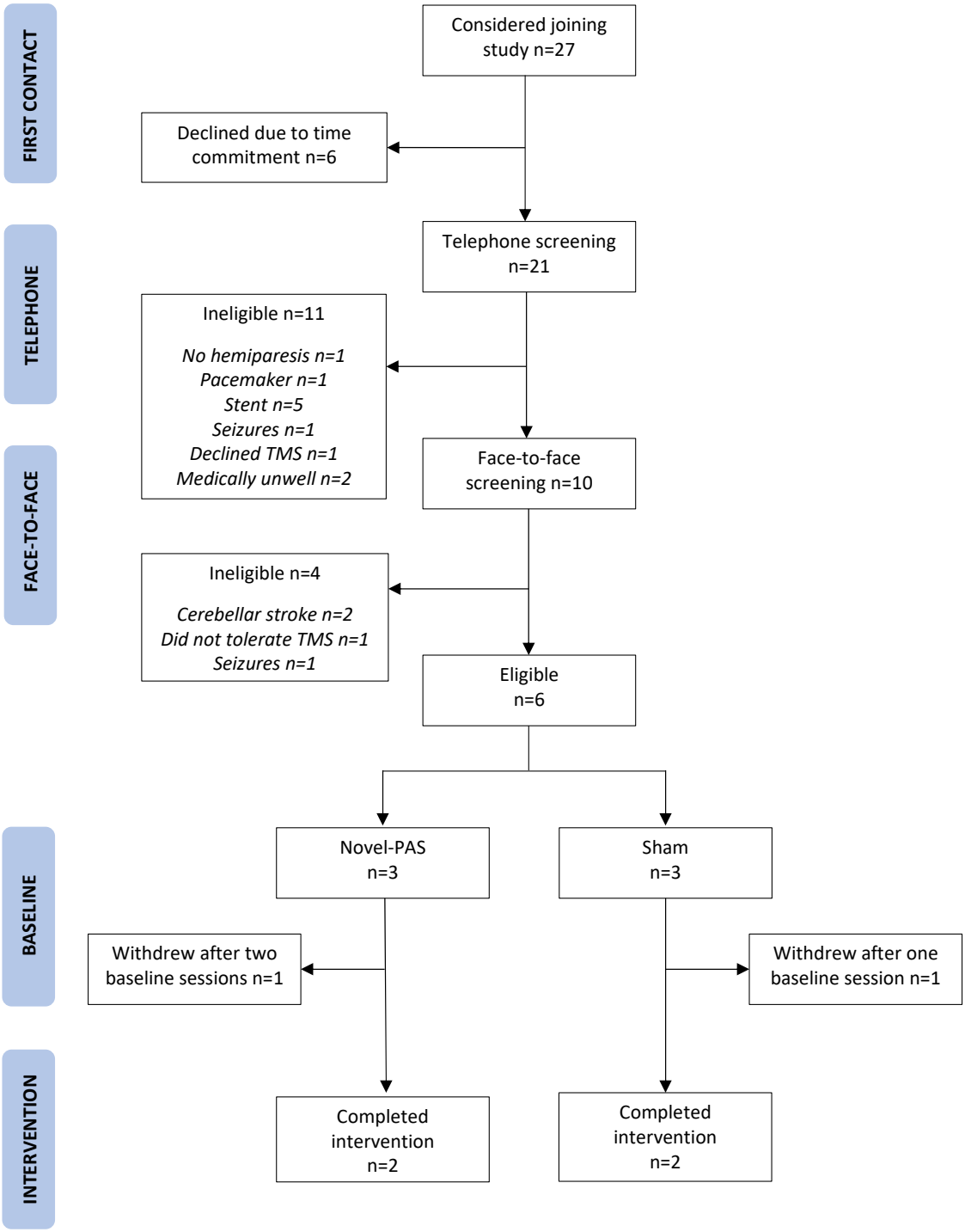



Figure 4-7 Recruitment and retention for Study B

## Sample characteristics

Sample characteristics are shown in Table 4-1. The participants had a mean age of 69.5 years, and a mean gait speed of 0.43 m/s, indicating substantial disability[214].

Table 4-1 Sample characteristics

| Participant | Gender | Age (years) | Hemiparesis | Time since stroke | Outdoor gait aids | Gait speed (m/s) |
|---|---|---|---|---|---|---|
| Completed four-week intervention (n=4) | | | | | | |
| 1 | Male | 75 | Right | 5 years | Stick | 0.35 |
| 2 | Female | 61 | Left | 17 years | Quad-stick | 0.29 |
| 4 | Male | 64 | Right | 1 year | 4-wheel frame | 0.75 |
| 6 | Female | 78 | Right | 9 months | 4-wheel-frame | 0.33 |
| | Male n=2 Female n=2 | Mean 69.5 years | Right n=3 Left n=1 | Mean 7.2 years | 4-wheel frame n=2 Quad-stick n=1 Stick n=1 | Mean 0.43 m/s |
| Drop-outs at baseline (n=2) | | | | | | |
| 3 | Female | 57 | Left | 7 years | Quad-stick | 0.22 |
| 5 | Female | 54 | Right | 7 years | 4-wheel frame | 0.23 |

## Protocol deviations

Protocol deviations are outlined in Table 4-2 and a full description is provided in Appendix L. The research team agreed to a major protocol deviation to reduce the time requirements of the study in response to participant feedback, as the original protocol required participants to complete eight measurement sessions, averaging 2.75 hours each. The length of these measurement sessions was longer than anticipated due to a range of factors including the technical requirements, equipment malfunction, the need for breaks, and extra time taken to move and position participants comfortably. Two protocol revisions were made, firstly to reduce TMS measures by recording only step-up MEPs in some sessions, and secondly to remove all MEP measures from weeks 2-4. This reduced the duration of the measurement sessions at the start of weeks 2-4 to 1.3 hours.

Table 4-2 Protocol deviations

| Stage of research process | Protocol deviation |
|---|---|
| Recruitment | Extended recruitment phase from 4-11 months |
| Measurement | Refined process for identifying TMS intensity when no isometric MEP was produced at maximum tolerable intensity (n=1) |
| Measurement | Skin preparation for electrode placement was not performed more than once for those at risk of skin breakdown |
| Measurement | Electrode impedance was not always below 5KΩ. |
| Measurement | Performed 6-m walk test next to wall (n=1) |
| Measurement | Used hip/knee flexion to recruit ankle dorsiflexors during TMS measures (n=1) |
| Measurement | Step height lowered for 3D motion analysis and TMS measures (n=1) |
| Measurement | Reduced number of outcome measurements during intervention phase |
| Measurement | Delayed and missed data collection (n=2) |
| Intervention | 20-day break during intervention phase (n=1) |
| Intervention | Potential miscalculation of PN timing due to missing data (week 1 and 2 of intervention, n=1) |
| Intervention | Miscalculation in PN timing due to miscommunication (6 intervention sessions, n=1) |
| Intervention | Error in pulse width used for electrical stimulation due to miscommunication (6 intervention sessions, n=1) |

## Data completeness

Total data completeness was 86%. Results for each outcome measure for all participants up to the point of withdrawal or study completion can be seen in Table 4-3. Missing data can be primarily ascribed to one participant missing two post-intervention measurement sessions due to an unrelated illness (4.6%), and due to technical difficulties recording and analysing the MRCP (1.1%) and EMG (7.5%) during cue-based ankle dorsiflexion movements. The lowest level of data completeness was 17% for TA EMG measures recorded during the MRCP recordings. This was due to the low level of visible EMG activity in people with stroke[294,295] and difficulty matching the EMG epochs with the MRCP epochs when some epochs were missing.

Table 4-3 Actual versus expected data completeness for outcome measures

| | | Comfortable gait speed | Fast paced gait speed | Step test | 3D motion analysis | EMG during gait | MVIC | MRCP | EMG during MRCP | TMS isometric | TMS step-ups | Interview |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | Expected | 6 | 6 | 6 | 6 | 6 | 9 | 8 | 8 | 9 | 9 | NA |
| | Actual | 6 | 6 | 6 | 6 | 6 | 9 | 6 Ø | 2 Ø | 9 | 8 Ø | NA |
| Intervention | Expected | NA | NA | NA | NA | NA | NA | 12 | 12 | NA | NA | NA |
| | Actual | NA | NA | NA | NA | NA | NA | 11 Ø | 1 Ø | NA | NA | NA |
| Post intervention | Expected | 8 | 8 | 8 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Actual | 7 ☆ | 7 ☆ | 7 ☆ | 4 | 4 | 3 ☆ | 3 ☆ | 1 ☆ Ø | 3 ☆ | 3 ☆ | 4 |
| % completed | | 92 | 92 | 92 | 100 | 100 | 92 | 83 | 17 | 92 | 85 | 100 |

Ø Missing data due to technical errors or poor data quality

☆ Missing data due to measures not being recorded for one participant due to unrelated illness

NA = Not applicable

### 4.4.2 FEASIBILITY OF THE NOVEL-PAS INTERVENTION

## Adverse events

There were no adverse events related to the novel-PAS or sham interventions.

## Adherence

Participants who started the intervention phase completed all 12 intervention sessions, with the exception of one session for one participant due to a public holiday.

### Intervention fidelity

Sessions which included just the intervention, but not outcome measures, lasted 27 minutes on average (range 19-46 minutes), where intervention delivery took 13 minutes. Seventy five percent of interventions were delivered according to the intervention protocol (50% of novel-PAS interventions and 100% of sham interventions). There were four deviations from the novel-PAS intervention protocol (Table 4-2). The first was an 11-day break midway through the intervention period for novel-PAS participant 4. The second deviation related to the loss of data during two MRCP recordings for novel-PAS participant 1, which may have affected the PN timing for the first two weeks of intervention. The third deviation related to a miscommunication about a minor change made to the MATLAB programme which plotted the MRCP, resulting in miscalculation of the PN for two intervention weeks for novel-PAS participant 4. A final deviation involved the use of a 2ms pulse width rather than 1ms. This deviation was considered unlikely to influence intervention efficacy[299] and was therefore excluded from intervention fidelity results.

In addition to these protocol deviations, there was a difference between the PN timing calculated *in-session* which was used to time the intervention, and the PN timing calculated *post-hoc* during the data processing phase, for the MRCP collected in week four for novel-PAS participant 1 (variation between the two PN values of 352ms). Differences between these two PN calculations was also observed for sham participant 2 during the first two intervention weeks, although this did not influence the fidelity of the sham intervention.

### Acceptability

Acceptability of the RCT protocol and the novel-PAS intervention will be discussed at the end of the results section (refer to 4.4.4).

## 4.4.3 ACTIVITY, IMPAIRMENT, AND NEUROPHYSIOLOGICAL OUTCOMES

As only four participants completed the trial, individual rather than group data is presented. Where available, reference values for the standard error of the measurement (SEM) and the smallest real difference (SRD) are given; these can be used to guide the interpretation of individual data[300]. The SEM represents the natural variation that occurs been two measurements as a result of biological variability and measurement error[301]. The SRD represents the range in which 95% of the differences between two measurements lie, and is used as an indication of whether true change has occurred beyond natural variation and

measurement error[300,302]. The SEM and SRD can also be expressed relative to the mean to give the SEM% and SRD%, which are irrespective of measurement units[302,303].

## Activity measures

- **Comfortable and fast-paced gait speed**

The results for comfortable- and fast-paced gait speed are presented in Table 4-4. In three participants, there were post-intervention decreases in comfortable-paced (n=2) and fast-paced (n=1) gait speed beyond the SEM, but these changes were not maintained one week later.

## Impairment measures

- **Step test**

The results for the step test are presented in Table 4-4. For two participants, the step test score on one leg *increased* beyond the SRD, and for one participant the step test score on one leg *decreased* beyond the SRD.

- **Ankle dorsiflexion strength**

The results for ankle dorsiflexion MVIC are presented in Table 4-5. As an indication of baseline stability, the change between the two baseline measures has been calculated, along with the post-intervention change. For participant 2, there was a post-intervention 34% increase in MVIC which exceeded the SEM%, but there was also a 21% change in baseline measures which also exceeded SEM%. For participant 6, the MVIC varied between 4.6N and 20.8N at baseline, and then returned to 5.8N post-intervention. These changes at such low force levels gave large percentage change values that exceeded the SEM%.

- **Gait pattern and gait variability for kinematic and temporal parameters**

The results for 3D motion analysis of walking and step-ups are presented in Table 4-6. For *peak dorsiflexion in swing*, *peak dorsiflexion during step-up* and *step-up time*, the mean and SD are representative of 11-20 gait cycles and 7-10 step-up cycles, with the exception of participant 6 who could only complete one step-up before and five step-ups after the intervention. For *step length*, *swing time*, and *gait speed*, the mean is representative of the means from 3-4 walking trials, each containing 3-5 steps.

Table 4-4 Clinical measures

| Group | Participant | Baseline | Post 5 days | Post 12 days | Change baseline to post 5 days | Change baseline to post 12 days |
|---|---|---|---|---|---|---|
| Comfortable-paced gait speed (m/s) | | | | | | |
| Novel-PAS | 1 | 0.35 | 0.31 | 0.33 | -0.04 ✝ | -0.01 |
| | 4 | 0.75 | 0.73* | NT | -0.02 | NT |
| Sham | 2 | 0.29 | 0.28 | 0.30 | -0.01 | +0.01 |
| | 6 | 0.33 | 0.27** | 0.32** | -0.06✝ | -0.02 |
| Fast-paced gait speed (m/s) | | | | | | |
| Novel-PAS | 1 | 0.37 | 0.35 | 0.35 | -0.02 | -0.02 |
| | 4 | 0.98 | 0.93* | NT | -0.05✝ | NT |
| Sham | 2 | 0.33 | 0.31 | 0.34 | -0.02 | +0.01 |
| | 6 | 0.38 | 0.37** | 0.37** | -0.02 | -0.01 |
| Step test (number of steps on hemiparetic/non-paretic leg) | | | | | | |
| Novel-PAS | 1 | 0/0 | 1/0 | 2/0△△ | Hemiparetic leg +1 ‡ | Hemiparetic leg +2 ‡‡ |
| | 4 | 7/0 | 0/0△ | NT | Hemiparetic leg -7 ‡‡ | NT |
| Sham | 2 | 4/5 | 4/5 | 4/6 | Non-paretic leg +1 ‡ | Non-paretic leg +2 ‡‡ |
| | 6 | 0/0 | 0/0 | 0/0 | No change | No change |

* Delayed by 7 days, ** Delayed by 11 days, NT = not tested, △ Reported had lost confidence to try due to recent illness, △△ Reported had been practising stairs

✝ Exceeds SEM 0.04m for people with stroke (SRD 0.11)[215]

‡ Exceeds SEM for hemiparetic leg 0.4 steps or non-paretic leg 0.6 steps, ‡‡ Exceeds SRD for hemiparetic leg 1.1 steps or non-paretic leg 1.6 steps[260]

Table 4-5 MVIC for ankle dorsiflexor muscles

| Group | Participant | Baseline 1 (N) | Baseline 2 (prior to delivery of first intervention) (N) | *Mean at baseline (N)* | *Change at baseline (% of mean)* | Post 3 days (N) | *Change mean baseline to post-intervention (% change)* |
|---|---|---|---|---|---|---|---|
| Novel PAS | 1 | 104.2 | 112.0 | 108.1 | +7.8 (+7%) | 104.8 | -3.3 (-3%) |
| | 4 | 88.3 | 63.0 | 75.7 | -25.3 (-33%) ✝ | NT | - |
| Sham | 2 | 138.0 | 111.6 | 124.8 | -26.4 (-21%) ✝ | 167.7 | +42.9 (+34%) ✝ |
| | 6 | 4.6 | 20.8 | 12.7 | +16.2 (128%) ✝ | 5.8 | -6.9 (-54%) ✝ |

✝ Exceeds SEM% of 9-39% calculated from isometric[263] or isokinetic[50,304] ankle dorsiflexion strength measurements in people with stroke.

Table 4-6 3D motion analysis

| Group | Participant | Measure | Baseline mean (SD) | Post 5 days mean (SD) | *Change in mean* | *Change in SD* |
|---|---|---|---|---|---|---|
| Novel PAS | 1 | Gait speed (m/s) | 0.32 | 0.31 | -0.01 | - |
| | | Step length during gait (metres (m)) | 0.27 | 0.26 | 0.00 | - |
| | | Swing time during gait (seconds (s)) | 0.52 | 0.50 | -0.02 | - |
| | | Peak dorsiflexion in swing during gait (degrees from neutral) | -1.48 (0.61) | 3.92 (0.60) | 5.41 ⌗ | -0.01 |
| | | Step-up time (s) | 2.82 (0.40) | 1.44 (0.27) | -1.38 ## | -0.13 |
| | | Peak dorsiflexion during step-up (degrees from neutral) | 2.47 (0.38) | 2.47 (0.60) | 0.00 | 0.22 |

*Continued on next page…*

Table 4-6 Continued from previous page

| Group | Participant | Measure | Baseline mean (SD) | Post 5 days mean (SD) | *Change in mean* | *Change in SD* |
|---|---|---|---|---|---|---|
| Novel PAS | 4 | Gait speed (m/s) | 0.65 | 0.66 | 0.01 | - |
| | | Step length during gait (m) | 0.40 | 0.45 | 0.05 | - |
| | | Swing time during gait (s) | 0.46 | 0.43 | -0.03 | - |
| | | Peak dorsiflexion in swing during gait (degrees from neutral) | -6.98 (1.51) | -9.88 (2.09) | -2.90 ‡ | 0.58 |
| | | Step-up time (s) | 1.36 (0.15) | 1.22 (0.20) | -0.13# | 0.04 |
| | | Peak dorsiflexion during step-up (degrees from neutral) | -0.27 (0.72) | -0.59 (1.61) | -0.32 | 0.88 |
| Sham | 2 | Gait speed (m/s) | 0.19 | 0.23 | 0.04✝ | - |
| | | Step length during gait (m) | 0.17 | 0.15 | -0.02 | - |
| | | Swing time during gait (s) | 0.50 | 0.51 | 0.01 | - |
| | | Peak dorsiflexion in swing during gait (degrees from neutral) | -1.74 (1.36) | -7.06 (1.68) | -5.32 ‡‡ | 0.32 |
| | | Step-up time (s) | 1.42 (0.16) | 1.09 (0.24) | -0.33 ## | 0.08 |
| | | Peak dorsiflexion during step-up (degrees from neutral) | -3.90 (3.01) | -6.55 (2.03) | -2.64 ‡ | -0.98 |
| Sham | 6 | Gait speed (m/s) | 0.28 | 0.26 | -0.01 | - |
| | | Step length during gait (m) | 0.24 | 0.26 | 0.02 | - |
| | | Swing time during gait (s) | 0.53 | 0.47 | -0.07 | - |
| | | Peak dorsiflexion in swing during gait (degrees from neutral) | -3.64 (0.78) | -2.34 (1.32) | 1.30 | 0.54 |
| | | Step-up time (s) | 6.12 (1 cycle) | 5.77 (4 cycles) ◆ | -0.35 ## | NA |
| | | Peak dorsiflexion during step-up (degrees from neutral) | -2.78 (1 cycle) | -0.40 (4 cycles) ◆ | 2.38 ‡ | NA |

‡ Exceeds SEM 1.8°, or ‡‡ exceeds SRD 4.9°, for peak ankle dorsiflexion during swing phase on treadmill in people with stroke (SRD 4.9°)[305]. Kinematic data not available for stairs

# Exceeds estimated SEM 0.11s, or ## exceeds estimated SRD 0.31s, for ascending two steps with rail. Based on 1/6 of values for 12-step ascent steps in people with chronic stroke[43].

✝ Exceeds SEM 0.04m for gait speed in people with stroke (SRD 0.11)[215]. Other SEM values: step length 0.11m and step time 0.11s in young people with neurological conditions[306]

◆ Participant 6 completed 5 step-ups post-intervention

## Neurophysiological measures

- **EMG measures**

The TA EMG linear envelopes during gait and their VRs are presented in Figure 4-8 and a descriptive analysis of the linear envelopes is presented in Table 4-7. The TA EMG linear envelopes during step-ups and their VRs are presented in Figure 4-9 and a descriptive analysis of the linear envelopes is presented in Table 4-8. The VR was not calculated for participant 6 as they could only perform one step-up at baseline, with hand support. The TA EMG rise during step-ups is presented in Figure 4-10. This measure improved post-intervention for all participants.

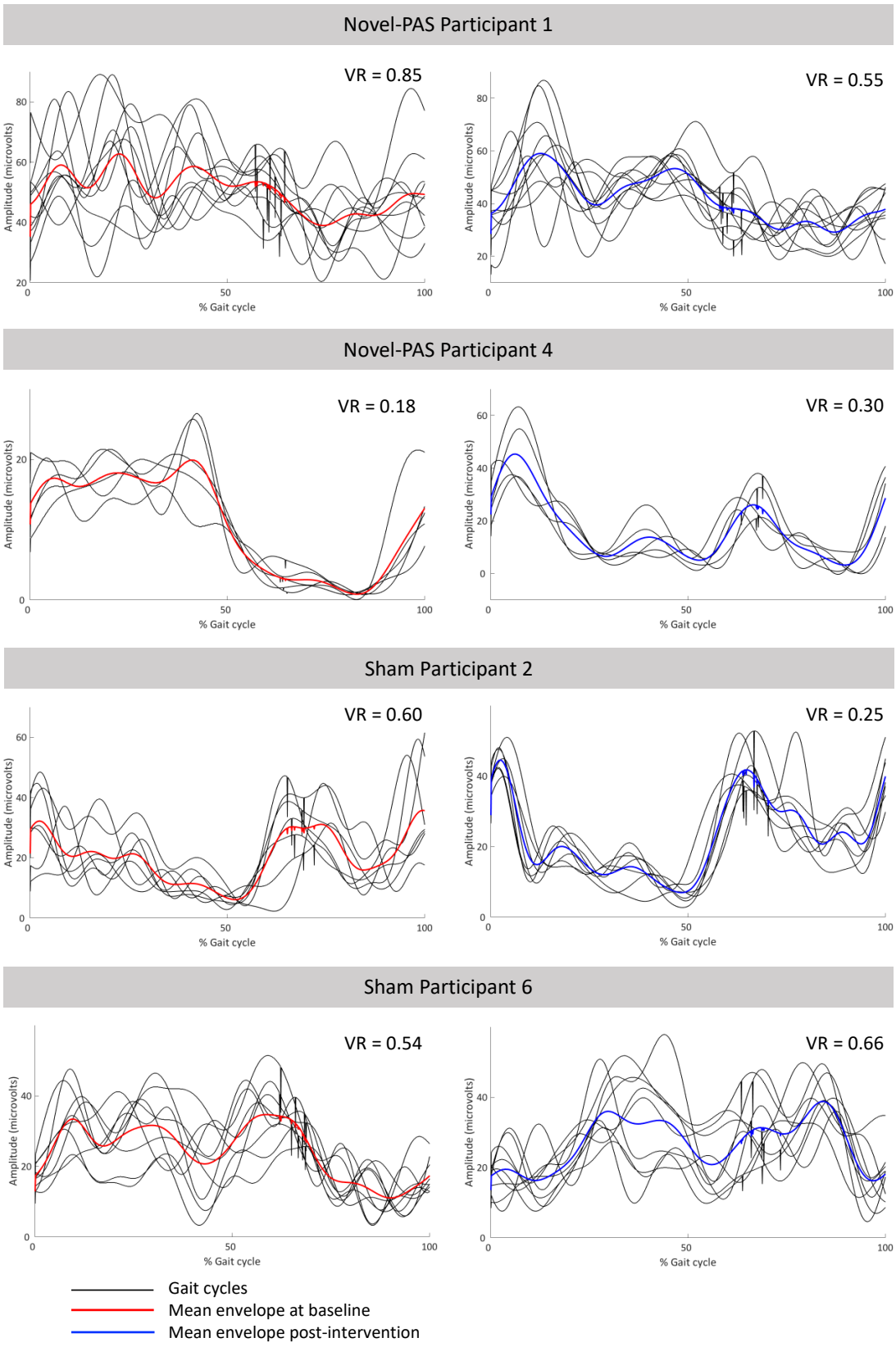



Figure 4-8 TA EMG linear envelopes and VRs during gait for individual participants

Table 4-7: Descriptive analysis and VRs for TA EMG linear envelopes during gait

| Group | Participant | Baseline | | | | Post-intervention | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Heel-strike burst | Toe-off burst | Comment on waveform | VR | Heel-strike burst | Toe-off burst | Comment on waveform | VR | VR comment in relation to healthy range (0.18-0.38[273]) |
| Novel-PAS | 1 | – 7/12 cycles | – 6/12 Narrow bursts. Not maintained through swing. | 4-5 small bursts through gait cycle. | 0.85 (10 cycles) | – 11/14 | – 2/14 Narrow bursts. Not maintained through swing. | Similar to baseline. | 0.55 (10 cycles) | Moving toward healthy range |
| Novel-PAS | 4 | ✓ 4/5 cycles | × | TA active in stance, but not swing phase. | 0.18 (5 cycles) | ✓ 7/8 | ✓ 2/8 have low amplitude. Not maintained through swing. | Change from single burst to double burst (addition of toe off burst). | 0.30 (5 cycles) | Within healthy range |
| Sham | 2 | ✓ Narrow bursts | ✓ Narrow bursts. Not maintained through swing. | Double burst. Narrow. Similar amplitude. | 0.60 (7 cycles) | ✓ Narrow bursts | ✓ Narrow bursts. Not maintained through swing. | Similar to baseline. | 0.25 (7 cycles) | Moving toward healthy range |
| Sham | 6 | – 6/9 cycles | ✓ 8/9 Narrow bursts. Not maintained through swing. | ≈ 4 small bursts through gait cycle. | 0.54 (9 cycles) | – 7/13 | ✓ More activity in mid-swing | Still multiple bursts, but more activity in swing phase. | 0.66 (9 cycles) | Moving away from healthy range |

✓ visible burst in upper 50% of amplitude range for >80% trials, × no burst, – inconsistent bursts in <80% trials

For heel-strike burst inspected 0-15% of cycle. For toe-off burst inspected 60-85% of cycle.

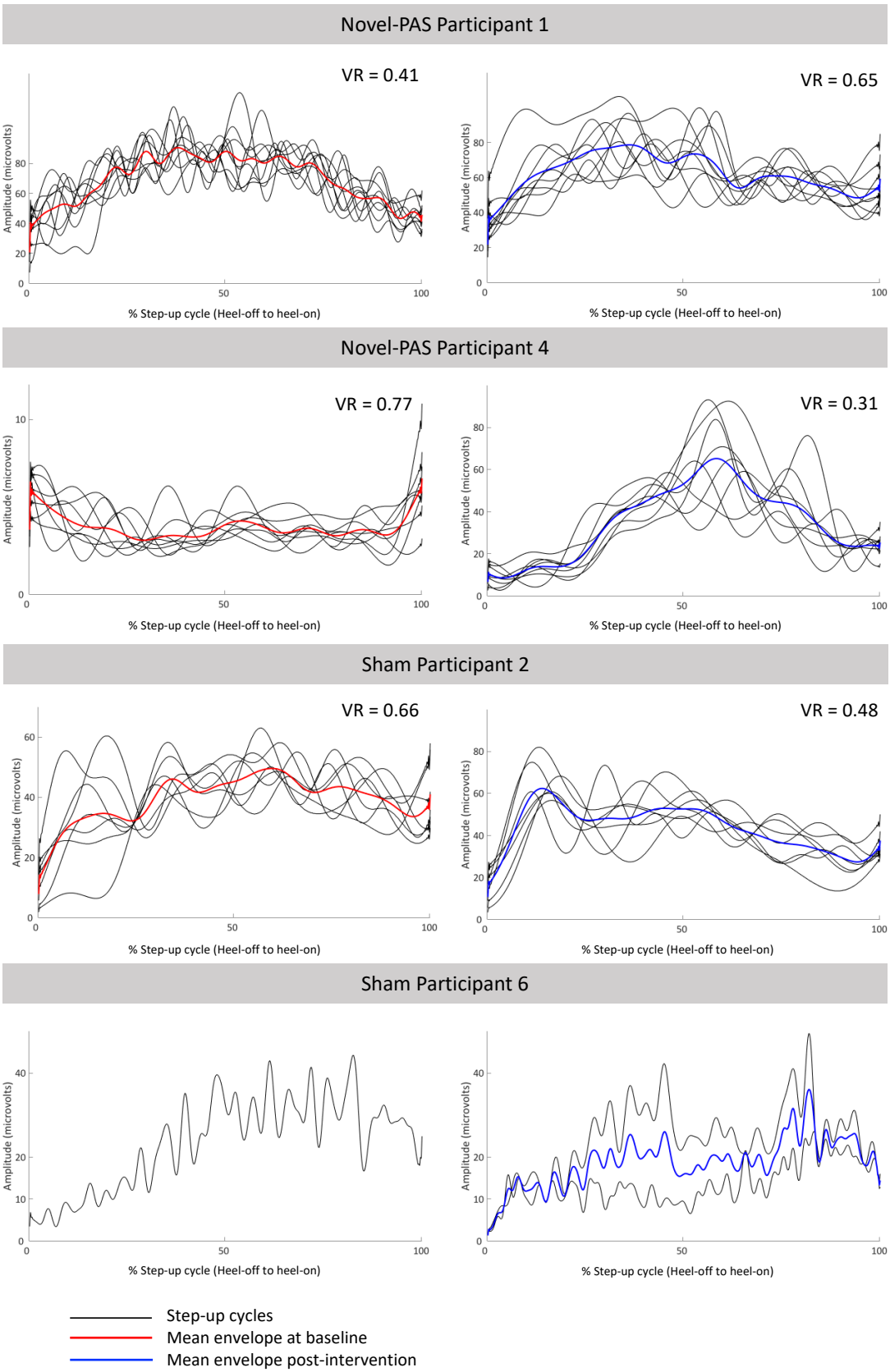



Figure 4-9 TA EMG linear envelopes and VRs during step-ups for individual participants

Table 4-8: Descriptive analysis and VRs for TA EMG linear envelopes during step-ups

| Group | Participant | Baseline | | Post-intervention | | |
|---|---|---|---|---|---|---|
| | | Swing burst comment | VR | Swing burst comment | VR | VR comment |
| Novel-PAS | 1 | ≈8 bursts each step | 0.41 (9 cycles) | 4 bursts each step. Less bursts to achieve the same movement, but step-up time also halved. | 0.65 (9 cycles) | Increasing variability |
| Novel-PAS | 4 | Small shallow bursts or flat . | 0.77 (8 cycles) | 1-2 bursts present on all steps. Peak amplitude middle swing. | 0.31 (8 cycles) | Decreasing variability |
| Sham | 2 | ≈2-4 bursts each step. Highest bursts early or middle swing. | 0.66 (7 cycles) | ≈2-3 bursts each step. Peak amplitude early swing. | 0.48 (7 cycles) | Decreasing variability |
| Sham | 6 | Many high frequency bursts. Peak amplitude mid to late swing | NA | Similar to baseline. | NA | NA |

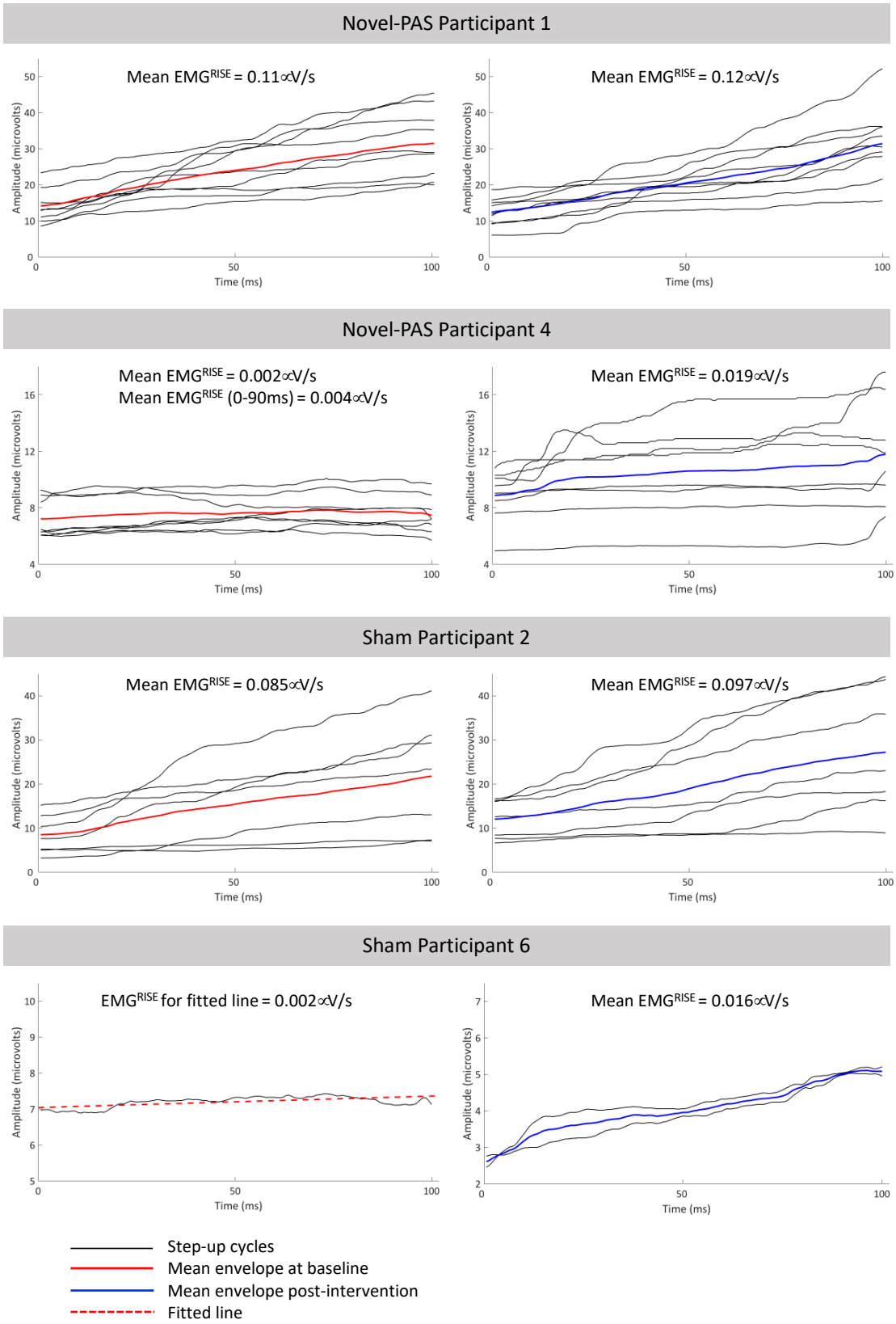



Figure 4-10 TA EMG moving average envelopes during first 100ms of step-ups for individual participants

- **MRCP**

The MRCP was time-locked to the cue to move, rather than the EMG onset, due to poor visibility of the EMG data. An example of the average MRCP for one participant is shown in Figure 4-11. The changes in the *PN timing* over the six MRCP measurements are shown in Figure 4-12. This shows increased variability at baseline for participant 4, and increased variability across all six measurements for participant 1 and 4. The PN timing for participant 2 and 6 remains more stable. The MRCP amplitude values for each participant, at each recording session, are presented in Figure 4-13. For participant 4 there was a progressive decrease in the amplitude of M1 and PN up to week 3, when a break occurred in the intervention. Whereas, for participant 2 there was a progressive increase in PN amplitude, and for participant 6 there was a progressive increase in MP1 and MP2 amplitude.

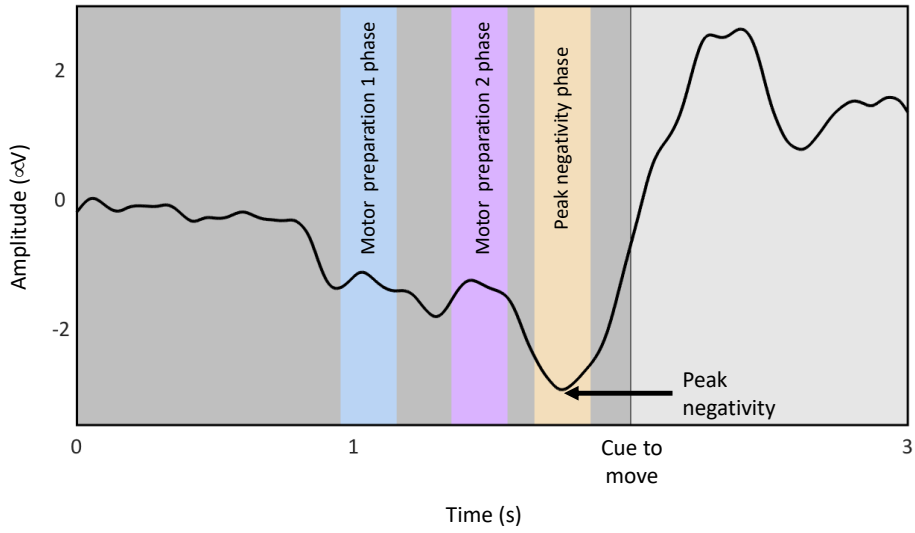



Figure 4-11 Example of average MRCP for one participant, showing phases of motor preparation phase 1, motor preparation phase 2, and PN.

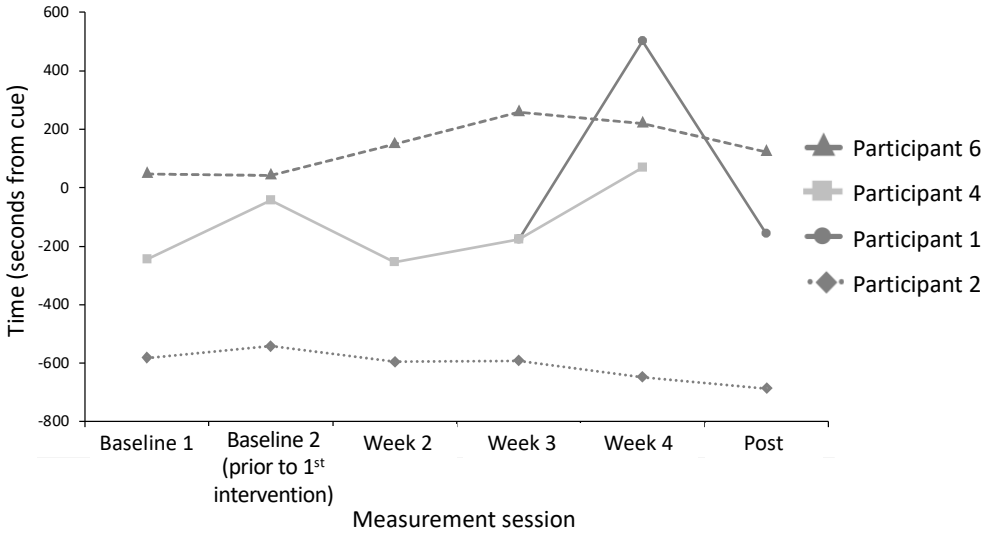



Figure 4-12 PN timing over six sessions for individual participants

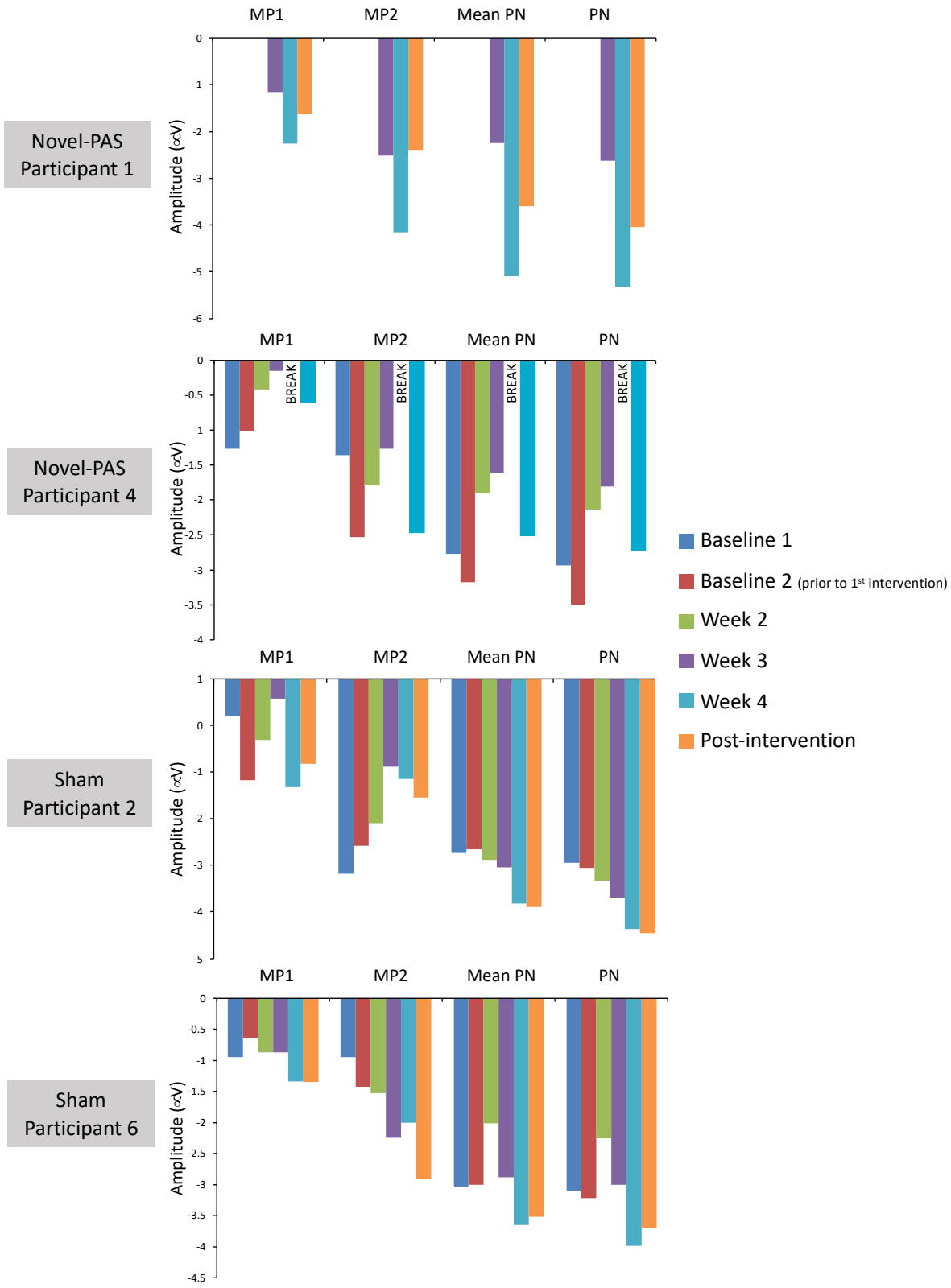



Figure 4-13 Mean MRCP values during the motor preparation phase 1 (MP1), motor preparation phase 2 (MP2), and the peak negativity phase (mean PN), and the amplitude of the PN (PN).

- **Between-session changes in corticomotor excitability**

Isometric and step-up MEPs for individual participants are shown in Figure 4-14. This figure shows the TA MEP area (red and blue columns) in relation to the background EMG area in the 40ms prior to the TMS pulse (grey columns). For participant 2, the background EMG during the 10% MVIC resembled EMG at rest, despite the active dorsiflexion movement being performed. The between-session changes in isometric and step-up MEPs can be seen by comparing the red columns for each time-point. As an indication of baseline stability, the between-session changes in background EMG and MEPs at baseline are also shown in Table 4-9. Baseline isometric MEPs exceeded the SEM% for three participants. Baseline step-up MEPs exceeded the SEM% for one participant.

Table 4-9 Variation in background EMG and MEPs between baseline measurements

| | | Isometric MEPs (10% MVIC) | | Step-up MEPs | |
|---|---|---|---|---|---|
| | | Change in background EMG at baseline | Change in isometric MEP at baseline | Change in background EMG at baseline | Change in step-up MEP at baseline |
| Novel | 1 | 17% | -44% ✝ | Lost data | Lost data |
| PAS | 4 | -18% | -23% | 0% | 27% |
| Sham | 2 | 10% | -54% ✝ | 4% | 23% |
| | 6 | 35% | 356% ✝ | -21% | 144% ‡ |

✝ Exceeds SEM% 38% for TA MEPs during 10% MVIC in people with stroke (intraclass correlation coefficient (ICC) 0.38)[236]

‡ Exceeds SEM% 42% for soleus MEPs during treadmill walking in people with stroke (ICC 0.91)[280]

- **Within-session changes in corticomotor excitability**

The within-session pre-post changes in isometric and step-up MEPs can be seen by comparing the red and blue columns at each time-point in Figure 4-14. The results show that isometric and step-up MEPs decreased following novel-PAS in nine out of 10 measurements. However, following the sham intervention there was an increase in isometric or step-up MEPs in five out of seven measurements. In most cases, the changes in step-up MEPs followed the direction of the fluctuation in background EMG. Isometric MEP changes exceeded the SEM% in three out of seven measurements, based on figures reported for isometric TA MEPs in the stroke population[280]. Within-session SEM values for step-up MEPs or a similar task are not available for comparison.

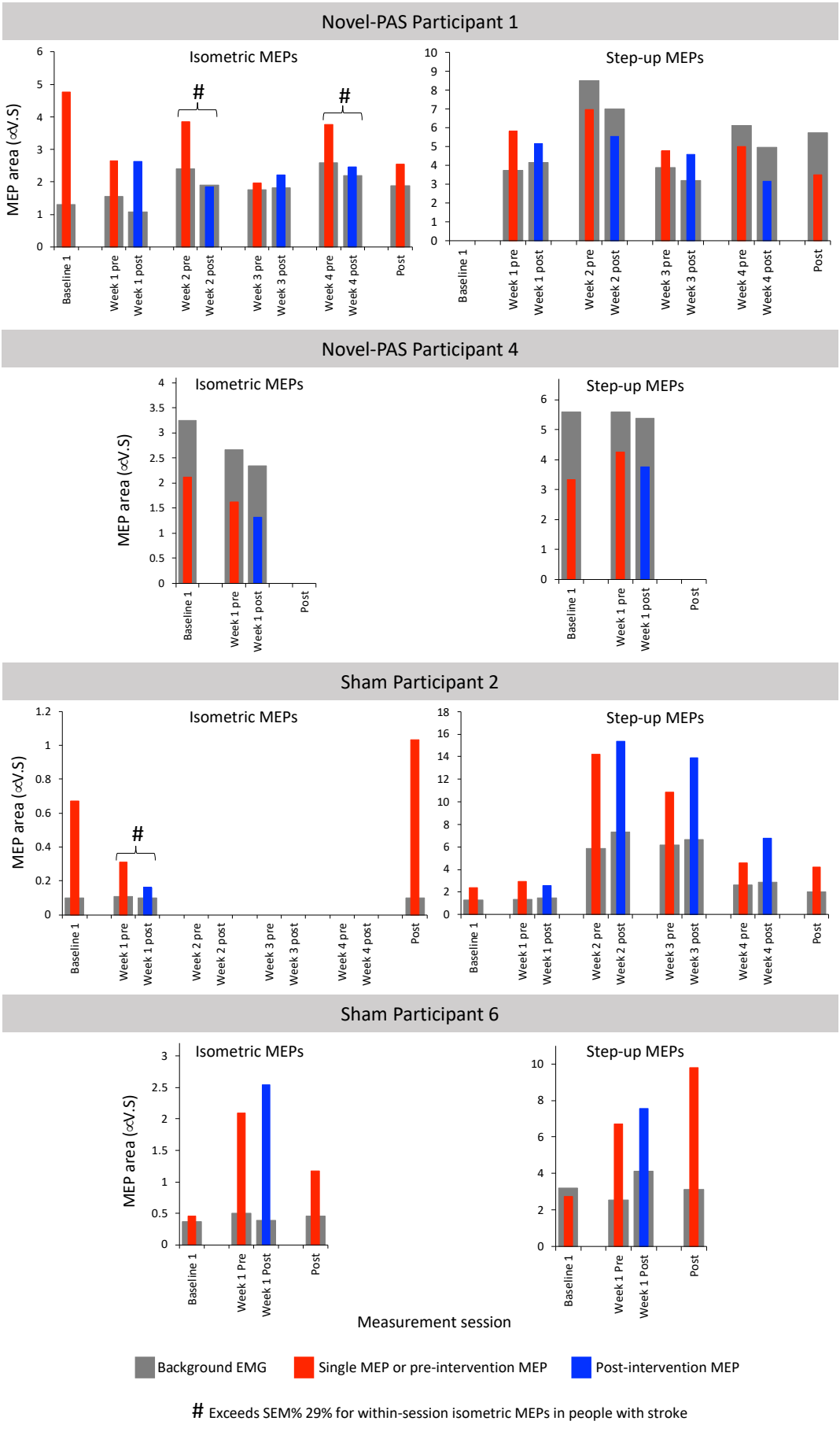



Figure 4-14 TA MEP area for isometric MEPs and step-up MEPs

### 4.4.4 ACCEPTABILITY OF THE RESEARCH PROTOCOL AND INTERVENTION

The interview data fitted into three broad themes: factors related to the participants personally, factors related to the intervention or research process, and the interaction between the person and the intervention/research. These three themes are illustrated in Figure 4-15.

The *interaction* was explored to answer the following research questions related to acceptability.

- *Is the novel-PAS research protocol acceptable to people with stroke?*
- *Is the novel-PAS intervention acceptable to people with stroke?*

Four themes which were embedded within the *interaction* worked together to produce full participation in the programme. Factors related to the *person* and the *intervention/research* influenced the interaction in different ways.

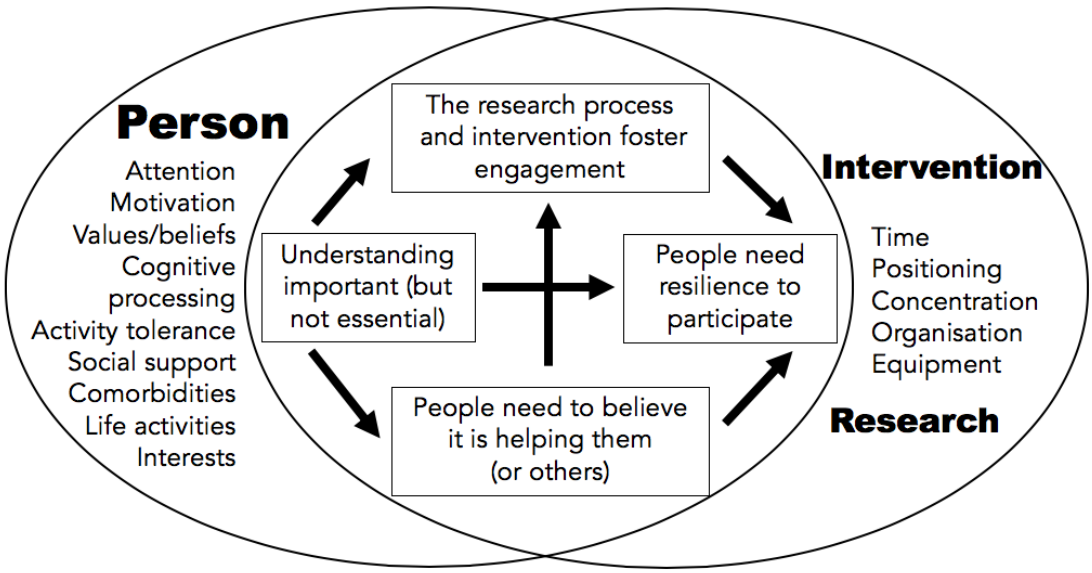



Figure 4-15 The interaction between the person with stroke and the intervention or research protocol, and the themes associated with the acceptability of this interaction.

## Theme 1. Understanding can be important but is not essential

> ***"Once people are able to get their head around it, then they'll come to the party."*** (Male, age 64, novel-PAS group)

This theme explores how understanding the intervention/research is a requirement for some people but not for others. Three out of four participants had a basic understanding of what they needed to do but could not explain how the intervention worked. They were hesitant to answer questions about the theory and how the research or intervention could be improved, and reported a lack of expertise with computers, and that they just 'did as they were told'. This illustrates that the participants' trust in the research staff and research process was not based on an in-depth understanding of the science, and that understanding was not a requirement for acceptability.

> "…I guess I've just gone along, do it." (Female, age 61, sham group)

However, one participant had a technical background and was motivated to make sense of the intervention.

> "I's thinking, now how's that gonna work?" (Male, age 64, novel-PAS group)

This participant initially found the information daunting, but soon gained an understanding of what was happening, and appreciated that the researchers kept him "in the loop". This illustrates that for those participants who have the desire and cognition to comprehend the processes, the researchers play an important role in guiding them towards understanding. Through this dialogue, the researcher earns the participant's trust and the participant becomes more engaged in the research process/intervention. This understanding feeds into the other three themes, as illustrated by the arrows in Figure 4-15.

## Theme 2: The research process and intervention foster engagement

> ***"…I'd never done anything like that before…it was all so new that it was fascinating in a way. You know, to see what they did."*** (Female, age 78, sham group)

This theme identifies the components of the intervention and research process that foster engagement. When someone is engaged, they attend to, and put effort into the task. Participants spoke of the novelty of the research, which sparked their interest, and enjoyed participating in the intervention/research process and working with the researchers.

"…I was having too much fun…just being part of a programme." (Female, age 61, sham group)

"…the people are really good eh. They are." (Male, age 75, novel-PAS group)

The visual cue helped participants attend to the dorsiflexion task and provided motivation to perform the task accurately. The visual biofeedback during strength testing also provided an incentive to improve performance. Participants felt that motivation might fall if the intervention was being performed alone (without 1:1 supervision), and that this could be enhanced in a competitive group situation, or with some monitoring and accountability to the physiotherapist.

*Personal factors* also fostered engagement. For one participant, their technical background and familiarity with the environment helped them maintain focus during the dorsiflexion task and fuelled their interest in the programme.

"…because of my background, I thought aw well, I's sort of like coming to work." (Male, age 64, novel-PAS group)

In addition, participants' altruistic values drove their desire to participate and engage in the research.

## Theme 3: People need to believe it is helping them (or others)

***"But once I could see some movement in my feet, from the intervention, then I realised oh something is working."*** (Male, age 64, novel-PAS group)

This theme explores the importance of people believing in the benefits of the intervention for themselves or others. The participants who received the novel-PAS intervention reported physical benefits and a preference to continue the novel-PAS intervention, whilst the participants who received the sham intervention reported no physical benefits and did not want to continue. This suggests that believing and seeing evidence that the intervention is helping may promote adherence. *Personal factors* also influenced this theme. One of the sham participants who noted she could not feel the electrical stimulation, had strong beliefs that rehabilitation should be hard physical work and felt that the intervention did not meet this standard.

"What you were calling therapy, I didn't feel any"….."it didn't feel like (treatment) to me, cos I like to get into, a day when you're really huh huh (panting sound)." (Female, age 61, sham group)

Despite this, both sham participants reported that they would still recommend the intervention to others because they believed it would be helpful to some people (e.g. immobile, acute patients), indicating an underlying belief that the research may have value for others.

> "there's got to be someone that it's going to be good for." (Female, age 61, sham group)

This may have been the result of the participants pre-existing beliefs about the organisation/research/intervention, or may have developed during the research process, as the participant developed trust in the researchers.

## Theme 4: People need resilience to participate

> ***"Just that the equipment that you use, but I mean, I can bear it, you know the chairs and things…yeah they're not the comfortable chairs. You know but, I mean, that's what it is."*** (Male, age 64, novel-PAS group)

This theme describes the difficulties that participants faced during the research that required them to be resilient in order to complete the programme. The dorsiflexion task was difficult for one participant, due to the high level of concentration required. Participants spoke of positions or procedures that produced feelings of discomfort or being out of control, but also used terms like "it was all bearable" (Female, age 78, sham group) which implied that they may not have been in pain, but they were uncomfortable.

Participants acknowledged that some of the sessions were long and that this would be tiring for some people. They recommended that in future the sessions should not exceed 90 minutes for research or 15 minutes for a novel-PAS intervention. One participant had other commitments in the afternoon which exacerbated their tiredness.

> "for some people it would be a long time, cos it's quite tiring." (Female, age 61, sham group)

One participant spoke of equipment used in another study that was smaller and easier to use, suggesting that the equipment in this study was too large and too time-consuming. A factor that promoted resilience was that one participant was accompanied by a family member who could provide extra help when needed.

### Summary of interview data

With regards to the acceptability of the *research protocol*, people with stroke deemed several aspects of the protocol unacceptable, such as the long sessions, the high level of concentration required, and the uncomfortable positioning, all of which increased the risk of 'tiredness'. It was recommended that future sessions should last not more than 90 minutes. Despite these barriers, a number of factors promoted participation, including the participant-researcher relationship, the novelty of the experience, visual feedback about performance, and personal factors such as altruism and family support. For one participant, understanding the underlying process also promoted participation and engagement.

With regards to the acceptability of the *intervention*, people with stroke found the novel-PAS or sham intervention enjoyable, but reported that the equipment size, efficiency and comfort could be improved. Aspects of the intervention that promoted participation included the participant-research relationship, the visual cue, perceived physical benefits, and the 1:1 support. It was recommended that the intervention might fit well within a group exercise setting, which would promote motivation, competition and accountability. For one participant, understanding the underlying mechanism of the intervention promoted participation. For another participant, participation and engagement was hindered because the intervention did not fit with their personal beliefs about what rehabilitation should entail. Overall, the intervention in its current form was not deemed acceptable for use in the rehabilitation environment.

## 4.5 DISCUSSION

The results related to the feasibility of the research protocol and the intervention will be discussed first, followed by an exploration of the activity, impairment and neurophysiological outcomes, and then a discussion regarding the usability and usefulness of these measures for future research. The main limitations of the study will be outlined, and then final conclusions and recommendations made.

### 4.5.1 FEASIBILITY OF THE RESEARCH PROTOCOL

While a range of studies have previously investigated the efficacy of novel-PAS in healthy people[200-203,205,206,210] and people with stroke[204], none have reported on feasibility issues such as recruitment and retention, participant burden, and the acceptability of the research process. This research is the first to examine the feasibility of a four-week novel-PAS research protocol. The purpose of assessing feasibility was to determine the protocol's

viability and acceptability for use in a fully-powered RCT. The protocol adopted in the study failed to meet all five criteria set for feasibility.

## Recruitment

The criterion for recruitment feasibility was that 20 participants would be recruited in a four-month period. Despite an extensive and multi-faceted recruitment strategy, this criterion was not met. The time commitment of 17 sessions over 6.5 weeks was thought to restrict the pool of potential participants; this applies particularly to those people with very low activity levels, who might have felt they lacked the endurance to participate, or those with high activity levels, who may already be engaged in work or other community activities. Six of the 27 people who initially showed an interest in the study withdrew their interest after learning about the trial requirements, including the number and length of sessions.

While recruitment difficulties associated with time requirements, travel constraints, and level of disability are common in studies of community-dwelling people with stroke[307], these have not been described in previous novel-PAS[204] or PAS[29-35] literature. Information about the selection of potential participants has been largely unreported in this body of literature; however, low sample sizes indicate that difficulties with recruitment may have occurred[29-35,204]. In addition, sample demographics, and the physical requirements of previous PAS protocols, indicate that the majority of novel-PAS and PAS studies enrolled participants with a relatively mild level of disability from stroke[29,30,32-35,204]. It is foreseeable that this selection bias is at least partially related to the use of TMS as an outcome measure, a factor which has been reported to limit recruitment in rTMS research[308]. The majority of novel-PAS and PAS studies have included only participants in whom a TMS-induced MEP could be produced in the target muscle at rest[29,30,32-35,204], yet many people with more severe stroke do not have an observable MEP[31,117]. Thus, the use of TMS in previous research protocols appears to have influenced participant selection. Findings from the present study support this assertion; the use of TMS was a major barrier to recruitment, accounting for 71% of exclusions. Concerns about possible selection bias in previous novel-PAS and PAS studies in people with stroke raise questions about the external validity of this body of literature, and in particular, whether this research is generalisable to people with more severe stroke.

Future novel-PAS research protocols should consider strategies to improve recruitment, including reducing the time-commitment involved and making interventions more accessible. In particular, researchers should carefully consider whether the use of TMS measures are prioritised over the selection bias that this measure brings.

## Retention

The criterion for retention feasibility was that drop-outs did not exceed 20%. This criterion was not met, as two out of six participants (33%) dropped out during the baseline phase due to unrelated injuries. This figure is comparatively high compared with other studies involving a four-week neuromodulatory intervention in people with chronic stroke, where drop-out rates of 4-20% have been reported[186,309,310]. However, the high drop-out rate in the present study may have been influenced by the low sample size.

The participants who dropped out chose not to re-join the study at a later date, due to the time commitment involved. In addition, interview feedback from participants was that some sessions were too long in duration. This reinforces the concerns noted above about the time-requirements of the protocol and the need to reduce these in future research. This is particularly important in stroke rehabilitation research, where a range of health, social, marital, occupational and financial issues can limit retention of participants[307].

## Protocol deviations

The criterion for protocol deviations was that any deviations could be addressed with minor modifications to the protocol. Small deviations related to measurements were resolved with minor protocol adjustments. There were also protocol deviations related to the intervention; these will be discussed in the next section related to intervention feasibility (refer to 4.5.2).

Major protocol revisions were required to reduce the duration of sessions. Measurement sessions were initially anticipated to last approximately two hours; however the inclusion of a number of different outcome measures, each with varying set up positions, equipment needs, and processing requirements, predisposed the protocol to running over time. This issue was managed by reducing the number of TMS measurements in weeks 2-4 of the intervention phase; these sessions were decreased from over 3 hours each to 1.3 hours each. However, the final revised protocol still included five measurement sessions averaging 2.75 hours each, which qualitative data indicated was still too high a time commitment for a future protocol. Difficulty with completing outcome measures in an acceptable time-period may have been a factor in previous novel-PAS research in people with stroke[204], where TMS data for three out of 13 participants was reported as incomplete and excluded from data analysis. Overall, the criterion related to protocol deviations was not met and further major protocol changes are required. These findings offer valuable insight into the challenges of collecting multiple outcomes in this field of research.

## Data completeness

The criterion for data completeness was that at least 90% of planned outcome measurements were recorded. This was not met; the overall data completeness for the study reached 86%. Data completion was reduced by the low level of usable EMG recordings during the MRCP collection. The implications of this lost data will be discussed in further detail later in the section on 'Outcome measures for future research' (refer to 4.5.3). The other factor which hindered data completeness was participant illness. It is possible that the low sample size resulted in a disproportionate level of participant illness compared with the wider stroke population, as previous novel-PAS and PAS studies in people with stroke have not reported illness as a barrier to completion of the protocol[29-35,204]. However, as discussed earlier, this body of literature may not be representative of people with more severe stroke. The one PAS study which included some participants with more severe disability reported that weariness limited the collection of multiple post-intervention TMS measures[31]. This suggests that had previous novel-PAS and PAS research been more representative of the wider stroke population, where people commonly experience a number of comorbidities and medical stroke-related complications[221], participant illness and fatigue may have further interfered with data completeness. The findings of the present study illustrate the importance of planning for participant illness when conducting research. Future studies should maintain a degree of flexibility in data collection time-points to minimise loss of data.

## Acceptability of the protocol

The criterion for acceptability was that people with stroke deemed the research protocol acceptable. This criterion was not met, and the interview findings offer valuable insight into the many unacceptable aspects of the four-week novel-PAS protocol. A major factor was the long data collection sessions which often exceeded three hours. The length of sessions did not interfere with data completeness due to the high level of resilience, commitment, and altruism of the participants. While the altruistic values of people with stroke are known to inspire their participation in research[311], this level of commitment was not considered acceptable for future novel-PAS research. Potential participants with stroke may already be experiencing fatigue as a result of their normal daily activities[62], and therefore involvement in research can add to this burden. Future protocols must prioritise participant comfort over collecting numerous measurements, and keep sessions under 90 minutes as recommended by people with stroke in this study.

Factors which promoted participation and engagement should also be incorporated into future research protocols, particularly visual feedback about performance, which can

enhance motivation[312], and education about the process, which can enhance engagement of people during stroke rehabilitation[313]. Lastly, the role of the relationship between the participant and researcher in promoting fun, trust, and engagement, must not be underestimated. This concept is supported by other stroke research which emphasises the importance of relationship in engagement[313-315].

### Summary of protocol feasibility

In summary, the five criteria for feasibility of the research protocol were not met. The protocol requires major revisions to improve its feasibility and acceptability to people with stroke.

## 4.5.2 FEASIBILITY OF THE NOVEL-PAS INTERVENTION

This study was the first to examine the feasibility of the novel-PAS intervention, which is essential to its development and potential implementation into rehabilitation practice. While novel-PAS was shown to be safe and had excellent levels of adherence, there were some challenges with its delivery and acceptability.

### Technical challenges

There were technical challenges with the timing of novel-PAS delivery, which meant that only 50% of novel-PAS interventions were delivered per protocol. As previous novel-PAS[200] and PAS literature[25,26] reinforces the importance of accurate timing of pairings, these deviations from protocol may have resulted in an ineffective intervention. Some difficulties were caused by equipment malfunction and were corrected early in the study (25%). Other errors arose due to a breakdown in communication within the team (25%) and could be prevented in future.

A more concerning factor related to the intervention timing, was the inconsistencies observed in the processing of the MRCP between the *in-session* calculation and the *post-hoc* calculation. This resulted in two different calculations of the PN timing for a single set of data. The PN of each MRCP trial is subject to large biological variability[316], and the subjective process involved in screening and excluding individual trials has potential to influence the PN of the *average* MRCP. The inconsistencies in the PN calculations may have resulted from errors in the processing of the MRCP during the data collection session, due to time pressure or level of expertise. This raises concerns about the intra- and inter-rater reliability of the method used to process the MRCP.

The data from the present study also showed significant *between-session* variability in the timing of the PN of the average MRCP for two participants (between-session SD of 386ms and 139ms, for participants 1 and 4 respectively, for *post-hoc* data) (refer to Figure 4-12). This contrasts with previous literature, where the timing of the PN of the average MRCP in people with stroke was considered a stable measure, based on no significant difference being found across group data over three days (n=7)[204]. However, the reliability of this measure has not been investigated with appropriate statistical methods[317], and has not been explored in more severely-impaired people with stroke, such as those enrolled in the present study. The between-session variability noted in the present study could be due to poor intra- or inter-rater reliability mentioned earlier, or larger biological variability between sessions than previously thought[204]. The between-session variability observed has significant implications for the method used to deliver novel-PAS; this is because the weekly MRCP recordings used in the present study may not be sufficient to accurately time the intervention.

These findings suggest that human error, poor reliability of the method, or large between-session variability may have influenced the timing of the novel-PAS intervention and its efficacy. This suggests that previous novel-PAS research in people with stroke[204], which utilised the same method for intervention delivery as the present study, may have been subject to similar challenges with carrying out the novel-PAS protocol. This raises questions about the internal validity of previous findings[204], and the degree to which inconsistencies in the method may have contributed to variability in the results. Across the wider PAS literature, feasibility issues related to intervention delivery go largely unreported[29-33,35]. However, one study did allude to technical challenges involved in timing the PAS intervention[34], indicating that the difficulties encountered in Study B are not unique to novel-PAS.

These feasibility findings highlight the importance of establishing a robust protocol for delivering novel-PAS, with equipment and procedures that are feasible and reliable, to ensure that novel-PAS can be implemented into rehabilitation practice in the future. Literature supports the early optimisation of complex health interventions to avoid progressing sub-optimal interventions to larger-scale trials and to anticipate potential implementation challenges[185,318]. To optimise the timing of the novel-PAS intervention, further research is required to determine the intra- and inter-rater reliability of the *PN timing* of the average MRCP, and also determine whether this has any bearing on the efficacy of the novel-PAS intervention. From there, the procedure for identifying the PN can be further refined to reduce errors associated with the measurement, possibly through automating the process rather than relying on subjective screening of epochs. This will also facilitate the development of the novel-PAS intervention delivered with a BCI, which can detect the onset of MRCPs

in real time, but relies on averaging MRCP data and identifying the PN[201]. Further refinement of the intervention using wearable technology and a BCI has potential to lower cost, improve efficiency, and increase effectiveness[319,320]; these factors are essential to the successful implementation of a neuromodulatory intervention[34].

## Acceptability of the intervention

An important component of intervention feasibility was to assess its acceptability to people with stroke. The intervention had poor acceptability, primarily due to concerns that equipment size, efficiency and comfort were not appropriate for the current rehabilitation environment. In addition, there was a concern that the intervention was not hard physical work. A sense of 'working hard' has been linked with improved motivation and engagement in rehabilitation[321], yet the novel-PAS intervention consists of a seated low-intensity exercise. While neuromodulatory interventions are often delivered in quiet sitting, they can be delivered during exercises or functional tasks[163,175,176], which could add intensity and meaningfulness to the intervention, and possibly improve acceptability. Further research and development is required to miniaturise the novel-PAS intervention, possibly into *wearable* technology[319,320], and explore whether it can be delivered during high-intensity exercise. A miniaturised version may also reduce the set-up time, which took an average of 14 minutes in this study; shorter set-up could leave more time to carry out the novel-PAS or other interventions within a rehabilitation session.

Other factors were raised that might further improve engagement with the novel-PAS intervention. Some participants felt that the intervention could be delivered within a group setting. Group delivery of rehabilitation interventions has been shown to improve engagement through a sense of accountability, competition, inspiration, and support[321]. Group delivery would also be more cost-effective than 1:1 supervision. One participant felt that understanding the mechanism of the intervention was important, aligning with literature which has linked knowledge about stroke rehabilitation with improved motivation[322]. Three out of four participants could not understand the novel-PAS intervention, and while this did not limit their engagement in the present study, future researchers should consider how to provide participants with more accessible information about the interventions mechanism. Participants felt the visual cue was a motivating component of the intervention. However, the cue currently takes a very simple visual form, and could be further developed to enhance motivation by adding features of *gamification*, such as play, fun, rewards, and feedback[323]. In line with findings about the acceptability of the research protocol, the participant-researcher relationship promoted engagement with the intervention; this echoes the

experiences of people with stroke undertaking a rehabilitation programme involving tDCS and gait training[186]. Given that an individual's motivation during stroke rehabilitation can be influenced by their interactions with both health professionals and the therapeutic environment[322], researchers should consider how to integrate factors that might foster engagement in the development of the novel-PAS intervention.

In the broader body of neuromodulation literature, studies that report on intervention feasibility tend to limit participants' opinions to information from questionnaires, or informal feedback, about their symptoms[324-326] and their experience of the intervention[327,328]. A more in-depth qualitative analysis of interview data is seldom seen in the neuromodulation stroke literature[186]. Yet the incorporation of patient perspectives into the design of complex interventions is strongly recommended, and likely to produce a more relevant intervention and facilitate implementation into practice[185]. Thus, the qualitative findings of this study offer a valuable starting point for researchers to work with clinicians and people with stroke, to continue developing the novel-PAS intervention in order to maximise its acceptability.

### Summary of intervention feasibility

Two of the four criteria related to feasibility of the novel-PAS intervention were not met: intervention fidelity and acceptability to people with stroke. Further research is needed to refine the delivery method for novel-PAS and identify and address barriers to its implementation into rehabilitation practice. This will facilitate the design of a more acceptable intervention.

## 4.5.3 ACTIVITY, IMPAIRMENT AND NEUROPHYSIOLOGICAL OUTCOMES

Due to the failure to recruit all 20 participants, the estimates of treatment effect and variance could not be calculated. However, an important aim of this study was to determine *which* measures might be the most appropriate and responsive for use in a future trial. This will be explored through interpretation of individual data. The purpose of this part of the discussion is not to make conclusions about efficacy, but rather to understand the potential usefulness of various outcome measures. Outcomes that apply to all participants will be discussed first, followed by a case presentation for each of the four participants, and a discussion about potential outcome measures for a future trial.

## Outcomes that improved for all participants

- **Step-up time**

All participants had improved hemiparetic step-up time. For one novel-PAS participant and two sham participants, the change exceeded an SRD estimated from a similar measure[43] (refer to Table 4-6), suggesting that a real improvement occurred. This change may have contributed to an improved ability to climb stairs. Because these effects on step-up time were common to both novel-PAS and sham conditions, they may have resulted from aspects common to both interventions, such as the active cue-based ankle movements, or from aspects of the research protocol, such as the step-up practice during TMS measures. This reinforces the importance of conducting further novel-PAS research in a well-controlled manner, to ensure that the effects of novel-PAS can be differentiated from the effects of the research protocol or the sham condition.

- **TA EMG rise during step-ups**

All participants had an increase in the TA EMG rise during step-ups between baseline and the end of the intervention. This may indicate an increase in the initial discharge rate of motor units[54], and may have contributed to the improved step-up time observed in all participants.

## Outcomes that did not exceed measurement error

- **Gait speed**

Some gait speed changes exceeded the SEM at the 5-day post-intervention time point but were not maintained one week later. No changes exceeded the SRD, suggesting that gait speed did not change as a result of either the novel-PAS or sham intervention.

- **Ankle strength**

Ankle strength measurements were prone to baseline variability, with variations of 21-128% for three participants (refer to Table 4-5), which exceeded the SEM of 9% for isokinetic Kin-Com ankle strength measures in people with stroke (intraclass correlation coefficient (ICC) 0.98)[50]. This suggests large within-subject variation and/or large measurement error in this study's method. Higher SEMs have been found in studies which use alternative devices to measure ankle strength in people with stroke; this includes an SEM of 22% with the Cybex II dynamometer (ICC 0.84)[304] and an SEM of 39% with a strain gauge mounted on a customised chair (ICC 0.71)[263]. This suggests ankle strength measurements may be prone to

greater error according to the measuring device used. Thus, the customised chair with mounted strain gauge used in the present study may have been prone to large measurement errors; the variation in baseline measures supports this possibility. Measurement errors may have been increased through inadequate blocking of toe extension; this has been shown to contribute to variation in isometric dorsiflexion force measurements[329]. In addition, hip flexion movements may have been inadequately blocked, as thigh movement was blocked by just the lower leg strap, rather than a thigh and lower leg strap used in other literature[304]. Future research must ensure that measurement errors associated with strength testing are minimised.

- **Between-session changes in corticomotor excitability**

There was high variability in isometric TA MEPs *between* baseline measurements. In three out of four participants, this variation exceeded the SEM%[236], reinforcing previous literature which has shown poor between-session reliability for isometric TA MEP amplitudes in people with stroke (ICC 0.38, SEM% 38%)[236]. Therefore, the fluctuations in isometric MEPs over the course of the intervention were not considered a reliable indicator of the between-session effect.

Step-up TA MEPs also varied at baseline. For two participants this variation fell within the SEM% reported for soleus MEPs during treadmill walking in people with stroke (ICC 0.91, SEM% 42%)[280]. However, for one participant there was a change of 144% between the two baseline step-up MEPs (refer to Table 4-9), which suggests larger between-session variability than that reported for treadmill MEP recordings. This may be due to fluctuations observed in the level of background EMG during the step-up task. A more continuous task, such as treadmill walking, may be required to generate a stable level of background activity prior to the delivery of TMS. Over the intervention period there were fluctuations in the step-up TA MEP measures between sessions; however due to a low sample size and no established SEM for this measure, it is not possible to use these measures to make conclusions about the cumulative effects of novel-PAS on corticomotor excitability. Further research about the cumulative effects of novel-PAS must use an outcome measure with high between-session reliability.

## Outcomes for individual participants

The following section explores outcomes for each individual participant. With regards to within-session changes in corticomotor excitability, only isometric TA MEP results will be

discussed; these have been previously shown to be reliable in people with stroke (ICC 0.81, SEM% 29%)[280].

- **Novel-PAS participant 1**

There was a concern with intervention fidelity for this participant, with the possibility that the interventions were mistimed in three out of four weeks, due to missing MRCP data and possible miscalculation of the PN. Nevertheless, this participant still experienced an improvement in the hemiparetic leg step test score (+2), which exceeded the SRD, and had the most significant improvement in step-up time of all four participants (-1.38s) (refer to Table 4-4). In line with these improvements, there was a reduced number of TA EMG bursts when stepping up, but increased variability between step-ups in both the EMG waveforms and ankle kinematics (refer to Table 4-8 and Table 4-6). This increased variability in the presence of functional improvement might reflect the variability associated with task acquisition; this is advantageous to the motor learning process[330]. During walking, this participant had increased peak ankle dorsiflexion angle during the swing phase and decreased variation between EMG waveforms (refer to Table 4-6 and Table 4-7); this reflects a movement toward a healthy range of variation[273] and more consistent activation of the TA post-intervention[250].

During the third intervention week, when the participant received correctly-timed novel-PAS, within-session isometric MEP measures showed a small increase in corticomotor excitability immediately following the intervention, but this did not exceed the SEM (refer to Figure 4-14). However, in the other three intervention weeks, when the intervention was potentially mistimed, there was a decrease in corticomotor excitability, which exceeded the SEM for two measurements. This raises the concern that the mistimed intervention had an inhibitory effect, although this is not supported by previous literature where mistimed novel-PAS had no effect[200,204]. Alternatively, this inhibition may have resulted from the long and physically-demanding session, either through post-exercise MEP inhibition[331] or by decreasing intervention efficacy due to the loss of attention to task, a factor which is known to influence neuromodulatory effects[212]. Another possibility is that MEPs recorded following the intervention fluctuated due to the change in background muscle activity, as the direction of the MEP changes followed the direction of changes in background activity in all four measurements. In consideration of the concerns with intervention fidelity, confounding variables, and MEP reliability, the meaning of changes in corticomotor excitability for this participant is unclear.

Overall, this participant experienced improvements in impairment and neurophysiological measures, but it is not clear whether these changes resulted from the intervention. Improvements may be attributable to aspects of the research protocol. For example, the improved ability to perform step-ups may have occurred as a result of the regular step-up practice during TMS measures, as it is well known that task-specific practice produces functional improvements[151,332,333]. Additionally, this participant reported practising stairs at home, which may have contributed to improvements.

- **Novel-PAS participant 4**

This participant experienced a number of unrelated illnesses which necessitated a 20-day break midway through the intervention period and also resulted in the final MEP, MRCP, and ankle strength measures not being collected. Thus, illness was a significant confounder for this participant, and likely influenced the deterioration in hemiparetic leg step test score (-7) (refer to Table 4-4). There were some concerns with timing of the intervention in the third and fourth intervention weeks. Nevertheless, a visible improvement was seen in this participant's EMG waveforms during walking, with baseline measures showing only a single heel-strike burst, and post-intervention measures showing both heel-strike and toe-off bursts (refer to Figure 4-8). In addition, the EMG waveforms during step-ups showed improvements in the amplitude and duration of TA burst activity, and a reduction in waveform variability (refer to Table 4-8), which indicates a more consistent pattern of activation. There were also changes in the MRCP over the course of the intervention. The amplitude of the early movement preparation phase (600-800ms before PN) and the PN decreased progressively between baseline and the week 3 measurement, the period in which the protocol was delivered continuously (refer to Figure 4-13). This may suggest that over time the task was becoming easier to perform and required less effort[275]. The single assessment of the within-session effects on isometric MEPs did not reveal any changes that exceeded measurement error (refer to Figure 4-14). Overall this participant experienced improvements in neurophysiological measures, despite some functional decline in balance. The role that the novel-PAS intervention played in these changes is not clear.

- **Sham participant 2**

Following the four-week sham intervention, this participant could perform step-ups more quickly with their hemiparetic leg. Neurophysiological data during step-ups showed reduced variability in EMG waveforms and ankle kinematics (refer to Table 4-8 and Table 4-6) which may indicate more consistent movement patterns. There was also a decrease in peak ankle dorsiflexion during step-ups, which might be considered a deterioration in gait pattern, but

when viewed with the other results could suggest the participant was using a more efficient movement strategy to step up. As for participant 1, regular step-up practice associated with the protocol may have been the source of these changes. The amplitude of the PN of the MRCP during ankle dorsiflexion increased progressively over time (refer to Figure 4-13), a trend which is seen during acquisition of a task in healthy people[251] and might indicate learning was taking place. The single assessment of within-session changes in isometric MEPs showed a decrease in corticomotor excitability, which exceeded the SEM (refer to Figure 4-14). This inhibition is not thought to result from the sham intervention, as previous sham interventions using voluntary movements[183] or novel-PAS with mistimed electrical stimulation[204] have not changed corticomotor excitability. As hypothesised with participant 1, this may be a result of the long data collection session.

- **Sham participant 6**

At baseline, this participant had a step-test score of zero, and during 3D motion analysis could complete one step-up with hand support. Following the four-week sham intervention they could complete five step-ups with hand-support, had improved step-up time, and increased peak ankle dorsiflexion during step-ups (refer to Table 4-6). Despite this improvement, their step-test score did not improve, which reinforces the floor effect of this measure[262]. During gait, this participant had increased TA burst activity during mid-swing (refer to Table 4-7). The single assessment of within-session changes in isometric MEPs showed an increase in corticomotor excitability, but the change did not exceed the SEM (refer to Figure 4-14). The amplitude of the preparation phase of the MRCP, 200-800ms before the PN, progressively increased over the course of the study (refer to Figure 4-13). As for the other sham participant, this may be related to task acquisition and learning[251].

- **Summary of individual outcomes**

Both novel-PAS and sham participants had improvements in a selection of impairment and neurophysiological outcomes, but it is unclear whether these can be attributed to the intervention or the other aspects of the research protocol. Although there were concerns with intervention fidelity, when novel-PAS was delivered correctly it did not induce the excitatory effect seen in people with less severe lower limb motor deficits[204]. While this study was not designed to determine efficacy, these individual results do raise the question of whether previous results can be replicated in people with more severe stroke, such as those in the present study. In the present study, a treatment effect may have been masked by the inhibitory effects of the protocol suggested above, or participants may have been non-responders[243].

## Outcome measures for future research

The following section will consider which of the activity, impairment and neurophysiological outcomes used in this study might be most appropriate for future research, in terms of being both feasible and responsive to the intervention.

- **Activity measures**

Gait speed measured with the 6-m walk test is a simple and efficient measure of walking activity. However, following the four-week intervention, there were no consistent changes in gait speed that exceeded the SEM. In contrast, there were changes in the *step test* and *step-up time*, indicating that these measures were sensitive to improvements in stepping activity. The novel-PAS intervention targets the TA, which has a high level of activity during stair-climbing[284,334]. Therefore, future research should incorporate a stair-climbing outcome measure. A possible measure is the *stair-climbing ascend test* which requires participants to ascend a flight of stairs with or without rails, and has high reliability in people with stroke (ICC 0.98, SEM 6.5%)[43,335]. This measure may be preferable to the *step test* which has a floor effect[262] and *step-up time* which requires 3D motion analysis or accelerometry, but is most reliable with 3D motion analysis[266,336].

- **Impairment measures**

In the present study, isometric ankle strength measures were potentially compromised by large measurement errors. However, other ankle strength testing methods have shown excellent reliability and low measurement error in people with stroke[50]. Isometric strength tests have advantages in terms of efficiency, and can be collected simultaneously with other outcome measures, such as the ROFD and EMG[292]. Therefore, isometric strength measures should be considered in future research and alternative testing methods with less measurement error should be explored.

3D motion analysis recorded during gait and step-ups provided a number of impairment measures but took approximately 2 hours to complete. A time-consuming 27-marker model was chosen to allow for kinematic analysis; however, between-session measures are prone to errors in marker placement[264], and differences in kinematics were small, possibly because improvements in TA activation need to be larger to overcome the passive stiffness that limits ankle dorsiflexion during the swing phase[337]. Thus, ankle kinematics may not be a feasible or responsive measure for a future novel-PAS study. If kinematic data is not being measured, then a simpler, less time-consuming marker system could be used to collect spatiotemporal data during gait and step-ups.

- **Neurophysiological measures**

The EMG burst pattern and EMG rise during gait and step-ups provide useful information for understanding changes at the impairment and activity level and should be considered in future research. However, when undertaking research with a larger sample, it may not be feasible to analyse burst patterns in individual data, and therefore future research may need to focus on measuring EMG rise which can be processed more efficiently. The EMG skin preparation protocol, which required an impedance of <5 KΩ, proved problematic for some participants with fragile skin. Based on EMG literature, impedance requirements in future research can be increased to 15 KΩ[338] or to 30 KΩ for simple conditions[271].

Whether measured at the impairment or neurophysiological level, the use of gait variability measures is limited by difficulty interpreting the results. While pathological conditions are usually associated with increased gait variability due to poor neuromuscular control[339], they can also cause decreased gait variability, for example, in a spastic muscle that is restricted to a certain activation pattern[250]. Given the high inter-individual variability in hemiparetic gait patterns[340], analysis of gait variability at a group level may be problematic, and analysis of subgroups with similar gait patterns may be required. Greater access to gait variability data from the wider stroke population would assist with interpretation.

As previously discussed, the use of TMS measures presented a major barrier to recruitment. In addition, TMS measures contributed approximately 1 hour 48 mins to the total session duration of just over 3 hours and are a major reason why the participant burden of the study was considered unacceptable. While TMS time requirements could have been reduced considerably by applying TMS to the resting muscle only, rather than during an active contraction or during step-ups, this would have restricted recruitment further. MEPs are more difficult to produce in the resting muscle in people with stroke[279] because they depend on a certain level of excitability at multiple sites: cortical axons, cortical synapses and spinal synapses[341]. Whereas, active MEPs are easier to produce, as the active contraction raises the excitability of spinal synapses[116,341]. In addition to these feasibility issues, the usefulness of TMS is limited by the poor between-session reliability of lower limb MEPs in people with stroke[236]. Thus, despite TMS being a widely accepted tool used to assess the excitability of corticospinal pathways[112-114], it presents major feasibility issues which appear to outweigh its usefulness as a measure of intervention efficacy.

The MRCP is an alternative measure of neural activity. While being a logical choice as an outcome measure, because it is already recorded as part of the novel-PAS intervention, there

were some technical issues with the concurrent TA EMG recording. This meant that the MRCP data could only be time-locked to the cue to move. While this is standard practice in cue-based movements in healthy people[192,342,343], in the stroke population who have some difficulty regulating the timing of movements, the MRCP is time-locked to the cue and the movement onset separately, and this can provide slightly different results[344]. Future research should ensure that the EMG and MRCP epochs are numbered so that any gaps in data collection do not limit the matching of the epochs. However, difficulty identifying EMG onset in stroke data with very low amplitudes may continue to limit the ability to time-lock MRCPs to movement onset. The usefulness of the MRCP as a potential outcome measure is limited by difficulty interpreting the meaning of changes. In this study there were both increases and decreases in MRCP amplitude (refer to Figure 4-13). Larger amplitude MRCPs could be interpreted as a positive outcome because they have been associated with task learning in healthy people[251] and with excitatory neuromodulation in people with stroke[345]. By contrast, smaller amplitude MRCPs could be interpreted positively, because they suggest the task requires less effort[275] and have been observed following a one-month rehabilitation programme in people with stroke[252]. Further research is required to understand the meaning of changes in the MRCP and explore its potential as a measure of the cumulative effects of novel-PAS on neural plasticity.

## Outcome measures summary

This section has described the changes observed in a number of activity, impairment, and neurophysiological measures following the intervention. Both novel-PAS and sham participants improved in a selection of measures, which indicates that future research should continue to make comparisons with an attention- and dose-matched sham intervention.

The TMS results did not concur with previous reports of increased corticomotor excitability immediately following novel-PAS[204], and therefore further research is warranted to confirm the excitatory effects of novel-PAS in a broader sample of people with stroke. Yet, because TMS has poor feasibility, other measures which might detect the within-session excitatory effects of novel-PAS should be explored.

A range of measures have been considered for future research into the cumulative effects of novel-PAS. In summary, to measures changes at the activity level, a stair-climbing measure is recommended. Researchers should consider alternative methods of measuring TA strength to reduce measurement errors of strength tests. Full 3D analysis of kinematic data is not recommended due to limited sensitivity and time requirements. However, a simplified 3D marker system could be considered to reduce the time-burden of recording spatiotemporal

parameters during step-ups. EMG can be simultaneously recorded during 3D motion analysis, and future work should focus on analysis methods that can be applied to group data. The MRCP and gait variability outcomes should continue to be explored as potential measures, but changes in these parameters should be interpreted with caution.

### 4.5.4 STUDY LIMITATIONS

With regard to the feasibility findings of this study, the main limitation was the low sample size. It is unlikely that a larger sample size would have altered the overall findings in relation to feasibility, but it may have provided further qualitative data related to acceptability. The low sample size also meant that group outcomes could not be analysed, but individual data provided some insight into the usefulness of the activity, impairment and neurophysiological outcome measures. Error of measurement data was used to determine whether individual changes were large enough to indicate a true change, but as SEMs were not available for some measures, the approach of using SEMs from similar measures may have led to an over- or under-estimation of the actual measurement error. There were limitations associated with a number of outcome measures used in this study. Kinematic results suggested that marker placement may have differed between sessions. Two participants wore shoes during 3D motion analysis due to discomfort walking barefoot, and this may have affected the reproducibility of foot marker placement. These issues were remedied by measuring the degree of change from a neutral ankle position. The VR of TA EMG was calculated from 5-10 gait cycles and 7-9 step-up cycles, which falls short of the 10-16 cycles reported in other literature[267,285]. Another limitation with the VR measure was that while the toe-off time was averaged within each recording of 4-5 steps, several recordings were combined to produce the VR, and this may have slightly raised the VR value due to marginally different toe-off times.

## 4.6 SUMMARY

This study was the first to explore the feasibility of the novel-PAS intervention and offers novel findings which will guide future research and possible translation to rehabilitation practice. The novel-PAS intervention in its current form was not acceptable to people with stroke and was vulnerable to delivery errors. In addition, there were concerns about the reliability of the method utilised to identify the PN of the MRCP. The technical challenges identified have raised questions about the extent to which difficulties carrying out the intervention protocol have influenced previous novel-PAS research. Further research should be carried out to optimise the novel-PAS intervention and continue to identify barriers to its

implementation into rehabilitation practice. Specific research should be carried out in the following areas:

- To improve consistency of intervention delivery, further research is required to assess the intra- and inter-rater reliability of the timing of the PN from the averaged MRCP in people with stroke. Recent developments in technology to automatically identify the PN (U. Rashid, unpublished data, 2019) should also be considered.
- To improve usability, efficiency and acceptability, the novel-PAS intervention should be miniaturised into a wearable BCI.
- To improve motivation and engagement, researchers should consider alternative methods to deliver novel-PAS, including in a group setting, and during higher-intensity exercise. This will better align the intervention with the rehabilitation expectations of people with stroke.
- To improve motivation, the visual cue should be modified to include principles of gamification.

This study also demonstrated that the RCT protocol was not feasible for future research. The main problems with feasibility arose due to the time requirements of the study, and the use of TMS as an outcome measure. The following recommendations have been made to improve the feasibility of future research protocols:

- To improve recruitment and retention, data collection sessions should be kept under 90 minutes. The overall time-commitment of the study and its accessibility to people with stroke should also be considered.
- To improve recruitment and reduce selection bias, TMS measures should be avoided.
- To avoid loss of data due to illness, the protocol should maintain a degree of flexibility with data collection time-points.
- To avoid measurement errors, any modifications to equipment or processes during the course of the study should be communicated to all team members.
- To improve acceptability, the physical requirements of the protocol must be considered, and the participants' comfort prioritised.
- To improve participation and engagement with the protocol, researchers should provide education about the research process, as guided by the participant's interest, provide feedback about performance, and maintain a positive and engaging environment.

Although the novel-PAS intervention was vulnerable to errors, when it was delivered correctly, it did not produce the within-session excitatory effects seen in previous stroke research conducted by the same research team in Aalborg University[204]. This previous work was undertaken with people with milder lower limb motor deficits. This chapter has raised concerns about the internal and external validity of this previous novel-PAS research, indicating further research is needed to confirm the within-session effects of novel-PAS in the wider stroke population. Specifically, this research should:

- Explore the within-session effects of novel-PAS on measures other than TMS MEPs, which limit recruitment and increase time requirements. This research will be the focus of Chapter 5.

Following exploration of the within-session effects of novel-PAS, further research should be undertaken to investigate the cumulative effects of novel-PAS. The design of this research should incorporate recommendations made in this chapter about selection of outcome measures. In addition, as participants from both the novel-PAS and sham groups in the present study showed some improvement in a selection of impairment and neurophysiological measures, future research should use an attention- and dose-matched sham intervention, to ensure the effects of novel-PAS can be distinguished from the effects of a sham intervention or the research protocol.

# Chapter 5.
# Study C. Immediate effects on strength, fatigue and voluntary activation

## 5.1 PROLOGUE

Chapter 4 presented Study B, which investigated the feasibility of a four-week RCT protocol. It was intended that this feasibility study would lead on to a fully-powered RCT, which would address the fourth research question identified in Chapter 2 concerning the cumulative effects of novel-PAS in people with stroke. However, the Study B protocol was not feasible for further research. In addition, Study B identified the need to conduct further research to confirm the within-session effects of novel-PAS in the wider stroke population. Chapter 5 will address one of the key feasibility issues identified in Study B; the use of TMS as an outcome measure. This chapter will explore alternative outcome measures to TMS and will then present Study C, which was undertaken to investigate the within-session effects of novel-PAS on a selection of impairment and neurophysiological measures.

## 5.2 INTRODUCTION AND OBJECTIVE

One of the key recommendations from the pilot RCT was that further research was required to determine the within-session effects of novel-PAS in the wider stroke population, using a measure other than TMS, and keeping data collection sessions under 90 minutes (refer to 4.6). While TMS measures are commonly used to assess the neurophysiological effects of neuromodulation, a range of other neurophysiological and impairment measures have been used to illustrate the effects of neuromodulatory interventions targeting the M1. This section will introduce potential outcome measures that could be used to measure the within-session effects of novel-PAS, and will then propose a research study which aims to explore the within-session effects of novel-PAS on measures which do not require TMS.

### 5.2.1 POTENTIAL NEUROPHYSIOLOGICAL MEASURES

While TMS measures of corticomotor excitability are most commonly used to illustrate the effects of neuromodulation, a number of other neurophysiological measures have potential to illustrate the immediate effects of interventions like novel-PAS.

The first potential measure is *voluntary activation* which represents the voluntary neural drive to a muscle during a voluntary contraction[346]. Voluntary activation is measured with the interpolated twitch technique, and involves applying supramaximal electrical stimulation to a motor nerve[346-348] or muscle[349-351] to produce two muscle twitches; the first twitch is applied while the target muscle is at rest, and the second is applied while the muscle is performing an active contraction. Figure 5-1 illustrates muscle twitches evoked at rest and during an MVIC.

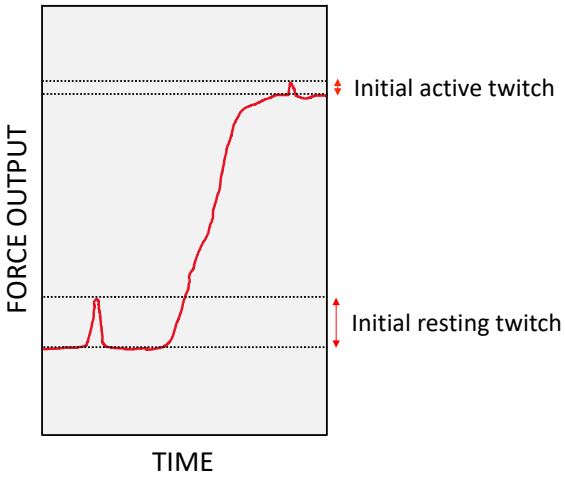



Figure 5-1 Schematic of force trace showing muscle twitches applied at rest and during an active MVIC for voluntary activation calculation

The calculation of voluntary activation involves presenting the torque produced during the active muscle twitch as a proportion of torque produced during the resting muscle twitch, and indicates the proportion of muscle activation that is not under voluntary control[346]. Voluntary activation deficits indicate incomplete activation of motor units due to insufficient recruitment or discharge rate[349], and can arise from dysfunction at any point proximal to the electrical stimulation, such as in the cortex, subcortical areas, descending tracts, or motor axons[352]. There is a body of literature linking voluntary activation deficits with conditions in which corticomotor excitability is reduced, such as in the hemiparetic limb following stroke[135,136,295,353], in healthy muscle following fatiguing exercise[354], and in the quadriceps muscle following anterior cruciate ligament injury[355-357]. This suggests that voluntary activation might change in response to neuromodulation. Findings from one study have

supported this idea, demonstrating that four days of tDCS produced an increase in voluntary activation in healthy participants[358]. For people with stroke, in whom voluntary activation deficits are associated with poor functional performance[295], improvements in voluntary activation may have functional consequences.

The next two potential measures are recorded during a sustained muscle contraction. Sustained exercise causes neuromuscular fatigue, that is, a decrease in a muscles capacity to generate force[352]. Neuromuscular fatigue can arise centrally, due to loss of supraspinal and spinal output, or can arise from peripheral changes[352]. The next potential outcome measure, *central fatigue*, can be used to evaluate the central component of neuromuscular fatigue[352]. Central fatigue is measured with the interpolated twitch technique and involves calculating voluntary activation at the start and end of a fatiguing exercise[352]. Central fatigue is the change in voluntary activation over the course of the exercise[352]. Figure 5-2 illustrates muscle twitches evoked at the start and end of a 30-second sustained contraction from which central fatigue can be calculated. Following stroke, central fatigue is more prominent in the hemiparetic limb[61]. Neuromodulatory interventions that modulate M1 excitability are thought to be able to influence neuromuscular fatigue at a supraspinal level, for example, by reducing intracortical inhibition[331,359]. Thus, measures of central fatigue have potential to illustrate the effects of novel-PAS in people with stroke. Only one study has investigated central fatigue following neuromodulation with PAS, and this showed no significant change in voluntary activation at the end of a 15-second soleus muscle contraction in healthy participants[174]. Although it is important to note that these findings were with a short-duration contraction and not in the stroke population.

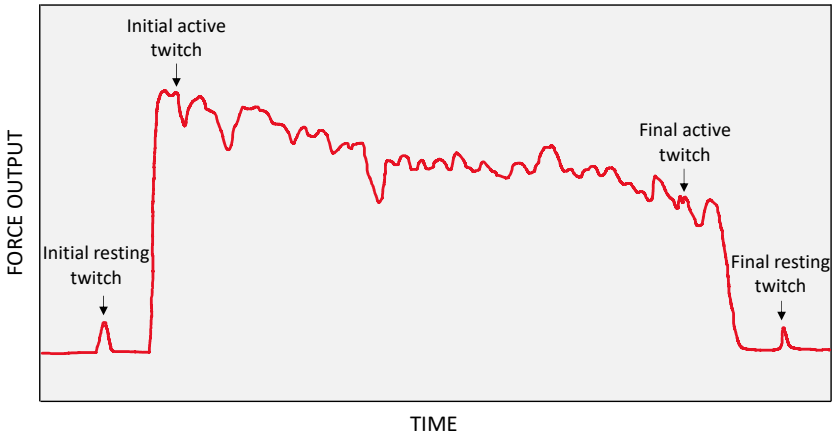



Figure 5-2 Schematic of force trace showing muscle twitches applied during a 30-second MVIC for calculation of central fatigue and peripheral fatigue

In contrast to central fatigue, *peripheral fatigue* is a measure that represents the loss of contractile ability of the muscle due to changes at, or distal to, the neuromuscular junction[352,360,361]. Peripheral fatigue is measured by applying supramaximal electrical

stimulation to the resting nerve or muscle, and presenting the twitch torque produced after exercise as a proportion of the twitch torque produced before exercise[352]. The twitches applied to the resting muscle in Figure 5-2 are used for this calculation. While neuromodulatory interventions are not thought to specifically target peripheral mechanisms, their effects on central fatigue may allow the muscle to be driven more fully, which in turn, would produce greater levels of peripheral fatigue[61]. Thus, both central and peripheral fatigue offer potential measures to explore the effects of novel-PAS.

The final two neurophysiological measures are extracted from surface EMG signals. The *EMG amplitude* provides a measure of motor unit activity[60] and is decreased in the hemiparetic limb after stroke[294,295]. EMG amplitude is potentially modifiable with neuromodulatory interventions, as evidenced by research in healthy people where tDCS applied over the M1 produced an immediate increase in peak EMG amplitude during an MVIC[253]. Another EMG measure is the *median frequency* of the power spectrum, which is the gold standard for assessing fatigue-related EMG changes[362], and is known to decrease during sustained exercise[363,364]. This measure has not been specifically investigated following neuromodulation, but given the potential for neuromodulatory interventions to influence supraspinal sources of neuromuscular fatigue[359], it is foreseeable that they might alter the EMG median frequency.

### 5.2.2 POTENTIAL IMPAIRMENT MEASURES

There are a range of impairment measures seen in the neuromodulation literature that have potential to illustrate the effect of novel-PAS. The first impairment measure is *isometric muscle strength*, measured with an MVIC. Studies have shown that tDCS targeting the M1 can produce immediate increases in muscle strength in healthy people[365,366] and people with stroke[248,249]. The second measure of interest is *total neuromuscular fatigue*, which quantifies the loss of capacity to generate force during sustained exercise, and is a gauge of neuromuscular endurance[367]. Studies have shown improved neuromuscular fatigue immediately following rTMS[368] and tDCS[359,369,370] to the M1 in healthy people. A third measure, *muscle power*, has received less attention but has been shown to improve immediately following tDCS over the healthy M1[371]. This literature suggests that the novel-PAS intervention, which also targets the M1, might produce immediate changes in isometric muscle strength, total neuromuscular fatigue and muscle power. A number of tDCS studies in people with stroke have also shown improvements in aspects of movement control, such as hand dexterity[372,373] and response time[374,375], but as these studies have targeted the upper limb, these measures will not be considered for novel-PAS research targeting the lower limb.

### 5.2.3 PROPOSED RESEARCH OBJECTIVE

Based on the outcome measures reviewed, the objective of the following study was to establish the within-session effects of novel-PAS on the primary outcomes of isometric muscle strength and total neuromuscular fatigue of the ankle dorsiflexor muscles. These primary outcome measures were chosen because they had the most literature to support their potential to illustrate the effects of neuromodulation. The primary research questions were:

1. *Does novel-PAS produce an immediate improvement in isometric muscle strength of the ankle dorsiflexors, more than an attention- and dose-matched sham intervention, in people with chronic stroke?*
2. *Does novel-PAS produce an immediate improvement in total neuromuscular fatigue of the ankle dorsiflexor muscles, more than an attention- and dose-matched sham intervention, in people with chronic stroke?*

The study also investigated, but was not powered to detect, the effects of novel-PAS on a range of secondary measures of impairment (neuromuscular fatigue and muscle power) and neurophysiology (voluntary activation, central fatigue, peripheral fatigue, EMG activity, and corticomotor excitability). Measures of corticomotor excitability were included to confirm previous findings but were only collected if deemed safe and tolerable for participants, to ensure this did not limit recruitment or retention.

## 5.3 METHOD

### 5.3.1 STUDY SETTING AND DESIGN

The study was a double-blind, within-subject, repeated-measures, cross-over experiment. Each participant received one *novel-PAS intervention* and one *sham intervention*, in a randomised order, at least seven days apart. Pre- and post-intervention measures were recorded during each session. Participants were aware they were receiving two different interventions but were unaware a sham intervention was being used, and instead were advised that the two interventions were *moderate intensity* and *low intensity*. The participants, the researcher performing outcome assessments, and the researcher performing data processing and analysis, remained blinded to randomisation. Data analysis did not proceed until all data had been collected. Unblinding took place after the completion of all data analysis. This study was undertaken at the Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand.

### 5.3.2 PARTICIPANTS

## Sample size

A sample size calculation was performed based on available evidence from previous studies investigating the efficacy of similar neuromodulatory interventions on isometric muscle strength in the lower limb of people with stroke[248,249] and on total neuromuscular fatigue measured as the force lost during an isometric MVIC in the upper limb of healthy people[368]. Evidence investigating total neuromuscular fatigue in people with stroke was not available. Studies that had determined neuromuscular fatigue using submaximal tasks did not inform the sample size calculation[359,369,370,376,377]. Based on the above data, a sample size of ten was would enable the detection of statistically-significant differences in within-session measures of isometric muscle strength and total neuromuscular fatigue (80% power, alpha 0.05). However, to account for limitations in the evidence-base and risk of drop outs, the sample size was elevated to 15 participants.

## Inclusion criteria

Volunteers were considered for inclusion in the study if they met the following criteria:

- Over 18 years of age
- Single stroke more than six months previously
- Hemiparesis affecting the ability to move the ankle

## Exclusion criteria

Volunteers were excluded from the study if they had any of the following conditions:

- Significant cognitive, perceptual or communication deficits.
- Cerebellar stroke
- Contra-indications to peripheral electrical stimulation
- Inability to generate ankle dorsiflexor force in the ankle dynamometer
- Medical conditions that would impact the safety of participant or the reliability of the results, as determined by the researcher during screening.

## Ethical and cultural considerations

The study protocol was peer reviewed by an external researcher and by the Matauranga Maori Committee. Ethical approval was obtained from the New Zealand Health and Disability Ethics Committees (HDEC) (Appendix M). Locality approval was received from AUTEC

(Appendix N). The study was registered with the Australian New Zealand Trials Registry (Trial ID ACTRN12617000838314).

### 5.3.3 STUDY PROCEDURE

#### Recruitment strategy

Participants were recruited through: a small database of previous research participants who were interested in taking part in research, liaison with private and public neurological physiotherapists, verbal presentations to health providers and support groups, and collaboration with Te Puna Hauora Medical Clinic with the aim of reaching potential Maori participants.

#### Screening and consent

All potential participants who expressed an interest in the study were provided with the participant information sheet (Appendix O). Potential participants were screened for eligibility over the telephone or in person by a trained research physiotherapist, who sought information about relevant medical conditions, medications, and contraindications or cautions to electrical stimulation and TMS (Appendix P). Potential participants who met the study criteria were offered a face-to-face appointment to screen health information in person, confirm presence of a hemiparesis, answer any questions, and gain written consent (see end of Appendix O).

#### Study flow

The study flow is outlined in Figure 5-3 and involved participants attending three sessions. The first session involved face-to-face screening, discussion about what the study involved, provision of written informed consent, recording of the MRCP, and a trial of TMS if applicable. Following consent, the order in which each participant would receive the novel-PAS and sham interventions was determined according to a randomisation schedule. The interventions were then delivered in two further sessions, 7 days apart. Outcome measures were collected before and after each intervention. After the conclusion of the study, participants were offered a free physiotherapy session, as thanks for their time.

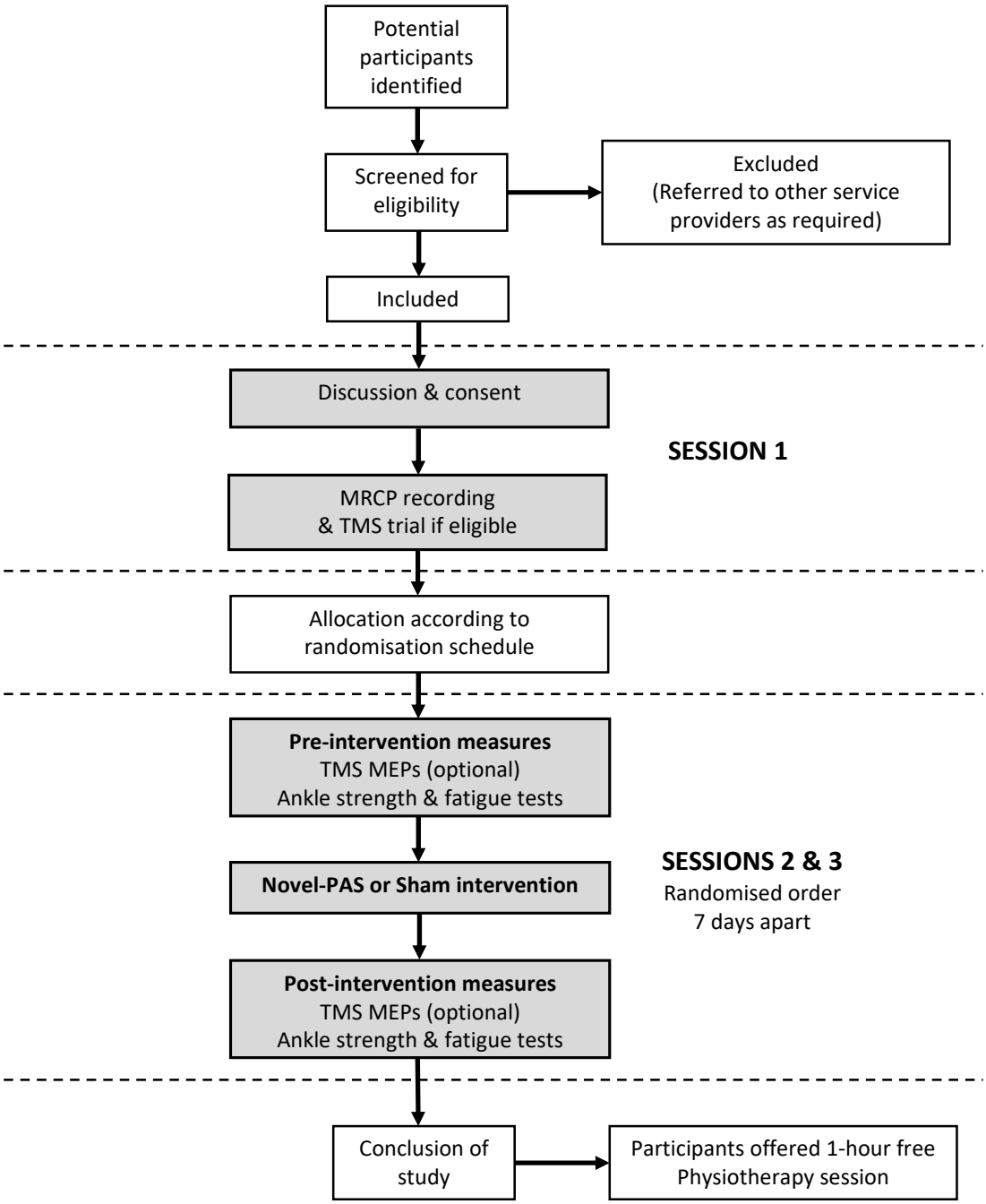



Figure 5-3 Study flow for Study C

## Session 1

Following consent, the MRCP was recorded according to the method described in Study B (refer to 4.3.5), with the only change being that participants sat in a height-adjustable armchair with their hemiparetic leg supported with the knee in approximately 50° of flexion. Potential participants had been advised that TMS measures were optional. Following the MRCP recording, participants who were eligible were given the opportunity to trial receiving TMS, to determine their ability to tolerate the stimulation. If TMS was not deemed safe, or

not deemed tolerable in terms of comfort or the extra time required, sessions 2 and 3 were conducted without TMS measures.

MRCP data was processed according to the method described in Study A (refer to 3.3.4), but to improve reliability, this was carried out independently by two experienced researchers. If the PN timing differed by more than 10ms, the two researchers repeated the MRCP processing together. If the PN timing differed by less than 10ms, an average of the two measures was used. If any disagreement occurred, a third researcher was consulted.

## Randomisation

The randomisation schedule was generated prior to the study via a randomisation website[378]. This schedule was held by a third party and only shared with the research assistants who delivered the interventions. At the point of consent, each participant was allocated a consecutive number between 1 and 15, and then the randomisation schedule was consulted to determine the order in which each participant would receive the interventions.

## Sessions 2 and 3

Participants attended two intervention sessions, at least 7 days apart. Outcome measures were collected immediately before and after each intervention. These included TMS measures for those participants who were eligible, three brief MVICs of the hemiparetic ankle dorsiflexor muscles, and one 30-second MVIC of the hemiparetic ankle dorsiflexor muscles. The order of measurements can be seen in Figure 5-4. A full description of each outcome measure will be presented in section 5.3.4 'Outcome measures and processing', and the procedures for collecting measurements will be presented in section 5.3.5 'Testing procedures'.

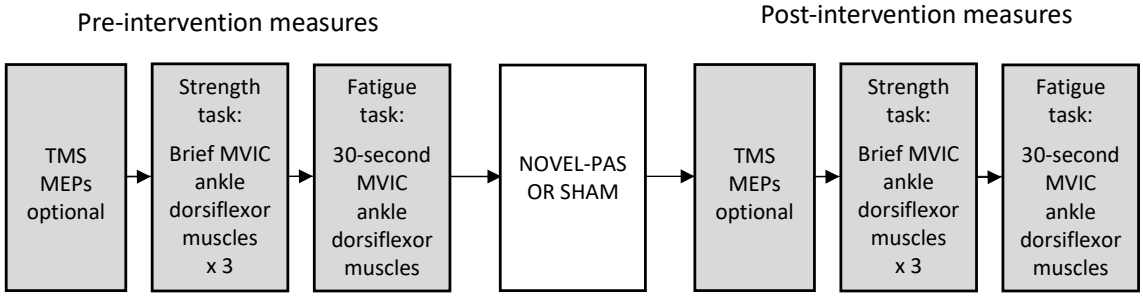



Figure 5-4 Order of procedures during sessions 2 and 3 for Study C

### 5.3.4 OUTCOME MEASURES AND PROCESSING

## Corticomotor excitability

TMS-induced MEPs of the TA were used as a measure in Study A and B and their within-session reliability has been previously described (refer to 4.3.4). TA MEPs were screened according to the method described in Study B (refer to 4.3.5), with the additional criteria that MEPs were excluded if there was TA EMG activity prior to the TMS pulse. The MEP onset was identified as the point where the rectified EMG signal exceeded the mean baseline by two SDs and this was confirmed visually. The background activity was measured as per the method described in Study A (refer to 3.3.1). The MEP area was calculated by measuring the area below the rectified EMG signal in a 30ms window from MEP onset. The MEP amplitude was determined by measuring the maximum peak-to-peak amplitude of the raw EMG signal. The 10 MEP area and 10 MEP amplitude measures were averaged to give a mean MEP amplitude and mean MEP area for each individual at each pre- and post-intervention measurement.

## Outcomes recorded during maximum voluntary isometric contraction

- **Maximum voluntary isometric contraction**

The primary outcome of MVIC has been previously described as a measure of isometric ankle strength in Study B (refer to 4.3.4). To improve accuracy and sensitivity of MVIC measures, a rigid device was utilised in the present study to ensure improved fixation of the thigh and foot. Three repetitions were performed and MVIC data was calculated by measuring the difference between the mean signal in a 500ms baseline period (or 1 second period if the baseline was unsteady) and the peak amplitude for each MVIC, using Spike2 software (CED, UK). Force values were converted from volts to Newtons according to a scaling factor determined from calibration data.

- **Muscle power - Rate of force development 0-200ms**

The ROFD in the first 200ms (0-200ms) of each of the three MVICs was used as a measure of muscle power, and is an indication of central nervous system drive to the muscle and motor unit discharge rates[379]. ROFD is reduced in the hemiparetic limb after stroke[55,380]. ROFD 0-200ms has excellent reliability in healthy adults[381]. MVIC force signals were exported from Spike2 software into LabVIEW software, and low-pass filtered at 15Hz. The onset of each MVIC was identified automatically as the point where the signal exceeded the baseline signal by 3 SDs, and then confirmed visually. The baseline window and the onset

threshold could be individualised to ensure the onset was identified correctly for each contraction. The ROFD 0-200ms was calculated for each MVIC in N/s.

- **Muscle power - Time to 90% of MVIC**

The time taken to reach 90% of peak force during each of the three MVICs was used as a gauge of muscle power over the majority of the muscle contraction. This measure is impaired following stroke[56] and in healthy people is a more reliable measure than the time taken to reach 100% force[382]. Deficits in lower limb muscle power are significantly correlated with reduced function after stroke[57,58]. Using the same LabVIEW processing described for the ROFD 0-200ms measure above, the time taken to reach 90% of peak force in seconds (s) was calculated for each MVIC. Measures of MVIC, ROFD 0-200ms, and time to 90% MVIC are illustrated in Figure 5-5.

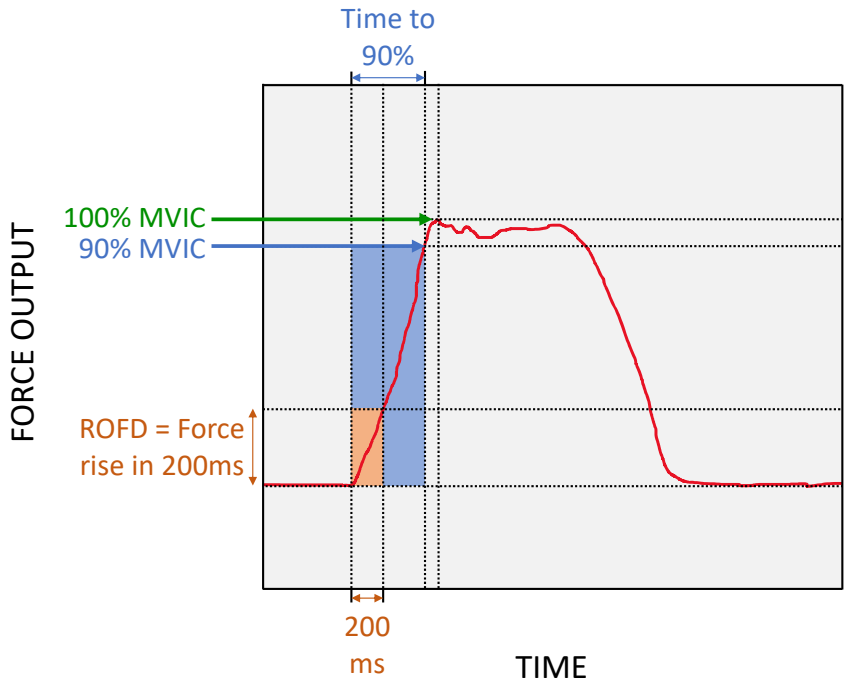



Figure 5-5 Schematic showing force trace during MVIC and outcome measures of ROFD 0-200ms and time to 90% MVIC.

- **Peak EMG amplitude**

The peak amplitude of the TA EMG signal during each of the three MVICs was used as a measure of motor unit activation. Peak EMG amplitude is reduced in people with stroke[294,295] and has been shown to be highly reliable in the TA of healthy adults[383]. Raw EMG signals were exported from Spike2 software into LabVIEW software, band-pass filtered (10-500Hz) and rectified. The peak root mean square (RMS) of the EMG signal for each MVIC trial was calculated by subtracting the RMS of the baseline signal in a window when the participant

was not moving, from the RMS of the signal in a 1-second window surrounding the point of peak force.

- **Voluntary activation**

Voluntary activation was collected at the start of the 30-second fatigue task. However, because the first part of the fatigue task involves an MVIC, this measure is described in this section with other MVIC measures. Voluntary activation is calculated with the interpolated twitch ratio, which involves delivering an electrically-stimulated muscle twitch during a period of rest (initial resting twitch), and then during an MVIC (initial active twitch). The additional force produced during these muscle twitches is illustrated in Figure 5-1. Voluntary activation has high inter-session reliability in the quadriceps muscle in participants with stroke using a doublet pulse[384] and in healthy participants using a single pulse[350]. It is acknowledged that an alternative calculation of voluntary activation exists, the central activation ratio[385-388]. While the central activation ratio has been shown to be reliable in healthy people[388], its reliability has not been investigated in people with stroke, and it may overestimate voluntary activation levels when compared with the interpolated twitch method[389]. Thus, the interpolated twitch ratio was used to calculate voluntary activation.

Using Spike2 software (CED, UK), resting and potentiated twitches were identified visually, but with consideration for the biologically feasible twitch duration and latency[347,348,352,386], to ensure the twitch was measured, and not any pre- or post-twitch muscle activity. Twitch amplitudes were exported into Microsoft Excel software and used to calculate voluntary activation, as per the following equation.

$$\text{Voluntary activation at start of task (\%)} = \left(1 - \frac{\text{Initial active twitch}}{\text{Initial resting twitch}}\right) \text{x } 100$$

## Outcomes recorded during fatigue task

- **Area under the curve fatigue index**

The second primary outcome was the area under the curve (AUC) fatigue index during a 30-second MVIC. This can be used to quantify neuromuscular fatigue[367,390]. While the loss of force between the start and end of a fatigue task is often used to index fatigue (refer to simple fatigue index below), research in people with multiple sclerosis has shown that the AUC fatigue index is a more reliable method and allows quantification of force changes that are not linear[367]. Thus, the AUC fatigue index was chosen as a primary measure. The AUC fatigue index presents the loss of force that occurs during an isometric contraction as a percentage

of the *potential* force that would be produced if the peak force was maintained throughout the exercise[367,390]. This is illustrated in see Figure 5-6 by the blue area above the force-time curve, representing the force lost during the task. The first 5 seconds of the exercise was excluded from the calculation so that the force generation phase was not measured[367]. If necessary, a slightly longer period was excluded to ensure the interpolated twitch was not included in the fatigue index calculation.

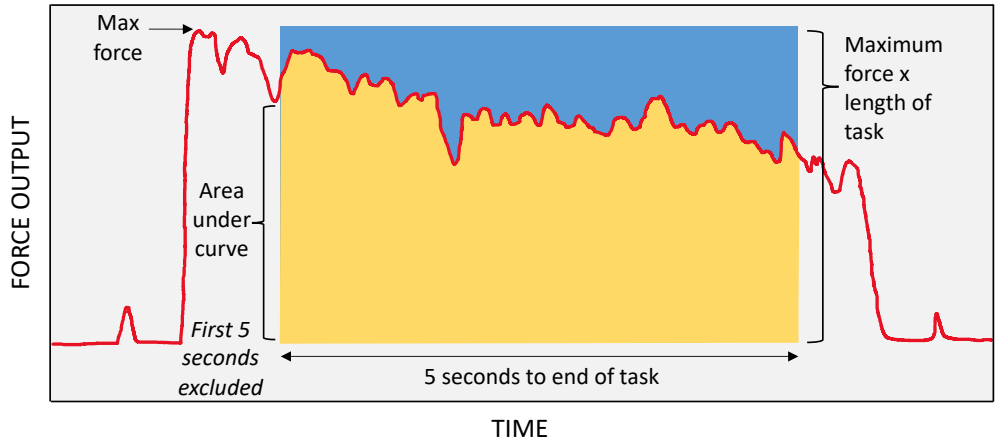



Figure 5-6 Schematic showing force trace during 30-second fatigue task and calculation of AUC fatigue index (blue area above force-time curve)

Using Spike2 software (CED, UK), the peak force and the area under the force-time curve was measured from 5 seconds into the task to the end of the task (just prior to the second active muscle twitch). This data was exported into Microsoft Excel where the AUC fatigue index was calculated with the following equation[367].

$$\text{AUC fatigue index (\%)} = \left(1 - \frac{\text{AUC}^{(\text{5 seconds to end of task})}}{\text{Max force x length of task}}\right) \text{x } 100$$

The peak force could occur anytime during the fatigue task, but if it occurred just after the interpolated twitch, then the next lowest point was used. The use of manual triggering to deliver twitches and variability in participants' ability to complete the task resulted in variation in the duration of the fatigue task between and within participants. To ensure the same level of fatigue was compared within each participant, the duration of data analysed was reduced to the minimum available for each participant.

- **Simple fatigue index**

In addition to using the AUC fatigue index as a primary outcome measure, neuromuscular fatigue was measured from the decline in force that occurs between the start and end of a fatiguing task[60]. This was calculated using the simple fatigue index, which represents the loss in force at the end of the task as a percentage of the force produced at the start of the

task[367,391]. This measure was included as a secondary measure because, unlike the AUC fatigue index, it has been used to evaluate fatigue in people with stroke[391,392]. A similar index of fatigue has shown good reliability in people with stroke (ICC 0.83)[384].

Force data was exported into LabVIEW software (National Instruments, USA), and low-pass filtered at 15Hz. Considering a baseline force value in a 200ms window prior to the initial resting twitch, the mean force was determined in a 400ms window before the initial active twitch and in consecutive 1-second windows after that until just before the final active twitch. This provided mean force values for each second of the task, which were imported into Microsoft Excel for further analysis. The simple fatigue index was calculated using the equation below, which represents the percentage loss of force between initial three epochs and the final three epochs[367]. As for the AUC fatigue index, the number of epochs analysed was reduced to the minimum available for each participant.

$$\text{Simple fatigue index (\%)} = \left(1 - \frac{\text{Mean force in final 3 epochs}}{\text{Mean force in initial 3 epochs}}\right) \text{x } 100$$

- **Central fatigue**

Central fatigue, is calculated as the difference between voluntary activation at the start and end of the fatigue task[352] and has good reliability in people with stroke (ICC 0.82)[384]. As well as applying electrically-stimulated muscle twitches at the start of the task for measuring voluntary activation, twitches were also applied just before the end of the fatigue task (final active twitch) and after the fatigue task when force had returned to baseline (final resting twitch). The additional force produced during these muscle twitches was illustrated in the introduction (refer to Figure 5-2). Twitch amplitudes were processed as described for voluntary activation above. Voluntary activation at the end of the task, and then central fatigue, were calculated using the following equations.

$$\text{Voluntary activation at end of task (\%)} = \left(1 - \frac{\text{Final active twitch}}{\text{Final resting twitch}}\right) \text{x } 100$$

$$\text{Central fatigue (\%)} = \text{Voluntary activation start task - Voluntary activation end task}$$

- **Peripheral fatigue**

Peripheral fatigue, described in the introduction, is calculated using twitch interpolation and is the difference between the twitch force evoked in the resting muscle at the start and end of a fatigue task[352]. This measure has fair reliability in people with stroke[384].

Twitch amplitudes were processed as described for voluntary activation. Peripheral fatigue was measured using the following equation.

$$\text{Peripheral fatigue (\%)} = \left(1 - \frac{\text{Final resting twitch}}{\text{Initial resting twitch}}\right) \text{x } 100$$

- **Decline in EMG amplitude**

The change in TA EMG amplitude during a fatigue task was used to measure the decline in motor unit activation associated with fatigue[60]. This measure presents the loss in TA EMG amplitude during a fatigue task as a percentage of the EMG amplitude at the start of the task, and has been shown to be more reliable than using the slope of the line of best fit[363].

Raw TA EMG signals were exported into LabVIEW software (National Instruments, USA), band-pass filtered (10-500Hz) and rectified. The EMG was divided into epochs, with the first epoch being a 400ms-window before the initial active twitch, and all other epochs containing consecutive 1-second windows between the initial and final active twitches. The RMS of the EMG was determined and the mean value in each epoch was calculated and normalised to the peak EMG RMS recorded during the pre-intervention MVIC task. As with the force data, the epochs were reduced to the minimum number collected for each participant. The percentage loss in EMG RMS during the fatigue task was calculated with the following equation.

$$\text{RMS EMG loss during fatigue task (\%)} = \left(1 - \frac{\text{RMS final epoch}}{\text{RMS initial epoch}}\right) \text{x } 100$$

- **Decline in EMG median frequency**

The change in TA EMG median frequency during a fatigue task was used to measure the change motor unit discharge rate associated with fatigue[393]. This measure presents the loss in TA EMG median frequency during a fatigue task as a percentage of the EMG median frequency at the start of the task, and has been shown to be more reliable than using the slope of this decline[363].

Using the processed TA EMG signals imported into LabVIEW software (described for EMG amplitude measures), the power spectrum was determined using a fast Fourier transform algorithm and the median frequency in each epoch was identified. As with the force data, the epochs were reduced to the minimum number collected for each participant. The percentage loss in median frequency of the EMG during the fatigue task was calculated with the following equation, using absolute values.

$$\text{Median frequency (MF) loss during fatigue task (\%)} = \left(1 - \frac{\text{MF final epoch}}{\text{MF initial epoch}}\right) \times 100$$

### 5.3.5 PROCEDURES FOR OUTCOME MEASURES

#### Measurement set-up

Participants were seated in an orthopaedic height-adjustable armchair. Their hemiparetic leg was positioned on a purpose-built dynamometer that was secured to the floor, with a fixed footplate angled 25° to the floor. For those participants who received TMS outcome measurements, these took place prior to the dynamometer measurements, with the foot positioned on foam padding overlying the force plate. For the subsequent outcome measures, the participant's leg was secured to the foot plate with three straps over the ankle, metatarsals and toes[329] and a knee guard over the anterior surface of the knee to prevent hip flexion (refer to Figure 5-7).

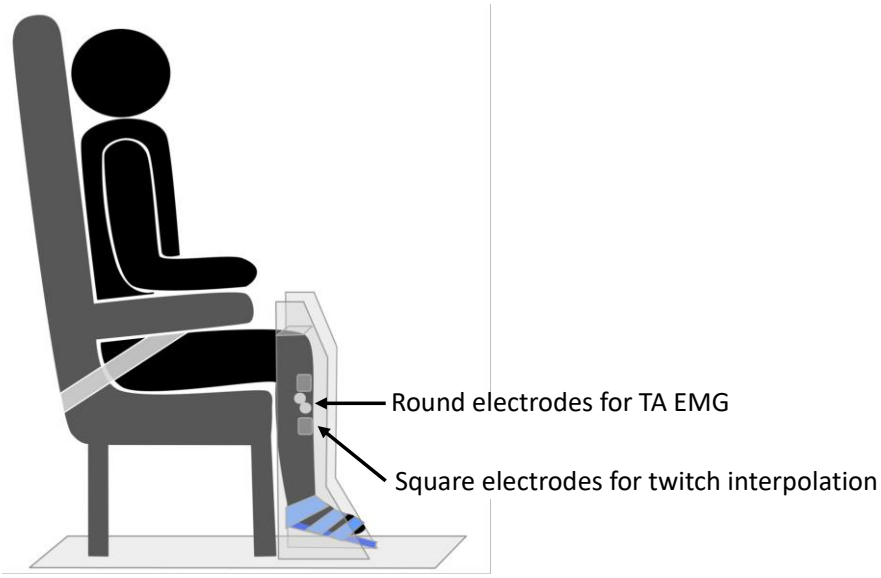



Figure 5-7 Set up for strength and fatigue tasks in Study C

The straps and knee guard were padded with neoprene to prevent skin damage. To ensure consistent positioning, the participant's popliteal fossa was in contact with the front of the

seat, and a belt was placed around the waist to prevent movement of the pelvis during testing. Joint angles were hip flexion ≈70°, knee flexion ≈80°, and ankle plantarflexion at a mean of 27°. The dynamometer measured isometric ankle dorsiflexion/plantarflexion force via a load cell (underneath the fixed footplate) with a capacity of 100lbs and error of <0.05% (Model MLP100, Transducer Techniques, California). Force signals were amplified (Forza, OT Bioelettronica, Italy) and sampled at 1961Hz using a data acquisition board (Micro 1401, CED, UK) and Spike2 software (CED, UK).

For the collection of EMG data, two sets of EMG surface electrodes (Blue sensor N, Ambu, Denmark) were placed over the hemiparetic TA and soleus muscle following skin preparation (shaving if needed, cleaning with abrasive gel and wiping with alcohol). For the TA, two electrodes were placed a third of the way along the line between the head of the fibula and the tip of the medial malleolus[231], and a reference electrode was placed on the lower third of the anterior border of the tibia. For the soleus muscle, two electrodes were placed two-thirds of the way along the line between the medial femoral condyle and the medial malleolus[231] with a reference electrode over the medial malleolus. For the TA only, impedance was checked with a digital multimeter with the aim of ensuring a level below 30KΩ[271]. If the level was higher, and the researcher deemed the participants skin integrity would not be compromised, additional abrasion was applied to reduce impedance. For TMS measures, TA EMG was amplified (AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz using a data acquisition board (Micro 1401, CED, UK) and Signal software (CED, UK). For strength and fatigue measures, TA and soleus EMG was amplified (AMT-8, Bortec Biomedical, Canada) and sampled at 1961 Hz using a data acquisition board (Micro 1401, CED, UK) and Spike2 software (CED, UK).

For the delivery of twitch interpolation, two muscle stimulation electrodes (5 x 5cm PALS, Axelgaard, USA) were placed over the hemiparetic TA muscle, just below the tibial plateau, and approximately midway down the tibia. Muscle stimulation was chosen over nerve stimulation to avoid stimulation of antagonist muscles[349]. Single 1ms pulses of electrical stimulation (DS7A, Digitimer Ltd, UK) were applied at increasing intensity until a twitch contraction was palpable at the tendon of the TA muscle, without concurrent twitches in the tendons of the peroneal, plantar flexor, or toe extensor muscles. If the desired muscle activation was not achieved, the electrodes were moved until the optimum position was located. The location of these electrodes was marked on the skin with an indelible pen. The participants were asked to watch a real-time force trace on a computer monitor while completing the strength and fatigue tasks.

### TMS testing procedure

The participant was asked to keep their ankle in a relaxed position. TMS was applied, as per the method described in Study A (refer to 3.3.4), to identify the TA *hot spot* and RMT. During each pre- or post-intervention measurement, monophasic pulses of TMS were applied at 120% RMT, eight seconds apart, to produce 10 TA MEPs.

### Maximum voluntary isometric contraction testing procedure

After securing the force plate straps, each participant completed two submaximal practices of voluntary isometric dorsiflexion, and then waited two minutes before starting the testing. Three MVICs were collected with 2-minute rests in between each. Participants were instructed to "pull as fast and hard as possible" and received loud verbal encouragement throughout the task while watching a real-time display of their force production.

### Fatigue testing procedure

After a 5-minute rest period, the intensity for delivering supramaximal electrical stimulation (DS7A, Digitimer Ltd, UK) was established. Doublet 1ms pulses (10ms inter-pulse interval, 300V) were applied to the resting TA muscle in increasing 5mA increments until there was a plateau in force production[350]. The amplitude reached was identified as 100% intensity, and subsequent electrical stimulation was delivered at 120% of this value. Participants completed a single 30-second MVIC while receiving loud continuous verbal encouragement. They viewed a real-time display of their force and were instructed to aim for a vertical cursor that was placed 2 seconds past the end point of the task. Using manual triggering, doublet pulses were applied to the TA during the initial resting period, at the start of the fatigue task once a plateau in force had been reached, at the end of the fatigue task, and after task completion (refer to Figure 5-2). As various methods are used in the ITT literature[347,348,350,351,386], this pulse method was determined during a piloting period where a comparison was made between a doublet pulse, 5-pulse burst (50Hz) and 10-pulse burst (50Hz) to determine the most effective but comfortable method. Two participants could not tolerate higher intensities of stimulation and so the maximum tolerated intensity was used[351].

## 5.3.6 PROCEDURES FOR INTERVENTIONS

### Intervention set-up

The straps and knee guard on the dynamometer were removed, and the participant's foot was positioned on foam padding overlying the force plate to allow for free ankle movement

(hip flexion ≈70°, knee flexion ≈50°). A movable bar electrode with electrode gel was placed over the dCPN, 2-5cm anterior and inferior to the head of the right fibula. For most participants this required that the proximal muscle stimulation electrode was partially peeled back to allow room for the bar electrode. Single 1ms pulses of electrical stimulation (DS7A, Digitimer Ltd, UK) were applied according to the method described in Study A (refer to 3.3.4) to determine the location and intensity of stimulation required to produce a twitch contraction at the tendon of the TA muscle. The electrode was secured with tape and the intensity determined was used in the subsequent novel-PAS intervention. Participants were oriented to the visual cue, which was identical to that used in studies A and B (refer to 3.3.4) and performed a short practice to familiarise with the technique. The blinded assessor left the laboratory prior to intervention delivery.

### Novel-PAS and sham interventions

The novel-PAS and sham interventions were delivered as described in Study B (refer to 4.3.6) and involved 50 repetitions of attempted ankle dorsiflexion in time with a visual cue, while receiving single pulses of real or sham electrical stimulation to the dCPN. Following the delivery of each intervention, the bar electrode and gel were removed, and the proximal muscle stimulation electrode was re-attached in its original position.

## 5.3.7 DATA ANALYSIS

### Data checking and completeness

Methodological errors resulted in excluded or missing data for two participants. For participant 2, incorrect timing of interpolated twitches and errors in the visual feedback resulted in the exclusion of twitch interpolation data and exclusion of the final three epochs of EMG and force data during the fatigue task. For participant 3, TA EMG data was not recorded during the MVIC task which resulted in missing EMG amplitude data for the MVIC and fatigue task.

During data collection it was noted that participant 8 was unable to complete the protocol consistently due to communication impairments that had not been apparent during the screening phase, but became problematic during data collection. Participant 15 was consistently sleepy during the experiment and required regular rousing.

Optional TMS measurements were completed for two participants. Reasons for exclusion from TMS were seizures (n=3), metalware (n=3), migraines (n=1), no resting MEP (n=2), declined (n=2), unable to tolerate (n=2).

## Statistical analysis

Descriptive statistics were performed for all outcome measures (mean, SD). As an exploratory study, data was analysed on a *per protocol* basis. Consequently, the data from participants 8 and 15 described above was removed from the analysis. The two primary outcomes, MVIC and AUC fatigue index, were analysed with univariate models. The absolute values for the three repeated measures of MVIC at each time point were analysed with a generalised linear mixed model with a log link. The fixed effects were *'intervention'* (novel-PAS and sham) and *'time'* (pre and post), and *'participant'* was a random effect. The log link was used to interpret relative change rather than absolute change. Individual MVIC data was also converted to percentage change values to allow comparisons with previous literature[248]. The AUC fatigue index data was analysed with a linear mixed model with fixed effects of *'intervention'*, *'time'*, and *'mean pre-intervention MVIC'*, while *'participant'* was a random effect. By including the pre-intervention MVIC as a fixed effect, the fatigue model adjusted for different levels of baseline strength.

As the study was not powered for the secondary outcome measures, the primary and secondary outcomes were pooled in two multivariate linear mixed models, to improve statistical power[394]. The first multivariate model included primary and secondary measures related to strength (MVIC, ROFD 0-200ms, time to 90% MVIC, peak RMS during MVIC, voluntary activation). Outcomes which had three measures at each time point were averaged before being entered in the model. The second multivariate model included primary and secondary measures related to fatigue (AUC fatigue index, simple fatigue index, central fatigue, peripheral fatigue, RMS EMG loss, median frequency loss). For both multivariate models, the fixed effects were *'intervention'* and *'time'* for each outcome, and the random effects were *'participant'* and *'each measure per participant'*. TMS measures were analysed descriptively.

## 5.4 RESULTS

Data collection was completed between July and October 2017.

### 5.4.1 SAMPLE CHARACTERISTICS

Participant demographics are shown in Table 5-1. Participants had a mean age of 69.9 years and were a mean of 6.4 years post-stroke. Eleven of the 15 participants had a left hemiparesis. The sample included people with a range of lower limb disability, from those with mild impairment requiring no walking aids, to those with severe impairment requiring a wheelchair for outdoor mobility. Three participants wore ankle AFOs for gait.

Table 5-1 Participant demographics

| Participant | Sex | Age (years) | Time since stroke | Hemiparesis | Outdoor walking aid | AFO |
|---|---|---|---|---|---|---|
| 1 | Male | 74 | 2 years | Left | Stick | No |
| 2 | Female | 64 | 19 years | Left | Quad stick | No |
| 3 | Female | 60 | 9 years | Left | Quad stick | Yes |
| 4 | Female | 79 | 8 months | Right | 4-wheel frame | No |
| 5 | Male | 76 | 10 years | Right | Nil | No |
| 6 | Male | 60 | 2 years | Left | Wheelchair | Yes |
| 7 | Female | 58 | 7 years | Left | Nil | No |
| 8 | Male | 79 | 3 years | Right | Wheelchair | Yes |
| 9 | Male | 70 | 12 years | Left | Nil | No |
| 10 | Female | 73 | 6 years | Right | 4-wheel frame | No |
| 11 | Female | 67 | 4 years | Left | Wheelchair | No |
| 12 | Male | 84 | 4 years | Left | Quad stick | No |
| 13 | Male | 46 | 2 years | Left | Nil | No |
| 14 | Female | 79 | 7 months | Left | Stick | No |
| 15 | Male | 79 | 7 years | Left | Wheelchair | No |
| | Male n=8<br>Female n=7 | Mean =<br>69.9 years<br>SD =<br>10.5 years | Mean =<br>6.4 years<br>SD =<br>4.8 years | Left n=11<br>Right n=4 | Nil n=4<br>Stick n=2<br>Quad stick n=3<br>Frame n=2<br>Wheelchair n=4 | AFO n=3 |

### 5.4.2 PRIMARY MEASURES

## Maximum voluntary isometric contraction

The group data for absolute MVIC values and percentage change values are presented in Table 5-2. Following the novel-PAS intervention there was a mean increase in ankle dorsiflexion MVIC of 7.33N or 9.75% from pre-intervention values. Following the sham intervention, absolute and relative changes in MVIC were negligible (+0.09N and -0.17% change from pre-intervention). The generalised linear mixed model analysis with log link revealed that the novel-PAS intervention resulted in 1.3% increase in isometric ankle dorsiflexion strength which was not statistically significant.

Table 5-2 Results for MVIC of ankle dorsiflexor muscles

| Outcome | Novel-PAS Mean (SD) | | | Sham Mean (SD) | | | Treatment Effect (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Change | Pre | Post | Change | | |
| Descriptive statistics | | | | | | | | |
| MVIC (N) | 137.73 (65.74) | 145.06 (58.09) | +7.33 (18.24) | 146.38 (64.98) | 146.48 (69.28) | 0.09 (14.45) | NA | NA |
| MVIC (% change) | 100 | 109.75 (14.00) | +9.75 (14.00) | 100 | 99.83 (9.01) | -0.17 (9.01) | NA | NA |
| Generalised linear mixed model with log link | | | | | | | | |
| MVIC (log) | 4.847 | 4.872 | +2.5% | 4.897 | 4.908 | +1.1% | +1.3% (-6.9 to 4.2) | 0.64 |

## Area under the curve fatigue index

During the fatigue task, most participants showed a slow decline in force (n=8), however for some participants the force trace fluctuated around a more or less flat line (n=3) or even increased slightly (n=2). These contrasting patterns are illustrated for two example participants in Figure 5-8. The group data for the AUC fatigue indices are presented in Table 5-3. Both the novel-PAS and sham interventions resulted in increases in neuromuscular fatigue, but effects were comparable for both groups.

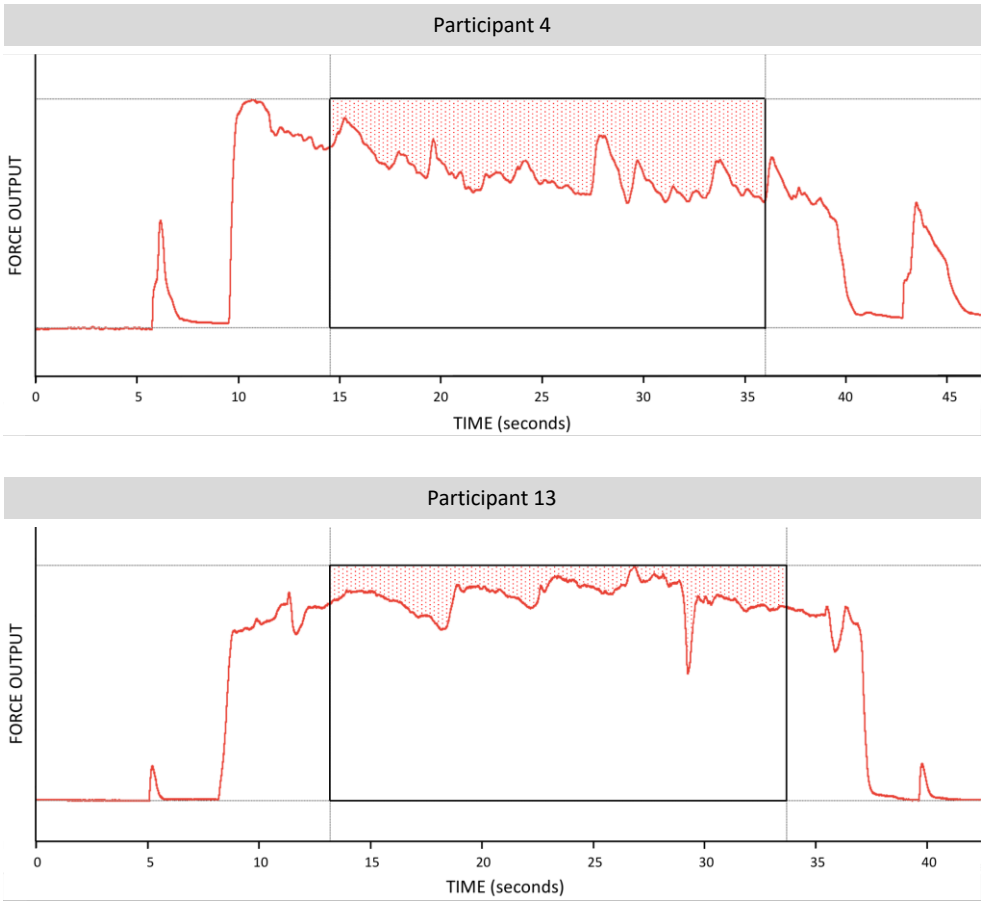



Figure 5-8 Contrasting changes in force during fatigue task for two participants (shaded area depicts AUC fatigue index)

Table 5-3 Results for the AUC fatigue index

| Outcome | Novel-PAS Mean (SD) | | | Sham Mean (SD) | | | Treatment effect (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Change | Pre | Post | Change | | |
| AUC fatigue index (%) | 23.17 (13.79) | 24.03 (13.45) | 0.86 (7.29) | 20.01 (7.44) | 21.93 (11.31) | 1.92 (7.64) | -1.06 (-5.38 to 7.50) | 0.74 |

### 5.4.3 SECONDARY MEASURES

## Multivariate analysis of measures recorded during MVIC

The multivariate analysis of primary and secondary outcomes recorded during the MVIC task can be seen in Table 5-4. There was no statistically significant difference between the interventions on these combined outcomes (p=0.14). However, novel-PAS had a significant effect of 6.99% on voluntary activation, as indicated by the confidence interval which did not cross zero. There were no significant effects on ROFD 0-200ms, time to 90% MVIC, or peak EMG.

Table 5-4 Multivariate analysis for outcomes related to MVIC task

| Outcomes | Novel-PAS Mean (SD) | | | Sham Mean (SD) | | | Treatment effect | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Change | Pre | Post | Change | | |
| MVIC (N) | 137.73 (65.74) | 145.06 (58.09) | +7.33 (18.24) | 146.38 (64.98) | 146.48 (69.28) | 0.09 (14.45) | +7.24 | -2.88 to 17.36 |
| ROFD 0-200ms (N/s) | 257.81 (151.62) | 224.93 (118.55) | -32.87 (91.81) | 254.43 (133.74) | 236.78 (127.81) | -17.65 (42.43) | -15.22 | -58.74 to 28.30 |
| Time 90% MVIC (s) | 1.68 (0.83) | 1.69 (0.99) | 0.01 (0.57) | 1.43 (0.75) | 1.60 (1.12) | 0.17 (0.89) | -0.16 | -0.54 to 0.23 |
| Peak RMS EMG during MVIC (V) | 0.18 (0.15) | 0.18 (0.10) | 0.00 (0.04) | 0.19 (0.13) | 0.18 (0.13) | -0.01 (0.02) | 0.00 | -0.03 to 0.04 |
| Voluntary activation (%) | 81.87 (19.45) | 85.36 (17.61) | 3.49 (8.12) | 87.37 (19.87) | 83.86 (23.22) | -3.50 (8.53) | 6.99 | 1.30 to 12.68 ** |

For multivariate linear mixed model of combined outcome p=0.14

** indicates statistically significant effect for voluntary activation outcome

## Multivariate analysis of fatigue measures

The multivariate analysis of outcomes related to the fatigue task can be seen in Table 5-5 and showed no effect of novel-PAS on these combined outcomes (p=0.53), and no significant effect on any individual outcomes as all confidence intervals cross zero.

Table 5-5 Multivariate analysis for outcomes related to fatigue task

| Outcomes | Novel-PAS Mean (SD) | | | Sham Mean (SD) | | | Treatment effect | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Change | Pre | Post | Change | | |
| AUC fatigue index (%) | 23.17 (13.79) | 24.03 (13.45) | 0.86 (7.29) | 20.01 (7.44) | 21.93 (11.31) | 1.92 (7.64) | -1.06 | -6.45 to 4.33 |
| Simple fatigue index (%) | 11.27 (23.93) | 21.72 (20.65) | 10.45 (20.38) | 18.73 (14.75) | 20.28 (21.74) | 1.55 (19.48) | 8.90 | -5.59 to 23.39 |
| Central fatigue (%) | 9.72 (22.22) | 17.26 (21.39) | 7.54 (26.55) | 17.83 (18.61) | 9.59 (28.53) | -8.24 (24.68) | 15.77 | -2.61 to 34.15 |
| Peripheral fatigue (%) | 4.99 (13.32) | 8.53 (15.62) | 3.54 (12.74) | 6.44 (7.27) | 11.16 (9.59) | 4.72 (7.82) | -1.18 | -10.30 to 7.94 |
| RMS EMG loss (%) | 25.00 (23.68) | 31.74 (24.16) | 6.74 (17.48) | 22.44 (21.87) | 35.51 (31.35) | 13.07 (39.41) | -6.33 | -26.43 to 13.77 |
| Median frequency loss (%) | 7.42 (17.74) | 4.19 (18.64) | -3.23 (21.97) | 2.77 (19.24) | 4.43 (18.31) | 1.67 (24.43) | -4.90 | -20.72 to 10.93 |

For multivariate linear mixed model of combined outcomes p=0.53

## Corticomotor excitability

TMS-induced MEPs were only collected for one of the 13 participants who completed the protocol. For this participant, TA MEP area increased following both interventions, but the increase was greater following the sham intervention (+18%) than the novel-PAS intervention (+10%). Changes in TA MEP amplitude were smaller, but also favoured the sham intervention (+5%), over the novel-PAS intervention (-2%).

## 5.5 DISCUSSION

This study aimed to explore the influence of novel-PAS on a range of primary and secondary outcomes, but importantly, was the first study to assess the within-session effects of novel-PAS on measures that do not require TMS. The findings revealed a significant effect of novel-PAS on voluntary activation. The following discussion will firstly focus on the findings related to measures of impairment, that is, muscle strength, neuromuscular fatigue, and muscle power. This will be followed by a discussion of the neurophysiological findings and the central mechanism underlying novel-PAS. Thereafter, the feasibility of the intervention will be discussed, and the limitations of the study will be addressed. Finally, the implications of the findings will be discussed in relation to future research and rehabilitation practice.

### 5.5.1 IMPAIRMENTS

#### Muscle strength

It was hypothesised that increases in corticomotor excitability in response to the intervention would result in a significant increase in muscle strength as measured by the MVIC. The novel-PAS intervention resulted in a 7 N increase in absolute strength or a 10% increase in relative strength. While estimates of minimal clinically important differences in lower limb strength for people with stroke are not available, it has been suggested that change scores of 10-15% represent meaningful improvement[395]. Thus, while the strength findings were not statistically significant, it is promising that within just a single session of novel-PAS, improvements approached the level deemed clinically important.

The statistical analysis in the present study utilised the absolute change in strength and failed to illustrate a significant difference between groups. Previous neuromodulation studies in stroke have found significant effects on lower limb strength following tDCS using percentage change data[248,249]. From a clinical perspective, the use of percentage change data may be preferred because small absolute changes may have greater meaning to people with greater impairment. However, converting data to percentage change values is cautioned in statistical analysis literature because it can distort the magnitude of change and violate the assumptions of the statistical analysis model[396,397]. These factors were considered in the present study and it was deemed appropriate to analyse the absolute data. Interestingly though, when the univariate statistical analysis was repeated on percentage change data, the result was statistically significant ($p=0.01$). It was notable that of the 13 participants in the study, the

three participants who responded less favourably to the novel-PAS intervention had the highest pre-intervention strength measures (>229 N). Thus, transforming the data resulted in smaller percentage change values for these three participants and provided less support for the sham intervention. This illustrates how the use of percentage change data can alter results and should be performed with caution[397,398].

There was large inter-individual variability in levels of pre-intervention impairment, with ankle dorsiflexion strength ranging from 57-262 N, or from minimal active movement to full range against resistance. The ten participants who responded more favourably to the novel-PAS intervention were weaker (<187 N), whereas the three participants who responded less favourably had strength within the healthy range[399]. This might imply that people with stroke with greater impairment have more potential to benefit from novel-PAS. Other tDCS studies have reported greater improvements in precision and reaction tasks in those more impaired following stroke[373-375]. Literature from the older adult population also supports the idea that people with greater impairments gain more from neuromodulation[400]. The method of pairing of stimuli during novel-PAS may also be important in understanding variations in the intervention response. In previous novel-PAS research in healthy people, *voluntary* ankle movements needed to be paired with *muscle* stimulation to have an excitatory effect, whereas *nerve* stimulation had no effect[202]. It was suggested in Chapter 2 that this may have occurred because voluntary movement produces higher levels of cortical activation which require pairing with afferent volleys of higher frequency or amplitude, such as that produced with muscle stimulation. Thus, for the three least impaired participants in this study, a different novel-PAS intervention using muscle, rather than nerve stimulation, may have produced an excitatory effect. This notion of tailoring neuromodulation parameters to each individuals level of impairment has been suggested in previous neuromodulation literature[137,401]. Future novel-PAS research should have a sufficiently large enough sample size to allow stratification of data according to impairment level. This could facilitate the optimisation of stimulation parameters for the level of impairment.

The method used to test strength may not have been appropriate for the muscle and the task being trained. The TA maintains a low level of activity during quiet standing and produces short bursts of activity during the stance and swing phase of gait[402] and in challenging balance tasks[403]. Therefore, the use of a maximum voluntary isometric contraction may not be appropriate to assess improvements in the *function* of the TA muscle. In addition, the task-specificity of neural plasticity[20] suggests that the isometric testing method may not be sensitive to changes in corticomotor excitability associated with novel-PAS intervention, which trains the ankle dorsiflexors in a phasic isokinetic contraction. Future studies should

consider assessing strength using a phasic isokinetic muscle contraction, which more closely resembles the function of the TA and the movement trained during the novel-PAS intervention.

It is possible the non-significant strength finding may relate to an insufficient sample size. Data from previous tDCS work by Tanaka et al[248] and Sohn et al[249] suggested that the sample size used in the present study would be sufficient to detect an immediate increase in muscle strength in people with stroke. However, other studies in people with stroke investigating the effects of ***bihemispheric*** tDCS on lower limb strength[404] or the effects of tDCS on ***upper limb*** strength[372,374,404,405], have failed to find statistically significant effects. This contrast in the literature may be due to the use of different tDCS methods, application to the upper rather than lower limb, or the large inter-individual variability in responses to neuromodulation[212,241-243]. Further research is required to determine if the immediate strength improvements following novel-PAS seen in this study can be confirmed in a larger sample of people with stroke.

## Total neuromuscular fatigue

The results for the primary outcome, the AUC fatigue index, and the secondary outcome, the simple fatigue index, were not statistically significantly different between novel-PAS and sham interventions. This suggests that a single session of novel-PAS has no effect on total neuromuscular fatigue in people with stroke. It was noted that the magnitude and direction of the treatment effect for the simple fatigue index differed from the AUC fatigue index (treatment effect +8.90% and -1.06% respectively). This reinforces that these measures represent different aspects of neuromuscular fatigue, with the simple fatigue index representing the linear change in force between the start and the end of the task, and the AUC fatigue index representing force fluctuations during the entire task[367]. These differences should be considered when selecting outcome measures in future research, particularly when researchers are interested in detecting changes in performance across the ***entire*** task.

As for the MVIC findings, the method for testing neuromuscular fatigue of the TA may have not been suited to the function of the TA. In the present study, neuromuscular fatigue was induced with a single sustained MVIC, which has been previously used to study ankle dorsiflexor muscle fatigue in healthy people[385], and people with diabetic neuropathy[406] and multiple sclerosis[367]. However, given the functional demands of the TA, it may have been more appropriate to induce fatigue with a phasic task, such as repetitive isokinetic movements used in other ankle muscle fatigue protocols[407-409]. Similar phasic tasks have been tested following tDCS over the M1, and shown improved fatigue resistance in the elbow

flexors of weightlifters[370] and the lower limb muscles of cyclists[410]. Another option for inducing fatigue would be to use a submaximal isometric task. Low load tasks preferentially recruit slow-twitch muscle fibres[411], which are more predominant in the TA[412,413], and therefore might be more suited to testing fatigue of this muscle. Several tDCS studies have shown improvements in the time to task failure during a submaximal isometric task[359,369,400,414]. While phasic and low-load isometric fatigue protocols are more time-consuming they should be considered for future research into the effects of novel-PAS on neuromuscular fatigue.

The sample size was deemed adequate according to previous tDCS work by Benwell et al[368]. However, as with strength findings, other similar sized studies have shown inconsistent effects of neuromodulation on neuromuscular fatigue[174,376,377]. Much of this work has investigated submaximal fatigue tasks in the upper and lower limb of healthy people[174,376,377]. Due to the mixed results in the literature, it is unclear whether a larger sample may have shown an effect of novel-PAS on neuromuscular fatigue.

## Muscle power

Muscle power, investigated as a secondary measure using the ROFD 0-200ms and time to 90% MVIC, was not significantly increased by a single session of novel-PAS. Prior research performed with healthy participants has shown improvements in muscle power following tDCS[371]. However, immediate improvements in muscle power may be more difficult to achieve in people with stroke. The ROFD depends on both the neural activation of motor units, and non-neural factors, such as the muscle fibre-type composition and muscle-tendon stiffness[379]. These *non-neural factors* could have limited the effects of novel-PAS on muscle power in the present study. However, evidence concerning non-neural changes after stroke shows that changes in muscle mass, muscle length, and muscle fascicle angle are not significant in the hemiparetic TA[348,412,415]. Also, changes in fibre-type composition are inconsistent, with studies showing both increases[412] and decreases[416] in type II fibres. There is a possibility that antagonist plantarflexor muscle stiffness, which is known to limit hemiparetic ankle dorsiflexion during gait[337], may also limit immediate improvements in muscle power. These factors raise uncertainty about whether non-neural factors might have influenced ROFD in the present study. If this were so, achieving significant changes in muscle power may require more than a single session of novel-PAS, as well as other standard interventions to address non-neural changes[417].

### 5.5.2 CENTRAL MECHANISM

The multivariate analysis found a significant 7% increase in voluntary activation following a single session of novel-PAS (95% confidence interval 1.30-12.68%). This effect was seen with only a single session of novel-PAS, whereas in other neuromodulation literature, there was no significant effect on voluntary activation after a single session[174,414,418,419], and a four-day intervention was needed to significantly increase voluntary activation[358]. The voluntary activation findings confirm that novel-PAS has a central mechanism, and fits with previous findings of its effects on corticomotor excitability in healthy people and people with stroke[200,201,204]. It is assumed that the mechanism for increased voluntary activation is supraspinal as previous novel-PAS work has shown no effect on spinal cord excitability[200,201]. In terms of the magnitude of change, the 7% increase in voluntary activation exceeded available values for the error of the measurement, of 1.3% in the healthy triceps surae[350] and 3.8% in the hemiparetic quadriceps[384]. It is not clear whether this change in voluntary activation has functional consequences; however, the link between voluntary activation deficits after stroke and poor functional performance[295] suggests this is possible.

Central fatigue did not differ significantly between novel-PAS and sham interventions, but there was a trend towards increased central fatigue in the novel-PAS group (treatment effect +15.77%, 95% confidence interval -2.61–34.15%). This may be explained by the increased voluntary activation that occurred in the novel-PAS group, as tasks which require greater voluntary activation induce greater levels of central fatigue[420]. It has been proposed that neuromodulatory interventions might prevent central fatigue by reducing the intracortical inhibition which acts on the M1 during sustained exercise[331,359,410]. The healthy response to this fatigue-induced inhibition is an increase in corticomotor excitability[61,331]. However, this compensatory response does not occur following stroke, and this may contribute to the greater levels of central fatigue seen in the hemiparetic limb[61,62]. Neuromodulation could potentially prevent central and neuromuscular fatigue by either increasing M1 excitability or increasing intracortical facilitation[359,410]. However, there was no evidence of this preventative effect on fatigue in the present study. As previously discussed, the effects of neuromodulatory interventions on neuromuscular fatigue are inconsistent[174,376,377] and studies which have specifically investigated central fatigue, have not shown significant effects in healthy people[174,414]. A greater understanding of the central mechanism underlying novel-PAS may help to identify if, and how, novel-PAS might influence central and neuromuscular fatigue.

The central mechanism underlying novel-PAS was not further elucidated by the EMG amplitude data, which is an indicator of CNS activation of motor units[60]. There was no significant effect of novel-PAS on EMG amplitude during the MVIC. This contrasts with previous work which has shown that peak EMG amplitude during an MVIC can significantly increase following tDCS, in line with increases in MVIC[253]. There were also no significant effects of novel-PAS on EMG amplitude and median frequency during the 30-second fatigue task, although for both interventions, these measures declined, which is in line with fatigue-related changes in motor unit activity in healthy adults[60,421,422]. These findings may be related to the insensitivity of EMG measures to detect small changes associated with neuromuscular fatigue, as demonstrated by tDCS studies which showed improved neuromuscular fatigue without any effects on EMG amplitude during the fatigue task[359,369]. Further research is needed to determine if novel-PAS and other neuromodulatory interventions have an effect on EMG measures.

### 5.5.3 FEASIBILITY

While this study did not specifically investigate feasibility, two participants were removed from analysis due to communication, cognitive, and attentional impairments, which limited their ability to complete the protocol. Although these impairments were not deemed significant enough during the screening phase to warrant exclusion from the study, their severity was much more pronounced during data collection, likely due to the unfamiliar environment and novel tasks that were being performed. Interestingly, this issue did not arise within the feasibility work completed in Study B, and in that study, recruitment barriers were deemed to be largely related to the research protocol rather than the intervention. This lack of engagement with the intervention has implications for the clinical feasibility of novel-PAS, as many people with stroke may not have the physical and cognitive skills to complete the intervention. In its current form, the novel-PAS intervention suits an individual who can perform isolated ankle dorsiflexion in time with a visual cue, without looking at their foot, and maintain attention for 15 minutes. In future, researchers should consider intervention delivery methods that are achievable for people with more severe impairments, to determine whether novel-PAS could be applied to a wider range of people with stroke.

Given the poor feasibility of TMS measures outlined in Study B, it was not surprising that these measurements were only collected for two out of 15 participants, and only one of the 13 participants included in data analysis. The results for this one participant unexpectedly favoured the sham intervention, and for MEP area, exceeded the error of the measure[235]. This result may reflect the variability in the individual responses to neuromodulatory

interventions (discussed in 3.5.2) especially given this participant was 84 years old, and age is known to limit PAS-induced changes in corticomotor excitability[423].

### 5.5.4 STUDY LIMITATIONS

It is acknowledged the voluntary activation measurement techniques have some limitations. The interpolated twitch method does not represent *true* levels of voluntary activation and is less sensitive at higher levels of MVIC[349,424], which may have resulted in an underestimation of voluntary activation changes for those with higher levels of strength. Another limitation was that voluntary activation was measured at the start of the fatigue task, and although participants were advised to contract maximally, they may have used submaximal effort in anticipation of the task ahead, which might have reduced their voluntary activation. This could be avoided in future by recording voluntary activation during a brief MVIC.

EMG amplitude measures are commonly normalised to the MVIC, to reduce between-session variability in signal quality[271,287] and reference the EMG activity during a fatigue task to that during a brief maximal task[253,359,369]. While amplitude-normalisation was performed on EMG RMS data during the fatigue task, in line with other neuromodulation studies of fatigue[253,359,369], the EMG RMS data during the strength task was not normalised to the pre-intervention MVIC, as this is not a requirement for assessing within-session effects[425], and would have involved conversion to percent changes, which can distort the magnitude of change[397,398]. This method could be criticised for being vulnerable to between-session differences in signal quality, however, the statistical model accounted for the pre-intervention values in each session.

### 5.5.5 IMPLICATIONS FOR RESEARCH AND REHABILITATION

With just a single session of novel-PAS, there was a significant improvement in voluntary activation in people with chronic stroke. This finding confirms the neuromodulatory effect of novel-PAS and provides support for the future investigation of novel-PAS as an adjunct to standard rehabilitation, applied either before or during other interventions. Improving the central nervous system drive to a muscle with novel-PAS has potential to improve motor performance during standard rehabilitation tasks, such as task-specific training or strength training, and with repetition has potential to lead to improved motor recovery[20]. Future research should investigate the effects of applying novel-PAS in combination with standard rehabilitation techniques.

This study was the first to explore the effects of novel-PAS on a range of outcome measures other than corticomotor excitability, and also to recruit a sample with a range of lower limb disability. This study demonstrates that the effects of novel-PAS can be investigated with measures other than TMS and provides guidance for the selection of outcome measures in future research. The use of MVIC and voluntary activation measures, instead of TMS measures, is likely to improve recruitment, reduce data collection time, and promote the generalisability of the research to the stroke population. In the present study, changes at the impairment level were not significant. However, significant changes in these measures may require more than a single session of novel-PAS, and therefore future research should investigate the effects of multiple sessions of novel-PAS.

## 5.6 SUMMARY

This study demonstrated that the novel-PAS intervention can significantly increase voluntary activation of the TA in people with chronic stroke, more than an attention- and dose-matched sham intervention. This provides important confirmation of the effects of novel-PAS on neural plasticity and supports its potential to be used as a rehabilitation adjunct for people with stroke.

# Chapter 6.
# Integrated discussion and conclusion

## 6.1 INTRODUCTION

This thesis has explored and extended the novel-PAS knowledge base through a literature review and three studies.

- Study A, a within-subject, repeated-measures experiment in healthy people, explored the immediate effects of novel-PAS in the 60-minute period following intervention delivery.
- Study B, a four-week pilot RCT in people with stroke, evaluated the feasibility of the research protocol and the novel-PAS intervention, and made recommendations regarding the selection of outcome measures in future research.
- Study C, a repeated-measures cross-over experiment in people with stroke, investigated the immediate effects of novel-PAS on measures of muscle strength and fatigue.

## 6.2 MOVING FROM THE RESEARCH LABORATORY TOWARD REHABILITATION PRACTICE

Interventions that arise out of neuroscience research generally fail to be implemented into rehabilitation practice; this reinforces the importance of translational research, which involves trialling an intervention in the clinical population, optimising its delivery, developing strategies to address barriers to its implementation, and integrating the intervention into health services[426]. At the outset of this research programme, the small body of existing novel-PAS literature was based on laboratory-based research, and had not considered how

the intervention would be integrated with standard rehabilitation practice. The research reflected in this thesis addressed this gap in the body of work.

Study A added to the body of knowledge by demonstrating that novel-PAS induced a 60-minute window of increased corticomotor excitability in healthy people. This finding indicates that the neuromodulatory effects of novel-PAS could be harnessed for up to 60 minutes following intervention delivery and provides researchers and clinicians with new insight into the possibilities for combining novel-PAS with standard rehabilitation practice. In addition, this finding provided important guidance for the design of research protocols where outcome measures need to be collected within this post-intervention period of increased corticomotor excitability.

There are a number of challenges to the translation of novel-PAS into the rehabilitation context and these were explored in Study B, which investigated the feasibility of delivering four weeks of novel-PAS to people with stroke in a pilot RCT. Novel-PAS was shown to be safe, and adherence levels high; however there were a number of technical challenges associated with its delivery which made it vulnerable to errors. This reinforced the need to establish a robust method for delivering novel-PAS to ensure that it can be effectively implemented in rehabilitation practice. Study C offered further insight into the difficulties with intervention delivery. Despite a rigorous screening process, two out of the 15 participants could not perform the novel-PAS task. This raised concerns that the current mode of delivery may not be appropriate for people with high-level cognitive and communication impairment and indicates that researchers should consider ways to make the intervention applicable to people with a wider range of stroke-related impairments.

Study B was the first to explore the acceptability of the novel-PAS intervention to people with stroke and has made a valuable contribution to the wider field of neuromodulation research, where the acceptability of neuromodulatory interventions has rarely been explored. Participants with stroke did not find the intervention acceptable in its current form, citing concerns related to the equipment size, efficiency and comfort, and the low intensity of the intervention. Insight into factors which could improve the acceptability of the intervention offers a significant contribution to the future development of the novel-PAS intervention. One potential solution is to miniaturise the novel-PAS intervention using wearable BCI technology[319,320]; this would reduce the set-up time and allow the intervention to be applied during exercises or functional tasks. Miniaturisation would not only improve intervention acceptability, but would allow the incorporation of motor learning principles such as intensity, task-specificity, and meaningfulness, which are important factors for driving neural

plasticity[20]. Another insight from this work was the importance of the relationship between the patient and the clinician, as well as the potential relationships between fellow patients, all of which can provide motivation, inspiration, and support. As researchers consider ways to further develop the novel-PAS intervention, they should not underestimate the relational component of rehabilitation, which can enhance motivation, enjoyment and engagement. The novel-PAS intervention requires considerable development before it can be used in the rehabilitation environment.

## 6.3 INSIGHTS INTO RESEARCH PROTOCOL DESIGN

One of the aims of this thesis was determine whether the RCT protocol carried out in Study B was viable for use in a future powered study. Study B revealed that this protocol failed to meet all pre-determined indicators of feasibility and that only six participants, of the planned sample of 20, could be recruited to the trial. Thus, the research protocol was deemed unfeasible for use in a larger study. However, the findings offered valuable insight into the challenges of evaluating the efficacy of a multi-week novel-PAS intervention in people with stroke, and these factors can be used to guide the design of future protocols. The components which posed the largest challenges to completing the protocol were the use of TMS outcome measures, and the time requirements of the protocol. To ensure the feasibility of future research, these factors must be addressed during protocol design.

## 6.4 THE RESPONSE TO NOVEL-PAS

Across the three studies in this thesis, there was variability in the individual response to the novel-PAS intervention. While the findings in this thesis are not contrary to the wider body of neuromodulation literature, where high between-subject variability has been observed[212,241-243], it is important to consider possible sources of variability that may have resulted from the experimental method, and which could potentially be controlled in future studies. One possible source of variability relates to intervention delivery. Study B raised the possibility that human error, poor reliability in the method used to process the MRCP, or large biological variability in the timing of the PN of the MRCP, may have led to mismatching of MRCPs with electrical stimulation. This has potential to influence the efficacy of the novel-PAS intervention, and therefore raised concerns about the internal validity of previous novel-PAS research[204]. It is essential that further work is carried out to explore whether

modifications to the method for identifying the PN have any bearing on the response to the intervention.

With regard to the immediate effects of novel-PAS on corticomotor excitability explored in Study B, the findings from individual data did not show the post-intervention excitatory effects seen in previous research on people with stroke[204]. In addition, previous research enrolled participants with less severe lower limb disability from stroke, possibly due to the use of TMS as an outcome measure. This raised concerns about the potential for selection bias in previous work and whether this research is generalisable to people with more severe stroke. This demonstrated the need to revisit previous conclusions about the effects of novel-PAS and confirm its immediate effects on people with stroke with a range of lower limb disability.

## 6.5 A REVISED APPROACH TO MEASUREMENT

The findings from Study B demonstrated that it was not feasible to carry out a fully-powered version of the RCT protocol. The use of TMS outcome measures, and the time requirements of the protocol, were particular barriers to feasibility, and these needed to be addressed before continuing to investigate the cumulative effects of novel-PAS. In addition, as discussed above, findings indicated that further research was needed to confirm the immediate effects of novel-PAS in the wider stroke population. These findings focused the thesis on exploring the immediate neuromodulatory effects of novel-PAS prior to exploring its cumulative effects. Of prime importance was to design a research protocol with feasibility in mind and to ensure recruitment of people with a range of lower limb deficits. The impact of TMS measurement on the feasibility of the protocol indicated that alternative outcome measures were required. The literature revealed a range of outcome measures which had potential to demonstrate the neuromodulatory effects of novel-PAS and this literature guided the design of the Study C.

Study C was the first to assess the immediate effects of novel-PAS on measures other than corticomotor excitability. The finding of increased voluntary activation makes a significant contribution to the body of knowledge by confirming the neuromodulatory effect of novel-PAS in people with stroke. This study demonstrated that a range of outcome measures that do not involve TMS can be used to investigate the effects of novel-PAS. The application of these findings will improve the feasibility and external validity of future research by ensuring that the use of TMS as an outcome measure does not drive a selection bias when recruiting people with stroke. While this study explored a range of alternative outcomes to TMS, an

important consideration when selecting measures is whether they effectively measure the task-specific nature of neural plasticity.

Study C offered insight into the between-subject variability in the response to novel-PAS, with some support for the idea that people with greater impairment have more to gain from neuromodulatory interventions[373-375,400], and for the need to individualise an intervention for each person. This reinforces the importance of considering the needs of people with stroke, and the rehabilitation environment itself, in the design and development of novel-PAS.

One of the strengths of this research is the collection of a range of outcome measures. The inclusion of feasibility measures allows for important consideration of the potential barriers to the implementation of future research protocols and the novel-PAS intervention itself. The robust analysis of qualitative data aligns this research well with the Medical Research Council's recommendations for the development of complex health interventions[185]. The research included quantitative measures of neurophysiological, impairment and activity outcomes, all collected according to a rigorous experimental method. The findings from both Study B and Study C offer valuable guidance for the selection of outcome measures in future novel-PAS research. For the most time-efficient assessment of within- and between-session effects, it is recommended that future research include MVIC measures, with simultaneous collection of voluntary activation and EMG amplitude. Cumulative effects should also be measured with an activity measure such as the stair-climbing ascend test. In addition, if timing allows, a simple 3D marker system could be used to measure step-up time, and the EMG rise and variation ratio of the EMG linear envelopes could be collected simultaneously. The MRCP should continue to be explored as a potential measure of the cumulative effects of novel-PAS; however further research is required to understand the meaning of changes in MRCP parameters.

## 6.6 LIMITATIONS

The recruitment of people with stroke for Study B and C was performed in a thorough and meticulous manner however recruitment of participants though the community meant the sample could not be described with respect to lesion size or location. Thus, these factors could not be considered when interpreting the results. The possibility that the underlying impairment may influence the response to neuromodulation[373-375] should be considered in future work. In addition, whilst the samples of people with stroke were heterogenous in terms of chronicity and severity of lower limb disability, the sample sizes were small, and the experiments were carried out in a University laboratory, which may limit the external validity

of the findings. Participants in the chronic phase of stroke were recruited, to ensure they had reached a plateau in their recovery; however future work should be carried out in a more acute population to assess whether novel-PAS might enhance early recovery.

## 6.7 DIRECTION OF FUTURE RESEARCH

Future research should focus on combining novel-PAS with standard rehabilitation techniques, assessing its cumulative effects on stroke recovery, optimising its delivery, and miniaturising the equipment. As recommended for the development of complex health interventions[185], researchers must consider the views and needs of people with stroke during this process, to ensure novel-PAS can be utilised with a diverse range of people with stroke and to facilitate its implementation into rehabilitation practice.

## 6.8 CONCLUSION

This research has extended the current body of knowledge regarding the efficacy and feasibility of the novel-PAS intervention and research protocols. Specifically, this thesis has:

- Demonstrated a 60-minute neuromodulatory effect of novel-PAS in healthy people
- Revealed a range of features of the current novel-PAS intervention that need to be addressed to improve intervention feasibility and the potential for translation into rehabilitation practice
- Exposed significant barriers to carrying out novel-PAS research and recommended strategies to address these issues when developing future research protocols
- Established the immediate neuromodulatory effect of novel-PAS in people with stroke using a more feasible outcome measure than previous research.

# PUBLICATIONS AND CONFERENCE PRESENTATIONS

1. Alder G, Signal N, Vandal AC, Niazi IK, **Olsen S,** Taylor D. Fine-tuning the delivery of a novel neuromodulatory intervention. Podium presentation at the Stroke Rehab: From No-Tech to Go-Tech Conference; January 2018; Christchurch.

2. **Olsen S,** Signal N, Niazi IK, Alder GA, Taylor D. From research laboratory towards clinical practice. Understanding patient perspectives of a novel neuromodulatory intervention. Podium presentation at New Zealand Rehabilitation Association Conference; September 2017; Christchurch.

3. **Olsen S,** Signal N, Niazi IK, Christensen T, Alder G, Jochumsen M, Taylor D. Measuring changes in neuromuscular control following neuromodulation. A feasibility study in people with stroke. Poster presentation at the Scientific Meeting of the Stroke Society of Australasia; August 2017; Queenstown.

4. **Olsen S,** Signal N, Niazi IK, Christensen T, Jochumsen M, Taylor D. Paired associative stimulation delivered by pairing movement-related cortical potentials with peripheral electrical stimulation: An investigation of the duration of neuromodulatory effects. *Neuromodulation: Technology at the Neural Interface*, 2017; June. doi:10.1111/ner.12616.

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6. **Olsen S,** Signal N, Niazi IK, Christensen T, Taylor D. Brain computer interface driven paired associative stimulation: An investigation of the duration of neuromodulatory effects. Podium presentation at the Physiotherapy New Zealand Conference; September 2016; Auckland.

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# APPENDICES

## Appendix A. Study A TMS screening sheet

**Participant Safety Checklist for using Transcranial Magnetic Stimulation**

Volunteer Name:_____

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

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

Medications checked for seizure threshold lowering effect? Yes / No

Checklist completed by: _____

Signature: _____

# Appendix B. Study A ethical approval

AUTEC
SECRETARIAT

18 February 2015

Denise Taylor

Faculty of Health and Environmental Sciences

Dear Denise

Re: Ethics Application: **14/255 The Aalborg BCI: a MRCP driven PAS protocol for people with stroke.**

Thank you for your request for approval of an amendment to your ethics application.

I have approved the minor amendment to your ethics application allowing additional testing with healthy volunteers.

I remind you that as part of the ethics approval process, you are required to submit the following to the Auckland University of Technology Ethics Committee (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 12 November 2017;
- 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 12 November 2017 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: Nada Signal; Gwyn Lewis

Ethical considerations for Study A:

- Possible discomfort during TMS. This was reduced by starting the stimulation at a low intensity and allowing participants time to habituate. Consent was sought before touching each participant's head, and earplugs were also available for comfort.
- Possible skin irritation due to skin preparation for electrode placement. Aloe vera gel was available to reduce this discomfort if required.
- Seizure risk associated with TMS. This was minimised by careful screening and exclusion of participants taking medications that lower seizure threshold, and those with a history of seizures or epilepsy.

## Appendix C. Study A. Participant information sheet

# Participant Information Sheet

**Date Information Sheet Produced:**

16 February 2015

**Project Title**

The Aalborg Brain Computer Interface: A rehabilitation strategy for people with stroke.

**An Invitation**

Kia ora, talofa lava and hello, you are invited to take part in a study aiming to explore the effects of a new rehabilitation approach to improve walking after stroke. 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 will in no way affect your current or future health care.

This information sheet will explain the research study. Please feel free to ask about anything you do not understand or if you have questions at any time.

**What is the purpose of this research?**

A brain computer interface (BCI) is a system that interprets brain signals generated by the person, allowing specific commands from the brain to be sent to an external device. Recent rehabilitation research has begun exploring whether BCI devices have potential as adjuncts to rehabilitation for people following stroke.

The Aalborg BCI interprets brain signals during movement of the leg and utilises this information to trigger external stimulation of the leg muscles. The Aalborg BCI has been shown to improve brain activity in the area of the brain which controls the affected leg following stroke. However, it is not clear whether this improvement in brain activity is long lasting and whether it results in meaningful improvements in walking ability for people with stroke.

Prior to implementing the intervention in people with stroke we are seeking to clarify how long after a single session of the Aalborg BCI Protocol brain activity is increased.

The outcomes of this study will be presented to rehabilitation health professionals and researchers at conferences and published in rehabilitation and neuroscience journals.

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

People are being invited to participate in the research study if they meet all the following criteria:

- Aged over 18 years

People may be excluded from taking part in the study if:

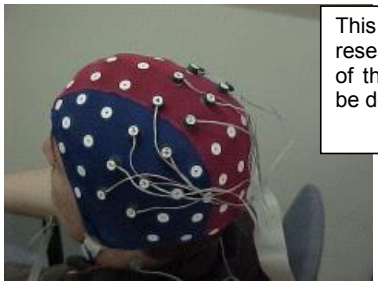
- they are unable to participate due to other problems such as significant communication, cognitive or perceptual impairment
- they are considered medically unsuitable to participate
- the researchers are unable to reliably record one of the study outcome measures

Ten people will participate in the study.

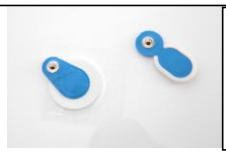
**What will happen in this research?**

The study involves being assessed using Transcranial Magnetic Stimulation, completing a single session of the Aalborg BCI rehabilitation programme, and then being assessed again

In the Aalborg BCI session, electroencephalography (EEG) electrodes will be placed on the participants scalp; these electrodes will record the person's brain activity during movement. Stimulating electrodes will be placed on the affected leg; these electrodes will be used to stimulate the leg muscles. Participants will then attempt to lift their foot and brain activity will be recorded. The participant will then attempt a further 50 foot lifts during which the muscles of the legs will be stimulated..



This is an EEG cap similar to that used in this research project. Conductive gel is placed in each of the electrodes allowing a good EEG signal to be detected by the computer.



These are similar to the electrodes that will be used on your calf to provide the low level electrical stimulation to the common peroneal nerve.

At the beginning and at three time points after the Aalborg BCI session measures of brain excitability using a technique called transcranial magnetic stimulation (TMS) will be undertaken. This technique involves the researcher delivering small magnetic pulses onto participant's head via the TMS machine. These pulses activate the nerve cells in the brain, which results in a twitch in the leg muscles. This technique will help us to understand how the brains control of movement changes after rehabilitation.

The entire session will take approximately two hours.

**What are the discomforts and risks? How will these discomforts and risks be alleviated?**

<u>The Study</u>

This study asks participants for a commitment of time and energy. Participants are able to stop the session at any stage and the researchers will monitor the participants comfort closely.

<u>Measurement of Brain Excitability using Transcranial Magnetic Stimulation</u>

Transcranial Magnetic Stimulation is painless; however it does cause the muscles to twitch, makes a clicking noise and involves the researchers touching the participants head. Some people find this uncomfortable. The intensity of the magnetic stimulator will begin at a very low level, allowing participants time to get used to the muscle twitches, and ear plugs will be offered.

It is recommended that certain people do not have transcranial magnetic stimulation, either because there is a slightly increased risk of seizure with it or because its effects are not known in that group. All participants will be screened using a TMS Safety screening questionnaire and anyone who is deemed to have an increased risk will be excluded from the study for their safety.

During testing small areas of skin on the leg need to be shaved, abraded and wiped with alcohol before adhesive electrodes can be attached. This can cause a temporary stinging sensation and may cause minor, temporary skin reddening. Aloe Vera lotion will be offered as required.

**What are the benefits?**

People who take part in this study are acting as co-researchers and will contribute to our understanding of the Aalborg BCI rehabilitation programme. Their contribution will aid the development rehabilitation approaches that are responsive to the needs of people with walking disability following stroke.

**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?**

Each participant will be assigned a specific code which is used to identify them on all documentation, rather than using their name. All data will be stored in a locked cabinet. Only members of the research team directly involved in data collection and analysis will have access to raw data.

**What are the costs of participating in this research?**

There are no direct costs to participants. Participants will contribute their time and be reimbursed for the cost of their transport to and from AUT University.

**What opportunity do I have to consider this invitation?**

All potential participants are encouraged to take time to consider this invitation and to discuss it with family/whanau. If you have any questions please feel free to contact one of the researchers listed below. If you would like to be considered for the study please respond to this invitation within two weeks.

**How do I agree to participate in this research?**

After contacting that research team and undergoing a brief screening assessment you will be asked to complete a consent form if you would like to participate in this research study.

**Will I receive feedback on the results of this research?**

At the end of the study, all participants will receive a summary of the findings, along with an opportunity to discuss the findings with a researcher.

**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, *Denise Taylor, denise.taylor@aut.ac.nz, 921 9680*.

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?**

***Researcher Contact Details:***


| | |
|---|---|
| Co-Investigator | Nada Signal<br>Health & Rehabilitation Research Institute<br>AUT University<br>Private Bag 92006<br>Auckland 1142<br>09 921 9999<br>nada.signal@aut.ac.nz |
| Co-Investigator | Imran K Niazi |

New Zealand College of Chiropractic
6 Harrison Road
Mt Wellington
Auckland
09 5262105
Imran.niazi@nzchiro.co.nz

***Project Supervisor Contact Details:***

Project Supervisor

Denise Taylor
Health & Rehabilitation Research Institute
AUT University
Private Bag 92006
Auckland 1142
09 921 9680
Denise.taylor@aut.ac.nz

**Approved by the Auckland University of Technology Ethics Committee on *12th February 2015***

**AUTEC Reference number *14/255*.**

## Appendix D. Study A written consent form

# Consent Form

| | |
|---|---|
| *Project title:* | ***The Aalborg Brain Computer Interface: A rehabilitation strategy for people with stroke*** |
| *Project Supervisor:* | ***Associate Professor Denise Taylor*** |
| *Researchers:* | ***Dr Imran Khan Niazi,*** |
| | ***Nada Signal,*** |
| | ***Dr Kim Demstrup,*** |
| | ***Associate Professor Gwyn Lewis*** |

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 16 February 2015.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ If I withdraw, I understand that all relevant information including all data, tapes and transcripts, or parts thereof, will be destroyed.
- ○ I have had the medical risks associated with this research project explained to me
- ○ I am aware of the reasons for potential exclusion from participation in this study
- ○ To the best of my knowledge I am not suffering from any contraindication to the use of Transcranial Magnetic Stimulation as outlined by the researcher.
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes○ No○

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if appropriate):

……..

……..

……..

Date:

***Approved by the Auckland University of Technology Ethics Committee on 12th February 2015 AUTEC Reference number 14/255***

*Note: The Participant should retain a copy of this form.*

# Appendix E. Study A SPSS analysis

## Analysis of background EMG activity prior to triggering MEP (30ms window)

**Tests of Normality**

| | Kolmogorov-Smirnov[a] | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Sig. | Statistic | df | Sig. |
| Back_pre | .463 | 10 | .000 | .508 | 10 | .000 |
| Back_post0 | .359 | 10 | .001 | .667 | 10 | .000 |
| Back_post30 | .332 | 10 | .003 | .852 | 10 | .061 |
| Back_post45 | .245 | 10 | .089 | .934 | 10 | .489 |
| Back_post60 | .213 | 10 | .200* | .896 | 10 | .198 |
| Log_Back_pre | .452 | 10 | .000 | .469 | 10 | .000 |
| Log_Back_post0 | .330 | 10 | .003 | .742 | 10 | .003 |
| Log_Back_post30 | .406 | 10 | .000 | .757 | 10 | .004 |
| Log_Back_post45 | .386 | 10 | .000 | .703 | 10 | .001 |
| Log_Back_post60 | .309 | 10 | .007 | .876 | 10 | .118 |
| Log10Ref_Back_pre | .463 | 10 | .000 | .508 | 10 | .000 |
| Log10Ref_Back_post0 | .359 | 10 | .001 | .667 | 10 | .000 |
| Log10Ref_Back_post30 | .332 | 10 | .003 | .852 | 10 | .061 |
| Log10Ref_Back_post45 | .245 | 10 | .089 | .934 | 10 | .489 |
| Log10Ref_Back_post60 | .213 | 10 | .200* | .896 | 10 | .198 |

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

**Descriptive Statistics**

| | N | Mean | Std. Deviation | Minimum | Maximum |
|---|---|---|---|---|---|
| Back_pre | 10 | .000090 | .0000238 | .0000 | .0001 |
| Back_post0 | 10 | .000111 | .0000316 | .0001 | .0002 |
| Back_post30 | 10 | .000097 | .0000417 | .0000 | .0002 |
| Back_post45 | 10 | .000122 | .0000553 | .0000 | .0002 |
| Back_post60 | 10 | .000123 | .0000764 | .0000 | .0003 |

# Friedman Test

**Ranks**

| | Mean Rank |
|---|---|
| Back_pre | 2.30 |
| Back_post0 | 3.15 |
| Back_post30 | 2.65 |
| Back_post45 | 3.40 |
| Back_post60 | 3.50 |

**Test Statistics[a]**

| | |
|---|---|
| N | 10 |
| Chi-Square | 6.014 |
| df | 4 |
| Asymp. Sig. | .198 |

a. Friedman Test

## Analysis of MEP amplitude data

- **Normality tests of raw data**

IBM SPSS Web Report - Output15

**Explore**

Explore - Descriptives - March 14, 2017

**Descriptives**

| | | | Statistic | Std. Error |
|---|---|---|---|---|
| pre | Mean | | .1752 | .02613 |
| | 95% Confidence Interval for Mean | Lower Bound | .1161 | |
| | | Upper Bound | .2343 | |
| | 5% Trimmed Mean | | .1745 | |
| | Median | | .1757 | |
| | Variance | | .007 | |
| | Std. Deviation | | .08262 | |
| | Minimum | | .06 | |
| | Maximum | | .30 | |
| | Range | | .24 | |
| | Interquartile Range | | .16 | |
| | Skewness | | .032 | .687 |
| | Kurtosis | | -1.214 | 1.334 |
| post0 | Mean | | .3445 | .06855 |
| | 95% Confidence Interval for Mean | Lower Bound | .1895 | |
| | | Upper Bound | .4996 | |
| | 5% Trimmed Mean | | .3410 | |
| | Median | | .2843 | |
| | Variance | | .047 | |
| | Std. Deviation | | .21677 | |
| | Minimum | | .08 | |
| | Maximum | | .67 | |
| | Range | | .59 | |
| | Interquartile Range | | .40 | |
| | Skewness | | .436 | .687 |
| | Kurtosis | | -1.046 | 1.334 |
| post30 | Mean | | .2703 | .05401 |
| | 95% Confidence Interval for Mean | Lower Bound | .1481 | |
| | | Upper Bound | .3925 | |
| | 5% Trimmed Mean | | .2612 | |
| | Median | | .2572 | |
| | Variance | | .029 | |
| | Std. Deviation | | .17061 | |
| | Minimum | | .08 | |
| | Maximum | | .63 | |
| | Range | | .55 | |
| | Interquartile Range | | .26 | |
| | Skewness | | .969 | .687 |
| | Kurtosis | | .797 | 1.334 |
| post45 | Mean | | .2671 | .04864 |
| | 95% Confidence Interval for Mean | Lower Bound | .1570 | |
| | | Upper Bound | .3771 | |
| | 5% Trimmed Mean | | .2637 | |
| | Median | | .2558 | |
| | Variance | | .024 | |

IBM SPSS Web Report - Output15

**Explore**

Explore - Tests of Normality - March 14, 2017

**Tests of Normality**

| | Kolmogorov-Smirnov[a] | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Sig. | Statistic | df | Sig. |
| pre | .127 | 10 | .200* | .965 | 10 | .731 |
| post0 | .193 | 10 | .200* | .914 | 10 | .309 |
| post30 | .167 | 10 | .200* | .918 | 10 | .339 |
| post45 | .117 | 10 | .200* | .974 | 10 | .929 |
| post60 | .214 | 10 | .200* | .797 | 10 | .013 |

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

IBM SPSS Web Report - Output15

**Explore**

Explore - Descriptives - March 14, 2017

| | | | | |
|---|---|---|---|---|
| post60 | Mean | | .3123 | .07306 |
| | 95% Confidence Interval for Mean | Lower Bound | .1470 | |
| | | Upper Bound | .4776 | |
| | 5% Trimmed Mean | | .2935 | |
| | Median | | .2460 | |
| | Variance | | .053 | |
| | Std. Deviation | | .23104 | |
| | Minimum | | .07 | |
| | Maximum | | .90 | |
| | Range | | .83 | |
| | Interquartile Range | | .19 | |
| | Skewness | | 2.028 | .687 |
| | Kurtosis | | 4.985 | 1.334 |

- **Normality tests of log-transformed data**

## Explore

Explore - Descriptives - March 15, 2017

**Descriptives**

| | | | Statistic | Std. Error |
|---|---|---|---|---|
| pre_log10 | Mean | | -.8098 | .07597 |
| | 95% Confidence Interval for Mean | Lower Bound | -.9817 | |
| | | Upper Bound | -.6380 | |
| | 5% Trimmed Mean | | -.8035 | |
| | Median | | -.7572 | |
| | Variance | | .058 | |
| | Std. Deviation | | .24025 | |
| | Minimum | | -1.21 | |
| | Maximum | | -.52 | |
| | Range | | .69 | |
| | Interquartile Range | | .44 | |
| | Skewness | | -.634 | .687 |
| | Kurtosis | | -.838 | 1.334 |
| post0_log10 | Mean | | -.5607 | .10499 |
| | 95% Confidence Interval for Mean | Lower Bound | -.7982 | |
| | | Upper Bound | -.3231 | |
| | 5% Trimmed Mean | | -.5525 | |
| | Median | | -.5465 | |
| | Variance | | .110 | |
| | Std. Deviation | | .33202 | |
| | Minimum | | -1.10 | |
| | Maximum | | -.17 | |
| | Range | | .92 | |
| | Interquartile Range | | .57 | |
| | Skewness | | -.594 | .687 |
| | Kurtosis | | -.653 | 1.334 |
| post30_log10 | Mean | | -.6514 | .09286 |
| | 95% Confidence Interval for Mean | Lower Bound | -.8615 | |
| | | Upper Bound | -.4414 | |
| | 5% Trimmed Mean | | -.6510 | |
| | Median | | -.5899 | |
| | Variance | | .086 | |

## IBM SPSS Web Report - Output2

## Explore

Explore - Descriptives - March 15, 2017

| | | | | |
|---|---|---|---|---|
| post60_log10 | Mean | | -.5955 | .09393 |
| | 95% Confidence Interval for Mean | Lower Bound | -.8080 | |
| | | Upper Bound | -.3830 | |
| | 5% Trimmed Mean | | -.5936 | |
| | Median | | -.6116 | |
| | Variance | | .088 | |
| | Std. Deviation | | .29703 | |
| | Minimum | | -1.18 | |
| | Maximum | | -.05 | |
| | Range | | 1.13 | |
| | Interquartile Range | | .31 | |
| | Skewness | | -.132 | .687 |
| | Kurtosis | | 1.588 | 1.334 |

IBM SPSS Web Report - Output2

Help

Log

Log

Explore

Case Processing Summary

Descriptives

Tests of Normality

pre_log10

Stem-and-Leaf Plot

Normal Q-Q Plot

## Explore

Explore - Tests of Normality - March 15, 2017

Tests of Normality

| | Kolmogorov-Smirnov[a] | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Sig. | Statistic | df | Sig. |
| pre_log10 | .153 | 10 | .200* | .921 | 10 | .368 |
| post0_log10 | .187 | 10 | .200* | .906 | 10 | .257 |
| post30_log10 | .169 | 10 | .200* | .952 | 10 | .687 |
| post45_log10 | .204 | 10 | .200* | .932 | 10 | .468 |
| post60_log10 | .158 | 10 | .200* | .964 | 10 | .825 |

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

- **Repeated-measures ANOVA for log transformed MEP data**

## Log

Log - Log - March 15, 2017

```
GLM pre_log10 post0_log10 post30_log10 post45_log10 post60_log10
  /WSFACTOR=time 5 Polynomial
  /METHOD=SSTYPE(3)
  /EMMEANS=TABLES(time) COMPARE ADJ(LSD)
  /CRITERIA=ALPHA(.05)
  /WSDESIGN=time.
```

## General Linear Model

General Linear Model - Within-Subjects Factors - March 15, 2017

Within-Subjects Factors

MEASURE_1

| time | Dependent Variable |
|---|---|
| 1 | pre_log10 |
| 2 | post0_log10 |
| 3 | post30_log10 |
| 4 | post45_log10 |
| 5 | post60_log10 |

## General Linear Model

General Linear Model - Multivariate Tests - March 15, 2017

Multivariate Tests[a]

| Effect | | Value | F | Hypothesis df | Error df | Sig. |
|---|---|---|---|---|---|---|
| time | Pillai's Trace | .672 | 3.073[b] | 4.000 | 6.000 | .106 |
| | Wilks' Lambda | .328 | 3.073[b] | 4.000 | 6.000 | .106 |
| | Hotelling's Trace | 2.049 | 3.073[b] | 4.000 | 6.000 | .106 |
| | Roy's Largest Root | 2.049 | 3.073[b] | 4.000 | 6.000 | .106 |

a. Design: Intercept
Within Subjects Design: time

b. Exact statistic

## General Linear Model

General Linear Model - Mauchly's Test of Sphericity - March 15, 2017

Mauchly's Test of Sphericity[a]

MEASURE_1

| Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. | Epsilon[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | Greenhouse-Geisser | Huynh-Feldt | Lower-bound |
| time | .300 | 8.935 | 9 | .455 | .686 | 1.000 | .250 |

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept
Within Subjects Design: time

IBM SPSS Web Report - Output3

## General Linear Model

General Linear Model - Tests of Within-Subjects Effects - March 15, 2017

**Tests of Within-Subjects Effects**

MEASURE_1

| Source | | Type III Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| time | Sphericity Assumed | .364 | 4 | .091 | 4.831 | .003 |
| | Greenhouse-Geisser | .364 | 2.743 | .133 | 4.831 | .010 |
| | Huynh-Feldt | .364 | 4.000 | .091 | 4.831 | .003 |
| | Lower-bound | .364 | 1.000 | .364 | 4.831 | .056 |
| Error(time) | Sphericity Assumed | .679 | 36 | .019 | | |
| | Greenhouse-Geisser | .679 | 24.690 | .028 | | |
| | Huynh-Feldt | .679 | 36.000 | .019 | | |
| | Lower-bound | .679 | 9.000 | .075 | | |

- **Post hoc tests for log-transformed MEP data**

IBM SPSS Web Report - Output3

## time

time - Pairwise Comparisons - March 15, 2017

**Pairwise Comparisons**

MEASURE_1

| (I) time | (J) time | Mean Difference (I-J) | Std. Error | Sig.[b] | 95% Confidence Interval for Difference[b] Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|
| 1 | 2 | -.249* | .070 | .006 | -.407 | -.091 |
| | 3 | -.158* | .045 | .006 | -.259 | -.057 |
| | 4 | -.150* | .057 | .027 | -.278 | -.021 |
| | 5 | -.214* | .076 | .020 | -.386 | -.043 |
| 2 | 1 | .249* | .070 | .006 | .091 | .407 |
| | 3 | .091 | .060 | .162 | -.044 | .226 |
| | 4 | .100 | .061 | .137 | -.038 | .238 |
| | 5 | .035 | .077 | .660 | -.138 | .208 |
| 3 | 1 | .158* | .045 | .006 | .057 | .259 |
| | 2 | -.091 | .060 | .162 | -.226 | .044 |
| | 4 | .009 | .050 | .862 | -.103 | .121 |
| | 5 | -.056 | .069 | .441 | -.213 | .101 |
| 4 | 1 | .150* | .057 | .027 | .021 | .278 |
| | 2 | -.100 | .061 | .137 | -.238 | .038 |
| | 3 | -.009 | .050 | .862 | -.121 | .103 |
| | 5 | -.065 | .039 | .128 | -.152 | .023 |
| 5 | 1 | .214* | .076 | .020 | .043 | .386 |
| | 2 | -.035 | .077 | .660 | -.208 | .138 |
| | 3 | .056 | .069 | .441 | -.101 | .213 |
| | 4 | .065 | .039 | .128 | -.023 | .152 |

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

P values adjusted according to Holm-Bonferroni method. Values adjusted from lowest to highest significant levels:

$p^1 = 0.0125$

$p^2 = 0.017$

$p^3 = 0.025$

$p^4 = 0.05$

# Appendix F. Study B ethical approval

AUT UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

AUTEC
SECRETARIAT

14 November 2014

Denise Taylor
Faculty of Health and Environmental Sciences

Dear Denise

Re Ethics Application: **14/255 The Aalborg BCI: a MRCP driven PAS protocol for people with stroke.**

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 12 November 2017.

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 12 November 2017;
- 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 12 November 2017 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: Nada Signal; Gwyn Lewis

Auckland University of Technology Ethics Committee
WA505F Level 5 WA Building City Campus
Private Bag 92006 Auckland 1142 Ph: +64-9-921-9999 ext 8316 email ethics@aut.ac.nz

Ethical considerations for Study B:

- Possible discomfort during TMS. This was reduced by starting the stimulation at a low intensity and allowing participants time to habituate. Consent was sought before touching each participant's head, and earplugs were also available for comfort.
- Possible skin irritation due to electrode placement. Aloe vera gel was available to reduce this discomfort if required.
- Seizure risk associated with TMS. This was minimised by screening of risk factors associated with increased risk of seizure.
- Safety considerations during functional assessments. This was minimised by having a trained research physiotherapist present during all functional assessments and using a safety harness during the application of TMS during step-ups.
- Deception involved in the use of the sham intervention. Participants were advised that there were two intervention conditions, one moderate intensity and one low intensity, and were unaware that the low intensity condition was a sham intervention. This was important to ensure that participants in the sham group behaved in the same way as those receiving the novel-PAS intervention. While it was anticipated that both intervention and sham protocols might improve brain activity and walking function, participants were unaware of the study's hypothesis that moderate intensity novel-PAS would induce greater changes.

## Appendix G. Study B participant information booklet

# Whom do I contact for further information about this study?


**Co-Investigator**

Nada Signal

Health & Rehabilitation Research Institute

AUT University

Private Bag 92006, Auckland 1142

09 921 9999

Nada.signal@aut.ac.nz

**Co- Investigator**

Imran K Niazi

New Zealand College of Chiropractic

6 Harrison Road, Mt Wellington, Auckland

09 526 2105

Imran.niazi@nzchiro.co.nz

**Project Supervisor**

Denise Taylor

Health & Rehabilitation Research Institute

AUT University

Private Bag 92006, Auckland 1142

09 921 9680

Denise.taylor@aut.ac.nz


12

# The Aalborg Brain Computer Interface

## A Rehabilitation Strategy for People with Stroke

## Participant Information

Please contact Sharon Olsen to register your interest on 09 921 9999 x 8935

AUT UNIVERSITY

# An invitation:

## Kia ora, talofa lava and hello.

You are invited to take part in a study aiming to explore the effects of a new rehabilitation approach to improve walking after stroke. 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 will in no way affect your current or future health care.

This information sheet will explain the research study. Please feel free to ask about anything you do not understand or if you have questions at any time.



# What is the purpose of this research?

A brain computer interface (BCI) is a system that interprets brain signals generated by the person, allowing specific commands from the brain to be sent to an external device. Recent rehabilitation research has begun exploring whether BCI devices have potential as adjuncts to rehabilitation for people following stroke.

The Aalborg BCI interprets brain signals during movement of the leg and utilises this information to trigger external stimulation of the leg muscles. The Aalborg BCI has been shown to improve brain activity in the area of the brain which controls the affected leg following stroke. However, it is not clear whether this improvement in brain activity is long lasting and whether it results in meaningful improvements in walking ability for people with stroke.

Therefore, the aim of this study is to explore the effect of the Aalborg BCI. Specifically we want to:

1. Explore whether the Aalborg BCI results in immediate, long term and retained changes in brain activity in people with stroke.
2. Explore whether the Aalborg BCI has potential to improve walking ability in people following stroke.
3. Explore the acceptability of the Aalborg BCI to people following stroke.
4. Consider the feasibility of carrying out a bigger research study investigating the Aalborg BCI in a large group of people with stroke.

The outcomes of this study will be presented to rehabilitation health professionals and researchers at conferences and published in rehabilitation and neuroscience journals.

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

People are being invited to participate in the research study if they meet all the following criteria:

- Aged over 18 years.
- Have had a single stroke more than 6 months ago.
- Are able to walk, but still have difficulty with walking since the stroke.

People may be excluded from taking part in the study if:

- They are unable to participate due to other problems such as significant communication, cognitive or perceptual impairment.
- They are considered medically unsuitable to participate.
- The researchers are unable to reliably record one of the study outcome measures.

Twenty people will participate in the study.



# What will happen in the research?

The study involves being assessed using a variety of measures, completing a four week Aalborg BCI rehabilitation programme, and then being assessed again. After the first set of assessments each person is assigned by chance, using a computer, to one of two groups; BCI low intensity and BCI moderate intensity.

**The Rehabilitation Programme**

The rehabilitation programme lasts for four weeks. People in both groups will come to the North Shore campus of AUT University to do their rehabilitation three times per week for four weeks. The total time spent doing the rehabilitation is 12 hours. The rehabilitation will be supervised by a trained researcher.

In each Aalborg BCI session, electroencephalography (EEG) electrodes will be placed on the participants scalp; these electrodes will record the person's brain activity during movement. Stimulating electrodes will be placed on the affected leg; these electrodes will be used to stimulate the leg muscles. Participants will then attempt to lift their foot and brain activity will be recorded. The participant will then attempt a further 50 foot lifts during which the muscles of the legs will be stimulated. Participants in both groups will receive leg muscle stimulation; one group will have stimulation at a low intensity and the other at a moderate intensity.

# What will happen in the research continued…

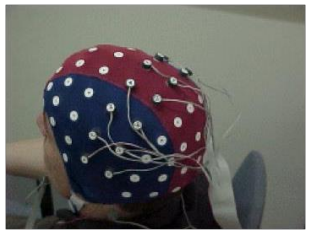
**The Assessments**

At the beginning and end of the rehabilitation programme everyone participating will attend AUT University to take part in a series of assessments and tests including:

- Tests of physical abilities, such as walking speed and balance.
- Measurement of leg muscle strength.
- Discussions with a researcher about your impressions and opinions of the Aalborg BCI rehabilitation programme.
- Measures of brain excitability using a technique called transcranial magnetic stimulation (TMS). This technique involves the researcher delivering small magnetic pulses onto participant's head via the TMS machine. These pulses activate the nerve cells in the brain, which results in a twitch in the leg muscles. This technique will help us to understand how the brains control of movement changes after rehabilitation. This measurement will also be repeated at the 1st, 4th, 7th, and 10th rehabilitation sessions to chart the changes in brain excitability with the rehabilitation programme.

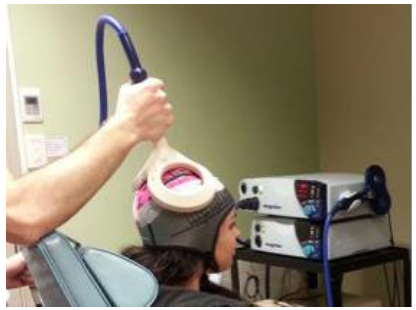
Assessment sessions can last 2-3 hours.





This is an EEG cap similar to that used in this research project. Conductive gel is placed in each of the electrodes allowing a good EEG signal to be detected by the computer.

These are similar to the electrodes that will be used on your leg to provide the low level electrical stimulation to the common peroneal nerve.



This is Transcranial Magnetic Stimulation. A coil is placed on the head and magnetic pulses are delivered. This is used to measure the excitability of the brain.

# What are the discomforts and risks? How will these be alleviated?

**The Study**

This study asks participants for a significant commitment of time and energy. People with stroke may experience some fatigue due to the amount and nature of this commitment. Participants are able to stop an experimental or rehabilitation session at any stage and the researchers will monitor all sessions closely.

**Measurement of Brain Excitability using Transcranial Magnetic Stimulation**

Transcranial Magnetic Stimulation is painless; however it does cause the muscles to twitch, makes a clicking noise and involves the researchers touching the participants head. Some people find this uncomfortable. The intensity of the magnetic stimulator will begin at a very low level, allowing participants time to get used to the muscle twitches, and ear plugs will be offered.

It is recommended that certain people do not have transcranial magnetic stimulation, either because there is a slightly increased risk of seizure with it or because its effects are not known in that group. All participants will be screened using a TMS Safety screening questionnaire and anyone who is deemed to have an increased risk will be excluded from the study for their safety.

During testing small areas of skin on the leg need to be shaved, abraded and wiped with alcohol before adhesive electrodes can be attached. This can cause a temporary stinging sensation and may cause minor, temporary skin reddening. Aloe Vera lotion will be offered as required.



# What are the benefits?

Whilst we cannot guarantee it, we hope that participants will experience improvement in their walking ability as a result of participating in the study. People who take part in this study are acting as co-researchers and will contribute to our understanding of the Aalborg BCI rehabilitation programme. Their contribution will aid the development rehabilitation approaches that are responsive to the needs of people with walking disability following stroke.

# 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?

Each participant will be assigned a specific code which is used to identify them on all documentation, rather than using their name. All data will be stored in a locked cabinet. Only members of the research team directly involved in data collection and analysis will have access to raw data.

## What are the costs of participating in the research?

There are no direct costs to participants. Participants will be offered petrol or taxi vouchers to assist with their travel costs to and from AUT. Participants will also contribute their time.

## What opportunity do I have to consider this invitation?

All potential participants are encouraged to take time to consider this invitation and to discuss it with family/whanau. If you have any questions please feel free to contact one of the researchers on the back page of this booklet. If you would like to be considered for the study please respond to this invitation within two weeks.

## How do I agree to participate in this research?

After contacting the research team and undergoing a brief screening assessment you will be asked to complete a consent form if you would like to participate in this research study.



## Will I receive feedback on the results of this research?

At the end of the study, all participants will receive a summary of the findings, along with an opportunity to discuss the findings with a researcher.

## 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, *Denise Taylor, denise.taylor@aut.ac.nz, 921 9680*.

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.

**This study was approved by the Auckland University of Technology Ethics Committee on *14 November 2014***

**AUTEC Reference number *14/255***

# Appendix H. Study B telephone screening tool

| | | |
|---|---|---|
| **Name** | | |
| **Address** | | |
| **Telephone Number** | | |
| **Email / Alternate Contact** | | |
| **How did you hear about the study?** | | |
| **Have you read an information sheet about the study?** | | |
| **Sex** | | |
| **DOB/Age** | | *Over 18 years?* |
| **Date of Stroke** | | *More than 6 months ago?* |
| **Single stroke** | | |
| **Type of Stroke (if known)** | | |
| **Hemiplegia** | | |
| **Able to walk 10m** | | |
| **10m Walking Speed** | | m/s |
| **Uses Aid?** | | What? |
| **Uses AFO?** | | |
| If you were eligible to participate would you be able to attend rehabilitation 3x per week at AUT's North Shore Campus (Monday, Wednesday and Friday or alternate days) ? | | |
| Are you comfortable with the idea of TMS? Do you have any questions about the assessments? | | |

| | |
|---|---|
| **Medical Conditions:**<br><br>Cardiac Conditions<br><br>Hypertension (160+/105+)<br><br>Uncontrolled metabolic disorders<br><br>Active acute infection<br><br>Musculoskeletal pain in LL's<br><br>*Do you have a history of significant lower limb trauma?*<br><br>Major depression/ psychiatric illness<br><br>Other neurological pathologies *Other than this stroke, have you had another stroke or neurological illness or muscle wasting disease?* | Cautions and contraindications to exercise |
| **Involved in another study?** | |
| **TMS Screening Questionnaire**<br><br>*The magnetic stimulator feels like a big tap on your head, and can cause the muscles in the leg and sometimes in the face to twitch. It is not recommended for people who have certain conditions so we need to complete a checklist first.*<br><br>Complete TMS Safety Questionnaire. | Cautions<br><br>Contraindications |
| **Medications (name and dose)** **(**Check against threshold lowering list)<br><br>Screened for seizure threshold lowering effect Y/N | |

## Screening Outcome

| | |
|---|---|
| Possibility | Needs Face to Face<br><br>Other: |
| Excluded from TMS? | Reason (s): |
| Excluded/ Included in Study | Reason (s): |
| Referred to | |

## Participant Safety Checklist for using Transcranial Magnetic Stimulation

Volunteer Name:_____

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

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

Medications checked for seizure threshold lowering effect? Yes / No

Checklist completed by: _____

Signature: _____

# Appendix I. Study B written consent form



# Consent Form

| | |
|---|---|
| *Project title:* | ***The Aalborg Brain Computer Interface: A rehabilitation strategy for people with stroke*** |
| *Project Supervisor:* | ***Associate Professor Denise Taylor*** |
| *Researchers:* | ***Dr Imran Khan Niazi,*** |
| | ***Nada Signal,*** |
| | ***Dr Kim Demstrup,*** |
| | ***Associate Professor Gwyn Lewis*** |

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 14 August 2014.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ If I withdraw, I understand that all relevant information including all data, tapes and transcripts, or parts thereof, will be destroyed.
- ○ I understand that notes will be taken during the interview and that they will also be audio-taped and transcribed.
- ○ I have had the medical risks associated with this research project explained to me
- ○ I am aware of the reasons for potential exclusion from participation in this study
- ○ To the best of my knowledge I am not suffering from any contraindication to the use of Transcranial Magnetic Stimulation as outlined by the researcher.
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes○ No○

Participant's signature: .....……

Participant's name: .....……

Participant's Contact Details (if appropriate):

……..

……..

Date:

**Approved by the Auckland University of Technology Ethics Committee on *14 November 2014.***

**AUTEC Reference number *14/255***

*Note: The Participant should retain a copy of this form.*

This version was last edited on 12 May 2015

# Appendix J. Study B 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.**

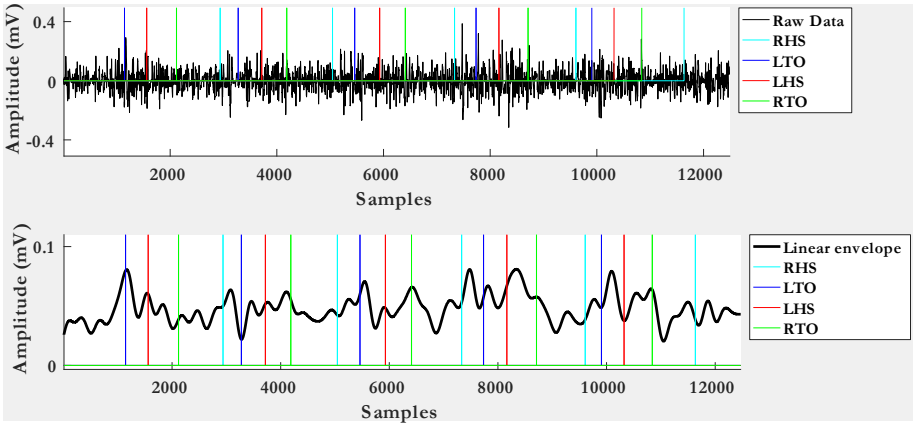
If such an event should occur, please report this by emailing the form below to nada.signal@aut.ac.nz as soon as possible.

| | |
|---|---|
| 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<br>Details: |
| Outcome: | Fatal/Recovered/Ongoing<br>Details: |
| Was the event related to the research session? | Related/Unrelated<br>Details: |
| Name/designation of person reporting: | |
| Date form completed: | |

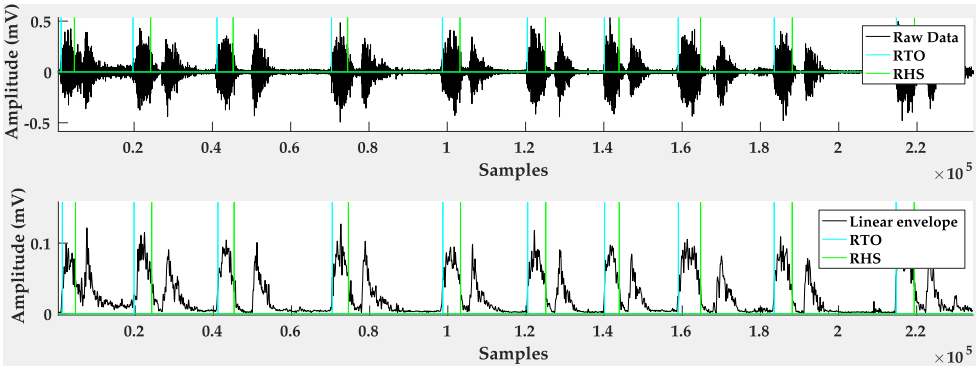
# Appendix K. TA EMG processing for gait and step-ups

## Linear envelopes for visual analysis and variation ratio

TA EMG data was was bandwidth filtered at 10-150Hz[250,271,282-284], full-wave rectified, and smoothed using a 10Hz low-pass (5th order Butterworth) to create a linear envelope[427]. Individual gait cycles, defined as heel strike to heel strike on the hemiplegic side, were time-normalised to 1001 samples[285]. This involved first calculating the "mean toe-off" time from all gait cycles. Then within each individual gait cycle, the data before and after the toe-off event was resampled separately, so that the toe-off event occurred at time of the "mean toe-off". This allowed the stance and swing phases to be compared across trials. Individual step-up cycles, defined as heel-off to heel-on, were normalised to a time frame of 501 points.

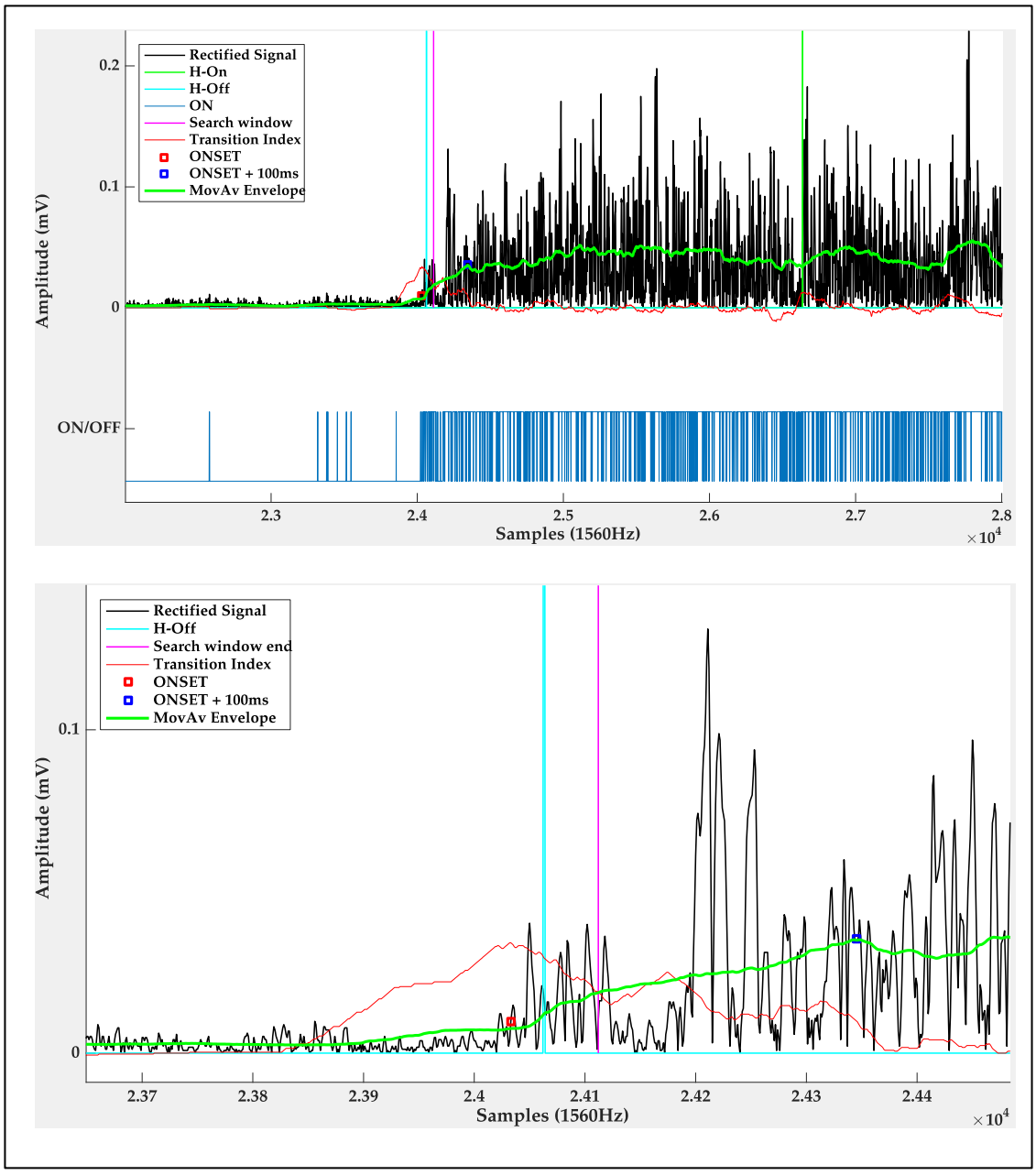



Example of raw TA EMG (above) and linear envelope (below) during gait with right heel-strike and toe-off (RHS and RTO) and left heel-strike and toe-off (LHS and LTO) events shown.




Example of raw TA EMG (above) and linear envelope (below) during step-ups with right toe-off (RTO) and right heel-strike (RHS) events shown.

**Moving average envelopes for rate of EMG rise**




Plot showing rectified TA EMG and moving average envelope (MovAv) during one trial of hemiparetic limb step-ups. Lower plot is zoomed in over the EMG onset. Heel-on (H-On) and heel-off (H-Off) events are marked. The peak of the transition index identifies the EMG onset.

# Appendix L. Study B protocol deviations

| Stage of research process | Protocol deviation | Description |
|---|---|---|
| Recruitment | Extended recruitment phase from 4-11 months | Due to difficulty with recruitment, the time-frame for recruitment was extended from 4 to 11 months. |
| Measurement | Refined process for identifying TMS intensity when no isometric MEP was produced at maximum tolerable intensity (n=1) | The method for finding the AMT for TMS measures was not suitable for one participant, who had no MEP at maximum tolerable intensity (during 10% MVIC). In this situation, the TMS intensity was set at 'maximum tolerable'. The MEP during the 10% MVIC was recorded as zero, but measurable MEPs were produced during step-ups. The participant withdrew after baseline, but it was planned that for future recordings, the TMS intensity would be set at that used in the first session. If the participant developed a MEP during a 10% MVIC over the course of the study, then MEPs would be recorded at AMT, and the TMS intensity used in the first session. |
| Measurement | Skin preparation for electrode placement was not performed more than once for those at risk of skin breakdown | In some participants routine skin preparation over the anterior lower leg caused mild blood spotting or skin inflammation. Therefore, all skin preparation was performed carefully, and for those considered at risk of skin breakdown, skin preparation was not performed more than once. |
| Measurement | Electrode impedance not always below 5KΩ. | Skin preparation was never performed more than twice, even if impedance was > 5KΩ, due to the risk of skin damage. |
| Measurement | Performed 6m walk test next to wall (n=1) | One participant was not confident to walk in the centre of the hallway, so they were permitted to walk with a wall on their non-paretic side and this was kept consistent for all measurement sessions. |
| Measurement | Used hip/knee flexion to recruit ankle dorsiflexors during TMS measures (n=1) | One participant could not perform isolated ankle dorsiflexion in the force plate, which meant they could not produce a 10% MIVC for AMT testing. They were instructed to perform a combined hip flexion, knee flexion, and ankle dorsflexion movement, which enabled dorsiflexion muscle activation. |
| Measurement | Step height lowered for 3D motion analysis and TMS measures (n=1) | One participant could not perform step-ups with 19cm step, so a 7.5cm step was used for 3D motion analysis and TMS measures. |

| Stage of research process | Protocol deviation | Description |
|---|---|---|
| Measurement | Reduced number of outcome measurements during intervention phase | The original protocol included 8 time-consuming measurements sessions. For the first participant, these lasted on average 2.77 hours (range 2-3.5 hours). In an attempt to reduce this time burden for participants, the protocol was revised for the second participant to exclude the isometric-MEP measures from three sessions during weeks 2-4. However, for participant 2 these three sessions still lasted an average of 3 hours. The protocol was modified from the third participant onwards, to exclude isometric- and stepping-MEPs from the week 2-4 measures. This second protocol revision reduced the measurement sessions in week 2-4 from 3 hours to 1.3 hours. The final protocol had five long measurement sessions (2.1 to 3.4 hours), and three medium length sessions (1.3 hours). |
| Measurement | Delayed and missed data collection (n=2) | Participant 4 experienced recurrent illness which caused a delay of 7 days for post-intervention session 2, and cancellation of post-intervention sessions 1 and 3.<br>Participant 6 had a delay of 11 days for post-intervention session 2 due to having an unrelated illness. |
| Intervention | 20-day break during intervention phase (n=1) | Participant 4 experienced recurrent illness which caused a delay of 20 days between intervention 8 and 9. |
| Intervention | Potential miscalculation of PN timing<br>(week 1 and 2 of intervention, n=1) | Due to technical errors, many MRCP epochs were lost for the first three MRCP recordings for participant 1, which meant that the PN was calculated from a reduced number of epochs for the first two weeks of intervention. |
| Intervention | Miscalculation of PN timing (6 interventions, n=1) | Due to miscommunication about a minor change made to the MATLAB programme, participant 4 received the intervention with incorrectly timed electrical stimulation (PN minus 200ms) for 6/12 interventions. |
| Intervention | Error in pulse width of electrical stimulation (6 interventions, n=1) | Due to error, participant 4 had electrical stimulation delivered in 2ms pulses, rather than 1ms pulses, for 6 out of 12 interventions. |

# Appendix M. 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

0800 4 ETHICS
hdecs@moh.govt.nz

31 May 2017

Mrs Sharon Olsen
HRRI
AUT University North Campus
90 Akoranga Drive
Northcote 0627

Dear Mrs Olsen

| Re: | **Ethics ref:** | **17/NTB/80** |
|---|---|---|
| | Study title: | An investigation of the effects of a Brain Computer Interface protocol on the brains ability to move the affected leg after stroke. |

I am pleased to advise that this application has been *approved* by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC-Expedited 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 Northern B 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.

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.

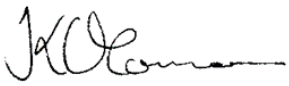
Your next progress report is due by 30 May 2018.

Participant access to ACC

The Northern B 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,



Mrs Kate O'Connor
Chairperson
Northern B 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* |
|---|---|---|
| CV for CI: CV for Sharon Olsen, Doctoral Student undertaking research. | 1 | 11 April 2017 |
| Screening assessment completed by Researcher to assess eligibility and record demographic data. | 1 | 11 April 2017 |
| Screening sheet for Transcranial Magnetic Stimulation to be completed by Researcher. | 1 | 11 April 2017 |
| Protocol: Research Protocol. | 1 | 11 April 2017 |
| Covering Letter: Cover Letter | 1 | 11 April 2017 |
| Evidence of scientific review: Peer review by Dr Kelly Holt | 1 | 24 April 2017 |
| PIS/CF: PIS version. This has been modified and all feedback has been incorporated. | 2 | 23 May 2017 |
| Advertisement (version 2) corrected based on feedback. | 2 | 27 April 2017 |
| Version 2 of advertisement with corrections based on feedback. | 2 | 22 May 2017 |
| Response to feedback about statistics. | 1 | 23 May 2017 |

**Appendix B**
**Statement of compliance and list of members**

Statement of compliance

The Northern B 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 00008715) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

| *Name* | *Category* | *Appointed* | *Term Expires* |
|---|---|---|---|
| Mrs Maliaga Erick | Lay (consumer/community perspectives) | 01/07/2015 | 01/07/2018 |
| Mr John Hancock | Lay (the law) | 14/12/2015 | 14/12/2018 |
| Dr Nora Lynch | Non-lay (health/disability service provision) | 24/07/2015 | 24/07/2018 |
| Miss Tangihaere Macfarlane | Lay (consumer/community perspectives) | 20/05/2017 | 20/05/2020 |
| Mrs Kate O'Connor | Lay (ethical/moral reasoning) | 14/12/2015 | 14/12/2018 |
| Mrs Stephanie Pollard | Non-lay (intervention studies) | 01/07/2015 | 01/07/2018 |
| Mrs Leesa Russell | Non-lay (intervention studies), Non-lay (observational studies) | 14/12/2015 | 14/12/2018 |
| Mrs Jane Wylie | Non-lay (intervention studies) | 20/05/2017 | 20/05/2020 |

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

The main ethical considerations included:

- Possible physical discomfort during testing. For TMS measurements, this was reduced by starting the stimulation at a low intensity and allowing participants time to habituate. Consent was sought before touching each participant's head, and earplugs were also available for comfort. Electrical stimulation was applied in very short bursts and only applied at an intensity the participant could tolerate.
- Possible skin irritation due to electrode placement. Aloe vera gel was available to reduce this discomfort if required.
- Seizure risk associated with TMS. This was minimised by screening risk factors associated increased risk of seizure.
- Risks associated with electrical stimulation. These were minimised by screening participants for contraindications to electrical stimulation.
- Deception involved in the use of the sham intervention.
- Participants were offered a 1-hour free session with a New Zealand registered physiotherapist as thanks for their time.

# Appendix N. 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

13 June 2017

Denise Taylor
Faculty of Health and Environmental Sciences

Dear Denise

Ethics Application: 17/187 **An investigation of the effects of a Brain Computer Interface protocol on the brains ability to move the affected leg after stroke**

I wish to advise you that a subcommittee of the Auckland University of Technology Ethics Committee (AUTEC) has **approved** your ethics application.

This approval is for three years, expiring 7 June 2020.

**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 You are reminded that it is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard.

For any enquiries, please contact ethics@aut.ac.nz

Yours sincerely,

Kate O'Connor
Executive Manager
**Auckland University of Technology Ethics Committee**

Cc: solsen@aut.ac.nz; Imran Niazi

# Appendix O. Study C participant information sheet and consent form

## Participant Information Sheet

| | | | |
|---|---|---|---|
| Study title: | **Usefulness of a Brain Computer Interface for Rehabilitation after Stroke** | | |
| Locality: | **AUT University, Auckland** | Ethics committee ref.: 17/NTB/80 | |
| Lead investigator: | **Professor Denise Taylor**<br>**AUT University** | Contact phone number: | **09 921 9999 x 9494** |

Kia ora, Talofa lava, and Hello.

You are invited to take part in a study about the **Usefulness of a Brain Computer Interface for Rehabilitation after Stroke**. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason, and it will not 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, whānau, 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 9 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 research is about a Brain Computer Interface. A Brain Computer Interface is a system that interprets brain signals, and then sends a command to another device. Research has begun exploring whether Brain Computer Interfaces can help improve rehabilitation for people following stroke.

Our Brain Computer Interface interprets brain signals while you are moving your ankle and then uses this information to trigger electrical stimulation to one of the ankle muscles. This approach can improve brain activity in the part of the brain that controls the affected ankle following stroke.

The purpose of this research study is to advance our knowledge about how the Brain Computer Interface improves the brains control over your ankle movement. All participants will be treated equally and will receive two intervention sessions. One session will use the Brain Computer Interface at a moderate intensity, and one will use the Brain Computer Interface at low intensity. The order of these sessions will be randomised so you will not know which is first. In addition, the person taking measures of your brain and muscle function will not know which intervention you have received, and this helps ensure the results are not influenced by the Researcher's opinion.

The information we gather will help us decide whether the Brain Computer Interface has potential to assist with rehabilitation following stroke.

This study will also contribute to the qualification of Doctor of Philosophy (PhD) for Sharon Olsen, at AUT University. Sharon is a Physiotherapist by background, and is co-ordinating the study. She can be contacted on 09 921 9999 x 9494. This study has received ethical approval from HDEC on 31 May 2017 and recruitment for the study is underway. 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 may have contacted us after seeing our advertisement or being told about this study by your healthcare provider. If you are interested in participating, we will need to conduct a screening assessment to check that you meet the following criteria:

- Aged over 18 years.
- Have had a single stroke more than 6 months ago.
- Have weakness on one side affecting ankle movement.

People may be excluded from taking part in the study if:

- They are unable to participate due to other problems such as significant communication, cognitive or perceptual impairment.
- Have had a cerebellar stroke.
- They are considered medically unsuitable to participate. For example, if they are acutely unwell, have other neurological conditions that may impact the testing, have significant pain, have a recent injury, damaged skin, or infection in their affected lower leg, have metal implants in their affected lower leg, or have implanted devices (e.g. pacemaker).
- They are unable to stand with assistance to transfer into the research chair, or would not tolerate the length of the research session (1- 1 ¾ hours).
- The researchers are unable to reliably record one of the study outcome measures.

If you are eligible to participate, and would like to participate in the study you will be asked to complete a consent form (at the end of this document). The Researcher will then send a letter to your GP to inform them about your participation in the study.

The study will involve attending three appointments at AUT University in Northcote, Auckland.

- The first session will involve two assessments.

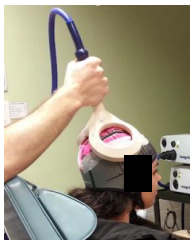
- The second session will involve a series of assessments, followed by one of the Brain Computer Interface interventions (moderate or low intensity), and then the assessments will be repeated.
- The third session will be the same as the second session, but you will receive the intervention that you have not tried yet.

The total time commitment is 4-6 hours.

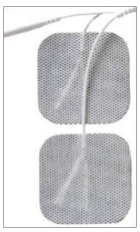
Assessments

The assessments will involve:

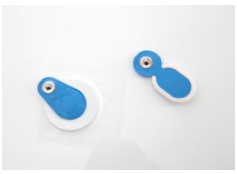
- Measurement of ankle muscle strength and endurance.
- Measurement of brain excitability using a technique called Transcranial Magnetic Stimulation. This technique involves the researcher delivering small magnetic pulses onto your head via the Transcranial Magnetic Stimulation machine (pictured). These pulses activate the nerve cells in your brain, which results in a twitch in the leg muscles. Not everyone can have Transcranial Magnetic Stimulation so we will check this at the first session. If we are unable to use the stimulation, you can still continue with the study.



- Measurement of the brains control over your ankle movement using a technique called Interpolated Twitch. This technique involves placing stimulating electrodes (similar to those pictured) over your lower leg (shin muscle), and then delivering short pulses of electrical stimulation while you are moving your ankle. This will feel like a small shock to the muscle, but it only lasts a very short time.



- Measurement of ankle muscle activity using Electromyography. This involves placing small sticky electrodes (pictured) on your lower leg and recording muscle activity while you are moving your ankle.



The Brain Computer Interface intervention

Firstly, brain activity is recorded with Electroencephalography (EEG). This involves placing a cap on your head that contains many small electrodes. These electrodes record brain activity while you are moving your ankle.

This is an EEG cap similar to that used in this research project. Conductive gel is placed in each of the electrodes allowing a good EEG signal to be detected by the computer.

The intervention involves using the EEG signals to trigger some electrical stimulation to your ankle muscle. Stimulating electrodes are placed on your affected leg just below the knee.

While you attempt to move your ankle 50 times, a small pulse of stimulation will be delivered to these electrodes.

## WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

You may experience some benefit from having one session of the Brain Computer Interface intervention, but we cannot guarantee this. However, your contribution will help move this research forward. Your contribution will further our understanding of the effects of the Brain Computer Interface, and will help develop this rehabilitation approach for people with stroke.

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

Time involved

This study asks participants' for a commitment of time and energy. People with stroke may feel fatigued due to this commitment. Participants are able to stop an experimental session at any stage and the researchers will monitor all sessions closely.

Transcranial Magnetic Stimulation

This can cause discomfort in some people. It feels like something is tapping your head, makes your muscles twitch, makes a clicking noise and involves the Researcher touching your head. At the first session, we will check that you can tolerate this. If you cannot tolerate it, then you can continue the study without it. To help make it more comfortable, we can offer you earplugs and increase the stimulation slowly, so you can get used to it.

It is recommended that certain people do not have Transcranial Magnetic Stimulation, either because there is a slightly increased risk of seizure with it or because its effects are not known in that group. All participants will be screened using a Safety questionnaire and anyone who is deemed to have an increased risk will be excluded from having the stimulation, but can continue the study.

There is also very low risk of fainting or headache. Participants' will remain seated during the stimulation and Researchers will monitor participants for signs of dizziness throughout the session. If you have a history of headaches, please discuss this with the Researcher as this may prevent you from having the stimulation.

Electrode placement

During testing small areas of skin on the front of your lower leg need to be shaved, abraded and wiped with alcohol before adhesive electrodes can be attached. This can cause a temporary stinging sensation and may cause minor, temporary skin reddening. Aloe Vera lotion will be offered as required.

Interpolated twitches

This technique involves giving electrical muscle stimulation at a level that produces a large twitch in the muscle. This may be uncomfortable but lasts for a very short time. The stimulation will start at a low level to allow people to get used to the stimulation. All participants will be asked questions about their skin and leg prior to having electrical stimulation, to ensure it is safe for them.

Electroencephalography

While setting up the electrode cap, electrode gel is injected into each electrode with a blunt needle. The blunt needle is rubbed against the scalp to remove dead skin and move hair

aside, so that the electrode is in good contact with the skin. This is not painful, and the researcher will perform this gently to ensure you are comfortable.

## WHO PAYS FOR THE STUDY?

There are no direct costs to participants. Participants will contribute their time. Either petrol or taxi vouchers will be offered to assist with transport costs to and from AUT University.

In recognition of your commitment to this study, after the completion of your three sessions, you will be offered a 1-hour free session with a NZ Registered Physiotherapist. This will involve a 30-minute assessment of either your arm or your leg (your choice) and prescription of a short home exercise programme. A summary of this assessment and exercise programme will be sent to your GP.

## WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. 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 in no way affect your future healthcare. 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 your data removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data will not be possible.

You have the right to privacy and confidentiality. Your personal details will be stored in a locked cabinet. You will be assigned a specific code, and all data collected will be recorded next to this code, rather than your name. Only members of the research team directly involved in data collection and analysis will have access to this data, and it will be stored in a locked cabinet. You will not be identifiable in any presentations or journal articles related to the study's findings.

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

During the study, if we become aware of any new benefits or adverse effects of the study protocol that may affect your health, we will advise you of this.

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

At the conclusion of the study, a summary of the study's findings will be sent to you. This is expected to take about 9 months.

Following the study, the Brain Computer Interface will not be available to you as an intervention. Further research and development will be required before it can be used for rehabilitation.

The data that is collected will be stored for 10 years at AUT University. The data will not be used for other studies. After 10 years, the data will be destroyed.

## 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 | Sharon Olsen<br>Health and Rehabilitation Research Institute<br>AUT University<br>Private Bag 92006<br>Auckland 1142<br>Ph 09 921 9999 x 9494<br>solsen@aut.ac.nz |
| Co-Investigator | Dr Nada Signal<br>Health and Rehabilitation Research Institute<br>AUT University<br>Private Bag 92006<br>Auckland 1142<br>Ph 09 921 9999<br>Nada.signal@aut.ac.nz |
| Project Supervisor | Professor Denise Taylor<br>Health and Rehabilitation Research Institute<br>AUT University<br>Private Bag 92006<br>Auckland 1142<br>Ph 09 921 9680<br>Denise.taylor@aut.ac.nz |


If you want to talk to someone who is not 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

For Maori health support please contact :

Anita Kumar

Te Puna Hauora

Phone: 09 489 3049

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.<br>Name of GP: _____<br>Medical Centre: _____ | | |
| I understand that following the Physiotherapy session, the Physiotherapist will send my GP a summary of their assessment and a copy of my exercise programme. | | |
| 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: |

**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 P. Study C participant screening sheet

## Participant Screening Sheet

Study criteria are noted in red

| | | |
|---|---|---|
| Name | | |
| Address | | |
| Telephone Number | | |
| Email / Alternate Contact | | |
| How did you hear about the study? | | |
| Have you read an information sheet about the study? | | |
| Sex | | |
| DOB/Age | | Over 18 years? |
| Date of Stroke | | More than 6 months ago? |
| How many strokes? | | Single stroke? |
| Type of Stroke (if known) | | Exclude cerebellar stroke |
| Hemiplegia | | |
| Lower limb affected? | | Must have ankle weakness |
| Mobility | | Consider ability to transfer |
| Uses Aid? | | What? |
| Uses AFO? | | |
| Communication, cognitive, perceptual impairments? | | If impairments will limit ability to perform tests or intervention then exclude participant |
| If you were eligible to participate would you be able to attend 3 sessions at AUT's North Shore Campus? | | |
| Are you comfortable with the idea of Transcranial Magnetic Stimulation? Do you have any questions about the research? | | |
| TMS Screening Questionnaire<br><br>*"The magnetic stimulator feels like a big tap on your head, and can cause the muscles in the leg and sometimes in the face to twitch. It is not recommended for people who have certain conditions so we need to complete a checklist first".* | | See TMS questionaire |

| | |
|---|---|
| **Screening for Electrical Stimulation:**<br><br>Metal in your affected leg?<br><br>Bleeding conditions?<br><br>Electronic devices?<br><br>Damaged skin?<br><br>Infection in leg?<br><br>Recent lower limb trauma, nerve injury, malignancy? | (Consider proximity of metal to stimulating electrodes) |
| **Medical Conditions:**<br><br>Cardiac Conditions<br><br>Hypertension (160+/105+)<br><br>Uncontrolled metabolic disorders<br><br>Active acute infection<br><br>Musculoskeletal pain in lower limbs<br><br>Spine or back problems<br><br>History of significant lower limb trauma<br><br>Major depression/ psychiatric illness<br><br>Other neurological pathologies or muscle wasting disease<br><br>Other | (Consider if any condition will limit participants ability to tolerate testing session, increase their risk, or affect the reliability of the measures). |
| Involved in another study? | |
| Medications (name and dose) (Check against threshold lowering list)<br><br>Screened for seizure threshold lowering effect Y/N | |

**Screening Outcome**

| | |
|---|---|
| Possibility | Needs Face to Face<br>Other:<br>Booked for 1st session:<br>Wear shorts, no caffeine/exercise |
| Excluded due to TMS? | Reason (s): |
| Excluded/ Included in Study | Reason (s): |
| Referred to | |

Note if the participant is excluded, then the previous two pages of health information must be shredded.

## Participant Safety Checklist for using Single Pulse Transcranial Magnetic Stimulation

Participant Name:_____

Participant D.O.B.:_____

| | YES/NO | Note about management of precautions |
|---|---|---|
| 1. Have you ever been diagnosed with epilepsy or suffered from epileptic seizures? | | |
| 3. Do you wear a pacemaker? | | |
| 4. Do you have any metal or other devices in any part of your body including your head (except tooth fillings)? Do you have any stents? | | |
| 5. Have you ever had a skull fracture? | | |
| 6. Do you have any known skull defects? | | |
| 7. Do you suffer from recurring headaches or migraines? | | |
| 8. Have you suffered a head injury or concussion within the last 6 months? | | |
| 9. Do you suffer from anxiety associated with medical procedures, needles etc | | |
| 10. Are you currently, or could you be, pregnant? | | |
| 11. Medications checked for seizure threshold lowering effect? | | |

Checklist completed by: _____

Signature: _____

Date: _____