Neuromodulation in the treatment of upper limb spasticity

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I. Official declaration

I, Sarah Massey confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that it has been indicated in the work.

II. Abstract

In this thesis I investigated neurophysiological changes following transcutaneous electrical nerve stimulation (TENS) at 100 Hz, and TENS and transcutaneous spinal cord stimulation (tSCS) applied with high-frequency (10 kHz) trains (HF-TENS and HF-tSCS, respectively). I also assessed literature studying neuromodulation for spasticity in SCI and developed a mobile application (app) which aimed to improve spasticity self-management through education of triggers.

Paired-pulses of cervical tSCS caused post-activation depression in posterior-root reflexes (PRRs) in wrist flexors and extensors at interstimulus intervals of < 2 s; showing a similar pattern of modulation observed in previous studies with H-reflex activity (8 healthy, able-bodied participants). Another study compared TENS, HF-TENS and HF-tSCS to sham stimulation. Changes in PRRs and motor-evoked potentials (MEPs) in the wrist flexor and extensor were assessed. HF-tSCS was most efficient at modulating corticospinal excitability immediately after intervention, causing a decrease in flexor MEPs lasting 30 minutes ($p = 0.015$), as well as a trend towards an increase in extensor MEPs. Late spinal inhibition of wrist flexors occurred following 60 minutes of HF-tSCS ($p = 0.018$).

An app was designed to support users in identifying factors which trigger their spasticity by logging and rating events (Penn spasm frequency scale). The design of the app was assessed using questionnaires sent to clinicians and people with spasticity. Results showed that all responders felt that the design of the app could have potential in benefitting symptoms of spasticity.

Bringing together neurophysiological and clinical measures of spasticity, a systematic review and meta-analysis of 27 studies assessed the effects of neuromodulation on spasticity in SCI. This revealed a lack of randomised control trials (RCTs). In 3 RCTs and 17 studies without a control group, there was a reduction in spasticity immediately following electrical stimulation according to clinical measures. Four studies included the H-reflex as an outcome measure, with 3/4 reporting no change, or varied results between participants.

III. Impact statement

Spinal cord injury (SCI) is the damage of the spinal cord from trauma or disease. This damage can lead to neurological dysfunction, including the development of spasticity. This research aimed to develop a neuromodulation protocol to manage upper limb spasticity in people with SCIs. Second to this, we aimed to understand changes to the underlying neurophysiological mechanisms caused by neuromodulation. Research studies completed and outlined within this thesis show the efficacy of kilohertz transcutaneous spinal cord stimulation (tSCS) in reducing corticospinal excitability in the wrist flexors; a desirable outcome which correlates with a reduction in spasticity. These results justify future clinical trials within this target population (upper limb spasticity arising from a SCI). There may also be a wider impact on those with lower limb spasticity, as well as those with spasticity arising from varying aetiologies.

The predominant method of spasticity management is the use of pharmaceuticals, such as botulinum toxin injections, which can cause a range of side-effects. Neuromodulation offers a complementary management technique, which may reduce a patient's reliability on these injections, potentially reducing the number of hospital appointments the patient must attend in their lifetime, and allowing rehabilitation to continue at home, following discharge.

Research presented in this thesis assessed the effects of kilohertz tSCS on the excitability of the central nervous system (CNS) in healthy, able-bodied participants. Kilohertz electrical stimulation has potential in modulating neurophysiological mechanisms which are lost or altered following SCI, known to change with spasticity, without paraesthesia, which is not tolerated by some people. This research marks a step towards creating these neuromodulation protocols to be used in clinical settings and by patients at home.

Much of the research already carried out within the field of neuromodulation for spasticity management focuses on those with lower limb spasticity. Few investigate the changes to the neurophysiological mechanisms following neuromodulation in the upper limb, due to the low reliability of the upper limb H-reflex as an investigatory tool, without a muscle contraction. Within the SCI population, people may not be able to sustain these muscle contractions throughout an investigation. Research carried out here presents an alternative method which may be translatable to this population, and may give further insight into

the neurophysiological changes which occur following neuromodulation in future experiments.

A systematic review and meta-analysis of studies which investigate the effects of non-invasive neuromodulation on spasticity in people with SCI was carried out. This resulted in several recommendations for the publication of future studies in this field. Specifically, these were to remain consistent in the use of clinical outcome measures for spasticity, to consider the addition of neurophysiological outcome measures, to include a control group in research if possible and to publish negative or non-statistically significant results.

Results from studies carried out in this thesis have been disseminated at 4 conferences, several cross-disciplinary research seminars and work has been submitted to one research journal. This ensures both formal peer-review of research, as well as many stimulating discussions across several research institutes.

IV. Acknowledgements

First and foremost, I'd like to thank my supervisors Lynsey and Anne as well as Yazi. I couldn't have hoped for a more supportive and inspiring team to guide me through my PhD. You've all made this the most enjoyable experience I could've hoped for.

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V. Contents

VI. List of figures

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VIII. List of abbreviations

AB – Able-bodied

AS – Ashworth scale

CI – Confidence interval

CNS – Central nervous system

CPG – Central pattern generator

CSS – Composite spasticity score

DF – Dorsiflexors

DI – Disynaptic inhibition

DTR – Deep tendon reflex

ECRL – Extensor carpi radialis longus

EMG - Electromyography

ES – Electrical stimulation

FCR – Flexor carpi radialis

FDS – Functional disability score

FES – Functional electrical stimulation

FIM – Functional independence measure

GL - Gluteals

H-reflex – Hoffman reflex

H-wave – Hoffman wave

HA - Hamstrings

HD – Homosynaptic depression

HF-tSCS – High-frequency transcutaneous spinal cord stimulation

HF-TENS – High-frequency transcutaneous electrical nerve stimulation

HTI- Highest tolerated intensity

ICC – Intraclass correlation coefficient

ITB – Intrathecal baclofen

ISI – Interstimulus interval

M-wave – Motor wave

MAS – Modified Ashworth scale

MEP – Motor evoked potential

MT – Motor threshold

MVC – Maximum voluntary contraction

NICE – National institute for health and care excellence

NMES – Neuromuscular electrical stimulation

PAD – Post-activation depression

PrAD – Primary afferent depolarisation

PF - Plantar flexors

PI – Presynaptic inhibition

PT- Pendulum test

PNS – Peripheral nervous system

PRR – Posterior-root reflex

PSFS – Penn spasm frequency scale

PT – Pendulum scale

QU - Quadriceps

RCT – Randomised control trial

RI – Reciprocal inhibition

rTMS – Repetitive transcranial magnetic stimulation

R_{2n} – Relaxation index

SCATS – Spinal cord assessment tool for spastic reflexes

SCI – Spinal cord injury

SCS – Spinal cord stimulation

SD – Standard deviation

SFS – Spasm frequency score

SOL – Soleus

ST – Sensory threshold

TA – Tibialis anterior

TENS – Transcutaneous electrical nerve stimulation

TMS – Transcranial magnetic stimulation

TS – Triceps surae

tSCS – Transcutaneous spinal cord stimulation

TUGT – Timed up-and-go test

UMN – Upper motor neuron

FCR – Flexor carpi radialis

VAS – Visual analogue scale

6MWT – 6-minute walking test

I. Context and research questions

1 A note to the reader

Due to the impact of the COVID-19 pandemic, a planned clinical study in 2020 could not go ahead. Details of this study are outlined in chapter V of this thesis, as well as in Appendix II. In cases where this work has impacted or changed the narrative of other studies presented in this thesis, it is indicated in the introduction of each section.

2 Background and thesis outline

Spinal cord injury (SCI) is the damage of the spinal cord from trauma or disease (World Health Organisation 2013). This damage can lead to neurological disorders such as spasticity. As well as people with SCI, spasticity also affects those with multiple sclerosis, stroke and traumatic brain injury. Globally, spasticity affects around 12 million people (American Association of Neurological Surgeons 2019), with a prevalence of around 65 % at discharge following traumatic SCI (Holtz et al. 2017) and 78 % for chronic SCI (Maynard, Karunas, and Waring 1990).

The classically cited definition of spasticity from Lance (1980) states that spasticity is 'a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neurone syndrome'. These symptoms include the presence of a constant muscle contraction, clonus or muscle spasms from external triggers. For people with spasticity, these symptoms affect the ability to carry out activities of daily living and consequently quality of life (Adams and Hicks 2005; Sadeghi and Sawatzky 2014).

Due to the plastic nature of our central nervous system (CNS), the pathophysiology of spasticity is ever-changing (J. B. Nielsen, Crone, and Hultborn 2007; Sheean 2002; Carlo Trompetto et al. 2014). These changes occur both immediately and gradually after a CNS lesion and contribute to mechanical changes of the muscle, tendon and surrounding soft tissues of the affected limb, which can cause concurrent pain in the limb (Gracies 2005).

Neuromodulation of the CNS via electrical stimulation (ES) delivered transcutaneously and invasively has been used for several decades to manage spasticity symptoms in several pathologies. A wide range of ES protocols across research groups, clinics and rehabilitation centres are used with little consensus of which protocols should be used in which circumstance.

This thesis aims to improve existing spasticity management using different transcutaneous ES protocols. This chapter will first review: the underlying neurological mechanisms which affect spasticity; the pathophysiology; neurophysiological and clinical measurement of spasticity, highlighting the lack of understanding in populations with upper limb spasticity; current management protocols; neuromodulation as an alternative to these protocols; and the research questions which this thesis aims to answer.

3 The nervous system: anatomy and circuitry

When there is a lesion to the CNS, such as in a SCI, reorganisation can occur at a cortical (Rossini et al. 2003) and spinal level (Shimada and Tokioka 1995; Topka et al. 1991). This reorganisation affects the neural mechanisms which modulate afferent and efferent pathways and keep our CNS and periphery in a state of homoeostasis. This section will first introduce these mechanisms; following this, the changes to these mechanisms will be introduced in consequent sections.

3.1 *Reciprocal Ia inhibition and disynaptic inhibition*

Reciprocal inhibition (RI) is the balance of activity of agonist-antagonistic pairs during movement. Activity is mediated by interneurons via Ia afferents projecting onto motoneurons during an action, say extending the elbow, such that during a triceps contraction, the activity of the biceps reduces and vice versa (Sherrington 1893; Lundberg 1970) (see Figure 1). Constant feedback to the synapse, suppresses bicep activity while the triceps are active, allowing for a balance between the agonist-antagonistic pair to create a smooth movement when extending the elbow.

There is also evidence of corticospinal influences which facilitate RI from projections onto Ia interneurons during tasks with both upper and lower limbs (J. Nielsen et al. 1993). Transcranial magnetic stimulation (TMS) of the primary motor cortex has been shown to reflect this balance of activity between agonistic-antagonistic pairs during movement (J. Nielsen et al. 1993).

Although the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) are considered to be an antagonistic pair, they are also a synergistic pair, as they are used together to perform wrist abduction movements. True RI does not occur between the two as the balance of activity between these muscles is not mediated by pure Ia interneurons, but by interneurons which modulate disynaptic inhibition (DI) (Aymard et al. 1995).

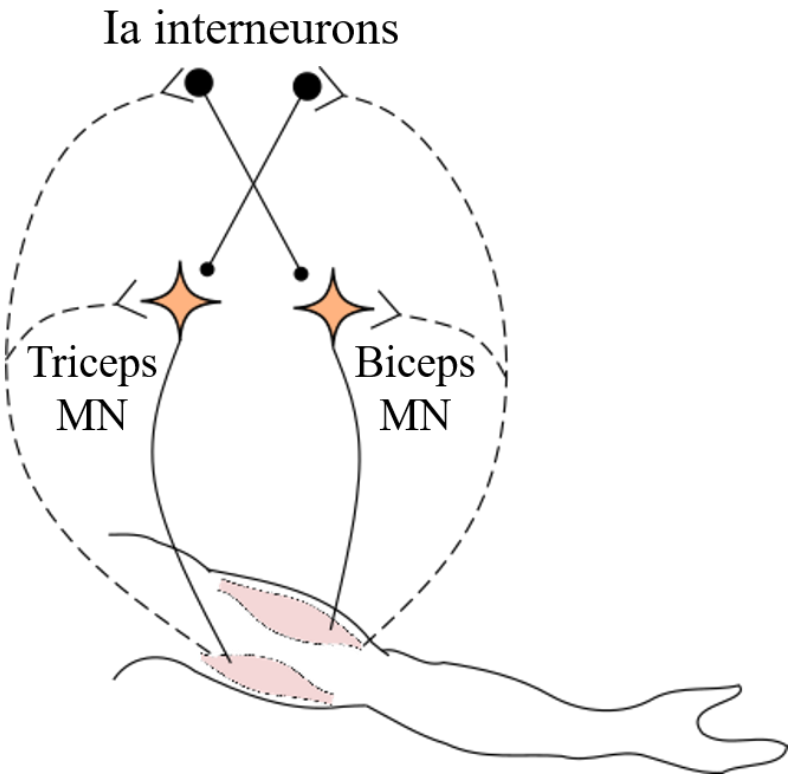

Figure 1:Pathway of reciprocal inhibition between motoneurons (MN) of the triceps and biceps. Y-shaped bars represent excitatory synapses, small filled circles show inhibitory synapses, large filled circles show inhibitory interneurons and dashed lines show the Ia afferent pathway. Replicated from (Pierrot-Deseilligy and Burke 2012).

3.2 *Recurrent inhibition*

Renshaw cells are the interneurons which, when excited, cause a hyperpolarisation of the motoneurons; thus causing inhibition of any activity following for approximately 35 ms (Burke 2016). This process of inhibition via Renshaw cells is known as recurrent inhibition. (J. B. Nielsen, Crone, and Hultborn 2007). In this process, following a motor discharge, a subsequent discharge will need to overcome a higher threshold level. There are also corticospinal influences on this mechanism.

Recurrent inhibition can be measured using the Hoffman reflex (H-reflex). A study in humans showed that stimulating the motor cortex using TMS influenced the H-reflex response, showing decreased recurrent inhibition (Mazzocchio, Rossi, and Rothwell 1994). This corticospinal influence on recurrent inhibition is illustrated in Figure 2 for the flexor carpi radialis (FCR).

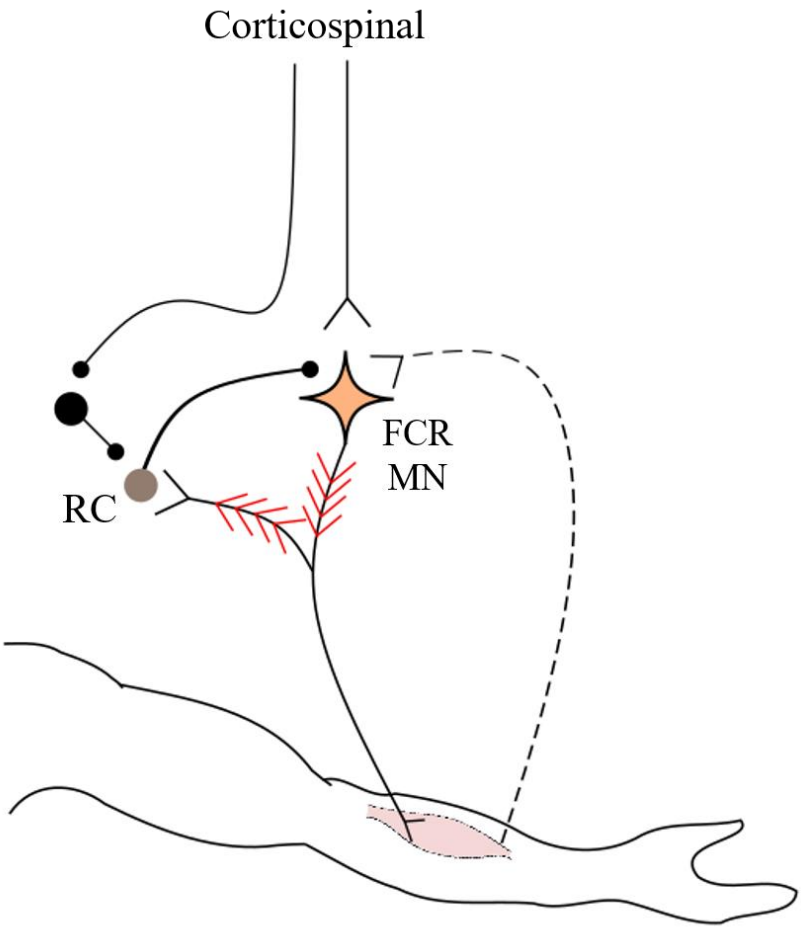

Figure 2: Pathway of homonymous recurrent inhibition occurring for the FCR. Y-shaped bars represent excitatory synapses, small filled circles show inhibitory synapses, large filled circles show inhibitory interneurons and dashed lines show the Ia afferent pathway. Recurring red arrows represent conditioning reflex discharges. Abbreviations: FCR = flexor carpi radialis, MN = motoneuron, RC = Renshaw cell. Replicated from (Pierrot-Deseilligy and Burke 2012).

3.3 *Presynaptic inhibition*

Presynaptic inhibition (PI) occurs when a motor response is inhibited by previous input, causing depolarisation of Ia terminals. This then causes the modulation of neurotransmitter release via $GABA_A$ receptors, causing inhibition for approximately 200-300 ms (Rudomin and Schmidt 1999). The interneurons which project onto these Ia terminals are known as primary afferent depolarisation (PrAD) interneurons. The excitation of primary PrAD interneurons from Ia and Ib afferent fibres acts to reduce neurotransmitter release from last-order PrAD interneurons mediating $GABA_A$ receptors and therefore cause PI (Rudomin and Schmidt 1999). Corticospinal and cutaneous input, however, have an inhibitory effect on the interneurons mediating PI, therefore acting to reduce it and having an overall excitatory effect (Rudomin and Schmidt 1999).

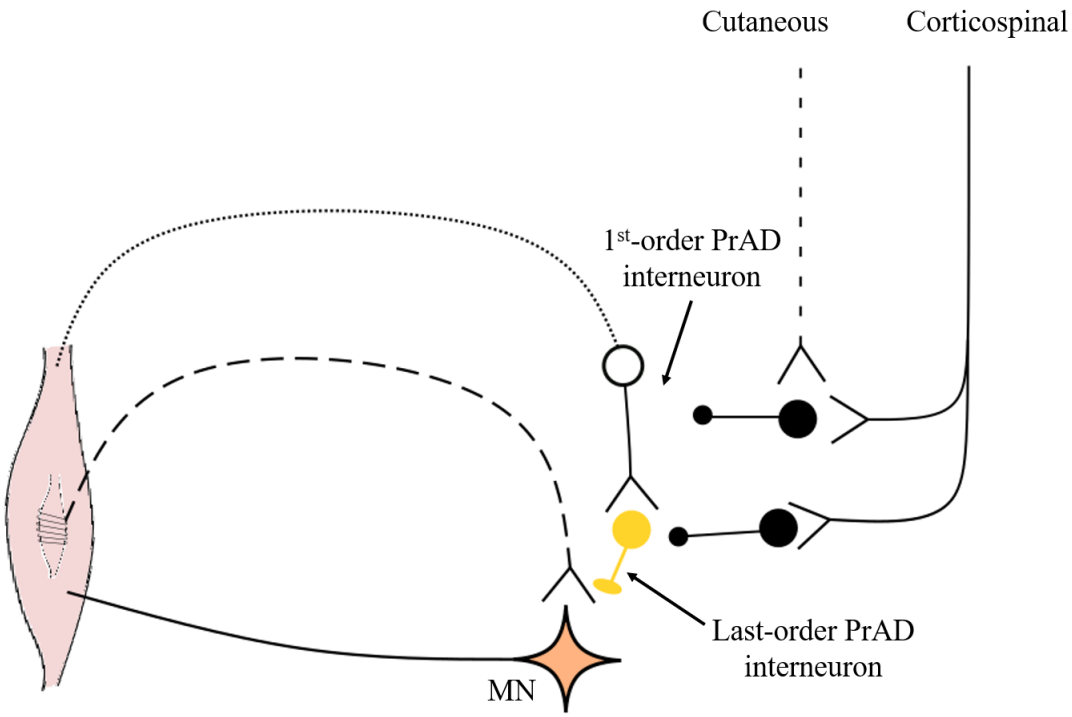

Figure 3: Pathway of presynaptic inhibition. Y-shaped bars represent excitatory synapses, small filled circles show inhibitory synapses, large filled circles show inhibitory interneurons, large open circles represent primary PrAD interneurons, large yellow circles represent last-order PrAD interneurons mediating $GABA_A$ receptors, dotted lines show the Ib afferent pathway and dashed lines show the Ia afferent pathway. Abbreviations: MN = motoneuron, PrAD = primary afferent depression, RC = Renshaw cell. Replicated from (Pierrot-Deseilligy and Burke 2012).

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4 Neurophysiological measurement

The neurophysiological measurement of spasticity is important because it deepens our understanding of the mechanisms behind any clinically measured improvements seen in spasticity following intervention. Understanding which mechanisms are linked with improvements in spasticity then allow for the design of experiments to assess potential spasticity management protocols in pre-clinical trials with healthy, able-bodied participants. This section will introduce established neurophysiological measurements which are known to change with spasticity, method of measurement and their limitations.

4.1 *The H-reflex*

The H-reflex can occur following either mechanical stimulation, or ES of a mixed nerve, and the response is measured via electromyography (EMG). Here, both the efferent and afferent pathways are stimulated, causing a muscle response from the efferents (M-wave), and a delayed response from Ia afferent fibres projecting onto their motoneurons once they have synapsed at the spinal cord (H-wave) (Hoffmann 1918; Buchthal and Schmalbruch 1970). It is a monosynaptic reflex, which crosses only one synapse and bypasses the muscle spindle; we can therefore assess the level of excitation occurring at a spinal level by measuring the change in amplitude of the H-wave (Burke 2016). Figure 4 shows the pathway of the H-reflex as it synapses at the spinal cord.

Since it is a monosynaptic reflex which is exhibited upon activation of Ia afferents, it can be used to investigate RI, DI, PI, recurrent inhibition, homosynaptic depression (HD – to be covered in subsequent sections) and spinal excitability within its reflex arc in any given muscle, where isolated stimulation is feasible (Burke 2016). The most common use of the H-reflex is in the soleus muscle, where the tibial nerve is easily electrically stimulated at the popliteal fossa, producing a reliable response (Burke 2016; Knikou 2008). Although its elicitation is possible in the upper limb, research groups have used varying stimulation sites, arm positions, stimulation parameters and the use of a muscle contraction, known as facilitation, to generate a more reliable response (see Table 1).

Using facilitation may cause crosstalk, which will lead to interference from other EMG activity (Hutton, Roy, and Edgerton 1988; Miller, Newall, and Jackson 1995), especially in the upper limb where it is more difficult to intentionally activate a single muscle at a time due to the innervation of several muscles through the same nerve and their close proximity. The between-day reliability of the flexor carpi radialis (FCR) H-reflex has

been studied using different arm positions, stimulation parameters and some use of facilitation (see Table 1), the results suggest that the FCR H-reflex may be reliable without facilitation in healthy, able-bodied adults. However, evidence for people with spasticity is not so clear. It may also be more difficult for populations with spasticity, especially those with upper limb impairments, to sustain a constant muscle contraction for a prolonged period.

When recording the H-reflex, many intrinsic and extrinsic factors also affect the amplitude of the response. For example, participating in mental tasks such as imagining a movement in the muscle where an H-reflex is being elicited has been shown to increase the response amplitude (Hale, Raglin, and Koceja 2003; Bonnet et al. 1997; Brunia 1971). Local changes in temperature also affect H-reflex amplitude; by warming the muscle of interest (36-37 °C), both the amplitude of the H-wave and the motor response (M-wave) are reduced (Dewhurst et al. 2005; Racinais and Cresswell 2013).

Alerting stimuli can also affect H-reflex amplitude; it is therefore recommended that recordings should be taken in a quiet room with little mental and motor effort (Pierrot-Deseilligy and Burke, 2012). As well as these factors, which should be taken into account when designing an experiment with the H-reflex as an outcome measure, the act of taking part in a study, which requires the participant to remain still, also affects the H-reflex (Crone et al. 1999). This study showed that amplitudes of both M- and H-waves decrease throughout an experimental period lasting 95-150 minutes, where participants were told to remain still throughout (Crone et al. 1999). The effect of these factors on the H-reflex show the difficulties in the practicalities of taking the measurement alone, and the importance of adding a control condition when using the H-reflex as an outcome measure.

Table 1: Variations in stimulation site, posture, use of facilitation and measured reliability of the FCR H-reflex in studies carried out with healthy, able-bodied participants. Abbreviations: FCR = flexor carpi radialis, ICC = intraclass correlation coefficient.

Author	Stim Site	Pulse width (ms)	Arm position	Facilitation	Reported reliability
Christie (2005) (N = 39)	Motor point of the FCR	1	Supine with arm 45 ˚ relative to the trunk	In 5% of participants	Good (ICC = 0.89-0.97)
Jaberzadeh (2004) (N = 15)	Cubital fossa	0.8	Seated, elbow flexion 135˚	Yes	Good (ICC = 0.66-0.89)
Stowe (2008) (N = 8)	1/3 from the lateral epicondyle to the biceps tendon	1	Seated, elbow flexion 90˚, shoulder flexion 15˚	Yes, 0.5 lb weight	Fair to good (ICC = 0.57-0.99)

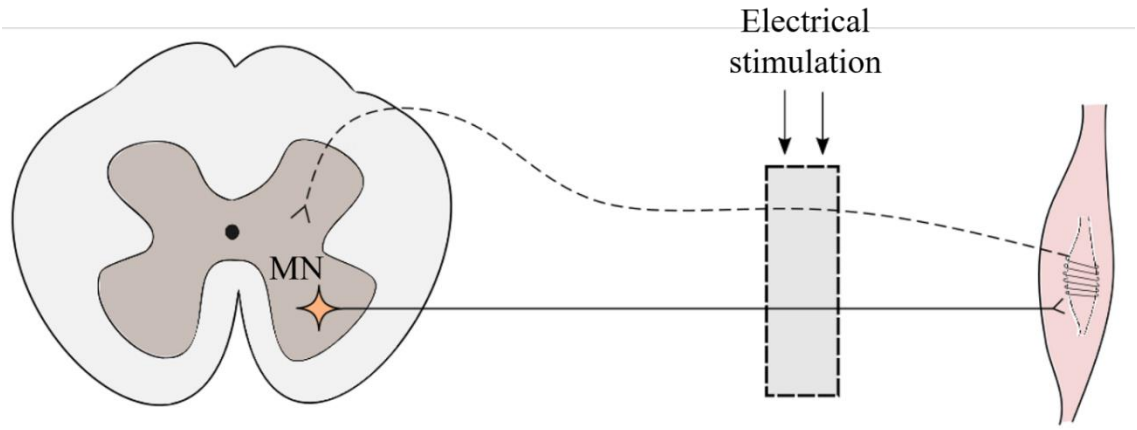

Figure 4: Pathway of the H-reflex. Y-shaped bars represent excitatory synapses, dashed lines show the Ia afferent pathway. Abbreviations: MN = motoneuron.

4.2 *Posterior-root reflexes*

The posterior-root reflex (PRR) is the response measured in a muscle when its posterior root is stimulated at the spinal cord. This can be through stimulation using single pulses, delivered via invasive spinal cord stimulation (SCS), or transcutaneous SCS (tSCS). Similar to the H-reflex, elicitation of a PRR involves stimulation of Ia afferent fibres; meaning that PI, DI and HD can be investigated using this response. However, several

posterior roots may be stimulated at once, leading to heteronymous influences on the PRR response (Minassian, Freundl, and Hofstoetter 2020).

4.3 *Homosynaptic depression (post-activation depression)*

HD occurs when paired-pulses of ES are delivered with an interstimulus interval of 1-2 s (Crone and Nielsen 1989). The first pulse of ES (control) depresses the response which occurs due to the second pulse of ES (conditioned) through activation of Ia fibres (Figure 5). This occurs due to the repetitive activation of the synapse, which reduces neurotransmitter release at the Ia fibre motoneuron synapse (Crone and Nielsen 1989).

This is also true for other Ia afferent input such as vibratory stimuli, passive and voluntary movements (Hultborn et al., 1996).

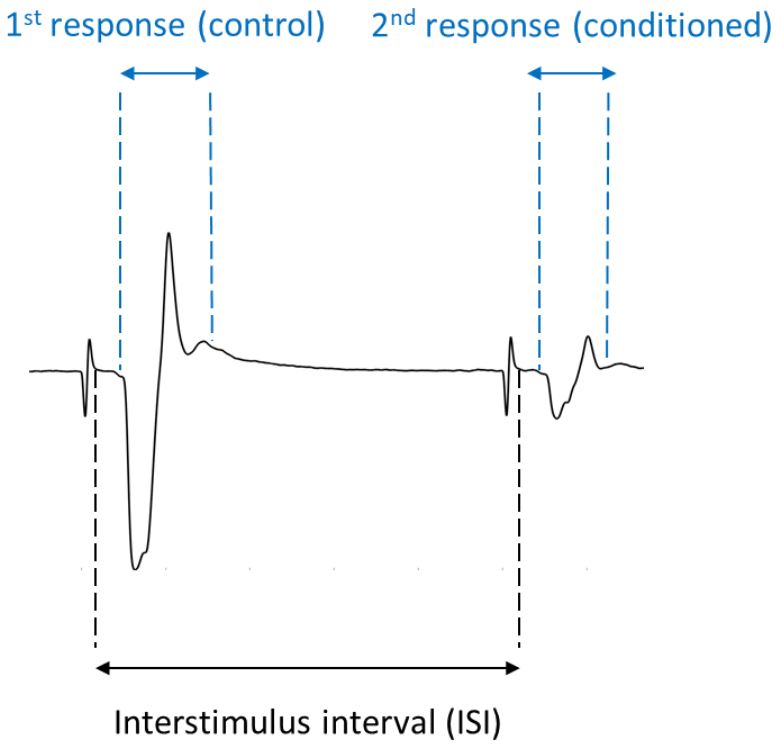

Figure 5: EMG trace showing homosynaptic depression. The second response is depressed by the first with an interstimulus interval of <10 s. Abbreviations: EMG = electromyography, ISI = interstimulus interval.

4.4 *Motor-evoked potentials*

Motor-evoked potentials (MEPs) are responses measured in a target muscle via EMG, when the primary motor cortex is stimulated using TMS. They give information about the excitability within the corticospinal pathway. Since spasticity may be of cerebral or spinal

origin – or a combination of both – using MEPs to assess this pathway is a valuable addition to the use of H-reflexes and PRRs (Garcia et al. 2019).

5 Spasticity: pathophysiology and mechanisms

5.1 *Components of spasticity*

Symptoms of spasticity arise due to a collection of influences, depending on the pathology. Collectively, these are known as spinal spasticity or cerebral spasticity. The former affects the processing of descending and ascending control at the spinal cord, whereas the latter affects descending control, originating at the brain, and also the processing of signals at the brainstem (Lapeyre, Kuks, and Meijler 2010). These factors ultimately lead to the exaggeration of reflexes, leading to increased involuntary muscle contracture.

There is also a non-neural component to spasticity which affects mechanical changes to the soft tissue. This includes shortening of muscles and fibrosis, which can contribute to hypertonia and is not related to neural reflexes (Carlo Trompetto et al. 2014; Gracies 2005; Bonikowski, Braendvik, and Brostr 2017). However, these neural and non-neural components of spasticity can be interconnected. This non-neural shortening of the muscle can increase propagation due to stretch to muscle spindles more readily, therefore affecting the neural component (Gracies 2005). This thesis will focus on the neural components of spasticity.

5.2 *Triggers of spasticity*

Uncontrolled contractions occurring as a result of spasticity can be triggered as an aberrant response to muscle stretch (Kheder and Nair 2012). Understandably, muscle stretch can occur in response to a range of movements, including during activities of daily living; and so, these triggered spasms can interfere with everyday life. Other intrinsic and extrinsic factors can also contribute to the onset of a spastic contraction, such as changes in temperature, bladder activity and tight clothing (Cheung et al. 2015; Kheder and Nair 2012; Phadke et al. 2013; Nair and Marsden 2014).

As well as external factors and movement, intrinsic factors such as stress and anxiety also play a role in the severity of spasticity (Malhotra et al. 2008), and has been identified as an intrinsic trigger in the SCI population (Phadke et al. 2013; Cheung et al. 2015; Nair and Marsden 2014). These emotional states are coupled with activity of the sympathetic nervous system (Kreibig 2010).

5.3 *Changes to neurophysiological mechanisms with CNS lesions*

When there is a lesion to the CNS, reorganisation can occur at a cortical (Rossini et al. 2003) and spinal level (Shimada and Tokioka 1995; Topka et al. 1991). This reorganisation can change in the days, weeks and months following the lesion, where reflexes may be more exaggerated. In the case of a SCI, this is known as spinal shock syndrome. This reorganisation affects the neural mechanisms which modulate afferent and efferent pathways and keep our CNS and periphery in a state of homoeostasis.

5.3.1 Reciprocal Ia inhibition and disynaptic inhibition

A loss of control over RI in those with spasticity may present itself in the form of co-contractions of muscles (Nair and Marsden 2014; Crone et al. 1994; Ashby and Wiens 1989; Ada et al. 1998). In people with asymmetric SCI, it has been shown that RI is reduced on the more affected side, compared to the side with good recovery, in the lower limbs (Okuma, Mizuno, and Lee 2002). At a spinal level, a reduction in RI may occur due to the loss of control over descending pathway which project onto interneurons, following CNS lesions (Ada et al. 1998), causing reduced mediation between agonistic pairs. However there is also evidence to show that the reduced mediation may be due to a loss of control over descending pathways which project onto these interneurons (J. Nielsen et al. 1993).

In those with incomplete SCI, it has been found that the extent of impairment of RI correlated with the amount of co-contractions occurring during dynamic contractions (Boorman et al. 1996). It has also been shown that in this population, those who have recovered some active function, have increased RI compared to those with an intact CNS (Boorman et al. 1991).

5.3.2 Recurrent inhibition

Following a SCI, recurrent inhibition has been found to increase, implying that there is decreased inhibition acting on Renshaw cells from interneurons, which may occur due to a decrease in supraspinal projections onto inhibitory interneurons (Katz and Pierrot-deseilligny 1982). Shefner et al., (1992) found that recurrent inhibition correlates with severity of spasticity, which decreases towards the level in participants with an intact CNS as spasticity improves.

5.3.3 Presynaptic inhibition

PI has been shown to decrease after a SCI; this is thought to be due to lessened supra-spinal control over first-order PrAD interneurons, leading to the excitation of last-order PrAD interneurons (Faist et al. 1994). This is thought to contribute towards the hyperexcitability of the stretch reflex in those with spasticity from an SCI (Angel and Hofmann 1963; Faist et al. 1994; Aymard et al. 2000), as motoneurons are more excitable under lessened PI (Volker Dietz and Sinkjaer 2007; Katz 1999).

5.3.4 Homosynaptic depression (post-activation depression)

For people with spasticity, depression of the conditioned response was found to be reduced, compared with people who are able-bodied (Grey, Klinge, Crone, Biering-sørensen, Jakob Lorentzen, et al. 2008). In people who have had a stroke, the extent of HD is correlated with the severity of spasticity, in both upper and lower limbs, according to the Ashworth scale (Lamy et al. 2009).

5.3.5 Motor-evoked potentials

Following stroke, spasticity can occur due to the cerebral lesion, meaning that it originates due to a lack of descending inhibition (Pierrot-Deseilligy and Burke, 2012:503). In this case, MEP amplitude is significantly lower, and with a longer latency, compared to those without spasticity (Cakar et al. 2016). In SCI, spasticity may have a different origin, depending on the nature of the lesion and whether it is complete or incomplete. In those with residual descending motor pathways, where MEPs can be measured, it has been found that the MEP amplitude correlates with the severity of spasticity (Sangari et al. 2019). The authors of this study also found that MEPs were not present in individuals who did not have spasticity, even for participants with a diagnosis of incomplete SCI.

5.4 *The H-reflex and posterior-root reflexes as measures of spasticity*

Increased excitability at a spinal level is known to be a contributing factor which causes spasticity, meaning that the H-reflex is an ideal way to monitor changes in hyperexcitability due to interventions intended to treat spasticity (Faist et al. 1994; Aymard et al. 2000; Angel and Hofmann 1963). However, the reliability of this measure in patients with pathologies such as SCI or stroke is limited (Goulet et al., 1996; Stowe *et al*., 2013). Goulet et al. (1996) reported difficulties in obtaining H-reflexes in 14 people who have had a SCI, not being able to elicit the reflex in 5 people and failing to show any significant results in the effect of transcutaneous electrical nerve stimulation (TENS) at

100 Hz on the H-reflex amplitude, but did show significant results in the reduction of Modified Ashworth Scale scores.

There has been some recent success in the use of PRRs as a measure of spinal excitability in people with SCI (Murray and Knikou 2019; Hofstoetter et al. 2019). Although there has not been investigation into their reliability in people with spasticity as there has been with the H-reflex, there is evidence showing the similarities in the characteristics of the H-reflex and PRRs (Minassian et al. 2007; Hofstoetter et al. 2019). Therefore, PRRs may be an acceptable alternative to the H-reflex as a measure of spasticity. This will be further investigated in upcoming chapters of this thesis.

Some groups have attempted to use the H-reflex as a biofeedback mechanism to reduce spasticity. Here, people with spasticity were trained to reduce their H-reflex through visual feedback of their H-reflex represented as a bar (Thompson and Wolpaw 2014; Segal and Wolf 1994). In some cases, a reward was given by turning the feedback bar green when the H-reflex is significantly reduced below a threshold amplitude; or negative feedback is given by turning a bar red, when it is not (Thompson and Wolpaw 2014). This has been shown to reduce the H-reflex for several months, reducing spasticity and improving walking in people who have had a stroke (Thompson and Wolpaw 2014) and SCI (Thompson, Pomerantz, and Wolpaw 2013).

5.5 *Differences between pathologies*

Mechanisms underlying spasticity are thought to differ between those who have had a stroke and those living with a SCI (Elbasiouny et al. 2010). Following a SCI, reflexes become isolated from inhibitory mechanisms (Lapeyre, Kuks, and Meijler 2010; Pierrot-Deseilligy and Burke 2012; Biering-Sørensen, Nielsen, and Klinge 2006). This causes an increased excitability, allowing muscle contractions to occur more easily (Pierrot-Deseilligy and Burke, 2012), resulting in the increased tone and exaggerated reflexes, including flexor reflex, which are characteristic of spinal spasticity. In those who have had a stroke, however, it is thought that the stiffening of muscle following the stroke is due to changes in the soft tissues, rather than changes in reflex control (Volker Dietz and Sinkjaer 2007; Ada et al. 1998)

Another factor influencing spinal spasticity is the abnormal processing of sensory feedback to the CNS (Sheean 2002). This lack of feedback leads to the loss of descending control over interneuronal circuits at the spinal level (Alonso and Mancall 1991). In the

intact spinal cord, these interneuronal circuits are those which control the inhibitory mechanisms to mediate over-activity. This lessened ability to mediate these circuits is also hindered by the dampening of inhibitory circuits, as well as an increased excitability (Trompetto et al., 2014).

One factor which influences the onset of co-contractions in those with spasticity is the loss of control over RI and DI (Nair and Marsden 2014; Crone et al. 1994; Ashby and Wiens 1989; Ada et al. 1998). In those with multiple sclerosis, this mechanism has been found to be abolished in most cases among 39 participants (Crone et al. 1994). Although RI is altered in people with SCI (to be discussed in section 4.42), it has not been found to be abolished in this way.

There is a decrease in PI of Ia terminals in SCI, but no change in the same mechanism in stroke (Faist et al. 1994). It has also been shown that there is a significant reduction in the HD of Ia terminals on the hemiplegic side of stroke patients with spasticity, and to a lesser extent on their unaffected side (Aymard et al. 2000). This reinforces the need to understand patients as individuals, also understanding how these characteristics change with each individual CNS lesion.

6 Clinical assessment of spasticity

Measures of spasticity taken by the patient's clinical team can be used to provide the patient with a descriptive measure of different components of spasticity, such as the muscle stiffness, frequency of spasms and severity of spasms.

6.1 *Clinical measures*

Primary outcome measures of spasticity include the Ashworth scale (AS) and modified Ashworth scale (MAS). The MAS includes an additional 1+ measure of spasticity, to include a measure of resistance to passive movement (SCIRE Professional Spinal Cord Injury Research Evidence 2010) (see Table 2). The assessments are subject to inter-rater variation, with consistencies of 86.7 % using the MAS for the elbow joint (Bohannon and Smith 1987). It has been shown that increasing MAS scores correlate with increasing EMG activity (Skold et al. 1998).

Table 2: Key descriptions of scores and their descriptive outcomes for the Modified Ashworth Scale (Enderby, John and Petheram, 2006).

0 (0)	**No increase in muscle tone**
1 (1)	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+ (2)	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement
2 (3)	More marked increase in muscle tone through most of the range of movement, but affected part(s) easily moved
3 (4)	Considerable increase in muscle tone passive, movement difficult
4 (5)	Affected part(s) rigid in flexion or extension

The pendulum test (PT) is another measure of spastic tone in the lower limb, first defined by Wartenberg (Wartenberg 1951). It is carried out by letting the leg swing at the knee against the resistance of its muscles. The assessor then measures the following components of knee angle: S1 = initial knee angle; S2 = peak angle of first swing; and S3 = final position of the leg. These components are used to calculate the Relaxation Index

(R_{2n}) using equation 1. Scores of $R_{2n} > 1$ indicate that an individual does not have spasticity, whereas a score of $R_{2n} = 0$ would be considered as an extreme case of spasticity (Bajd and Vodovnik 1984).

$$Relaxation\ Index = S2 - \frac{S1}{1.6(S3 - S1)} \quad \textit{Eq. 1}$$

The spinal cord assessment tool for spastic reflexes (SCATS) is used to assess issues which are specific to SCI. This involves rating each of the following features on a scale from 0 (no spasm) to 3 (severe spasm): clonus, flexor spasms, extensor spasms (Eng and Chan 2013). For two physiotherapists with ≥ 5 years of experience, there has been found to be an almost perfect inter-rater reliability when tested with 47 people with SCI resulting in either paraplegia or tetraplegia (Akpinar et al. 2017). Although this has only been assessed in one study, it has also been found to have moderate to high correlation with the MAS (SCIRE Professional Spinal Cord Injury Research Evidence 2010), which is more commonly used.

6.2 *Self-evaluated clinical measures*

Scoring spasticity with either the MAS or SCATS can only be done by a suitably qualified person, such as a physiotherapist. Since the degree of spasticity varies throughout the day (Phadke et al. 2013), an assessment of the long-term, day-to-day effects of an intervention requires a shorter, self-assessment method. The Penn Spasm Frequency Scale (PSFS) is a self-assessment of spasticity, which is generally carried out with a clinician present; spasticity is rated based on the frequency and severity of their spasms (SCIRE Professional Spinal Cord Injury Research Evidence 2005). Table 3 shows the scores for each component of this scale and their relevant observations. For novice raters, who have been trained in using the PSFS, this measure has been found to have good inter- and intra-rater reliability when used in SCI (Patricia B. Mills et al. 2018). However, this measure does not report on aggravating factors and noxious stimuli which may influence the patients' spasticity, making it difficult for clinicians to determine whether other factors may be affecting their patient's spasms (SCIRE Professional Spinal Cord Injury Research Evidence 2005).

Table 3: Penn spasm frequency scale scores for frequency and severity components.

Spasm Frequency score	Observation	Spasm severity score	
1	Mild spasms induced	**1**	Mild
2	Infrequent full spasms occurring less than once per hour	**2**	Moderate
3	Spasms occurring more than once per hour	**3**	Severe
4	Spasms occurring more than 10 times per hour		

Clinicians also use treatment goals, which are developed between the patient and their therapy team (Royal National Orthopaedic Hospital Trust 2019). Using this within a management protocol gives more focus on the aim of the therapy used, and may increase patient engagement (Richardson 2002).

7 Current spasticity management

There are a wide range of management methods available to people with spasticity. These vary from physiotherapy and exercise, to pharmacological intervention, surgery and the use of neuromodulation. Several of the following management techniques can be combined to create a management programme for each individual (Royal National Orthopaedic Hospital Trust 2019; University College London Hospitals and Trust 2018). This will vary from person to person and will ultimately be a collective decision made by the individual and their clinical care team. A summary of the commonly used management techniques for spasticity and the route generally taken to implement each of them is shown in Figure 6. Subsequent sub-sections will describe the techniques listed here

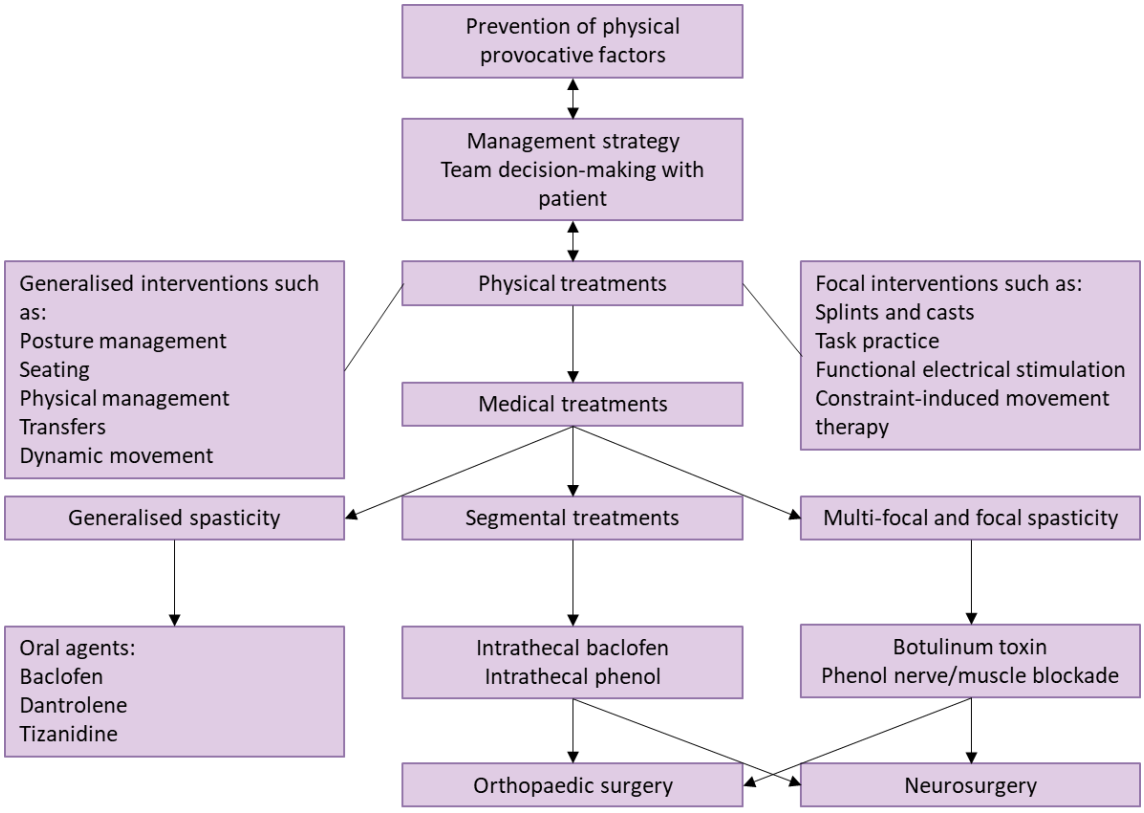

Figure 6: Clinically suggested spasticity management protocols and the routes to take. Adapted from (Adams & Hicks, 2005; National Institute for Health and Care Excellence, 2019; A. B. Ward, 2002).

7.1 *Management of exasperating triggers*

In many treatment centres, the first means of spasticity management, before physiotherapy and medication, are to identify the factors affecting the individual through patient education (Royal National Orthopaedic Hospital Trust 2019; University College

London Hospitals and Trust 2018; A. B. Ward 2002). This is an important first line of treatment since some management protocols can give benefits in clinical measures without influencing triggers of spasticity.

Bhimani, McAlpine and Henly (2012) asked people with spasticity (arising from various causes) about their perspectives of their spasticity throughout a year. This study found that most participants actively avoided triggers of spasticity, which they discovered through trial and error. The authors suggest that spasticity changes throughout one's life and awareness of the triggers of spasticity is important for lifetime management.

Interventions for spasticity management may not address these factors. Therefore, a reduction in spasticity measured by the MAS or PT scores may not reduce the amount of spasms occurring due to the triggers which affect an individual. This line of spasticity management will therefore be addressed in future chapters of this thesis.

7.2 *Physiotherapy, splints and orthoses*

Active function is important for independence in activities of daily living, as well as in social contexts. Improvement of active function can be achieved with range of motion exercises and stretching, which are reported to be beneficial and possibly cause mechanical changes in the muscle, tendon and soft tissue (Adams and Hicks 2005; Elbasiouny et al. 2010). Maintaining optimal biomechanics will allow for ease of movement at the joint, increase dexterity and ease pain.

The use of splints and orthoses will also help to keep the affected limb in a position which does not elicit spasm; this is important as it can increase functionality as well as reduce pain due to spasm (Adams and Hicks 2005; Thomas and Joseph 2020). However, there is little evidence for the benefits in active function when splinting patients, with some studies showing no statistically significant changes in MAS scores or H-reflex amplitude in patients who have had a stroke (Khan et al. 2019; Basaran et al. 2012).

Physiotherapy is one of the first-line of treatments recommended by the UCL hospitals trust, as well as the NICE guidelines for under-19s with spasticity and those following stroke (National Institue for Health and Care Excellence 2019b; 2016; University College London Hospitals and Trust 2018). A physiotherapy session gives the patient stretch, exercise, good positioning and engages the patient with their own management protocol (Boyd and Ada 2008). This active form of therapy promotes proper movement of the limb and increases flexibility of soft tissues (University College London Hospitals and Trust

2018). However there is low evidence of its efficacy (Khan et al. 2019; Barbosa et al. 2021). Since it is standard practice to offer physiotherapy to those with spasticity, there may be a lack of research carried out within the healthcare institutes where this therapy is often carried out (Barbosa et al. 2021).

7.3 *Pharmacological intervention*

Oral medications can act either at the level of the spinal cord, affecting neurotransmitter release or by supressing activity (baclofen, diazepam, tizanidine), or on the muscle directly (dantrolene sodium) (Lapeyre, Kuks, and Meijler 2010). However all of these medications can cause side-effects; balancing the potency of these side-effects with the effectiveness of the drug for spasticity management is done through dose management with the patient's clinical team (Royal College of Physicians 2018).

Botulinum toxin is a muscle relaxant which is commonly used in the management of spasticity (University College London Hospitals and Trust 2018). Benefits of this type of treatment are that relaxation occurs shortly after injection, and that these injections only need to be 'topped-up' every 2-3 months (Santamato and Panza 2017). This form of pharmacological intervention is useful for those with focal spasticity, as it targets the specific area where it is injected, by blocking the release of the neurotransmitter acetylcholine, which in turn blocks or weakens muscle contraction (Kheder and Nair 2012).

Some patients may prefer other forms of spasticity management due to the adverse effects which may occur with the use of botulinum toxin (see Table 4). Evidence suggests that it does not improve active function, or activities of daily living, particularly for those with upper limb spasticity (Levy et al. 2018; Deltombe, Lejeune, and Gustin 2018; Adams and Hicks 2005).

To lessen the dose taken through oral medications, implantation of an intrathecal baclofen (ITB) pump can be an alternative. This involves surgical implantation of a drug delivery device, which enables the drug to be excreted close to the spinal cord, where it regulates muscle tone through smaller doses of baclofen (Kheder and Nair 2012; Zahavi et al. 2004).

There is good evidence for the effectiveness of ITB for spasticity, especially in the lower limb (Lapeyre, Kuks, and Meijler 2010; Rekand 2010). However, as with botulinum

toxin, there is no correlation between ITB with active function of the upper limb (Balsara, Jea, and Raskin 2018).

Table 4: Pharmacological intervention for spasticity. Adapted from Lapeyre, Kuks and Meijler, 2010.

Name	Route	Dose range (daily)	Action	Side-effects
Botulinum toxin	Injection	-	Prevention of the release of acetylcholine from the pre-synaptic nerve terminal, blocking muscle contraction	Spread to other parts of the body, muscle weakness. For use in upper limb spasticity: aphasia, dysphasia
Baclofen	Oral	30-100 mg	Decreases activity in motoneurons and interneurons to depress monosynaptic and polysynaptic transmissions	Sedation, excessive weakness, vertigo, depression, hallucinations
Diazepam	Oral	2-30 mg	Supresses GABA mediated activity in the spinal reflex pathways	Sedation, hypotonia
Dantrolene sodium	Oral	25-400 mg	Decreases calcium release, causing uncoupling of excitation and contraction	Diarrhoea, nausea, vomiting, weakness, liver damage
Gabapentin	Oral	300-2400 mg	Unknown	Drowsiness, fainting, ataxia
Intrathecal baclofen	Intrathecal catheter	50-100 μg		
Tizanidine	Oral	2-36 mg	Supresses polysynaptic transmission at spinal and supra-spinal levels	Hypotension, light-headedness, liver damage

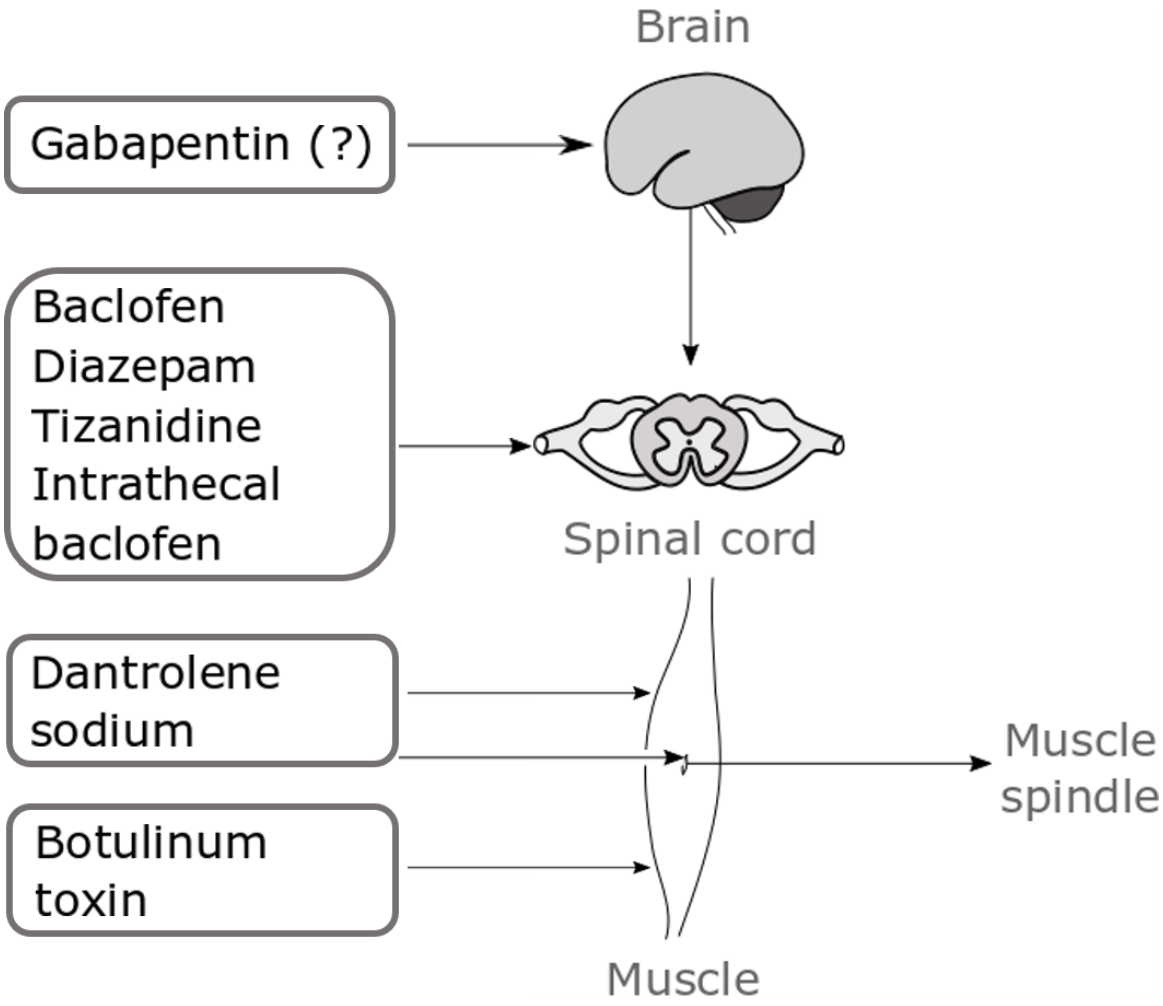

Figure 7: Illustration of the levels of the mechanisms of actions of varying anti-spastic drugs. Adapted from Lapeyre et al. (2010).

7.4 *Surgery*

In extreme circumstances, once other management techniques have been exhausted, surgical intervention such as rhizotomy and orthopaedic surgery may be required to alleviate symptoms of spasticity (Rekand 2010). The former is an irreversible process, which involves destroying nerve roots which innervate spastic muscles causing particular issue; the latter involves either lengthening of the tendon, or release of soft tissues in the problem areas (Rekand 2010). Surgery may not be a desirable management technique for spasticity due to its associated risks and some of its procedures being irreversible.

8 Neuromodulation

Neuromodulation is a method which regulates or alters neurological signals or excitability within peripheral nervous system (PNS) or the CNS. The mechanisms of action behind this are not fully understood, however, it may work by interrupting excitatory signals, increasing inhibitory mechanisms and by increasing afferent feedback both at cortical and spinal levels.

Non-invasive forms of neuromodulation include: transcutaneous electrical nerve stimulation (TENS) and neuromuscular electrical nerve stimulation (NMES); transcutaneous spinal cord stimulation (tSCS); transcranial direct current stimulation (TDCS); repetitive transcranial magnetic stimulation (rTMS); focal vibration, applied to a muscle or tendon; and whole-body vibration. In this thesis, I will discuss the use of forms of neuromodulation with ES only.

TENS is the application of ES to a nerve or muscle, using electrodes placed on the skin, for therapeutic effects. NMES may refer to ES delivered to a nerve or muscle, either through invasive, or non-invasive methods. In this thesis, the term TENS will be used to refer to ES delivered over a nerve or muscle. The term NMES will not be used for the remainder of this thesis.

Research groups who investigate the use of ES for spasticity management use a variety of stimulation parameters such as frequency, pulse width, dose, stimulation intensity and site of activation. This makes it difficult to pin-point the effects of changing one parameter versus another. The following sub-sections will first introduce the main types of ES investigated throughout this thesis, followed by a discussion of the extent of the variation of stimulation parameters, and the possibility of varying effects on spasticity management through their use.

The following sections will first introduce the clinical recommendations for the use of neuromodulation, before discussing the research into the use of these therapies for spasticity. I will then more specifically discuss the variations in stimulation parameters between these forms of neuromodulation, and their possible influence on spasticity management.

8.1 *Clinical use of neuromodulation*

There is a limited use of ES in the clinical management of spasticity given by the National Institute for Health and Care Excellence (NICE) guidelines, the University College London Hospitals Trust and the Royal National Orthopaedic Hospital. Published reports recommending the use of TENS and FES for the rehabilitation of people with SCI (National Institue for Health and Care Excellence 2019a) and those who have had a stroke (National Institue for Health and Care Excellence 2016) focuses on its use for increasing strength and function, not for spasticity management.

FES cycling is noted to be commonplace for SCI rehabilitation in some clinical settings, however may be considered as novel technology in other settings (National Institue for Health and Care Excellence 2019a; Royal National Orthopaedic Hospital Trust 2021). The NICE guidelines currently do not recommend the routine use of ES for the rehabilitation of people who have had stroke (National Institue for Health and Care Excellence 2016); however, in some more severe cases, it has been recommended for use for improving strength during functional tasks.

SCS, whether delivered invasively or through the skin, is not included in the NICE guidelines as a method of spasticity management. Its primary recommendation of use is for pain management (National Institute for Health and Care Excellence 2019; 2009; 2020).

The following sections will briefly introduce research into the use of various forms of neuromodulation, including kHz SCS, and their possible benefits or translations to people with spasticity. The effects of varying stimulation parameters of non-invasive ES for spasticity will then be discussed in sections 7.5 – 7.9.

8.2 *Research studying the efficacy of transcutaneous electrical nerve stimulation for spasticity*

Repeated sessions of TENS therapy has been shown to decrease ankle spasticity, muscle tone (Laddha et al. 2016) and increase walking speed (Ng and Hui-Chan 2009) compared to a placebo group in populations with impairment due to stroke affecting the lower limb. For people with SCI, this has given improvements in spasm frequency scores, Ashworth scale (Aydin et al. 2005), composite spasticity scores and muscle tone (Oo 2014). TENS is typically used for people with upper limb spasticity following stroke (Mills and Dossa 2016; Mahmood et al. 2019).

TENS has also been shown to improve motor control, and reduce spasticity and pain in those with CNS lesions (Schuhfried et al. 2012). However, when used for upper limb spasticity specifically, it may be more effective to involve a functional task (FES), compared with use of TENS alone (de Kroon et al. 2005). There is also evidence showing that the use of TENS enhances upper limb spasticity management with the use of botulinum toxin, compared to the use of botulinum toxin alone in people after stroke (Hesse et al. 1998).

8.3 *Research studying the efficacy of functional electrical stimulation for spasticity*

FES may be used for gait training or cycling for lower limb rehabilitation, or in reaching and grasping tasks for the upper limb. Potential benefits of FES include increase muscle strength, muscle bulk and cardiovascular health in people with SCI (for a recent systematic review, see Luo et al., 2020), improved function and strength in young adults with cerebral palsy (Moll et al. 2017) and upper limb activity in those who have had a stroke (Howlett et al. 2015). However, there are mixed reports for its efficacy at reducing spasticity.

For people with spasticity arising from an SCI, 10 participants with incomplete SCI were shown to have an overall reduction in spasticity after 3 months of FES cycling, which were maintained 3 months following the end of the trial (Yaşar et al. 2015). A single session of FES cycling has also been shown to decrease R_{2n} scores in people with complete SCI, in a crossover study, compared to passive cycling only (Krause et al. 2008). However, 8 participants with complete SCI showed either increased or unchanged MAS scores following 8 weeks of FES cycling (Gant et al. 2018). It is unclear what may cause this variation of results between studies, however an increase in muscle bulk may lead to an increase in the intensity or strength of spastic contractions.

8.4 *Research studying the efficacy of spinal cord stimulation for spasticity: drawing on findings from pain management*

Due to the plastic nature of our CNS, after a lesion, a huge reorganisation occurs (Rossini et al. 2003; Shimada and Tokioka 1995). In some cases, these changes lead to a breakdown of the spinal inhibitory mechanisms already discussed; in others, they lead to a lack of sensory feedback to the brain. In both cases, there is a loss of control over descending pathways and an inability to regulate signals at interneurons (Pierrot-

Deseilligy and Burke 2012). As well as leading to spasticity, these alterations in the CNS can lead the brain to feel pain without a physical cause, known as neuropathic pain (Baron, Binder, and Wasner 2010; Campbell and Meyer 2006).

Ascending noxious (pain) sensory inputs are modulated in the spinal cord by afferent pathways, controlling the amount of pain perceived (Kandel, Schwartz and Jessell, 2000). Gate theory states that both nociceptive and nonnociceptive fibres are involved in the perception of pain, and that the nonnociceptive fibres (Aβ fibres, which transmit other sensory information) mediate this perceived pain (Melzack and Wall 1965).

With common mechanisms affecting both spasticity and neuropathic pain, there is some overlap and interferences in treatment and management protocols. In a study with people with SCI, ITB, which is used to decrease spasticity, was shown to decrease neuropathic pain (Kumru et al. 2018). Similarly, Gabapentin is commonly used to treat both neuropathic pain and spasticity (Finnerup 2017). However, amitriptyline, which is used to treat neuropathic pain, is said to increase spasticity (Finnerup 2017).

Cortical changes due to neuropathic pain can lead to changes in the dominant frequencies of the brain signal associated with specific activities (Vuckovic et al. 2014). This information was used to develop a biofeedback training programme for patients to relieve their own pain (Hassan et al. 2015). This type of intervention is similar to the operant conditioning of spasticity using biofeedback using stretch reflexes (Segal and Wolf 1994) and H-reflexes (Hoseini, Koceja, and Riley 2011) to re-regulate brain activity.

Implanted SCS for pain management is mostly used in populations with chronic pain of neuropathic origin (Malinowski et al. 2020; Baron, Binder, and Wasner 2010). This is generally delivered at frequencies of 40 – 100 Hz (Malinowski et al. 2020). An RCT consisting of 1000 participants compared conventional medical treatment of neuropathic pain and treatment using SCS at 49 Hz over 12 months (Kumar et al. 2007). The team found that SCS was more effective at improving pain relief compared to conventional medical treatment alone, with some participants using both conventional treatment and SCS combined.

Table 5: Varying parameters for kHz stimulation in current literature. Abbreviations: SCS = spinal cord stimulation, tSCS = transcutaneous spinal cord stimulation.

Author	Stimulation type	Frequency (Hz)	Pulse Width (ms)	Stimulation site	Intended outcome	Session
Al-Kaisy (2014)	Epidural SCS	10 k	Not reported	T4-5 to C2-7	Relieve neuropathic pain	6 months
Gad (2018)	tSCS	30 with 10 k carrier frequency	1	C3-4 to C6-7	Voluntary control	2, 1-2-hour sessions/ week for 4 weeks
Kapural (2016)	Epidural SCS	10 k	0.03	T9/10 to T8-T11	Relieve chronic pain	24 months
Van Buyten (2013)	Epidural SCS	Up to 10 k	Not reported	T8-T12	Relieve back pain	6 months

Previous sections show that there are currently no clinical recommendations for implanted SCS for spasticity arising from any aetiology. Although there is some evidence for the benefits of epidural SCS for spasticity (Dimitrijevic et al. 1986; Pinter, Gerstenbrand, and Dimitrijevic 2000), in recent years, much of the research uses non-invasive SCS for its use for spasticity management.

Studies investigating a single session of tSCS have shown a potential to decrease spasticity, in several outcome measures, in people with both complete and incomplete SCI (Hofstoetter et al. 2014; 2020; Vargas Luna et al. 2016). Hofstoetter et al. (2020) continued their study in one participant with an incomplete SCI for 6 weeks. This participant had continued decreases in MAS scores every week and overall improved EMG-evaluated outcomes from baseline to the end of the 6 weeks of stimulation, however had varied results across the stimulation period for their PT scores. Most outcome measures also remained improved from the baseline measure at the 2-week follow-up, however most had worsened from the end of the stimulation period.

SCS may have potential for spasticity management in those with SCI, however there are currently no randomised-control trials (RCTs) within this field investigating its efficacy (Nagel et al. 2017).

Using SCS, both invasively and non-invasively, is known to alter the sympathetic nervous system, which is thought to occur due to the modulation of neurotransmitters within the dorsal horn of the spinal cord (Parekh 2017). For spasticity management, SCS is currently

the only intervention which interacts with neural circuits which regulate interneurons (Nagel et al. 2017).

Transcutaneous SCS can be used as an investigatory tool. To use tSCS in this way, we can use a series of tests to confirm which neural structures are being stimulated. For instance, by eliciting paraesthesia in targeted dermatomes, we can associate this sensation with activation of particular nerve roots. This is useful for spasticity management using SCS, as we can select the pathways involving the Ia afferent that are affected in people who present with spasticity (Barolat, Myklebust, and Wenninger 1988; Pinter, Gerstenbrand, and Dimitrijevic 2000; Hofstoetter et al. 2020).

8.5 *Site of activation*

Application of ES to different sites on the body may have different therapeutic or functional effects. Much like pharmaceutical intervention, it may be possible to target spasticity originating at a cortical level or at a spinal level, depending on where stimulation is being delivered, and its stimulation intensity. A summary of the proposed mechanisms resulting in spasticity relief from different sites of activation is shown in Table 6.

Table 6: Proposed mechanisms of action for spasticity management using varying sites of electrical stimulation.

Site of activation	Mechanisms of action
Brain	• Modulation of oscillatory brain rhythms (Cortes et al. 2017); • Overall increase of neural activity in the primary motor cortex (Kumru et al. 2010) ; • Increased excitability of descending corticospinal activity with interaction with local motoneurons (I. F. Nielsen, Sinkjaer, and Jakobsen 1996)
Muscle/nerve	• Stimulation of afferent fibres (via mixed fibres) increases feedback to the motor pathways which decreases excitability of the reflex system (Mima et al. 2004); • Reciprocal inhibition activated when stimulating an agonist-antagonist pair through activation of interneurons via afferent stimulation (Perez, Floeter, and Field-Fote 2004; Schuhfried et al. 2012); • Decrease of cortical excitability (Tinazzi et al. 2005)
Spinal cord	• Stimulation of Ia afferents activate Ia inhibitory interneurons, increasing presynaptic inhibition (Hofstoetter et al., 2014) and homosynaptic depression (Knikou and Murray 2019); • Reciprocal inhibition activated through spinal circuits which mediate this mechanism (Minassian et al., 2007); • Decrease of neurotransmitter release within the dorsal horn, affecting motoneurons (frequency dependent) (U. S. Hofstoetter et al. 2020; Parekh 2017)

Although TENS can be delivered with the intention of targeting certain muscle groups, there may be differences in the activation threshold of different muscle groups (Pitcher, Ridding, and Miles 2003). This adds more complexity to the difficult task of selecting appropriate stimulation parameters for spasticity management. The stimulation of mixed nerve fibres using TENS and its varying effects with stimulation intensity and frequency will be discussed in upcoming sections.

With few groups using tSCS for neuromodulation in spasticity, the orientation of stimulating electrodes is another differing factor across research groups using tSCS. For spasticity management, the cathode has been placed on the back, with its anode placed

on the abdomen (Hofstoetter et al. 2014; 2020). For function, the cathode can be placed over the targeted level, with the anode being placed over the anterior superior iliac spine (for hand function) (Freyvert et al. 2018); or with the anode over the iliac crests (for locomotion) (Gerasimenko et al. 2018); or electrodes placed paraspinally, either side of the spinal cord (Murray and Knikou 2019). Whereas for investigatory studies, where spinal reflexes were measured, electrodes have been placed with a pair of cathodes over the target vertebrae, and a pair of anodes over the lower abdomen (Hofstoetter et al. 2019), either side of the spinal cord (Einhorn et al. 2013), or over the target vertebrae and the navel (Estes, Iddings, and Field-Fote 2017).

Delivering stimulation using different orientations affects the charges delivered to both afferent and efferent pathways, due to the orientation of the spinal cord within the body. The orientations discussed may intend to increase function, where stimulation of efferents is more crucial compared to spasticity management, where modulation afferent fibres is necessary. There may also be an effect on the neural activation threshold, and therefore the stimulation intensity required (Zander et al. 2020; Minassian, Freundl, and Hofstoetter 2020). This in turn affects uptake of tSCS in populations with intact sensory pathways, or those with hypersensitivity.

8.6 *Stimulation intensity*

For the use of TENS, there is variation between research groups on how to select the stimulation intensity. Some studies use a set percentage above motor threshold (MT) (Koyama et al. 2016; A M Stowe et al. 2013), while others use a set percentage above sensory threshold (ST), but below MT (Tinazzi et al. 2005; Mima et al. 2004; Dewald, Given, and Rymer 1996; Aydin et al. 2005; Sivaramakrishnan, Solomon, and Manikandan 2018).

For research groups who opted to use intensities above MT, the choice of stimulation intensity, either producing a visible muscle contraction (A M Stowe et al. 2013), or ‘just above’ MT (Koyama et al. 2016), was not justified. Both studies were investigating the effects of TENS on people after stroke (A M Stowe et al. 2013; Koyama et al. 2016). For those who use stimulation intensities below MT, the selection of intensity varied, summarised in Table 7 and Table 8. For many of these studies, the method of determining the stimulation intensity was through asking the participant to inform the researcher of

their sensations. The desired outcome here was for paraesthesia to be present, but without any pain being inflicted.

It may be argued that lower intensities are needed for the management of spasticity, since sensory fibres have a lower stimulation threshold in comparison to motor fibres (Kantor, Alon, and Ho 1994; A. R. Ward and Robertson 1998). Modulation of the mechanisms which are altered in those with spasticity, discussed in section 1, stimulation of sensory pathways is required.

By using higher intensities and stimulating the motor pathway, muscle bulk and strength may be increased (for a recent systematic review, see Ricardo et al., 2019); which could worsen spastic contractions when they occur. However, using FES may train the motor pathway in order to increase motor control (Luo et al. 2020). This is not yet clear in current literature, since some studies report reduction of spasticity through FES over 12 weeks (Sabut et al. 2011), and others report improvement in some participants, but not others over a 6-month period (Skold et al. 2002).

For the use of tSCS for spasticity management, there seems to be a consensus among researchers to use a stimulation intensity which is below motor threshold, but evokes the feeling of paraesthesia in the participant (Hofstoetter et al. 2014; 2020; Serrano-Munoz et al. 2019).

Many studies shown in Table 7 and Table 8 describe a desired sensation felt by their participant when setting the stimulation intensity. To achieve a similar sensation, there should be a correlation between the stimulation intensity and pulse widths used (Geddes and Bourland 1985). However, this is not the case and there does not seem to be a logical pattern between studies, or any justification. This makes it particularly difficult to understand which stimulation parameters may be optimal for spasticity management and can also hinder future research as justifications are often not given in research papers.

8.7 *Stimulation dose*

Many studies investigate the effects of a single session of neuromodulation, with delivery times varying from 10 to 60 minutes for TENS (Dewald, Given, and Rymer 1996; Chung and Cheng 2010), and 30 to 40 minutes for tSCS (Hofstoetter et al. 2014; 2020; Serrano-Munoz et al. 2019). Studies with repeated sessions of TENS showed a more beneficial effect on clinical measures of spasticity (A M Stowe et al. 2013; Aydin et al. 2005). One study showed cumulative effects across 15 days of 15-minute daily sessions of TENS in

the lower limb (Aydin et al. 2005). In another study (A M Stowe et al. 2013), TENS was delivered in 9 30-minute sessions over 14 days. Here, outcome measures were taken at baseline, on day 14 and 2 weeks after the last session. An improvement was seen between baseline and day 14 measurements; however, this was not retained after 2 weeks. This may indicate that benefits following TENS may be dose-dependent, however retention may not be.

Single-session studies allow researchers to determine the effects of a neuromodulation protocol before using this information to inform a longitudinal study. Where longitudinal studies are used, two important questions should be asked: 1) does the dose of neuromodulation over the sessions have a cumulative effect? 2) is there a retention period? By taking advantage of the opportunity to answer these questions in a longitudinal study, the parameters being discussed can be further analysed for these accumulative and lasting effects.

8.8 *Stimulation frequency*

In the current literature, a large range of frequencies are used for TENS (20-200 Hz) and tSCS (50-100 Hz) for targeting mechanisms believed to affect spasticity in studies with healthy, able-bodied people, or for managing spasticity in clinical studies (see Table 7 and Table 8). Where neurophysiological outcome measures in healthy, able-bodied participants are used, ES using different frequencies have been found to affect some neural pathways more than others. For example, using TENS at 100 Hz has been shown to be more effective at increasing corticospinal excitability, measured by MEPs, in the lower limb compared to 10, 50 and 200 Hz (Mang, Lagerquist, and Collins 2010).

TENS has been shown to improve PI in stroke populations at 200 Hz, compared to 50 and 100 Hz stimulation (Koyama et al. 2016). Stimulation at 50, 100 and 200 Hz were all shown to decrease motoneuron excitability of the soleus (measured via the H-reflex) during and immediately following 30-minutes of TENS (Koyama et al. 2014). However at 50 Hz stimulation only, this decrease was seen for up to 20 minutes after stimulation had been stopped (Koyama et al. 2014). The outcomes found by Mang et al. (2010) and Koyama et al. (2016) show that there may be several mechanisms triggered which lessen spasticity following TENS at 100 Hz; with an increase in corticospinal excitability and a decrease in motoneuron excitability.

The modulatory effects seen following neuromodulation delivered at kHz frequencies has been increasingly investigated in recent years (Serrano-Munoz et al. 2019; Russo and Van Buyten 2015). With much of its therapeutic use seen in neuropathic pain (Russo and Van Buyten 2015; Nagel et al. 2017), there may also be possible benefits in its use to manage spasticity (Nagel et al. 2017). The similarities between neuropathic pain and spasticity, and therefore the translation of the use of kHz ES for spasticity management will be further discussed in chapter III, where kHz frequencies are investigated in healthy, able-bodied adults.

*Table 7: Varying stimulation and study parameters in clinical studies assessing the effects of TENS on upper and lower limb spasticity. Authors labelled with a * represent papers where the population investigated were healthy, able-bodied individuals, the results of which were based on neurophysiological measures whose implications affect research in spasticity management. Abbreviations: MT = motor threshold, ST = stimulation threshold, TA = tibialis anterior.*

Author	Stimulation site	Stimulation intensity	Pulse Width (ms)	Frequency (Hz)	Session
Aydin (2005) (N = 11)	Tibial nerve	50 mA – below MT	0.1	100	15 mins once per day for 15 days
Chung (2009) (N = 18)	Common peroneal nerve	15 mA – 2x average ST in healthy, able-bodied participants	0.25	100	60 mins
Dewald (1996) (N = 9)	Biceps brachii muscle	Below MT and above ST	0.1	20	10-15 mins
Goulet (1996) (N = 14)	Common peroneal nerve	15 mA – 2x average ST in healthy, able-bodied participants	0.25	99	30 mins
***Koyama (2014) (N = 40) 10 per group**	Deep peroneal nerve	Slightly above MT	0.25	50, 100, 200	30 mins
Koyama (2016) (N = 20)	TA muscle belly	Slightly above MT	0.25	50, 100, 200	30 mins TENS (40 s on, 10 s off)
***Mang (2010) (N = 8)**	Common peroneal nerve	The lowest intensity that evoked an M-wave or H-wave in TA	1	10, 50, 100, 200	40 mins (20 s on, 20 s off)
***Mima (2004) (N = 8)**	Thenar eminence muscle group	Below MT, with paraesthesia	0.25	90	30 mins
Sivaram-akrishnan (2017) (N = 10)	Quadriceps	Below MT, just below pain threshold	0.3	100	30 mins
Stowe (2013) (N = 18)	Wrist flexor/extensor muscles	Visible muscle contraction produced	0.3	40	30 mins, 9 sessions in 9 days, 60 muscle contractions per day
***Tinazzi (2005) (N = 16)**	Forearm flexor muscles	2.5 x ST – MT	0.1	150	30 mins (2 s on, 2 s off)

Table 8: Varying stimulation and study parameters for tSCS for spasticity. Abbreviations: MT = motor threshold. Abbreviations: MT = motor threshold.

Author	Stimulation site	Stimulation intensity	Pulse Width (ms)	Frequency (Hz)	Session
Estes (2017) (N = 10)	T11/T12	Producing paraesthesia or highest tolerated intensity	Not reported	50	30 mins
Hofstoetter (2014) (N = 3)	T11/T12	Below MT with, paraesthesia	1	50	30 mins
Hofstoetter (2020) **(N = 12)**	T11/T12	Below MT with, paraesthesia	1	50	30 mins
Vargas Luna (2016) (N = 4)	T11/T12	90 % of MT	1	50	30 mins

8.9 *Summary*

Considering the benefits of TENS and tSCS interventions seen in several studies introduced in this section, there may be potential in its incorporation in the clinical management of spasticity. Since there are no known side-effects to the use of therapeutic ES (disregarding any side-effects in those with hypersensitivity, from surgical implantation or skin reactions to transcutaneous electrodes) (Nagel et al. 2017; Estes, Iddings, and Field-Fote 2017; Fernández-Tenorio et al. 2016), including its use in combination with pharmaceutical intervention (Khan et al. 2019), Figure 8 introduces possible routes that could be followed, with consideration of neuromodulation as a protocol, with boxes in green highlighting where boxes in Figure 6 have been edited.

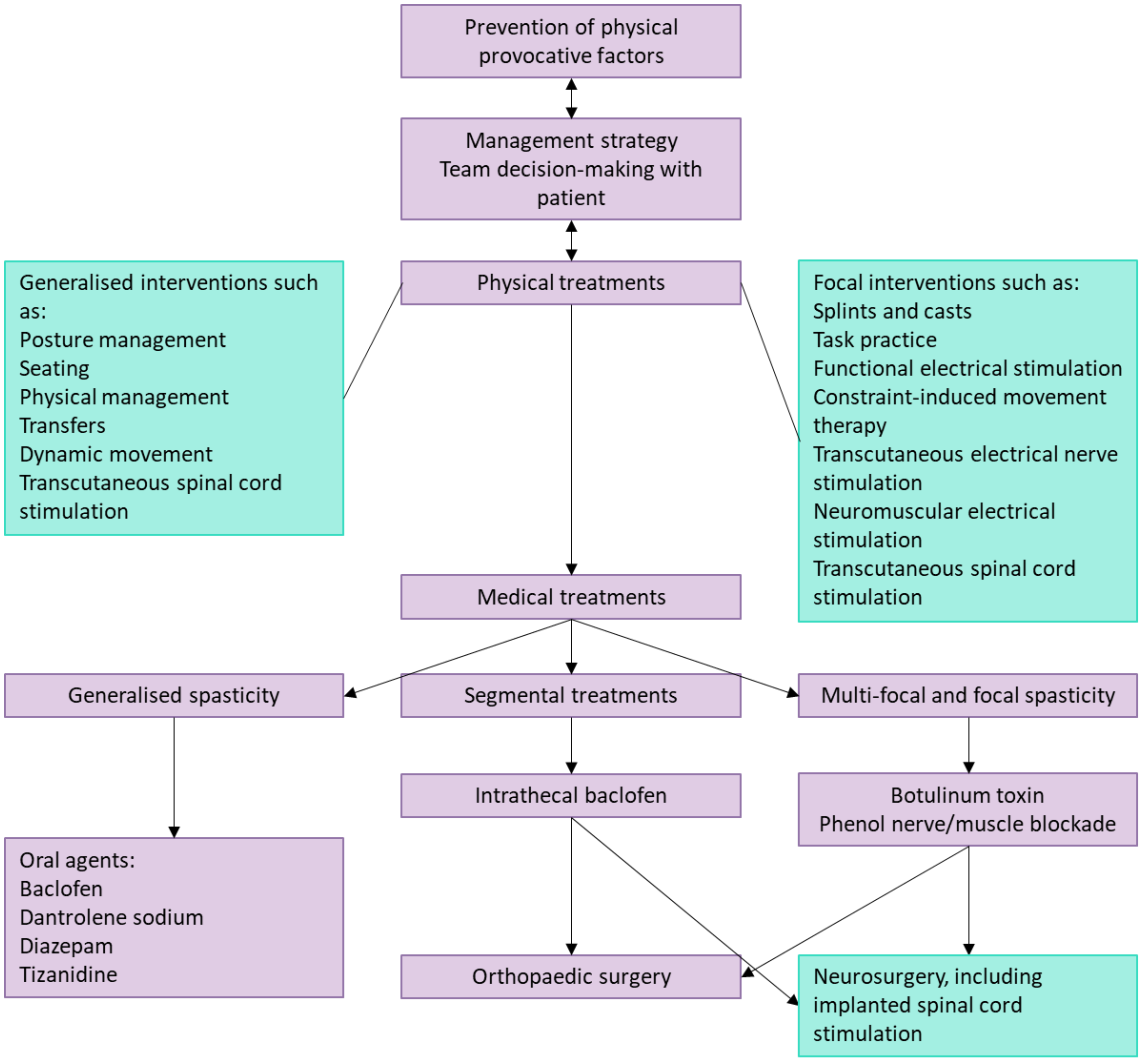

Figure 8: Clinically suggested spasticity management protocols and the routes to take (purple). Addition of neuromodulation as a management protocol (green). Adapted from (National Institue for Health and Care Excellence 2019b; Adams and Hicks 2005; A. B. Ward 2002).

9 Summary and Research questions

From this chapter, we have seen that methods suggested by medical institutions, such as the use of botulinum toxin and oral medications for spasticity management (Stevenson and Farrell 2011; University College London Hospitals and Trust 2018) may not be sufficient for active function of the upper limb (Picelli et al. 2017).

Non-invasive methods which could be self-administered or administered by a caregiver may give an alternative management protocol with fewer side-effects and fewer interactions with medical professionals, for re-administration of pharmaceuticals, for example. This form of self-management may also enable continued rehabilitation at home. Thus far, research into non-invasive methods such as neuromodulation has been under-represented in the upper limb, with some upper limb spasticity studies quoting low participant numbers and a need for larger clinical studies (A M Stowe et al. 2013).

The use of transcutaneous ES gives us a safer and cheaper alternative to those delivered invasively, such as epidural SCS, which interacts more directly with the underlying neuroanatomy, in comparison to tSCS.

These types of interventions, for the self-management of spasticity, must be assessed by the user, as well as the researcher or clinician. By involving the end-user in assessment of these technologies, we can measure how the user perceives their own spasticity and its impact on their life before and after intervention. By doing this, we may increase uptake of these types of intervention, and increase integration into a long-term management protocol.

From this, the research questions which this PhD thesis aims to answer are: 1) are upper limb PRRs an appropriate tool to assess changes in HD following neuromodulation? 2) Which stimulation parameters and site of activation is most effective at modulating cortical and spinal excitability in healthy, able-bodied adults? 3) Can the design of a mobile application (app) be used to manage spasticity symptoms through education of exasperating factors? 4) Which stimulation parameters and site of activation is most effective at improving clinical and neurophysiological outcome measures of spasticity in people with SCI?

10 Research objectives and hypotheses

The following section will outline the aims and hypotheses for consequent experimental chapters.

10.1 *Chapter 2: Preliminary research: an investigation into the use of posterior-root reflexes to elicit homosynaptic depression via cervical roots*

This study aimed to determine whether upper limb PRRs may be used as a neurophysiological tool to assess changes in HD following a neuromodulation intervention. Seventeen interstimulus intervals (ISIs) (30, 50, 100, 250, 500 ms, 1 – 12 s) were delivered via cervical tSCS to determine whether HD would be triggered in PRR responses.

This experiment assessed the extent to which upper limb PRRs reflect previous results in the literature using the H-reflex, and therefore its usefulness as an investigatory tool for future experiments.

10.2 *Chapter 3: The effects of neuromodulation on corticospinal and spinal excitability of the upper limb: a preliminary study in healthy, able-bodied adults*

This study aimed to assess the effects of 30 minutes of 3 forms of non-invasive electrical stimulation (TENS, high-frequency TENS (HF-TENS), delivered over the forearm, and HF-tSCS) on MEPs, PRRs and HD in healthy, able-bodied adults.

This experiment assessed the potential mechanisms of action which occur when non-invasive electrical stimulation is delivered over the forearm, or the spinal cord, and with or without a HF carrier frequency. The neuromodulation protocols were compared to highlight the most efficacious intervention for a potential treatment of spasticity in a person with SCI, based on changes in spinal and corticospinal excitability.

10.3 *Chapter 4: Design of a mobile application for the self-management of spasticity through education of triggers*

The aim of this chapter was to design and develop a mobile app where users could log their triggers of spasticity, and rate them using a clinical, self-assessed spasticity measure (PSFS). The design was explained to clinicians and people living with spasticity. Questionnaires were sent to these cohorts to assess its potential usability, perceived usefulness, efficacy, and the potential methods of use of the app.

Results of this study will influence future iterations of the design of this app, such that it can be used to aid in the education of exacerbating factors which affects people with spasticity.

10.4 *Chapter 5: Impact of non-invasive electrical stimulation on spasticity in people with spinal cord injury. A comparison between neurophysiological and clinical outcome measures: systematic review and meta-analysis*

This systematic review and meta-analysis aimed to determine which forms of non-invasive electrical stimulation may be more effective in reducing clinical and neurophysiological measures of spasticity in people with SCI. Specifically, this review addressed the following research questions: i) can non-invasive ES delivered to the PNS improve MAS, PT and PSFS scores? ii) is there a specific non-invasive ES protocol which is more effective at reducing spasticity (according to these outcome measures) in people with SCI? iii) are there any correlations between clinical outcome measures of spasticity, such as the MAS, PT and PSFS score, and neurophysiological measures, such as H-reflex, PRR and MEP amplitude? iv) does the current literature allow us to draw clinically meaningful conclusions?

This systematic review allows for comparison between neurophysiological outcomes assessed in healthy, able-bodied participants in experiments outlined previously in this thesis, and clinical outcomes of spasticity in people with SCI.

II. Preliminary research: an investigation into the use of posterior-root reflexes to elicit homosynaptic depression via cervical roots

This study aims to determine whether PRRs elicited in the upper limb could exhibit HD in healthy, AB participants. HD is known to be altered in people with spasticity (Grey et al., 2008); giving an additional understanding of the mechanisms which may occur following a neuromodulatory therapy. A secondary question, if HD is present, is which ISI is appropriate to measure changes in HD of the upper limb PRR for future investigations.

This chapter starts with a brief explanation on using HD, and how this work contributes to the overall aim of the PhD, before detailing the experimental methods, results and discussion.

1 Homosynaptic depression: selection of interstimulus interval

The overall aim of this PhD is to determine a form of neuromodulation which may be used by people with SCI for the self-management of upper limb spasticity. To this end, the effects of 30 minutes of 3 forms of neuromodulation on the excitability of the CNS were compared, in healthy, AB participants (see chapter III). In that study, spinal (measured through PRRs) and corticospinal (measured through MEPs) excitability were compared prior to neuromodulation, just after, and for up to one hour afterwards.

However, reductions in these measurements (PRRs and MEPs) may occur due to participants remaining still for prolonged period (Crone et al. 1999). As discussed in chapter I, HD occurs when paired pulses of ES are delivered; with the first (control) pulse activating Ia fibres, which causes the depression of the response to a second (conditioned) pulse of ES. When using this as an outcome measure for CNS excitability, we measure the extent of the depression of the conditioned pulse as a percentage of its control pulse. Therefore, any reduction in excitability due to prolonged sitting would be accounted for, because the conditioned response is expressed relative to the test response at the same timepoint.

Various literature demonstrating HD in the upper limb uses the H-reflex (Aymard et al., 2000; Lamy et al., 2009; Trompetto et al., 2014). However, eliciting H-reflexes in the

upper limb can be unreliable in people with spasticity, or may require a sustained muscle contraction, which may not be suitable for people with SCI (Goulet et al. 1996; Ann Marie Stowe et al. 2008; A M Stowe et al. 2013). In experiments outlined in this thesis, we have chosen to use the PRR, since this type of response also occurs due to the stimulation of Ia afferents and has similar characteristics as the H-reflex (Minassian et al., 2007; Hofstoetter et al., 2019).

When paired pulses of electrical stimulation are delivered to nerve or spinal root afferents, the control pulse (1st pulse) will excite Ia fibres, leading to a decreased probability of neurotransmitter release (Crone and Nielsen 1989), causing a depressed response in the conditioned pulse (2nd pulse) at ISIs of 1 – 10 s, known as HD (Burke 2016; Crone and Nielsen 1989). A similar effect is seen for ISIs up to 400 ms, caused by the depolarisation of primary afferent terminals (PI) (Crone and Nielsen 1989; Burke 2016). Since both inhibitory mechanisms occur due to previously activated Ia fibres, and so will be termed as post-activation depression (PAD) for the duration of this chapter. The potency of both HD and PI reduce with spasticity (Lamy et al. 2009; Faist et al. 1994; Rose Katz 1999), which may be a mechanism behind the characteristic exaggerated stretch reflex (Tansey et al. 2012).

HD has been successfully measured in PRR in the lower limb in healthy, AB participants (Andrews, Stein, and Roy 2015; Hofstoetter et al. 2019) and those with SCI (Hofstoetter et al. 2019; Murray and Knikou 2019). In the upper limb, some studies have found that the PRR did not exhibit HD with ISIs at 1, 3, 5 and 8 s in 12 out of 13 healthy, AB participants (Einhorn et al. 2013). However, HD was seen in 10 / 10 participants with an ISI of 50 ms (Milosevic, Masugi, Sasaki, et al. 2019). Figure 9 shows the placement of the stimulating electrodes in these studies. In the study presented here, however, we will use the electrode placement shown in Figure 11. This is to increase the comfort for the participant while receiving tSCS, as electrical stimulation through the cervical column has been uncomfortable in previous experiments we have carried out; this also maintains precision in the pathways activated.

Evaluating HD in upper limb PRRs would be an invaluable addition for experiments assessing the effects of neuromodulation on CNS excitability. The single ISI required to elicit HD for these types of experiments would ideally depress the conditioned pulse such that HD is measurable when the general spinal excitability has been lowered, without

causing the conditioned response to disappear completely. This experiment is a novel approach to eliciting HD in upper limb PRRs using tSCS, and tests a wide range of ISIs.

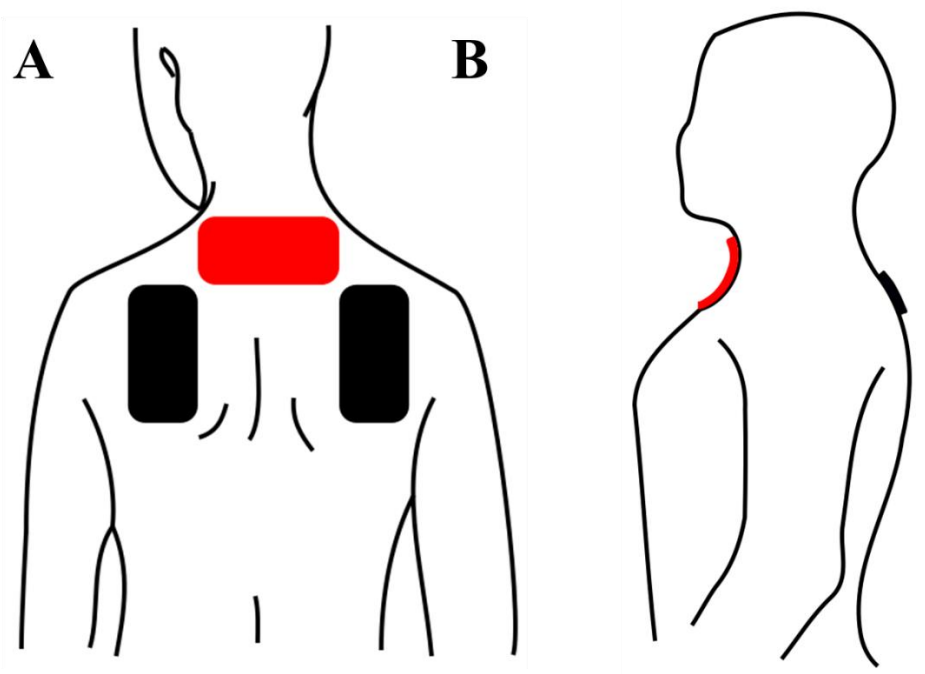

Figure 9: Electrode placement of anodes (red) and cathodes (black) used in (a) Einhorn et al. (2013) and (b) Milosevic et al. (2019). Not drawn to scale.

1.1 *Methods*

1.1.1 Participants and ethical approval

Ethical approval for this study was granted by the University College London Research Ethics Committee and informed consent was given by all participants who took part.

1.1.2 Experimental set-up

With the participant laying supine, EMG recordings were taken from the left flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) via adhesive electrodes (Ø 24 mm, Covidien, Medtronic, MI, USA) placed over the belly each muscle (see Figure 10). EMG data was recorded through LabChart 8 software (ADInstruments, Dunedin, New Zealand) at a sampling rate of 10 kHz. All EMG data was subject to first order digital filters in LabChart 8. This consisted of a low pass filtering with a cut-off frequency of 500 Hz, as well as high pass filtering, of cut-off frequency 0.5 Hz.

1.1.3 Transcutaneous spinal cord stimulation

ES was provided by a Digitimer DS8R research stimulator (Hertfordshire, UK) and was delivered using adhesive circular surface electrodes (PALS Neurostimulation adhesive

electrodes, Ø 50 mm), with the cathode placed over the C6 and the anode over the T1 vertebrae (see Figure 11). Pulses were configured in Signal 6 software and were triggered via a 1401 mini (Cambridge Electronic Designs, Cambridge, UK).

For each participant, ES using monophasic, 1 ms pulses, delivered every 7 s were used to determine PRR threshold. Stimulation intensity was increased gradually, while making sure the participant was comfortable, until PRRs were elicited in both the FCR and ECRL. If PRRs were not elicited, stimulating electrodes were moved marginally from the midline, or the anode was moved towards the T2 vertebrae. Once this had been achieved, the stimulation intensity was decreased until the PRR disappeared. This was determined to be the reflex threshold. Stimulation intensity was then set at 1.4x reflex threshold, or at 1.2x threshold or 1.3x threshold if participants could not tolerate 1.4x.

To determine which nerve was being stimulated, participants were asked if they had any sensation in their arm or hand. If participants experienced sensation in the thumb or index finger, it was deemed that the median nerve was being stimulated (Gray 1977). However, in some cases, participants were not able to tolerate high enough levels of stimulation for this sensation, but PRRs were still measurable.

Three paired-pulses of tSCS were delivered at ISIs of 30, 50, 100, 250, 500 ms and 1-12 s (at 1 s intervals) at random, giving a total of 51 paired-pulses delivered to each participant. An interval of 15 s was left between each pair of pulses.

1.1.4 Data analysis

Data analysis and visualisation was carried out using MATLAB 2019b software (Mathworks, MA, USA). Normality of data was assessed using a quantile-quantile (Q-Q) plot. A Wilcoxon signed rank test was used to determine the difference between the peak-to-peak amplitudes for the conditioned pulse versus peak-to peak amplitudes of its control, for both muscles, for each ISI condition. This was carried out within groups of participants who experienced sensation in the index finger and thumb, those who did not experience this sensation, and across all participants. Results were considered as statistically significant for $p < 0.05$. Statistical analysis was carried out using SPSS statistics software (IBM Corporation, version 26, Armonk, NY, USA).

To determine any differences between groups of people who experienced sensation in the index finger and thumb and those who did not, a Mann-Whitney U test was carried out

on percentage changes of the conditioned pulse from its control pulse, across each ISI condition.

For data visualisation, the percentage change in the conditioned PRR from its control response was calculated, then averaged over the 3 repeats for each ISI.

Latency of each response was calculated as the period from the start of the stimulation artefact, to the point at which a change in the root-mean-squared value was detected, following the repolarisation of the stimulation artefact. This detection was visually inspected and confirmed for each pulse. This was compared, using a one-way ANOVA between the control and conditioned pulses. A repeated measures ANOVA was also carried out between each ISI condition.

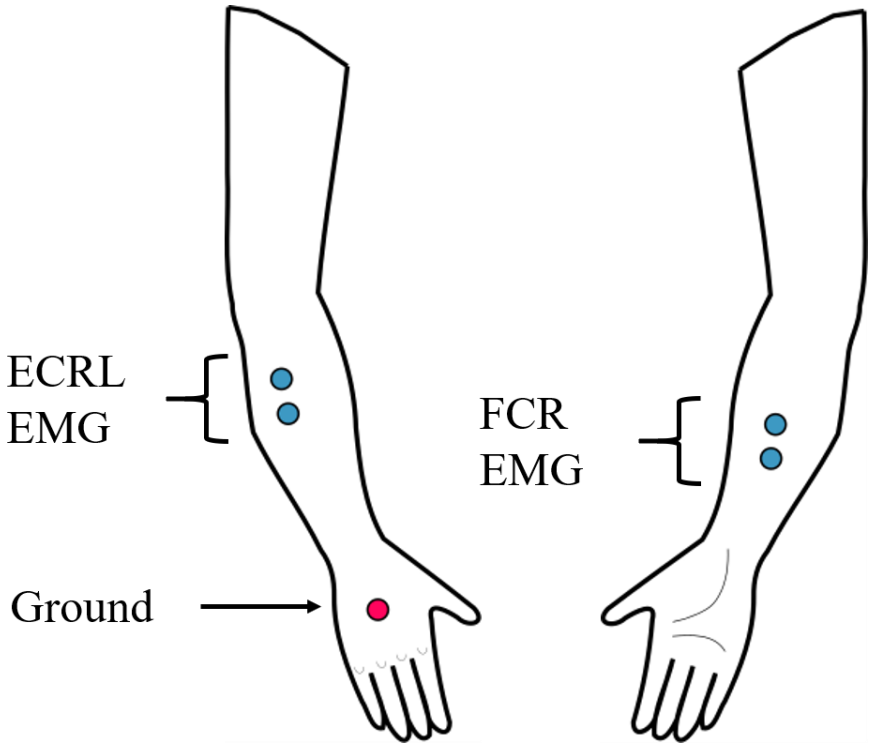

Figure 10: EMG electrode placement. Abbreviations: ECRL = extensor carpi radialis longus, EMG = electromyography, FCR = flexor carpi radialis.

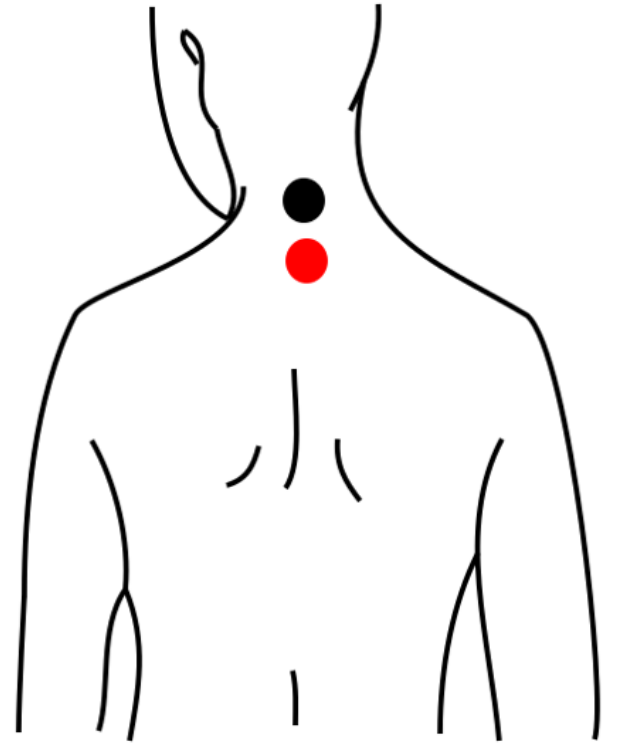

Figure 11: Electrode placement of anodes (red – T1) and cathodes (black – C6). Not drawn to scale.

1.2 *Results*

1.2.1 Participants

Eight adults (2 males, 6 females) aged 22-35 years (25.88 ± 4.66; mean ± SD) with no known neurological disorders participated in this study. Stimulation intensities ranged from 52.3-84.5 mA (63.8 ± 10.2 mA; mean ± SD), a summary of these parameters for individuals are shown in Table 9. Figure 12 shows example PRR responses in one participant (participant 2).

Table 9: Participant electrical stimulation characteristics. PRR amplitudes presented were calculated as an average of 3 control pulses delivered at an ISI of 12 s. Abbreviations: ISI – interstimulus interval, PRR = posterior-root reflex.

Participant	Stimulation amplitude (mA)	Threshold multiple	FCR PRR amplitude (mV)	ECRL PRR amplitude (mV)	Sensation present
1	46.6	1.2	0.093	0.026	Yes
2	66.2	1.4	2.167	0.507	Yes
3	84.5	1.3	0.045	0.148	No
4	65.1	1.4	0.054	0.052	No
5	69.7	1.4	0.115	0.132	No
6	58.8	1.4	0.236	0.274	No
7	55.2	1.2	0.191	0.196	Yes
8	52.3	1.2	0.123	0.075	No

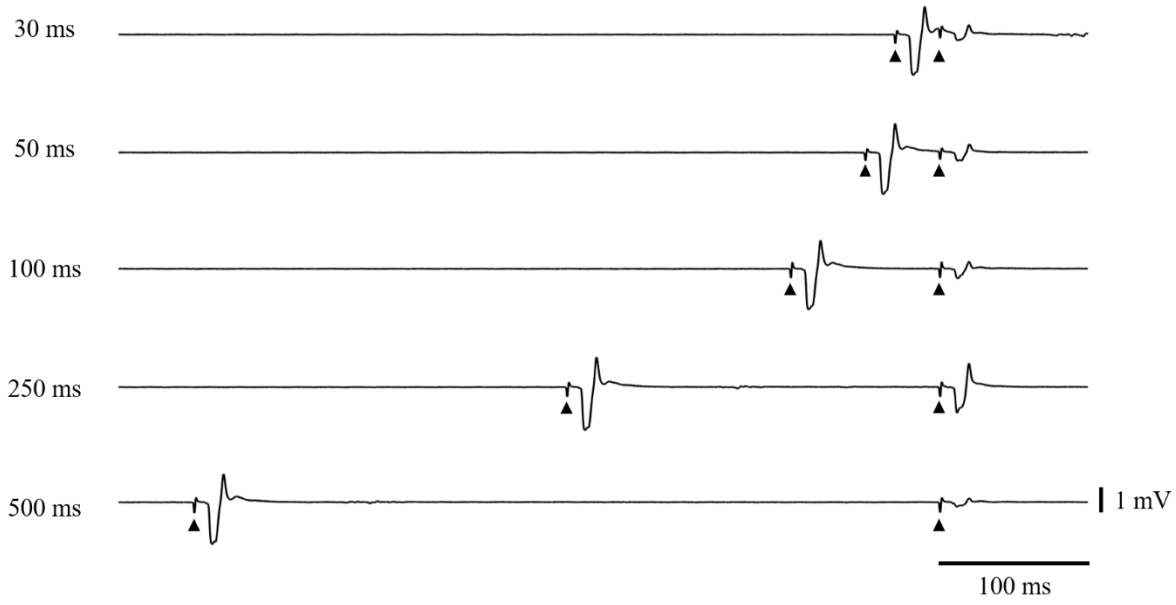

Figure 12: Example FCR EMG traces for ISIs of 30 to 500 ms, showing paired-pulse PRR responses. Arrowheads show where the electrical stimulus occurred. Abbreviations: EMG = electromyography, FCR = flexor carpi radialis, ISI = interstimulus interval, PRR = posterior-root reflex.

1.2.2 Changes in peak-to-peak amplitude

Figure 13 shows the mean percentage differences from the conditioned pulse to its control, averaged over the 3 stimuli for each ISI, for the FCR and ECRL. For results averaged across all participants, depression of the conditioned pulse occurred in the FCR at 30 (74.77 %, $p = 0.001$) and 50 ms (71.77 %, $p = 0.001$); and also in the ECRL at 30 (85.97 %, $p = 0.016$), 50 (94.60 %, $p = 0.137$) and 500 ms (88.88 %, $p = 0.006$).

In the FCR, there was an increase in percentage change at 5 – 12 s, with a maximum mean percentage change occurring at a 6 s ISI (151.95 %, $p = 0.047$). In the ECRL, the maximum mean percentage change occurred at 11 s (107.80 %, $p = 0.026$).

Figure 14 and Figure 15 show results for individuals who experienced sensation in the thumb and the index finger (n = 3), and those who experienced no particular sensation (n = 5) in the FCR and ECRL respectively. For ISIs < 2 s, percentage changes were larger in participants who experienced this sensation, versus those who did not. For the sensation group, statistically significant results occurred at 30 ms (51.74 %, $p = 0.025$), 50 ms (53.92 %, $p = 0.012$) and 5 s (84.10 %, $p = 0.012$) in the FCR, and at 30 ms (71.00 %, $p = 0.012$), 50 ms (76. 55 %, $p = 0.011$), 500 ms (72.86 %, $p = 0.021$) and 3-5 s (83.14 %, $p = 0.051$; 80.14 %, $p = 0.008$; 90.24 %, $p = 0.021$) in the ECRL. For those who did not experience sensation, there was a statistically significant reduction in the conditioned pulse at 30 ms only (76.21 %, $p = 0.015$) in the FCR.

Differences between these groups were statistically significant at 100 ms ($p = 0.001$), 500 ms ($p = 0.025$) and 5s ($p = 0.035$) for the FCR, and at 4 s ($p = 0.021$) in the ECRL.

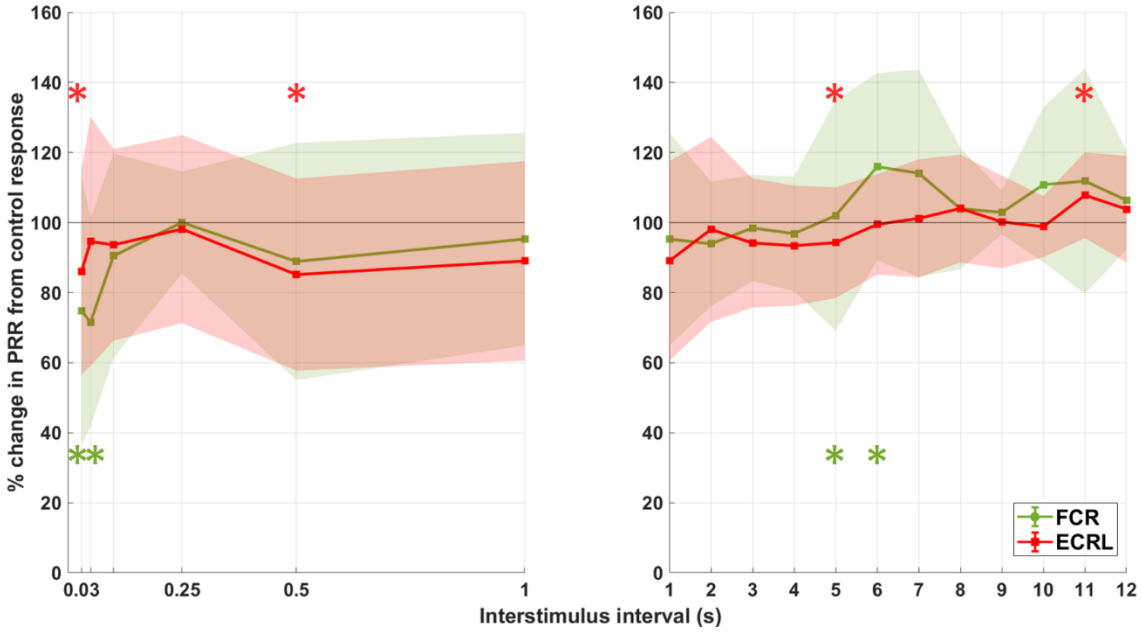

*Figure 13: Average percentage change in the conditioned response following the control stimulus in the FCR (green) and ECRL (red) across all participants. Shaded area represents the standard deviation. * denotes results for which there is a statistically significant difference between control PRR amplitude and conditioned PRR amplitude ($p < 0.05$) Abbreviations: ECRL = extensor carpi radialis, FCR = flexor carpi radialis, PRR = posterior-root reflex.*

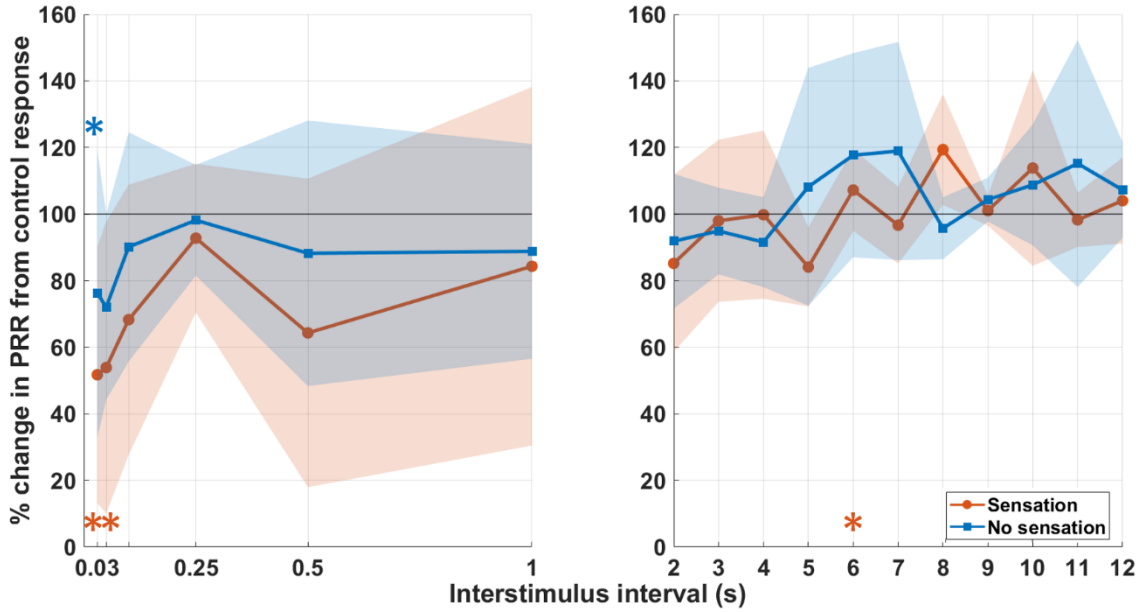

*Figure 14: Percentage change in the conditioned response following the control stimulus in the FCR for participants with sensation in the index finger and/or thumb (n = 3) (orange), those with no particular sensation (n = 5) (blue). Shaded area represents the standard deviation. * denotes results for which there is a statistically significant difference between control PRR amplitude and conditioned PRR amplitude ($p < 0.05$). Abbreviations: FCR = flexor carpi radialis, PRR = posterior-root reflex.*

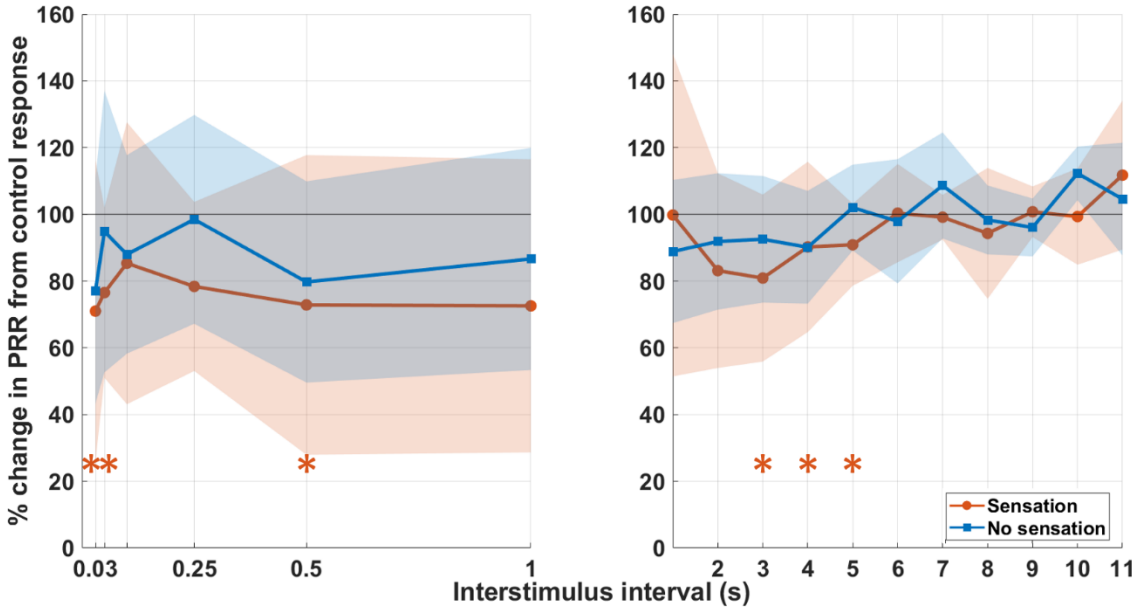

*Figure 15:Percentage change in the conditioned response following the control stimulus in the ECRL for participants with sensation in the index finger and/or thumb (n = 3) (orange), those with no particular sensation (n = 5) (blue). Shaded area represents the standard deviation. * denotes results for which there is a statistically significant difference between control PRR amplitude and conditioned PRR amplitude (p < 0.05). Abbreviations: ECRL = extensor carpi radialis, PRR = posterior-root reflex.*

Figure 16 shows the results from one participant, who did experience sensation in the thumb and index finger. For this participant, a more marked depression occurred, compared to the average across the other participants. In this participant, the same decrease in percentage change at 250 ms, seen across averaged data, is also present.

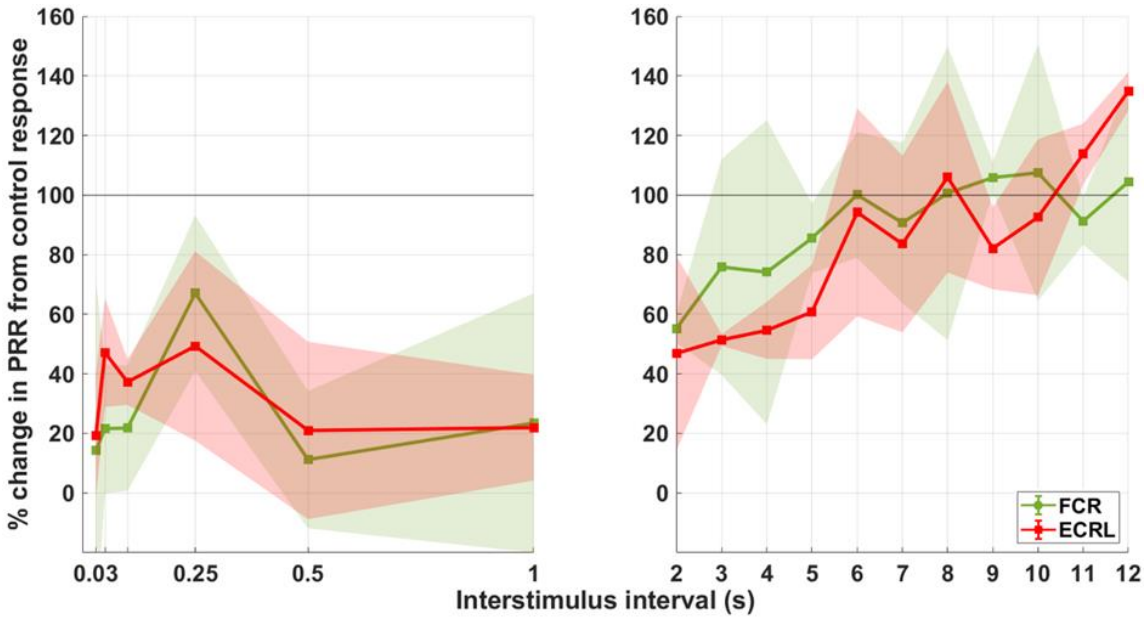

Figure 16: Average percentage change in the conditioned response following the control stimulus in the FCR (red) and the ECRL (blue) for participant 2 only. Shaded area represents the standard deviation. Abbreviations: ECRL = extensor carpi radialis, FCR = flexor carpi radialis.

1.2.3 Changes in latency

Latencies averaged across all participants and ISIs for the control PRR response were 9.2 ± 0.093 ms and 9.7 ± 0.17 ms for the FCR and ECRL respectively. For the conditioned PRR response, the same value was 9.1 ± 0.11 ms and 9.8 ± 0.21 ms for the FCR and ECRL respectively (mean ± SD). Following a one-way ANOVA, no statistically significant differences were found between control and conditioned PRR latencies across all ISI conditions, for either muscle.

1.3 *Discussion*

1.3.1 Elicitation of HD in upper limb PRRs

Results of this study show that HD of PRRs in the upper limb can be elicited in some participants. In those who experienced sensation in their thumb and index finger, depression of the conditioned PRR was largest with smaller ISIs, with deceasing depression as ISIs were increased. This is similar to results in experiments with the H-reflex (Hultborn and Nielsen 1998; Aymard et al. 2000) and in PRRs (Hofstoetter et al. 2019). Inconsistency with eliciting HD between participants is reflected in the study by Einhorn et al. (2013), where PRRs in the upper limb are also investigated. For investigation into PRRs in the lower limbs, HD is elicited in all participants using an ISI of 50 ms (Milosevic et al., 2019), at ISIs 25 – 250 ms (Andrews, Stein, and Roy 2015), and at 20 ms – 5 s (Hofstoetter et al. 2019).

When comparing HD between upper and lower limb H-reflexes of healthy, AB participants, no statistically significant difference has been found in the amount of HD at ISIs 1- 10 s, with a similar amount of HD seen at each ISI (Aymard et al., 2000). This suggests that HD should have similar effects for nerves originating at cervical and thoracic levels. When delivering ES via transcutaneous electrodes over the spinal cord, however, many structures are subject to stimulation, making it difficult to isolate each structure. More consistency in HD seen in the lower limb, compared to the upper limb, could be due to the closer proximity of different nerve roots within the cervical vertebrae, compared with the thoracic vertebrae (Gray, 1977). This allows for a better isolation for the ES of the desired nerve for PRRs; similar to the elicitation of the H-reflex.

With a higher degree of specificity required for the stimulation of upper limb spinal roots, differences in the underlying anatomy between participants may have a larger effect. This could attribute to the more exaggerated responses seen in participant 2, compared to other participants. When comparing the current study to the work of Einhorn et al. (2013), we saw a larger number of participants who exhibited HD. In the Einhorn study, stimulating electrodes covered a much larger area (see Figure 9A) compared to the current study (see Figure 11). Delivering ES in this way also means that higher stimulation intensities are required, with an average of 159.15 mA used in the study by Einhorn et al. (2013), and 63.8 mA in the current study. The arrangement used by Einhorn et al. (2013) may amount to a larger spread in current to other underlying anatomy, as well as more discomfort to

the participant. It is unclear from this study whether the participants experienced sensation associated with stimulation of the dermatomes associated with the median nerve. This, as well as the lack of precision of tSCS, may have led to HD being elicited in fewer participants compared to the current study.

In our study, PRRs exhibited HD at shorter ISIs <2 s. However, for participants who did not experience sensation in their thumb and index finger, HD at 30 ms was present in the FCR for 3 out of 5 participants, and 1 in the ECRL; compared to all 3 participants who did experience sensation. Since PRRs were elicited in all participants, we know that stimulation was producing activity in one of, or a mixture of, nerves originating at the brachial plexus (Gray, 1977). For participants who had sensation in their thumb or index finger; this sensation can only be attributed to stimulation of the median or radial nerve, which innervate the FCR and ECRL respectively (Gray, 1977). Therefore, the increased HD seen in this participant cohort may be due to a more precise stimulation of targeted structures. This decreased spread of current to other surrounding nerves may potentially cause crosstalk between innervated muscles to be measured via EMG and therefore lead to a lessened measurement of HD. We can therefore propose that this sensation is recommended to confirm the targeted stimulation of the median nerve via tSCS, therefore eliciting HD through the stimulation of afferents.

1.3.2 Reduction of HD at 250 ms

The reduction in HD seen 250 ms in the current study has also been seen in lower limb PRRs at the same ISI (Hofstoetter et al. 2019) and in the lower limb H-reflex at 250 – 300 ms (Kagamihara et al. 1998). In the current study, PRRs were elicited at 1.2 – 1.4 x reflex threshold, where a muscle response was observed in most participants. This is similar to that of Hofstoetter et al. (2019); where this facilitation was seen at 200 – 500 ms in neurologically intact people, and 200 – 300 ms in those with a SCI. The authors suggest that facilitation occurs at 250 ms since the muscle twitch causes ascending afferent input, synapsing at the spinal cord at approximately this time, which in turn facilitates motoneurons, causing the larger conditioned response at this interval. The amount of afferent input causing excitation here surpasses the reduced activity from Ia afferent input attributed to PAD. At an ISI of 500 ms, however, the muscle twitch has already occurred as a result of the control pulse, meaning there is little or no afferent input at the time of the conditioning pulse, and reduced spinal excitability associated with PAD has an overriding effect. Tábořík̆ova and Sax (1969) suggest that this same facilitation at ~250

ms occurs in the H-reflex below motor threshold, with increasing facilitation for increasing control stimulus intensity.

This facilitation has been shown to be increased in people with spasticity as a result of Parkinson's disease, stroke (Olsen and Diamantopoulos 1967; Yap 1967), as well as SCI (U. S. Hofstoetter et al. 2019). For people with spasticity, HD is reduced compared to those without spasticity (Grey et al., 2008). As well as this, exaggerated reflexes can occur due to an increased motoneuron excitability (J. B. Nielsen, Crone, and Hultborn 2007), which can cause an increase in ascending afferent input. However, more investigation is required to determine if this is the true mechanism behind the facilitated response in conditioned response at an ISI of 250 ms.

1.3.3 Selection of ISI to elicit HD in a study investigating the effects of neuromodulation

From preliminary results on 4 participants, when PRRs were measured following 30 minutes of neuromodulation, PRR response were reduced by up to 50 % from its baseline, due to the decrease in spinal excitability (Massey et al. 2018). Based on the findings in this study, the optimal ISI for future studies is 1 s. This is because it reduced the conditioned response by less than 50 % in both muscles, so would still measure HD if neuromodulation were to reduce spinal excitability. Although this amount of reduction in the conditioned response also occurred at 100 and 500 ms, a reduction in HD occurred at 250 ms in the current study, and at 200 – 300 ms in a study by Hofstoetter et al. (2019). The mechanism behind this is little understood, so ISIs of 100 and 500 ms should be avoided to ensure this mechanism does not influence HD as an outcome measure.

1.4 *Implications for future studies*

Results of this study are in line with other studies, with similar trends to changes in HD with ISI as results in the H-reflex (Táboříkova and Sax 1969; Schieppati 1987; Hultborn and Nielsen 1998; Kagamihara et al. 1998; Aymard et al. 2000) and PRRs (Andrews, Stein, and Roy 2015; Hofstoetter et al. 2019). Difficulties in eliciting HD in all participants also occurred in a study by Einhorn et al. (2013); attributing this to differences in the underlying anatomy between participants.

To increase the number of participants who exhibit PRR HD in future experiments, we will also include a preliminary test, where short ISIs of 30 – 100 ms will be used to attempt to elicit HD, as recommended by Hofstoetter et al. (2014). If HD is elicited, this confirms

the stimulation of afferents. Stimulating electrodes will be repositioned if this is not seen. If HD occurs during this test, we can then confirm stimulation of afferents when delivering neuromodulation to the participant. This differs from the 1 s HD outcome measure as it is a confirmatory test and the short ISIs will be required to be tolerated by the participant for a much shorter period.

To measure HD in a study to determine the effects of 30 minutes of 3 forms of neuromodulation with healthy, AB participants, an ISI of 1 s has been chosen. At this ISI, there was enough depression in the conditioned response such that it may be measurable in some participants but would still be measurable should there be a decreased excitability due to 30 minutes of neuromodulation.

1.5 *Conclusion*

Results presented here describe a method which successfully triggered HD in upper limb PRRs. Participants who experienced sensation in the desired dermatomes were more likely to display HD compared to those who did not. It is therefore recommended that future studies aiming to elicit HD in upper limb PRRs verify whether this sensation is felt in the participants, as well as to confirm stimulation of afferent fibres using ISIs of 30 – 100 ms (Hofstoetter et al., 2014). These results also provide evidence that upper limb PRRs elicited using this method may have comparable characteristics to lower limb H-reflexes and PRRs.

III. The effects of neuromodulation on corticospinal and spinal excitability of the upper limb: a preliminary study in healthy, able-bodied adults

This chapter presents the design and outcomes of an experiment with 9 healthy, able-bodied, participants. This study sought to determine which form of neuromodulation would be most effective in reducing spinal excitability, to guide towards the most appropriate parameters in the management of upper limb spasticity. The forms of neuromodulation tested were: i) TENS delivered over the FCR at 100 Hz (pulse width 0.25 ms); ii) HF-TENS delivered over the FCR at 100 Hz, with a carrier frequency (see Figure 19 for visualisation of a HF carrier frequency) of 9090 Hz (pulse width 0.05 ms) and iii) HF-tSCS, delivered over the C6 and T1 vertebrae, at 100 Hz, with a carrier frequency of 9090 Hz (pulse width 0.05 ms). These were all compared to a sham intervention, where no ES was given.

1 Neurophysiological comparatives with spasticity

As discussed in chapter I, there is a large amount of variety in the stimulation parameters used for spasticity management. For this study, TENS at a frequency of 100 Hz and pulse width of 0.25 ms was chosen, as this is a common set of parameters across several researchers (Goulet et al. 1996; Chung and Cheng 2010; Mima et al. 2004; Koyama et al. 2016; 2014; Mang, Lagerquist, and Collins 2010). There has also been more use of kHz ES for the management of neuropathic pain in recent years (Kapural and Al-Kaisy 2018; Van Buyten et al. 2013; Al-Kaisy et al. 2015), with potential for translated benefits to populations with spasticity (Nagel et al. 2017). By testing both HF and 'conventional' forms of neuromodulation, we can compare between more frequently used interventions against novel, HF forms.

To speculate potential effects of these interventions in populations with spasticity, it is useful to first investigate the effects on intact neurophysiology, to discover the mechanisms through which they may potentially relieve spasticity symptoms. Therefore, measures of spinal and corticospinal excitability have been measured through PRRs and MEPs respectively, as well as HD in a subset of participants.

Neurophysiological outcome measures of spinal and corticospinal excitability are known to differ in people with spasticity, compared to those without, for example: spinal reflexes

(Angel and Hofmann 1963; Faist et al. 1994; Aymard et al. 2000), MEPs (Sangari et al. 2019; Cakar et al. 2016) and HD (Faist et al., 1994; Schindler-Ivens and Shields, 2000; Grey et al., 2008).

Following continuous ES, there exist some common findings between healthy, AB participants and participants with spasticity. For example, a total of 30 minutes of 25 Hz TENS delivered to the common peroneal nerve may cause an increase in tibialis anterior MEPs in both people with incomplete SCI (Thompson et al. 2011), and in the intact CNS, following 40 minutes of TENS at 100 Hz (Mang, Lagerquist, and Collins 2010). Both studies have also found little or no change in H-reflex amplitude following TENS. No changes were found despite reductions in clinical measures of spasticity being reported, following both single (Goulet et al. 1996) and multiple (Aydin et al. 2005) TENS sessions. This collective evidence suggests that TENS may impact descending input through corticospinal tracts, but not spinal tracts; which may have a positive effect on spasticity.

When comparing between more commonly used frequencies (25-200 Hz) and kHz frequencies, recent research has focussed on the use of tSCS (Serrano-Munoz et al. 2017; Benavides et al. 2020). In healthy, AB participants, reduction of H-reflex amplitude in the lower limb was seen following 40 minutes of 100 Hz and 10 kHz tSCS, compared to sham tSCS (Serrano-Munoz et al. 2019), differing from aforementioned studies which used TENS (Mang, Lagerquist, and Collins 2010; Thompson et al. 2011). Another study measured responses elicited at the primary motor cortex (MEPs) and subcortical measures from the cervicomedullary junction, investigated the use of 20 minutes of cervical tSCS, at 30 Hz with and without a 5 kHz carrier frequency to improve function in people with SCI (Benavides et al. 2020). This study found that 30 Hz tSCS increased both cortical and subcortical excitability, whilst a 5 kHz carrier frequency increased subcortical excitability, and not cortical excitability, in both populations with and without SCI (Benavides et al. 2020). They also found that tSCS with a 5 kHz carrier frequency increased intracortical inhibition, which did not occur without this carrier frequency. The authors suggest that the 5 kHz carrier frequency may contribute to the cortical inhibitory effects. Therefore, more traditionally used frequencies of tSCS, without a kHz carrier frequency, may not modulate these pathways. In participants with SCI, single sessions of tSCS has been shown to give functional improvements when delivered at 50 Hz (Hofstoetter et al. 2014; 2020) and at 30 Hz, with more marked improvements at 30 Hz with a 5 kHz carrier frequency (Benavides et al. 2020).

Epidural SCS, delivered with kilohertz carrier frequencies, has been utilised for neuropathic and chronic pain, and has been shown to have a higher responder rate compared with SCS at 40-60 Hz (76.5 versus 49.3 % respectively, for back pain), as well as larger decreases in pain (66.9 versus 41.1 % respectively, for back pain) (Kapural and Al-Kaisy 2018). It also causes reductions in chronic back pain (Van Buyten et al. 2013) and neuropathic pain (Al-Kaisy et al. 2015), without paraesthesia, which can cause dropout. This has had some success, with reductions in pain following 1 month (Al-Kaisy et al. 2015) and 6 months (Van Buyten et al. 2013) of invasive SCS, and larger reductions in chronic pain following 24 months of epidural SCS, compared to stimulation at 40-60 Hz (Kapural et al. 2016). The mechanism for the reduction of neuropathic pain using this method requires further investigation (Nagel et al. 2017). Considering its success in reduction of pain, and some similarities between neuropathic pain and spasticity, the unknown mechanisms through which it does work may affect those occurring in spasticity.

Summarising this evidence, tSCS at conventionally used frequencies may increase cortical and subcortical, and decrease spinal excitability (Hofstoetter et al. 2014; 2020; Serrano-Munoz et al. 2019; Benavides et al. 2020). Whereas TENS may only increase descending drive, with inhibitory pathways being modulated at the cortical level (Thompson et al. 2011; Mang, Lagerquist, and Collins 2010). When tSCS is delivered with kHz carrier frequencies, there may again be a difference in modulated structures. This may be due to differences in current density delivered, and therefore the spread of current to afferent pathways (Serrano-Munoz et al. 2019).

Potential differences in the neurophysiological effects of non-invasive ES delivered with and without kHz carrier frequencies is not yet clear from the current literature, with few studies investigating the underlying mechanisms occurring following these types of non-invasive ES. Therefore, this study aims to determine the effects of delivering 30 minutes of TENS, HF-TENS and HF-tSCS on corticospinal and spinal excitability.

When testing for differences between kHz and 100 Hz TENS and kHz tSCS interventions in the current study, we used measures of corticospinal (MEPs) and spinal excitability (PRRs, HD) to speculate the location of modulation, as well as the potential neurophysiological mechanisms causing these changes.

2 Methods

2.1 *Participants and ethical approval*

Healthy, able-bodied participants with no known neurological conditions were recruited to take part in this study. Ethical approval was granted by the University College London Research Ethics Committee and informed consent was obtained from all participants.

2.2 *Experimental set-up*

Interventions and outcome measures were carried out with the participant in supine position. For each participant, 4 different 30-minute interventions were compared on separate days, and in a random order. The 4 interventions were: i) TENS; ii) HF-TENS; iii) HF-tSCS and iv) sham ES (summarised in Figure 17). In all participants, corticospinal excitability was determined by evoking MEPs and spinal excitability was determined by evoking PRRs. Following the experiment outlined in chapter II, in a sub-set of participants, HD of PRRs were measured using an ISI of 1 s.

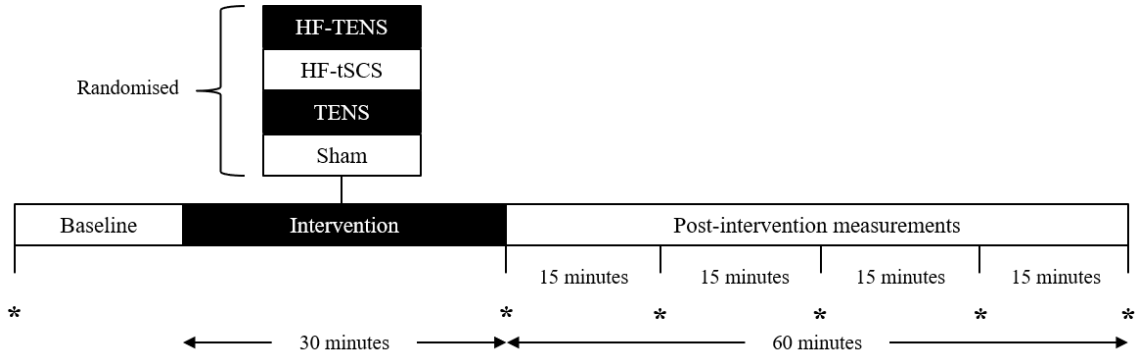

*Figure 17: Experimental timeline. * represents when outcome measures of 20 MEPs, PRRs and HD were taken. Abbreviations: HD = homosynaptic depression, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential, PRR = posterior-root reflex.*

2.2.1 Electromyography

Outcome measures were assessed via adhesive EMG electrodes, (Ø 2.4 mm) placed over the FCR and ECRL (see Figure 18). EMG data was recorded through LabChart 8 software (ADInstruments, Dunedin, New Zealand) at a sampling rate of 10 kHz. All EMG data was subject to first order digital filters in LabChart 8. This consisted of a low pass filtering with a cut-off frequency of 500 Hz, as well as high pass filtering, of cut-off frequency 0.5 Hz.

2.2.2 *Electrical stimulation electrode placement*

ES was delivered using a Digitimer DS8R stimulator (Hertfordshire, United Kingdom). Stimulating electrodes were placed over the FCR for HF-TENS and TENS interventions (Ø 24 mm) (see Figure 18). For HF-tSCS, the cathode was placed over the C6 vertebrae and the anode was placed over T1 (Ø 50 mm). Pulses were configured in Signal 6 software and were triggered via a 1401 mini (Cambridge Electronic Designs, Cambridge, United Kingdom).

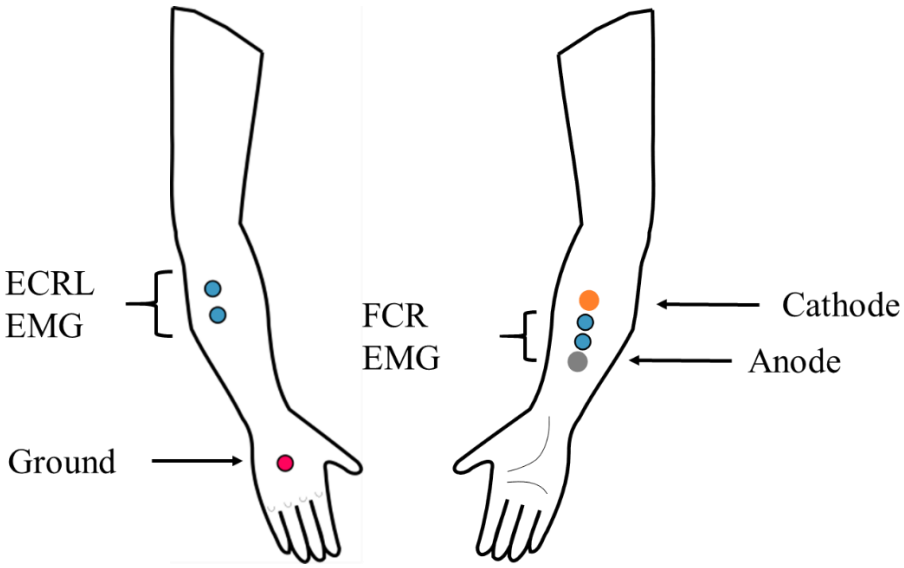

Figure 18: EMG electrode placement and stimulating electrode placement for HF-TENS and TENS interventions. Abbreviations: ECRL = extensor carpi radialis longus, EMG = electromyography, FCR = flexor carpi radialis.

2.3 *Outcome measures*

Timepoints at which outcome measures were taken were: immediately following the intervention (post0), and 15 (post15), 30 (post30), 45 (post45) and 60 (post60) minutes post intervention.

2.3.1 *Posterior-root reflexes*

For PRRs, stimulating electrodes were positioned in the same way as for the HF-tSCS intervention (described above), and single pulses of tSCS were applied (pulse width 1 ms). For each participant, single pulses of tSCS, delivered every 7 s were used to determine PRR stimulation intensity for use throughout the experiment. Stimulation intensity was increased gradually, while making sure the participant was comfortable, until PRRs were elicited in both the FCR and ECRL. If PRRs were not elicited in either muscle, stimulating electrodes were moved marginally from the midline, or the anode was moved towards the T2 vertebrae.

Once a stimulation intensity was set, participants were asked if they felt they could tolerate paired pulses at an ISI of 30, 50 or 100 ms at the same stimulation intensity used to elicit PRRs. If participants agreed to this, 3 paired pulses at 30, 50 or 100 ms were delivered. Presence of HD was used to determine whether the tSCS was targeting afferent fibres (Hofstoetter et al., 2014, 2019). In this preliminary test, HD was confirmed by visual inspection. Stimulating electrodes were repositioned if HD was not seen. In some cases where the stimulating electrodes were repositioned several times, if HD was not present, the experiment continued, and a recruitment curve, measuring PRRs was then taken. Stimulation intensity was determined to be either the minimum intensity where the recruitment curve plateaued, or the highest tolerated intensity, if the plateau was not reached.

Twenty of each of these measures were taken prior to each intervention, at post0, post15, post30, post45 and post60 (see Figure 17). Between outcome measures, a 7 s interval was used for the first 4 participants, and a 12 s interval was used for the remaining 5 participants, following the results of the experiment outlined in chapter II.

2.3.2 Motor-evoked potentials

MEPs were triggered by evoking responses in the primary motor cortex via a circular transcranial magnetic stimulation coil (Ø 90 mm). The stimulation point over the primary motor cortex was found by measuring the mid-point, at the crown of the head, between the ears and between the inion and the nasion, with induced current flowing anti-clockwise in the brain. Single pulses of TMS were delivered over and around this point until an MEP was seen in FCR and ECRL EMG. The coil was then moved about this point until the maximum MEP was achieved at the same stimulation intensity. This point was marked on a cap, on the participant's head, so the coil would be placed in approximately the same position between measurements.

Once this position had been determined, a recruitment curve was taken. TMS intensity used to elicit MEPs for the remainder of the experiment was selected as either the minimum intensity where the recruitment curve plateaued, or the highest tolerated intensity if the plateau was not reached.

For the first 4 participants, TMS pulses were delivered via a Magstim 200 (Ø 130 mm); for the remaining 5 participants, a Magstim 200^2 was used. Between outcome measures,

a 7 s interval was used for the first 4 participants, and a 12 s interval was used for the remaining 5 participants.

2.3.3 Homosynaptic depression

HD of PRRs were measured using paired pulses, delivered via the same stimulating electrodes used to evoke PRRs, at the same stimulation intensity used to evoke PRRs, with an ISI of 1 s. Twenty of each of these measures were taken prior to each intervention, immediately following intervention, and every 15 minutes thereafter, for up to an hour (see Figure 17).

2.4 *Interventions*

HF-tSCS and HF-TENS were delivered as a biphasic square wave at 100 Hz, with a 9090 Hz carrier frequency and a 50 μs pulse width (1 ms total pulse width for a total of 10 trains – see Figure 19). TENS was delivered as a biphasic square wave at 100 Hz with a 250 μs pulse width. During the sham intervention, the participant was told that low-intensity stimulation would be delivered, which they may not be able to feel, to account for any placebo effects.

Stimulation intensity for HF-TENS and TENS were set at 80 % of the stimulation intensity inducing muscle twitch using single pulses of stimulation (250 μs pulse width). HF-tSCS, intensity was determined using single pulses of tSCS (1 ms pulse width). Stimulation was set at 80 % of the intensity which elicited PRRs in the FCR and ECRL.

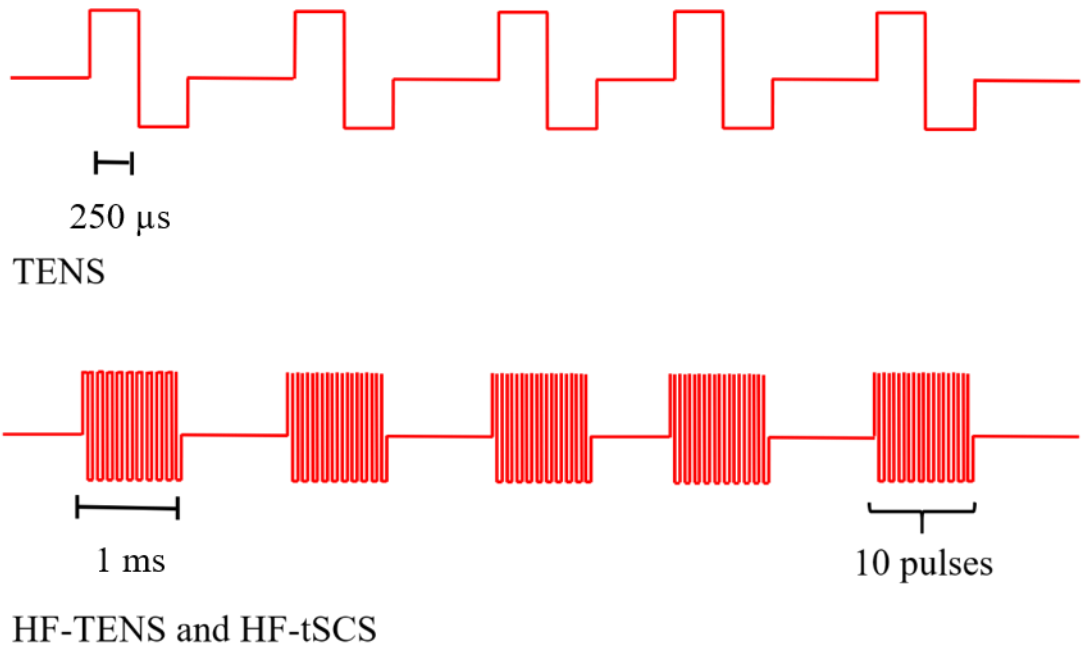

Figure 19:Example traces of TENS, HF-TENS and HF-tSCS interventions. Abbreviations: HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation.

2.5 *Data analysis*

Data analysis and visualisation was carried out using MATLAB 2019b software (Mathworks, MA, USA). All data is presented as mean ± SD unless stated otherwise.

For each block of 20 MEPs and PRRs taken, the percentage change of peak-to-peak amplitudes were measured from the average of their corresponding baseline measure were calculated for data visualisation.

Current density for each active intervention was calculated for individual participants using equation 2 and was averaged.

$$Current\ density\ = \frac{Current\ amplitude}{Surface\ area} \qquad Eq.\ 2$$

Normality of data was assessed using a quantile-Q-Q plot. A Wilcoxon signed rank test was carried out on raw MEP and PRR amplitudes measured at each time point, following each intervention, and compared to their corresponding baseline measure. A two-way ANOVA was performed on MEP and PRR amplitudes, measuring differences between timepoints and intervention, or the interaction of these two factors. Where a statistically significant difference was found between time points or intervention using this test, further analysis on the same data used a one-way ANOVA with a Bonferroni correction on the same data to break down any potential differences occurring.

To assess changes in HD throughout the experiment, the ratio of the conditioned response (i.e. the response measured at the muscle from the 2nd stimulus) to its control response (i.e. the response measured at the muscle from the 1st stimulus) measured after the intervention, were compared to their corresponding baseline measure. Statistical significance between these changes were assessed using a Wilcoxon signed rank test. Statistical analysis was carried out using SPSS statistics software (IBM Corporation, version 26, Armonk, NY, USA). For all statistical analyses, statistical significance was considered for $p < 0.05$.

3 Results

3.1 *Participants and preliminary HD test*

A total of 9 adults (2 males, 7 females) aged 27-40 years (33 ± 4.63; mean ± SD) with no known neurological disorders participated in this study. Data of 4 participants from this protocol was presented at the International Functional Electrical Stimulation Society conference 2018 (Massey et al. 2018).

For the subset of participants who were offered the preliminary test (n = 5), some participants, during some sessions, felt that they would not tolerate the more intense sensation of pairs of pulses. Therefore, this preliminary test was carried out in a total of 9 sessions, of a potential 20, in 3 participants. In these tests, HD was elicited during 7 of these 9 sessions. Example responses of those for whom HD was and was not elicited is shown in Figure 22.

Two participants felt that they could not tolerate PRRs, meaning they were measured in 7 of the 9 participants who took part; of these, ECRL MEP and PRR data from 1 participant during the sham intervention was corrupted during data collection and so was not included in the results and data analysis.

Examples of MEP responses and recruitment curves are shown in Figure 20 and Figure 21, respectively. Average stimulation intensity delivered to elicit PRRs and HD was 61.23 ± 8.53 mA (mean ± SD) for 7 participants. Average stimulation intensity to elicit MEPs was 68.69 ± 5.04 % of maximum stimulator output for 9 participants. Table 10 shows mean, SD and range of stimulation amplitudes and current densities delivered to participants for each intervention.

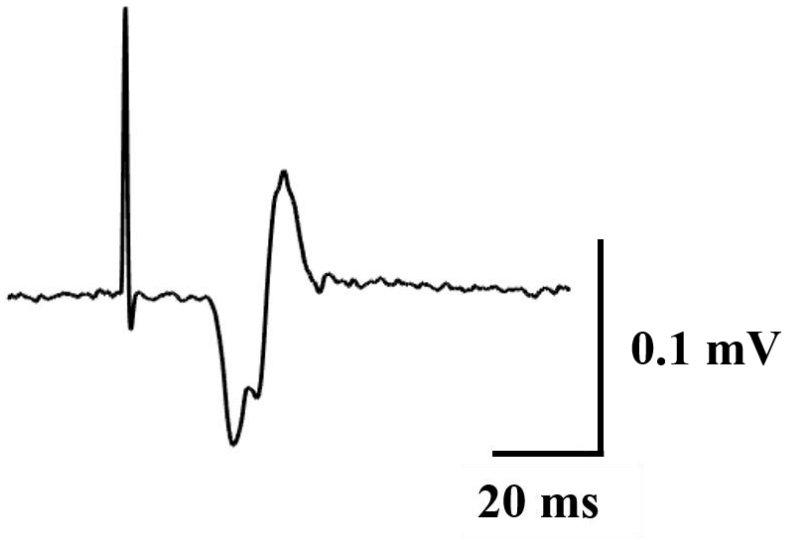

Figure 20: Example MEP trace from the FCR from participant 3. Abbreviations: FCR = flexor carpi radialis, MEP = motor-evoked potential.

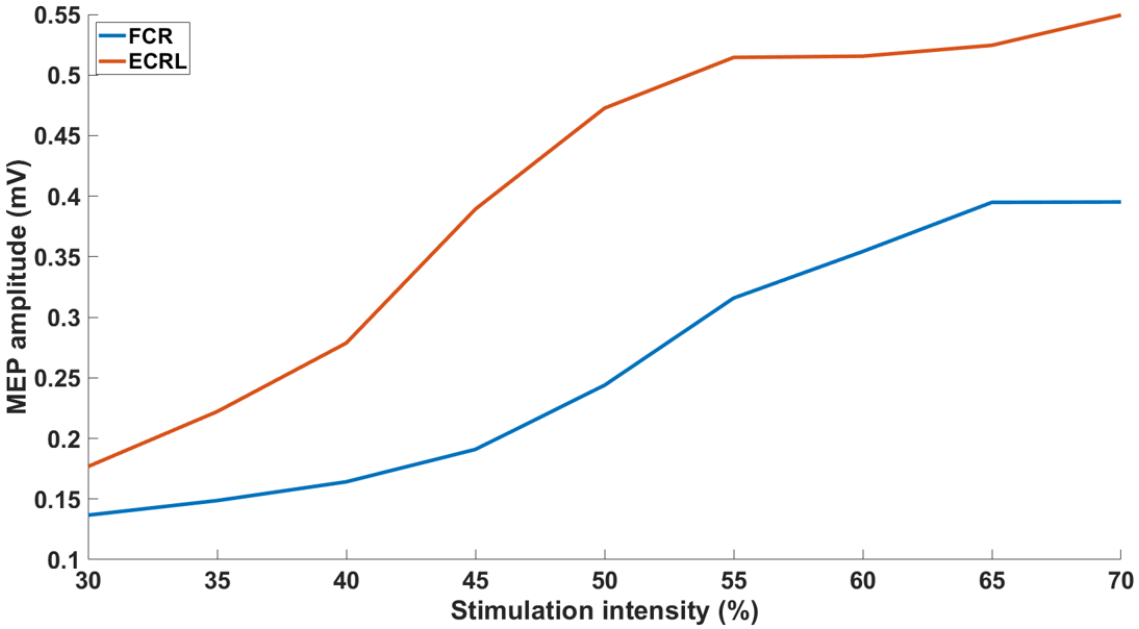

Figure 21:Example MEP recruitment curves in the FCR and ECRL for participant 1 prior to HF-tSCS intervention. A stimulation intensity of 70 % was used for the remainder of the experiment for this participant. Abbreviations: ECRL = extensor carpi radialis longus, FCR = flexor carpi radialis, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential.

Table 10: Stimulation parameters across participants for each active intervention (n = 9). Abbreviations: HF-tSCS = high-frequency transcutaneous spinal cord stimulation, HF-TENS = high-frequency transcutaneous electrical stimulation.

Variable	Intervention	Range	Mean	Standard deviation
Current	HF-tSCS	32.2 – 48.8 mA	37.3 mA	5.1 mA
	HF-TENS	1.5 – 5.9 mA	4.5 mA	1.3 mA
	TENS	3.3 – 6.7 mA	4.6 mA	1.1 mA
Current density	HF-tSCS	1.6 – 25 Am^{-2}	19 Am^{-2}	2.6 Am^{-2}
	HF-TENS	3.3 – 13 Am^{-2}	9.5 Am^{-2}	2.7 Am^{-2}
	TENS	7.2 – 11 Am^{-2}	10 Am^{-2}	2.2 Am^{-2}

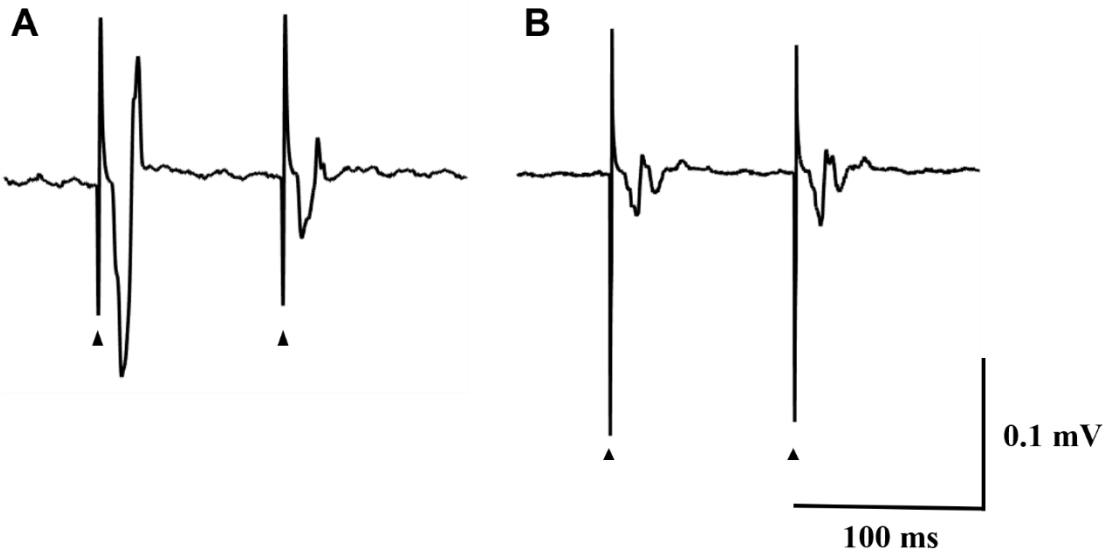

Figure 22: Example traces of FCR PRRs showing A) participant 8, where HD was present and B) participant 9, where HD was not observed. Both examples are using ISI = 100 ms. Arrowheads show where the electrical stimulus was triggered. Abbreviations: FCR = flexor carpi radialis, HD = homosynaptic depression, ISI = interstimulus interval, PRR = posterior-root reflex.

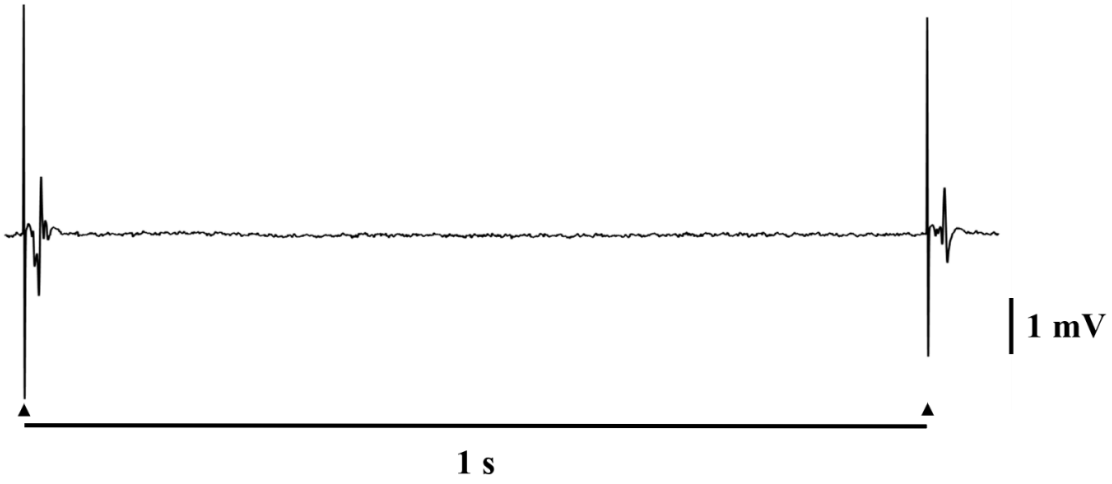

Figure 23: FCR PRR responses to paired pulses of tSCS, with an ISI of 1 s, in participant 6. Arrowheads show when the electrical stimulus was triggered. Abbreviations: FCR = flexor carpi radialis, ISI = interstimulus interval, PRR = posterior-root reflex, tSCS = transcutaneous spinal cord stimulation.

3.2 *Changes in MEPs*

Changes in MEP amplitude compared to baseline are shown for individual participants in Figure 24 and Figure 25, for the FCR and ECRL respectively. Figure 26 and Figure 27 show the percentage change in MEP amplitude from baseline for each of the active interventions, compared with the sham intervention, in the FCR and ECRL respectively. Statistically significant changes in MEP amplitudes from baseline were seen at post0, following HF-tSCS (80.66 ± 22.96 %, $p = 0.036$) and at post30 (77.21 ± 22.06 %, $p = 0.015$) in the FCR. No significant changes were observed in the ECRL.

For MEP amplitude, a two-way ANOVA found no significant difference in time point, or intervention, with no interaction.

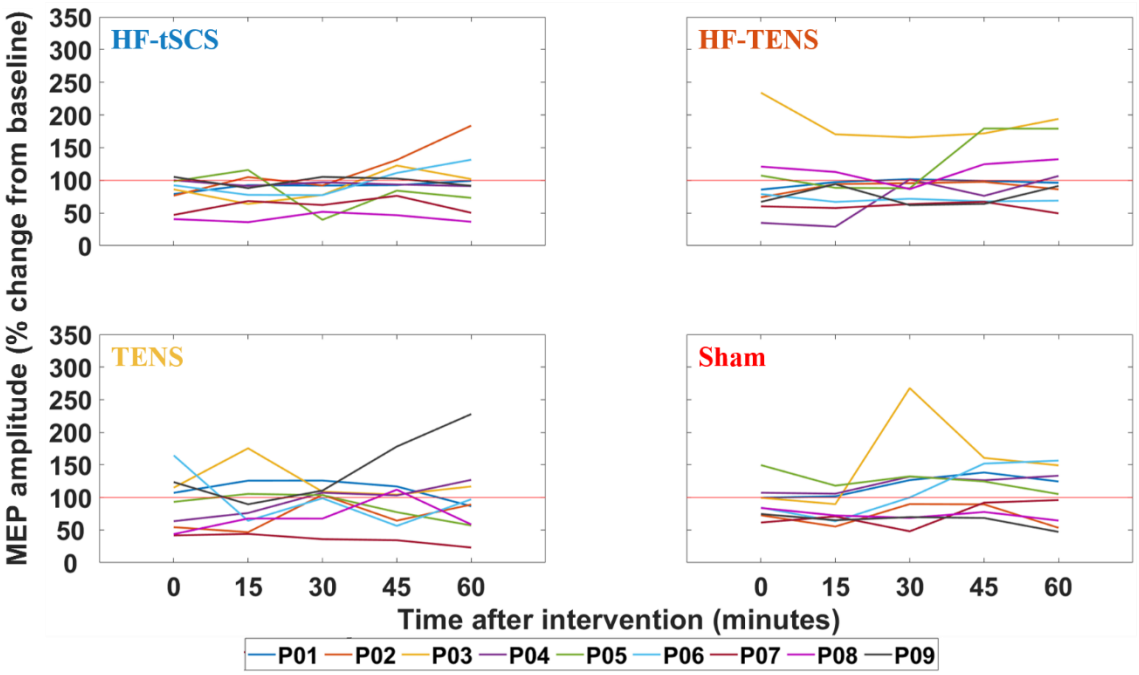

Figure 24: MEP amplitude (% change from baseline) in the FCR for individual participants in each intervention. (n = 9). Abbreviations: FCR = flexor carpi radialis, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential.

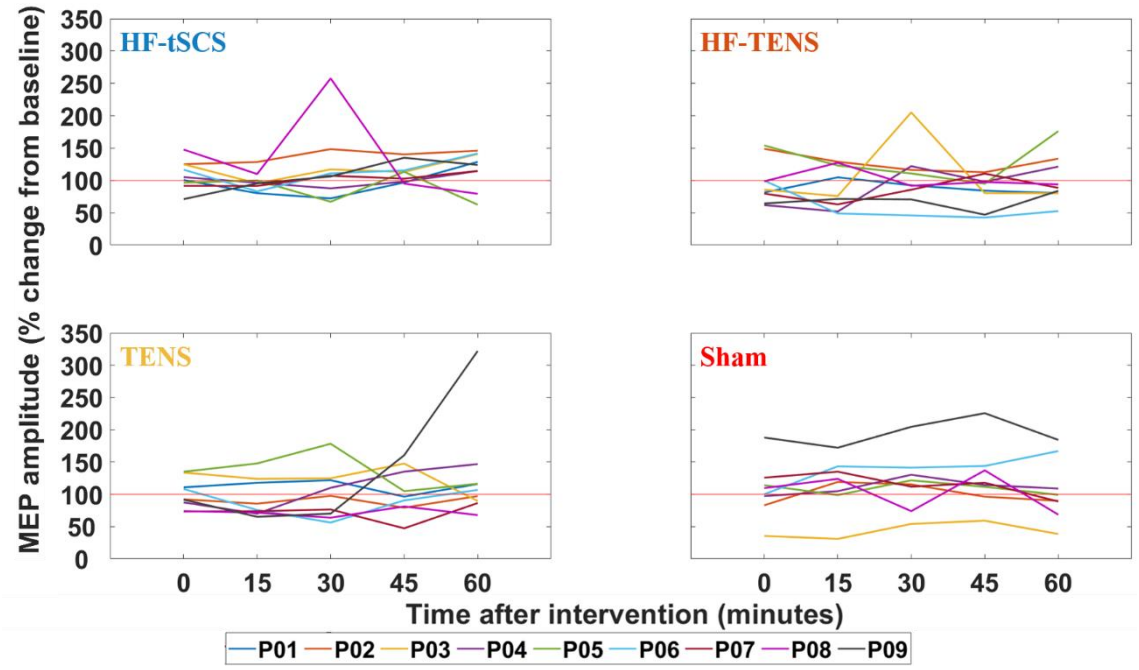

Figure 25: MEP amplitude (% change from baseline) in the ECRL for individual participants in each intervention. (n = 8). Abbreviations: ECRL = extensor carpi radialis longus, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential.

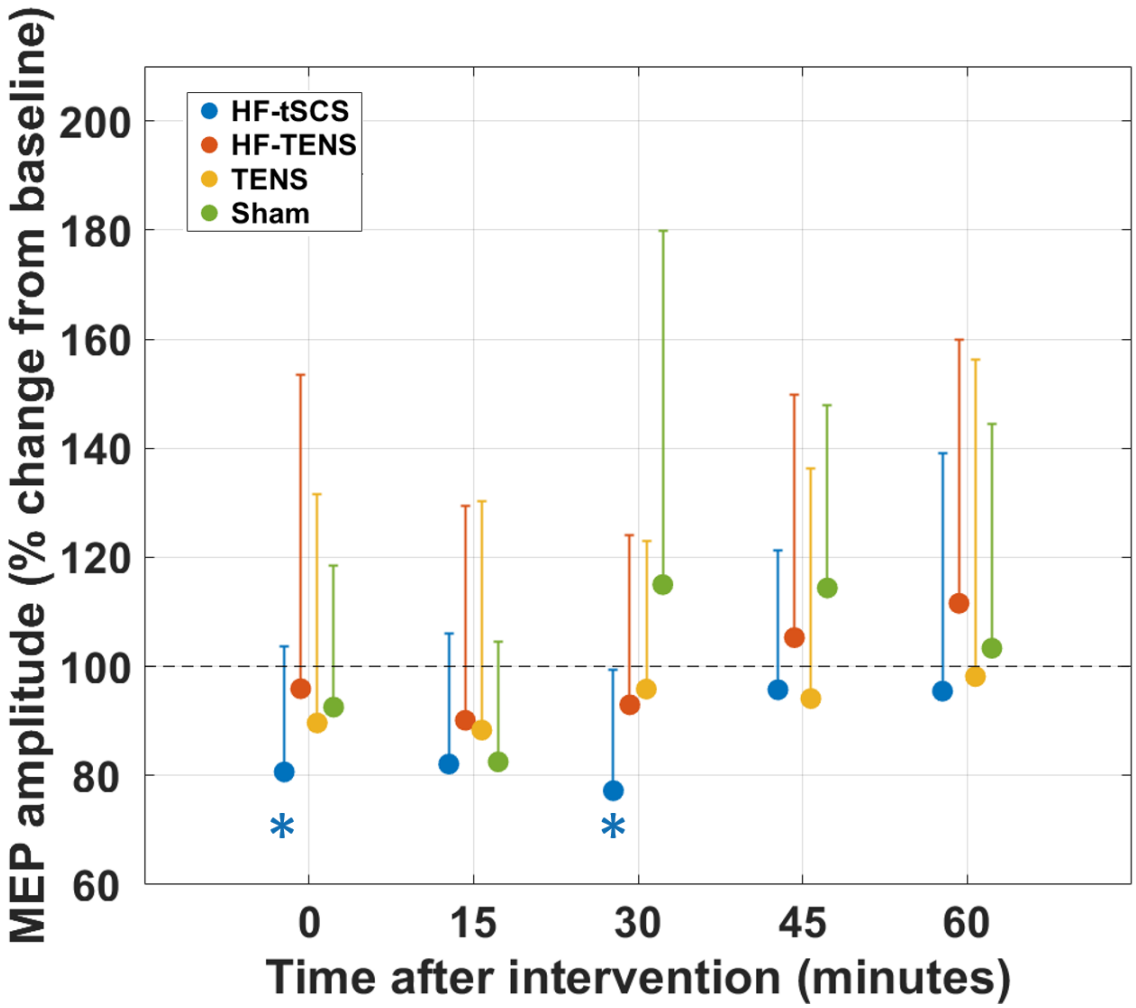

*Figure 26: Mean (SD) MEP amplitude (% change from baseline) in the FCR following each 30-minute intervention or sham. * represents a statistically significant difference in MEP amplitude from baseline ($p < 0.05$) following a Wilcoxon signed-rank test. (n = 9). Abbreviations: FCR = flexor carpi radialis, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential.*

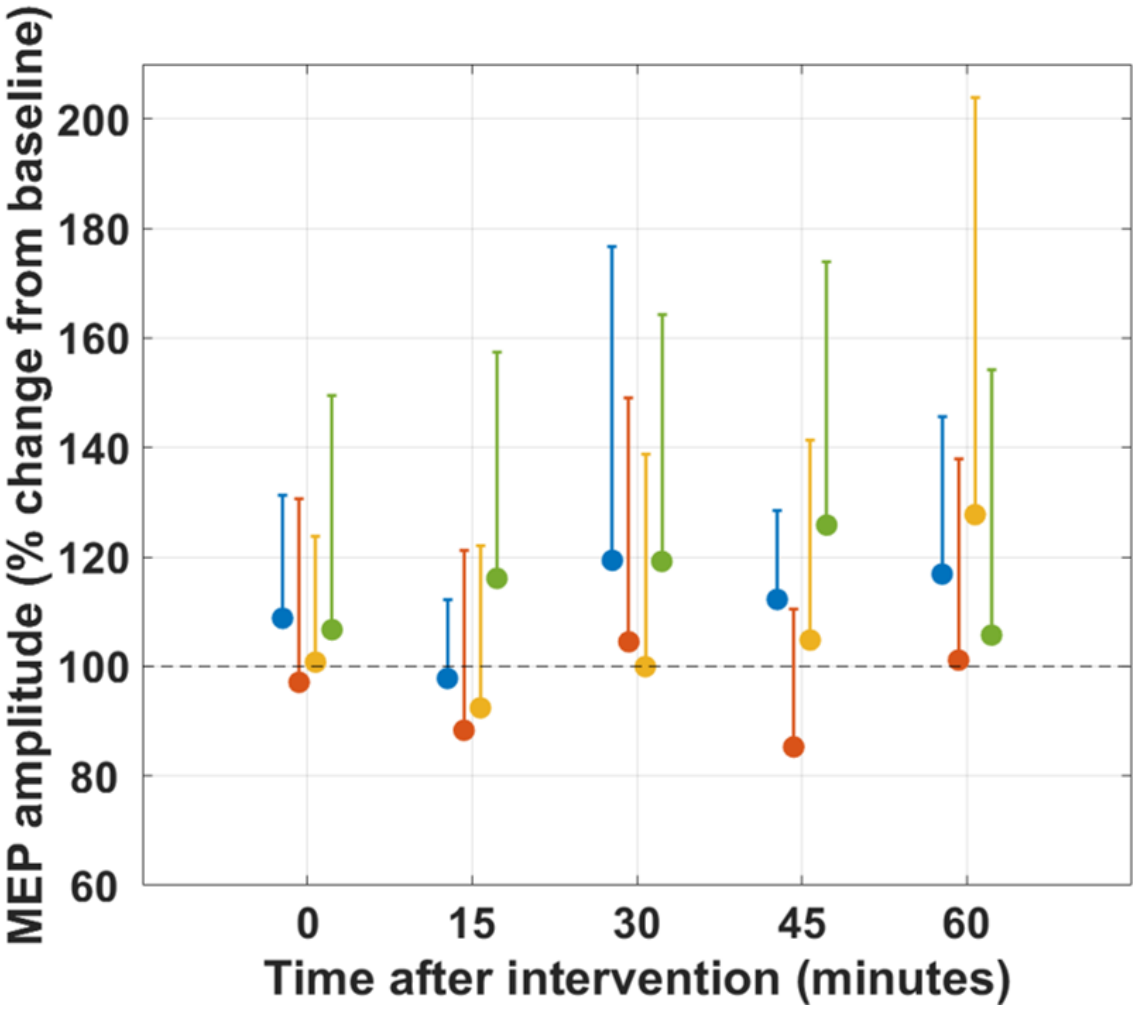

Figure 27: Mean (SD) MEP amplitude (% change from baseline) in the ECRL following each 30-minute intervention or sham. (n = 8). Abbreviations: ECRL = extensor carpi radialis longus, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, MEP = motor-evoked potential.

3.3 *Changes in PRRs*

Individual changes in PRR amplitude (relative to baseline) are shown in Figure 28 and Figure 29 for the FCR and ECRL respectively. These show large increases in PRR amplitude for participants 2 and 6. These results are up to 8 times that of other participants. Since this change was not seen in other participants, or in the same participants within different interventions, this data has been excluded. This exclusion will be further considered in the discussion. With these participants excluded, Figure 30 and Figure 31 show averaged changes of PRR amplitude for the FCR and ECRL respectively. After HF-tSCS, PRR amplitude reduced significantly at post60 (54.97 ± 27.63 %, $p = 0.018$) in the FCR, and at post15 (83.57 ± 20.86 %, $p = 0.028$), post30 (78.94 ± 18.53 %, $p = 0.028$) and post60 (72.15 ± 19.04 %, $p = 0.018$) in the ECRL. After HF-TENS, PRR amplitude reduced significantly at post45 (80.05 ± 14.84 %, $p = 0.028$) in the FCR.

A two-way ANOVA showed that intervention had a significant impact on PRR change from baseline in both the FCR and the ECRL ($p < 0.001$), however time point, nor a combination of these variables had a statistically significant impact. Further analysis on this data using a one-way ANOVA showed statistically significant differences occurring for ECRL PRRs between sham stimulation and active interventions (HF-tSCS and TENS) ($p < 0.001$). This was not seen in FCR PRRs.

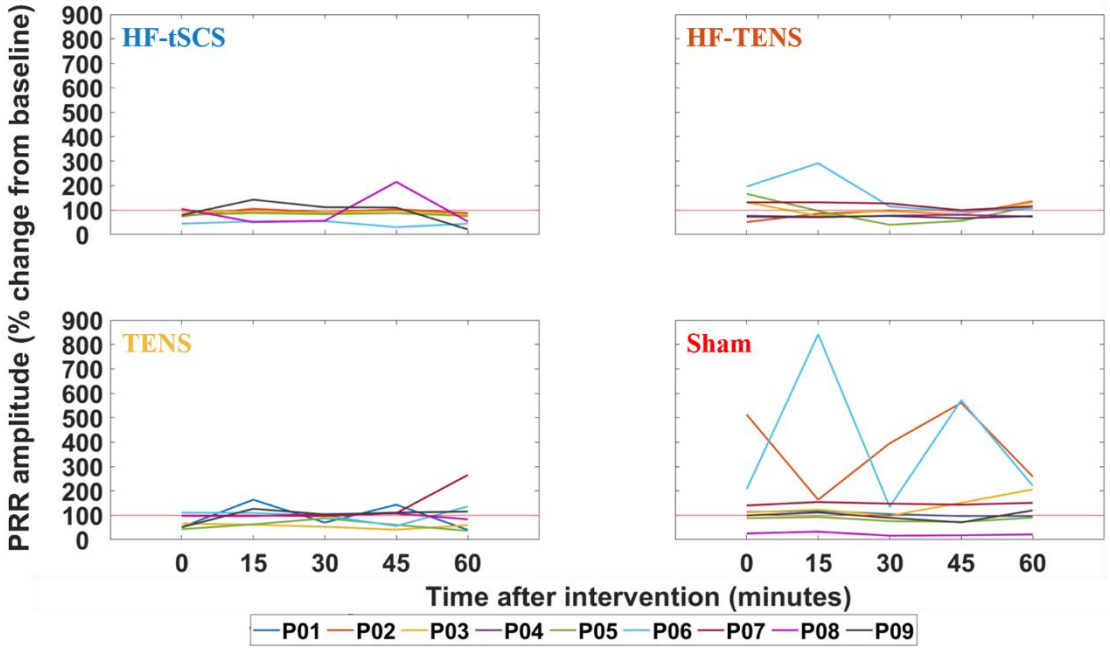

Figure 28: PRR amplitude (% change from baseline) in the FCR for individual participants in each intervention. (n = 7). Abbreviations: FCR = flexor carpi radialis, PRR = posterior-root reflex.

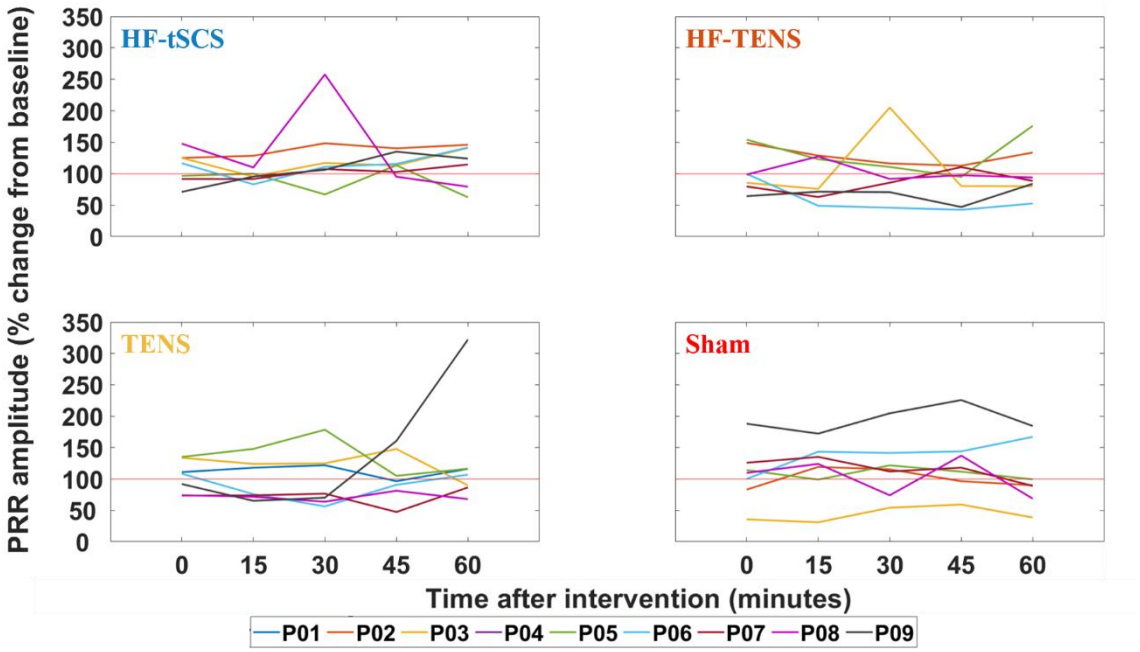

Figure 29: PRR amplitude (% change from baseline) in the ECRL for individual participants in each intervention. (n = 7), except for sham intervention, where (n = 6). Abbreviations: ECRL = extensor carpi radialis longus, PRR = posterior-root reflex.

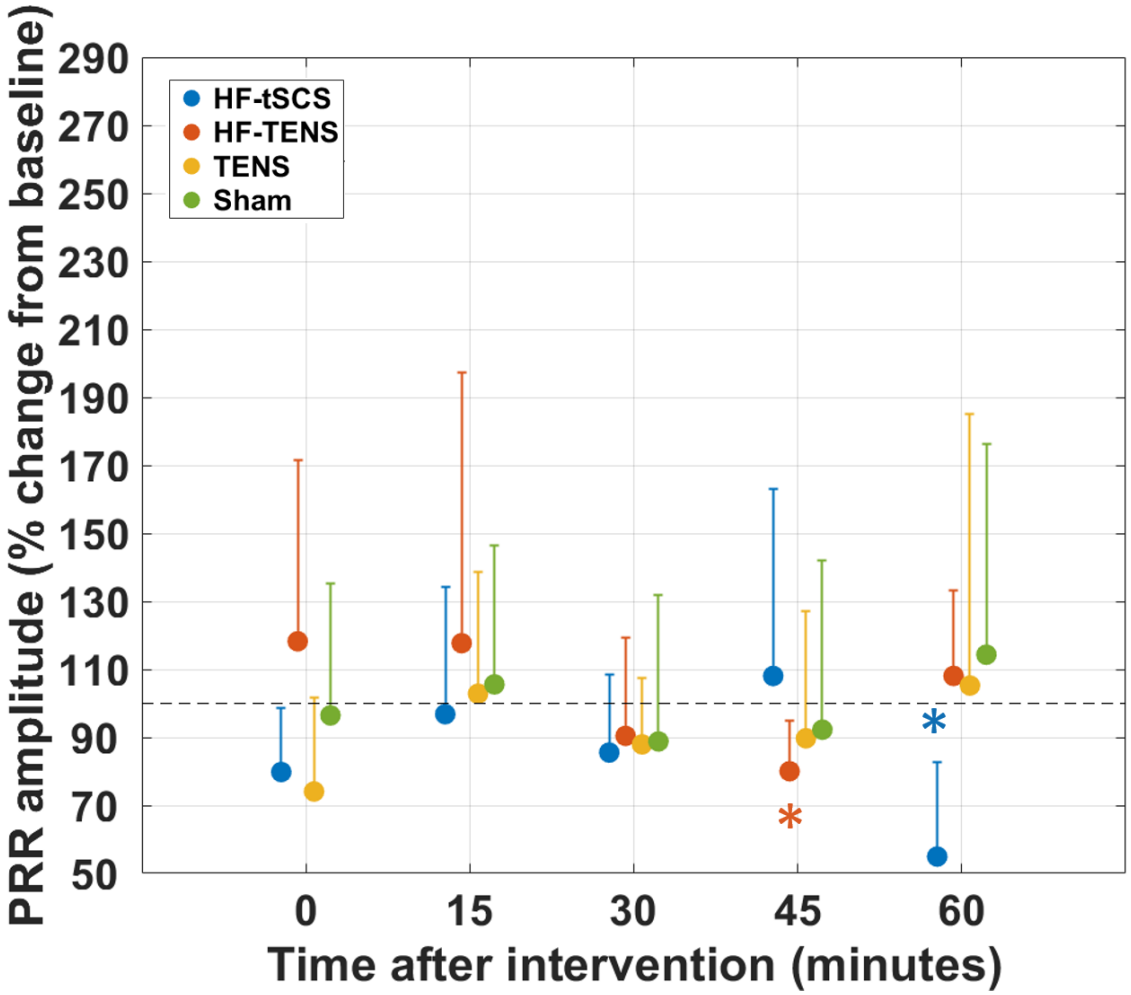

*Figure 30: Mean (SD) PRR amplitude (% change from baseline) in the FCR following each 30-minute intervention or sham. * represents a statistically significant difference in PRR amplitude from baseline ($p < 0.05$) following a Wilcoxon signed-rank test. (n = 7). Abbreviations: FCR = flexor carpi radialis, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, PRR = posterior-root reflex.*

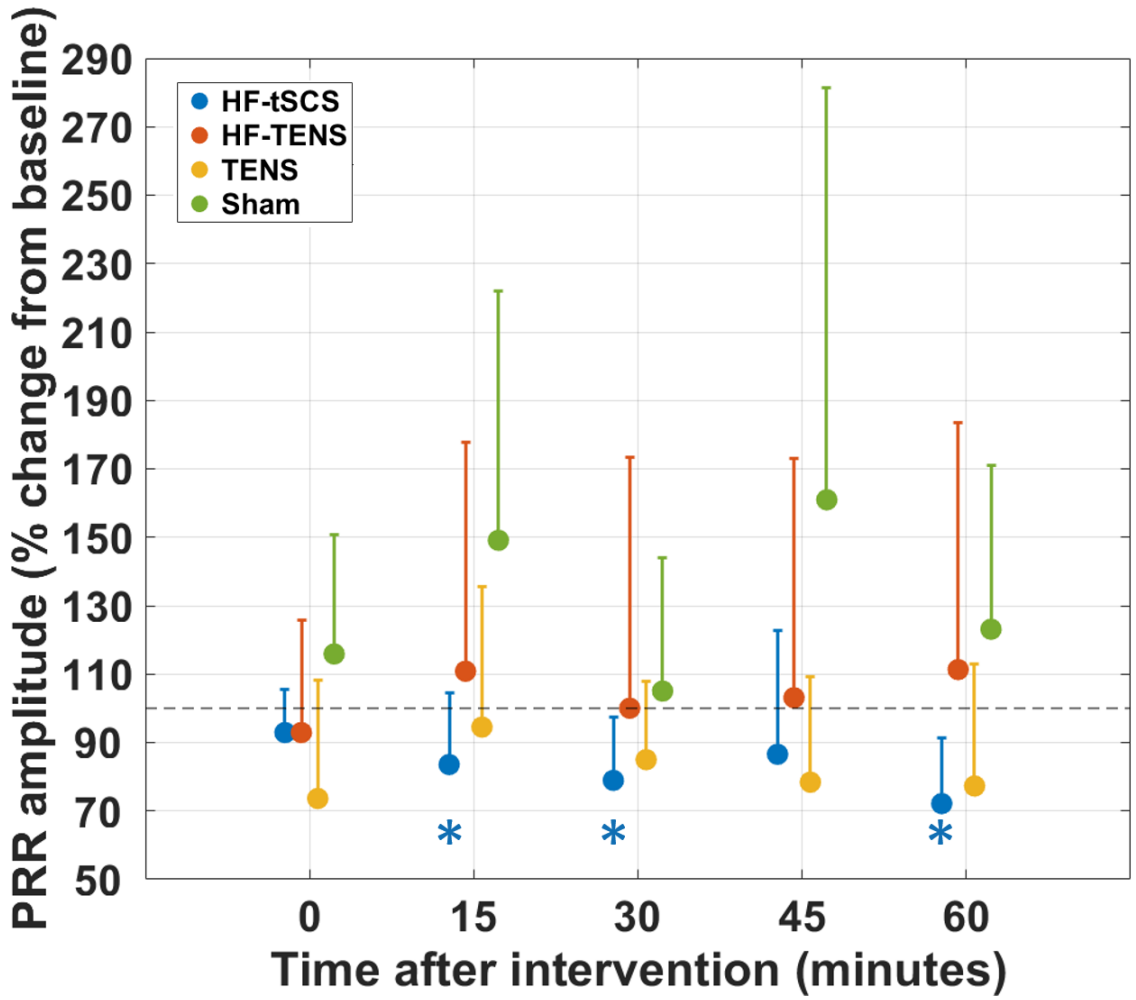

*Figure 31: Mean (SD) PRR amplitude (% change from baseline) in the ECRL following each 30-minute intervention or sham. * represents a statistically significant difference in PRR amplitude from baseline ($p < 0.05$) following a Wilcoxon signed-rank test. (n = 6). Abbreviations: ECRL = extensor carpi radialis longus, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, PRR = posterior-root reflex.*

3.4 *Changes in HD*

For participants where the preliminary test was carried out (n = 5), changes in the conditioned pulse from its control, at each time point of the experiment, are shown in Figure 32 and Figure 33. A reduction in HD represents greater spinal inhibition. Significant reductions in ECRL HD were found following HF-TENS at post0 (97.42 ± 5.12 %, $p = 0.043$) and following TENS at post60 (94.30 ± 11.87 %, $p = 0.043$). For participants who showed HD during the preliminary test, results are shown in Figure 34 and Figure 35.

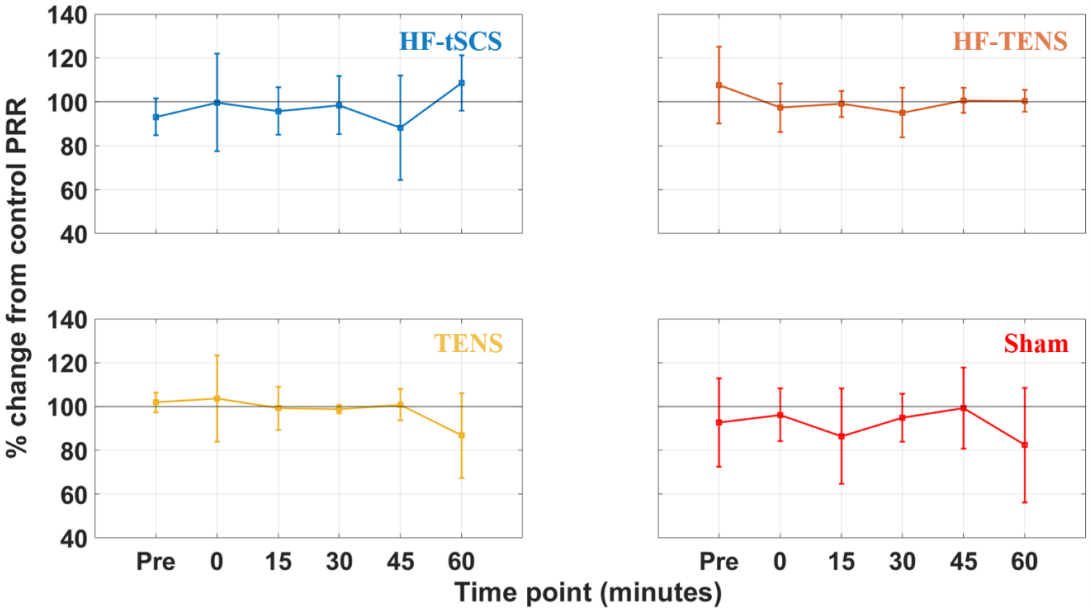

Figure 32: Mean (SD) HD (% change of conditioned PRRs relative to their control) in the FCR at each time point for all interventions, at an ISI of 1 s. (n = 5). Abbreviations: FCR = flexor carpi radialis, HD = homosynaptic depression, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, ISI = interstimulus interval, PRR = posterior-root reflex.

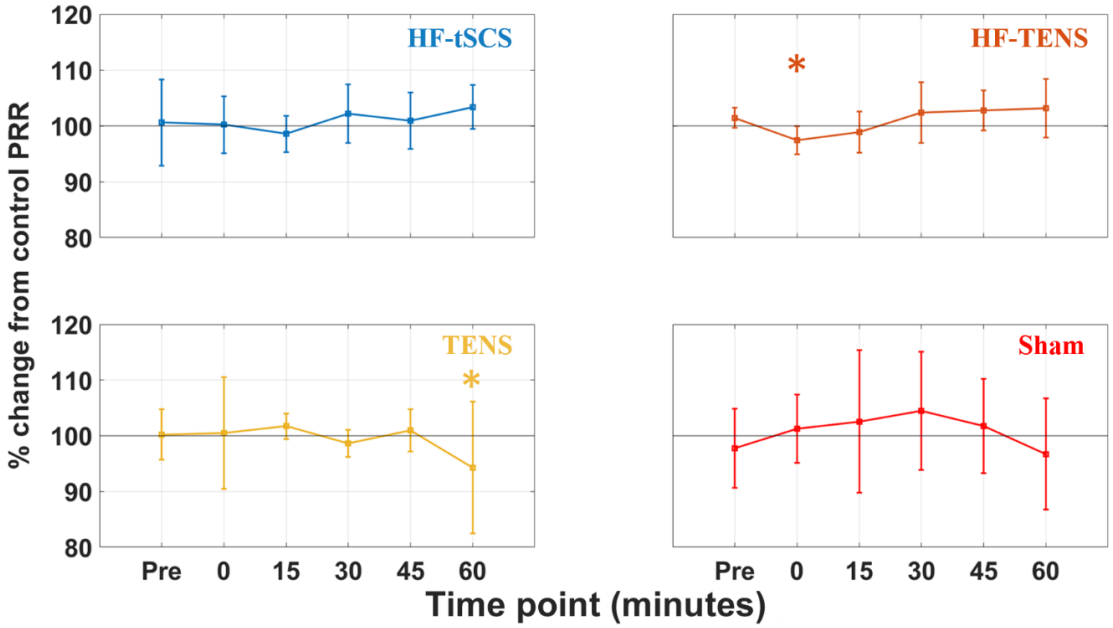

*Figure 33: Mean (SD HD (% change of conditioned PRRs relative to their control) in the ECRL at each time point for all interventions, at an ISI of 1 s. * represents a significant difference between baseline PRR amplitude for which $p < 0.05$. ($n = 5$) Abbreviations: ECRL = extensor carpi radialis longus, HD = homosynaptic depression, ISI = interstimulus interval, PRR = posterior-root reflex.*

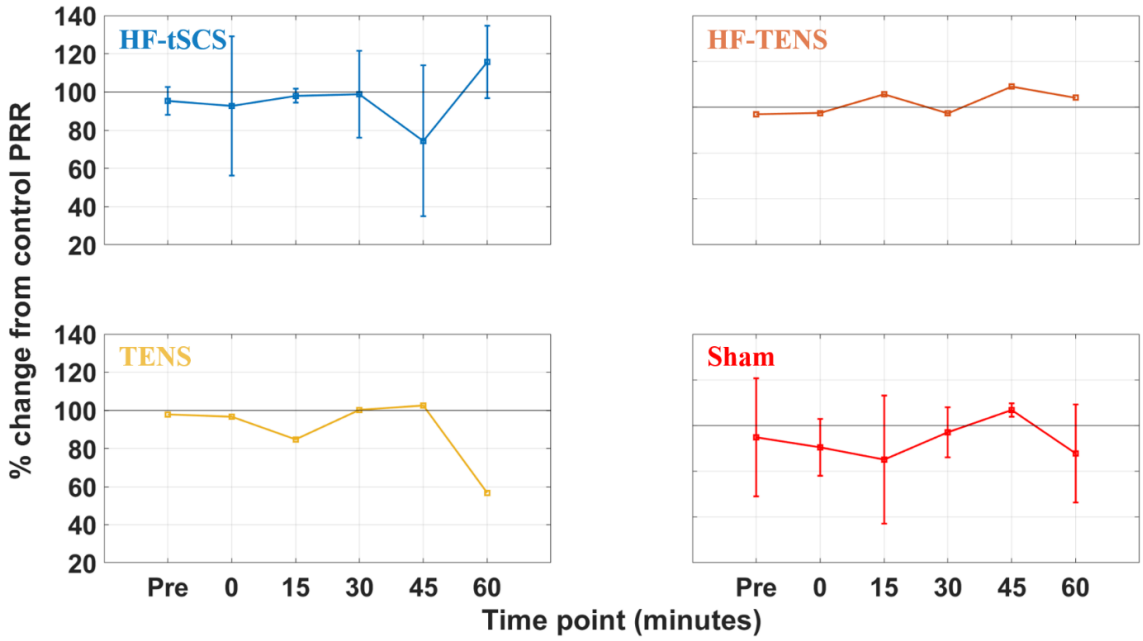

Figure 34:Percentage changes of conditioned PRRs from their control in the FCR at each time point in the experiment for participants who showed HD in preliminary tests. HF-tSCS (n = 2), HF-TENS (n = 1), TENS (n = 1) and sham (n = 3) interventions. Abbreviations: FCR = flexor carpi radialis, HD = homosynaptic depression, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, PRR = posterior-root reflex.

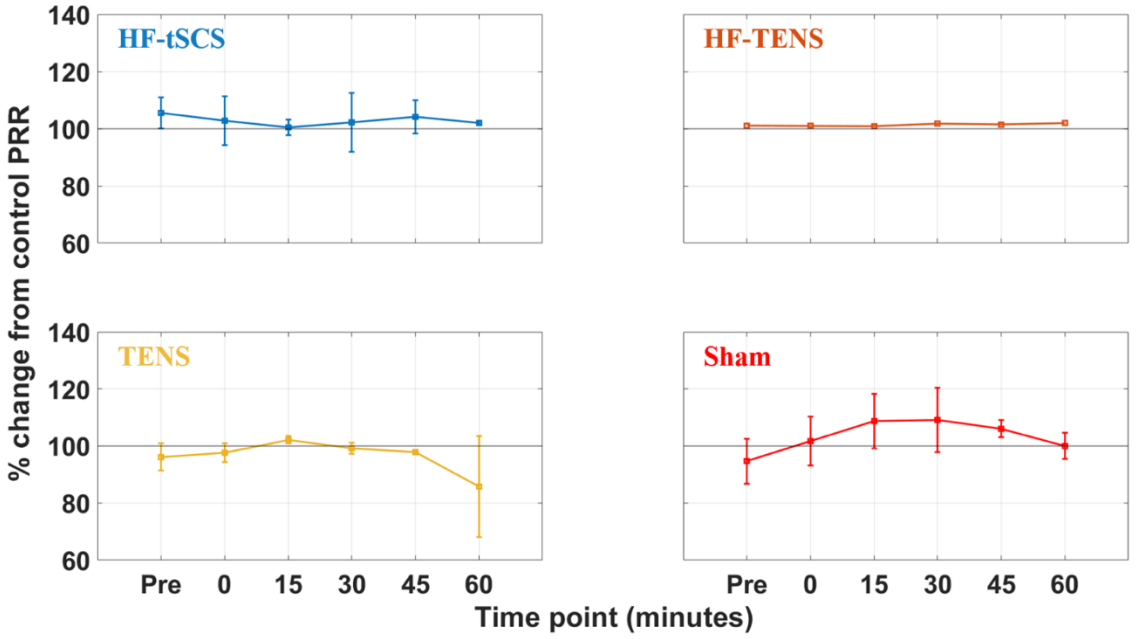

Figure 35: Percentage changes of conditioned PRRs from their control in the ECRL at each time point in the experiment for participants who showed HD in preliminary tests. HF-tSCS (n = 2), HF-TENS (n = 1), TENS (n = 2) and sham (n = 3) interventions. Abbreviations: ECRL = extensor carpi radialis longus, HD = homosynaptic depression, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, PRR = posterior-root reflex.

4 Discussion

4.1 *Summary of findings*

Results from this study show that corticospinal excitability may be modulated, and spinal excitability may be decreased, following 30 minutes of HF-tSCS. Mean FCR MEPs were significantly reduced from baseline. Following HF-tSCS, there was a significant decrease in ECRL PRRs at post15, post30 and post60, as well as a non-significant reduction in PRRs at post0, which agrees with findings from similar studies (Bertolasi et al. 1998; Tinazzi et al. 2005). These results are summarised in Table 11.

The results presented of changes in HD using PRRs were inconclusive in the current study. The low number of participants where HD was measured may have contributed to this uncertain finding.

Table 11: schematic summarising changes in MEPs and PRRs following each intervention. Dark green fields represent statistically significant reduction from baseline in the outcome measure, light green fields represent a reduction from baseline, blue fields represent no change from baseline and red fields represent an increase from baseline. Abbreviations: FCR = flexor carpi radialis, HD = homosynaptic depression, HF-TENS = high-frequency transcutaneous electrical nerve stimulation, HF-tSCS = high-frequency transcutaneous spinal cord stimulation, PRR = posterior-root reflex.

Measure	Muscle	Intervention	Post0	Post15	Post30	Post45	Post60
MEPs	FCR	HF-tSCS					
		HF-TENS					
		TENS					
		Sham					
	ECRL	HF-tSCS					
		HF-TENS					
		TENS					
		Sham					
PRRs	FCR	HF-tSCS					
		HF-TENS					
		TENS					
		Sham					
	ECRL	HF-tSCS					
		HF-TENS					
		TENS					
		Sham					

4.2 *Changes in MEP amplitude*

Results from this study show how different waveforms of ES delivered over the spinal cord and peripheral nerves have varying effects on centrally mediated neurophysiological signals. Although changes in MEP amplitude following HF-TENS and TENS were not

statistically significant, there was a trend of decreased excitability in the FCR up to post30, with a trend of increased corticospinal excitability in the ECRL following HF-tSCS. Data from each active intervention suggests that HF-tSCS was most effective at triggering DI in MEPs; i.e., increasing excitability in the extensor while decreasing excitability in the flexor. This has also been reported in several other studies (Bertolasi et al. 1998; Tinazzi et al. 2005).

In sham stimulation, there was a large variability in MEP amplitude, suggesting that MEPs may vary simply by taking part in this experiment. A two-way ANOVA revealed no statistically significant differences between interventions (including sham), time points or their interaction, showing that no intervention is more effective than another at altering corticospinal excitability. By comparing directly between each active intervention and sham stimulation, this finding was reinforced in MEP data.

A reduction of at least approximately 50 % of flexor MEP amplitude following neuromodulation has been reported following TENS at 10-200 Hz (Mang, Lagerquist, and Collins 2010) and 90 Hz (Mima et al. 2004) in the upper limb, and at 150 Hz for the lower limb (Tinazzi et al. 2005). This extent of depression was not seen in averaged results here, however reductions of approximately 50 % of baseline, following HF-tSCS and TENS, is seen in some individuals (see Figure 24).

A potential difference causing DI in the aforementioned studies, but not with TENS in the current study may be the current density delivered to participants. This can either differ due to a smaller surface area of stimulation electrodes, or higher stimulation intensities being used. The average current density of TENS in our study was 10 Am^{-2}. Other studies delivered considerably more (29 Am^{-2} (Mima et al. 2004) and 55 – 80 Am^{-2} (Tinazzi et al. 2005)). Current activates more afferent nerve fibres, therefore leading to more afferent input, which may increase triggering of inhibitory mechanisms. Mima et al. has proposed a correlation between a decrease in sensory threshold and a decrease in corticospinal excitability, when TENS is applied over the hand (Mima et al. 2004). They suggest that TENS decreases the probability of excitatory inputs to corticospinal neurons; results from the current study compared others, imply that this reduction may be dose dependent.

A study by Serrano-muñoz et al. (2019) investigated differences between H-reflex amplitude and latency when tSCS was delivered to the lower limbs at 100 Hz and 10 kHz,

compared to sham stimulation. These authors measured a significant inhibition of the H-reflex following 40 minutes of 100 Hz tSCS. This study also showed a significant increase in H_{max} latency of 0.23 ms following 10 kHz stimulation, versus 100 Hz and sham stimulation. This delay was observed 10 minutes after the intervention.

This study used current densities of 13.1 Am^{-2} and 21.2 Am^{-2} for 100 Hz and 10 kHz tSCS respectively. They hypothesise that a higher stimulating intensity is required when stimulating with higher frequencies (Serrano-Munoz et al. 2019). For HF-tSCS, a current density of 19 Am^{-2} was used. This may explain the more pronounced effect in this participant cohort following HF-tSCS compared to TENS.

4.3 *Changes in PRR amplitude*

Although there is no consistent trend among participants for changes in PRR amplitude following each intervention; some participants showed a generalised reduction in this measure, and therefore spinal excitability (see Figure 28 and Figure 29). This inconsistency has been found in similar studies, investigating the effects of TENS on the H-reflex (Goulet et al. 1994; Tinazzi et al. 2005) and PRRs (Milosevic, Masugi, Obata, et al. 2019). For experiments carried out by Tinazzi et al., MEPs were also measured in the FCR and ECRL, where DI was also seen (Tinazzi et al. 2005). This will be further discussed in upcoming sections.

Results showed statistically significant differences in ECRL PRR amplitudes when delivering sham stimulation, compared to delivering HF-tSCS and TENS. This direct comparison suggests that HF-tSCS and TENS interventions are capable of reducing spinal excitability in the ECRL, beyond the effects caused by taking part in the experiment alone.

Data from sham stimulation in participants 2 and 6, which were excluded from the averages used for the statistical analysis, show a large increase in PRR amplitude from baseline, with values ranging from approximately 200 % and 850 %. During the experiment performed on participant 2, temperatures were approximately 29 °C. Participant 6 stood up during a 15-minute interval during their experiment. The room temperature varied between participants, ranging between 17 °C and 32 °C, Cooler temperatures are thought to have a greater impact on H-reflex amplitude compared to warmer temperatures; with cooler temperatures acting to increase amplitude (Dewhurst et al. 2005). However, room temperature would have been similar during individual

sessions, and results have been presented as relative change from baseline. Although this may be a factor influencing the overall extent of changes seen in outcome measures, the significant changes seen across all participants are likely to be due to the interventions given.

Movement during the experiment may also have increased PRR response. Body position is known to influence which underlying structures are stimulated by tSCS (Danner et al. 2016). It is possible that when the participant stood up during the experiment, their resting position was altered compared to their position during set-up, causing this change in excitability.

4.4 *Changes in HD*

The results show that a change in HD from its baseline measured only occurred in the ECRL at post0 for HF-TENS ($p = 0.043$) and at post60 for TENS ($p = 0.043$). These results are based on 5 participants. Figure 34 shows a more pronounced reduction in PRR from its baseline at post60, compared with other time points in one participant (participant 7). Further testing is required to determine whether future results would agree with the large decrease in HD, seen in this participant, as it can be seen in Figure 33 that there is a large variation between participants at this time point, following TENS.

4.5 *Stimulated structures and modulated pathways*

DI triggered in MEPs and not in spinal reflexes has been cited in studies which investigated the effects 30 minutes of 150 Hz TENS in the upper limb (Tinazzi et al. 2005). This result was also seen in the current study, with DI present in corticospinal signals, and a trend of reduced spinal excitability in the antagonistic muscle pair. This suggests that, in the current study, HF-tSCS may have modulated DI within the motor cortex (Tinazzi et al. 2005; Bertolasi et al. 1998). This is supported by Benavides et al. (2020), where tSCS with a 5 kHz carrier frequency was shown to contribute to cortical inhibitory effects, whereas tSCS without this kHz carrier frequency did not. Although the current study did not include a direct comparison between tSCS with and without the 10 kHz carrier frequency (to be discussed in the following sub-section), this potential to modulate the cortical pathway using a kHz carrier frequency is shown in the significant changes in MEP amplitude seen following HF-tSCS.

A reduction in PRRs following HF-tSCS were seen until post60 in the ECRL, and a trend in the reduction of FCR PRRs was seen at post60. This may have occurred due to a

reduction in motoneuron excitability, however further investigation is required. This is a change known to coincide with the increase of DI in populations with spasticity (Nielsen, Crone, and Hultborn 2007; Crone et al. 2003).

Changes in MEPs measured in other studies using TENS interventions show that afferent input to the nerve may also cause ascending input (Tinazzi et al. 2005; Mima et al. 2004; Bertolasi et al. 1998; Mang, Lagerquist, and Collins 2010). Results from the current study show a non-statistically significant reduction in FCR MEPs of approximately 90 % of baseline until post30, following TENS, as well as reductions in FCR and ECRL PRRs at post0. Further investigation is required to determine whether TENS and HF-tSCS may have similar effects on the CNS.

Statistically significant reductions in FCR MEPs show that there may be potential that HF-tSCS could be most beneficial in upper limb spasticity management of the 3 forms of neuromodulation tested here. Its superiority over TENS and HF-TENS may be due to its higher current density, causing a larger amount of afferent input.

4.6 *Limitations*

This study aimed to determine the neurophysiological effects of 30 minutes of neuromodulation for up to an hour after it had been administered. However the design of this study gives rise to possible changes in CNS excitability, since it requires participants to remain supine for this period (Crone et al. 1999). Although there were significant differences in ECRL PRRs between HF-tSCS and TENS and the sham intervention, this was not the case for any other outcome measure. It is difficult to alleviate this issue, however, since giving participants breaks, allowing them to move during the experiment, may give rise to its own issues due to the marginal shifts of the underlying anatomy in respect to the stimulating electrodes (Danner et al. 2016).

There was no direct comparison between HF-tSCS and a 100 Hz equivalent in this study. This is due to the higher current density which would be delivered in this case, which would activate the back muscles and potentially cause pain to participants when continuously delivered for 30 minutes. Due to the potential dose-dependency (Mima et al. 2004), delivering 100 Hz tSCS to populations with spasticity may give rise to larger increases in DI, decreases in spinal excitability, and therefore may have the potential to mitigate symptoms of spasticity more effectively (in those whose spinal lesions allows them to tolerate the sensation of tSCS at 100 Hz). This has been shown with 50 Hz tSCS

in populations with lower limb spasticity, arising from SCI (Hofstoetter et al. 2020; Hofstoetter et al. 2014).

5 Conclusion

Results from this study show the potential benefits of using HF-tSCS for spasticity management. FCR MEPs and ECRL PRRs were reduced. We can therefore speculate that DI has been modulated at a cortical level, with a generalised reduction in spinal excitability, in agreement with other studies (Bertolasi et al. 1998; Tinazzi et al. 2005).

However, the current density of TENS delivered in this study is significantly less compared to others in the literature (Mima et al. 2004; Tinazzi et al. 2005). This, with the superiority of HF-tSCS compared to TENS in this experiment, implies that there may be a dose dependency, which may increase afferent inputs, when modulating desirable mechanisms known to reduce symptoms of spasticity.

Although further study is required to strengthen these findings, literature using kHz tSCS has also shown its potential in modulating CNS excitability (Benavides et al. 2020) and reducing spasticity in the lower limb (Hofstoetter et al. 2014; 2020).

IV. Design of a mobile application for the self-management of spasticity through education of triggers

This chapter presents the development of a mobile app which logs intrinsic and extrinsic triggers of spasticity. Once the user has logged an event, they are able to view these as easy-to-read graphs. The aim of developing this app was to enable remote, self-assessed outcome measure during our planned clinical trial. However, it was also designed to allow much wider applications; in particular, as a clinical too to assess whether people with spasticity manage their symptoms through the awareness of the exasperating factors which trigger their spasticity. Subsequent sections of this chapter outline the initial design of this app and its assessment using questionnaires designed for potential app users and clinicians who work with people with spasticity.

Uncontrolled muscle contractions occurring from spasticity can be triggered as an aberrant response to muscle stretch (Kheder and Nair 2012). This muscle stretch can occur with a variety of movements, including during activities of daily living. Other intrinsic and extrinsic factors can also contribute to the onset of a spastic contraction, such as changes in temperature, bladder activity and stress (Phadke et al. 2013; Cheung et al. 2015; Kheder and Nair 2012; Nair and Marsden 2014). At the Royal National Orthopaedic Hospital, the first means of spasticity management, before exercise and medication, are to identify the factors affecting the individual (Royal National Orthopaedic Hospital Trust 2019).

In recent years, there has been an increase in the use of healthcare apps, both for general use (Free et al. 2013), and for the management of chronic diseases (Agarwal et al. 2021). Methods of monitoring or managing one's health using an app include: users messaging via text and video with their clinicians; automated reminder or motivational messages; medication monitoring; food diaries and nutritional information (Hamine et al. 2015; Free et al. 2013). The efficacy of apps whose purpose is to manage chronic diseases is often underreported due to the lack of summative evidence (i.e. there has been no quantitative assessment of the effect of the app on the disease being investigated) (Agarwal et al. 2021).

Apps which use self-reported data as feedback have had previous success in the management of diabetes. In one study, users could log their diet, blood glucose levels,

medication, physical activities and mood (Nes et al. 2012). Users would receive individual feedback from a therapist who had immediate access to each user's log. It was found that the use of feedback and app promoted positive lifestyle changes and benefitted user's management of their diabetes. A meta-analysis of the use of mobile phones for self-management of diabetes also found improvement in blood sugar levels and self-care (Liang et al. 2011); with little difference in improvement found between the type of intervention, such as: feedback via text message, monitoring of blood sugar levels and diet and personalised and goal-orientated messages. This example of diabetes shows that self-management of health through mobile phones can have a significant impact on education and management techniques adopted by the users.

Previous studies have shown success in the development of apps for pressure sore prevention (Amann et al. 2020) and other self-management programmes for people with SCI (Mortenson et al. 2019). However, an app which aims to aid self-education and self-management of spasticity through identification of the user's triggers has not yet been developed.

The primary outcome measure of spasticity used in this app is the Penn Spasm Frequency Scale (PSFS). This self -assessed measure takes < 5 minutes to complete (Patricia B. Mills et al. 2018). This scale has two components: the frequency of the spasm (from 1 being mild spasms, to 4 being spasms occurring more than 10 times per hour), and the severity of the spasm (from 1 being mild, to 3 being severe) (see Table 3 for detailed description of this scale). The app enables users to log the trigger of a spasm, rate it according to the PSFS, select the time of day it occurred and where on their body it occurred. Relating this outcome measure to a trigger, time of day and body part may support self-education and promote self-management of spasticity.

The app was developed such that it could be used in two different scenarios: by people taking part in a clinical trial where the effects of an intervention on spasticity were being assessed; and by people who would be using the app for self-management of spasticity through understanding intrinsic and extrinsic triggers causing muscle spasms. In the former case, users would be able to log triggers of their spasticity and rate the triggered spasms using the PSFS, but not be able to look at the data that had been previously logged. In the latter cases, users would have access to the feedback from data that had been previously logged. Since the clinical study which was planned to be part of this thesis

could not take place due to the COVID-19 pandemic, this chapter will focus on the latter case only.

Following an initial design of the app, questionnaires were sent to potential users and the clinicians who work with people with spasticity. This was to include end-users and their clinicians in the design process. Should a second version of this app be developed, it could be done so with this information in mind, creating a user-centred designed app.

The following sections present the initial design of this novel app, followed by assessment by potential users and clinicians who work with people with spasticity.

1 Design process: towards user-centred design

1.1 *App design and process*

An initial design of the app was created. The back- and front-end of the app was then developed with a team of UCL Computer Science MSc students.

Following the initial design outlined in subsequent sections, two questionnaires were developed to assess the feasibility and usability of the app design, function and feedback tools. These were aimed at 2 separate populations: people with spasticity (potential app users) and for clinicians who work with people with spasticity.

1.2 *App development considerations*

The populations which this app is intended for are those who have spasticity. Since this population may also have functional upper limb impairments, selectable functions within the app have large buttons, so that they would be easier to select for those with low dexterity, or with the use of other smartphone accessibility features such as switch input control. Switch input allows users with low dexterity to interact with their phones using a single switch.

The initial app design allows users to log a spastic contraction linked to a trigger, which they can either select from a list, derived from the literature (Cheung et al. 2015; Kheder and Nair 2012; Phadke et al. 2013; Nair and Marsden 2014), or add a trigger themselves. The user then rates this spasm using the PSFS, selects where on the body the spasm occurred and the time of day this occurred. They may also add a comment, which may be used for logging changes to anti-spasticity medication, for example.

1.3 *Setting up a user profile and personal data handling*

This app is designed to log and store triggers of spasticity, the severity and frequency of the triggered spams, using the PSFS, the time of day the spasm occurred, where on the body this occurred, and any comments the user may have. This data may be considered as sensitive as it relates to the user's medical condition and so is protected under the General Data Protection Regulations.

Therefore, to create a secure and safe way to log this data, the app was designed so that users would need to create a unique username and password to log into the app. When a user would log their data, this was then stored and hosted on Azure (Microsoft, Washington, USA). For the researcher to access this data, the user would have to

voluntarily share this data by exporting a report as a PDF file, via an email, which is created for them within the app. This gives the user control over their own data, as well as creates a secure email, which is not linked to their own private email.

When the participant registers with their username and password to use the app, they are also asked whether they are using this app as part of a clinical trial, shown in Figure 36. If the user selects that they are a part of a clinical trial, they will not have access to their logged data within the app (other than in the PDF report). This is to prevent the app influencing the clinical trial, where feedback from the app may alter any effects of the intended intervention. If the app user deselects the 'Clinical Trial' box, they will have access to their logged data.

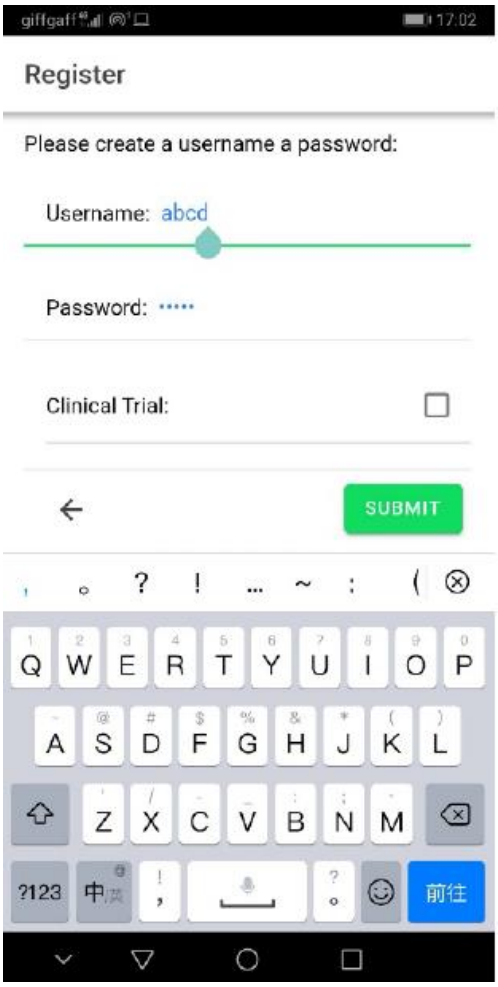

Figure 36: Registration screen. Users can choose their own username and password and select whether they are using this app as part of a clinical trial. Shown on Android platform.

1.4 *Logging an event*

Once a user has set up their own profile, they are then ready to use the app. In this initial design, the ‘Main Menu’ icon is where triggers of spasticity can be logged. The triggers available in the app are categorised as: bladder/bowel/sexual function; temperature; time of day; posture; skin; or the user has the option of adding their own trigger (Table 12), which will be saved for later use (see Figure 37 (left)). Once the user has chosen their category, they are then shown the specific triggers within that category (Figure 37 (right)). See Table 12 for the full list of available specific triggers. They can also add their own specific trigger here, which will be saved for later use.

Once the user has chosen their specific trigger, they will be asked to select a rough estimate of where their spasticity occurred on their body, as shown in Figure 38. They will then be taken to the screen shown in Figure 39, where they will select the time of day their spasticity occurred.

The user will then be asked to rate their spasm using the PSFS. The two components of the PSFS are shown in Figure 40.

The user will then be asked if they would like to enter any comments regarding their input, or they can skip this section. Once submitted, this input will be time stamped.

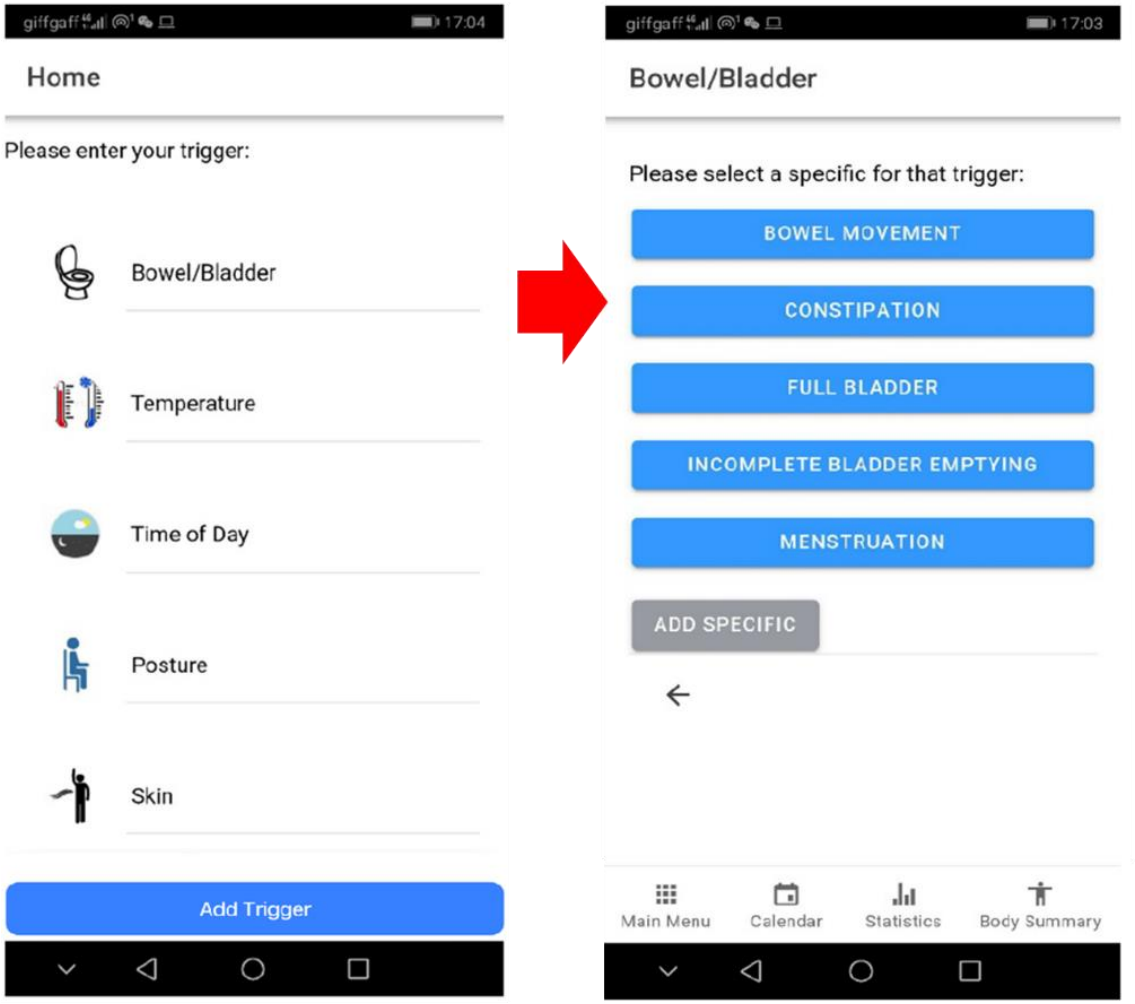

Figure 37: (Left) user home screen where categories of triggers, or the option to add their own trigger is available. (Right) the specific triggers available to log for one category. The user also has an option to add their own specific trigger in this category. Shown on Android platform.

Table 12: Categories and specific triggers of spasticity available as default on the app.

Category	Specific trigger
Bladder/bowel/sexual function	Bowel movement
	Constipation
	Full bladder
	Incomplete bladder emptying
	Menstruation
	Urinary tract infection
Temperature	Inside cold
	Outside cold
	Outside heat
Time of day	Morning
	Afternoon
	Night
Posture	Changing position
	Lying on your back
	Making transfers
	Sitting (improper?)
Skin	Pressure ulcers
	Tight clothing
	Loose clothing
	Tight splint/orthosis
	Light touch

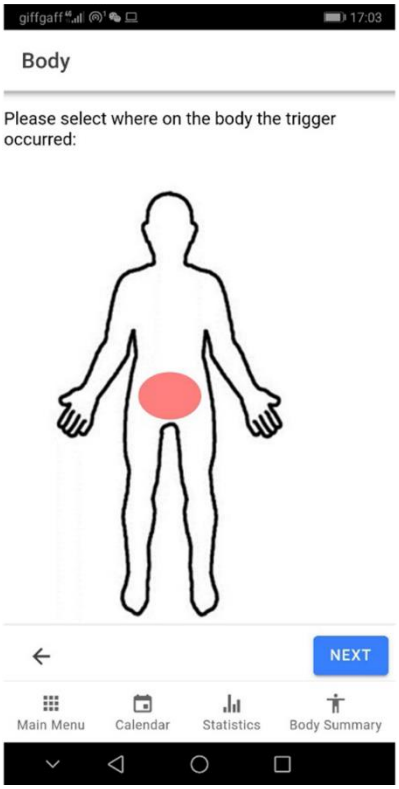

Figure 38: Users select an approximation of where on their body their spasticity occurred. Shown on Android platform.

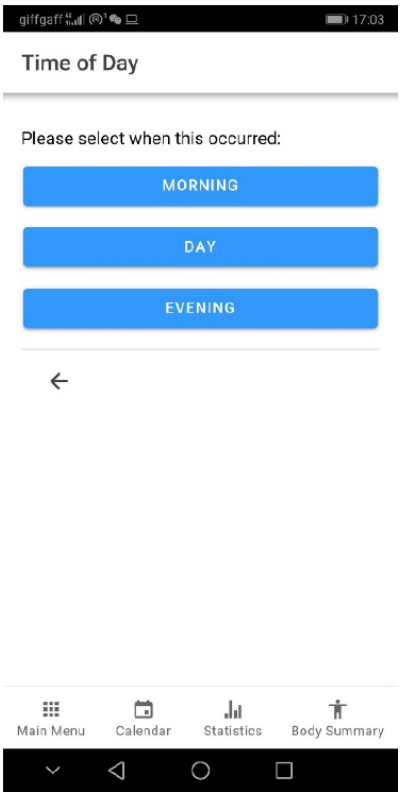

Figure 39: The user will be asked to select the time of day their specific trigger affected them. Shown on Android platform.

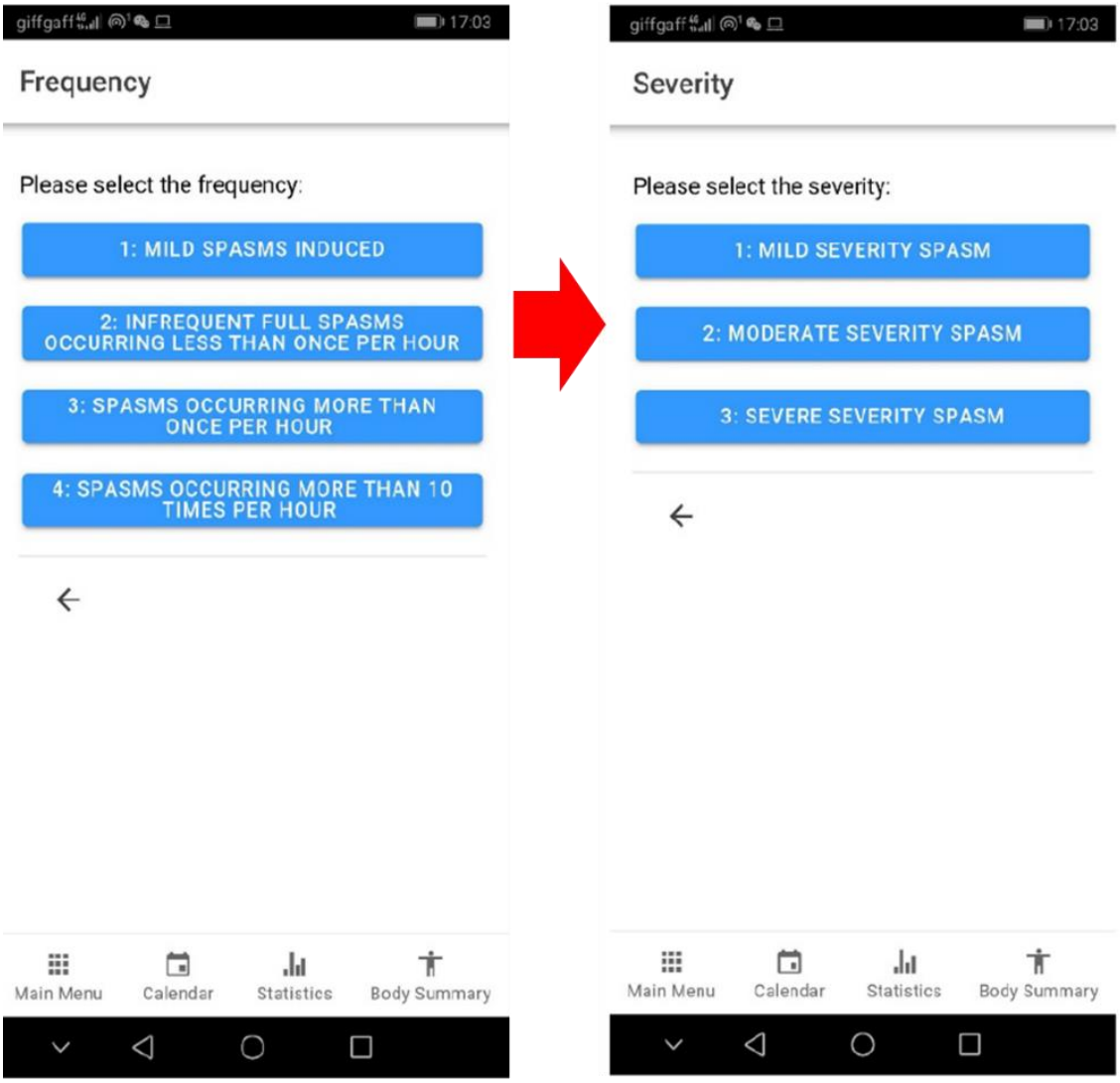

Figure 40: (Left) the frequency aspect of the PSFS and the descriptions for each scale point. The user will then progress to the severity aspect of the PSFS (Right) and the description for each scale point. Shown on Android platform.

1.5 *Reviewing logged events for feedback*

For users who are not part of a clinical trial, feedback of their logged triggers of spasticity will be available to them by selecting the 'Calendar' icon in the toolbar. This data will be available in the form of a summary of the number of events on a specific day. The day summary will categorise these in the initial trigger categories available, or for the new trigger category the user may add, as shown in Figure 41. A user may click on each category shown in the red boxes, which will then show the specific triggers, shown in the blue box.

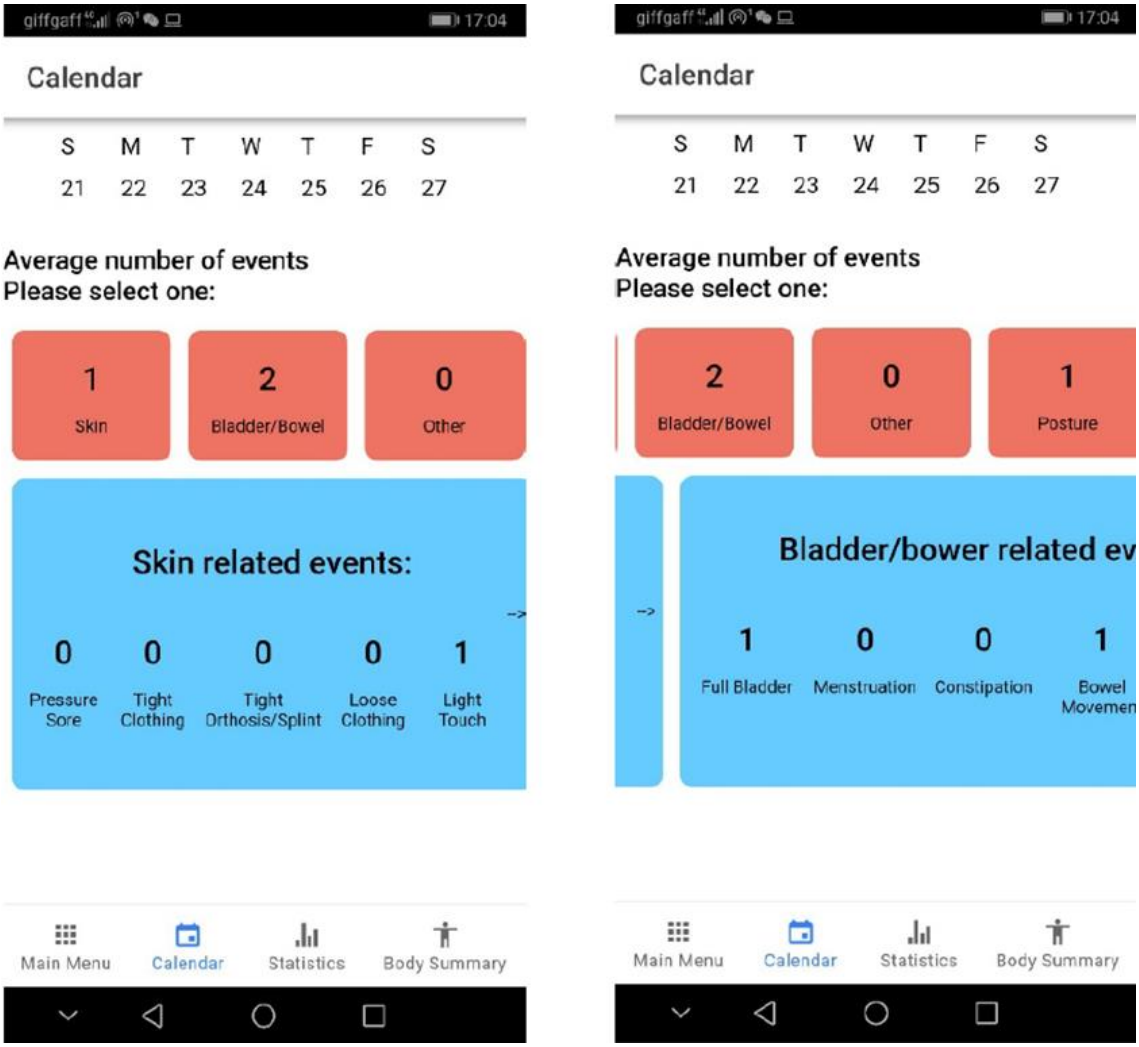

Figure 41: Day summary of triggers within their categories (red boxes). Users may select a category to view which specifics triggered spasticity (blue box). Left shows a summary for skin-related events and right shows a summary for bladder/bowel/sexual function-related events.

A summary of their ratings of each spastic event can also be seen by selecting the 'Statistics' icon in the toolbar. This will give you a choice of selecting the day (D), week (W) or month (M) view of your triggers and their rating according to each aspect of the PSFS, which are shown in separate graphs (see Figure 42). Each graph will show an individual trigger category. The coloured bars on the graph represent specific triggers for a category which are also presented in the legend. The user will scroll through these graphs to view each category.

Figure 42:Day and week summaries of spasticity triggers for skin-related events.

When the ‘Body Summary’ icon is selected, the user will be able to view a summary of where on their body their spasticity occurred (Figure 43). In this section, the deeper red shapes represent locations on the body where a spastic event is more frequently logged. This summary is also available for day (D), week (W) and month (M) view.

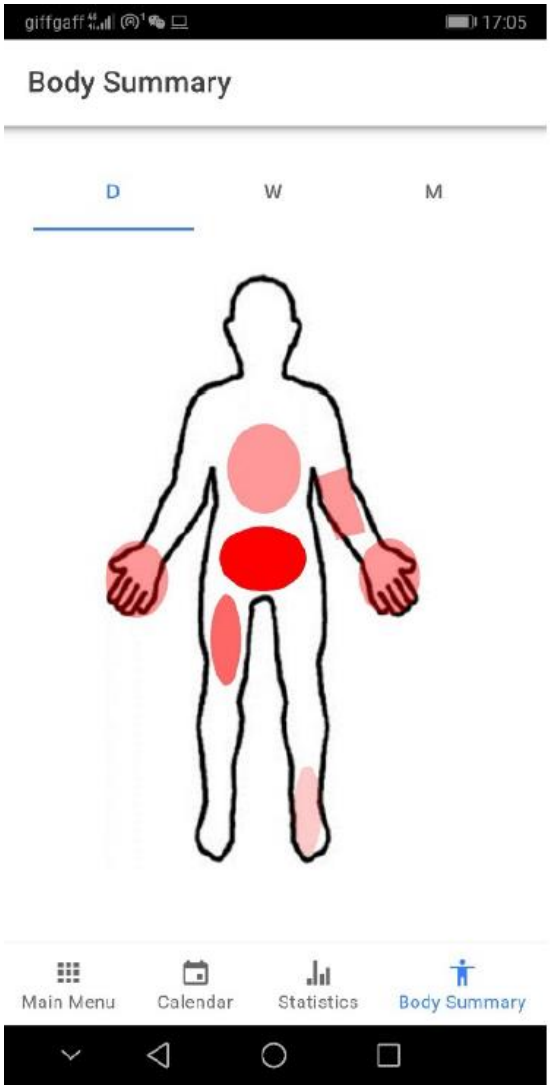

Figure 43: Body summary of where on the body spasticity occurred. Red patches will appear a deeper red when users log their spasticity in that location more frequently, and a more translucent red when they are logged less often.

2 Assessment of app design

The app design presented above shows the early stages of its development. The aims of the following assessment were to assess: i) the user acceptance; ii) user interpretation of feedback; iii) potential efficacy of the app; iv) clinical use of the app and its relevance to their patient; v) awareness of triggers of spasticity and vi) relevance of the triggers listed in the app.

2.1 *Methods*

2.1.1 Participants

Ethical approval for this study was granted by the UCL ethics committee. People with spasticity and clinicians who work with people with spasticity (e.g. physiotherapists, occupational therapists, nurses) were asked to watch an instructional video, or attend a demonstration, and fill in one questionnaire. The questionnaire they were asked to complete was different depending on whether they were a person with spasticity or a clinician.

Potential participants were recruited via email, poster advertisements, social media and in research seminars, where the video (although not in the case of the seminars) and questionnaires were made available to them via a URL link or a QR code. Consent to take part in this study was assumed upon completion of the questionnaire.

2.1.2 Questionnaire and instructional video

To investigate the feasibility of this app as a spasticity management tool, an instructional video was created to guide to viewer through how to log an event (spasticity occurring) and how to view logged events. This video was also given as a talk in research seminars. Questionnaires were created using the web-based survey tool Opinio (UCL). Participants complete their questionnaires on this website where their answers were stored, and a summarising report was created.

The themes assessed in the questionnaire given to both people with spasticity and clinicians were:

1. Perceived usefulness of the app for spasticity management,
2. Awareness of spasticity triggers,
3. Clarity of the app design (including the graphs presented),

4. Relevant triggers of spasticity (see Table 13 and Table 14 for the full questionnaire).

The themes relevant only to people with spasticity were:

5. Methods of app use,
6. User acceptance.

Themes assessed relevant to clinicians only were:

7. Reliability of the data collected within the app,
8. How the app may benefit outpatient appointments.

Table 13: Questionnaire for people with spasticity.

1. Do you think this app would be useful for your spasticity management?

☐ Yes ☐ No ☐ Maybe

2. Do you think you'd only use this app if a clinician told you to?

☐ Yes ☐ No ☐ Maybe

3. Are you aware of what triggers your spasticity?

☐ Yes ☐ No ☐ To some extent

4. How many times in a day is your spasticity triggered?

☐ Never ☐ Once ☐ Twice ☐ Three or more

5. How many times in a day would you use this app to **review** the triggers of your spasms?

☐ Never ☐ Once ☐ Twice ☐ Three or more

6i. Would you **update** the triggers of your spasticity each time they occur during the day?

☐ Yes ☐ No ☐ Maybe

6ii. Would you prefer to **update** the triggers just **once**, at the end of the day?

☐ Yes ☐ No ☐ Maybe

7. Do you think this app would be easy to use?

☐ Yes ☐ No ☐ Maybe

8. Do you think you will be more aware of your triggers with this app?

☐ Yes ☐ No ☐ Maybe

9. Are the triggers listed below relevant in your opinion?	Yes	No
Bowel movement	☐	☐
Changing position	☐	☐
Constipation	☐	☐
External temperature	☐	☐
Frequent naps during the day	☐	☐
Full bladder	☐	☐
Incomplete bladder emptying	☐	☐
Ingrown toenail	☐	☐
Lying on your back	☐	☐
Making transfers	☐	☐
Menstruation	☐	☐
Muscle fatigue	☐	☐

Pressure ulcers	☐	☐
Sitting	☐	☐
Skin	☐	☐
Stress and anxiety	☐	☐
Tight clothes	☐	☐
Tight splint/orthosis	☐	☐
Tiredness/drowsiness	☐	☐
Time of day	☐	☐
Unable to sleep at night	☐	☐
Urinary tract infection	☐	☐

Other?

……

……

10. Is the design of this app simple and clear?

☐ Yes ☐ No

11. Are the graphs presented here easily interpretable?

☐ Yes ☐ No

12. Are the graphs presented here useful?

☐ Yes ☐ No

13. Would you want to use this app?

☐ Yes ☐ No ☐ Maybe

14. Would you consider it to be useful to have information about where your spasticity occurred each time it was triggered?

☐ Yes ☐ No

15. Would you want feedback from the app when your spasticity has decreased?

☐ Yes ☐ No

16. Are there any other comments you would like to add?

……

……

Table 14: Questionnaire for clinicians who work with people with spasticity.

1. Do you think using this app could benefit your patient's spasticity management?

☐ Yes ☐ No ☐ Maybe

2. Would you encourage your patients to use this app?

☐ Yes ☐ No ☐ Maybe

3i. How many of your patients do you think recognise the triggers of their own spasticity?

☐ All ☐ Many ☐ Half ☐ Some ☐ None

3ii. To which extent do you think these patients can recognise the triggers of their spasticity?

☐ Not at all ☐ Somewhat ☐ Fully

4. Do you think this app would make it easier for your patients to identify triggers of their spasticity?

☐ Yes ☐ No ☐ Maybe

5. Are the triggers listed below relevant in your opinion?	Yes	No
Bowel movement	☐	☐
Changing position	☐	☐
Constipation	☐	☐
External temperature	☐	☐
Frequent naps during the day	☐	☐
Full bladder	☐	☐
Incomplete bladder emptying	☐	☐
Ingrown toenail	☐	☐
Lying on your back	☐	☐
Making transfers	☐	☐
Menstruation	☐	☐
Muscle fatigue	☐	☐
Pressure ulcers	☐	☐
Sitting	☐	☐
Skin	☐	☐
Stress and anxiety	☐	☐
Tight clothes	☐	☐
Tight splint/orthosis	☐	☐
Tiredness/drowsiness	☐	☐
Time of day	☐	☐
Unable to sleep at night	☐	☐

Urinary tract infection	☐	☐
Other? …… ……		

6. Do you think the self-reported data collected will be reliable?

☐ Yes ☐ No ☐ Maybe

7. Are the graphs easily interpretable?

☐ Yes ☐ No

8. Is the design of this app simple and clear?

☐ Yes ☐ No ☐ Maybe

9. Could the graphs displayed in this app be useful in your sessions with patients?

☐ Yes ☐ No ☐ Maybe

10. Could the graphs displayed in this app be useful for treatment planning?

☐ Yes ☐ No ☐ Maybe

11. Would this app be useful for outpatients as a complementary report in the time running up to a session?

☐ Yes ☐ No ☐ Maybe

12. Are there any other comments you would like to add?

……

……

2.1.3 Data analysis

Responses to each questionnaire were grouped according to the themes outlined in 2.1.2, summarised in Table 15.

Responses to question 9 in the questionnaire for people with spasticity and question 5 for clinicians (see Table 13 and Table 14) were grouped by the responder type and plotted by their selection frequency for each trigger.

Free text responses given (in questions 16 and 12 for the questionnaire for people with spasticity and for clinicians respectively) were also grouped by these themes where relevant.

Table 15: Themes assessed in both questionnaires and the relevant questions for each theme.

Theme	App user questionnaire	Clinician questionnaire
Perceived usefulness of the app	Q1, Q7, Q8, Q12	Q1, Q2, Q4
Awareness of spasticity triggers	Q3, Q4	Q 3i, Q3ii
Clarity of app design	Q10, Q11	Q7, Q8
Relevant triggers of spasticity	Q9	Q5
Methods of app use	Q5, Q6i, Q6ii, Q14, Q15	-
User acceptance	Q2, Q13	-
Reliability of the data collected within the app	-	Q6
How the app may benefit outpatient appointments	-	Q9, Q10, Q11

2.2 *Results*

A total of 12 participants completed the questionnaire. This included 2 potential app users and 10 clinicians. For individual results, see Appendix I.

2.2.1 Theme 1: perceived usefulness of the app for spasticity management

Overall, people with spasticity responded with *Yes* or *Maybe* to all relevant questions, with both responding *Yes* when asked if the presented graphs were useful (see Figure 44A).

Clinicians also all responded with *Yes* or *Maybe* to all relevant questions, with 8/10 responding with *Yes* when asked if they would encourage their patients to use this app (see Figure 44B).

Two clinicians, who both responded *Yes* when asked if they would encourage their patients to use the app, also added the following comments:

> *"The app is good and I think it would be useful self management tool for some patients and help to target spasticity treatment."*

> *"... It may also help patients learn more about their own patterns of spasticity and triggers"*

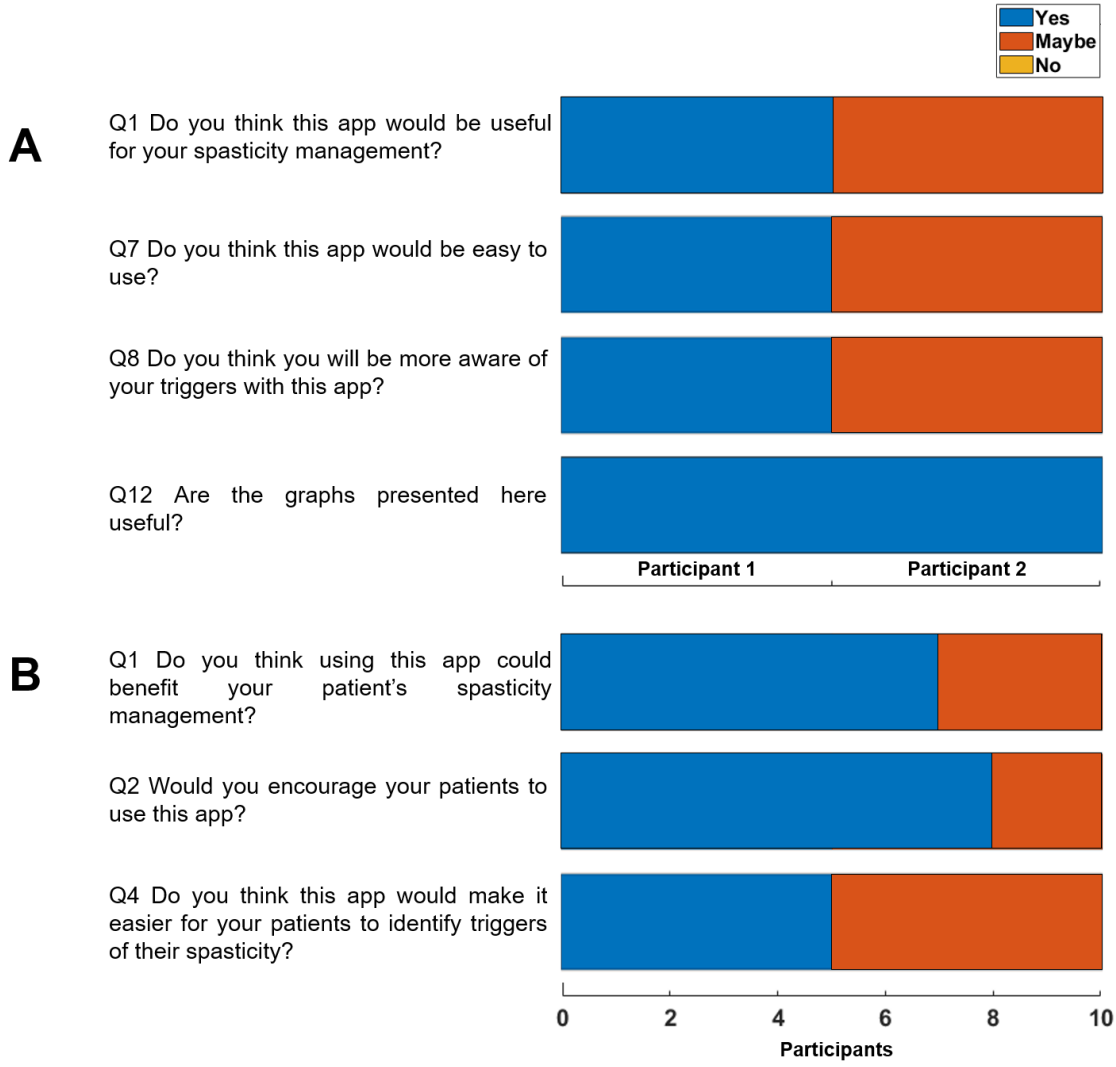

Figure 44:Summary of responses for indicated questions in the questionnaire given to A) people with spasticity (n = 2) and B) clinicians who work with people with spasticity (n = 10).

2.2.2 Theme 2: awareness of spasticity triggers

People with spasticity either responded *Yes* or *To some extent* when asked if they were aware of what triggers their spasticity, with their spasticity being triggered either twice a day, or 2 times or more.

Figure 45 summarises responses to the question "how many of your patients do you think recognise the triggers of their own spasticity?". Nine out of 10 clinicians said that their patients can *Somewhat* recognise the triggers of their spasticity and 1 said that their patients *Fully* recognise this.

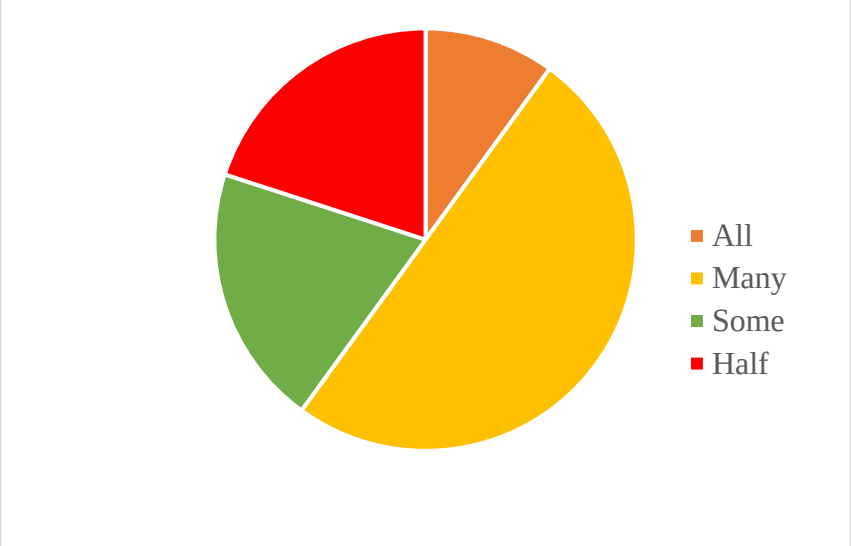

Figure 45: Representation of clinicians' responses to question 3i: 'To which extent do you think these patients can recognise the triggers of their spasticity?' (n= 10).

2.2.3 Theme 3: clarity of the app design

Both people with spasticity and all clinicians responded with *Yes* to all questions assessing the simplicity and clarity of the app design and the graphs presented in Figure 42.

2.2.4 Theme 4: relevant triggers of spasticity

People with spasticity and clinicians considered the triggers shown in Figure 46 to be relevant. 'Frequent naps during the day' was not selected by any participants.

Under 'other', one clinician added 'medically unwell' to the list of triggers given, and another added a relevant comment in the free text at the end of the questionnaire:

> *"I work with patients using electrical stimulation and this can sometimes induce spasms. I would encourage patients to add this as a category to see how often different modes of the electrical stimulation device are provoking spasms"*

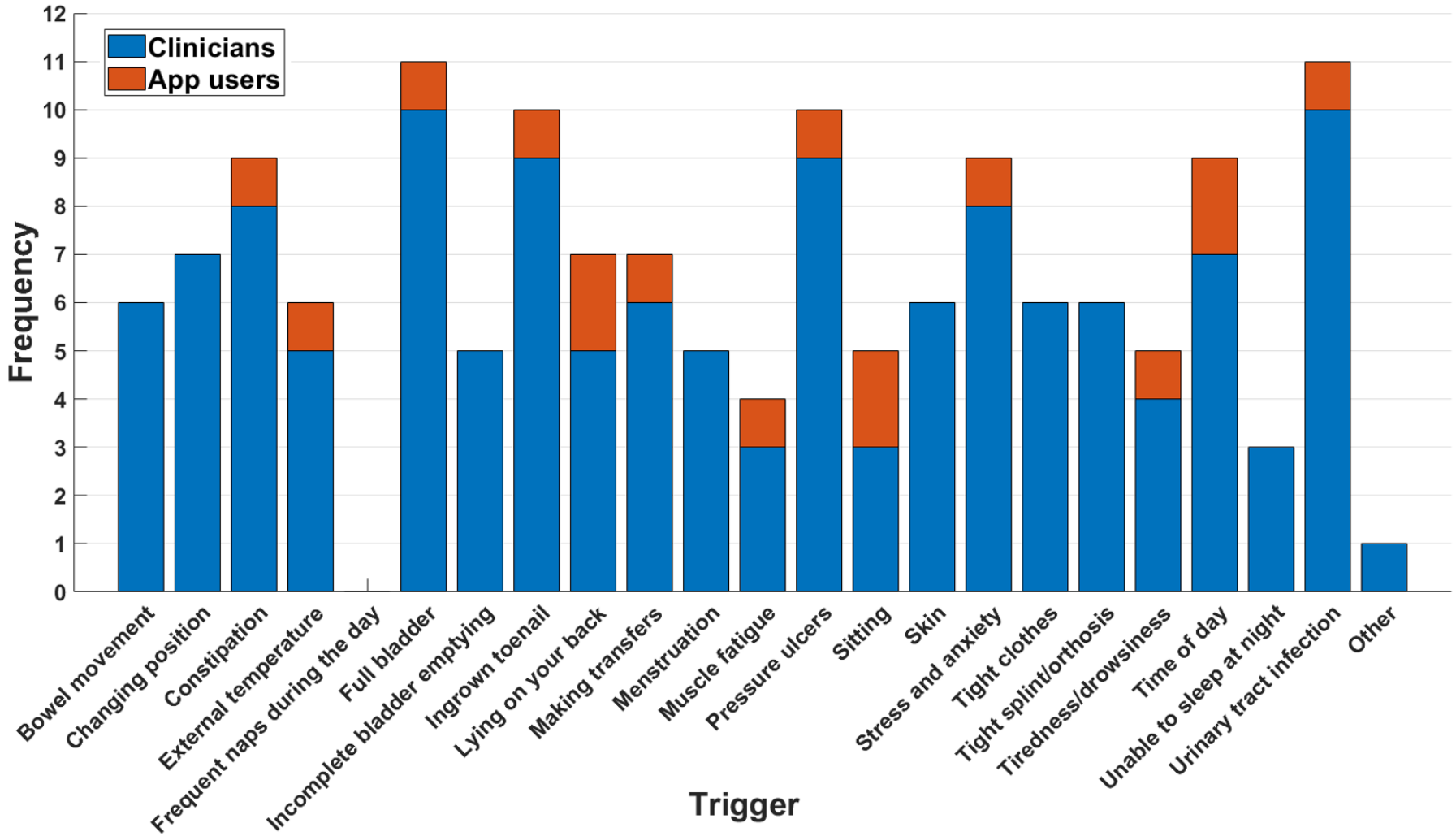

Figure 46: Frequency of selected triggers by clinicians (n = 10) and potential app users (n = 2).

2.2.5 *Theme 5: methods of app use*

Participants reported that they would like to review the triggers of their spasms either once or twice per day. Other responses related to how the participants would like to use the app are summarised in Figure 47.

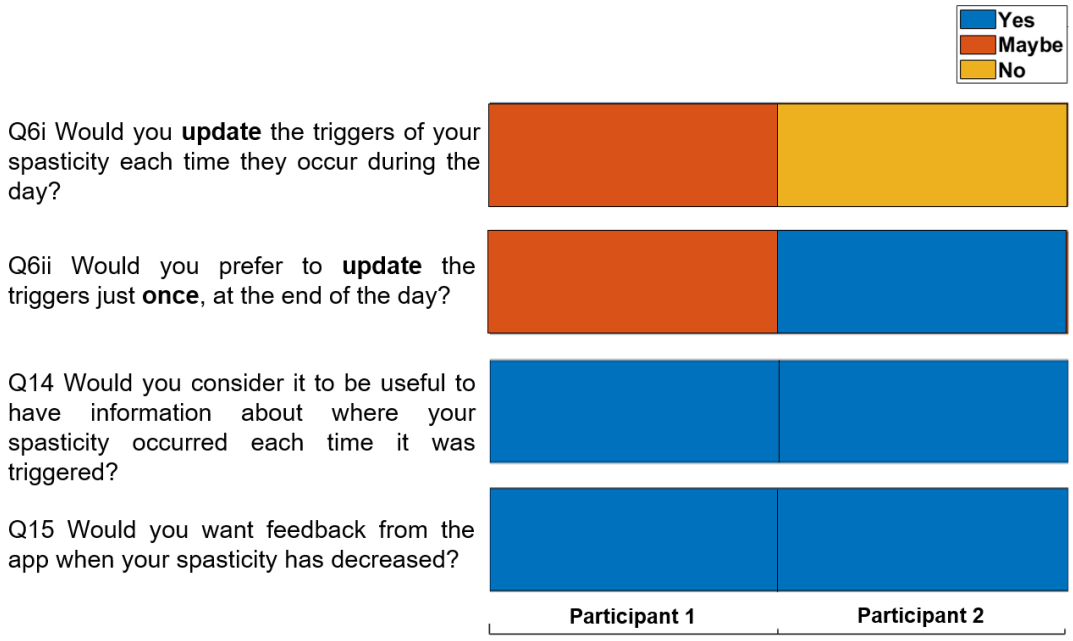

Figure 47: Summary of responses for indicated questions in the questionnaire given to people with spasticity (n = 2).

2.2.6 *Theme 6: user acceptance*

People with spasticity reported that they would not only use this app if told to do so by a clinician. Responders either reported that they would like to use the app, or that they would *Maybe* like to use the app.

The person who reported that they would like to use the app also added the following comment:

> *"I think it's a great idea!"*

A clinician also added the following relevant comment:

> *"For someone who was very self aware it may be beneficial prior to clinic to aid change of management or medication but I feel there may be a big population who are unable to access, use and engage with this system"*

2.2.7 Theme 7: reliability of the data collected within the app

Six of the 10 clinicians responded *Maybe* when asked if they thought that the self-reported data collected would be reliable, the remaining responded with *Yes*.

2.2.8 Theme 8: how the app may benefit outpatient appointments

Responses relevant to this theme are summarised in Figure 48. Two clinicians also added the potential role of this app within research and for intervention assessment:

> *"I think it could also be useful as a pre and post spasticity intervention, and also for research projects…"*

> *"Useful tool to evaluate treatment effectiveness. Similarly for trial of equipment, exercise and swimming etc. Could be used for evidence in other research and evidence to support provision of an intervention, such as FES."*

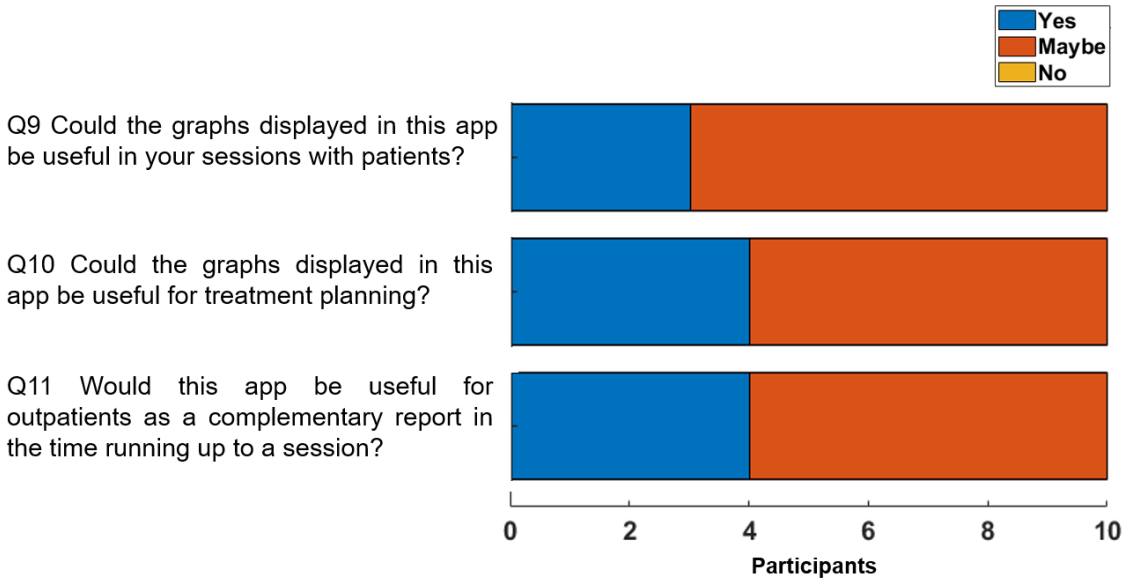

Figure 48: Summary of responses for indicated questions in the questionnaire given to clinicians who work with people with spasticity (n = 10).

2.3 *Discussion*

2.3.1 Summary of results

Overall, both app users and clinicians had a positive response to the current design of the app. There was some tentativeness among both parties when responding to questions regarding how useful the app would be towards spasticity management. A comment from

one clinician highlighted the likely variation of engagement between their patients, and another praised the design as a “useful management tool for some patients”.

2.3.2 Theme 1: perceived usefulness of the app for spasticity management

There were mixed responses to questions surrounding this theme, however all responses were either *Yes* or *Maybe*, with most responses being *Yes*. A potential source of uncertainty for responders may be due to the lack of evidence supporting the efficacy of this app for spasticity management. Once the design of this app has been finalised, this, as well as the reliability of the data collected using this app should be assessed.

Both potential app users perceived the graphs presented in Figure 42 to be useful. The interpretation of these graphs is incredibly important for this app to be used as a feedback tool.

2.3.3 Theme 2: awareness of spasticity triggers

Participants with spasticity perceived that they either are aware or somewhat aware of what triggers their spasticity. Half of the clinicians suggested that many of their patients recognise their triggers of spasticity, with the majority describing that their patients are somewhat aware of their triggers of their spasticity.

These results suggest that there is perhaps a need for an app, such as the one described here, for populations who are less aware of what may trigger their spasticity. Increasing the awareness of triggers of spasticity is suggested to be an important for lifetime management (Phadke et al. 2013).

2.3.4 Theme 3: clarity of the app design

All responders found the app design, as well as the feedback graphs, to be clear, simple and easy to interpret. The simplicity of the app design may allow for higher accessibility among those with SCI who have decreased dexterity, as well as for those who use accessibility features and assistive devices with their smartphones. This may facilitate user acceptance and lower abandonment, however this must be assessed.

The fact that all responders found the feedback graphs easily interpretable increases the potential efficacy of this app for self-management. If the input data is easily understood, users will be able to understand which triggers may be affecting their spasticity more than others.

2.3.5 Theme 4: relevant triggers of spasticity

The results presented in Figure 46 show that clinicians selected more triggers from the list provided compared to people with spasticity. This may be due to the low number of people with spasticity who responded to the questionnaire (n = 2), and these participants only selecting those which were relevant to themselves.

One other trigger was noted by a clinician, which was 'medically unwell'. Another clinician commented that ES is a trigger in some patients and that logging this using the app may be a useful way to manage the effects of different modalities using ES. Other than these, overall results suggest that the list given in this first design of the app is comprehensive.

2.3.6 Theme 5: methods of app use

For the feedback aspect of the app, one responder said they would review the triggers for the spasms once per day, and the other twice. The responder who would review this once said they would prefer to update the app just once, at the end of the day, rather than as their spasms occur. The other responder did not reply with this certainty. The current design of the app allows for this level of flexibility. The user is asked to add the time of day (morning, afternoon, or evening) the spasm occurs as they log it.

Both responders said that they would find it useful to have information about where their spasticity occurs each time it is triggered. This question was added to determine whether the information given in the 'Body Summary' section would be useful for app users (see Figure 43). From these two responses, we can see that this additional information may be a useful contribution to the feedback aspect of the app.

Both participants would also want notified feedback from the app when their spasticity had decreased. This is not yet a feature in this design of the app. Studies investigating self-management of diabetes via self-input data using an app have showed that individual feedback helped to reinforce the coping strategies adopted by their participants, ultimately improving their management of their diabetes (Nes et al. 2012). This should be a consideration for the next design of the app, to ensure effective feedback.

2.3.7 Theme 6: user acceptance

Potential users of the app responded either *Yes* or *Maybe* when asked whether they would want to use this app. Both also responded *No* when asked if they would only use the app

if told to do so by a clinician. This is relatively positive for user acceptance. However, this questionnaire cannot appropriately assess the likelihood of abandonment for this app.

One clinician noted that "there may be a big population who are unable to access, use and engage with this system". There is currently no literature assessing abandonment rates of apps of this nature for the SCI community. However, an assessment of abandonment of healthcare apps in general show that the most common reason that these apps are abandoned is the user abandoning the heath goal itself (Murnane, Huffaker, and Kossinets 2015). Likelihood of abandonment of this app should be assessed by a pilot group of users.

2.3.8 Theme 7: reliability of the data collected within the app

Most clinicians felt that the data collected in the app may be reliable. Physiotherapists or occupational therapists will often ask their patients the questions outlined in the PSFS themselves. In this setting, the PSFS has been found to have a good inter- and intra- rater reliability (Patricia B. Mills et al. 2018). This app will ask its users to complete these questions unsupervised. It may be appropriate to ensure that potential app users have previously rated their spasticity using the PSFS under supervision from a clinician prior to using this app. The reliability of the data collected using this app should be assessed in a pilot study.

2.3.9 Theme 8: how the app may benefit outpatient appointments

Clinicians felt that the graphs displayed in the app may be useful during sessions with their patients and treatment planning. Most also thought the data collected in the app would be useful as a complementary report in the time leading to a session with a patient. Results from theme 3 showed that all responders for these questionnaires found the feedback graphs to be easily interpretable. If a report were to be used during clinical sessions with a patient, the ease of interpreting these graphs reduces the workload on the clinician to understand potential changes to their patient's spasticity.

This theme was assessed to gauge the potential use of this app in a clinical setting. Evidence shows that patient involvement in their own rehabilitation and patient-centred goals improves their outcomes (Levack et al. 2006). This app may increase patient involvement and engagement, and therefore improve their spasticity management.

2.3.10 Adjustments to the current app design

From this first assessment of the app design, there are no changes to make to the process of logging a trigger, or the data presented for feedback purposes. However, 'Medically unwell' will be added to the list of triggers.

Both potential app users said that they would find it useful to be notified when their spasticity had improved. This would involve the app calculating when the severity or frequency of spasms related to a particular trigger had decreased over a prolonged period. This may help to reinforce the user's approach towards avoiding a particular trigger.

Although it was not noted by any responders presented here, under the list of triggers provided, 'No trigger identified' will also be added to future iterations of the app, to give users the option of adding an event which did not arise for any particular reason.

2.4 *Limitations*

A main limitation of this study is the low number of participants with spasticity who responded to their questionnaire (n = 2). This makes it difficult to interpret the user perceptions appropriately, as these responders may not be representative of the population. However, the next steps for the app development are to run user assessments, with this population.

One comment from a clinician stated that "there may be a big population who are unable to access, use and engage with this system". However, there was no overall negative responses from both potential app users who completed the survey, with one participant commenting that they "think it's a great idea!". To address this comment, it is important that future assessment of this app should include an assessment of user engagement.

The app currently does not have a feature where the user is able to log changes to their anti-spasticity medication, other than if they choose to do so themselves in the notes section. This is due to the sensitivity of this data. Under future assessment of this app, users will be encouraged to log any changes in their medication, however user satisfaction on this topic will be evaluated.

The use of assistive technologies and functional considerations were not addressed in the questionnaire. For a future user assessment of this app, varying smartphone accessibility features should also be assessed.

2.5 *Conclusion*

This chapter presents a novel, user-focussed assessment of the design of a spasticity management tool, evaluated by both potential users and relevant clinicians in the field. Overall, the current design of the app was accepted by both groups of participants. Following the suggested changes to the app, its use as a measurement tool, the reliability of the data, user acceptability and engagement will be assessed.

V. Impact of non-invasive electrical stimulation on spasticity in people with spinal cord injury. A comparison between neurophysiological and clinical outcome measures: systematic review and meta-analysis

In this thesis, I have explored the possible pathways involved in modulating spinal and corticospinal excitability when non-invasive ES is delivered over the forearm or spinal cord, as well as the possible role of self-education for spasticity management at home. This chapter aims to assess the effects of neuromodulation in people with spasticity arising from an SCI; measuring spasticity using both neurophysiological and clinical outcome measures of spasticity.

Initially, I had planned a clinical study, investigating the effects of a single-session of cervical HF-tSCS on neurophysiological outcome measures (PRRs, MEPs, HD and a brain motor control assessment) and on clinical outcome measures (MAS, PSFS and pain questionnaires) in people with upper limb spasticity, arising from a SCI (see Appendix II – The effects of kilohertz transcutaneous spinal cord stimulation on neurophysiological and clinical outcome measures in people with spasticity in spinal cord injury). I hoped that these case studies on a small cohort of participants (up to 5) would determine the feasibility of HF-tSCS as a potential method of managing symptoms of spasticity. If HF-tSCS were effective in reducing spasticity using clinical outcome measures, the addition of neurophysiological measures would have given an insight into the neural mechanisms behind this reduction in spasticity.

Since this study was no longer possible amid the COVID-19 pandemic and within the timeframe of this PhD, this systematic review was carried out on the effects of non-invasive ES delivered to the PNS (including tSCS) on limb spasticity in people with SCI. Meta-analyses on clinical and neurophysiological outcome measures aimed to investigate how these two interlink and change following non-invasive ES. Specifically, the outcome measures assessed are MAS, Pendulum Test (PT) and PSFS scores (clinical outcome measures), H-reflex, PRR and MEP amplitudes (neurophysiological outcome measures).

With advances being made with the use of implanted SCS for spasticity management over the last 50 years (Nagel et al. 2017), it is also important to assess its efficacy when

delivered transcutaneously. Focussing on non-invasive methods enables uptake of a low-cost treatment with minimal risk.

There are limited RCTs exploring the benefits of non-invasive ES for spasticity in people with SCI. The low number of participants within this cohort does not owe itself to the large-scale studies seen in other research fields. Furthermore, there are no systematic reviews on this topic which have combined results from available RCTs in a meta-analysis.

Existing reviews which analyse similar data include: systematic reviews on the effects of TENS on limb spasticity arising from various prognoses (Mills et al. 2016); the treatment of FES for people with SCI, (Luo et al. 2020); and the effects of ES parameters on lower limb spasticity in people with SCI (Bekhet et al. 2019). These provide some evidence into the success in decreasing spasticity in populations with SCI of neuromodulation, such as SCS and TENS without exercise (Fernández-Tenorio et al. 2016; Mahmood et al. 2019; Nagel et al. 2017; Bekhet et al. 2019; Mills et al. 2016), as well as with exercise, such as FES cycling and gait (Luo et al. 2020; Bekhet et al. 2019). However, these reviews do not consider the neurophysiological changes when non-invasive electrical stimulation is used for spasticity management. This systematic review will consider the effects of all non-invasive forms of ES on clinical outcomes of spasticity, in people with SCI. It will also assess possible correlations between clinical changes in spasticity and neurophysiological outcome measures.

Primary outcome measures of this systematic review are the MAS, the PT and the PSFS. These outcome measures have been chosen as they are commonplace when spasticity is assessed by a physiotherapist or occupational therapist (MAS and PT scores) (Tancredo et al. 2013; Adams and Hicks 2005) and the PSFS is a self-assessed measure which is used in chapter IV, promoting continuity across studies included in this thesis. Secondary outcome measures include the H-reflex, PRRs and MEPs, to explore whether these neurophysiological measures are good indicators of clinically meaningful results. H-Reflexes and MEPs are useful tools to monitor changes in CNS excitability with ES interventions; however, their correlation with changes in clinical measures of spasticity, due to an ES intervention, has not been investigated in a systematic review and meta-analysis.

The research questions this systematic review and meta-analysis aims to answer are: i) can non-invasive ES delivered to the PNS improve MAS, PT and PSFS scores? ii) is there a specific non-invasive ES protocol which is more effective at reducing spasticity (according to these outcome measures) in people with SCI? iii) are there any correlations between clinical outcome measures of spasticity, such as the MAS, PT and PSFS score, and neurophysiological measures, such as H-reflex, PRR and MEP amplitude? iv) does the current literature allow us to draw clinically meaningful conclusions?

1 Methods

This systematic review and meta-analysis has been carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines (Higgins et al., 2020). It has been registered with PROSPERO international prospective register of systematic reviews (registration number CRD42020186215).

1.1 *Search criteria*

In July 2020, PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) databases were searched, using the following search strategy: electric* AND stimulation AND spastic* AND spinal AND (injury OR lesion) AND ((posterior root) OR (h reflex) OR (motor evoked potential) OR (Ashworth scale) OR (pendulum test) OR (Penn spasm frequency scale)). No restrictions for publication date were used.

1.2 *Eligibility criteria and study selection*

Search results from all databases were combined in EndNote X9 software and duplicates were removed. These were then initially screened by title and abstract using the inclusion criteria: i) human adults with SCI; ii) provided an intervention of continuous, non-invasive ES, delivered to the PNS, either alone or in combination with movement therapy iii) investigating limb spasticity (i.e. exclude studies investigating bladder spasticity); iv) use of the Modified Ashworth Scale, Pendulum test and/or Penn Spasm Frequency scale to assess changes in spasticity due to intervention; v) in English language.

Only RCTs which used the MAS, PT or PSFS as outcome measures were included in meta-analyses and statistical analysis. Data from studies that only used an intervention group (i.e. observational or case studies), which used the same outcome measures, were collated and reviewed but not statistically analysed.

1.3 *Methodological quality*

Methodological quality of RCTs was assessed using the Physiotherapist Evidence Database (PEDro) scale. This included assessment of studies which had more than 1 intervention group, where other groups either received an alternative intervention, or were control groups. The PEDro scale is an 11-point scale, which scores studies based on whether they have: explicitly stated their eligibility criteria; randomly allocated

participants into groups; concealed allocation; ensured participants are similar at baseline; blinded all subjects; blinded all therapists who administered the intervention; blinded all assessors; measured at least 1 intervention in more than 85 % of initial participants; given the participants the intervention they were initially allocated; reported between-group statistical analysis; carried out point measures and assessed variability (Physiotherapist Evidence Database 1999) (see Appendix III for full description of criterion). Each study was given a score of 1 if it was completely clear that they satisfied the criterion; if it was not explicitly stated, they did not receive the point. Where the analysis of an outcome measure in a study was assessed, only outcome measures relevant to this systematic review were assessed.

Heterogeneity of RCTs was measured using the I^2 statistics when using a random-effects model. Due to the low number of RCTs included in this systematic review, heterogeneity of studies was considered for $I^2 > 30$ % and for $p < 0.10$ (Higgins et al. 2020b). If studies are deemed to be heterogenetic, sources of variation between protocols (e.g. methodological and statistical diversity) will be assessed.

1.4 *Outcome measures*

The primary outcome measures for meta-analyses were the MAS (including the AS), the PT and the PSFS. The AS is a 5-point scale, with scores of 0-4 (inclusive), which measures the muscle tone. The MAS is a 6-point scale, with the addition of 1+, which indicates the resistance to movement during measurement (SCIRE Professional Spinal Cord Injury Research Evidence 2010). The PSFS is a self-assessment of spasticity which measures 2 components: the severity and frequency of muscle spasms (SCIRE Professional Spinal Cord Injury Research Evidence 2005).

The PT is also a measure of spastic tone in the lower limb. It is carried out by letting the leg swing at the knee against the resistance of its muscles. The assessor then measures the following components of knee angle: S1 = initial knee angle; S2 = peak angle of first swing; and S3 = final position of the leg. These components are used to calculate the Relaxation Index (R_{2n}) using equation 1 (see chapter I). Scores of $R_{2n} > 1$ indicate that an individual does not have spasticity, whereas a score of $R_{2n} = 0$ would be considered as an extreme case of spasticity (Bajd and Vodovnik 1984).

The secondary outcome measures are the H-reflex amplitude, Hmax/Mmax ratio, PRR and MEP amplitude. For meta-analysis, these measures will only be considered if the

study also includes either of the primary outcome measures, to allow for effective comparison of clinical and neurophysiological measures of spasticity.

1.5 *Data extraction and management*

Data extracted from included studies were methodological design; number of participants; ASIA score of participants; time since SCI of participants; ES location; ES parameters (frequency, pulse width and duration of stimulation). Depending on the methodological design, studies were categorised as either RCTs or non-RCTs (i.e. case studies and observational studies with no control group comparator). Data from each of these groups were only analysed once – either as part of the meta-analysis, or as a summary of non-RCT data.

Studies were sub-categorised depending on the duration of the study: whether they were acute or long-term studies. Acute studies were defined as those where a single dose of neuromodulation was delivered in one session. Long-term studies were defined as those where neuromodulation was delivered over multiple sessions, over several days or weeks.

Mean ± SD data of each outcome measure were extracted from each study. The corresponding authors of studies which did not publish their data in this format were contacted via email for their raw data. If the author did not respond, data presented in figures were estimated, or the study was not included in the meta-analysis. If data were presented as mean ± SE, the SD was calculated.

For studies who used compound scoring for the MAS scores (i.e. the MAS score measured for each individual muscle was summed), if the raw data for individual participants were available, this data was divided by the number of muscles measured, from which the mean and SD was calculated.

For studies which presented separate results for left and right limbs, or for several muscles, the mean and SDs of these results were combined within each study, in accordance with the Cochrane guidelines, using Equations 3 and 4 (Higgins et al. 2020b). In cases where more than 2 groups were needed to be combined, these equations were used to combine groups 1 and 2 to make group ‘1+2’, which was then combined with group 3 to create group ‘1+2+3’ and so on (Higgins et al. 2020b).

$$Mean = \frac{N_1 Mean_1 + N_2 Mean_2}{N_1 + N_2} \qquad \textit{Eq. 3}$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}} \quad \textit{Eq. 4}$$

For analysis of the acute effects of non-invasive ES on the MAS score, the mean change in score was calculated for each study, shown in Equation 5. The standard deviation of this change was then calculated as the propagation of error (Equation 6, where $Corr$ is the correlation coefficient and $1 \leq Corr \leq -1$).

The correlation coefficient is defined as the similarity in outcome measures between participants (Higgins et al. 2020b). $Corr = 1$ would indicate high correlation between participants and $Corr = -1$ a negative correlation. For the purposes of this meta-analysis, it is assumed that there cannot be perfect correlation between participants in different studies, therefore SD_{change} will be considered for $Corr = 0$ and $Corr = -1$.

$$Mean\ difference = Post\ measure - Baseline\ measure \quad \textit{Eq. 5}$$

$$SD_{change} = \sqrt{SD_{baseline}^2 + SD_{final}^2 - (2 \times Corr \times SD_{final})} \quad \textit{Eq. 6}$$

1.6 *Statistical analysis*

Meta-analysis of RCTs were carried out using Review Manager 5.4 software. Analysis of the mean differences of continuous outcome measures were carried out using a random-effects model, using 95 % confidence intervals. The mean difference was calculated as the change from baseline to the post-intervention value (see equation 6). A minimum of two studies were required to carry out this analysis. Where a single study investigated several non-invasive ES interventions, the same control group was used as the comparator for each intervention. Statistical significance was considered for $p < 0.05$.

For analysis of non-RCTs, studies were grouped depending on their outcome measure and type of trial (single-session (acute) or multi-session, over several days (long-term)). Results for individual participants in each study were amalgamated and graphically presented. Data from studies presented as mean ± SD were also included if data for individuals was not available.

Studies were included in one type of analysis only. If a study qualified to be included in the RCT meta-analysis, it was not included in results for non-RCT studies.

2 Results

2.1 *Study selection*

A total of 369 papers were identified through database searches. A further 12 papers found through personal databases. A PRISMA flow diagram is presented in Figure 49. Once duplicate papers had been removed, 241 papers were screened by their title and abstract and 189 were removed as it was clear that they did not meet the inclusion criteria. Fifty-two full-text articles were reviewed, and 25 were removed (see Figure 49 for the reasons for exclusion). This left 27 studies to be included in the systematic review. Of these, 3 studies were included in the meta-analysis and 17 in the amalgamation and presentation of results from non-RCT studies. The remaining 7 studies were not included in the meta-analysis nor the amalgamation, either because results were not presented or because the outcome measures presented were not consistent with the other included studies (see Table 16 for a summary of which studies were included in which analysis).

2.2 *Included studies*

Of the 27 studies included in this systematic review, the spread of interventions used were as follows: 10 studies assessed the effects of TENS on spasticity (9 for the lower limbs and 1 for the upper limbs) (Aydin et al. 2005; Bajd et al. 1985; Franek, Turczynski, and Opara 1988; Goulet et al. 1996; Khanna and Kaur 2017; Perdan et al. 2010; Robinson, Kett, and Bolam 1988b; Sivaramakrishnan, Solomon, and Manikandan 2018; Van Der Salm et al. 2006; Vodovnik, Bowman, and Hufford 1984; Oo 2014); 4 used tSCS, all targeting the lower limbs (Estes, Iddings, and Field-Fote 2017; Hofstoetter et al. 2014; 2020; Vargas Luna et al. 2016); 9 used FES cycling (Skold et al., 2002; Krause et al., 2008; Mazzoleni et al., 2013; Ralston et al., 2013; Kuhn, Leichtfried and Schobersberger, 2014; Mazzoleni et al., 2017; Gant et al., 2018; Duffell et al., 2019); 3 for FES gait (Granat et al. 1993; Kapadia et al. 2014; Murray et al. 2018); and 1 which also assessed FES for the lower limbs as well as TENS (which has already been counted) (Sivaramakrishnan, Solomon, and Manikandan 2018).

It should be noted that the study by Mazzoleni et al. (2017) studied the effects of 20 sessions of FES cycling followed by 20 sessions of robot-assisted FES gait training. For the purposes of this systematic review and meta-analysis, results were only taken from the FES cycling phase of this trial, since this training may have influenced results obtained during the FES gait phase of this study.

Seventeen studies used the MAS score and 3 used the AS as an outcome measure. Of these, 4 studies used compound scoring, 2 studies assigned the 1+ score used in the MAS the value of 1.5 and 1 study assigned 1+ score with 2, 2 with 3 and so on. Eight of these studies were included in the quantitative synthesis; 3 were RCTs and 13 were non-RCTs. Four studies were excluded from these analyses because data were not presented (Granat et al. 1993; Kapadia et al. 2014; Oo 2014), or because compound scoring was used and averaged across participants (Mazzoleni *et al.*, 2017). In these cases, the author was contacted to request access to their data, however this was not successful for all studies.

Twelve of the included studies used the PT to measure changes in spasticity. Of these 12 studies, 8 reported PT results as the R_{2n} (Bajd et al. 1985; Granat et al. 1993; Hofstoetter et al. 2014; 2020; Phillip Krause et al. 2008; Vargas Luna et al. 2016) (with one reporting results as the change in R_{2n} (Vodovnik, Stefanovska, and Bajd 1987)), 2 as the first swing excursion (Gant et al. 2018; Estes, Iddings, and Field-Fote 2017), (defined as "the angle at which the lower leg transitions from flexion to extension during after the heel of the test leg is released" (Estes, Iddings, and Field-Fote 2017)), one only reported statistical analysis of their PT results (Kapadia et al. 2014) and the remaining study did not report their results as they were statistically non-significant (Franek, Turczynski, and Opara 1988).

The PSFS was included in one study as an outcome measure, however it was reported as a single value and it was not clear whether the 2 components of the PSFS were averaged together (Mazzoleni et al., 2017).

Four studies included the H-reflex as an outcome measure (Goulet et al. 1996; Aydin et al. 2005; Van Der Salm et al. 2006; Gant et al. 2018). All studies reported their results as H_{max}/M_{max}. No studies included in the final systematic review included MEPs or PRRs in their outcome measures.

2.3 *Methodological quality of RCTs*

Assessment of randomised trials (whether the group comparator was a control group or assessing another form of non-invasive ES) is shown in Table 17.

It should be considered that, due to the nature of non-invasive ES as an intervention, it was noted by most assessed studies that blinding the participant and the therapist who administered the intervention was not possible. For some studies, one assessor was blinded and others were not (Khanna and Kaur 2017; Krause et al. 2008).

2.4 *Participants*

A total of 373 participants with a SCI were included in this systematic review. Seventeen studies included people with AIS A SCIs and 8 included people who had incomplete injuries. Participants in 10 studies were at least 1-year post-injury, at least 6-months post-injury in 2 studies, and at least one participant was less than 6-months post-injury in 8 studies. A summary of these parameters is given in Table 18.

Only 10 studies included information on whether participants were permitted to continue taking anti-spasticity medication (Estes, Iddings, and Field-Fote 2017; Hofstoetter et al. 2014; 2020; Khanna and Kaur 2017; Krause et al. 2008; Robinson, Kett, and Bolam 1988a; Sivaramakrishnan, Solomon, and Manikandan 2018; Skold et al. 2002; Thompson et al. 2011; Van Der Salm et al. 2006). In one study, taking anti-spasticity medication was an exclusion criteria (Krause et al. 2008). All other studies allowed participants to continue taking their medication.

2.5 *Stimulation parameters*

The range of ES frequencies used in studies included in this systematic review were 5-1000 Hz. The range of pulse widths used was 0.01-100 ms, with 1 study investigating the effects of TENS delivered with varying frequency/pulse width (ms) pairs, which were as follows: 100/0.1, 100/0.01, 100/1, 1000/0.1, 1000/0.01, 10/0.1, 10/0.01, 10/1 (Vodovnik, Stefanovska, and Bajd 1987).

The range of ES intensity reported in included studies was 8 – 160 mA (discounting studies which reported ES intensity as ‘up to’ and Krause et al. (2008) as their reported stimulation intensities included their passive cycling arm (0-99 mA)). Reported methods of determining ES intensity included: below MT; producing paraesthesia; highest tolerated intensity; 2x sensory threshold in healthy, able-bodied participants; sub-PRR threshold; at MT, or below when muscle spasticity occurred; 0.9x lowest MT in all stimulated muscles; 3x MT; and 0.8x MT. Where studies did not report a method for setting the stimulation intensity for each participant, they quoted the value of stimulation intensity. Table 18 shows a summary of all stimulation parameters of included studies.

2.6 *Summary of results from included studies*

Overall, 20 of the 27 studies included in this systematic review showed an improvement in at least one measure of spasticity following non-invasive ES, 13 of which were statistically significant changes, either from their baseline measure, or when compared to

a control group (see a summary of all results in Table 18). Twelve studies showed no change in at least one included outcome measure and 2 studies showed a possible, non-statistically significant, worsening of spasticity (Gant et al. 2018; Robinson, Kett, and Bolam 1988b). A summary of the studies included in each analysis carried out are summarised in Table 16.

Table 16: Studies included in each quantitative analysis carried out. Acute studies were defined as those where a single dose of neuromodulation was delivered in one session. Long-term studies were defined as those where neuromodulation was delivered over multiple sessions, over several days or weeks. Abbreviations: MAS = modified Ashworth scale, RCT = randomised-control trial, R_{2n} = relaxation index.

Analysis	Studies
Meta-analysis (RCTs)	• Van der Salm et al. (2006) • Krause and Straube (2008) • Ralston et al. (2013)
Acute changes in MAS scores (non-RCTs)	• Goulet et al. (1996) • Kuhn, Leichtfried and Schobersberger (2014) • Khanna and Kaur (2017) • Murray et al. (2018) • Sivaramakrishnan, Solomon and Manikandan (2018) • Hofstoetter et al. (2020)
Long-term changes in MAS scores	• Skold et al. (2002) • Aydin et al. (2005) • Perdan et al. (2010) • Mazzoleni et al. (2013) • Yaşar et al. (2015) • Gant et al. (2018) • Duffell et al. (2019)
Acute changes in R_{2n}	• Bajd et al. (1985) • Granat et al. (1985) • Hofstoetter et al. (2014) • Vargas Luna et al. (2016) • Hofstoetter et al. (2020)
Long-term changes in H_{max}/M_{max} ratio	• Aydin et al. (2005) • Gant et al. (2018)
Not included an any quantitative analysis	• Franek, Turczynski and Opara (1988) • Robinson, Kett and Bolam (1988) • Kapadia et al. (2014) • Oo et al. (2014) • Estes, Iddings and Field-Fote (2017) • Mazzoleni et al. (2017)

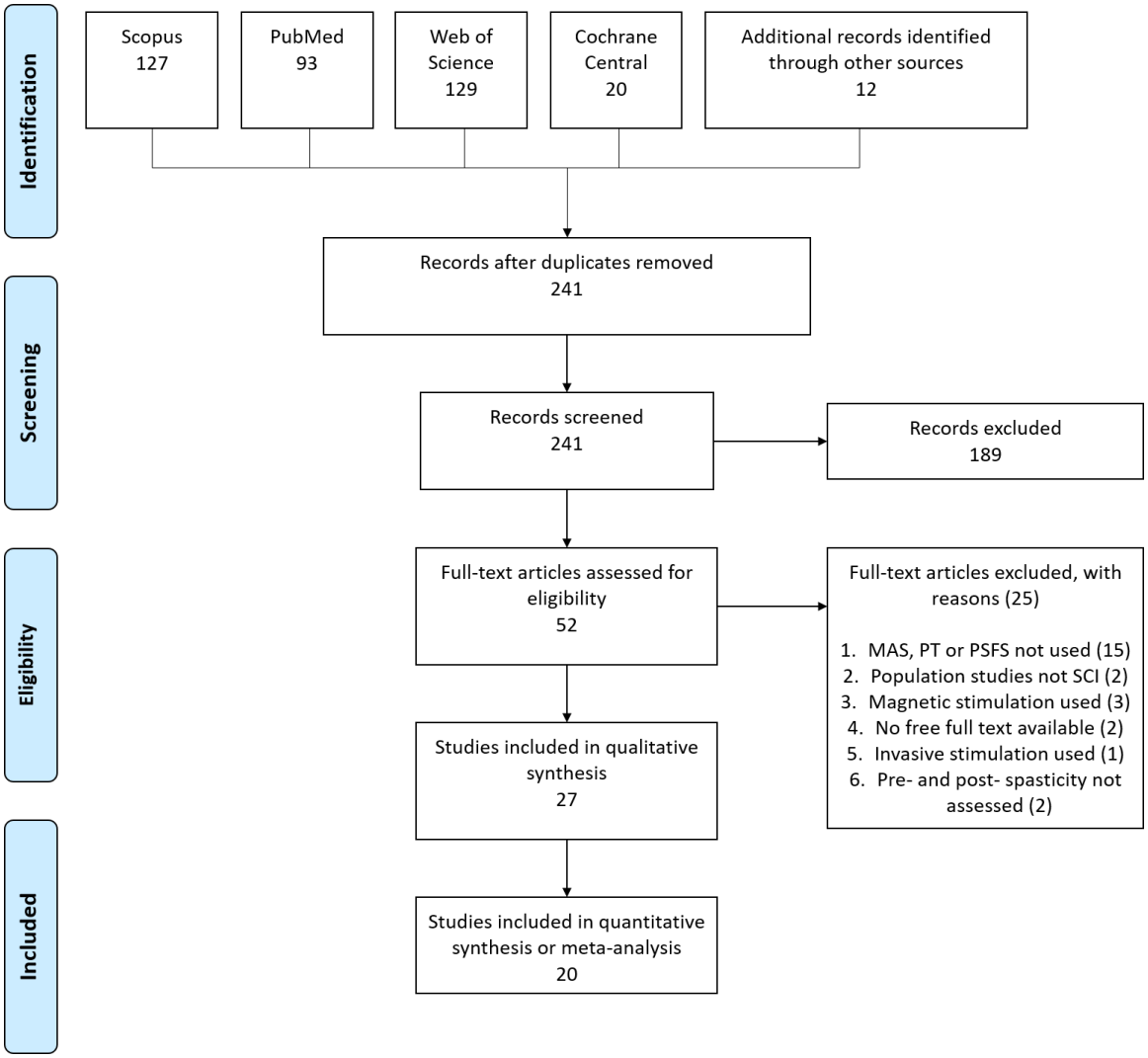

Figure 49: PRISMA flow diagram of included studies.

Table 17: Methodological quality assessment of randomised trials included in the systematic review according to the PEDro scale. Total scores are out of a possible 11 points.

	Aydin 2005	Estes 2017	Franek 1988	Kapadia 2014	Khanna 2017	Krause 2008	Oo 2014	Ralston 2013	Sivara-makris-hnan 2018	Van der Salm 2006	Vodovnik 1987
Eligibility criteria specified		✓		✓	✓	✓	✓	✓	✓	✓	
Random allocation	✓	✓		✓	✓		✓	✓	✓		
Concealed allocation				✓			✓	✓	✓		
Groups similar at baseline (in terms of important prognostic indicators)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
All subjects were blinded									✓		
Therapists who administered intervention blinded											
All assessors blinded				✓			✓	✓	✓		
≥1 outcome measure obtained from >85 % of initially allocated participants	✓				✓	✓	✓	✓	✓	✓	✓
Intervention was given as allocated			✓		✓	✓	✓	✓	✓	✓	✓
Between-group statistics performed	✓	✓		✓	✓	✓	✓	✓	✓	✓	
Point measures and variability assessed	✓	✓		✓	✓	✓		✓		✓	✓
Total score	**5**	**5**	**2**	**7**	**7**	**6**	**8**	**9**	**9**	**6**	**4**

*Table 18: Main characteristics of included studies. Abbreviations: AS = Ashworth scale, CSS = composite spasticity score, DF = dorsiflexors, DTR = deep tendon reflex, EMG = electromyography, FDS = functional disability score, FES = functional electrical stimulation, FIM = functional independence measure, GL = gluteals, HA, = hamstrings, HTI = highest tolerated intensity, MAS = modified Ashworth scale, MT = motor threshold, NR = not reported, PF = plantar-flexors, PT = pendulum test, QU = quadriceps, SCATS = spinal cord assessment tool for spastic reflexes, SFS = spasm frequency scale, ST = sensory threshold, TA = tibialis anterior, TS = triceps surae, TUGT = timed up-and-go test, VAS = visual analogue scale, 6MWT = 6-minute walking test. ✓denotes an improvement in the outcome measure, O denotes no change and ✗ denotes a worsening, * denotes a statistically significant result, unless stated otherwise.*

Study	Study design	N =	AIS	Time since injury	Form of ES	Stimulat-ion location	Freq. (Hz)	Pulse width (ms)	Intensity	Duration	Result
Aydin (2005)	Pre-post	10 SCI, 20 healthy	A		TENS	Bilateral tibial nerves	100	0.3	50 mA	15 mins/dy for 15 dy	✓* AS, SFS, DTR, FDS, FIM Most improvement seen following 15th session of TENS ✓* Hmax
Bajd (1985)	Pre-post	6			TENS	Above and below the knee	100	0.3	≤ 50 mA, < MT	20 mins	✓* PT
Duffell (2019)	Pre-post	11	C-D	2 mnth-49 yr	FES cyclin g	QUs, HA, GL	30	0.2	Gradual-ly increased from minim-um to HTI	20-45 minutes, 3x/ wk over 4 wk	✓ MAS ✓* Voluntary power output, motor scores
Estes (2017)	Random-ised	10	B-D	>2 yr	tSCS	T11/T12	50	NR	Producin g	30 mins	✓* PT for 45 minutes following tSCS

	crossov-er								paraesth-esia/HTI		
Franek (1988)	RCT	44 ES, 35 control	A-D	6-96 mnth	TENS	Hip abductors, anterior thigh, GL	5 to 7	NR	10-15 V	18x for 2.5 min/dy for 6 dy, 2x/dy for 6 dy	✓ PT, own spasticity scale Reduction in PT more marked in TENS group than in control group
Gant (2018)	Pre-post	8	A/B	≥1 yr	FES cyclin g		35	0.35	100-140 mA	12 wk	✗ MAS increased in most participants, or was unchanged O PT and H/M ratio varied between participants
Goulet (1996)	Pre-post	14	A-D	2-194 mnth	TENS	TS	99	0.25	15 mA (2x ST in healthy particip-ants)	30 mins	✓* MAS, Achilles DTR, (clonus - non-significant) O H-reflex
Granat (1993)	Pre-post	6	C/D	≥ 2 yr	FES gait	QU, hip abductors, HA, erector spinae	25	0.3	NR	30 mins/dy, <5 dy/wk for 6 mnth	✓* PT O AS varied between participants

Hofstoetter (2020)	Pre-post	12	A, C, D	≥ 1 yr	tSCS	T11/T12	50	1	16-100 mA, Sub-PRR threshold	30 mins. 6-week protocol in 1 participant. 30mins/dy, 4 dys/wk	✓* MAS, PT immediately after and 2 hours after tSCS ✓* Clonus, cutaneous-input evoked spasms, passive joint movement immediately after and 2 hours after tSCS O 10 m walk test
Hofstoetter (2014)	Pre-post	3	D	9-12 yr	tSCS	T11/T12	50	1	Producing paraesthesias, < MT	30 mins	✓ PT, stretch reflex
Kapadia (2014)	Randomised control trial	16	C-D	≥ 1.5 yr	FES gait	QU, HA, DF, PF	40	0-0.3	8-125 mA, > MT	45 mins per session, 3 dy/wk, 16 wk	O MAS, PT, SCIM over time, or between intervention groups
Khanna (2017)	Crossover trial	30	A-D	>6 mnth	TENS	TS, TA	30	0.3	At MT, or just below is spasms occurred	20 mins, 5x/wk for 2 wks	✓* MAS, DTR No difference between stimulation groups O Clonus
Krause (2008)	Crossover trial with	5	A	3-9 yr	FES cycling	QU, HA, glutes	20	0.5	0-99 mA	60-100 mins	✓* MAS, PT MAS reduced after both

	passive cycling										FES and passive cycling sessions
Kuhn (2014)	Pre-post	30	A-D	< 4 wk-122 mnth	FES cycling	QU, HA, GL	30	0.25	10-130 mA	20 mins 2 dy/wk for 4 wks	✓* MAS, muscle circumference (non-significant for AIS A & B)
Mazzoleni (2013)	Pre-post	20	A-C		FES cycling	QU, femoral biceps	NR	0.05-0.5	Up to 140 mA	20 sessions, 3/wk	O MAS, PSFS, SCIM
Mazzoleni (2017)	Pre-post	7	A		FES cycling	QUs, femoral biceps, GL	50	0.5	Quads: 35-75mA, femoral biceps: 25-50mA	20 sessions, 3/wk	✓* MAS, 6MWT, TUGT, standing time, number of steps (PSFS - non-significant)
Murray (2018)	Pre-post	3	A and C		FES gait	QU, GL, HA, TA, trunk	40	0.2-0.35	22-70 mA	15-25 mins	✓ MAS
Oo (2014)	RCT	8	A-D	~2-4 mnth	TENS	Common peroneal nerve	100	0.1-0.3	15 mA (2x ST in healthy participants)	60 mins	✓* CSS and clonus score in the experimental group compared to the control
Perdan (2010)	Case studies	2	C, D	3 and 4 mnth	TENS	Whole hand	50	0.2	ST	20 mins, 5 dy/wk for 4 wk	✓ Strength, motor control, hand function

											O MAS
Ralston (2013)	Random-ised crossov-er	14	A-C	64-135 dy	FES cyclin g	QU, HA, GL	33	NR	≤ 140 mA	30-45 mins, 4x/wk for 2 wk	O AS, no clear difference between FES cycling and standard rehabilitation
Robinson (1988)	Pre-post	31 (8 for 8 wks)	A-D	15 < 1 yr, 16 > 1 yr	TENS	QU	20	0.4	120-160 mA	20 mins, 2x/dy 6 dy/wk for 4-8 wks	O/✗ PT in most participants, which decreased by week 8
Sivaram-krishnan (2018)	Double blind random-ised crossov-er	10	A-E	1-26 mnth	TENS and FES	TENS: QUs, adductors, PF. FES: QU, adductors, PF	TENS : 100 Hz, FES: 35 Hz	0.3	TENS: ≤ 20 mA, < MT FES: 3x MT	30 mins	✓* MAS, SCATS for up to 4 hours No difference found between TENS and FES interventions
Skold (2002)	Pre-post	15		> 1 yr	FES cyclin g	Quads, hams, glutes	60	0.35	≤ 130 mA, > MT	NR	O MAS, VAS O EMG activity
Van der Salm (2006)	Placebo-controll-ed crossov-er	10	A and C	28-275 mnth	TENS	TS, TA, or S1 dermatom e (lateral side of the foot)	30	TS, TA stim: 0.03 ms, S1: 0.01 ms	TS and TA stim: 300 % MT, S1 stim: 80 % MT	45 mins	✓* MAS Statistically significant differences found between TENS and placebo group O H/M ratio

Vargas Luna (2016)	Pre-post	4	B-D	> 1 yr	tSCS	T11-T12	50	1	90 % of min. MT in all muscle groups	30 mins	✓ PT in 2 out of 3 the participants who presented with spasticity
Vodovnik (1987)	Compari-son crossov-er	7	A	4-60 mnth	TENS	QU	100, 100, 100, 1000, 1000, 10, 10, 10	1, 0.1, 0.01, 0.1, 0.01, 1, 0.1, 0.01	≤ 30 mA, > MT	4s on 4s off for 20 mins	✓ PT for all but 1 participant. 100 Hz was most effective at improving PT at various pulse widths ✓ EMG activity
Yasar (2015)	Pre-post	10	C-D	> 2 yr	FES cyclin g	QU, HA, GL	20	0.25	10-140 mA, > MT	1 hour, 3x/week for 16 weeks	✓* MAS, FIM compared to baseline after 3-month intervention and at 3-month follow-up

2.7 *Meta-analysis of RCTs for MAS scores*

The systematic review included results from 3 RCTs which used the MAS as an acute measure of spasticity (Krause and Straube 2008; Van Der Salm, Veltink, Ijzerman, et al. 2006; Ralston et al. 2013). All studies used a crossover design. The study by Van der Salm et al. (2006) measured MAS scores immediately following, 1 and 2 hours after 45 minutes of 3 forms of TENS delivered to tibialis anterior, triceps surae, the S1 dermatome (delivered over the side of the foot) and a control intervention. This study was included in acute results of RCTs due to the short post-intervention intervals, and to increase the power of the meta-analysis. The study by Krause and Straube (2008) compared the effects of FES cycling with passive cycling and Ralston et al. (2013) compared FES cycling to no FES cycling.

Figure 50 shows forest plots from the forms of non-invasive ES in these RCTs. The exact value of the correlation coefficient is unknown. Therefore, Figure 50 shows results for two cases: where there is a negative correlation between results for individual participants (Figure 50A; $Corr = -1$) and where this correlation between participants is not considered (Figure 50B; $Corr = 0$). The former case, however, is less likely since the nature of the outcome measures included in this meta-analysis are similar. Therefore, the latter case (see Figure 50B) shows a more accurate representation of these results. This is reinforced by the lack of heterogeneity found in these results (I^2 = 0 %).

The overall effect in Figure 50A shows a trend which may favour the intervention over the control groups, however this is a non-statistically significant result ($p = 0.26$). Figure 50B shows that if $Corr = 0$, the results from the included studies favour the intervention ($p = 0.03$). In both cases, FES cycling delivered by Krause and Straube (2008) showed the largest change in MAS score (n = 5), which was the most heavily weighted result in this random-effects model. Excluding S1 dermatome stimulation (Van Der Salm et al. 2006), mean differences in MAS scores for all other forms of non-invasive ES showed an improvement.

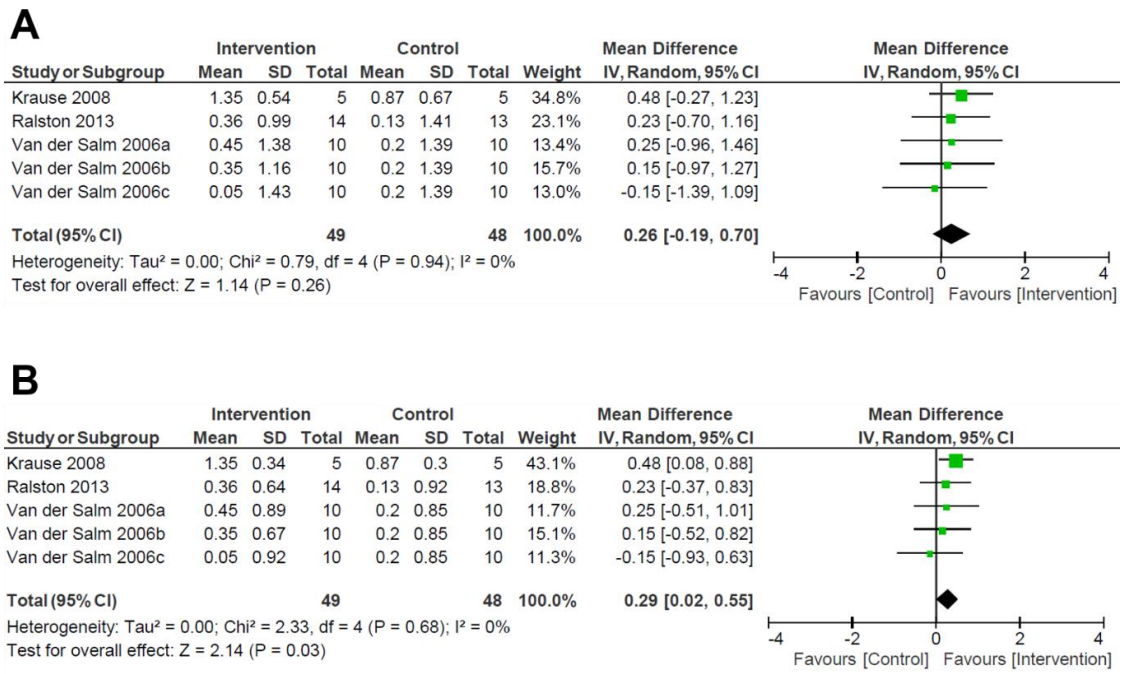

Figure 50: Forest plot using a random effects model of RCT studies using the MAS to test for the acute effects of non-invasive electrical stimulation. 2006a-c represent the 3 interventions that were tested in the single study performed by Van der Salm et al. (2006): TENS delivered to the agonist, antagonist and the S1 dermatome respectively. The black diamond represents the average effect of non-invasive electrical stimulation. A) shows results for Corr = -1 and B) for Corr = 0. Abbreviations: CI = confidence interval, MAS = modified Ashworth scale, RCT = randomised-control trial, TENS = transcutaneous electrical nerve stimulation.

2.8 *Acute changes in MAS score in non-RCT studies*

Results from acute non-RCT studies using the MAS score are shown in Figure 51; this shows data from studies for individual participants (Hofstoetter et al. 2020; Murray et al. 2018) and averaged results (Goulet et al. 1996; Khanna and Kaur 2017; Kuhn, Leichtfried, and Schobersberger 2014; Sivaramakrishnan, Solomon, and Manikandan 2018). Datapoints below the dashed line show results for which the MAS score was reduced following intervention. This figure shows results for a total of 122 participants (12 in Hofstoetter *et al* (2020), 3 in Murray et al. (2018), 14 in Goulet et al. (1996), 30 in Khanna and Kaur (2017), 30 in Kuhn et al. (2014) and 34 in Sivaramakrishnan et al.(2018)). Coloured bars above this figure and following, similar figures represent the frequency used in each study (i.e. for higher frequencies, the bar is shorter).

Results in the study by Sivaramakrishnan et al. (2018) are counted as separate muscles in individual legs, where spasticity was measured in the hip adductors in 19 legs across 10 participants, in the 11 legs for the knee extensors and 4 legs for plantar flexors. Figure 51 shows results for N = 34 for both FES and TENS interventions.

Results from individual participants show that most participants demonstrate a reduction in spasticity. For averaged results in studies by Khanna and Kaur (2014) and for the TENS intervention by Sivaramakrishnan et al. (2018), results for all participants showed a decrease in spasticity. Averaged results in studies by Goulet et al. (1996), and for the FES intervention used by Sivaramakrishnan et al. (2018) show large standard deviations, indicating a large variance across results for individual participants, where some may not have benefitted from the intervention.

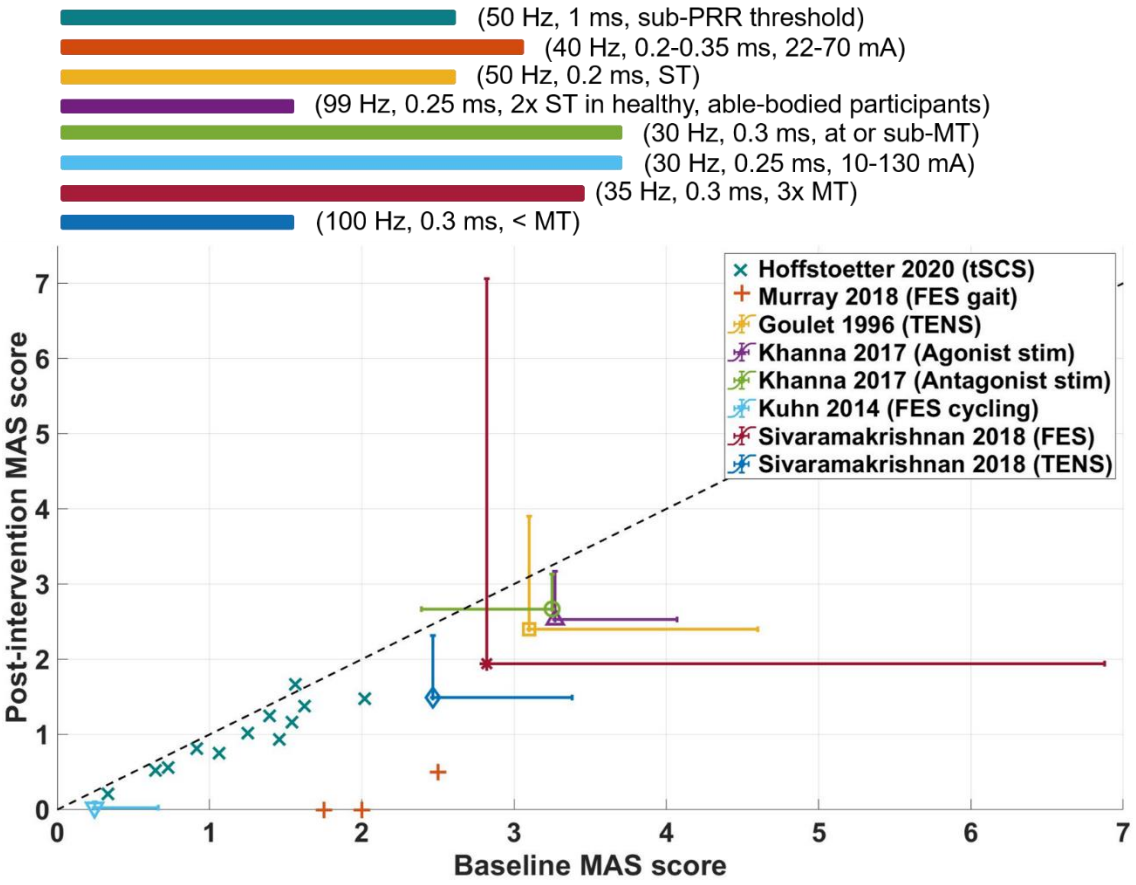

Figure 51:Changes in the MAS score of acute non-RCT studies. Datapoints with error bars represent studies where data has been presented as mean ± SD and those without show results for individual participants. The dashed line indicates no change in MAS score following intervention. SD for post-intervention MAS scores in the study by Kuhn et al (2014) = 0.077. Coloured bars above the plot represent the frequency used for each study. Abbreviations: FES = functional electrical stimulation, MT = motor threshold, PRR = posterior-root reflex, ST = sensory threshold, TENS = transcutaneous electrical nerve stimulation, tSCS = transcutaneous spinal cord stimulation.

2.9 *Long-term changes in MAS score in non-RCT studies*

Results from long-term studies for which data from studies were available for individual participants (Aydin et al. 2005; Duffell et al. 2019; Perdan et al. 2010) as well as averaged results (Mazzoleni et al. 2013) are shown in Figure 52. These figures show data for long-term trials under 8 weeks long in total. Trials lasted for 16-50 days from baseline measure

to follow-up measures. There is a total of 44 participants represented (11 in Aydin et al. (2005), 11 in Duffell et al. (2019), 2 in Perdan et al. (2010) and 20 in Mazzoleni et al. (2013)).

For most participants, there is a reduction in their MAS score from baseline to the end of the trial; this includes averaged results from the study by Mazzoleni et al. (2013). Results found by Duffell et al. also show that some reductions in spasticity following 4-weeks of FES cycling were retained 4-weeks after the trial had ended (2019). For 2 of the 11 participants in this study, spasticity had worsened following FES cycling, with their follow-up MAS score reduced compared to their post-intervention measure; but with an overall negative impact on their spasticity compared to baseline. Of individual results, there were a total of 2 participants for whom TENS intervention had no effect on their spasticity throughout the trials (Aydin et al. 2005; Perdan et al. 2010). Averaged results in the study by Mazzoleni et al. showed increasing standard deviations for successive readings, resulting in non-statistically significant results.

Figure 53 shows changes in MAS score for trials over 8 weeks long. A total of 49 participants took part in studies longer than 8 weeks (8 in Gant et al. (2018), 21 in Sköld et al. (2002) and 20 in Yaşar et al. (2015)). Results in the study by Sköld et al. (2002) represent the combination of averaged MAS scores measured in knee flexors and extensors in left and right legs, which were not measured in every participant, giving N = 21, although only 15 participants took part in the study. Similarly, for Yaşar et al. (2015), averaged results for the MAS score measured in knee flexors and extensors for all participants, giving N = 20 for results shown in Figure 53B, although only 10 participants took part in this study.

Averaged results for studies where interventions last > 8 weeks show a decrease in their end of trial measure compared to their baseline measure (Skold et al. 2002; Yaşar et al. 2015). In both studies, averaged participants' MAS scores increased from their end-of-trial measure to the follow-up, however both showed an overall improvement from their baseline measure. For participants who took part in the study by Gant et al. (2018), MAS scores of all participants were either increased or unchanged following 19 weeks of FES cycling.

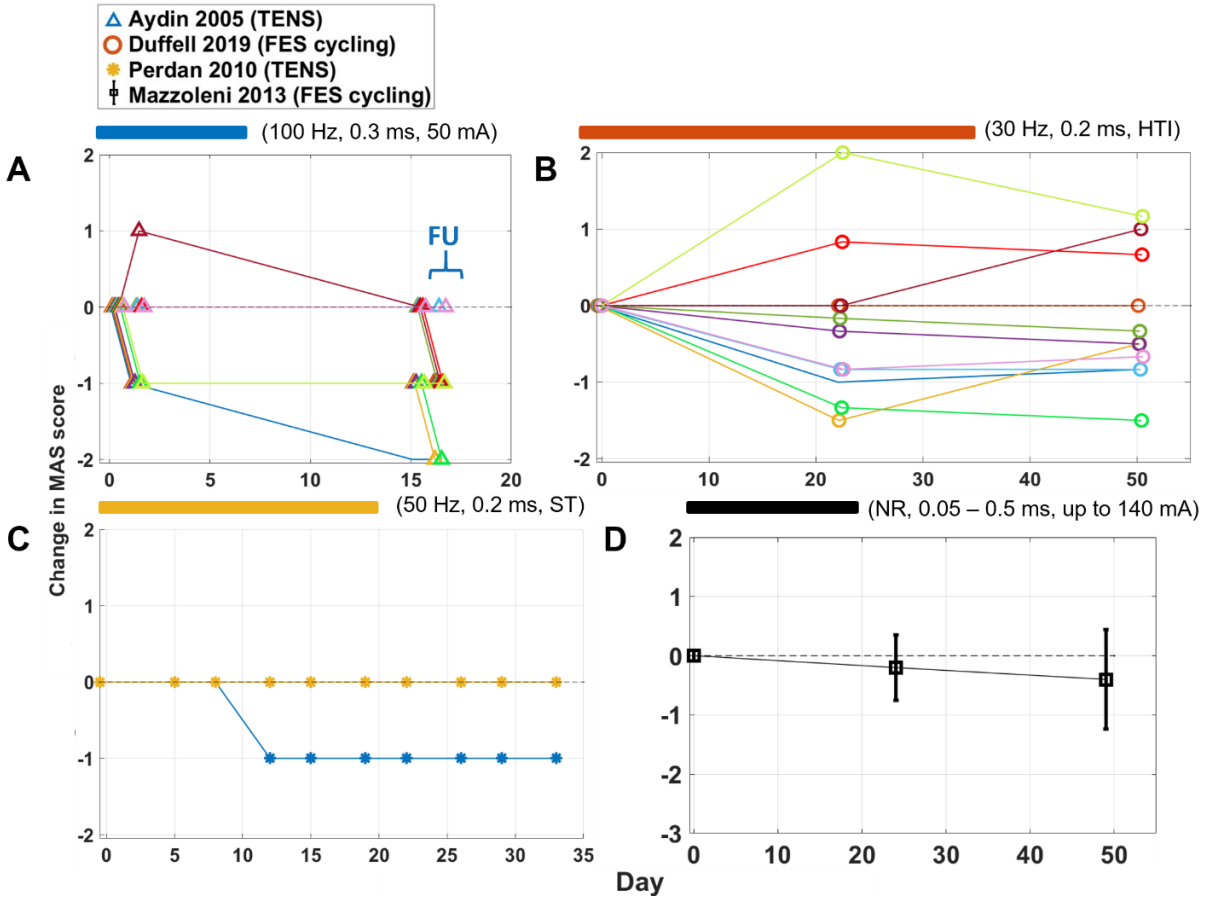

Figure 52:Individual changes in MAS scores from baseline of long-term non-RCT studies < 8 weeks in duration for: A) Aydin et al., (2005), B) Duffell et al., (2019), C) Perdan et al., (2010) and D) Gant et al., (2018). Datapoints plotted below the black dashed line represent a decrease in MAS score from baseline. Different colours of each symbol represent a different participant. Coloured bars above each plot represent the frequency used for each study. It should be noted that datapoints for Aydin et al. (2005) and Duffell et al. (2019) have been displaced so that points do not overlap. Results for Aydin et al. (2005) measure their outcomes at day 0, 1, 15 and 16. 'FU' denotes datapoints which were follow-up outcomes, measured after the intervention took place. Abbreviations: FES = functional electrical stimulation, MAS = modified Ashworth scale, RCT = randomised control trial, TENS = transcutaneous electrical nerve stimulation.

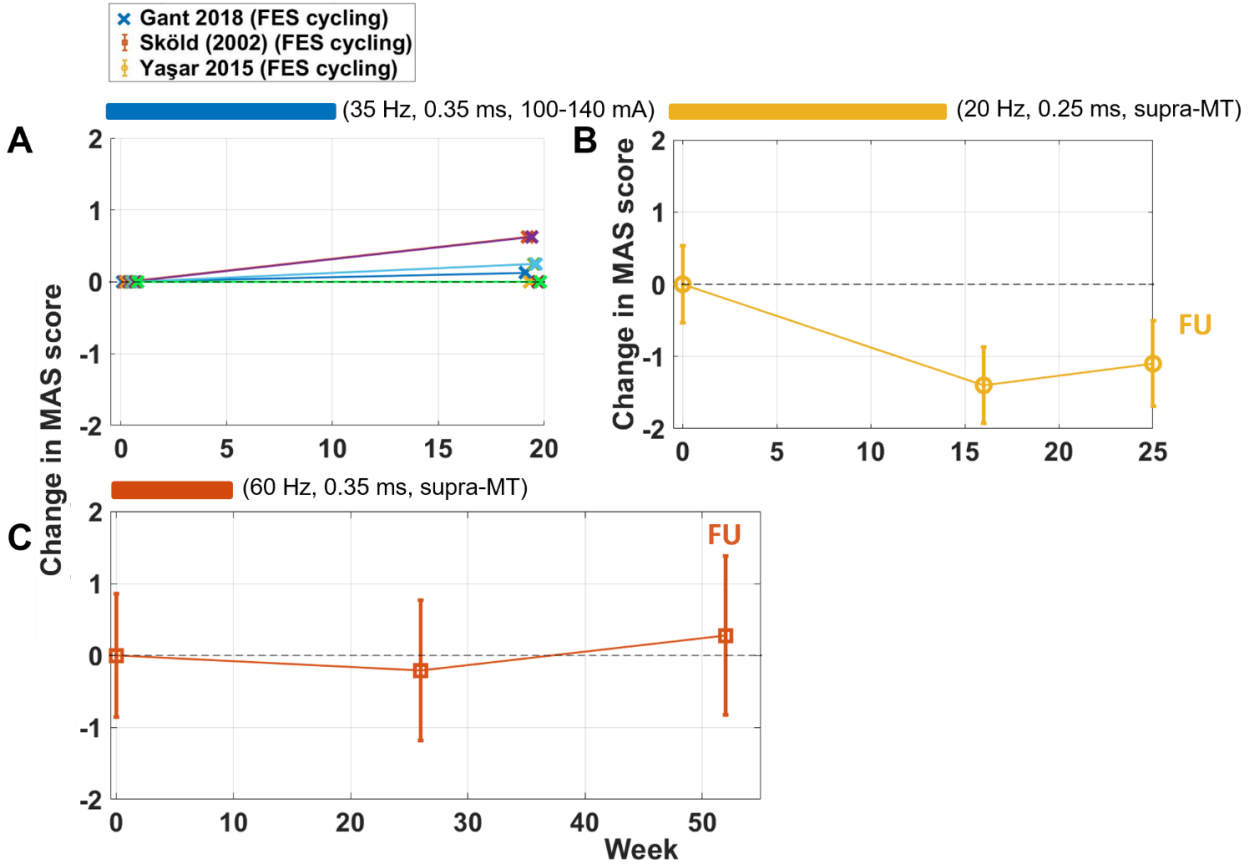

Figure 53: Change in MAS scores from baseline (represented as the black dashed line at y = 0) of long-term non-RCT studies which had >8 weeks of outcome measures for: A) Gant et al., (2018), B) Sköld et al.,(2002) and C) Yaşar et al. (2015) . Datapoints plotted below the black dashed line represent a decrease in MAS score from baseline. Datapoints with error bars represent studies where data has been presented as mean ± SD and those without show results for individual participants. Different colours of each symbol represent a different participant. Coloured bars above each plot represent the frequency used for each study. 'FU' denotes datapoints which were follow-up outcomes, measured after the intervention took place. It should be noted that all datapoints for Gant et al. (2018) have been displaced in the x-axis and that baseline datapoints for Sköld et al. (2002) and Yaşar et al. (2015) have also been displaced so that datapoints do not overlap. Abbreviations: FES = functional electrical stimulation, MAS = modified Ashworth Scale, RCT = randomised control trial.

2.10 *Acute changes in the R_{2n} in non-RCT studies*

Data from non-RCT studies is shown in Figure 54. All datapoints plotted are from studies for which PT results for individual participants were available and reported as R_{2n} (Bajd et al. 1985; Granat et al. 1993; Hofstoetter et al. 2014; 2020; Vargas Luna et al. 2016). Points above the dashed line show where R_{2n} measures have increased, indicating a decrease in spasticity. This figure shows results for a total of 31 participants (6 in Bajd et al. (1985), 6 in Granat et al. (1993), 3 in Hofstoetter et al. (2014), 12 in Hofstoetter et al. (2020) and 4 in Vargas Luna et al. (2016)). No results from included studies were plotted for R_{2n} as mean ± SD.

For the majority of studies, the intervention decreased the level of spasticity measured by R_{2n} (Bajd et al. 1985; Hofstoetter et al. 2020; Granat et al. 1993; Hofstoetter et al. 2014). Results reported by Vargas Luna et al. showed that 1 out of 3 of their participants had worsened spasticity, 2 had improved spasticity, and the authors determined that one participant did not have spasticity at baseline, since their value of $R_{2n} \sim 1$.

The most marked changes were in Bajd et al. (1985). In this study, participants had a higher level of spasticity at baseline compared to the other studies, which may have contributed to this larger change following intervention.

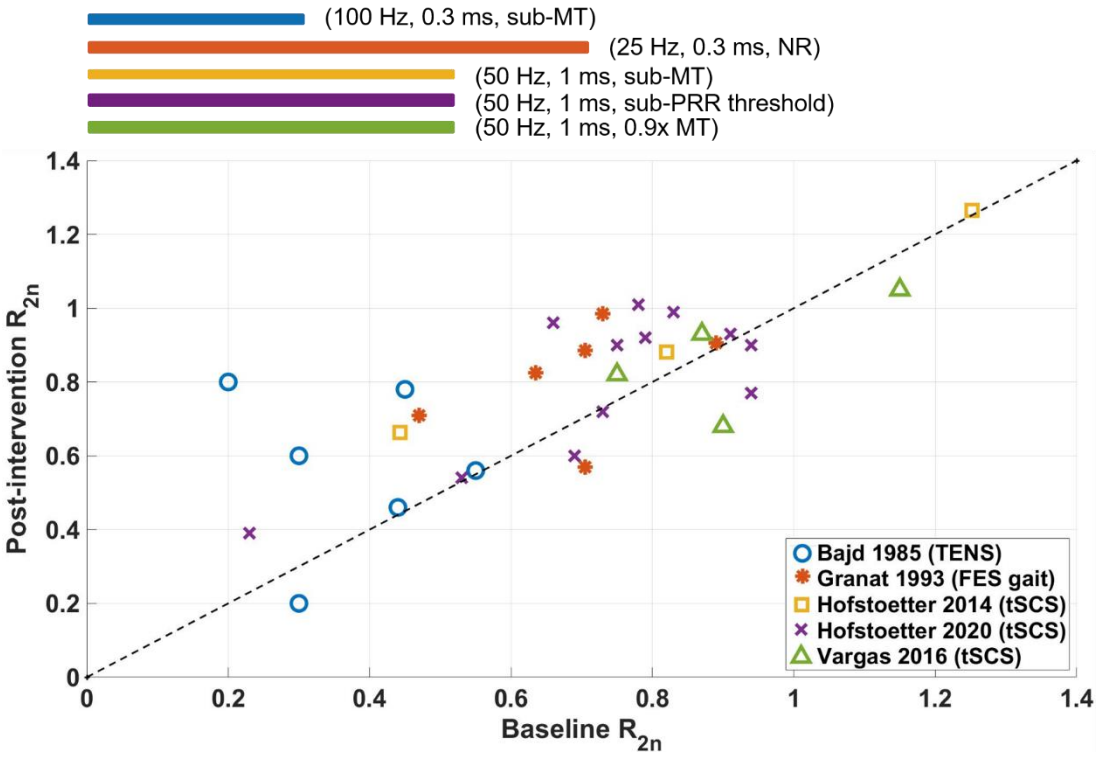

Figure 54: Changes in the R_{2n} of non-RCT studies. Datapoints along the dashed line signify no change in R_{2n} following intervention. Coloured bars above the plot represent the frequency used for each study. Abbreviations: FES = functional electrical stimulation, MT = motor threshold, NR = not reported, PRR = posterior-root reflex, TENS = transcutaneous electrical nerve stimulation, tSCS = transcutaneous spinal cord stimulation.

2.11 *Long-term changes in the H_{max}/M_{max} ratio in non-RCT studies*

Results from non-RCT studies which used the Hmax/Mmax ratio as an outcome measure are shown in Figure 55 for studies where results for individual participants were available. These figures show data from 19 participants in total (11 in Aydin et al. (2005), see Figure 55A) and 8 in Gant et al. (2018), see Figure 55B).

Seven participants in the study by Aydin et al. (2005) and 2 in Gant et al. (2018) show a reduction in H_{max}/M_{max} ratio from their baseline measure to the final measure (the follow-up measure for Aydin et al.), which evidence suggests is characteristic of a reduction in spasticity (Faist et al. 1994; Aymard et al. 2000; Angel and Hofmann 1963; Pierrot-Deseilligny et al. 2009). However, remaining participants showed either no change or an increase from their baseline measure, indicating that these interventions had either no effect or a negative impact on the majority of participants presented in Figure 55.

When comparing this data with that shown in Figure 52 and Figure 53, MAS scores for participants in the Aydin study show that 9 of 11 participants had an improved MAS score

and 2 unchanged, and 5 of 8 of Gant's participants having worsened MAS scores and 3 unchanged.

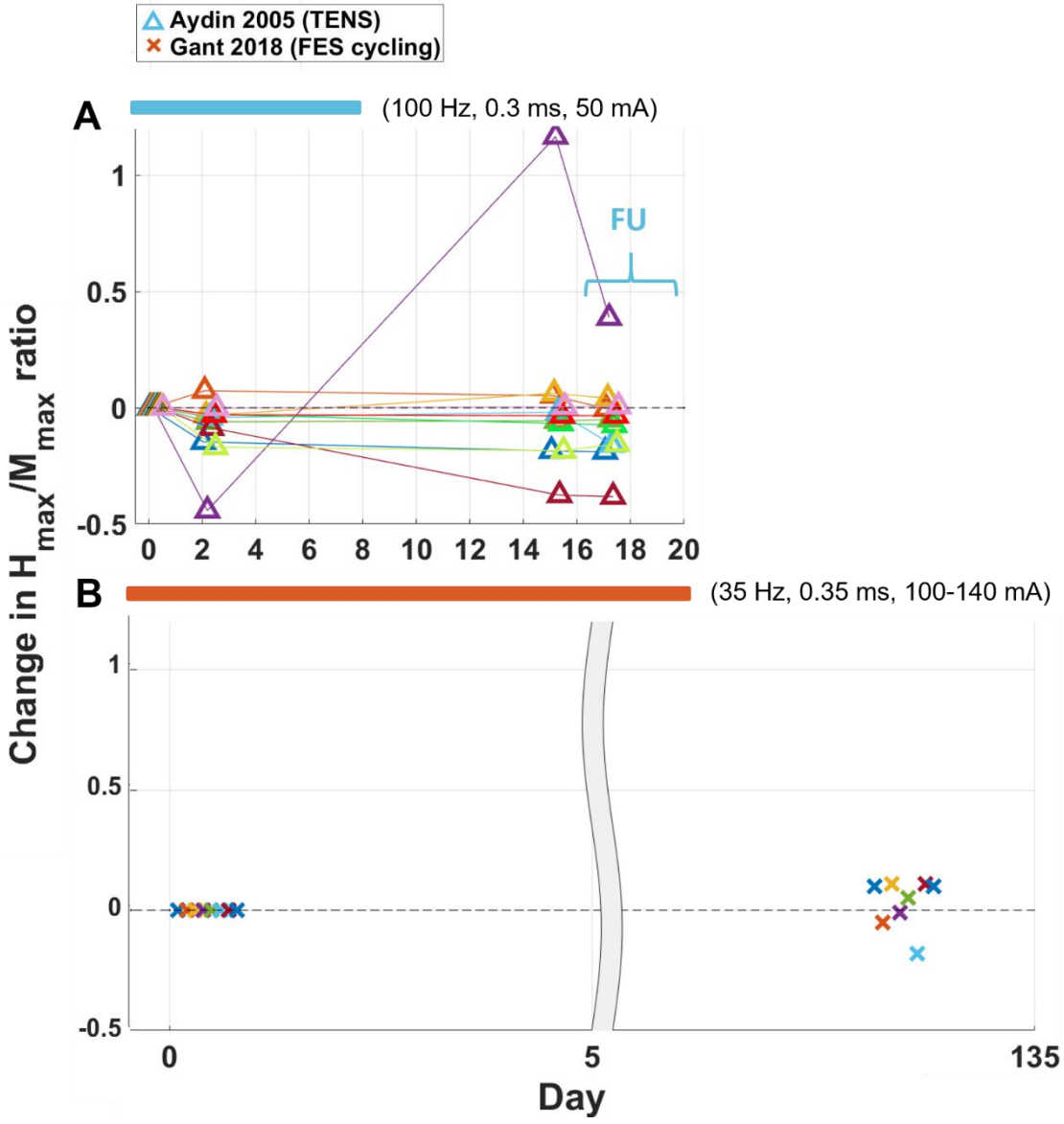

Figure 55: Changes in H_{max}/M_{max} ratio of long-term non-RCT studies for: A) Aydin et al., (2005) and B) Gant et al., (2018). Different colours of each symbol represent a different participant (the same colours have been used between outcome measures). Coloured bars above each plot represent the frequency used for each study. 'FU' denotes datapoints which were follow-up outcomes, measured after the intervention took place. It should be noted that all datapoints have been displaced so that points do not overlap. Aydin et al. (2005) measure their outcomes at day 0, 1, 15 and 16 and Gant et al. (2018) at day 0 and 133 (19 weeks). Abbreviations: FES = functional electrical stimulation, FU = follow-up, TENS = transcutaneous electrical nerve stimulation.

2.12 *Other reported outcome measures*

Most studies included in this systematic review also reported benefits to their participants in measures other than those required for eligibility in this review. Aydin et al. (2005) and Yaşar et al. (2015) found statistically significant reductions in the Functional Independence Measure following TENS and FES cycling respectively and clonus scores

were reduced in Goulet et al. (1996) and Oo et al. (2014) following TENS, and in Hofstoetter et al. (2020) following tSCS. A summary of changes in all reported outcome measures is shown in Table 18.

3 Discussion

3.1 *Summary of findings*

Results from this systematic review showed that there are not enough adequately powered RCTs to draw definitive conclusions. However, from the data presented here, non-invasive ES for the management of spasticity in people with SCI seems to be effective. From the RCTs, results may favour non-invasive ES with statistical significance, depending on the chosen value for the correlation coefficient. Results from non-RCTs overall showed a reduction in spasticity immediately following non-invasive ES. An overall reduction in spasticity measured by MAS scores was also seen in long-term trials. However, there was one study in these results where a 19-week programme of FES cycling caused either an increase or no change in MAS scores (Gant et al. 2018), as well as 4 cases where spasticity remained unchanged at the end of the study, compared to baseline measures (Robinson, Kett, and Bolam 1988b; Mazzoleni et al. 2013; Skold et al. 2002; Ralston et al. 2013).

Most participants also benefitted from non-invasive ES where spasticity was measured by the PT. Only Gant et al. (2018), reported no change in the PT following intervention (FES cycling), the same study also reported no changes or a worsening of MAS scores.

Only 4 studies in this systematic review included the H-reflex as a neurophysiological outcome measure (Aydin et al. 2005; Gant et al. 2018; Goulet et al. 1996; Van Der Salm et al. 2006). Of these, only one reported a reduction in the H_{max}/M_{max} ratio from baseline (Aydin et al. 2005), the remaining 3 reported no change, or varied results between participants. See Table 18 for more details.

The following sections discuss variations in stimulation protocols, the impact of the variation in reported outcome measures, any correlation found between clinical and neurophysiological outcomes and the consideration of errors and limitations in this systematic review and meta-analysis. It will further hypothesise on the impact of the reviewed literature in the field of spasticity self-management and give recommendations to future studies investigating non-invasive ES on spasticity in people with SCI. A discussion on the implications of results found in this systematic review and those given in chapter II and III of this thesis will follow in chapter VI.

3.2 *Variation between intervention protocols*

Although this systematic review covered only 4 methods of non-invasive ES (TENS, tSCS, FES cycling and FES gait), there exist many differences between protocols for the same intervention. Across all interventions, these differences were the frequency, pulse width, duration of intervention, stimulation intensity and the method of determining stimulation intensity.

With the exception of 2 studies (Gant et al. 2018; Robinson, Kett, and Bolam 1988b), overall, FES interventions tended to reduce spasticity. Similarly, with TENS and tSCS interventions, spasticity was generally reduced across the included studies. This shows that the efficacy of non-invasive ES in reducing spasticity may not be dependent upon its pairing with movement, the frequency, pulse width, or intensity of stimulation. With this wide range of protocols leading to similar outcomes, there may be many mechanisms at work across these protocols, and perhaps across types of SCI.

A huge variation in frequency and pulse width parameters is seen across the included studies. For studies included in this systematic review, those which used an FES intervention used a mean frequency of 34.8 Hz and stimulation intensity of 118.8 mA, whereas TENS and tSCS forms of intervention used a mean frequency of 56.5 Hz and mean stimulation intensity of 65.8 mA; all forms of intervention used a mean pulse width of 0.5 ms (see Table 19). Here, FES was given with lower frequencies and higher stimulation intensities compared to TENS and tSCS. These parameters may have been selected so that, at a minimum, an isometric muscle contraction was achieved, and at a maximum, muscle fatigue is minimised. For TENS and tSCS, there is a much larger range of frequencies used, however generally, most studies used frequencies >30 Hz (see Table 18 for an overview of all included studies).

Table 19: Mean (range) of frequencies, pulse widths and stimulation intensities used by all studies which use FES and TENS or tSCS. Where studies report a range of frequencies or pulse widths being used, the average has been taken. Where studies reported a range of stimulation intensities, the maximum intensity was used to account for interventions which included sham stimulation or passive movement (i.e. used 0 mA). In the case of stimulation intensity, only 16 studies reported a quantitative value (see Table 18). These values exclude those studied by Vodovnik et al. (1987) due to the large variation in frequencies and pulse widths investigated. Abbreviations: FES = functional electrical stimulation, TENS = transcutaneous electrical nerve stimulation, tSCS = transcutaneous spinal cord stimulation.

	FES interventions	**TENS/tSCS**
Frequency (Hz)	34.8 (20-60)	56.5 (5-100)
Pulse width (ms)	0.5 (0.05-0.5)	0.5 (0.3-1)
Stimulation intensity (mA)	118.9 (75-140)	65.8 (15-160)

Research carried out by Vodovnik, Stefanovska and Bajd (1987), compared varying combinations of frequencies and pulse widths, at similar stimulation intensities (up to 30 mA) during TENS (10-1000 Hz; 0.01-1 ms – see Table 18). This showed that spasticity assessed by the R_{2n} was reduced in 6 out of 7 participants for all variants of combinations, with 100 Hz having the largest effect (however, this was not statistically assessed). However, this was the only study included in this systematic review which directly compared several frequencies and pulse widths for the same form of non-invasive ES and no statistical analysis directly compared the efficacy of different frequencies at reducing spasticity.

From this systematic review, 5 of 6 studies using TENS, which obtained statistically significant improvements in spasticity, used a 99 or 100 Hz frequency (Aydin et al. 2005; Tadej Bajd et al. 1985; Goulet et al. 1996; Oo 2014; Sivaramakrishnan, Solomon, and Manikandan 2018), and the other used a 30 Hz frequency (Khanna and Kaur 2017). Of the remaining 4 studies which used TENS (excluding Vodovnik. Stefanovska and Bajd (1987)), all frequencies used were ≤ 50 Hz; results from these studies were not significant reductions, and in one case, spasticity was worsened (Robinson, Kett, and Bolam 1988b).

Other review papers share varying opinions on the topic; with some suggesting that frequencies of ~100 Hz are more effective at reducing spasticity in other aetiologies (Fernández-Tenorio et al. 2016; Mahmood et al. 2019) and others suggesting that TENS delivered at 4 Hz is superior to TENS at 25 Hz in spasticity arising from varying prognoses (Patricia Branco Mills and Dossa 2016). In an educational review, Nagel et al. (2017) suggest that SCS and tSCS at kHz frequencies may be the future of spasticity management. Clearly not enough is yet understood to determine which stimulation

parameters may be optimal for spasticity management in those with SCI. However, from this systematic review, results suggest that 100 Hz TENS may be superior to frequencies ≤ 50 Hz.

Reduction in spasticity seen across many different ES protocols may not be dependent on stimulation intensity. For FES, participants must sustain a useful muscle contraction and TENS or tSCS is expected to at least activate afferent fibres. For TENS and tSCS protocols, there were some studies which elicited muscle contractions during intervention and others which did not. Some studies used a fixed current amplitude across all participants and did not make it clear whether this amplitude caused muscle contraction (Aydin et al. 2005; Goulet et al. 1996; Robinson, Kett, and Bolam 1988b). Results presented in Figure 50-Figure 55 do not reveal distinct differences between FES interventions and TENS and tSCS protocols.

For TENS and tSCS studies where the intensity of ES was determined using a subjective method which was repeatable across participants (such as using motor or sensory threshold), 2 studies used a supra-MT stimulation intensity for TENS (Vodovnik, Stefanovska, and Bajd 1987; Khanna and Kaur 2017) and 7 studies used a sub-MT intensity (Bajd et al. 1985; Estes, Iddings, and Field-Fote 2017; Hofstoetter et al. 2014; 2020; Goulet et al. 1996; Perdan et al. 2010; Vargas Luna et al. 2016). Results presented by Khanna and Kaur (2017) still show a statistically significant reduction in spasticity following supra-MT TENS delivered to the agonist and antagonist separately in 30 participants, with no differences between these two groups. Non-statistically significant improvements in spasticity were also found in 7 participants presented by Vodovnik, Stefanovska and Bajd, 1987. Similarly, the above studies which used sub-MT intensities all saw decreases in clinical measures of spasticity (excluding Vargas Luna et al., 2016).

It is not clear whether the use of sub- or supra- MT stimulation is superior in the reduction of spasticity from the results presented in this meta-analysis. Spasticity may reduce following ES because of mechanisms such as presynaptic inhibition, recurrent inhibition and RI, all of which rely on the activation of afferent fibres (Pierrot-Deseilligy and Burke 2012). When ES is delivered supra-MT, antidromic firing, due to the stimulation of efferents, blocks afferent feedback, reducing the liklihood of these mechanisms being activated (Knikou 2008; Pierrot-Deseilligy and Burke 2012). Therefore, these mechanisms may not contribute towards spasticity reduction following supra-MT

threshold ES. However, both sub- and supra-MT ES, at least activate afferent fibres. Results from this systematic review show that both stimulation intensities reduced spasticity. This shows that the activation of efferent fibres using ES may not be necessary for reducing spasticity in people with SCI.

In the case of supra-MT ES paired with movement, the stimulation of afferents may not be the primary factor in the reduction of spasticity. With some studies reporting greater voluntary control and increased muscle bulk, as well as improvements in spasticity (Granat et al., 1993; Kuhn, Leichtfried and Schobersberger, 2014; Mazzoleni et al., 2017; Duffell et al., 2019), a training effect may increase modulation of descending and ascending control; leading to less uncontrolled spasms and increased voluntary movement.

Krause, Szecsi and Straube (2007) found a statistically significant difference in spasticity reduction, following FES cycling compared to passive cycling alone in 5 AIS A participants. Similar results were also seen in 7 AIS A SCI participants in a non-RCT study by Mazzoleni et al. (2017). There were no neurophysiological outcome measures in either study and both measured pre-post changes (in a single-session study (Krause, Szecsi, and Straube 2007) and multi-session study (Mazzoleni et al., 2017)). It cannot, therefore, be determined whether a reduction in spasticity due to plastic changes which may have occurred, or due to fatigue.

It has been theorised that improvements in function due to lower limb FES training following SCI may occur due to the stimulation of central pattern generators (CPGs) (Luo., 2020). Stimulating CPGs may promote increased control of spinal reflexes and therefore increased voluntary control (V. Dietz 2003). This may also result in a reduction in involuntary muscle spasms. The stimulation of CPGs has not yet been shown to improve spasticity, however, patterned ES delivered to the common peroneal nerve at 100 Hz (selected to reflect firing frequencies during walking) was shown to increase RI in healthy, able-bodied participants (Perez, Field-fote, and Floeter 2003). This theory may be a factor influencing the reduction in spasticity when supra-MT ES targets these CPGs.

Another factor to consider when discussing the modulated mechanisms is whether participants have a complete or incomplete SCI. Most FES studies which showed improvements in spasticity involved motor-incomplete SCI participants (Duffell et al. 2019; Kuhn, Leichtfried, and Schobersberger 2014; Murray et al. 2018; Yaşar et al. 2015).

For participants where an increase in muscle bulk was seen, stronger muscle spasms may have also occurred. However, both MAS and PT scores measure velocity-dependent components of spasticity. Had an increase in muscle tone resulted in stronger muscle spasms, these measures would have also increased. The addition of the PSFS allows for self-reported spasticity, which may be due to cutaneous-input spasms or spasms occurring due to other triggers, such as a full bladder or a change in temperature. It therefore may be hypothesised that this measured reduction in spasticity occurred due to increased control of mechanisms such as PI, recurrent inhibition and RI, thus increasing modulation both mediated by supra-spinal pathways as well as interneurons.

Following 30 minutes of tSCS, Hofstoetter et al. (2020) found similar results in AIS A participants and AIS C-D participants. This may indicate that, at least for AIS A participants (although this study has not considered whether these participants may have a discomplete injury), changes in spasticity may be occurring due to modulated pathways at a spinal level, below the level of injury, rather than increased modulation of descending pathways.

There is future potential to personalise these ES protocols based on an individual's presentation of spasticity and their type of SCI. There is severe inconsistency across groups of protocols (such as supra-MT and sub-MT protocols, or FES and TENS or tSCS protocols) which may be targeting a single group of mechanisms. Further research into which neurophysiological changes result in clinical improvements in spasticity may allow for personalised medicine within this field in the coming years.

3.3 *Variation in reporting of outcome measures*

Studies were included in this systematic review if they used the MAS, PT or PSFS. However, these measures were not reported in the same manner across studies. For the MAS, studies reported results using compound scoring (the sum of MAS scores across muscles), the average score across several muscles, or for individual muscles or participants. For the PT, studies reported results as the FSE, or as the R_{2n}. In some cases, studies did not report the values of these outcomes if their results were non-significant.

This variation in the reporting of outcome measures in research studies reduces the accuracy and precision of meta-analyses. Seven studies which qualified for this systematic review were not included in the meta-analysis because their results were reported in this way, or because they could not share their original data. Future studies

should report their outcome measures for individual participants, or ensure that this data is available for authors of future systematic reviews, as well as aiming to publish their work through open-access journals.

3.3.1 Correlation between clinical and neurophysiological outcome measures

Only 2 studies could be considered for analysis which included both the MAS score and the H_{max}/M_{max} ratio in their outcome measures (Aydin et al. 2005; Gant et al. 2018). Results presented by Aydin et al. (2005) show statistically significant decreases in both AS scores and the H_{max}/M_{max} ratio, whereas Gant et al. (2018) shows an increase in MAS scores and no overall change in H_{max}/M_{max} ratio.

Studies suggest H-reflex, and therefore spinal excitability, should correlate with spasticity, however much of this evidence exists for people with spasticity arising from a stroke (Angel and Hofmann 1963; Faist et al. 1994; Aymard et al. 2000). One acute study in this systematic review did not find any correlation between H_{max}/M_{max} ratio and MAS scores and were only able to elicit H-reflexes in 5 of 14 participants (Goulet et al. 1996). There is clearly a lack of research taking place which uses the MAS and PT scores as well as neurophysiological measures in people with SCI.

Investigating both clinical and neurophysiological measures in people with SCI would give an insight into the mechanisms occurring when a clinically meaningful reduction in spasticity is obtained. This would allow for more pre-clinical studies in people with an intact CNS to draw more meaningful conclusions. Developing these protocols in pre-clinical studies allows for refinement of neuromodulation protocols, testing for the most effective frequencies, pulse widths and stimulation intensities without the need for large-scale clinical RCTs. The large variation in the stimulation parameters for studies included in this systematic review has shown the need for such studies.

3.4 Consideration of errors

Data presented in the meta-analysis of RCTs, which used the MAS score as an outcome measure, counted the study by Van der Salm et al. (2006) 3 times. This is not recommended by the Cochrane resources (Higgins et al. 2020b), but it was necessary to assess separately each intervention used in the study. An alternative would have been to combine the effects of the 3 forms of TENS used, using Equations 3 and 4. Since the aim of this meta-analysis was to compare the efficacy of varying non-invasive ES protocols, this was not appropriate.

The specificity of MAS data was decreased through combining scores for individual muscles to obtain a single score for analysis. The intervention used may have affected some muscle groups and not others. Therefore, by combining these scores, analysis may include both positive and negative effects on different muscles. For consistency in the presentation of data, this review chose to combine data for those reported as separate muscles or legs as these studies were in the minority of those included. Where this was carried out (Kuhn, Leichtfried, and Schobersberger 2014; Krause et al. 2008; Sivaramakrishnan, Solomon, and Manikandan 2018; Skold et al. 2002; Yaşar et al. 2015), SDs did not often vary between time-points for each muscle or leg (i.e. SDs were similar for baseline measures or post-intervention measures). We can therefore consider that this amalgamation of data did not introduce significant errors into this analysis, however it did reduce its specificity and accuracy due to information being lost for specific muscles or legs of participants.

Figure 50 shows results for $Corr = -1$ and $Corr = 0$. The correlation coefficient describes the similarities between results obtained from different studies (Higgins et al. 2020a). A low correlation coefficient ($Corr \rightarrow -1$) is characteristic of high variability between baseline and post-intervention measures (i.e. the intervention has an effect on the variability of the outcome measure) (Higgins et al. 2020a). It can be argued that the correlation coefficient for the results presented is unlikely to be < 0 as all studies included were randomised-crossover trials, meaning that outcome measures are less likely to significantly differ for the same participant when they receive the control and active intervention. Additionally, at least one assessor was blinded to the intervention, decreasing bias between groups (Ralston et al. 2013; Krause et al. 2008; Van Der Salm et al. 2006), with one study using two assessors and reporting the average value (Phillip Krause et al. 2008) and another using one assessor to measure outcome measures, to further increase reliability in this measurement (Van Der Salm et al. 2006). Taking this into account, it is likely that results presented in Figure 50B, where $Corr = 0$ are a better representation of the true effect of non-invasive ES on spasticity in people with SCI ($p = 0.03$).

3.5 *Limitations*

The most important limitation of this systematic review and meta-analyses is the reliance upon data from non-RCT studies to come to the conclusions drawn here. It is recommended that meta-analyses are performed on RCT studies since these are least

likely to be biased (Higgins et al. 2020b). There is also a limitation on drawing conclusions relevant to this thesis. Although the evidence suggest that non-invasive ES is effective at reducing spasticity measured by MAS and PT scores, 26 of the 27 included studies were targeting lower limb spasticity, with only one paper reporting on 2 case studies using whole-hand TENS (Perdan et al. 2010). This is partially due to the inclusion of the PT as one of the primary outcome measures in this systematic review. However, the MAS is commonplace for measuring upper limb spasticity as well as lower limb and was expected to produce many more upper limb studies following an initial literature search.

This systematic review excluded papers which did not have any of the 3 chosen clinical measures of spasticity. This meant that studies were excluded which did include neurophysiological measures of spasticity but without clinical measures. Although there is evidence of these neurophysiological measures correlating with some clinical measures of spasticity (Cakar et al. 2016; Sangari et al. 2019; Pierrot-Deseilligy and Burke 2012), this systematic review aimed to prioritise clinically meaningful reductions in spasticity, thus assessing the efficacy of the 3 forms of neuromodulation investigated in chapter III of this thesis and the translation from results in healthy, able-bodied participants to those with spasticity.

This systematic review has also revealed that there are fewer RCTs available for spasticity arising from SCI compared to stroke. In a systematic review by Mahmood et al. (2019), 7 RCTs were included in meta-analysis and they were able to draw conclusions on: appropriate duration of intervention, frequency of intervention and electrode placement. This range of evidence does not exist in RCTs for the SCI population where studies do not report their outcome measures consistently, making it difficult to draw similar conclusions. Other systematic reviews assessing the effects of ES for spasticity in people with SCI did not carry out meta-analyses due to this lack of available data (Luo et al. 2020; Mahmood et al. 2019; Fernández-Tenorio et al. 2016; Bekhet et al. 2019; Mills and Dossa 2016). Although the amalgamation of evidence reported here and in other available systematic reviews reports on the efficacy of non-invasive ES, the coming years of research will be paramount for research teams developing conclusive evidence.

Some studies included in this systematic review did not include data where non-statistically significant results were reported (Granat et al. 1993; Kapadia et al. 2014;

Franek, Turczynski, and Opara 1988) (where Granat et al. (1993) reported results for the PT, but not the MAS). This may introduce bias when carrying out meta-analyses as this data cannot be included unless it is provided, meaning that there is less evidence available which reports the possible negative impact of non-invasive ES on spasticity.

3.6 *Pathway to self-management of spasticity?*

The aim of this chapter is to assess which form of non-invasive neuromodulation may be most effective as a self-management protocol for people with spasticity to use at home. Research carried out in most of the included studies is an important step towards developing these protocols, with some noting that future directions should include home-based therapy for their respective interventions (Mazzoleni et al. 2013; Duffell et al. 2019; Kuhn, Leichtfried, and Schobersberger 2014; Gant et al. 2018). For 2 studies, home-based interventions were delivered, to one participant as tSCS (Hofstoetter et al. 2020) and in 6 participants using an FES gait system (Granat et al. 1993), for 6 weeks and up to 6 months respectively. These 7 participants all had incomplete SCIs. In both cases, participants were given a period of instruction before they were able to take the equipment for home use.

Participants who used an FES gait system for at least 6 months saw mixed results (Granat et al. 1993). While participants saw an increase in voluntary muscle strength and stride length, there were mixed results for spasticity outcome measures. There was a statistically significant decrease in R_{2n} values, but mixed results for AS scores. This may indicate that spastic tone was decreased, however resistance to passive movement still remained in some participants (Bajd and Vodovnik 1984; Pandyan et al. 1999).

Following 6 weeks of tSCS, in one participant, the R_{2n} score increased from week 3-5, followed by a decrease at week 6, and at their week 1 follow-up; however their MAS sum scores continually decreased throughout the intervention period, followed by increases at 1 and 2 week follow-up, which were less than their baseline measure (Hofstoetter et al. 2020). In this study, EMG evaluations also showed a decrease in clonus, cutaneous-input evoked spasms and stretch reflexes, which increased in follow-up evaluations, but remained below the baseline level.

Results from these studies show that both clinically relevant decreases in spasticity, as well as decreases in neurophysiological activity for home-based therapies could be effectively delivered in those with incomplete SCI (Granat et al. 1993; Hofstoetter et al.

2020). The participant in the study by Hofstoetter et al. (2020) also continued to take their anti-spasticity medication throughout the study, showing that tSCS may still be effective when used in conjunction with other self-management protocols. These studies mark an important and progressive step towards delivering varying types of non-invasive ES for spasticity management and their integration into home-life.

3.7 *Recommendations for future studies*

This systematic review and meta-analysis have shown that the disparity between research protocols and reporting practices leads to a lack of specificity when amalgamating the data available in this field. Future research protocols should adhere to a standard, using common clinical outcome measures such as the MAS and PT scores, making this data readily available as supplementary material when it is inappropriate to publish all data. This systematic review suggests that future research studies should report their results using the R_{2n} and MAS scores for individuals.

Future studies should also consider the addition of neurophysiological outcome measures. This component of spasticity measurement may allow for a deeper understanding of the location and neural pathways involved in spasticity modulation following non-invasive ES. By understanding which pathways may contribute to a reduction in spasticity, our understanding of the effect of varying the stimulation intensity and frequency in activating these pathways may be developed, allowing for the refinement of ES protocols.

Where possible, researchers should be encouraged to develop any research protocols as RCTs, as control data gives an important and clear comparator for appropriate statistical analysis with matched participants.

The most important recommendation for future studies is to report negative and non-significant results. Unpublished negative results, or no data given for non-statistically significant results can be dangerous as it can bias meta-analyses to report on available data, which is more likely to report on positive results (Mlinaric, Horvat, and Smolcic 2017).

4 Conclusion

This systematic review and meta-analysis found that TENS, tSCS, FES cycling and FES gait were effective at reducing spasticity in people with SCI, according to MAS scores and R_{2n} values. There was little data available to assess how these results may correlate with neurophysiological measures; however, results from two studies showed some similar implications for spasticity from both MAS scores and H_{max}/M_{max} ratios.

Reductions in spasticity following sub-MT tSCS and TENS spasticity show that activation of afferent fibres is at least required for ES to be an effective intervention for spasticity management in people with SCI. Pairing ES with functional movement may not be necessary, however results do not show a negative effect on spasticity in this case.

This review concludes that more evidence is required for specific stimulation parameters to be recommended (frequency, pulse width and stimulation dose) and for the effects of these parameters on varying levels and severities of SCI.

VI. Overall discussions and conclusions

1 Summary

The proposed research questions for this thesis were: 1) are upper limb PRRs an appropriate tool to assess changes in HD following neuromodulation? 2) Which stimulation parameters and site of activation is most effective at modulating cortical and spinal excitability in healthy, able-bodied adults? 3) Can a mobile app be used to manage spasticity symptoms through education of exasperating factors? 4) Which stimulation parameters and site of activation is most effective at improving clinical and neurophysiological outcome measures of spasticity in people with SCI?

Subsequent sections will outline how results presented in this thesis addressed each of these research questions. It will also bring together results from healthy, able-bodied studies and those from the systematic review. The future directions these studies may take will be discussed and the overall conclusions of this thesis will be given.

2 Are upper limb PRRs an appropriate tool to assess changes in HD following neuromodulation?

Elicitation of HD in upper limb PRRs was investigated in 8 healthy, able-bodied participants in chapter II. HD was successfully elicited for ISIs < 2 s for 3/5 participants who did not experience sensation related to median nerve stimulation, and for 3/3 participants who did experience this sensation. Overall results from this study were consistent with results from studies investigating lower limb PRRs (Hofstoetter et al. 2019), as well as upper and lower limb H-reflexes (Hultborn and Nielsen 1998; Aymard et al. 2000). However, similar difficulties with the consistency of this method were shown in upper limb PRRs in a study by Einhorn et al. (2013).

A preliminary test was introduced, testing paired-pulses of tSCS at ISIs of 30, 50 or 100 ms to ensure the stimulation of afferents at the tSCS electrode site, as recommended by Hofstoetter et al. (2014). The method described in chapter II was then used as an investigatory tool for 5 participants in the study carried out chapter III.

The preliminary test was carried out in 7 out of a possible 20 sessions (4 sessions for 5 participants) as not all participants could tolerate these paired pulses at such short ISIs. There was clear HD in results from 4 of these 7 sessions. However, this did not lead to conclusive changes in HD following 30 minutes of neuromodulation in those where HD was seen in this preliminary test, nor those where it was not.

It can therefore be concluded that upper limb PRRs elicited via tSCS can exhibit HD in some participants. This method was not a useful investigatory tool in further participants due to the sensation of paired-pulses not being tolerated by all participants in this small cohort.

3 Which stimulation parameters and site of activation is most effective at modulating cortical and spinal excitability in healthy, able-bodied adults?

In chapter III, the assessment of 30 minutes of 3 forms of neuromodulation (HF-tSCS applied over the cervical vertebrae, TENS and HF-TENS applied over the FCR) in 9 healthy, able-bodied adults concluded that TENS and HF-tSCS may be more effective at mediating central pathways compared to HF-TENS and sham ES.

Specifically, HF-tSCS reduced corticospinal excitability in the targeted muscle (FCR), increased this measure in its antagonist (ECRL) and showed an overall reduction in both muscles for spinal excitability. This may indicate that HF-tSCS modulated DI at a cortical level, lasting for up to 30 minutes, and reduced overall spinal excitability. This was also the case following TENS, but to a lesser extent. Similar results were also seen following neuromodulation in other studies (Bertolasi et al. 1998; Tinazzi et al. 2005).

It was therefore concluded that HF-tSCS was most effective at modulating neurophysiological mechanisms in healthy, able-bodied participants which would be associated with reduced spasticity in populations with SCI.

A clinical study in up to 5 participants with SCI was planned and is fully outlined in Appendix II. This study aimed to investigate the effects of 4 weeks of 30 minutes of HF-tSCS, delivered 1-2 times per week. Both clinical (MAS) and neurophysiological (PRRs, HD, MEPs) outcomes would be assessed at week 0, week 4 and at a follow-up of 2 weeks following the final session (week 6). Self-assessed spasticity would be measured using the PSFS throughout by the participant, using the app described in chapter IV. This study marks the next steps of this research question. Its completion would determine whether the results from the able-bodied study were translatable to the SCI population, and the inclusion of neurophysiological outcomes in this clinical study would improve our understanding of the relationship between changes in clinical and neurophysiological outcome measures with changing spasticity.

4 Can a mobile app be used to manage spasticity symptoms through education of exasperating factors

A novel mobile app was successfully created where users could log an event which triggered their spasticity, select the time of day and location of the spasm, and rate their spasms using the PSFS. Users could then access their logged events as a summary, or through graphs. These graphs show how triggers of spasticity were rated according to the two components of the PSFS (frequency and severity), and can be viewed for each day, week or month.

This app can also be used in future studies assessing the effects of neuromodulation on spasticity, as a tool to measure self-reported spasticity through the PSFS. In this case, feedback would be disabled to reduce its influence on changes in spasticity.

The initial design of the app was assessed by potential app users (n = 2) and their clinicians (n = 10) through online questionnaires. The questionnaires showed that the design of the app, including feedback data, was clear and easy to interpret by both potential users and clinicians. All responders thought the app may or would benefit the management of triggers of spasticity.

Overall, these results showed that the initial design of the app does not need significant modifications. The next steps would be to assess the usability and reliability of the app. Although the PSFS has shown good intra- and inter-rater reliability in people with SCI (Patricia B. Mills et al. 2018), this has not been shown for participants independently using the PSFS at home.

The effects of using this app as an educational and feedback tool should also be assessed. With educational apps for healthcare showing success in diabetes management (Liang et al. 2011), this app has potential to decrease occurrence of spasticity by teaching its users which factors may be exasperating their spasticity.

5 Which stimulation parameters and site of activation is most effective at improving clinical and neurophysiological outcome measures of spasticity in people with SCI?

The systematic review of 27 studies and quantitative synthesis of 20 studies presented in chapter V revealed that non-invasive ES is effective at reducing spasticity in people with SCI, both immediately following single sessions and after participation in long-term trials, according to the MAS and R_{2n} measures. However, only 4 of these studies included neurophysiological outcome measures, with 2 of these 4 showing correlations between H_{max}/M_{max} ratios and MAS scores.

Recommendations to future studies in this field from this systematic review are to: be consistent with the already published literature when selecting outcome measure of spasticity – MAS and R_{2n} scores are commonly used and scores for individual participants should be accessible; consider the inclusion of neurophysiological outcomes as well as clinical outcomes in future studies; include a control group where possible; and publish negative or non-statistically significant results.

6 Comparison between healthy, able-bodied studies and the reviewed literature

Results from the systematic review highlight the shortfall of published research available which assesses both the clinical benefits of non-invasive ES for people with spasticity arising from a SCI, as well as neurophysiological outcomes.

Analysis of results presented in chapter III shows DI occurring in corticospinal pathways, as well as a trend towards a generalised reduction in spinal excitability. Two studies obtained through systematic review of the literature assessed spasticity using both H_{max}/M_{max} ratios and MAS scores. For one study, a statistically significant reduction was seen in both the H_{max}/M_{max} ratio as well as the MAS scores, following TENS (Aydin et al. 2005). This reduction in the H_{max}/M_{max} ratio indicates a reduced spinal excitability, which is desirable to reduce spasticity (Faist et al. 1994; Aymard et al. 2000; Angel and Hofmann 1963). A reduction in spinal excitability was also seen in our PRR study of 9 healthy participants, although this result was not statistically significant. This shows some potential for the translation of work carried out in chapter III to people with SCI.

However, this reduction in both the H_{max}/M_{max} ratio and MAS scores was not seen in the study by Gant et al. (2018), following FES cycling, with results varying between participants and time points. Gant et al. (2018) reported an increase in lower limb muscle strength as well as an increase in M_{max} across most participants. This may have led to the unclear change in the H_{max}/M_{max} ratio and the overall increase in MAS scores. These changes to the muscles, occurring across a long-term training protocol (19 weeks), may influence the variation in spasticity outcome measures.

As discussed in chapter I, the upper limb H-reflex remains a difficult outcome measure to obtain reliably within the SCI population (Goulet et al., 1996; Stowe et al., 2013). For healthy, able-bodied adults, its reliability improves when facilitation (sustained muscle contraction) is used (Ann Marie Stowe et al. 2008; Jaberzadeh et al. 2004). Facilitation may be difficult to achieve in populations with an SCI causing upper limb spasticity, as the muscles may be weakened, or the muscle stretch may induce spasticity itself.

In chapters II and III of this thesis, we chose to use the PRR as a measure of spinal excitability, comparable to the H-reflex (Minassian et al., 2007; Hofstoetter, Freundl, Binder, et al., 2019a). Although the PRR was not included as an outcome measure in

studies included in the systematic review, reductions in lower limb PRR amplitude following non-invasive ES have been shown (Milosevic, Masugi, Obata, et al. 2019).

MEPs were also not measured by any studies included in the systematic review. Although there have been some studies showing correlation between MEP amplitude and severity of spasticity in SCI (Sangari et al. 2019) and stroke (Cakar et al. 2016). These studies did not use MAS, PT or PSFS scores to assess spasticity. DI occurring at a corticospinal level following HF-tSCS, seen in chapter III is also seen in other studies in healthy, able-bodied participants (Bertolasi et al. 1998; Tinazzi et al. 2005).

Further investigation into influences of neuromodulation on MEPs and PRRs and how they change with respect to clinical outcome measures is required to determine whether PRRs are a reliable method of assessing changes in spinal excitability in those with SCI.

Although it is difficult to assess the potential of HF-tSCS as a means of spasticity management in people with SCI using the results obtained in chapter III, the systematic review carried out in chapter V clearly shows the efficacy of non-invasive ES at reducing spasticity. Four of these showed reductions in spasticity following tSCS (Hofstoetter et al. 2014; 2020; Vargas Luna et al. 2016; Estes, Iddings, and Field-Fote 2017), 2 of which reported statistically significant reductions in their clinical measures of spasticity (Hofstoetter et al. 2020; Estes, Iddings, and Field-Fote 2017).

Although these studies did not use kHz tSCS, its benefits for neuropathic pain have been shown in recent years (Kapural and Al-Kaisy 2018; Van Buyten et al. 2013; Al-Kaisy et al. 2015), with potential for translated benefits to populations with spasticity (Nagel et al. 2017). The decreased paraesthesia which comes with the use of kHz tSCS may also increase uptake in its use or reduce abandonment.

Results in chapter V showed that TENS is also effective at reducing spasticity in people with SCI, where 6 of 10 studies included in the systematic review obtained statistically significant improvements in spasticity measures (Aydin et al. 2005; Bajd et al. 1985; Goulet et al. 1996; Oo 2014; Sivaramakrishnan, Solomon, and Manikandan 2018; Khanna and Kaur 2017). Four of 10 studies using FES also showed statistically significant reductions in spasticity (Granat et al. 1993; Phillip Krause et al. 2008; Kuhn, Leichtfried, and Schobersberger 2014; Mazzoleni, Battini, et al. 2017). This suggests that TENS is at least as effective as FES at reducing spasticity. Therefore, efferent activation, nor ES paired with movement may be necessary for effective spasticity management.

However, HF-tSCS does not activate afferents to the same extent as ES without kHz carrier frequencies and therefore does not stimulate back muscles, nor cause discomfort. This collation of evidence shows the potential for spasticity management in adults with SCI using HF-tSCS. Primary outcome measures for future studies should be focussed on clinical measures, such as the MAS, to ensure a participant-focussed trial. However, the inclusion of neurophysiological measures as secondary outcomes will give us an important insight into how the neurophysiology changes with spasticity.

7 Overall conclusion

The results presented in this thesis contribute towards future developments of neuromodulation protocols for the management of upper limb spasticity in adults with SCI.

Further work is required to evaluate the effectiveness of HF-tSCS for spasticity in people living with SCI. This investigation should focus on clinical outcome measures as they are most relevant to patients, following the recommendations for future studies outlined in chapter V. This will allow for direct comparison between published techniques of spasticity management using non-invasive ES, including HF-tSCS, as well as increasing our understanding of the underlying mechanisms of action, which will benefit the patients, and the research in this field.

VII. References

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VIII. Appendix I – Triggers of spasticity questionnaire: complete results from clinicians

Table 20: Responses 1-4 and 6-11 from clinicians in the questionnaire outlined in chapter IV.

Participant	1	2	3	4	5	6	7	8	9	10
Q1 Do you think using this app could benefit your patient's spasticity management?	Maybe	Yes	Maybe	Yes	Yes	Yes	Yes	Yes	Yes	Maybe
Q2 Would you encourage your patient to use this app?	Yes	Yes	Maybe	Yes	Yes	Yes	Yes	Yes	Yes	Maybe
Q3i How many of your patients do you think recognise he triggers of their own spasticity?	Many	Some	Some	Half	Many	Many	Many	Many	Half	All
Q3ii To which extent do you think these patients can recognise the triggers of their spasticity?	Some what	Some what	Some what	Some what	Some what	Some what	Some what	Some what	Some what	Fully
Q4Do you think this app would make it easier for your patients to identify triggers of their spasticity?	Maybe	Yes	Maybe	Yes	Yes	Yes	Maybe	Maybe	Yes	Maybe
Q6 Do you think the self-reported data collected will be reliable?	Maybe	Yes	Maybe	Maybe	Yes	Yes	Maybe	Maybe	Maybe	Yes
Q7 Are the graphs easily interpretable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q8 Is the design of the app simple and clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q9 Could the graphs displayed in this app be useful in your sessions with patients?	Maybe	Yes	Maybe	Maybe	Yes	Yes	Maybe	Maybe	Yes	Maybe
Q10 Could the graphs displayed in this app be useful for treatment planning?	Maybe	Yes	Maybe	Maybe	Yes	Yes	Maybe	Maybe	Yes	Maybe
Q11 Would this app be useful for outpatients as a complementary report?	Yes	Yes	Yes	Maybe	Yes	Yes	Yes	Maybe	Yes	Maybe

Table 21: Responses to question 5 (are the triggers outlined below relevant in your opinion?) in the questionnaire for clinicians outlined in chapter IV. 1 denotes a 'yes' response and a 0 denotes no response (i.e. the trigger was not selected by the responder).

Participant	1	2	3	4	5	6	7	8	9	10
Bowel movement	1	0	0	1	0	1	1	1	1	0
Changing position	1	0	0	1	1	1	1	1	1	0
Constipation	0	1	1	1	1	1	1	1	1	0
External temperature	1	0	0	1	1	0	0	1	0	1
Frequent naps during the day	0	0	0	0	0	0	0	0	0	0
Full bladder	1	1	1	1	1	1	1	1	1	1
Incomplete bladder emptying	0	1	0	1	0	0	1	1	1	0
Ingrown toenail	1	1	1	1	1	1	1	1	1	0
Lying on your back	0	0	0	0	1	1	0	1	1	1
Making transfers	0	0	1	1	0	1	1	1	1	0
Menstruation	0	0	0	1	1	0	0	1	1	1
Muscle fatigue	0	0	0	1	1	0	0	1	0	0
Pressure ulcers	1	1	1	1	1	1	1	1	1	0
Sitting	1	0	0	0	0	0	1	1	0	0
Skin	1	0	0	0	1	1	0	1	1	1
Stress and anxiety	0	1	1	1	1	1	0	1	1	1
Tight clothes	1	0	1	1	0	0	1	1	1	0
Tight splint/orthosis	1	0	1	1	0	0	1	1	1	0
Tiredness/drowsiness	0	0	0	1	0	1	0	1	0	1
Time of day	0	0	0	1	1	1	1	1	1	1
Unable to sleep at night	0	0	0	0	0	0	0	1	1	1
Urinary tract infection	1	1	1	1	1	1	1	1	1	1
Other(s)									Medically unwell	

Table 22: responses to question 20 in the questionnaire for clinicians outlined in chapter IV. Participants who are not shown in the above table did not leave any comments.

Participant	Q12 Are there any other comments you would like to add?
3	Very dependent on individual patient, diagnosis and engagement in self management. For someone who was very self aware it may be beneficial prior to clinic to aid change of management or medication but I feel there may be a big population who are unable to access, use and engage with this system
4	The app is good and I think it would be useful self management tool for some patients and help to target spasticity treatment. Spasticity is often very complex and may be triggered by more than one thing e.g. a full bladder may not cause spasms in the morning, but in the afternoon when someone may be more fatigued, the combination of a full bladder and fatigue may trigger a spasm. This would be hard to identify in the app, unless logged under both categories. I work with patients using electrical stimulation and this can sometimes induce spasms. I would encourage patients to add this as a category to see how often different modes of the electrical stimulation device are provoking spasms. Good luck with the rest of your research!
5	Useful tool to evaluate treatment effectiveness. Similarly for trial of equipment, exercise and swimming etc. Could be used for evidence in other research and evidence to support provision of an intervention, such as FES.
8	I think it could also be useful as a pre and post spasticity intervention, and also for research projects. It may also help patients learn more about their own patterns of spasticity and triggers

IX. Appendix II – The effects of kilohertz transcutaneous spinal cord stimulation on neurophysiological and clinical outcome measures in people with spasticity in spinal cord injury

This study will consist of single case studies of people with SCI who experience upper limb spasticity to determine the feasibility of either electrical stimulation delivered over the spinal cord with a kilohertz carrier frequency (HF-tSCS). Each participant will receive the same 30-minute intervention, which consists of 1 or 2 sessions per week (whichever is possible for the participant), for 4 weeks, with 1 follow-up session 1-2 weeks following their last session.

Participants will answer the Spasticity and Pain Assessment questionnaire prior to each session they attend throughout the study. Before and after the intervention, the participant will undergo a neurophysiology assessment and their MAS score will be measured. Figure 57 shows an overview of the study timeline.

Results of this study will explore the efficacy of the chosen form of neuromodulation for the management of upper limb spasticity in people with SCI. If successful, there is potential for a future randomised clinical trial to determine its use for home use and self-management of upper limb spasticity.

Inclusion criteria for taking part in this study are:

1. Over the age of 18

2. Spinal cord injury for > 1 year

3. Spinal cord injury level C1-C6

4. AIS A-D

5. Clinically diagnosed with abnormal rigidity of the wrist, Modified Ashworth Scale score at least 1+

6. Willing and able to provide written informed consent

Exclusion criteria for taking part in this study are:

1. Women who are pregnant, planning pregnancy or breastfeeding

2. Those who have a cardiac pacemaker

3. Implanted metal or active device at electrode site (caudle to T1; e.g. screws, metal plates)

4. Any other musculoskeletal diagnosis affecting the upper limbs

5. Spinal malignancy

6. Uncontrolled autonomic dysreflexia

7. Complex regional pain syndrome

8. Neurological degenerative diseases

9. Peripheral nerve damage affecting the upper limbs

10. People who do not present with spasticity during their first session

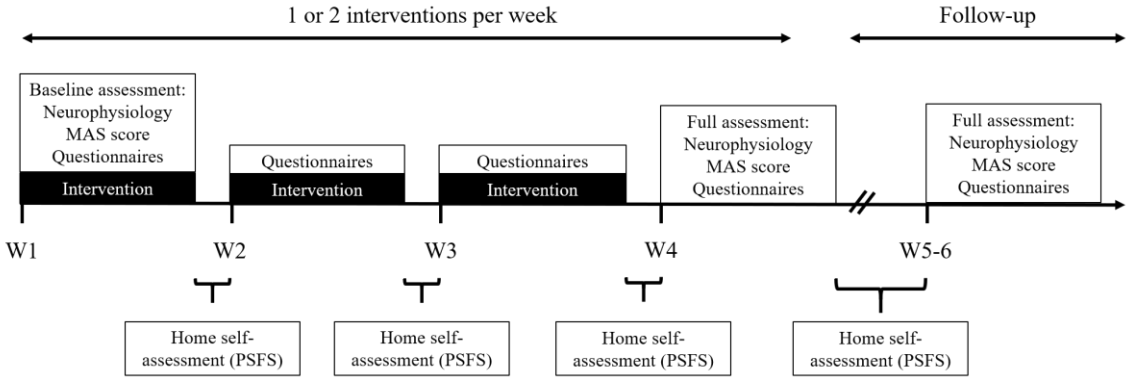

Figure 56: Study timeline, showing the first session of each week. Participants will be asked to carry out a self-assessment of their spasticity using a mobile app, which will ask them to rate their spasms according to the Penn Spasm Frequency Scale.

X. Appendix III – PEDro scale

Criterion:

1. eligibility criteria were specified
2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)
3. allocation was concealed
4. the groups were similar at baseline regarding the most important prognostic indicators
5. there was blinding of all subjects
6. there was blinding of all therapists who administered the therapy
7. there was blinding of all assessors who measured at least one key outcome
8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"
10. the results of between-group statistical comparisons are reported for at least one key outcome
11. the study provides both point measures and measures of variability for at least one key outcome

Notes on administration of the PEDro scale:

All criteria Points are only awarded when a criterion is clearly satisfied. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.

Criterion 1 This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.

Criterion 2 A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.

Criterion 3 Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".

Criterion 4 At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.

Criteria 4, 7-11 Key outcomes are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.

Criterion 5-7 Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.

Criterion 8 This criterion is only satisfied if the report explicitly states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.

Criterion 9 An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

Criterion 10 A between-group statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.

Criterion 11 A point measure is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. Measures of variability include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

XI. Appendix IV – Study information sheets and consent forms

- Neuromodulation studies with healthy, able-bodied adults information sheet
- Neuromodulation studies with healthy, able-bodied adults consent form
- App questionnaire information sheet
- Neuromodulation for people with spinal cord injury information sheet
- Neuromodulation for people with spinal cord injury consent form

Aspire CREATe Lab
Royal National Orthopaedic Hospital (RNOH)
Brockley Hill
Stanmore HA7 4LP

Participant Information Sheet For Participants

UCL Research Ethics Committee Approval ID Number: 6864/005

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: The Effects of Neuromodulation on the Upper Limb H-reflex in Healthy, Able-bodied Adults
Department: Surgery and Interventional Science
Name and Contact Details of the Researcher(s): Sarah Massey (sarah.massey.13@ucl.ac.uk)
Name and Contact Details of the Principal Researcher: Lynsey Duffell (l.duffell@ucl.ac.uk)

Invitation Paragraph

You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the project's purpose?

We are investigating the effects of different types of neuromodulation on the excitability of the central nervous system. These include neuromuscular electrical stimulation (NMES), which is applied to the muscle or nerve; conventional transcutaneous spinal cord stimulation (tSCS); high-frequency 'Russian' tSCS, both applied close to the spinal cord and focal vibration (FV) applied to the muscle, tendon or bone.

To measure the effects of these types of therapies on central excitability, we will measure your upper limb H-reflex, which is a well-known response in muscles, reflecting how excitable the nerves are. We will also measure the effects on upper limb motor-evoked potentials (MEPs), which tell us how signals travel from the brain to the periphery and therefore the excitability along this path. This will help us to understand the effects of this type of therapy for people with spasticity.

Why have I been chosen?

You have been invited to take part because you are healthy and over the age of 18 years with no problems involving your back or upper limbs. You also fall under the exclusion

criteria outlined in the form 'Exclusion Criteria for Healthy Adults taking part in TMS studies'.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw at any time without giving a reason and without it affecting any benefits that you are entitled to. If you decide to withdraw you will be asked what you wish to happen to the data you have provided up that point.

What will happen to me if I take part?
Should you choose to take part, you will be invited to the Aspire CREATe Lab at the Royal National Orthopaedic Hospital, Stanmore. We ask that you wear a t-shirt, vest or loose-fitting clothes. When you arrive, you may ask the researcher any questions you have. Self-adhesive recording electromyography (EMG) will be placed on your arm and electrical stimulation (ES) electrodes and/or a vibrating motor will be placed on the arm, or ES electrodes will be placed to your back, depending on which session you are attending.

Each session will start with baseline measurements by applying single or pairs of pulses of ES to your arm and also by applying single or pairs of pulses of transcranial magnetic stimulation (TMS) to your motor cortex. You will then be given 30-45 minutes of NMES, tSCS, high-frequency 'Russian' tSCS, FV, and/or a combination of these, or no intervention at all. Depending on which session you are attending, measures of H-reflex and MEPs will be systematically repeated throughout the form of neuromodulation intervention. You will then have a resting period after the intervention, where these measures will be taken at regular intervals. If you feel uncomfortable with the level of TMS, form of ES and/or FV at any time, please inform the researcher and the intensity levels will be adjusted or stopped.

Unfortunately, we are unable to provide reimbursement for travel expenses to the Royal National Orthopaedic Hospital.

What are the possible disadvantages and risks of taking part?
There is a small risk of reddening or irritation of the skin under the stimulation electrodes. Slight reddening which fades after about 10 minutes is normal. Please inform the researcher and seek medical advice if you notice any prolonged skin reddening or

soreness. In rare cases you may not be able to continue in the study or may need to take a break for a few days before recommencing once the skin reaction has resolved.

You may experience some discomfort during the TMS and electrical stimulation. Please inform the investigator if you experience any discomfort. If you do feel discomfort, we will decrease the level of stimulation to a more comfortable level for you.

There are some possible side effects of TMS, which are generally mild, including:

- Headache
- Scalp discomfort at the site of stimulation
- Tingling, spasms or twitching of facial muscles
- Lightheadedness
- Discomfort from noise during treatment

Serious side effects are rare. They can include:

- Seizures (TO NOTE: all drivers participating should stop driving and inform the DVLA if this happens. For HGV drivers this could affect their licence)
- Mania, particularly in people with bipolar disorder
- Hearing loss due to inadequate ear protection during treatment

What are the possible benefits of taking part?

Whilst there are no immediate benefits for those people participating in the project, it is hoped that this work will benefit people with spasticity. You may choose to receive a copy of the final report of this study.

What if something goes wrong?

Please inform the investigator if you have any health concerns due to your participation in this research study. If you experience any side-effects during your participation, we will stop the experiment immediately until the effects have resolved. We will then only continue if you choose to and if it is deemed safe to do so. In the event of an emergency, the RNOH medical emergency team will be called immediately. If you wish to raise a complaint about the research study, please contact the principal researcher (Dr Lynsey Duffell). If you feel your complaint has not been handled to your satisfaction, you may contact the Chair of the UCL Research Ethics Committee (ethics@ucl.ac.uk).

Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential. You will not be able to be identified in any ensuing reports or publications.

Limits to confidentiality

Confidentiality will be respected subject to legal constraints and professional guidelines.

What will happen to the results of the research project?
The results will be disseminated through seminars, conference presentations and publications. You will not be identified in any report or publication. The data collected during the course of the project may also be used for additional or subsequent research. You may choose to receive a copy of any publications arising from this research when you complete the consent form.

Data Protection Privacy Notice
The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk. UCL's Data Protection Officer is Lee Shailer and he can also be contacted at data-protection@ucl.ac.uk**.**

Your personal data will be processed for the purposes outlined in this information sheet. The legal basis that would be used to process your personal data will be the provision of your consent. You can provide your consent for the use of your personal data in this project by completing the consent form that has been provided to you.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

Who is organising and funding the research?
This research is being organised and sponsored by UCL. The research is funded by the Leslie Trust.

Contact for further information
If you would like further information on the study, please contact Lynsey Duffell (l.duffell@ucl.ac.uk). You will be given a copy of this information sheet and your signed consent form to keep.

Thank you for reading this information sheet and for considering to take part in this research study. Please read our additional information sheet updating you on the procedures now in place in light of the Covid-19 pandemic.

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: The effects of Neuromodulation on the Upper Limb H-reflex in Healthy, Able-bodied Adults
Department: Surgery and Interventional Science
Name and Contact Details of the Researcher(s): Sarah Massey (sarah.massey.13@ucl.ac.uk)
Name and Contact Details of the Principal Researcher: Dr Lynsey Duffell (l.duffell@ucl.ac.uk)
Name and Contact Details of the UCL Data Protection Officer: Lee Shailer (data-protection@ucl.ac.uk)
This study has been approved by the UCL Research Ethics Committee: Project ID number: 6864/005

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box below I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes means that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element that I may be deemed ineligible for the study.

		Tick Box
1.	I confirm that I have read and understood both Information Sheets for the above study. I have had an opportunity to consider the information and what will be expected of me. I have also had the opportunity to ask questions which have been answered to my satisfaction	
2.	I confirm that I have read and understood the Information Sheet for procedures in place for reducing COVID-19 transmission risks. I have had an opportunity to consider the information and what will be expected of me. I have also had the opportunity to ask questions which have been answered to my satisfaction.	
3.	**Personal Information** I understand that: For purposes of Government-led contact tracing, I will need to supply my mobile phone number, address and email address. These data will be stored in accordance with General Data Protection Regulation (2018) that protects the privacy of personal information. No one other than the researchers (and authorized government officials, if necessary) will have access to this data. This data will be securely deleted 3 weeks after the participation date as shown on this form.	
4.	I consent to the processing of my personal information *(age, height, weight, hand dominance)* for the purposes explained to me. I understand that such information will be handled in accordance with all applicable data protection legislation.	
5.	**Use of the information for this project only** I understand that confidentiality will be respected subject to legal constraints and professional guidelines. I understand that my data gathered in this study will be pseudonymised and stored securely. It will not be possible to identify me in any publications.	

6.	I understand that my information may be subject to review by responsible individuals from the University (to include sponsors and funders) for monitoring and audit purposes.	
7.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason. I understand that if I decide to withdraw, any personal data I have provided up to that point will be deleted unless I agree otherwise.	
8.	**COVID-19 transmission risk:** I understand that whilst every effort is made to reduce COVID-19 transmission risks down to manageable levels, the risk cannot be abolished completely.	
9.	I understand the potential risks of participating and the support that will be available to me should I become distressed during the course of the research.	
10.	I understand that the data will not be made available to any commercial organisations but is solely the responsibility of the researcher(s) undertaking this study.	
11.	I understand that I will not benefit financially from this study or from any possible outcome it may result in in the future.	
12.	I agree that my psuedonymised research data may be used by others for future research.	
13.	I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. Yes/No	
14.	I hereby confirm that I understand the inclusion criteria as detailed in the Information Sheet and explained to me by the researcher.	
15.	**My responsibility:** I confirm that I will adhere to the instructions detailed in the information sheet including those that relate to face covering, hand sanitizing and social distancing. I understand that my contact details will be shared with Government officials in case contact tracing is necessary. I will inform the experimenter, using the contact details provided to me, in the event that I test positive for COVID-19 within 1 week of today's date.	
16.	I hereby confirm that: (a) I understand the exclusion criteria as detailed in the Information Sheet and explained to me by the researcher; and (b) I do not fall under the exclusion criteria.	
17.	I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.	
18.	I am aware of who I should contact if I wish to lodge a complaint.	
19.	I voluntarily agree to take part in this study.	
20.	Use of information for this project and beyond I would be happy for the data I provide to be archived at UCL. I understand that other authenticated researchers will have access to my pseudonymised data.	

If you would like your contact details to be retained so that you can be contacted in the future by UCL researchers who would like to invite you to participate in follow up studies to this project, or in future studies of a similar nature, please tick the appropriate box below.

	Yes, I would be happy to be contacted in this way	
	No, I would not like to be contacted	

Participant details for contact tracing:

Name:

Email:

Address:

Mobile phone number:

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of witness (If applicable)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Participant Information Sheet for Participants

UCL Research Ethics Committee Approval ID Number: 14277/001

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: Development of an application to log triggers of spasticity
Department: Aspire Centre for Rehabilitation Engineering and Assistive Technology

Name and Contact Details of the Researcher(s):
Sarah Massey (sarah.massey.13@ucl.ac.uk)
Nadia Sciacca (nadia.sciacca.17@ucl.ac.uk)

Name and Contact Details of the Principal Researcher:
Anne Vanhoestenberghe (a.vanhoest@ucl.ac.uk)

Invitation Paragraph
You are being invited to take part in a research project. Before you decide it is important for you to understand why the research us being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the project's purpose?
Spasticity is a neurological disorder which causes increased tone and involuntary muscle contractions. It is present in populations with spinal cord injury, and those who have suffered a stroke. Symptoms of spasticity can be triggered by: temperature; pressure on the skin; a full bladder and stress. Although there are interventions which ease the symptoms, it is unclear how they affect the triggers, if at all.

We would therefore like to create an accessible smart phone application (app) for people with spasticity to be able to easily input the triggers for their spasticity as and when they experience it in their everyday life. The app will process this information into easy-to-read statistics, which we hope will support patient education and self-management, as well as increase our understanding. It is important that this app has a simple user interface to encourage user acceptance.

To meet this goal, we would like to send you information about the current design of the app and an anonymous online questionnaire to people with spasticity and clinicians who work with them. In this questionnaire, we will ask you to identify triggers of spasticity, how you would use the app and whether you think the app would be useful for the self-management of spasticity. The answers to this questionnaire will be used to develop the app and its interface.

Why have I been chosen?
You have been chosen to participate in this study because you have been identified as a person with spasticity or a clinician who works with people with spasticity. We feel that your input is precious to the development of this app.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep. You can withdraw at any time without giving a reason and without it affecting any benefits that you are entitled to. If you decide to withdraw you will be

asked what you wish to happen to the data you have provided up that point. The questionnaire you fill in will not ask for any information that will make you identifiable. You do not have to complete all questions if you do not wish to do so.

What will happen to me if I take part?
If you choose to take part, you will be asked to watch a short video explaining what the app does and how it would work. After this, you will be asked to fill in a short, anonymous online questionnaire.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risks of taking part.

What are the possible benefits of taking part?
Whilst there are no immediate benefits to participating in this project, it is hoped that this work will help to develop an effective app which will help people to manage their own spasticity at home.

What if something goes wrong?
Please inform the investigator if you have any concerns about your participation in this research. If you wish to raise a complaint this study, please contact the principal researcher (Dr Anne Vanhoestenberghe). If you feel your complaint has not been handled to your satisfaction, you may contact the Chair of the UCL Research Ethics Committee (ethics@ucl.ac.uk).

Will my taking part in this project be kept confidential?
All the information that we collect about you during the course of the research will be kept strictly confidential. You will not be able to be identified in any ensuing reports or publications.

Limits to confidentiality
Confidentiality will be respected subject to legal constraints and professional guidelines.

What will happen to the results of the research project?
The results will be disseminated through seminars, conference presentations and publications. You will not be identified in any report or publication. The data collected may also be used for additional or subsequent research.

Local Data Protection Privacy Notice
The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data and can be contacted (data-protection@ucl.ac.uk).

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice: www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.

Your personal data will not be used for this research study. We will contact you via email or in person and your questionnaire will be completed anonymously online. Your results will not be connected to your email in any way and so you will not be identifiable from your data.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the ICO. Contact details, and further details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

Who is organising and funding the research?

This research is being organised and sponsored by UCL. The research is funded by the Leslie Trust.

Contact for further information

If you would like further information on the study, please contact Sarah Massey (sarah.massey.13@ucl.ac.uk). You will be given a copy of this information sheet.

Thank you for reading this information sheet and for considering to take part in this research study.

Participant Information Sheet For Adults in Clinical Studies

UCL Research Ethics Committee Approval ID Number: _____

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: Mechanisms of neuromodulation for spasticity management in people with spinal cord injury

Department: Aspire Centre for Rehabilitation Engineering and Assistive Technology (Aspire CREATe) **Name and Contact Details of the Researcher(s):**
Sarah Massey (sarah.massey.13@ucl.ac.uk)
Anne Vanhoestenberghe (a.vanhoest@ucl.ac.uk)
Name and Contact Details of the Principal Researcher:
Lynsey Duffell (l.duffell@ucl.ac.uk)

Invitation Paragraph

You are being invited to take part in a research project. Before you decided it is important for you to understand why the research is being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the project's purpose?

Spasticity is a neurological condition which occurs in people with spinal cord injuries (SCIs) due to a lack of control over muscle activity from the central nervous system. Neuromodulation, in the form of non-invasive stimulation delivered over the muscle or spinal is thought to decrease spasticity in people with SCI. We are investigating the effects of electrical stimulation delivered **either** over the wrist flexor, **or** over the spinal cord, on upper limb spasticity. You will be informed of where the stimulation will be delivered **before** you agree to take part in the study.

We would like to evaluate how the chosen form of neuromodulation could be used as a part of a selfmanagement protocol. This will be assessed through changes in clinical measures of spasticity using the Modified Ashworth Scale (MAS) and through neurophysiological measures to help us to understand why this treatment changes spasticity in people with SCIs.

Why have I been chosen?

You have been asked to take part in this study because you identify yourself as someone with upper limb spasticity due to a spinal cord injury level C1-C6.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw from the study at any time without giving a reason and without penalty or loss of benefits that you are entitled to. If you do decide to withdraw, you will be asked what you wish to happen to that data that you have provided up to that point, provided it has not been anonymised at that point.

What will happen to me if I take part?

If you do choose to take part, you will be asked to attend **2 sessions**. Each session will take place at the Aspire CREATe lab at the Royal National Orthopaedic Hospital in Stanmore, HA7 4LP.

During these sessions, we will be measuring your muscle activity, through electrodes which are placed on the skin, and ask you to attempt to perform various movements with your arms and hands. This will give us a baseline measure of your muscle spasms. A physiotherapist will also be present to measure your Modified Ashworth Scale (MAS) score, a clinical measure of spasticity. You will then receive 30 minutes of electrical stimulation, delivered **either** over the forearm muscles, **or** over the spinal cord: you will be informed of which you will receive **before** your first session. At both sessions you attend, you will be receiving two types of stimulation, delivered at the same location (either the forearm or over the spine). You will also be asked to fill in the Spasticity and Pain questionnaire.

You will receive up to £50 towards your travel to each of the sessions you attend once you provide your travel receipts.

Will I be recorded and how will the recorded media be used?
With your permission, video recordings and photographs will be taken during your activities in this research. These will be used only for analysis and for illustration in conference presentations and lectures. No other use will be made of them without your written permission, and no one outside of the project will be allowed access to the original recordings. These recordings and photographs, should you agree to them, will be stored on a password protected external hard drive.

What are the possible disadvantages and risks of taking part?
There is a small risk that electrical stimulation can bring on autonomic dysreflexia (AD). Symptoms of AD may be a sudden increase in blood pressure and a severe headache. If you experience any symptoms of AD, electrical stimulation will be discontinued. You will be asked to bring your AD medication to each of your sessions and will be advised to take your medication for AD if symptoms do not resolve. Clinicians and first aiders will also be on site should an AD event occur.

There is a small risk of reddening or irritation of the skin under the stimulation electrodes. Slight reddening which fades after about 10 minutes is normal. Please inform the researcher and seek medical advice if you notice any prolonged skin reddening or soreness. In rare cases you may not be able to continue in the study or may need to take a break for a few days before recommencing once the skin reaction has resolved.

What are the possible benefits of taking part?
We cannot promise that taking part in this study will benefit you directly, however the information that we gain from your participation will help us to develop self-management protocols for upper limb spasticity involving electrical stimulation.

What if something goes wrong?
Please inform the investigator if you have any health concerns due to your participation in this research study. If you experience any side-effects during your participation, we will stop the experiment immediately until the effects have resolved. We will then only continue if you choose to and if it is deemed safe to do so. In the event of an emergency, the RNOH medical emergency team will be called immediately. If you wish to raise a complaint about the research

study, please contact the principal researcher (Dr Lynsey Duffell). If you feel your complaint has not been handled to your satisfaction, you may contact the Chair of the UCL Research Ethics Committee (ethics@ucl.ac.uk).

Will my taking part in this project be kept confidential?
All the information that we collect about you during the course of the research will be kept strictly confidential. You will not be identified in any ensuing reports or publications.

Limits to confidentiality

- Please note that assurances on confidentiality will be strictly adhered to unless evidence of wrongdoing or potential harm is uncovered. In such cases the University may be obliged to contact relevant statutory bodies/agencies.
- Please note that confidentiality will be maintained as far as it is possible, unless during our conversation I hear anything which makes me worried that someone might be in danger of harm, I might have to inform relevant agencies of this.
- Please note that confidentiality may not be guaranteed; due to the limited size of the participant sample.
- Confidentiality will be respected subject to legal constraints and professional guidelines.
- Confidentiality will be respected unless there are compelling and legitimate reasons for this to be breached. If this was the case we would inform you of any decisions that might limit your confidentiality.
- Confidentiality may be limited and conditional and the researcher has a duty of care to report to the relevant authorities possible harm/danger to the participant or others.

What will happen to the results of the research project?
The results will be disseminated through seminars, conference presentations and publications. You will not be identified in any report or publication. The data collected during the project may also be used for additional or subsequent research. You may choose to receive a copy of any publications arising from this research when you complete the consent form.

Data Protection Privacy Notice

Notice:
The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice:

For participants in research studies, click here

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.

The lawful basis that will be used to process your personal data are: 'Public task' for personal data and' Research purposes' for special category data.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk

If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protectionreform/overview-of-the-gdpr/individuals-rights/

Who is organising and funding the research?
This research is being organised and sponsored by UCL, and is funded by the Leslie Trust.

Contact for further information
If you would like further information on the study, please contact Sarah Massey (sarah.massey.13@ucl.ac.uk). You will be given a copy of this information sheet and your signed consent form to keep.

Thank you for reading this information sheet and for considering to take part in this research study.

CONSENT FORM FOR PARTICIPANTS IN CLINICAL STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: Mechanisms of neuromodulation for spasticity management in people with spinal cord injury

Department: Aspire Centre for Rehabilitation Engineering and Assistive Technology (Aspire CREATe)

Name and Contact Details of the Researcher(s):
Sarah Massey (sarah.massey.13@ucl.ac.uk)
Anne Vanhoestenberghe (a.vanhoest@ucl.ac.uk)

Name and Contact Details of the Principal Researcher:
Lynsey Duffell (l.duffell@ucl.ac.uk)

Name and Contact Details of the UCL Data Protection Officer: Alexandra Potts data-protection@ucl.ac.uk

This study has been approved by the UCL Research Ethics Committee: Project ID number: 14277/002

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box below I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes means that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element that I may be deemed ineligible for the study.

		Tick Box
1.	I confirm that I have read and understood the Information Sheet for the above study. I have had an opportunity to consider the information and what will be expected of me. I have also had the opportunity to ask questions which have been answered to my satisfaction	
2.	I understand that I will be able to withdraw my data at any time during and following the study.	
3.	I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified. I understand that my data gathered in this study will be stored anonymously and securely. It will not be possible to identify me in any publications.	
4.	I understand that my information may be subject to review by responsible individuals from the University (to include sponsors and funders) for monitoring and audit purposes.	
5.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without the care I receive or my legal rights being affected. I understand that if I decide to withdraw,	

	any personal data I have provided up to that point will be deleted unless I agree otherwise.	
6.	I understand that I will not benefit financially from this study or from any possible outcome it may result in in the future. I will only receive up to £50 towards travel expenses following the provision of travel receipts.	
7.	I agree that my pseudonymised research data may be used by others for future research. [No one will be able to identify you when this data is shared.]	
8.	I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. Yes/No	
9.	I consent to videos or photos being taken, and understand that the recordings will be:	
	Stored anonymously, using password-protected software and will be used for training, quality control, audit and specific research purposes. **To note: If you do not want your participation photographed or recorded you can still take part in the study**.	
10.	I hereby confirm that I understand the inclusion criteria as detailed in the Information Sheet and explained to me by the researcher.	
11.	I hereby confirm that: (a) I understand the exclusion criteria as detailed in the Information Sheet and explained to me by the researcher; and I do not fall under the exclusion criteria.	
12.	(b) I agree that my GP may be contacted if any unexpected results are found in relation to my health.	
13.	I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.	
14.	I am aware of who I should contact if I wish to lodge a complaint.	
15.	I voluntarily consent to take part in this study. I understand that according to data protection legislation, 'public task' will be the lawful basis for processing, and 'research purposes' will be the lawful basis for processing special category data.	

If you would like to subscribe to our 'Participate in Research' email list, please tick the box below to indicate this and provide your email address. You will then be informed of new research studies being carried out at the Aspire CREATe lab and choose to take part. You can also opt out of this email list whenever you like.

	Yes, I would be happy to be added to the 'Participate in Research' email list	
	No, I would not like to be contacted	

If yes, please provide your email:
……..

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of witness (If applicable)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

XII. Appendix V – Journal articles

- Massey, S., Al'joboori, Y., Vanhoestenberghe, A. and Duffell, L. (2020). Eliciting homosynaptic depression in upper limb posterior root reflexes using transcutaneous spinal cord stimulation. Journal of Neurophysiology. In progress.
- Al'joboori, Y., Massey, S., Knight, S., Donaldson, N., Duffell, L. (2020). The effects of adding transcutaneous spinal cord stimulation to sit-to-stand training in people with spinal cord injury. Journal of Clinical Medicine, 9(9), p.2765.

XIII. Appendix VI – Conference abstracts

- Massey, S., Sciacca, N., Liu, Y., Nicholson, S., Sanders, S., Duffell, L., and Vanhoestenberghe, A. (2019). Development of a mobile application to assess the use of neuromodulation for the self-management of upper limb spasticity. In BioMedEng19 conference.
- Massey, S., Al'joboori, Y., Vanhoestenberghe, A and Duffell, L. (2018). The effects of neuromodulation on central excitability of the upper limb in healthy, able-bodied adults. In IFESS conference.

BioMedEng19

Development of a mobile application to assess the use of neuromodulation for the self-management of spasticity

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Introduction

Spasticity is a neurological disorder affecting voluntary motor control (Thompson et al., 2005). Clinical features of spasticity, such as clonus (rhythmic contractions), occur as an aberrant response to muscle stretch (Kheder et al., 2012). Consequently, this interferes with day-to-day activities. Other triggers such as temperature, bladder emptying and stress are also known to affect spasticity (Cheung et al., 2015; Phadke et al., 2013).

Studies of new methods to treat spasticity should assess changes in the severity and frequency of spastic events, related to the trigger which caused them. Recording this outcome measure through a mobile application (app) allows participants to provide this information at any time of the day, from anywhere.

We therefore propose the design of an app which can record this information. Our focus is on spasms as the spastic event monitored as part of a study to measure the effects of electrical neuromodulation on spasticity.

Design

Following a spasm, or at the users' own convenience, they will input the nature of the trigger which caused this spasm, either from a list provided, or by entering their own trigger description. They will then rate the severity and frequency of this event using the Penn Spasm Frequency Scale and select where on the body it occurred using a diagram. Following this, users will be asked to add a comment, or skip this step. The data will be time-stamped, therefore creating a day-by-day diary of severity and frequency of spasms, with optional diary inputs, as well as building a picture of intrinsic and extrinsic triggers affecting each app user.

Discussion & conclusion

When using this app as an outcome measure in a clinical study, we cannot ignore the fact that by asking the participants to input a trigger of their spasticity, we are making them more aware of the possibility of spastic events occurring, therefore creating a modality for self-management of spasticity. Conversely, raising awareness of certain triggers may cause anxiety and an increased spastic response to those triggers. To address this, we will include formal questionnaires before and after the intervention to assess awareness and attitudes towards intrinsic and extrinsic triggers of spasticity.

This app is currently being developed for a clinical study assessing the effects of neuromodulation on spasticity. Besides the obvious advantages of ease of data collection for the outcome measure, the app will also allow the participants in this clinical study to engage in the self-management of their spasticity.

Acknowledgements

We would like to give thanks to the Leslie Trust for funding this project and to Dr Yun Fu for providing support for the development of this app.

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Development of a mobile application to assess the use of neuromodulation for the self-management of spasticity

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Introduction

- Spasticity is a neurological disorder affecting voluntary motor control [1].
- Uncontrolled contractions can be triggered as an aberrant response to muscle stretch [2], which can occur during day-to-day activities.
- Other triggers such as temperature, bladder activity and stress are also known to affect spasticity [3].
- People with spasticity may be able to better manage their condition if triggers were identified as they occur.
- This type of self-management may be enhanced through education using mobile phones applications (or Apps) [4], which allow triggers to be recorded at any time of the day, from anywhere.

The aim of this study was to design an App for patients to self-report spasms, using the Penn Spasm Frequency Scale (PSFS).

App Overview

Following a spasm, or at the users' own convenience, they may input the nature of the trigger which caused a spasm (Figure 1). The severity and frequency of the event can be rated using the PSFS, and where on the body it occurred can be indicated in a diagram. Following this, users can add a comment, or skip this step (Figure 2). The data is time-stamped, therefore creating a day-by-day diary of severity and frequency of spasms.

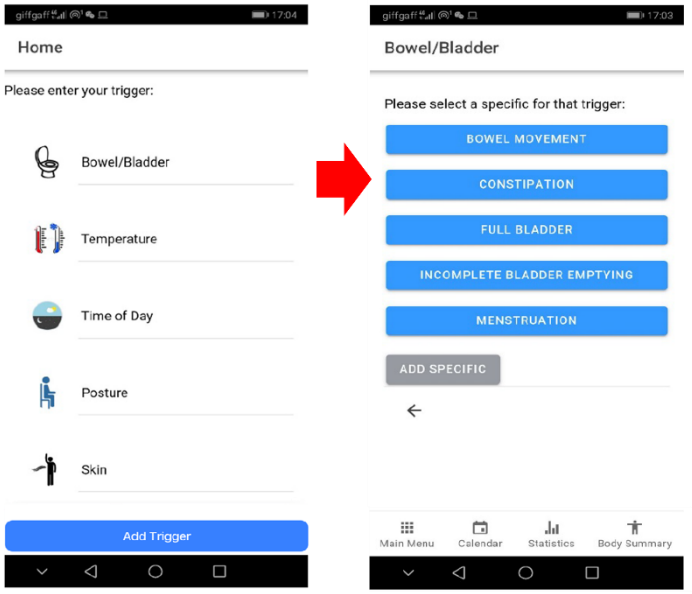

Figure 1: home page used to select the trigger category (left) and the succeeding page used to choose a specific trigger (right) (shown on Android).

Figure 2: information input in the process of logging a trigger in the App. Users can return to previous screens if necessary and can also choose not to add a comment.

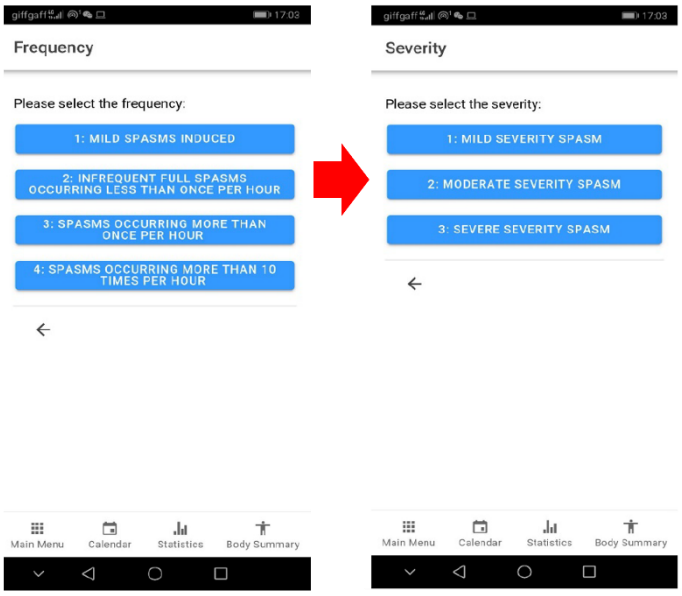

Figure 3: Penn Spasm Frequency Scale shown when user is logging a trigger-related spasm.

Functionality

This App can be used as an outcome measure to assess the efficacy of an intervention such as neuromodulation to manage upper limb spasticity. By using a mobile App, the participant's perspective on the effects of the intervention can be measured at home, using a clinically recognised scale (PSFS, Figure 3).

Educational Tool

This App can also be used as an educational intervention; by linking spasms to intrinsic and extrinsic triggers, we are raising the participants awareness of their triggers.

The App provides an overview of logged data (Figure 4), allowing the user to see how their spasms (frequency, severity and trigger) change overtime. This feedback may enable the user to alter their behaviour and better manage their spams. This overview feature may be disabled if required in a clinical study.

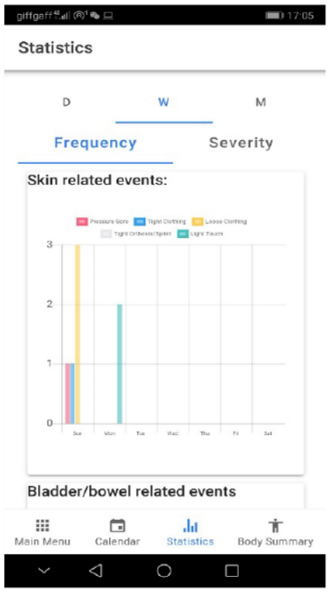

Figure 4: overview of logged data displayed.

Discussion & Conclusion

- We have developed a mobile phone App, which may be used as an outcome measure in a clinical study, or as an educational tool in the self-management of spasticity.
- This App will be used in a clinical study to assess the effects of neuromodulation on spasticity in daily life.
- We must acknowledge that, used in this way, the App may allow participants to engage in the self-management of their spasticity; the effects of the neuromodulation and the use of the App therefore need to be distinguished.
- Conversely, raising awareness of certain triggers may cause anxiety and an increased spastic response to those triggers.
- To address this, we will include formal questionnaires before and after the intervention to assess awareness and attitudes towards intrinsic and extrinsic triggers of spasticity.
- In addition, the feedback aspect of the App (reviewing logged data) will be disabled during a clinical study assessing a separate intervention.
- The interface and use of the App are currently being assessed in people with spasticity and clinicians, through questionnaires.

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The Effects of Neuromodulation on Central Excitability of the Upper Limb in Healthy, Able-bodied Adults

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Abstract: *Transcutaneous electrical nerve stimulation (TENS) has been shown to inhibit corticospinal mechanisms for the management of upper limb spasticity at frequencies > 90 Hz. Delivering transcutaneous spinal cord stimulation (tSCS) in kHz frequency bursts (HF-tSCS) has been proposed as an alternative therapy. This study compares the effects of TENS and HF-tSCS on upper limb motor-evoked potential (MEP) and H-reflex amplitude in 2 participants. Wrist extensor MEP amplitude decreased for 60-mins following TENS. However, this increased following HF-tSCS. The effects of both therapies on wrist flexor MEP amplitude were inconclusive, however H-reflex amplitude decreased immediately after both in one subject. Preliminary results suggest that HF-tSCS may not be as effective as TENS for spasticity management.*

Keywords: *Spasticity management, upper limb, neuromodulation, high-frequency stimulation*

Introduction

Neurological components of spasticity occur due to a lack of descending control over interneuronal circuits in the spinal cord [1]. Forms of neuromodulation effective in the management of upper limb spasticity range from neuromuscular electrical stimulation [2], to central stimulation of the spinal cord [3] or brain [4]. However, synergies between agonist-antagonist pairs following stimulation via alternative routes and using varying frequencies is lacking in the upper limb. Spasticity has been characterised by evaluations of motor-evoked potentials (MEPs) [5] and H-reflex amplitude [6]. These measures allow for the assessment of inhibitory and excitatory mechanisms at both cortical and spinal level.

Transcutaneous electrical nerve stimulation (TENS) has been shown to decrease MEPs after 30-minutes of intervention at 90 Hz [7]. At 200 Hz, TENS was also shown to have a positive effect on presynaptic inhibition [8]. These effects on cortico-spinal excitability help towards relieving symptoms of spasticity.

More recently, the use of transcutaneous spinal cord stimulation (tSCS) has been proposed as a therapy for the treatment of spasticity and neuropathic pain [3,9]. However, 49-71% of people who have experienced conventional tSCS for the treatment of neuropathic pain find the sensation unpleasant [9]. High-frequency tSCS (HF-tSCS) (up to 10 kHz) has been shown to have effects on chronic back pain without this unpleasant sensation [10]. The use of HF-tSCS may increase uptake in the use of this type of therapy for spasticity management.

This study investigated the effects of HF-tSCS compared to TENS in the upper limb. This will help us to understand the extent of alteration to inhibitory and excitatory pathways that HF-tSCS is able to achieve.

Methods

Participants

In this abstract, we present two participants for whom the effects of both interventions were measured on MEP amplitude and one participant whose H-reflex amplitude was also assessed. For the larger study, we will recruit 20 participants over the age of 18, with no known neurological conditions. Ethical approval for this study has been granted by the University College London Research Ethics Committee and informed consent will be sought from all participants who take part.

Data Collection

Electromyography (EMG) electrodes were placed over the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) muscles (figure 1). The electrodes over the FCR were the same adhesive electrodes used for the TENS intervention, only the EMG recording cables were replaced with stimulating cables. EMG data were sampled at 10 kHz and recorded through LabChart 8 software via a Powerlab (ADInstuments). This was externally triggered using Signal software (Cambridge Electronics Design) and a Power1401 ADC (Cambridge Electronics Design). Low pass filtering, with a cut-off frequency at 50 Hz, was implemented in LabChart 8 software.

TENS intervention
The participant was sitting upright in a comfortable chair. TENS was delivered via adhesive electrodes (Covidien adhesive electrodes, 2.4 cm diameter) placed over the FCR (figure 1). Stimulation was delivered at 150 Hz and pulse width 100 µs with 2 seconds of stimulation on and 2 seconds off for 30-minutes of intervention [11]. Threshold was defined as the intensity at which muscle twitch was first induced when stimulating. The stimulation amplitude was set at 80 % of threshold and kept constant for the duration of the intervention.

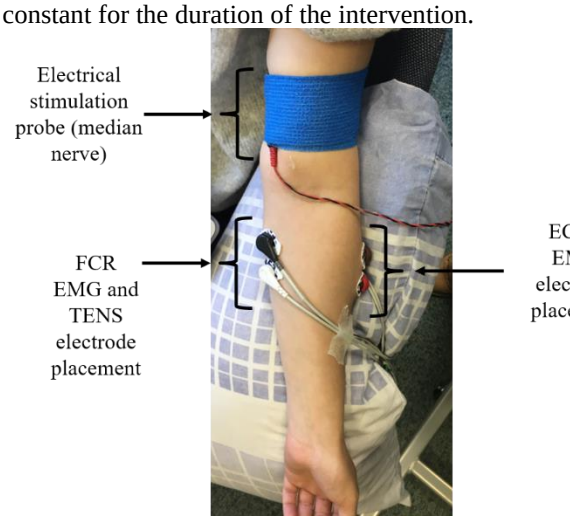

Figure 1: set-up showing EMG recording electrodes, TENS electrodes and the stimulating probe array used for H-reflex elicitation.

HF-tSCS intervention
In a separate session, HF-tSCS was supplied with a research stimulator (Digitimer DS8). Threshold was determined using conventional tSCS with a biphasic square wave at a frequency of 1 Hz and a 1 ms pulse width. This was the lowest intensity at which posterior root reflexes were elicited in the desired muscles. The high-frequency tSCS was then delivered at 30 Hz, with a 9090 Hz carrier frequency (biphasic square wave, pulse width 50 µs), with each high frequency burst lasting 1ms. This was supplied via self-adhesive surface electrodes (PALS Neurostimulation adhesive electrodes, 5cm diameter) placed over C6 and T1 vertebral levels (figure 2), and delivered in 2 second bursts following 2 seconds of no stimulation for 30-minutes at 80 % of threshold intensity.

H-reflex protocol
The H-reflex was evoked in the FCR by stimulating the median nerve with a 1 ms monophasic pulse at 7 s intervals via a bar electrode array. Two stimulation sites were tested: the cubital fossa [12] and approximately one third of the distance from the elbow to the shoulder [13], to select one where the H-reflex could be evoked.

Before intervention, a recruitment curve was obtained for the H-reflex in the FCR. The stimulation intensity where the H-reflex was largest relative to the M-wave was used for the remainder of the experiment. This was used to elicit 20 baseline H-reflexes, 20 immediately following intervention and at 15-minute intervals thereafter for 60 minutes. This is illustrated in figure 3.

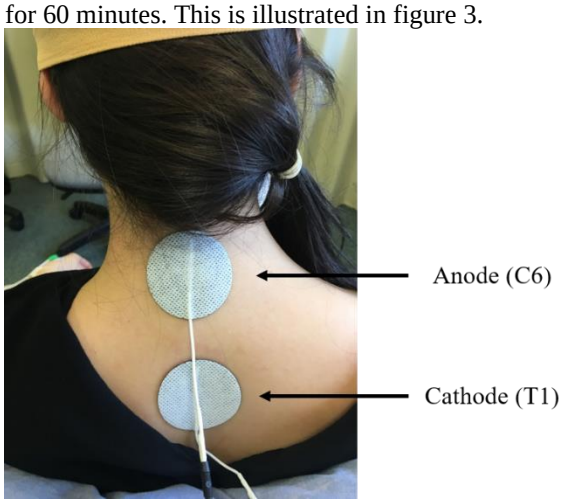

Figure 2: stimulating electrode placement over the vertebrae for HF-tSCS.

Measurements of the H-reflex amplitudes of each stage were averaged and peak-to-peak values were calculated for each of these points and represented as a percentage of the baseline measurement.

MEP protocol
MEPs were triggered in the FCR and ECRL using a circular transcranial magnetic stimulation TMS coil (13 cm external diameter) to stimulate the primary motor cortex via a Magstim 200.

Before intervention, the hotspot for eliciting MEPs in the FCR and ECRL was identified, and MEP recruitment curves were carried out to identify resting threshold. Stimulation intensity for the remainder of the experiment was 1.2x threshold. Twenty MEPs were elicited before, immediately following intervention, and at 15-minute intervals thereafter for 60 minutes (figure 3).

Results
The stimulation intensities used for outcome measures and interventions are displayed in table 1.

Table 1: Stimulation parameters for outcome measures and intervention.

Participant	H-reflex (mA)	MEP (%)	TENS (mA)	High-frequency tSCS (mA)
1	4.0	54	11.2	35
2	5.6	60	7.0	40.5

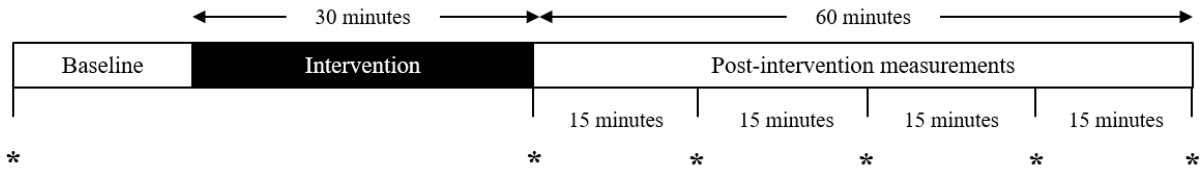

Figure 3: experimental timeline. * represents the times where measurements of MEP and H-reflex amplitude were taken.

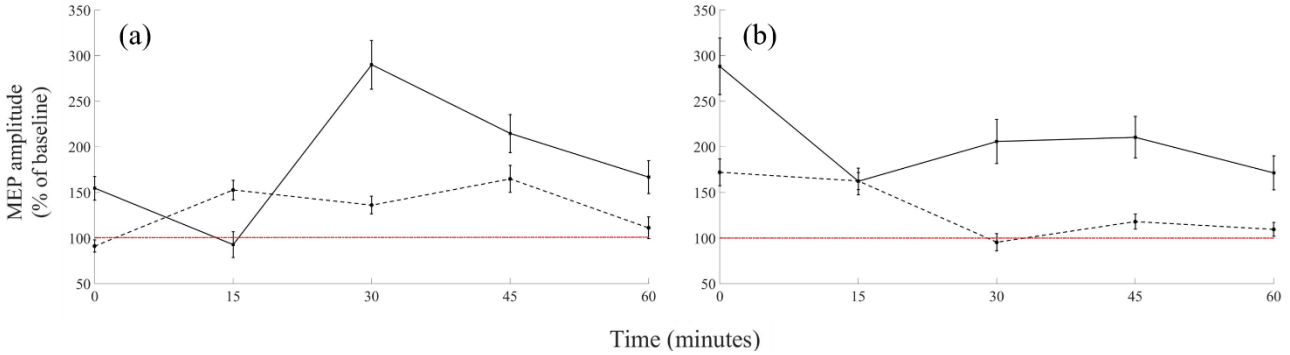

Figure 4: Mean (SEM) normalised FCR MEP amplitude (% of baseline) following HF-tSCS (dashed line) and TENS (solid line) intervention for Participant 1 (a) and Participant 2 (b).

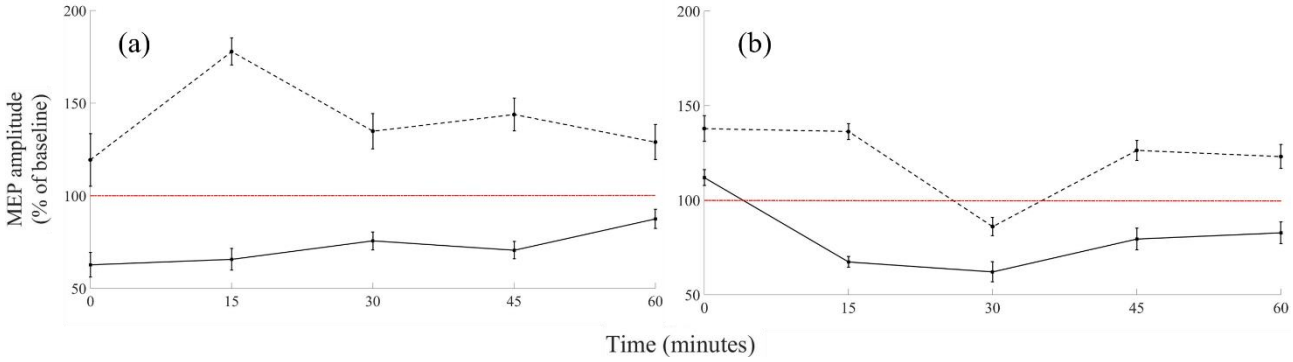

Figure 5: Mean (SEM) normalised ECRL MEP amplitude (% of baseline) following HF-tSCS (dashed line) and TENS (solid line) intervention for Participant 1 (a) and Participant 2 (b).

FCR MEP amplitude was not inhibited by either intervention (figure 4), remaining at or above baseline amplitude for 60-minutes following both interventions. This was true for both subjects tested. The data indicated that the interventions may have facilitated MEP amplitude in this muscle, particularly following TENS, but the data was rather variable between the two subjects tested.

For both subjects, ECRL MEP amplitude had decreased at 15-60 minutes following TENS intervention (figure 5). This effect was not seen following HF-tSCS, with MEP amplitude remaining close to or above baseline for 60minutes following the intervention. As with the wrist flexors, the data indicates that HF-tSCS may have facilitated MEP amplitude in the ECRL.

Following HF-tSCS and TENS intervention, H-reflex amplitude decreased to 42 % and 35 % of baseline respectively, immediately after the intervention (figure 6). H-reflex amplitude remained below baseline for 60 minutes after TENS intervention, but increased after HF-tSCS.

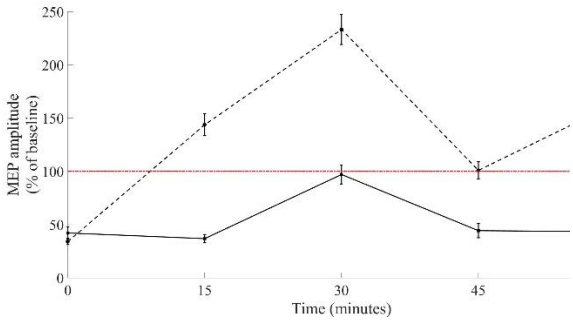

Figure 6: Mean (SEM) normalised H-reflex amplitude (% of baseline) following HF-tSCS (dashed line) and TENS (solid line) intervention for Participant 1 (a) and Participant 2 (b).

Discussion

Our results indicate that TENS therapy has inhibited H-reflex and ECRL MEP amplitudes, and has facilitated FCR MEP amplitude in both participants. This is contrary to previous findings of Tinazzi et al. [11] with the same stimulation parameters. With the exception of ECRL MEP amplitude measured immediately after intervention for participant 2, MEP amplitude has been inhibited following TENS. This indicates that this intervention has triggered reciprocal inhibition in the ECRL and had an excitatory effect on the FCR.

The effects of HF-tSCS on both H-reflex and FCR MEP amplitude indicate a facilitation of ECRL MEP amplitude in both participants. In the study by Tinazzi et al. [11], an increase of 64 % from ECRL MEP baseline was observed after TENS. An increase of 19 % and 38 % were seen here following HF-tSCS in the two participants respectively. Further investigation will determine whether this type of therapy could cause a statistically significant reduction in ECRL MEP amplitude and therefore be effective in the management of upper limb spasticity with less discomfort.

Results for changes in H-reflex amplitude following both interventions are highly variable, and the H-reflex could only be elicited in one participant. The H-reflex is a notoriously difficult measure to obtain in the upper limb and many studies have investigated its reliability [12, 13]. However, this measure allows us to investigate spinal excitability, which is altered in those with spasticity [14]. Using both H-reflex and MEP amplitude as outcome measures gives further relevance when investigating the potential effects of electrical stimulation on spasticity.

Our further investigation will assess the impact of HF-tSCS on spinal and cortical excitation compared to TENS. Results presented here indicate that HF-tSCS may have faciliatory effects on antagonist muscles. For effective treatment of spasticity, it is important for us to gain a better understanding of the neurophysiological effects of different interventions.

Acknowledgements

We would like to give thanks to the Leslie Trust for funding this project. We would also like to thank Digitimer Ltd for the loan of the DS8 stimulator.

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The Effects of Neuromodulation on Central Excitability of the Upper Limb in Healthy, Able-bodied Adults

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Introduction

Transcutaneous electrical nerve stimulation (TENS), at frequencies >90 Hz has been found to reduce cortico-spinal excitability [1,2], and is used clinically to treat symptoms of spasticity. Transcutaneous spinal cord stimulation (tSCS) has also been used to relieve symptoms of spasticity [3].

Conventional tSCS however recruits the underlying back muscles, which can be uncomfortable [4]. High-frequency tSCS (HF-tSCS) (up to 10 kHz) may improve spasticity, without this unpleasant sensation [4]. The use of HF-tSCS may increase uptake of this type of therapy for spasticity management.

Aims

- To compare the effects of 30 minutes of HF-tSCS HF-TENS, TENS and sham stimulation on upper limb spinal and cortical excitability.
- To determine an effective therapy for upper limb spasticity management.

Method

Motor Evoked Potentials (MEP) and Posterior Root Reflexes (PRR) were measured from electromyography (EMG) of the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) in four participants. This determines cortico-spinal and spinal excitability respectively. These were taken before each intervention, immediately following intervention, and at 15-minute intervals thereafter for 60 minutes, as illustrated in figure 1.

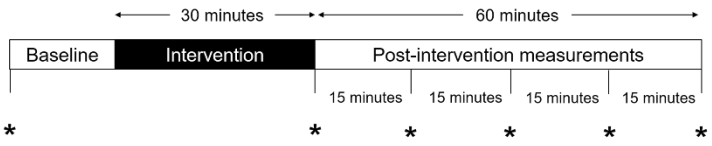

*Figure 1: experimental timeline. The * indicates when measurements (MEPs and PRRs) were taken.*

Each of the 4 interventions were delivered, in separate sessions, at 80 % of threshold intensity, and in the following manner:

- HF-tSCS – biphasic HF stimulation, C6 and T1 vertebrae levels (fig. 2a).
- HF-TENS – biphasic HF stimulation, over the FCR (fig. 2a). Threshold set with conventional TENS stimulation (fig.2b).
- TENS – conventional biphasic stimulation, over the FCR (fig. 2b).
- Sham – the participant was told that they would receive an intervention which they might not feel, however no stimulation was delivered.

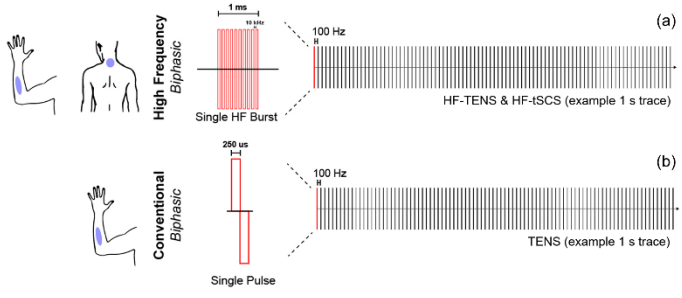

Figure 2: example traces of 30-minute HF-tSCS and HF-TENS (a) and TENS (b). HF stimulation was delivered at 100 Hz with a 9090 Hz carrier frequency.

Twenty PRRs and MEPs were taken at each measurement timepoint. To assess the change in MEP amplitude, with respect to baseline, paired t-tests were carried out on transformed MEP data. This was not carried out for PRRs since they were only elicited in two participants for three of the interventions.

To present the data, the peak to peak amplitudes were averaged, and normalised to the baseline average, giving percentage ratios.

Results

Immediately following HF-tSCS, MEP amplitude tended to decrease in the FCR and increase in the ECRL (fig. 3). This tendency for inhibition lasted 30 minutes, but these results were not statistically significant. However facilitation in the ECRL was statistically significant at 60 minutes.

A similar effect may be seen immediately following TENS, however this data has larger standard deviations compared to HF-tSCS.

There were no changes to cortico-spinal excitability following HF-TENS or sham stimulation.

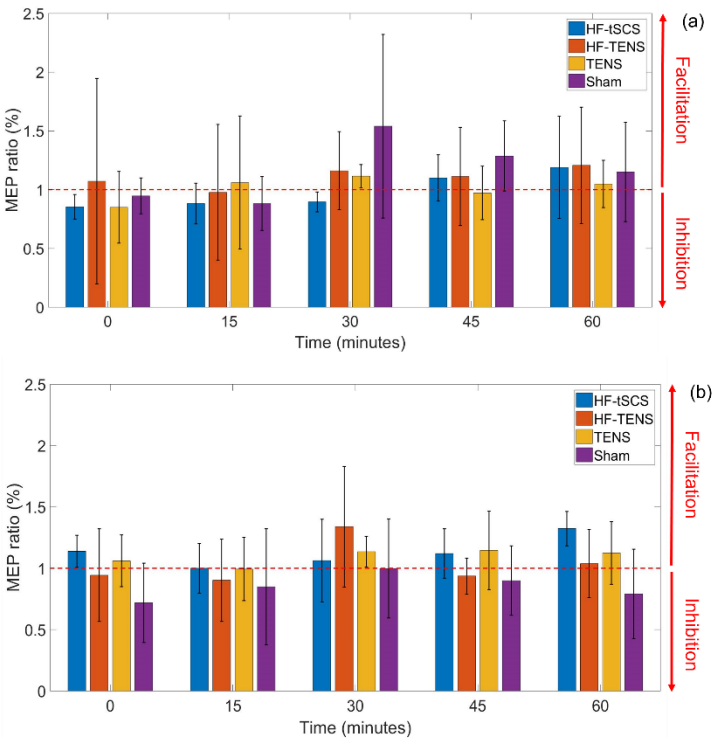

Figure 3: average (SD) FCR (a) and ECRL (b) MEPs (ratio normalised to baseline) over time. N=4, except for the sham intervention where N=3.

Discussion

These pilot results indicate that HF-tSCS and TENS may induce reciprocal inhibition. This data is in agreement with work by Mima et al. [1]. The effect is more pronounced immediately following HF-tSCS. Since this form of tSCS has been reported to be less painful than conventional tSCS [4], further studies are warranted.

The effects of HF-TENS were investigated to directly compare the effects of conventional and HF forms of the same intervention at similar intensities. The inclusion of this intervention also allowed us to assess the effects of HF stimulation at the muscle as well as over the spinal cord.

HF-TENS had no effect on central excitability. This may be due to the HF and conventional TENS threshold being set in the same way. There may, therefore, be an argument for increasing the intensity used for HF-TENS in future studies.

Conclusion

- Both HF-tSCS and TENS may be effective in inducing reciprocal inhibition, which is useful for spasticity management.
- The spread of the data indicates that HF-tSCS may be a more effective intervention compared to TENS, however further investigation is needed.
- Low stimulation intensities for HF-TENS may account for its apparent lack of effect. Using supra- conventional TENS threshold may produce results similar to that of HF-tSCS and TENS.

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