The effect of 30 minutes of peripheral electrical stimulation on excitability of the sensorimotor cortices and sensory threshold of healthy adults

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Attestation of Authorship

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

Signed:

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February 2012

Abstract

Aim:

To evaluate the effect of peripheral electrical stimulation (PES), with directed or diverted attention, on excitability of the sensorimotor cortices and sensory threshold in healthy adults.

Study design:

Within participant repeated measures design. Motor evoked potentials (MEP), somatosensory evoked potentials (SSEP) and sensory threshold were measured before and after 30 minutes of PES. Three different stimulation paradigms were applied in a random order, at least 48 hours apart.

Participants:

Twelve healthy participants (seven women, five men, mean age = 40 ± 12 years).

Interventions:

Three different stimulation conditions were tested using low frequency, wide pulse width, below motor threshold stimulation.

1. Thirty minutes of PES with directed attention
2. Thirty minutes of PES with diverted attention
3. Thirty minutes of sham PES.

Main measures:

Corticomotor excitability using single pulse transcranial magnetic stimulation (TMS), excitability of the primary somatosensory cortex using median nerve SSEPs, and sensory thresholds using Semmes-Weinstein monofilaments.

Results:

There were no significant changes in motor evoked potentials, somatosensory evoked potentials and sensory threshold following PES with directed or diverted attention.

Conclusion:

In healthy adults, 30 minutes of PES with directed or diverted attention did not result in an increase in corticomotor excitability, excitability of the primary somatosensory cortex or a decrease in sensory threshold. PES parameters such as duration, frequency, pulse width and intensity and / or the combination of these parameters are likely to have contributed to the findings of the current study. Further research is required to determine optimal PES parameters before it can be implemented clinically.

Abbreviations

ADM: Abductor digiti minimi

APB: Abductor pollicis brevis

CV%: Coefficient of variation

ECG: Electromyography

ECR: Extensor carpi radialis

FCR: Flexor carpi radialis

FDI: First dorsal interosseous

ICC: Intraclass correlation coefficients

LOA: Limits of agreement

MEP: Motor evoked potentials

PES: Peripheral electrical stimulation

SEM: Standard error of measurement

SSEP: Somatosensory evoked potentials

SWM: Semmes-Weinstein monofilaments

TMS: Transcranial magnetic stimulation

TE: Typical error

Operational definitions

For this study the following operational definitions were adopted:

Directed attention: the participants' attention was directed towards the stimulation.

Diverted attention: the participants' attention was distracted away from the stimulation.

Peripheral electrical stimulation: any prolonged, repetitive electrical stimulation applied as a standalone intervention over muscle or nerve in the upper limb resulting in perception of the stimulus, with or without a muscle twitch and in the absence of pain. It does not include stimulation that results in passive or active full range movement, functional movement, or is combined with motor training.

Sensory threshold: the lowest point at which a response to a pressure stimulus can be perceived. It was measured using Semmes-Weinstein Monofilaments.

Chapter 1: Introduction

Recovery of sensorimotor function in the upper limb following stroke is often incomplete, leaving patients with movement, function and participation limitations (Connell, Lincoln, & Radford, 2008; Lai, Studenski, Duncan, & Perera, 2002). Recovery depends on behavioural modification and the central nervous systems (CNS) ability to reorganise functionally and structurally, a process referred to as neuroplasticity (Ward, 2005). Increased understanding of neuroplasticity and the role that it plays in the recovery of sensorimotor function has facilitated the development of interventions aimed at inducing neuroplasticity in order to optimise rehabilitation outcomes.

One such intervention is peripheral electrical stimulation (PES) which generates afferent input to the CNS and has been shown to induce reorganisation of the CNS that is associated with changes in sensory threshold in the upper limb in healthy adults (Kaelin-Lang et al., 2002; McKay, Brooker, Giacomin, Ridding, & Miles, 2002; Mima et al., 2004; Pyndt & Ridding, 2004; Ridding, Brouwer, Miles, Pitcher, & Thompson, 2000; Ridding, McKay, Thompson, & Miles, 2001; Ridding & Uy, 2003). PES has also been shown to induce reorganisation of the CNS and enhance functional improvements in the upper limb following stroke (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007; Conforto, Cohen, dos Santos, Scaff, & Marie, 2007; Conforto et al., 2010; Conforto, Kaelin-Lang, & Cohen, 2002; Klaiput, Kitisomprayoonkul, Klaiput, & Kitisomprayoonkul, 2009; Sawaki, Wu, Kaelin-Lang, & Cohen, 2006; Wu, Seo, & Cohen, 2006). Despite these positive outcomes, the application of PES in the clinical setting is limited as researchers have used stimulation equipment and parameters that are currently not available to or feasible for clinicians.

The aim of the current study was to assess the clinical feasibility of PES using electrical stimulation units that are currently available and clinically feasible parameters to bridge the gap between research and clinical rehabilitation.

1.1 Aim

The aim of the study was to examine the immediate effects of 30 minutes of PES with directed attention, compared to PES with diverted attention and sham stimulation, on corticomotor excitability, excitability of the primary somatosensory cortex and sensory threshold in healthy adults. Corticomotor excitability was measured using single pulse transcranial magnetic stimulation; excitability of the somatosensory cortex was measured using somatosensory evoked potential techniques and sensory threshold using Semmes-Weinstein monofilaments. Previous studies have investigated the use of PES in healthy participants for a period of two hours. The current study is novel as it investigates whether PES using clinically available equipment and clinically feasible timeframes is effective in increasing corticomotor excitability, excitability of the somatosensory cortex and sensory threshold in healthy participants.

1.2 Hypotheses

The studys experimental hypotheses are:

1. In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased corticomotor excitability.

2. In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in corticomotor excitability compared to PES with attention diverted.

3. In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased excitability of the somatosensory cortex.

4. In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in excitability of the somatosensory cortex compared to PES with attention diverted.

5. In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased sensory threshold in the index finger of the right hand.

6. In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in sensory threshold in the index finger of the right hand compared to PES with attention diverted.

1.3 Limitations

The following limitations apply to this study:

1. Data collection was limited to corticomotor excitability, excitability of the somatosensory cortex and sensory threshold.

2. Cortical excitability was measured using single pulse TMS, therefore the contribution of cortical interneurons and/or spinal motoneurons will not be able to be ascertained.

3. Excitability of the somatosensory cortex was measured using peak to peak N20 - P25 amplitude, therefore the contribution of other areas of the sensory pathway will not be identified.

4. Sensory threshold was measured using Semmes–Weinstein monofilaments, therefore changes in sensations other than pressure threshold will fail to be detected.

5. Only healthy adults aged 20-70 years of age, without neurological injury and without any contraindications to the intervention and measures participated in the study.

6. The PES parameters used in our study were based on the literature but were limited by the clinical stimulation unit.

7. In the clinical setting PES would be applied immediately prior to rehabilitation techniques therefore, the duration of stimulation needs to be considered in the context of the therapy session as a whole. Following discussion with clinical experts, thirty minutes of stimulation was selected for the current study as this was deemed to be a clinically feasible timeframe. However, this duration may have been inadequate to elicit an increase in corticomotor excitability. Previous research suggests that 45 minutes of stimulation is required to demonstrate increased corticomotor excitability (McKay et al., 2002) however, this study

varied several other stimulation parameters (site of electrodes, pulse width and intensity) making it difficult to determine the importance of the duration of stimulation alone.

8. Bonferoni correction was applied to post hoc analyses. This correction is conservative increasing the probability of accepting the null hypothesis when the alternative is true (type II error).

9. Aspects of equipment set up were determined by participant comfort and therefore not standardised.

10. Participants were recruited by convenience sampling, which could have introduced significant selection bias resulting in a sample representing more compliant or cooperative participants.

11. An inherent problem when using interventions such as electrical stimulation is the difficulty blinding the investigator and participants. Lack of blinding may potentially result in expectation bias affecting the in internal validity of the study (Deyo, Walsh, Schoenfeld, & Ramamurthy, 1990; Rakel et al., 2010). The current study attempted to address investigator blinding by asking participants to not discuss interventions with the investigator, by using a research assistant to apply all interventions whilst the investigator left the room and by unblinding participants' data only once all data had been collected. More challenging perhaps was the blinding of participants. Participants were unaware of the study's hypotheses and were informed that different intensities of electrical stimulation were being tested and that sometimes they would feel the stimulation and sometimes they would not. Previous studies indicate that participants do not consistently remain blinded to these types of interventions, particularly if the sham intervention occurs after active stimulation (Deyo et al., 1990; Rakel et al., 2010). As the current study was a repeated measure within participant design with participants receiving each intervention twice, it is possible that participants were aware of the sham intervention and this may have biased the results.

Chapter 2: Literature review

2.1 Introduction

The purpose of this study was to examine the effects of PES on corticomotor excitability, excitability of the somatosensory cortex and sensory threshold in healthy adults. The following chapter presents a synopsis of cortical neuroplasticity to provide context to this study and a rationale for the use of PES. A review of the literature evaluating the effect of PES, applied to the upper limb, on corticomotor excitability, excitability of the somatosensory cortex and sensorimotor function in healthy adults will be presented. A summary of the PES parameters required to elicit such changes will be provided followed by a rationale for the stimulation parameters used in the current study.

2.2 Neuroplasticity

Neuroplasticity relates to reorganisation of the central nervous system's structure or function in response to experience (Nudo, 2007; R. J. Seitz et al., 2004). Advancements in the use of neurophysiological and neuroimaging techniques such as TMS, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) have enabled researchers to study neuroplasticity in humans. Reorganisation may manifest itself as an expansion or shift in cortical representations or a change in excitability of ascending/descending pathways, and has been demonstrated in both the sensory and motor cortices as a consequence of factors such as motor training (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Karni, Meyer, Jezzard, Adams, & al, 1995; Pascual-Leone et al., 1995; Pascual-Leone, Grafman, & Hallett, 1994), enhanced or altered sensory input (Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998; Ridding et al., 2000) or following injury (Cicinelli, Traversa, & Rossini, 1997; Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997). Such reorganisation results in focal somatotopic change within the cortices that outlast the period of manipulation and may be short term and reversible, or long lasting. The mechanisms underlying neuroplasticity include unmasking of existing, but latent synapses, the modulation of synaptic efficiency, such

as long term potentiation or long term depression, and the growth of new axons and connections (Caramia, lani, & Bernardi, 1996; Hess & Donoghue, 1994; Sanes & Donoghue, 2000).

2.2.1 Neuroplasticity and changes in function in healthy adults

Whether reorganisation of the sensorimotor cortices is associated with changes in function is of interest clinically, as this would suggest that interventions capable of inducing reorganisation may also facilitate changes in function. Several studies have investigated the correlation between cortical reorganisation and functional change. Pascual-Leone et al (1995) utilised TMS mapping techniques to study changes in cortical organisation associated with the acquisition of a fine motor skill over a period of several weeks. Practice of a five finger piano exercise, two hours a day for five days, resulted in increased motor skill which was associated with a progressive increase in the size of the primary motor cortex representation of the trained muscles. Following brief motor training Muellbacher, Ziemann, Boroojerdi, Cohen, and Hallett (2001) demonstrated a correlation between increased finger pinch force and acceleration, and increased corticomotor excitability in the trained muscle but not in a muscle unrelated to the task. Similar results have been found in the primary somatosensory cortex. Sensory training (passive tactile coactivation) resulted in improvements in somatosensory perception that were correlated with increased cortical representations within the primary somatosensory cortex that were specific to the stimulated skin area (Hodzic, Veit, Karim, Erb, & Godde, 2004; Pleger et al., 2001). These studies provide evidence of focal somatotopic reorganisation of the sensorimotor cortices following training and suggest that such changes underlie changes in sensorimotor function. It seems plausible, therefore, that an intervention capable of inducing cortical reorganisation is also capable of modifying sensorimotor function.

2.2.2 Neuroplasticity induced by afferent input

Afferent input, either naturally occurring during movement, or experimentally induced, seems to play an important role in the induction of neuroplasticity within the sensorimotor cortices. For example, in string players the digits of the left hand, which manipulate the strings resulting in increased sensory input, have a larger representation within the primary somatosensory cortex when compared to the right hand, which holds

the bow (Elbert et al., 1995). In addition, cortical representation is larger than the left hand finger representation in non musician controls (Elbert et al., 1995). Experimentally induced increased afferent input in the form of passive tactile coactivation (simultaneous tactile stimulation) or electrical stimulation has also been shown to increase representations within the primary somatosensory (Golaszewski et al., 2004; Hodzic et al., 2004; Pleger et al., 2001) and motor cortices (Golaszewski et al., 2004) and induce rapid, long term increases in corticomotor excitability (Fraser et al., 2002; Hamdy et al., 1998). In contrast, a reduction in afferent input following amputation (Cohen, Babdinelli, Findley, & Hallett, 1991) or ischemic nerve block (Brasil-Neto, Cohen, Pascual-Leone, et al., 1992) results in a focal reduction in primary motor cortex representations. These studies demonstrate that afferent input is capable of inducing neuroplastic change within the sensorimotor cortices and provides a rationale for utilising interventions that manipulate afferent input to modulate neuroplasticity.

2.2.3 Section summary

The sensorimotor cortices are capable of neuroplastic change, which can be measured as an expansion or shift in cortical representations or a change in excitability. Evidence suggests that training, such as motor or sensory training, results in focal somatotopic reorganisation of the sensorimotor cortices, and that such changes underlie changes in function. Naturally occurring or experimentally induced afferent input seems to play an important role in the induction of neuroplasticity, stimulating research into the use of interventions that manipulate afferent input to modulate neuroplasticity and facilitate changes in function. Clinically, such interventions are of great interest as they may provide a tool to facilitate improvements in function and enhance rehabilitation outcomes following brain injury. Peripheral electrical stimulation is one such intervention that is currently showing promise and will be reviewed in detail in the following section.

2.3 Peripheral electrical stimulation

Peripheral electrical stimulation (PES) is a method of applying specific afferent input to induce neuroplastic changes within the central nervous system. For the purpose of this review, it is defined as any prolonged, repetitive electrical stimulation applied as a

standalone intervention over muscle or nerve in the upper limb resulting in perception of the stimulus, with or without a muscle twitch and in the absence of pain. Electrical stimulation that results in passive or active full range movement, functional movement, or is combined with motor training is excluded from this definition as it is difficult to ascertain whether the effects observed are attributable to stimulation alone.

The literature search that pertains to the following review was undertaken between January 2009 and June 2010. Databases searched included: MEDLINE (via OVID), AMED (via OVID), and CINAHL (via EBSCOHost). Key citations and authors were also sourced using SCOPUS. A hand search of references was undertaken to identify any studies that had been overlooked. Studies were included if they evaluated: the effect of peripheral electrical stimulation applied to the upper limb; excitability or reorganization of the sensorimotor cortices; sensorimotor function in the upper limb, in healthy adults. Eligible studies published from 2000 through to commencement of the research (June 2010) were included. The cutoff date of 2000 was selected as PES was first referred to by Ridding et al. (2000) who investigated the effect of PES on corticomotor excitability. A summary of the PES parameters used in the reviewed studies and their main effects is provided in Table 1.

2.4 The effect of peripheral electrical stimulation on corticomotor excitability in healthy adults

PES can be applied above motor threshold, resulting in strong but comfortable paraesthesias and muscle twitch in the target muscle or below motor threshold, evoking strong but comfortable paraesthesias in the hand without muscle twitch. This section will begin by reviewing the effect of PES applied above motor threshold on corticomotor excitability as measured by TMS. This will be followed by a review of PES applied below motor threshold. Throughout this review important stimulation parameters will be highlighted in an attempt to determine PES parameters that optimise an increase in corticomotor excitability.

2.4.1 The effect of PES applied above motor threshold on corticomotor excitability

Seven studies were identified that evaluated the effect of PES applied above motor threshold on corticomotor excitability. Three studies applied PES to peripheral nerves at the wrist (McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001), three applied PES to motor points (Pyndt & Ridding, 2004; Ridding & Uy, 2003; Schabrun & Ridding, 2007) and one study compared nerve to motor point stimulation (Charlton, Ridding, Thompson, & Miles, 2003).

The first study by Ridding et al. (2000) investigated the effect of two hours of ulnar nerve stimulation in six healthy adults. Corticomotor excitability was measured using TMS in abductor digiti minimi (ADM), first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles twice before and immediately following PES. Ulnar nerve stimulation was applied at the wrist using trains of 1000 μs pulse width, square wave pulses, at a frequency of 10 Hz, with an on/off cycle of 500 ms and an intensity that resulted in small visible contractions of the ulnar nerve innervated muscles (ADM, FDI). Immediately following stimulation there was a significant increase in motor evoked potentials (MEP) amplitude for the ulnar innervated muscles in the absence of significant changes to APB. In order to evaluate the persistence of such changes, corticomotor excitability measures were repeated in three participants 15 minutes following stimulation and revealed that increased MEP amplitudes in FDI and ADM were still evident.

In a separate experiment the effect of electrode placement was investigated in four participants who received digital nerve stimulation of the 4^{th} and 5^{th} digits using identical parameters to the main experiment. In contrast to mixed nerve stimulation, digital nerve stimulation resulted in no significant increase in MEP amplitude, suggesting that mixed nerve stimulation, which includes the stimulation of muscle afferents, is more effective than the stimulation of cutaneous afferents alone. These results must be interpreted with caution as the small sample size may have resulted in reduced statistical power.

Table 1 Summary of stimulation parameters and main effects in healthy adults.

Author	Year	Type	Waveform	Site	Freq (Hz)	Pulse width (μs)	Intensity	Duration (h)	Attention to stim	Main effect
Ridding, et al.,	2000	PC	Square	UN	10	1000	M	2	-	↑ MEP FDI,ADM
		PC	Square	DN	10	1000	M	2		No change
Ridding, et al.,	2001	PC	Square	UN/RN	10	1000	M	2	-	↑ MEP FDI
Kaelin-Lang et al.,	2002	PC	-	UN	10	1000	S	2	x	↑ MEP ADM
McKay, et al.,	2002	PC	Square	UN/RN	10	1000	M	0.75	-	↑ MEP FDI
Uy & Ridding	2003	PC	-	UN	10	1000	M	0.1	-	No change
Ridding & Uy	2003	AS	Square	MP	0.35-6.7	1000	M	1	✓	↑ MEP FDI,APB
		NAS	Square	MP	0.35-6.7	1000	M	1	✓	No change
Charlton et al.,	2003	AS	-	UN/RN	10	1000	M	2	-	Variable results
		PC	-	MP	10	1000	M	2	-	Variable results
Pyndt & Ridding	2004	AS	Square	MP	0.35-6.7	1000	M	1	-	↑ MEP FDI,APB
Mima et al.,	2004	TENS	-	MP	90	250	S	0.5	-	↓ MEP APB ↑ ST & ↑ 2pt DST

Freq = frequency, PC = pulsed current, AS = associative stimulation, NAS = non associative stimulation, TENS = transcutaneous electrical stimulation, UN = ulnar nerve, RN = radial nerve, MN = median nerve, MP = motor point, M = stimulation above motor threshold, S = stimulation below motor threshold, MEP = motor evoked potential, FDI = first dorsal interosseous, ADM = Adductor digiti minimi, FCR = flexor carpi radialis, ECR = extensor carpi radialis, BOLD = blood oxygen level dependent, fMRI = functional magnetic resonance imaging, EMG = electromyography, ST = sensory threshold, 2pt DST = 2point discrimination sensory threshold, - = not mentioned, ✓ = attention directed towards PES, x = attention diverted away from PES.

Author	Year	Type	Waveform	Site	Freq (Hz)	Pulse width (μs)	Intensity	Duration (h)	Attention to stim	Main effect
Tinazzi et al.,	2005	TENS	Rectangular	MP	150	100	S	0.5	-	↓ MEP FCR
										↑ MEP ECR
Wu et al.,	2005	PC	-	MN	10	1000	S	2	-	↑ fMRI perfusion/
										BOLD responses.
		PC	-	DN	10	1000	S	2	-	No change
Dean et al.,	2006	TENS	-	MN	100	200	S	0.1	-	↑ ST
Schabrun &	2007	AS	Square	MP	0.35-6.7	1000	M	1	✓	↑ MEP FDI,ADM
Ridding		AS	Square	DN	0.35-6.7	1000	M	1	✓	No change
		NAS	Square	MP	0.35-6.7	1000	M	1	✓	No change
Murakami et al.,	2007	PC	Rectangular	MN	150	100	S	0.5	-	↓ MEP APB
Fernandez et al.,	2008	TENS	Rectangular	MP	150	100	S	0.5	-	- MEP FCR
										- MEP ECR
Dickstein & Kafri	2008	PC	-	MP	100	200	S	0.15	-	↑ EMG

Freq = frequency, PC = pulsed current, AS = associative stimulation, NAS = non associative stimulation, TENS = transcutaneous electrical stimulation, UN = ulnar nerve, RN = radial nerve, MN = median nerve, MP = motor point, M = stimulation above motor threshold, S = stimulation below motor threshold, MEP = motor evoked potential, FDI = first dorsal interosseous, ADM = Adductor digiti minimi, FCR = flexor carpi radialis, ECR = extensor carpi radialis, BOLD = blood oxygen level dependent, fMRI = functional magnetic resonance imaging, EMG = electromyography, ST = sensory threshold, 2pt DST = 2point discrimination sensory threshold, - = not mentioned, ✓ = attention directed towards PES, x = attention diverted away from PES.

This study provides evidence that two hours of low frequency PES applied above motor threshold to a mixed nerve, is capable of inducing a significant increase in corticomotor excitability that is specific to the stimulated muscles and outlasts the period of stimulation by at least 15 minutes. The stimulation of muscle afferents seems to be important in inducing such changes.

A second study conducted by Ridding et al. (2001) found similar results following two hours of simultaneous ulnar and median nerve stimulation at the wrist. A rationale for the simultaneous stimulation of two nerves was not provided. Fourteen healthy adults participated, eight of whom received stimulation using identical parameters to the previous study (Ridding et al., 2000) with an intensity three times perceptual threshold that evoked small motor responses in the ulnar innervated muscles. The authors stated that the parameters were developed to preferentially stimulate FDI and predicted that the effects of PES would be specific to this target muscle, however, it is unclear how this was achieved. The remaining six participants were used as controls and were connected to the stimulator but received no stimulation for a period of two hours. TMS was utilised to measure corticomotor excitability in FDI, ADM and APB prior to, immediately following, and in six participants, 24 hours after stimulation. Immediately following stimulation a significant increase in FDI MEP amplitude was found in the absence of significant changes in ADM, APB or the control participants. Increased FDI MEP amplitude outlasted stimulation by at least 30 minutes, which was the time taken to map the cortex, however it was no longer significant when measured at 24 hours. These results confirm previous findings (Ridding et al., 2000) that PES can induce an increase in corticomotor excitability in the target muscle, however are somewhat confusing as it is unclear how FDI was preferentially targeted as both median and ulnar nerves were stimulated. The lack of change in the median nerve innervated APB may be explained by the intensity of stimulation which was set at a level to evoke small motor responses in ulnar nerve innervated muscles only. The lack of significant change in excitability in the ulnar innervated ADM, which was present in the previous study, is difficult to explain and highlights the importance of detailed descriptions of PES parameters. Despite this, the study provides further support that two hours of low frequency PES, applied above motor threshold, is capable of

increasing corticomotor excitability. It provides new evidence that such changes outlast stimulation by 30 minutes but are no longer present at 24 hours, highlighting the reversibility of such changes.

Shorter durations of PES have also been investigated. Uy and Ridding (2003) investigated the effect of 10 minutes of PES applied to the ulnar nerve at the wrist, using parameters that were identical to previous studies (Ridding et al., 2000; Ridding et al., 2001). No change in corticomotor excitability in the target muscles was found, suggesting that 10 minutes of PES is insufficient to induce changes in corticomotor excitability.

McKay et al. (2002) conducted a study in ten healthy adults to determine the rate of change of corticomotor excitability during nerve stimulation. PES was applied simultaneously to the radial and ulnar nerves at the wrist, utilising parameters that were identical to previous studies (Ridding et al., 2000; Ridding et al., 2001). MEP amplitude was recorded from FDI prior to stimulation, and during stimulation at 15, 30, 45, 60, 75, 90, 105 and 120 minutes. During the experimental intervention, MEP amplitude increased steadily, was significantly larger in FDI between 45-105 minutes, and tended to plateau at about 60 minutes. Seven participants returned two weeks later for a control session and were tested using an identical protocol except that the peripheral nerves were not stimulated. Following the control session no change in corticomotor excitability was found. As these participants had already received the intervention it is likely that they were aware that they were not receiving stimulation during the control intervention and this may have influenced their results.

These results demonstrate that shorter durations of PES (45 minutes) are capable of inducing increased corticomotor excitability. This study used simultaneous stimulation of two nerves and it is unclear if results would be similar following stimulation of one nerve. These results are important as shorter durations of stimulation are more clinically feasible than longer durations such as two hours. The authors suggest that the time course of excitability changes seen in this study are similar to the time course of neuroplastic changes occuring during motor learning, such as the modulation of synaptic efficiency involving long term potentiation (Hess

& Donoghue, 1994). These results suggest that similar mechanisms are occurring during PES.

The application of PES above motor threshold using different stimulation parameters has been investigated by some authors in an attempt to optimise stimulation protocols. In three studies (Pyndt & Ridding, 2004; Ridding & Uy, 2003; Schabrun & Ridding, 2007) associative motor point stimulation was used as it has been demonstrated that correlated inputs are important for the induction of neuroplasticity (Godde, Spengler, & Dinse, 1996). Associative stimulation involved the simultaneous stimulation of FDI and APB motor points using square wave stimuli with a pulse width of 1000 μs, for one hour at an intensity three times perceptual threshold. This intensity evoked minimal visible motor responses in both muscles. The frequency of PES was modulated using a range of 0.35-6.7 Hz with the timing between successive pairs of stimuli randomised between 0.15 and 2.85 seconds. Modulation of frequency and timing of PES was used to minimise habituation which can reduce the response of the CNS to stimulation over time (Godde et al., 1996).

The effect of associative motor point stimulation on corticomotor excitability was assessed by Ridding and Uy (2003). Thirteen participants received associative stimulation as described above. As a control, participants also received non-associative stimulation using identical parameters, with the muscles receiving the same number of stimuli at the same rate, however never simultaneously. Interventions were delivered in a randomised order, one week apart, and participants were unaware of the study hypothesis. In an attempt to control for cognitive and attentional influences, participants received each intervention in a distraction free, quiet room and were repeatedly encouraged to pay attention to the stimulus during each session. Corticomotor excitability was measured using TMS stimulus response curves which were constructed before, immediately following, and at 15 minutes, one hour, and two hours following intervention. One hour of associative motor point stimulation resulted in significantly increased MEP amplitude in the stimulated muscles immediately following, at 15 minutes and at one hour following the intervention. In contrast, non-associative stimulation had no effect on corticomotor excitability.

The results of this study demonstrate that one hour of associative motor point stimulation resulted in increased corticomotor excitability that was specific to the stimulated muscles, and outlasted the stimulation by one hour. This is similar to McKay et al. (2002) that demonstrated increased corticomotor excitability following 45 - 60 minutes of simultaneous nerve stimulation. In contrast, non-associative stimulation had no effect on corticomotor excitability suggesting that correlated inputs are important for inducing excitability. This does not seem to be the case however when using mixed nerve stimulation as single and simultaneous nerve stimulation have both demonstrated increased corticomotor excitability (McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001).

Pyndt and Ridding, (2004) and Schabrun and Ridding, (2007) also evaluated the effect of associative motor point stimulation on corticomotor excitability using identical PES parameters to the previous study (Ridding & Uy, 2003). The results of both studies were consistent with Ridding and Uy (2003) and demonstrated that associative motor point stimulation results in increased corticomotor excitability that is specific to the stimulated muscles and outlasts stimulation.

Schabrun and Ridding (2007) compared associative motor point stimulation, to associative digital nerve stimulation and non-associative motor point stimulation in 24 healthy adults. Digital nerve stimulation was applied via ring electrodes on digits two and five. The results of this study demonstrated that one hour of associative motor point stimulation induced an increase in corticomotor excitability in the target muscles (FDI and ADM) whereas non-associative stimulation did not. Associative digital nerve stimulation had no effect on corticomotor excitability which is consistent with the results of the study by Ridding, Brouwer et al., (2000) and again suggests that the stimulation of muscle afferents is an important factor in driving changes in excitability.

It is unclear from the above studies whether mixed nerve or motor point stimulation is more effective at exciting the corticomotor pathway. Therefore, Charlton, Ridding, Thompson, and Miles (2003) investigated this further. In 12 healthy adults two hours of associative ulnar and superficial radial nerve stimulation was compared

to two hours of FDI motor point stimulation and 30 minutes of FDI motor point stimulation paired with low frequency TMS. PES parameters that have previously been used during mixed nerve stimulation were utilised (Ridding et al., 2000), however the intensity continued to be adjusted to evoke a twitch in FDI and ADM muscles during the two hour stimulation period. A separate control experiment was conducted on each participant using an identical protocol but without stimulation. MEP amplitudes were measured using TMS before stimulation, immediately following and then at 15 minute intervals for 120 minutes.

The results of this study were variable with all three protocols demonstrating significant increases in corticomotor excitability for some participants, significant decreases in corticomotor excitability for some participants, and inconsistency across the muscles tested. This is in contrast to all of the previously reviewed studies that consistently demonstrated increased excitability following nerve and associative motor point stimulation, which was specific to the target muscles. The authors suggested that attention, which they did not control for, may have influenced the results. Electrode placement and the intensity of stimulation differed from previous studies and may have had an impact. The subtly different protocols utilised in this study make it difficult to draw further conclusions.

2.4.2 The effect of PES applied below motor threshold on corticomotor excitability

Five studies were identified that evaluated the effect of PES applied below motor threshold on corticomotor excitability. One study used identical parameters to Ridding et al. (2000) with an intensity below motor threshold and demonstrated increased corticomotor excitability (Kaelin-Lang et al., 2002). In contrast, four studies used high frequency (90-150Hz), narrow pulse width stimulation, and demonstrated decreased corticomotor excitability, (Mima et al., 2004; Murakami, Sakuma, Nomura, & Nakashima, 2007; Tinazzi et al., 1998) or no change in corticomotor excitability (Fernandez-del-Olmo et al., 2008). These studies will be discussed further below.

In a repeated measures cross over design, Kaelin-Lang et al. (2002) compared the effect of two hours of ulnar nerve stimulation at the wrist to two hours of no

stimulation in 11 healthy participants. Stimulation parameters were identical to Ridding et al. (2000) with stimulus intensity below motor threshold evoking strong but comfortable paraesthesias in the hand, in the absence of visible muscle twitch. This stimulus intensity resulted in small compound muscle action potentials of 50-100 μV from ADM. Attention was directed away from the stimulation by participants reading books or magazines of their choice during the intervention. Details of the no stimulation control protocol were not provided. Corticomotor excitability was measured using TMS recruitment curves for ADM, APB, and FDI before and immediately following the intervention. Immediately following two hours of PES there was a significant increase in MEP amplitude for ADM in the absence of significant changes to FDI, APB, or following control stimulation. The authors concluded that the lack of change in excitability in the ulnar innervated FDI suggests that cutaneous and joint afferent fibres, not muscle afferents which are conducted from FDI via the ulnar nerve, are important for mediating changes in corticomotor excitability. This is in contrast to the studies reviewed previously that have demonstrated the importance of stimulating muscle afferents (Ridding et al., 2000; Schabrun & Ridding, 2007). An alternative explanation may be the intensity of stimulation, which was set at a level to evoke small compound muscle action potentials in ADM, and may not have been appropriate to elicit effects in FDI. The intensity of stimulation influences the number of sensory axons that are depolarised and therefore the size of the afferent volley to the CNS. These results suggest that PES intensity plays an important role in inducing corticomotor excitability.

In order to evaluate the persistence of increased corticomotor excitability, Kaelin-Lang et al. (2002) repeated MEP amplitude measures at 8-20 minute, 21-35 minute, and 36-50 minute time intervals following stimulation in six participants. The varied time intervals across individuals occurred due to the time it took to determine optimal scalp position and perform TMS. The results revealed that increased ADM MEP amplitudes were still evident 20 minutes following stimulation but were no longer significant at later time periods. These results are consistent with previous studies that used PES above motor threshold and demonstrate that two hours PES applied to a mixed nerve, below motor threshold, is capable of inducing a significant increase in corticomotor excitability that is specific to the stimulated muscle and

outlasts the period of stimulation. The lasting effect of stimulation was slightly shorter following PES below motor threshold and suggests that stimulus intensity has an impact on the maintenance of such neuroplastic change.

In contrast, studies that have used high frequency (90-150 Hz), narrow pulse width PES applied below motor threshold have demonstrated a decrease in corticomotor excitability (Mima et al., 2004; Murakami et al., 2007; Tinazzi et al., 1998), or no change in corticomotor excitability (Fernandez-del-Olmo et al., 2008). These studies suggest that the frequency of stimulation influences the direction of change in corticomotor excitability.

Murakami et al. (2007) evaluated the effect of 30 minutes of high frequency (150 Hz), narrow pulse width (100 μs) stimulation delivered in two second trains followed by a two second rest. Stimulation was applied at the median nerve at the wrist in 11 healthy participants at an intensity that evoked a tingling sensation in the area stimulated without muscle twitch or pain. TMS was used to measure MEP amplitudes in APB, FDI and ECR before stimulation and at 0-10, 15-25, 30-40, 45-55 and 60-70 minutes following stimulation. The results demonstrated a decrease in MEP amplitude in APB immediately and ten minutes following stimulation in the absence of changes to FDI and ECR. These results suggest that short duration (30 minutes) PES is capable of inducing changes in corticomotor excitability that outlast the period of stimulation. The effect on corticomotor excitability is influenced by the PES parameters used, with high frequency, narrow pulse width stimulation resulting in decreased excitability. In addition, the shorter duration of stimulation resulted in excitability changes that were sustained for a shorter period of time.

Similar results have been found following high frequency motor point PES (Mima et al., 2004; Tinazzi et al., 1998). Mima et al. (2004) investigated the effect of two 15 minute sessions of continuous stimulation, separated by three minutes rest, on corticomotor excitability in eight healthy adults. PES was applied to the right thenar eminence using high frequency (90 Hz), narrow pulse width (250 μs) stimulation applied below motor threshold. MEP amplitude was measured in APB before stimulation, immediately following each 15 minute session of stimulation and at five,

ten, 15 and 30 minutes following stimulation. Immediately following the first 15 minutes of stimulation, MEP amplitude in APB reduced significantly. MEP amplitude was also significantly reduced immediately following the second 15 minute session and at five minutes following stimulation. These results confirm the previous findings of Murakami et al. (2007) that high frequency, narrow pulse width PES applied below motor threshold results in a reduction in corticomotor excitability that outlasts stimulation.

Tinazzi et al. (1998) also found a reduction in corticomotor excitability of the stimulated muscle following 30 minutes of stimulation. PES was applied over the flexor compartment of the forearm, using similar stimulation parameters to the study by Murakami et al. (2007). MEP amplitude was measured in flexor carpi radialis (FCR), extensor carpi radialis (ECR) and FDI before and at 5-20, 21-35, 36- 50, and 51-65 minutes following stimulation. Time intervals varied across individuals due to the time required to perform TMS stimulation. The results of this study showed a significant reduction in corticomotor excitability in FCR that persisted for 35 minutes following stimulation, while MEP amplitude in ECR increased. The MEP amplitude for FDI did not change. These results are in agreement with other studies (Mima et al., 2004; Murakami et al., 2007). Tinazzi et al. (1998) found that decreased MEP amplitudes were maintained for up to 35 minutes following stimulation which is much longer than in other similar studies. The authors suggested that this may reflect differences in method such as the use of one 30 minute session versus two 15 minute sessions, slightly different frequency of stimulation (150 versus 90 Hz) and site of stimulation (muscle versus nerve).

More recently Fernandez-del-Olmo et al. (2008) repeated the study by Tinazzi et al. (1998) in an attempt to confirm their observations and explore the effects of PES on intracortical circuits. MEP amplitude was measured in FCR and ECR before and immediately following stimulation. Despite the use of identical stimulation parameters, Fernandez-del-Olmo et al. (2008) found that PES had no effect on MEP amplitude in FCR or ECR. In a complementary experiment, in the same study, the pulse width was increased to 500 μs to selectively activate more sensory afferents while all other PES parameters remained the same. The results of this experiment

also demonstrated no change in corticomotor excitability following PES. These results are in contrast to other similar studies (Tinazzi et al., 1998) and suggest that the effect of high frequency PES on corticomotor excitability is inconsistent. It is unclear why these results differ as the PES parameters were identical to Tinazzi et al. (1998). Ferandez-del-Olmo et al. (2008) suggested that these results demonstrate that the effects of PES are highly variable and unreliable.

The location of corticomotor excitability changes

TMS measures the excitability of the entire corticomotor pathway, therefore researchers have conducted complementary studies to determine the location of such excitability changes following PES (Kaelin-Lang et al., 2002; Mima et al., 2004; Ridding et al., 2000; Ridding et al., 2001; Tinazzi et al., 1998). The following section will begin by briefly discussing the location of changes in corticomotor excitability following PES applied above motor threshold, followed by a discussion of PES applied below motor threshold.

Very few studies have investigated the location of changes in corticomotor excitability following PES applied above motor threshold (Ridding et al., 2000; Ridding et al., 2001). Ridding et al. (2000) measured spinal motorneuron excitability by recording F-waves from FDI following two hours of ulnar nerve stimulation which had resulted in increased corticomotor excitability. No significant increases in F-wave characteristics (incidence, amplitude, area) were found, suggesting that the observed increases in MEP amplitude were not due to increases in spinal motoneuron excitability (Ridding et al., 2000). The excitability of the corticospinal tract below the foramen magnum has also been examined using TMS applied at the foramen magnum. No significant changes in MEP amplitude were observed following sub cortical stimulation despite significantly increased corticomotor excitability following TMS at the cortex. These results suggest that increased MEP amplitudes are due to structures above the brainstem (Ridding et al., 2001). Although extensive investigations into other potential sites of excitation have not been conducted, the above findings suggest that the location of increased corticomotor excitability following PES above motor threshold is supraspinal.

Similar results have been found following PES applied below motor threshold (Kaelin-Lang et al., 2002; Tinazzi et al., 1998). Maximal peripheral M-waves have been used to measure changes within the muscle or the neuromuscular junction (Kaelin-Lang et al., 2002; Tinazzi et al., 1998). Following PES, M-waves remained unchanged suggesting that the observed changes in corticomotor excitability were not due to changes within the muscle or neuromuscular junction. H-reflex amplitudes and F-wave amplitudes have been used to investigate spinal motoneuron excitability (Mima et al., 2004; Tinazzi et al., 1998). No change in H-reflexes or F-waves was found following PES, suggesting that the observed changes in corticomotor excitability did not occur in the spinal cord. Lastly, brainstem electrical stimulation was used in two participants to excite descending motor axons directly at the level of the brainstem (Kaelin-Lang et al., 2002). The amplitude and area of the cervicomedullar evoked potentials did not change following two hours of PES that resulted in an increase in corticomotor excitability measured by TMS over the cortex. These results suggest that changes in corticomotor excitability that are observed following PES applied at intensities above and below motor threshold are supraspinal in origin.

2.4.3 The effect of PES on excitability of the primary somatosensory cortex in healthy adults

Only one study was found that investigated the effect of PES on the primary somatosensory cortex (Wu, Van Gelderen, Hanakawa, Yaseen, & Cohen, 2005). Wu et al. (2005) conducted a crossover study to evaluate the effect of two hours of PES of the median nerve at the wrist on cortical activation using fMRI perfusion and blood oxygenation level (BOLD) responses during active thumb movements. Nineteen participants were allocated to three randomly ordered interventions; two hours of median nerve stimulation, stimulation of the skin overlying the deltoid muscle at the shoulder, and no stimulation. Stimulation parameters were identical to Kaelin-Lang et al. (2002) and consisted of trains of electrical stimuli delivered every second at 10 Hz with a pulse width of 1000 μs and an intensity below motor threshold. This intensity resulted in mild paraesthesias and evoked 50-100 μV compound muscle action potentials in the absence of any visible muscle twitches or pain.

Median nerve stimulation resulted in increased activation of the contralateral primary somatosensory, primary motor and dorsal premotor cortices compared to baseline, in the absence of change following stimulation of the skin overlying deltoid, or no stimulation. Increased activation in the somatosensory and primary motor cortices was specific to the stimulated body part representation and outlasted stimulation for up to 60 minutes. These results are consistent with other studies that have demonstrated specific and lasting changes in corticomotor excitability following PES (Ridding et al., 2000; Ridding et al., 2001; Ridding & Uy, 2003). These results provide evidence that PES applied below motor threshold is capable of inducing neuroplastic change within the primary somatosensory cortex and provides support for its use as a method of modulating plasticity. The lack of increased cortical activity following PES on the skin overlying deltoid suggests that input from large afferents are important in driving neuroplastic changes. Despite the assumption that PES is relayed to the motor cortex via the somatosensory cortex, this is the first piece of evidence that demonstrates the effect of PES on the somatosensory cortex.

2.4.4 The effect of PES on sensorimotor function

PES results in increased corticomotor excitability and increased activity of the sensorimotor cortices. Such cortical changes have been associated with changes in function following other types of training, however, very few studies have investigated the effect of PES on sensorimotor function in healthy adults. Two studies were found that examined the effect of PES on sensory thresholds (Dean, Bowsher, & Johnson, 2006; Mima et al., 2004) and one examined the effect on motor function (Dickstein & Kafri, 2008). All of these studies used high frequency, narrow pulse width stimulation applied below motor threshold. No studies were found that evaluated the functional effect of PES aimed at increasing excitability or applied at intensities above motor threshold.

Mima et al. (2004) applied continuous stimulation to the right thenar eminence at 90 Hz, with a pulse width of 250 μs and an intensity below motor threshold for two 15 minutes sessions in eight healthy males. Sensory threshold, measured using Semmes-Winstein monofilaments, and 2 point discrimination were measured at the site of stimulation (thenar eminence) before stimulation, during the first and second

stimulation sessions (approximately seven minutes after onset of PES), immediately following and at 15 and 30 minutes following the second stimulation session.

Alongside the decrease in corticomotor excitability of APB, as mentioned in section 2.4.2, sensory threshold was also affected by stimulation with a significant increase in sensory threshold during both stimulation sessions and immediately following the second session. Additionally 2-point discrimination threshold significantly increased during both sessions, immediately and at 15 minutes following the second stimulation session. This is the only study found that investigated both the cortical and functional effects of PES. It provides evidence that high frequency, narrow pulse width PES, applied below motor threshold, is capable of inducing an increase in sensory threshold that is specific to the stimulated area, outlasts stimulation, and is associated with a decrease in corticomotor excitability. It is currently unknown if PES parameters that have been shown to increase corticomotor excitability are associated with increased sensory function.

A change in sensory function was also demonstrated by Dean et al. (2006) following 10 minutes of continuous PES applied below motor threshold over the median nerve at the wrist. Slightly different stimulation parameters were used, including a frequency of 100 Hz and a pulse width of 200 μs. Sensory threshold, using Semmes-Weinstein Monofilaments (SWM), sharpness using weighted needles and thermal perception, using a Somedic thermal analyser, were measured from the ipsilateral and contralateral thenar eminence before, during, and 10 and 30 minutes following stimulation. The results of this study revealed that ipsilateral sensory threshold in the distribution of the median nerve increased significantly during and at 10 minutes following stimulation when compared to baseline and the contralateral hand. Sharpness detection worsened significantly during stimulation and thermal perception worsened during and 10 minutes following stimulation. The results of this study are consistent with Mima et al. (2004) and provide further evidence that very short durations of PES are capable of inducing a reduction in sensory function that outlasts stimulation.

Only one small pilot study investigated the effect of PES on motor function. Dickstein and Kafri (2008) examined the effects of unilateral and bilateral high frequency (100 Hz) PES on wrist flexor muscle electromyography (EMG) activity and grip force in 12 healthy participants. Three stimulation conditions; unilateral, bilateral or placebo were applied for 15 minutes to each participant, on three separate, randomly assigned occasions. Stimulation was applied on the forearm flexors using a pulse width of 200 μs and intensity below motor threshold. During the placebo condition the intensity was zero. EMG activity and grip force was measured at baseline, immediately and 15 minutes following stimulation. Testing consisted of four one second long repetitions of maximal voluntary grip contractions. Peak grip force of the four contractions was recorded at each time point.

The results of this study demonstrated that 15 minutes of unilateral or bilateral stimulation was associated with an immediate increase in EMG activity in the wrist flexor muscles during a subsequent maximum voluntary grip task. No change in EMG activity was recorded following placebo stimulation. Peak grip force was significantly increased immediately following unilateral stimulation in the absence of significant change following bilateral and placebo stimulation, which suggests that unilateral but not bilateral stimulation is capable of inducing an immediate significant change in motor function. The results at 15 minutes are less clear. All three conditions demonstrated significant increases in peak grip force however it is unclear if this was compared to baseline or immediately following stimulation making it difficult to evaluate the findings. It is possible that the increase in peak force in all three conditions may be explained by the practice effect of doing repetitive maximal voluntary grip contractions. The results of this study suggest that PES increases EMG activity in the target muscle however the effect on motor function is less clear.

2.4.5 Section summary

This review suggests that low frequency, wide pulse width PES applied above or below motor threshold to nerves or associatively to motor points results in increased corticomotor excitability. Stimulation below motor threshold has been found to increase activity in the somatosensory and motor cortices. This evidence is

suggestive of rapid, focal, reversible neuroplastic changes similar to those seen following motor learning and provides a rationale for the use of PES to enhance neuroplasticity in healthy and brain injured populations. No studies were found that evaluated the effect of PES parameters aimed at increasing excitability and activity on sensorimotor function, and the effect that attention may have on PES not yet been evaluated. In addition, all of the reviewed studies used equipment that is not clinically available and some parameters that would not be clinically feasible, such as stimulation duration of two hours. The purpose of this current thesis therefore was to evaluate the effect of PES with directed and diverted attention on corticomotor excitability, excitability of the primary somatosensory cortex and sensory function in healthy adults. In order to assess the current clinical feasibility of PES the study was carried out using a clinically available stimulation unit and parameters that are feasible in the current clinical environment.

2.5 Development of the intervention for the current study

It is evident from the review of the literature that a variety of stimulation parameters have been used with varied effects. Low frequency, wide pulse width stimulation above or below motor threshold has been shown to increase corticomotor excitability and activity in the somatosensory cortex. Development of the intervention in the current study was based on parameters that were found to be effective in the literature however needed to be modified in some cases to ensure feasibility in a clinical setting. The following section will briefly review key stimulation parameters and provide a rationale for the parameters used in the current study.

2.5.1 Site of stimulation

Stimulation has been applied via electrodes to cutaneous nerves, mixed nerves or motor points and using associative and non-associative stimulation. Single and simultaneous mixed nerve stimulation and associative motor point stimulation in the upper limb are effective at increasing MEP amplitude (Kaelin-Lang et al., 2002; McKay et al., 2002; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding et al., 2001; Ridding & Uy, 2003; Schabrun & Ridding, 2007). In addition, single mixed nerve stimulation increases activity in the primary somatosensory and primary motor cortices (Wu et al., 2005). As nerve stimulation recruits afferent fibres based on their

diameter (large fibres recruited first), mixed nerve stimulation results in the activation of a greater proportion of muscle afferents (Robertson, Ward, Low, & Reed, 2006). The stimulation of muscle afferents seems to influence the efficacy of PES therefore mixed nerve stimulation was selected for the current study.

2.5.2 Waveform

Common waveform shapes include square, rectangular and triangular. Square and rectangular waveforms are more efficient for nerve stimulation due to the instantaneous increase in current to maximal intensity, which increases the chance of an action potential occurring and limits nerve accommodation (Robertson et al., 2006). Square wave, pulsed current was most commonly used in the literature and was therefore selected for the current study.

Waveforms can be biphasic with the current flowing in both direction, or monophasic with the current flowing in one direction. Biphasic waveforms can be symmetrical or asymmetrical which determines if both or one of the electrodes is active during stimulation and is an important consideration when selecting the location of electrodes. The majority of previous studies did not provide any information regarding waveform and those that did used monophasic (Fernandez-del-Olmo et al., 2008), symmetrical and asymmetrical biphasic waveforms (Murakami et al., 2007; Tinazzi et al., 1998). It is unclear from the literature if a particular waveform is more effective in inducing neuroplasticity. For the current study, monophasic waveform was selected to target the median nerve as it results in only one electrode acting as the cathode. Therefore the cathode was placed over the median nerve at the wrist, proximal to the anode, to reduce the possibility of anodal block (Robertson et al., 2006).

2.5.3 Stimulation intensity

Stimulation intensities above and below motor threshold have been used in previous studies with varied results. Stimulation above motor threshold has been shown to consistently increase MEP amplitude (McKay et al., 2002; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding et al., 2001; Ridding & Uy, 2003; Schabrun & Ridding, 2007), whereas intensities below motor threshold have demonstrated increased and

decreased MEP amplitudes (Kaelin-Lang et al., 2002; Mima et al., 2004; Murakami et al., 2007; Tinazzi et al., 1998), increased activation of the primary motor and somatosensory cortices (Wu et al., 2005), and increased sensory thresholds (Dean et al., 2006; Mima et al., 2004). The conflicting results seen following stimulation below motor threshold however are due to the differing parameters, other than intensity, such as pulse width and frequency.

When studies using identical parameters are compared, both intensities of stimulation result in increased MEP amplitude (Kaelin-Lang et al., 2002; McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001). It is currently unclear from the literature which intensity is optimal. As the current study was primarily interested in the effects of direct afferent stimulation, stimulation below motor threshold was selected.

2.5.4 Pulse width

Changing the width of pulses alters the relative recruitment of motor and sensory axons, with narrow pulse widths (50-400 μs) preferentially activating motor axons and wider pulse widths (500-1000 μs) recruiting relatively more sensory axons (Grill & Mortimer, 1996; Mogyoros, Kiernan, & Burke, 1996; Panizza, Nilsson, Roth, Basser, & Hallett, 1992; Veale, Rees, & Rees, 1973). The majority of studies that demonstrated neuroplasticity following PES used wide pulse widths of 1000 μs. Unfortunately this was unable to be replicated in the current study due to the limitations of the stimulation unit therefore the highest pulse width (400 μs) available was selected.

2.5.5 Frequency of stimulation

The frequency of stimulation varied considerably in the literature, ranging from 0.35 Hz to 150 Hz, with 10 Hz the most commonly used frequency. Low frequency stimulation (0.35-10 Hz) resulted in increased MEP amplitude and increased cortical activation, whereas high frequency stimulation (20-150 Hz) had the opposite effect. Therefore a stimulation frequency of 10 Hz was selected for the current study.

2.5.6 Modulation

Modulation is the systematic variation in parameters such as frequency, intensity or pulse width. The purpose of modulation is to limit the rate of habituation which results in a decrease in response to a repeated stimulus (Robertson et al., 2006). Very few studies modulated the duration, frequency or intensity of the stimulation to limit habituation and it is unclear if modulation increases the effectiveness of PES. The stimulation unit in the current study did not have a modulation setting therefore modulation was not used.

2.5.7 Duration of stimulation

Studies that demonstrated increased corticomotor excitability or increased cortical activity used durations ranging from 45 minutes to 2 hours (Kaelin-Lang et al., 2002; McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001; Wu et al., 2005). In the clinical setting however, PES would be applied immediately prior to rehabilitation techniques therefore the duration of stimulation was considered in the context of the therapy session as a whole. Following discussion with clinical experts, thirty minutes of stimulation was selected for the current study as this was deemed to be realistic in the clinical setting.

2.5.8 Attention

Previous studies have shown that attention may optimise the effectiveness of sensory interventions (Rosenkranz & Rothwell, 2004; A. R. Seitz & Dinse, 2007; Stefan, Wycislo, & Classen, 2004). Despite this, very few studies evaluating the effect of PES have considered attention. Only three out of the 15 studies reviewed mentioned attention in their method, and of these one diverted attention away from the stimulus (Kaelin-Lang et al., 2002) and two actively directed attention towards the stimulus (Ridding & Uy, 2003; Schabrun & Ridding, 2007). None of the studies compared PES with or without attention directed at the stimulus and it is currently unknown if attention enhances the induction of neuroplastic change during PES. Therefore, for the purpose of this study attention was directed towards or diverted away from the stimulation to evaluate the effect of attention on PES.

Chapter 3: Test re-test reliability of sensory threshold testing using Semmes-Weinstein Monofilaments

3.1 Introduction

Semmes-Weinstein Monofilaments (SWM) are a hand held tool consisting of filaments of varying diameters that bend at specific repeatable force thresholds and allow the measurement of sensory threshold. The design of filaments accommodate vibration of the examiners hand and control for variable application forces (Bell-Krotoski & Tomancik, 1987). They are used to measure the function of part of the sensory system which includes mechanoreceptors of the skin, large myelinated (Aβ) afferent fibers, peripheral nerve function and the dorsal column medial leminiscal tract to the thalamus and primary somatosensory cortex (Johansson, Vallbo, & Westling, 1980; Weinstein, 1993). SWM compliment the use of SSEPs by providing a functional measure of sensation.

SWM have been used extensively in the literature to detect and measure the degree of sensory disturbance following brain injury, nerve injury or neuropathy and have been found to be valid and reliable in these populations (Jerosch-Herold, 2005; Patel & Bassini, 1999; Semmes, Weinstein, Ghent, & Teuber, 1960). Reliability in healthy adults is less clear due to conflicting results in the literature. Intra-rater reliability has been found to range from excellent to poor (Collins, Visscher, De Vet, Zuurmond, & Perez, 2010; Felix & Wilderstrom-Noga, 2009; Massy-Westropp, 2002; Rozental, Beredjiklian, Guyette, & Weiland, 2000; Semmes et al., 1960) and inter-rater reliability from excellent to fair (Novak, Mackinnon, Williams, & Kelly, 1993; Rozental et al., 2000).

A review of the literature suggests that the reliability of sensory threshold testing using SWM is dependent on several factors such as the calibration of filaments prior to use, environmental humidity, the method of application, assessors' experience, and the length of time that the force is applied. Studies that addressed the majority of

the above factors (Felix & Wilderstrom-Noga, 2009; Novak et al., 1993; Semmes et al., 1960) demonstrated excellent to moderate intra- and inter-rater reliability suggesting that SWM is a reliable tool in healthy adults when these factors are controlled. As reliability is influenced by assessor experience it was decided to conduct a study to establish the reliability of sensory threshold testing by our assessor using SWM prior to the main study.

3.2 Aim

The aim of this study was to establish the intra- and inter-session reliability of sensory threshold testing using SWM by our assessor, in healthy adults.

3.3 Methods

3.3.1 Participants

Twenty healthy participants (6 men and 14 women) aged 20 to 65 years (mean = 43 ± 12 years) participated in the study. All volunteers were verbally screened over the phone to determine eligibility, and were given the opportunity to discuss the study and ask any questions. Volunteers were invited to participate in the study if they were aged 20-70 years with no neurological disorders or cognitive deficits. The study was approved by the AUT University Ethics Committee, approval number 09/94 (see Appendix A), and all participants gave written informed consent.

3.3.2 Equipment

Testing was carried out with a standard kit of SWM (Monofilament kit, Sammons Preston Rolyan, USA) containing 20 filaments calibrated to forces ranging from 1.65-6.65 $\log^{10}$ force (mg/10). Previous studies have stressed the importance of calibration of monofilaments prior to use as errors in monofilament length may result in inaccurate forces (Bell-Krotoski & Tomancik, 1987); therefore, prior to the study, each monofilament was measured to confirm the appropriate length (38 mm) from rod to tip.

3.3.3 Procedure

Participants were measured on three occasions. Trial 1 and 2 were measured on the same day, separated by a five minute rest. Trial 3 was conducted two days later. See

Figure 1 for a summary of assessment points. At the first session all participants were screened for hand dominance using the Edinburgh Handedness Questionnaire (Appendix B) (Oldfield, 1971).

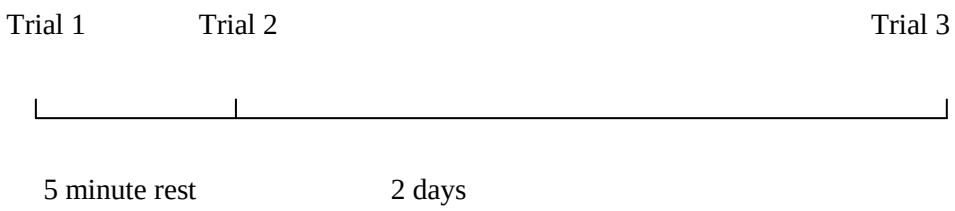

Figure 1: Timeline of assessment points for sensory threshold testing.

Sensory threshold was assessed on three separate occasions with a five minute rest between trial 1 and trial 2 and a two day rest between trial 1 and 3.

Participants were comfortably seated in a semi-reclined modified podiatry chair with a pillow to support the head and a table in front to support both arms (refer to Figure 2 below).

Figure 2: Participant set up for sensory threshold data collection.

The procedure was explained to the participant and the pulp of both index fingers marked with permanent marker to indicate the area to be tested. To ensure

consistency within and between trials, this point was defined as the apex of the arch of the fingerprint. The assessor assessed sensory threshold using a standardised procedure (refer to Appendix C). Participants were instructed to close their eyes and say "yes" when they perceived that their index finger was being touched. Starting with the right index finger, the filaments were applied perpendicular to the skin, to the point of bending, for 3 seconds (applied for 1 second, held for 1 second and released for 1 second) (Bell-Krotoski, 1991; Bell-Krotoski & Buford, 1997; Semmes et al., 1960). A staircase procedure was utilised to determine sensory threshold starting with a noticeable stimulus. Filaments were decreased in a stepwise manner until the participant no longer perceived a stimulus (lower boundary) and then increased until the stimulus was perceived again (upper boundary). The timing of application between filaments was varied so that participants could not predict the stimulus. This procedure was repeated three times and the first and last filaments perceived were recorded, resulting in six values per hand. The left hand was then tested followed by a five minute rest before the procedure was repeated again for both hands. During measurement, noise was kept to a minimum and the room temperature was maintained at 20-24°C. This procedure has been described previously by Semmes et al. (1960) and has been shown to have excellent test re-test reliability in healthy adults.

3.4 Data processing and analysis

The lower and upper boundary scores for each index finger were recorded in Excel (Microsoft Office Excel 2007) and the six values for each finger, at each assessment point, were averaged to provide the sensory threshold. Data was sorted into dominant and non-dominant hands to control any variations that may have occurred due to handedness. Sensory thresholds were double checked against raw data to ensure accuracy of data entry.

Data were analysed with SPSS software package (SPSS 16.0 for Windows, SPSS Inc., Chicago, USA). Intra and inter-session reliability was evaluated using intraclass correlation coefficients (ICC) (two-way mixed effects model, terms of absolute agreement). ICC provides an indication of relative error by assessing how closely the scores from one trial replicate the scores in another trial (Atkinson &

Nevil, 1998; Hopkins, 2000). Data from the Trial 1 were compared to data from Trial 2 to assess intra-session reliability, and Trial 1 to Trial 3 to assess inter-session reliability. The interpretation for the level of reliability was based on Shrout's recommendations with an ICC between 0.41-0.60 considered "fair", between 0.61-0.80 considered "moderate", and between 0.81-1.00 considered "substantial" (Shrout, 1998). The literature suggests that the use of ICCs alone for the analysis of reliability is not sufficient as it is influenced by the heterogeneity of values between participants and fails to assess the agreement between repeated measurements (de Vet, Terwee, Knol, & Bouter, 2006; Hopkins, 2000). Therefore, typical error, coefficient of variation (CV%), standard error of measurement (SEM), SEM% and Bland-Altman plots were also used.

Typical error (TE) and CV% were calculated to analyse the agreement between measurements and quantify the within participant random variation between trials (Lexell & Downham, 2005). TE and CV% were calculated using the equations: typical error = SDdiff/$\sqrt{2}$ and CV% = (TE/mean) x 100. SEM and SEM% were also calculated as measures of agreement to allow comparison with a previous intra-rater reliability study (Collins et al., 2010). SEM and SEM% were calculated using the equations SEM = $\sigma\sqrt{(1\text{-ICC})}$ and SEM% = (SEM/mean) x 100 (de Vet et al., 2006; Lexell & Downham, 2005).

To analyse the agreement between measurements, assess the presence of systematic bias and heteroscedasticity, data were presented graphically in Bland-Altman plots using Excel (Microsoft Office Excel 2007). The differences between measurements from two trials were plotted against the mean of the two measurements for each participant. The 95% limits of agreement (LOA) were calculated as the range of differences falling within the mean difference ± 1.96 standard deviations (Bland & Altman, 1986; Bland & Altman, 1996). The 95% LOA represent the test re-test differences for 95% of the population and provides an indication of the magnitude of measurement error between trials (de Vet et al., 2006).

3.5 Results

3.5.1 Sample Characteristics

Participant characteristics are presented in Table 2. Twenty participants were assessed.

Table 2: Summary of participant characteristics.

Participant characteristics	
Gender	
Male	6
Female	14
Age (years)	22-68
	M = 43 (SD = 12)
Handedness	
Left	3
Right	11

Note. M = mean, SD = standard deviation.

3.5.2 Test-retest reliability

The mean sensory threshold was 3.16 ± 0.43 log ^{10} in the dominant hand and 3.16 ± 0.44 log ^{10} in the non-dominant hand. The intraclass correlation coefficients (ICC), 95% confidence interval, TE, CV%, SEM and SEM% for intra-session and inter-session reliability in the dominant and non dominant hands between each trial are presented in Table 3 below.

Table 3: Reliability statistics for SWM sensory threshold testing.

		ICC (95 % confidence interval)	TE	CV%	SEM	SEM %
Intra-session reliability (T1- T2)	Dominant hand	0.96 (.90-.98)	0.10	3.46	0.07	2.5
	Non dominant hand	0.94 (.85 - .97)	0.13	4.47	0.09	2.9
Inter-session reliability (T1- T3)	Dominant hand	0.85 (.65-.94)	0.21	6.76	.19	6.0
	Non dominant hand	0.82 (.62 - .93)	0.23	7.53	.20	6.4

Note. ICC: intra class correlation coefficient, TE: typical error, CV%: coefficient of variation, SEM: standard error of measurement.

ICCs were high for intra- and inter-session reliability and were similar in dominant and non dominant hands. Intra-session reliability was substantial with correspondingly high confidence intervals. The inter-session ICCs also indicated substantial reliability however were lower, ranging from 0.82 - 0.85 with wider 95% confidence intervals. Reliability was slightly higher in the dominant hand when compared to the non-dominant hand for both testing intervals.

The TE and CV% ranged from 0.10 - 0.23 and 3.46 - 7.85 % respectively, with higher values for inter-session when compared to intra-session reliability. Slightly lower TE and CV% values were observed for the dominant hand when compared to the non-dominant hand for both testing intervals. SEM and SEM % results were similar.

Bland-Altman plots for intra-session reliability and inter-session reliability in dominant and non dominant hands are presented below. The bias was positive and ranged from 0.05 - 0.07 with the largest mean difference observed for inter-session reliability in the dominant hand. These results indicate a slightly higher sensory threshold for Trial 2 and 3 compared to Trial 1, and greater inter-session variability.

No heteroscedasticity was observed in any of the plots. Ninety five percent LOA were narrow and contained zero for all analyses.

In the dominant hand the mean difference between Trial 1 and 2 was .05 ± 0.3 (95% LOA) and between Trial 1 and 3 0.07 ± 0.5 (95% LOA). In the non dominant hand the mean difference between Trial 1 and 2 was .06 ± 0.3 (95% LOA) and between Trial 1 and 3 0.5 ± 0.6 (95% LOA). One outlier was detected for intra-session reliability in the dominant (Figure 3), and non-dominant hand (Figure 4), and for inter-session reliability (Figure 6) in the non-dominant hand.

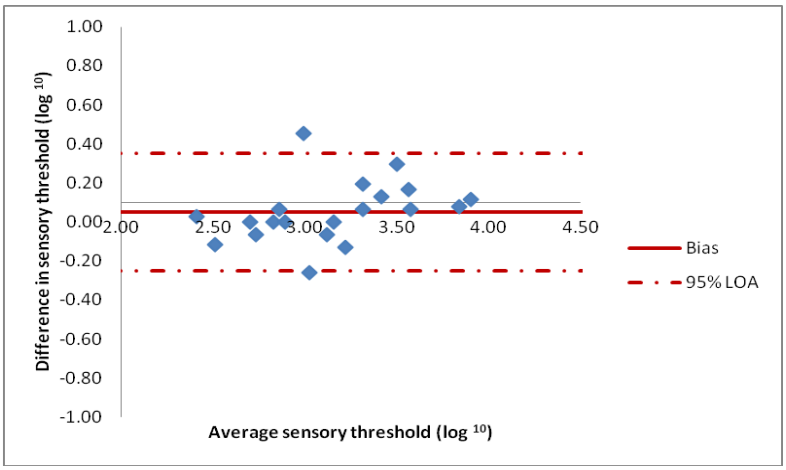

Figure 3. Bland-Altman plot for the intra-session reliability in the dominant hand.

Note: The differences between the trials are plotted against each individuals mean for the two trials. The solid line represents the bias between the two trials. The dotted lines represent the 95% limits of agreement (± 1.96 standard deviations).

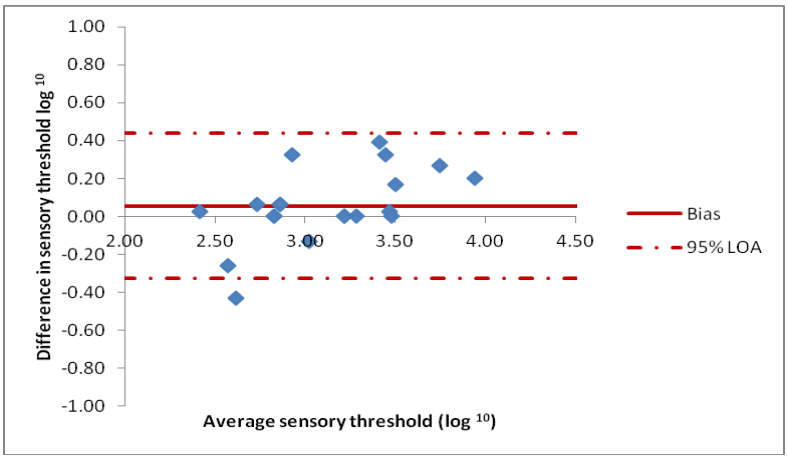

Figure 4. Bland-Altman plot for the intra-session reliability in the non-dominant hand.

Note: The differences between the trials are plotted against each individuals mean for the two trials. The solid line represents the bias difference between the two trials. The dotted lines represent the 95% limits of agreement (± 1.96 standard deviations).

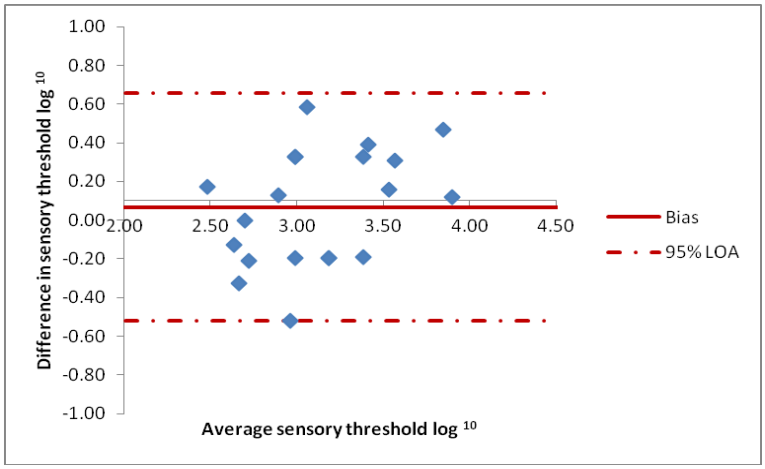

Figure 5. Bland-Altman plot for the inter-session reliability in the dominant hand.

Note: The differences between the trials are plotted against each individuals mean for the two trials. The solid line represents the bias between the two trials. The dotted lines represent the 95% limits of agreement (± 1.96 standard deviations).

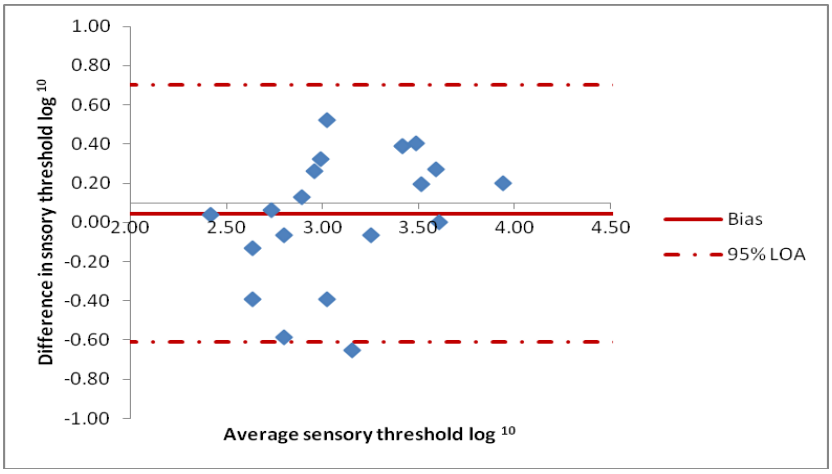

Figure 6. Bland-Altman plot for the inter-session reliability in the non-dominant hand.

Note: The differences between the trials are plotted against each individuals mean for the two trials. The solid line represents the bias between the two trials. The dotted lines represent the 95% limits of agreement (± 1.96 standard deviations).

3.6 Discussion

The test re-test reliability of SMW sensory threshold testing was substantial in both hands and between all trials. These results are higher than previous intra-session and inter-session reliability results (Collins et al., 2010; Felix & Wilderstrom-Noga, 2009), and may reflect different methods such as different sets of SWM, measurement of sensory threshold at different sites and differing methods of calculating threshold. In the current study, ICCs were lower and 95% confidence intervals wider (ranging from moderate to substantial reliability) for inter-session reliability than intra-session reliability. This is consistent with Collins et al. (2010) who also reported lower ICCs (0.52- 0.78) and wider 95% CI (0.42 - 0.83) when reliability was assessed by the same assessor on separate occasions. The results of the current reliability study indicate that the range of the ICC in the true population is wider, possibly reflecting more within participant variation, when measurements are conducted on two separate occasions compared to two consecutive trials on one occasion.

Absolute error was assessed using TE, CV% and Bland-Altman plots. TE in the present study indicates low levels of error in both hands and between all trials with slightly higher error apparent for inter-session measurements. No other studies were

found that measured TE and CV% of sensory threshold testing, therefore no comparisons can be made. SEM and SEM% also demonstrated low levels of error and allowed comparison to the previous study by Collins et al. (2010). The intra-session SEM in the our study is slightly lower than Collins et al. (2010) that reported a SEM of 0.25 and 0.33 following intra-rater reliability testing in the feet of healthy adults. The higher SEM found in the study by Collins et al. (2010) however may have been due to the measurement of sensory threshold from several sites and differing protocols. Despite these subtle differences both studies suggest a low level of error when testing sensory threshold with SWM. The variation observed in the present study is most likely due to a slight variation in the site of application of the filaments or subjectivity in the evaluation of sensation by participants. It is unlikely that our study's protocol was a major source of variability as a standardised protocol was followed during all trials. The addition of a practice session before formal testing may reduce participant subjectivity, therefore reducing error further.

The Bland-Altman plots displayed considerable agreement between trials confirming low systematic and random error. The mean difference between trials is located close to zero but was positive in all plots, indicating that sensory threshold at Trial 2 or 3 tended to be higher than at Trial 1. This may be due to a transient decrease in participants' concentration or motivation on subsequent trials. These results are consistent with Collins et al. (2010) who also found slightly higher sensory threshold at Trial 3 when compared to Trial 1. Heteroscedasticity was not present which suggests that there is no relation between the magnitude of the measured value and the size of the difference between measurements. The 95% LOA are narrow between all trials with the widest 95% LOA apparent between inter-session measurements. These results suggest that 95% of the difference measurements are located within a range of 0.3 - 0.6 higher or lower than the mean difference suggesting low between session variation. These results represent less variation when compared to Collins et al. (2010) who reported slightly higher 95% LOA, ranging from ± 0.6 - 0.9 between Trial 1 and 3.

Reliability studies can also be used to estimate the magnitude of change in a measure following an intervention that reflects a true change rather than measurement error.

Bland-Altman 95% LOA can be used to estimate true change in sensory threshold. Wide 95% LOA reflect increased measurement error, due to participant variability or measurement inaccuracy, for the same measure at different occasions. This increased measurement error means that true changes due to an intervention may be obscured or that change due to the variability of the measure may be misinterpreted as true change. The current study demonstrated narrow 95% LOA suggesting that changes of more than ± 0.3 - 0.6 $\log^{10}$ represent a true change in sensory threshold. Hopkins (2000) argues that 95% LOA are too large to use as a threshold for estimating a true change and suggests 1.5- 2.0 times the typical error as a more realistic threshold. Based on the largest typical error in the current study and using 2.0 as the more conservative estimate of true change, a change of more than ± 0.4 $\log^{10}$ would represent a true change in sensory threshold.

3.7 Conclusion

Measurement of sensory threshold in healthy adults, by our assessor, using SWM has been found to be reliable, with considerable agreement between measurements and low levels of error. The addition of a practice trial prior to testing may reduce error further. These results support the use of this measure in the main study.

Chapter 4: Method

4.1 Introduction

The purpose of the study was to examine the immediate effect of 30 minutes of PES with attention focused on stimulation, compared to PES with attention diverted away from the stimulation, and sham PES, on corticomotor excitability, excitability of the primary somatosensory cortex, and sensory threshold in the hand of healthy adults. The following chapter outlines the method used in our research by describing the study setting and design, participants, procedure, data management and statistical analysis.

4.2 Study Setting and Design

This study was undertaken at the Health and Rehabilitation Research Institute, AUT University, Auckland, New Zealand. A repeated measures, within-participant design, with experimental and control interventions was used.

4.3 Study participants

4.3.1 Sample size

Sample size calculation was undertaken assuming an alpha level of 0.05 and power of 0.8 using an online power calculator (StatisticalSolutions, 2009). Based on a MEP amplitude of 1 mV (± 0.5) and an effect size of 0.8, a sample size of ten participant's was required. An effect size of 0.8 was selected as this was deemed to be a physiologically meaningful result and is similar to previous studies in this field (7.5 - 9.1). The sample size was increased to 12 participants as the study required a significant time commitment from participants and it was anticipated that there may be drop outs.

4.3.2 Recruitment

Participants were recruited through advertisement at AUT University via posters (Appendix D). Posters included the study title, brief information on the study, eligibility criteria and an invitation to volunteer for the study.

4.3.3 Inclusion and exclusion criteria

Participants were included in the study if they satisfied the following inclusion criteria:

- Aged between 20-70 years

Participants were excluded if they had any of the following:

- Neurological disorders
- Contraindications and precautions to electrical stimulation. This excluded participants with: uncontrolled epilepsy, cardiac arrhythmia, cardiac pacemaker or metal implants in the hand region.
- Known contraindications to transcranial magnetic stimulation (TMS). This excluded from participation people with: pacemaker, intracardiac lines, artificial heart valves containing conductive material, cranial-facial reconstruction or metal implants in the head region (not including dental fillings) (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).
- Known precautions to TMS. This excluded participants with: history of epilepsy or seizure, concussion within the last six months, skull fracture or known skull defects, taking medication that lower seizure threshold and/or a history of severe or recurring headaches (Rossi et al., 2009; Wassermann, 1998).

4.4 Ethical and Cultural Considerations

Ethical approval was obtained from the AUT University Ethics Committee (AUTEC), approval number 09/94 (Appendix A). During the design and implementation of the study the principles of the Treaty of Waitangi, including partnership, participation and protection were applied, and the recruitment process ensured that all eligible participants had equal opportunity to take part in the study regardless of ethnicity.

4.5 Study procedure

The following section describes the study procedure including a detailed outline of pre- and post-intervention measures and experimental and control interventions. Refer to Figure 7 for an outline of the procedure.

All volunteers whom met the inclusion criteria were informed of the study purpose and procedure verbally and in writing (Appendix E). Eligible participants were invited to attend the first of six sessions. At the first session participants were asked relevant personal details, screened again for inclusion, and provided written informed consent (Appendix F). To ensure that participants were blinded to the interventions participants were deceived. They were not informed of the study hypotheses and were told that different intensities of electrical stimulation were being tested. At the completion of the study participants were fully informed verbally and in writing of the study hypotheses and provided informed consent again for their data to be used (Appendix G).

Participants were screened for hand dominance and allocated to intervention protocols (see section 4.7 for a detailed description of the three intervention protocols). The order of interventions was randomised using a computer generated random list within Excel (Microsoft Office, 2007). A research assistant delivered the interventions following a standardised procedure which allowed the researcher to remain blinded to intervention protocols throughout the study. Corticomotor excitability, excitability of the primary somatosensory cortex and sensory threshold were assessed before and after each intervention (see section 4.6 for a detailed description of pre and post intervention testing). To ensure that there was sufficient time to assess all measures immediately following each intervention the study was carried out in two parts. Corticomotor excitability and sensory threshold were assessed in sessions 1-3 and excitability of the somatosensory cortex was assessed in sessions 4-6 (see Figure 7).

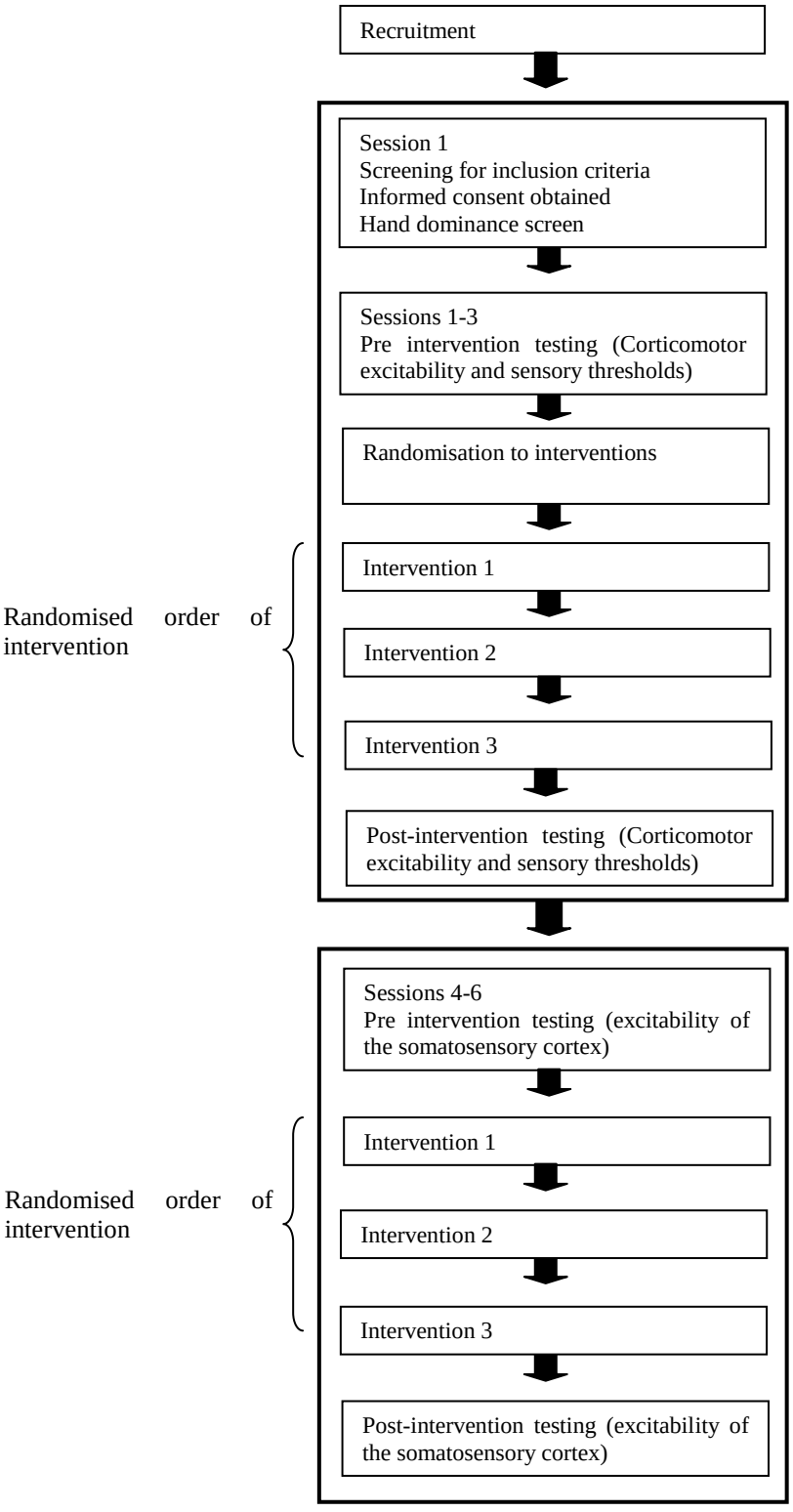

Figure 7: Outline of study procedure.

4.6 Measures

4.6.1 Hand dominance

At the first session all participants completed The Edinburgh Handedness Questionnaire (Appendix B) to determine hand dominance. A laterality quotient (LQ) of +100 represented extreme right hand preference, whereas a LQ of -100 represented extreme left hand preference (Oldfield 1971).

4.6.2 Assessment of corticomotor excitability

Participants were comfortably seated in a semi reclined modified podiatry chair with a table in front supporting both arms (refer to Figure 8 below).

Figure 8: Participant set up for MEP amplitude data collection.

Corticomotor excitability was assessed using single pulse TMS to elicit motor evoked potentials (MEP) in the right abductor pollicus brevis (APB) of all participants. Participants were tested twice at baseline, five minutes apart, to ascertain the stability of responses. Following the intervention corticomotor excitability was measured immediately and again at 15 minutes. The purpose of post-intervention testing was to determine the immediate and persisting effects of each intervention on corticomotor excitability. See Figure 9 for a summary of assessment points.

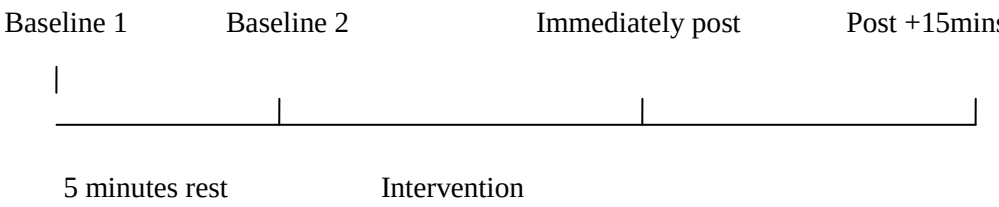

Figure 9: Timeline of assessment points for corticomotor excitability.

Corticomotor excitability was assessed twice at baseline prior to the intervention and once immediately and at fifteen minutes following the intervention.

Recording techniques

MEPs were recorded via EMG collected from APB of the right hand. Skin was prepared for electromyography (EMG) using standard skin preparation techniques. This involved shaving to remove hair, exfoliation of the skin using fine sandpaper, cleansing with alcohol and wiping dry to remove any residue. A Nortrode 20^{TM} Ag/AgCl 20 mm bipolar self-adhesive surface electrode (Myotronics Inc, Kent, WA) was placed over the muscle belly of APB and a ground electrode was placed over the lateral epicondyle at the elbow. APB was located by palpation during active thumb abduction by the participant.

EMG signals were amplified (AMT-8 EMG Wire telemetry system, Bortec Biomedical Ltd, Canada), filtered (10-1000 Hz) and sampled at a rate of 5000 Hz via an AD converter (Micro1401 MkII, CED Ltd, Cambridge, UK). EMG data were collected for 150 ms which included 50 ms prior to the stimulation.

Stimulation techniques

MEPs were elicited by TMS to the left motor cortex. A Magstim 200² (Magstim Company, Dyfed, UK) was used to deliver stimuli via a figure-of-eight stimulation coil (70 mm diameter each coil). The stimulating coil was positioned tangentially over the participant's left motor cortex, with the handle orientated posteriorly and laterally at a 45° angle away from the midline. This orientation was utilised as it enduces a posterior to anterior current flow within the brain and is optimal for activating the hand region of the motor cortex (Brasil-Neto, Cohen, Panizza, et al., 1992; Pascal-Leone, 1994).

At the beginning of each session the optimal position for stimulation was identified by systematically moving the coil over the motor cortex until the site that elicited the largest MEP from APB was established. This site was defined as the 'hotspot' and was marked on each participants scalp by permanent marker. For the remainder of the session the 'hotspot' was used as the stimulation site. The intensity of stimulation was then reduced until the minimum intensity required to elicit MEPs of $\geq$ 50 μV in the APB muscle in at least four out of eight consecutive stimuli was determined (resting motor threshold) (Rossini, 2007). Test stimulus intensity for TMS was then set at 130% of resting motor threshold and for the remainder of the session ten single pulse TMS were used to assess corticomotor excitability at each assessment point. Muscle activation has been show to alter cortical excitability (Ridding, Taylor, & Rothwell, 1995), therefore participants were asked to relax during TMS and relaxation of APB was monitored by the observation of continuous EMG traces via an oscilloscope (TDS2014B, Tektronix Inc, Beaverton, OR). Similar TMS protocols have been used in the literature and have been found to be reliable for assessing MEP amplitude in the hand muscles of healthy participants (Lefebvre, Pepin, Louis, & Boucher, 2004; Lewis, Byblow, & Carson, 2001; Malcolm et al., 2006).

4.6.3 Assessment of sensory threshold

Sensory threshold of the index finger on both hands was measured twice at baseline five minutes apart, and once immediately and at 15 minutes following each intervention, using Semmes-Weinstein monofilaments (Sammons Preston Rolyan, USA). See Figure 10 for a summary of assessment points for sensory threshold testing. Testing was carried out with a standard kit of SWM (Monofilament kit, Sammons Preston Rolyan, USA) containing 20 filaments calibrated to forces ranging from 1.65-6.65 $\log^{10}$ force (mg/10).

Sensory threshold testing was applied by an experienced assessor using the standarised procedure that was found to have substantial test re-test reliability in our reliability study (section 3.5). Participants were comfortably seated in a semi-reclined modified podiatry chair with a pillow to support the head and a table in front to support both arms. The procedure was explained to the participant and the pulp of

both index fingers marked with permanent marker to indicate the area to be tested. To ensure consistency, this point was defined as the apex of the arch of the fingerprint. Participants were instructed to close their eyes and say "yes" when they perceived that their index finger was being touched. Starting with the right index finger, the filaments were applied perpendicular to the skin, to the point of bending, for 3 seconds (applied for 1 second, held for 1 second and released for 1 second) (Bell-Krotoski, 1991; Bell-Krotoski & Buford, 1997; Semmes et al., 1960). A staircase procedure was utilised to determine sensory threshold starting with a noticeable stimulus. Filaments were decreased in a stepwise manner until the participant no longer perceived a stimulus (lower boundary) and then increased until the stimulus was perceived again (upper boundary). The timing of application between filaments was varied so that participants could not predict the stimulus. This procedure was repeated three times and the first and last filaments perceived were recorded, resulting in six values per hand. The left hand was then tested. During measurement, noise was kept to a minimum and the room temperature was maintained at 20-24°C.

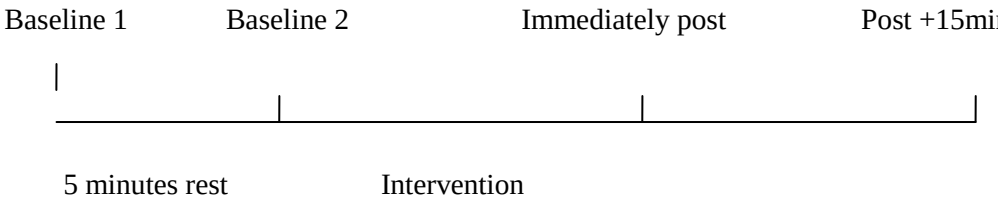

Figure 10: Timeline of assessment points for sensory threshold.

Note: Sensory threshold was assessed twice at baseline prior to the intervention and again immediately and at 15 minutes following the intervention.

4.6.4 Assessment of the excitability of the primary somatosensory cortex

Somatosensory evoked potentials have been used in previous studies to assess experimentally induced changes in excitability (Enomoto et al., 2001; Pleger et al., 2001; Ragert, Becker, Tegenthoff, Pleger, & Dinse, 2004; Tsuji & Rothwell, 2002), with different SSEP components enabling the site of plastic change to be located within the somatosensory system (Tinazzi et al., 1998). For the purpose of this study, median nerve SSEP N20-P25 peak to peak amplitudes were used to assess the excitability of the left primary somatosensory cortex. SSEP guidelines and current literature were used to standardise the procedure for the current study (American Clinical Neurophysiology Society, 2008).

Participants were tested twice at baseline, five minutes apart, to ascertain the stability of responses. This was repeated once immediately following the intervention and again at five, ten and 15 minutes. The timely nature of SSEP measurement allowed for the addition of two extra assessment points. The purpose of post-intervention testing was to determine the immediate and persisting effects of each intervention on the excitability of the somatosensory cortex. See Figure 11 for a summary of assessment points.

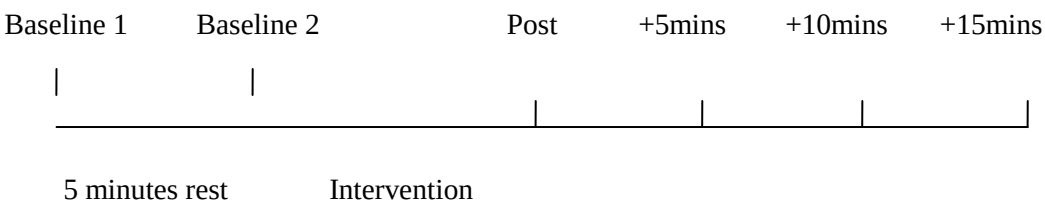

Figure 11: Timeline of assessment points for excitability of the somatosensory cortex.

Note: Excitability was assessed twice at baseline prior to the intervention and again immediately and at five, ten and fifteen minutes following the intervention.

Participants were orientated to the equipment and process and comfortably seated in a semi-reclined modified podiatry chair with an armrest supporting the left upper limb and table supporting the right forearm. Pillows were placed under the head, right upper limb and knees to provide support and reduce muscle activity (refer to Figure 12) (American Clinical Neurophysiology Society, 2006; Leeman, 2007). During recording participants were asked to close their eyes and relax. Noise was kept to a minimum and the lights were dimmed (American Clinical Neurophysiology Society, 2008).

Figure 12: Participant set up for SSEP data collection.

Note: The stimulating electrodes at the wrist were secured by tape and a small bandage. The recording electrodes on the head were secured in place by high density foam and a bandage.

Stimulation techniques

Skin over the median nerve was prepared for electrical stimulation using standard skin preparation techniques. This involved shaving to remove hair, exfoliation of the skin using fine sandpaper, cleansing with alcohol and wiping dry to remove any residue. An EEG cup electrode filled with Ten20 conductive EEG paste (DO Weaver & Co, USA) was used as the cathode and placed over the median nerve on the ventral surface of the wrist, 2 cm proximal to the palmar crease (Cruccu et al., 2008; Leeman, 2007; Nuwer, 1994). A second carbon rubber, reusable, 2 cm diameter electrode (PALS, USA) was prepared with gel (Lectron II, Pharmaceutical innovations, Inc. USA) and placed on the dorsum of the wrist (American Clinical Neurophysiology Society, 2008). The correct location of the electrodes was confirmed by electrical stimulation resulting in a visible abduction muscle twitch of the thumb. Skin impedance was evaluated using an Ohmmeter (Dick Smith Electronics, Auckland, NZ) and was accepted when below 5 kΩ to reduce discomfort and stimulus artifact (American Clinical Neurophysiology Society, 2008).

Electrical stimulation was delivered (Digitimer DS7A, Digitimer Ltd, UK) to the median nerve at the wrist using constant current, monophasic square wave pulses 200 μs in duration, at a rate of 4 Hz, and a stimulus intensity sufficient to produce a visible muscle twitch (abduction of the thumb) (American Clinical Neurophysiology Society, 2008; Cruccu et al., 2008; Leeman, 2007).

Recording techniques

Skin was prepared for SSEP using standard skin preparation techniques. This involved exfoliation of the skin using fine sandpaper, cleansing with alcohol and wiping dry to remove any residue. Silver/silver chloride EEG electrodes (Gereonics inc. California) filled with Ten20 conductive EEG paste (DO Weaver & Co, USA) were placed according to the international 10-20 system (American Electroencephalographic Society, 1994). The recording electrode was placed on the scalp over the left somatosensory cortex, 2 cm posterior to C4 and a reference electrode situated over the midline frontal region of the forehead (Fz). This recording montage was selected as it results in reduced artifacts, clear N20 onset times and large amplitudes (Cruccu et al., 2008; Sonoo, Kobayashi, Genba-Shimizu,

Manen, & Shimizu, 1996; Yamada, Yeh, & Kimura, 2004). A ground electrode was placed on the right earlobe. Electrodes were secured in place by placing a square of high density foam over each scalp electrode and the application of a bandage around the head. Skin impedance was evaluated using Ohmmeter (Dick Smith Electronics, Auckland, NZ) and was accepted when below 10 kΩ. This is slightly higher than the recommended 5 kΩ (American Clinical Neurophysiology Society, 2008); however, it was acceptable for this study as participants were required to attend three lab sessions at least 48 hours apart and more vigorous skin preparation resulted in skin irritation and prohibited participants from attending subsequent sessions.

Signals were amplified using a Grass AC amplifier (P511/CP511, Astro-med, USA), band pass filtered (30 Hz-3000 Hz) and sampled at a rate of 5000 Hz via an AD converter (Micro1401 MkII, CED Ltd, Cambridge, UK). A total number of 500 stimulus related epochs were recorded at each assessment point. One hundred milliseconds of SSEP data were collected per electrical stimulation, which included 50 ms prior to the stimulus (American Clinical Neurophysiology Society, 2008; Cruccu et al., 2008; Yamada et al., 2004).

4.7 Experimental and control interventions

There were three interventions that each participant received on separate days, in a random order, and at least 48 hrs apart to reduce the risk of carry over effects. The three interventions were:

- Experimental: Thirty minutes of PES applied below motor threshold, with attention directed towards the stimulation;
- Attention control: Thirty minutes of PES applied below motor threshold, with attention diverted away from the stimulation;
- Stimulation control: Thirty minutes of sham PES with attention diverted away from the stimulation.

4.7.1 PES electrode placement

Each participant's right forearm was prepared following standard skin preparation techniques which included shaving to remove hair, exfoliation of the skin using fine sandpaper, cleansing with alcohol and wiping dry to remove any residue. Self adhesive 3.2 cm round electrodes (PALS Platinum, Axelgaard Manufacturing Co Ltd, USA) were applied to the ventral aspect of the forearm, with the anode approximately 2.5 cm proximal to the palmer crease at the wrist and the cathode 1 cm proximal to the anode. This position was selected to stimulate the median nerve whilst still allowing for the placement of stimulating electrodes for the measurement of excitability of the somatosensory cortex.

4.7.2 PES parameters

Thirty minutes of PES was delivered via the Empi 300PV stimulator (Empi, USA) to the median nerve at the wrist. Stimulation consisted of monophasic pulses, with a pulse width of 400 μs, frequency of 10 Hz, repeated in an on-off mode (1 s on: 1 s off). For the experimental and attention control interventions the stimulus intensity was increased above motor threshold and then adjusted down until visual and tactile muscle contraction disappeared. Mild paraesthesias, without pain were reported in digits 1, 2, 3 and possibly 4. During all interventions the stimulation unit was hidden from view in a box. Participants were asked to relax their arm during the 30 minute intervention.

4.7.3 Sham stimulation parameters

In an attempt to control for the effects of the application of the electrical stimulation machine a sham stimulation intervention was used. During sham stimulation identical electrode placement and parameters were used however the stimulus intensity was adjusted down to 0 mA.

4.7.4 Attention during stimulation

Previous studies have shown that attention may optimise the effectiveness of sensory interventions (Rosenkranz & Rothwell, 2004; A. R. Seitz & Dinse, 2007; Stefan et al., 2004) therefore, an attention control was incorporated into the current study to ascertain the impact of attention on PES.

During the experimental intervention, participants' attention was directed towards the stimulation by instructing them to look at the stimulated hand and count the number of sets of 20 stimuli that they felt. Participants' were cued every five minutes to continue counting and the numbers of sets of 20 stimuli were recorded to assess their accuracy. During the attention control (diverted attention) and sham stimulation interventions participants were required to look at the computer screen and count the number of sets of 20 random computer generated auditory tones, therefore effectively diverting their attention away from the stimulation. Similar methods of focusing or diverting attention have been used in the literature (Conte et al., 2007; Stefan et al., 2004).

4.8 Data management

All written data were stored in a locked cabinet in the researcher's office. Computer data were stored on the password controlled laboratory computer with a back up copy kept on a portable data device and stored with the written data. Participant confidentiality was maintained through the allocation of a numerical code which appeared on all information related to each participant. Participant details and codes were able to be matched via a database that could only be accessed by the principle researcher.

4.9 Data processing

4.9.1 Corticomotor excitability

Analysis of corticomotor excitability measures was performed using Signal software (CED, Cambridge, UK). MEP recordings were visually screened for background muscle activation and recordings that displayed muscle activity were removed prior to processing. This represented approximately 5 % of the recordings. Raw MEP data were rectified and processed by averaging the ten MEPs from each time period. The averaged MEP was then used to measure the root mean square amplitude of background EMG (background RMS), peak to peak MEP amplitude and MEP latency at each assessment point. Background RMS was defined as the RMS amplitude of EMG during a 30 ms pre-stimulus window. MEP amplitude was defined as the maximum peak to peak amplitude in a 40 ms window following MEP

onset. MEP latency (onset) was defined as the first point following the stimulus artifact that the EMG signal exceeded background RMS by three standard deviations. All measurements were confirmed by visual analysis of the data. This method of MEP analysis was selected as it is commonly used in the literature (Benwell et al., 2006; Lewis et al., 2001). Figure 13 provides an example of an averaged MEP signal from the APB of one participant showing the measurement parameters.

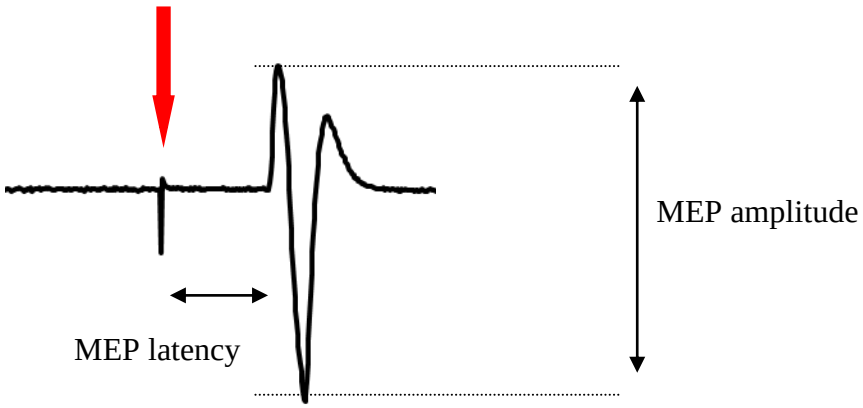

Figure 13: Averaged MEP from one participant.

Note: The averaged MEP signal is an average of 10 responses. MEP= motor evoked potential, mV=millivolts, ms= milliseconds. The stimulus artifact is indicated by the vertical arrow.

4.9.2 Sensory threshold

The lower and upper boundary scores for each index finger were recorded in Excel (Microsoft office Excel 2007) and the six values (lower and upper boundaries, three repetitions) for each finger were averaged at each assessment point to provide the sensory threshold (Semmes et al., 1960).

4.9.3 Excitability of the primary somatosensory cortex

Analysis of SSEP amplitudes was performed using Signal software (CED, Cambridge, UK). All SSEP recordings were visually screened for artifact and recordings that displayed artifact were removed prior to further processing. Five hundred SSEPs from each assessment point were averaged. This represented approximately 5 % of the recordings. The averaged SSEP was then used to measure

N20 latency and the peak to peak amplitudes for N20-P25. N20 latency (onset) was defined as the point of maximum negativity occurring at about 17-22 ms following the stimulus and preceding a large positive deflection. N20 was defined as the largest reproducible negative peak between 17 and 22 ms followed by a large positive deflection and P25 as the positive trough following N20 occurring at between 23-29 ms. The N20-P25 peak to peak amplitude was determined by measuring the distance between N20 peak and P25 trough (Haseeb et al., 2007; Nuwer, 1994). All responses were confirmed by visual analysis of the data. These components were selected as they reflect excitability of the primary somatosensory cortex (Mochizuki et al., 2004; Ozaki, Suzuki, Tanosaki, Baba, & Matsunaga, 2000; Tsuji & Rothwell, 2002). Figure 14 provides an example of an averaged SSEP signal from the primary somatosensory cortex of one participant showing the measurement parameters.

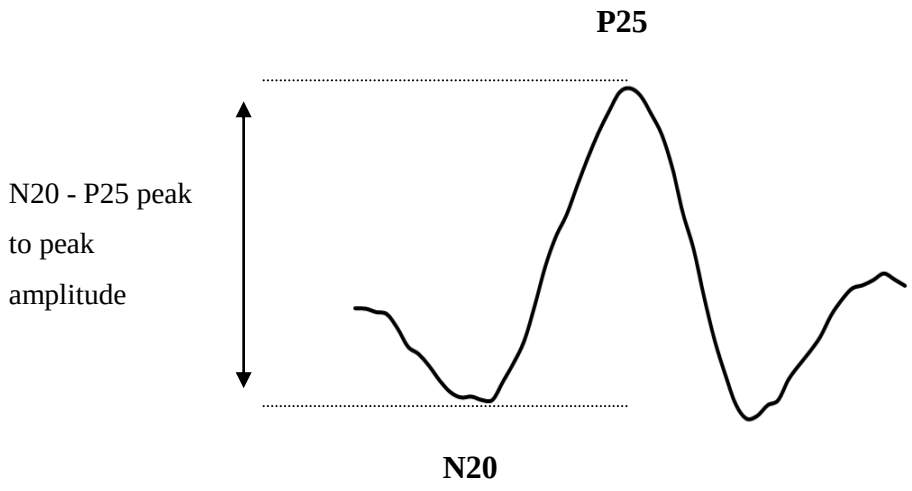

Figure 14: Averaged SSEP from one participant.

Note: The SSEP is an average of 500 stimulus related epochs recorded from the primary somatosensory cortex. SSEP= somatosensory evoked potential, mV=millivolts, ms= milliseconds. N20 and P25 are labeled and the N20-P25 peak to peak amplitude is indicated by the arrow.

4.10 Data analysis

Following data processing the researcher was unblinded to the interventions and data were entered into SPSS software package (SPSS 16.0 for Windows, SPSS Inc.,

Chicago, USA) for analysis. To ensure accuracy, data were double checked against the raw data. Data were then screened by a visual check of the range of scores, mean, standard deviation and standard error. Histograms and boxplots were plotted to view the distribution of data, and any outliers were referenced to raw data and confirmed as correct. Kolmogorov-Smirnov tests were used to assess the normality of data distribution, with a p-value of > 0.05 indicating a normal distribution (Field, 2005). This test revealed that the distribution of two variables (sensory threshold and SSEPs) were normal, whereas the distribution for MEP amplitude was non-normal. Therefore, natural log-transformations were used transform the MEP amplitude data prior to statistical analysis (Field, 2005). Parametric statistics were selected for all statistical analyses and an α level of 0.05 was used to determine statistical significance.

Analysis involved two phases, first a descriptive analysis of the participants' characteristics followed by statistical analysis of the variables of interest. The primary dependent variables were: MEP amplitude, right and left sensory thresholds, and N20-P25 peak to peak amplitude. The independent variables for corticomotor excitability and sensory thresholds were intervention (PES with focused attention, PES with attention diverted and sham PES with attention diverted), and time (baseline 1, baseline 2, post-intervention and post-intervention +15 minutes). The independent variables for excitability of the primary somatosensory cortex were intervention (PES with focused attention, PES with attention diverted and sham PES with attention diverted), and time (baseline 1, baseline 2, post-intervention, post-intervention +5 minutes, post-intervention +10 minutes and post-intervention +15 minutes).

Descriptive analysis of participants' characteristics identified the range, mean and standard deviation for the continuous data of age. Descriptive analysis also included summaries of the nominal characteristics of gender and handedness.

The effect of intervention on the dependant variables was analysed using a two way repeated measures ANOVA with within-subject factors of time and intervention. Sphericity of all data was determined by applying Mauchly's test. Where the

assumption of sphericity was violated, and Epsilon <1, Greenhouse-Geisser corrections were applied to the degrees of freedom (Field, 2005). Significant main effects were investigated using a Bonferroni correction to ensure control over the type I error rate (Field, 2005). All data is presented as mean ± standard deviation.

Chapter 5: Results

5.1 Introduction

The purpose of the current study was to evaluate the effect of 30 minutes of peripheral electrical stimulation, with directed or diverted attention, on corticomotor excitability, excitability of the primary somatosensory cortex and sensory threshold in the hand of healthy adults. The following chapter presents the main findings of the study. It will provide an overview of recruitment and retention, followed by a description of the participants' characteristics. Finally, analysis of the effect of the interventions on corticomotor excitability, excitability of the primary somatosensory cortex and sensory thresholds will be presented.

5.2 Recruitment and retention

Fourteen people volunteered for the study and of these 12 met the inclusion criteria. All eligible participants (n = 12) completed TMS and sensory threshold assessments but two participants were unable to complete the SSEP assessments. One participant was unable to return for the final two sessions of SSEP assessment, and the other could not tolerate SSEP stimulation. Therefore the results for SSEP were determined from 10 participants. Data collection took place from November 2009 to February 2010. Figure 15 below provides an overview of participant recruitment and retention.

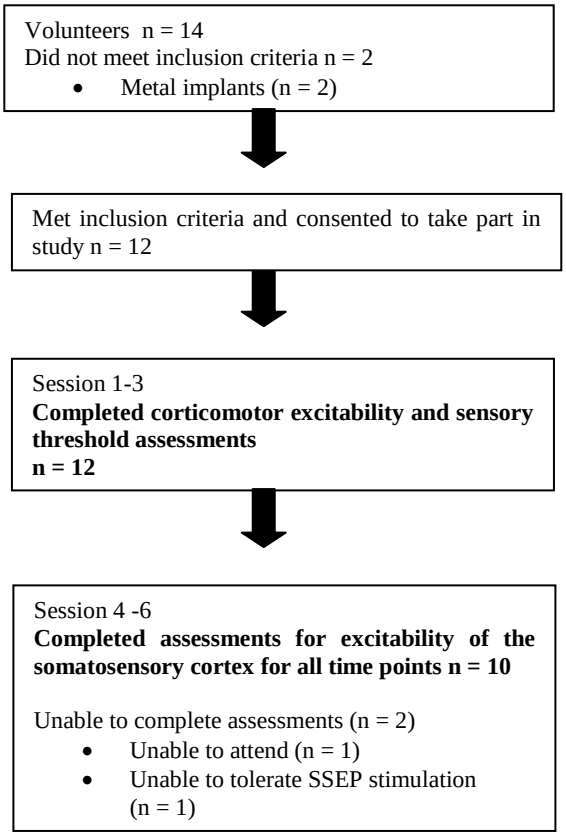

Figure 15. Flow diagram of participant recruitment and retention.

Note: SSEP = somatosensory evoked potentials

5.3 Sample characteristics

The characteristics of the participants are presented in Table 4 below. The age of participants ranged from 22 – 64 years (M = 40, SD = 12 years), with 5 males and 7 female participants. Two participants were left handed and 10 right handed.

Table 4: Participants' characteristics

Participant	Gender	Age (years)	Handedness
P1	F	47	R
P2	F	36	L
P3	F	39	R
P4	F	40	R
P5	M	35	R
P6	M	27	L
P7	M	22	R
P8	M	55	R
P9	M	36	R
P10	F	34	R
P11	F	50	R
P12	F	64	R
Mean	7 F	40	10 R
SD		12	

Note. M = male/ female, L = left, R = right, SD = standard deviation.

5.4 Corticomotor excitability

Across all sessions the average baseline MEP amplitude was 0.56 ± 0.45 mV with an average latency of 22 ± 1 ms. Figure 16 shows an example of MEP traces from one participant before and after PES with attention directed towards the stimulation.

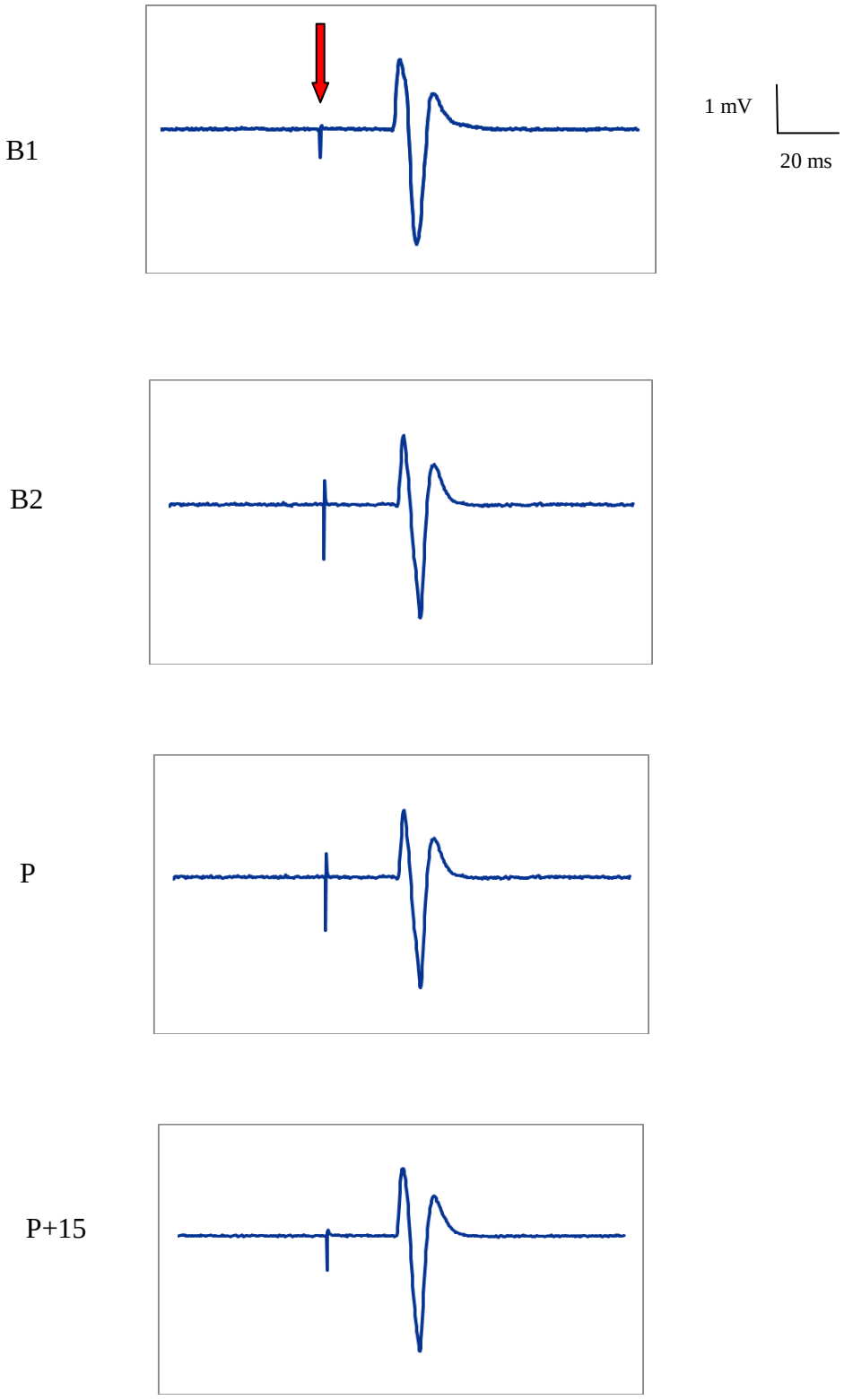

Figure 16: Example of MEP traces from one participant before and after PES with attention directed towards the stimulation.

Note: Traces are an average of ten responses. The arrow indicates the stimulus artifact. B1 = baseline 1, B2 = baseline 2, P = immediately post intervention, P+15 = post intervention +15 minutes.

Comparison of the three interventions is displayed graphically in Figure 17. There was no significant main effect of intervention ($F(2,22) = .276$, $p = .761$), time ($F(3,33) = 1.95$, $p = .141$), or interaction effect of intervention x time ($F(6,66) = 1.199$, $p = .318$) on MEP amplitude.

These results do not support the hypotheses that PES with directed attention, and PES with diverted attention results in increased corticomotor excitability post intervention. Neither does it support the hypothesis that PES with directed attention, demonstrates greater increases in corticomotor excitability compared to PES with diverted attention.

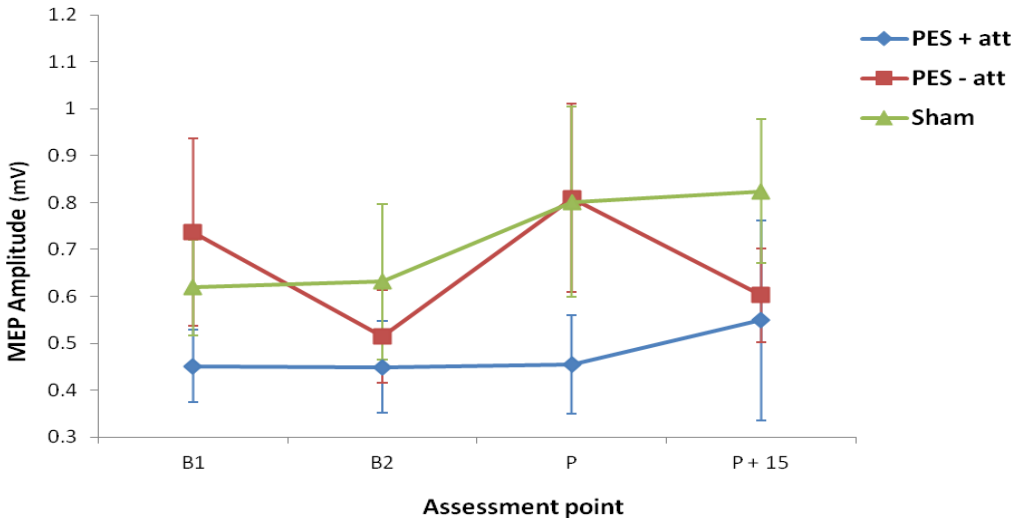

Figure 17: Group results for MEP amplitude at the four time periods.

Note: MEP amplitude are an average of 10 responses. Error bars show standard error of the mean. PES +att = peripheral electrical stimulation with attention focused on the stimulation, PES -att = peripheral electrical stimulation with attention diverted away from the stimulation, PES sham= no stimulation and attention diverted away from the stimulation. B1 = baseline 1, B2 = baseline 2, P = immediately post intervention, P+15 = post intervention +15 minutes.

5.5 Sensory threshold

The stimulated (right) and control (left) hand sensory thresholds were analysed separately. Across all sessions the average baseline sensory threshold was 3.14 ± .4 $\log^{10}$ in the right hand and 3.02 ± .4 $\log^{10}$ in the left hand. Group comparisons of the

effects of the three interventions in the stimulated hand are displayed in Figure 18. There was no significant main effect of intervention ($F(2,22) = 714$, $p = .501$), or interaction effect of intervention x time ($F(6,66) = .286$, $p = .942$) on sensory thresholds. There was a significant main effect of time ($F(3,33) = 6.497$, $p = .001$) on sensory thresholds in the stimulated hand. Post hoc paired t-tests analysis was performed to analyse whether there was a significant difference in sensory thresholds in the stimulated hand between the four time points. Baseline 1, was compared to all other time points and revealed no significant difference in sensory thresholds between any of the time points assessed (p >0.05).

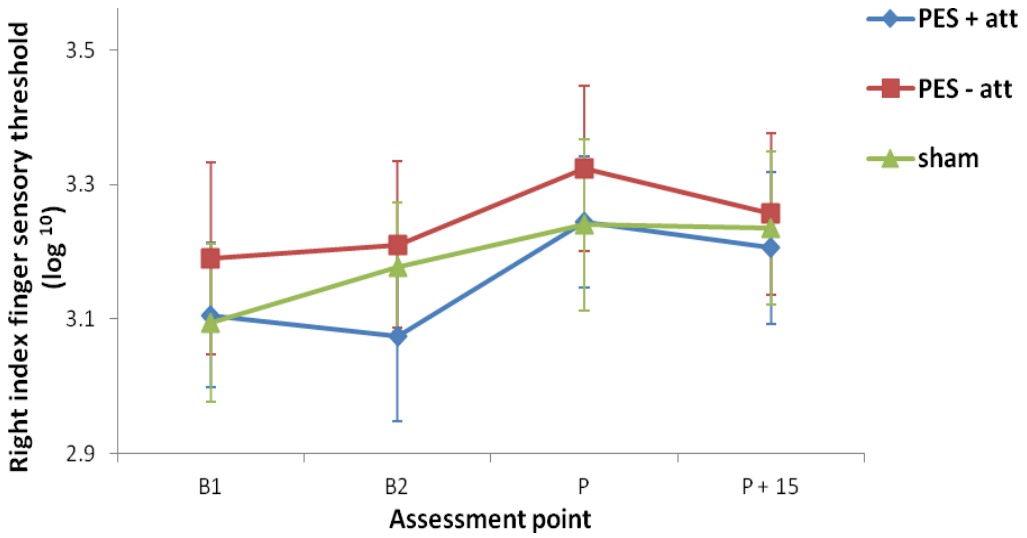

Figure 18: Group results for sensory threshold in the stimulated (right) hand over time.

Note: Sensory threshold is an average of six scores. Error bars show standard error of the mean. PES +att = peripheral electrical stimulation with attention focused on the stimulation, PES -att = peripheral electrical stimulation with attention diverted away from the stimulation, PES sham= no stimulation and attention diverted away from the stimulation. B1 = baseline 1, B2 = baseline 2, P = immediately post intervention, P+15 = post intervention +15 minutes.

For the control (left) hand there was no significant main effect of intervention ($F(2,22) = 368$, $p = .696$), time ($F(3,33) = 2.762$, $p = .058$), or interaction effect of intervention x time ($F(6,66) = 1.514$, $p = .187$) on sensory thresholds.

These results do not support the hypotheses that PES with directed attention, and PES with diverted attention results in decreased sensory threshold post intervention. Neither does it support the hypothesis that PES with directed attention, demonstrates greater decreases in sensory threshold compared to PES with diverted attention.

5.6 Excitability of the primary somatosensory cortex

Across all sessions the average baseline N20-P25 amplitude was 2.60 ± 0.001 μV with an average N20 latency of 20 ± 1 ms. Figure 19 displays an example of SSEP average traces from one participant before and after PES with attention directed towards the stimulation.

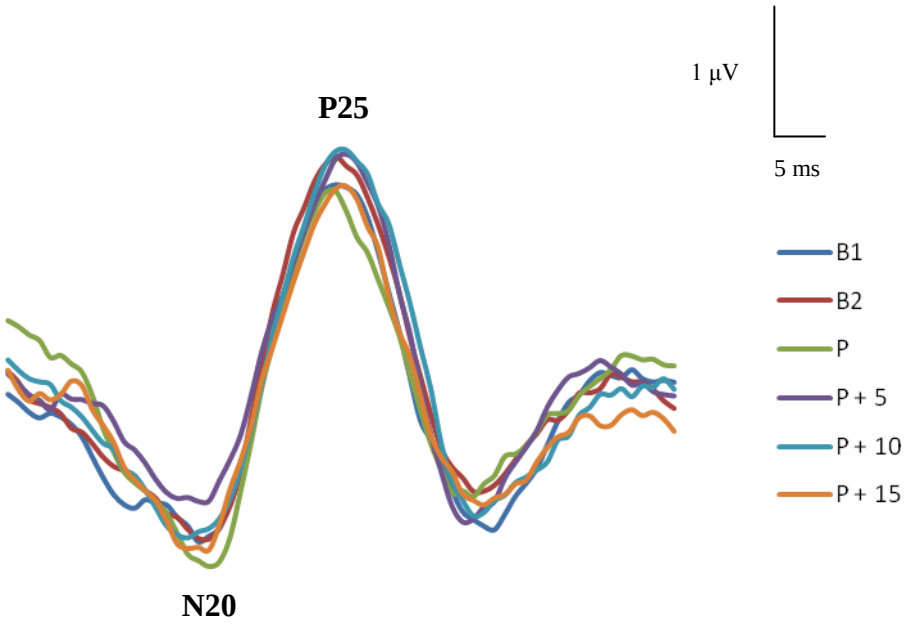

Figure 19: Example of SSEP traces from one participant before and after PES with attention directed towards the stimulation.

Note: Traces are an average of 500 responses. N20-P25 SSEP amplitude is labeled. B1 = baseline 1, B2 = baseline 2, P = immediately post intervention, P+5 = post intervention +5 minutes. P+10 = post intervention +10 minutes, P+15 = post intervention +15 minutes.

Comparison of the effect of the three interventions is displayed graphically in Figure 20. There was no significant main effect of intervention ($F(2,18) = 691$, $p = .514$), time ($F(5,45) = 2.224$, $p = .068$), or interaction effect of intervention x time ($F(10,90) = 1.251$, $p = .311$) on N20-P25 amplitude.

These results do not support the hypotheses that PES with directed attention, and PES with diverted attention results in increased excitability of the primary somatosensory cortex post intervention. Neither does it support the hypothesis that PES with directed attention, demonstrates greater increases in excitability of the primary somatosensory cortex compared to PES with diverted attention.

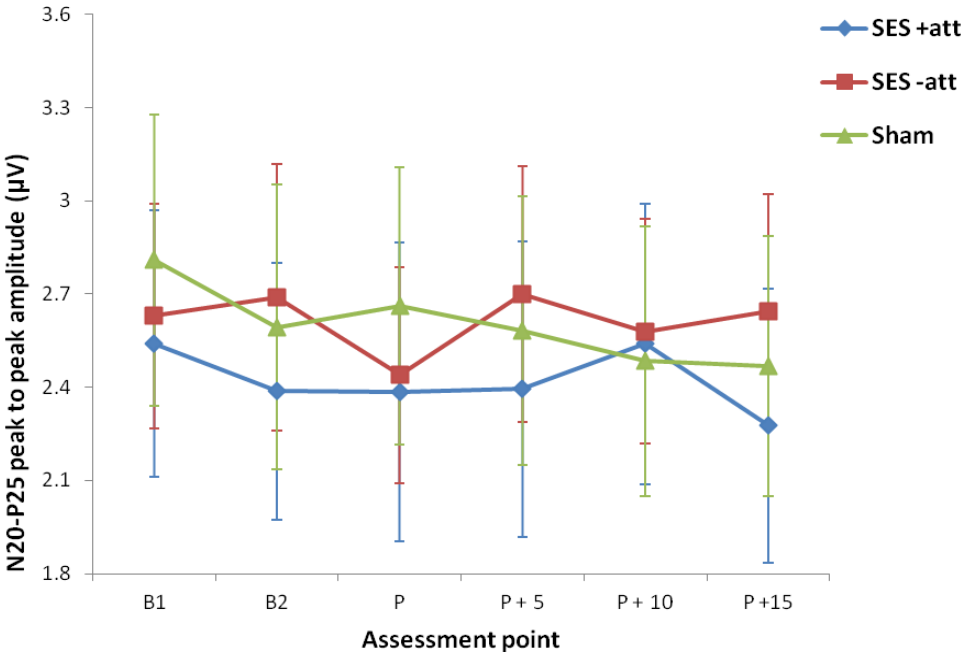

Figure 20: Group results for SSEP N20-P25 amplitude over time.

Note: SSEP amplitude are an average of 500 responses. Error bars show standard error of the mean. PES +att = peripheral electrical stimulation with attention focused on the stimulation, PES -att = peripheral electrical stimulation with attention diverted away from the stimulation, PES sham= no stimulation and attention diverted away from the stimulation. B1 = baseline 1, B2 = baseline 2, P = immediately post intervention, P+5 = post intervention +5 minutes. P+10 = post intervention +10 minutes, P+15 = post intervention +15 minutes.

Chapter 6: Discussion

6.1 Introduction

The purpose of this study was to examine the effect of 30 minutes of PES with directed attention, PES with attention diverted and sham PES on corticomotor excitability, excitability of the primary somatosensory cortex and sensory threshold in healthy adults. The following chapter will examine each hypothesis in relation to the results of the current study. Comparison will be made with previous research investigating the effect of PES in the upper limb and potential explanations for our findings will be explored. To conclude this chapter, suggestions for future research will be made.

6.2 Corticomotor excitability

Hypothesis One: In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased corticomotor excitability.

Hypothesis Two: In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in corticomotor excitability compared to PES with attention diverted.

The results of the current study suggest that 30 minutes of PES below motor threshold, regardless of attentional focus, had no effect on corticomotor excitability in healthy adults. These results are in contrast to the majority of previous studies that have demonstrated increased corticomotor excitability following PES (Chipchase, Schabrun, & Hodges, 2011; Kaelin-Lang et al., 2002; McKay et al., 2002; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding et al., 2001; Ridding & Uy, 2003; Schabrun & Ridding, 2007; Uy & Ridding, 2003), but are consistent with three studies that found no change in corticomotor excitability following short duration (10 - 30 minutes) PES (Chipchase et al., 2011; Fernandez-del-Olmo et al., 2008; Uy & Ridding, 2003). Possible explanations for the findings in the current study will be discussed in the following section.

6.2.1 Stimulation parameters and corticomotor excitability

In the current study, PES parameters were selected based on previous literature and clinical feasibility, which resulted in parameters that differed somewhat from those used in previous research. It is possible that the stimulation duration, intensity, frequency and pulse width utilised in the current study explain the lack of increased corticomotor excitability.

A minimum duration of PES may be required to induce changes in corticomotor excitability. Ten and 30 minutes of stimulation have been found to be insufficient to elicit changes in corticomotor excitability (Chipchase et al., 2011; Uy & Ridding, 2003), whereas 30, 45 and 120 minutes of stimulation resulted in significant increases (Chipchase et al., 2011; Kaelin-Lang et al., 2002; McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001). These results are somewhat conflicting and closer inspection of the literature suggests that the combination of stimulation parameters, not just duration, is influential. Five of the studies mentioned above (Kaelin-Lang et al., 2002; McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001; Uy & Ridding, 2003) used similar parameters to the current study, with the majority demonstrating increased corticomotor excitability following two hours of stimulation. McKay et al. (2002) investigated the induction of excitability over time and found that corticomotor excitability increased steadily but did not become significantly different until 45 minutes of stimulation. This study suggests that 30 minutes of stimulation, using the stimulation parameters of the current study, is too short to induce significant changes in corticomotor excitability.

However in support our selection of 30 minutes duration, a recent study by Chipchase et al. (2011) demonstrated that 30 minutes of stimulation is capable of inducing changes in corticomotor excitability but that the combination of stimulation parameters influences the outcome. The parameters used were different to the current study with stimulation delivered using a monophasic waveform, a pulse width of 100 μs, and applied to the biceps brachii muscle. Six different stimulation paradigms were investigated with varied frequency and intensity. The results of this study demonstrated that 10 and 100 Hz stimulation applied at perceptual threshold, and 10 Hz applied at noxious threshold decreased corticomotor excitability. Thirty

Hz applied to elicit muscle contraction increased corticomotor excitability, and 10 Hz applied at a similar intensity just producing a muscle twitch and at a higher intensity producing a maximal muscle twitch had no effect. This study demonstrates that 30 minutes of stimulation can increase corticomotor excitability but future research is required to determine the optimal combination of stimulation parameters to elicit the desired effect within clinically feasible timeframes.

The stimulation intensity used in the current study may have been inadequate. A recent systematic review concluded that the intensity of stimulation was an important parameter for the modulation of corticomotor excitability and that there was a trend for intensities above motor threshold to be effective (Chipchase, Schabrun, & Hodges, 2010). Previous studies that have used intensities above motor threshold have demonstrated increased corticomotor excitability (McKay et al., 2002; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding & Taylor, 2001; Ridding & Uy, 2003; Schabrun & Ridding, 2007), whereas intensities below motor threshold have resulted in varied outcomes (Chipchase et al., 2011; Dean et al., 2006; Kaelin-Lang et al., 2002; Mima et al., 2004; Murakami et al., 2007; Tinazzi et al., 1998). Kaelin-Lang et al. (2002) used similar stimulation parameters to the current study and demonstrated increased corticomotor excitability following two hours of PES at an intensity below motor threshold. This is in contrast to the remaining studies that used intensities below motor threshold (Chipchase et al., 2011; Dean et al., 2006; Mima et al., 2004; Murakami et al., 2007; Tinazzi et al., 1998) that demonstrated decreased MEP amplitudes. It is important to note however that the stimulation parameters used in these latter studies differed considerably to our study as their aim was to reduce corticomotor excitability. It is difficult therefore to evaluate the effect that changes in intensity alone may have had. It is possible that the submotor threshold intensity, in combination with the 30 minute duration, was too low to induce changes in corticomotor excitability. Future studies are required to investigate the effect of stimulus intensity on excitability with all other stimulation parameters remaining constant.

A frequency of 10 Hz was used for the current study which is consistent with the majority of studies that have demonstrated an increase in MEP amplitude following

PES (Kaelin-Lang et al., 2002; McKay et al., 2002; Ridding et al., 2000; Ridding et al., 2001). It is important to note that the configuration of the trains in the current study differed due to the limitations of the stimulation unit. Previous studies have used 10 Hz applied at a rate of 1 train per second, 5 pulses per train, with 500 ms on/off ratio, whereas the current study used 10 Hz applied at a rate of 1 train per second, 10 pulses per train, with a 1 sec on/off ratio. The configuration of trains in the current study would have resulted in the same number of impulses over a 30 minute period, however, the train duration was longer. Suprathreshold stimulation results in the initiation of an action potential, depolorisation, repolorisation and hyperpolorisation of axons prior to returning to resting potential (Robertson et al., 2006). The delivery of trains of 10 impulses may have resulted in more hyperpolorisation of axons. Maximal hyperpolorisation occurs following trains of 10-20 impulses resulting in axons that are more difficult to recruit, therefore reducing afferent input, until axons return to their resting potential at about 100 ms following stimulation (Burke, Kieran, & Bostock, 2001). It is possible that the configuration of trains applied in the current study resulted in more hyperpolorisation than previous studies and may explain the lack of change in corticomotor excitability. Future studies should investigate the effect of different frequencies of PES on corticomotor excitability, with all other stimulation parameters remaining constant.

Pulse width may have had an effect on the outcome of the current study. The pulse width used in the current study (400 μs) was limited by the capabilities of the stimulation unit and was considerably shorter than previous similar studies that have demonstrated an increase in corticomotor excitability (Kaelin-Lang et al., 2002; McKay et al., 2002; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding & Taylor, 2001; Ridding & Uy, 2003; Schabrun & Ridding, 2007). Pulse widths of 500 - 1000 μs preferentially stimulate sensory axons over motor axons (Panizza et al., 1992). The pulse width used in the current study would not have been optimal for stimulating sensory axons and may have resulted in comparatively reduced afferent input to the CNS.

It is possible that the method of directing attention used in the current study was insufficient to optimise the effects of PES. Previous studies have found that directed

attention significantly increased MEP amplitudes following a period of paired associative stimulation or low amplitude vibration (Rosenkranz & Rothwell, 2004; Stefan et al., 2004). These studies directed attention by instructing participants to detect random changes in the intensity or frequency of stimulation, which would have required more active attention than the method used in our study.

6.2.2 Participant characteristics and corticomotor excitability

Corticomotor plasticity reduces significantly with advancing age (Muller-Dahlhaus, Orekhov, & Ziemann, 2008; Rogasch, Dartnall, Cirillo, Nordstrom, & Semmler, 2009; Sawaki, Yassen, Kopylev, & Cohen, 2003), therefore, the age of participants may have contributed to the lack of change in corticomotor excitability that was observed. Participants in the current study were older, ranging from 22-64 years (M =40) when compared to previous studies that have that have investigated corticomotor excitability following PES (range = 18-50 years) (Fernandez-del-Olmo et al., 2008; Kaelin-Lang et al., 2002; McKay et al., 2002; Mima et al., 2004; Murakami et al., 2007; Pyndt & Ridding, 2004; Ridding et al., 2000; Ridding & Taylor, 2001; Ridding & Uy, 2003; Tinazzi et al., 1998).

6.3 Excitability of the primary somatosensory cortex

Hypothesis Three: In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased excitability of the primary somatosensory cortex.

Hypothesis Four: In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in excitability of the primary somatosensory cortex compared to PES with attention diverted.

The results of the current study suggest that 30 minutes of PES, delivered at an intensity below motor threshold, regardless of attentional focus, had no effect on the excitability of the primary somatosensory cortex in healthy adults. Only one other study was found that evaluated the effect of PES on the primary somatosensory cortex and demonstrated increased cortical activation of the primary somatosensory cortex as measured by fMRI (Wu et al., 2005). Possible explanations for the findings of the current study will be discussed in the following section.

6.3.1 Stimulation parameters and excitability of the primary somatosensory cortex

The stimulation parameters used in the current study differed somewhat to those used by Wu et al. (2005) and it is possible that the duration, frequency and pulse width utilised in the current study explain the lack of increased excitability of the primary somatosensory cortex.

A possible explanation for the lack of increased excitability observed in the current study is the use of a considerably shorter duration of stimulation. Wu et al., (2005) found that two hours of stimulation effectively increased activity in the primary somatosensory cortex. No other studies were found that evaluated the effect of PES on the somatosensory cortex and the minimum duration to induce such changes is currently unknown. The results of the current study suggest that 30 minutes of stimulation is insufficient to increase excitability of the primary somatosensory cortex. Future studies should investigate the time course required to induce changes in excitability. In addition, it is likely that the combination of stimulation parameters affects outcomes as discussed previously (see section 6.2.1), therefore various combinations of stimulation parameters should also be evaluated in an attempt to determine the stimulation parameters that induce increased excitability in the shortest amount of time.

A frequency of 10 Hz was used for the current study which is consistent with the study by Wu et al. (2005). As discussed in section 6.2.1 however, the configuration of the trains differed due to the limitations of our stimulation unit which may have induced more hyperpolorisation of axons. It is unclear, due to the lack of evidence, if 10 Hz is the optimal frequency for increasing excitability of the somatosensory cortex. Future studies should investigate the effect of different frequencies of stimulation with all other stimulation parameters remaining constant.

Lastly, the pulse width used in the current study (400 μs) was narrower than that applied by Wu et al. (2005) (1000 μs) and as discussed previously in 6.2.1, was not optimal for stimulating sensory afferents. This may have resulted in comparatively reduced afferent input to the somatosensory cortex therefore influencing the results.

6.4 Sensory threshold

Hypothesis Five: In healthy participants, 30 minutes of PES with directed and diverted attention will result in increased sensory threshold in the index finger of the right hand.

Hypothesis Six: In healthy participants, 30 minutes of PES with directed attention will result in a greater increase in sensory threshold in the index finger of the right hand compared to PES with attention diverted.

The current study is the first study to evaluate the effect of one session of PES using stimulation parameters designed to increase cortical excitability and decrease sensory threshold. The results suggest that 30 minutes of PES below motor threshold, regardless of attentional focus, had no effect in healthy adults. Very few studies have investigated the impact of PES on sensory threshold and the majority of these studies have used stimulation parameters designed to increase threshold (Dean et al., 2006; Mima et al., 2004). Only one other study was found that used stimulation parameters aimed at decreasing sensory threshold (Cuypers, Levin, Thijs, Swinnen, & Meesen, 2010). This study differs considerably to the current study but has been included in the discussion as it allows comparison and provides insight into possible reasons for the findings in the current study.

Cuypers et al. (2010) used high frequency (100 Hz), narrow pulse width stimulation at an intensity below motor threshold, for durations of one hour a day for three weeks, and demonstrated no effect on sensory threshold in healthy participants but a significantly decreased threshold in participants with multiple sclerosis. These results are in agreement with the current study and suggest that PES has no effect on sensory threshold in healthy adults. However, these findings are most likely explained by participants' scores at baseline which were already at a minimum resulting in any decreases in sensory threshold being unable to be measured. In contrast, a decrease in sensory threshold was observed in participants with multiple sclerosis. These results must be interpreted with caution as they may not be directly comparable to healthy adults due to the underlying disease process however they do provide evidence that PES is capable of decreasing sensory threshold. The following

section will compare the current study to previous research and will provide possible explanations for the lack of change in sensory threshold observed.

6.4.1 Stimulation parameters and sensory threshold

The stimulation parameters used in the current study differed considerably to those used in the previous study by Cuypers et al. (2010). It is possible that the duration and frequency of stimulation used in the current study explain the lack of decreased sensory threshold.

As discussed in previous sections 6.2.1and 6.3.1, the duration of stimulation used in the current study may have contributed to the findings. Protocols using as little as 10 or 15 minutes of stimulation have observed an increase in sensory threshold (Dean et al., 2006; Mima et al., 2004). This suggests that the duration of the PES intervention in the current study would have been sufficient to demonstrate similar changes if they had occurred. In contrast, decreased sensory threshold has only been demonstrated following one hour of PES per day for a period of three weeks in participants with multiple sclerosis (Cuypers et al., 2010). Unfortunately this study did not evaluate sensory threshold following a single one hour session of PES, therefore it is unknown if a decrease in sensory threshold was present at this time point. The results of the current study suggest that 30 minutes of stimulation, designed to decrease sensory threshold, is insufficient. Further research is required to investigate varied durations of stimulation in an attempt to clarify this issue.

The stimulation frequency used in the current study (10 Hz) may not have been optimal for inducing a decrease in sensory threshold. Cuypers et al. (2010) used a frequency of 100 Hz and demonstrated decreased sensory threshold. This is in conflict to the majority of other studies that have demonstrated increased sensory threshold when using high frequency stimulation (Dean et al., 2006; Mima et al., 2004). Closer inspection of the literature revealed that Cuypers et al., (2010) modulated the frequency and pulse width of stimulation by alternating between 50 and 100 Hz, and 250-125 μs every 0.5 seconds to reduce CNS habituation. This study suggests that higher frequencies are required to decrease sensory threshold; it also suggests that modulation of stimulation parameters may be important. The

current study was unable to modulate stimulation parameters due to the limitations of the stimulation unit, therefore habituation may have occurred limiting the effect of the intervention.

6.4.2 Participant characteristics and sensory threshold

Sensory threshold increases significantly and is more variable with increasing age (Thornbury & Mistretta, 1981), therefore, the age of participants in our study may have contributed to the lack of change in sensory threshold. Participants were older, ranging from 22-64 years (M =40, ±12 years), than the participants in the study by Mima et al., (2004) 26-36 years (M =31) and were similar in age to the study by Dean et al. (2006) (18-60 years), and Cuypers et al. (2010) (22-74 yrs) (M=47, SD=13 yrs). The use of an older sample with a wide age range was reflected in participant's sensory threshold scores with an average baseline sensory threshold in the intervention hand index finger, across all sessions, of 3.14 $\log^{10}$ (range = 2.44-3.96). These thresholds were higher than anticipated and according to (Bell-Krotoski, Ewing Fess, Figarola, & Hiltz, 1995) and would be interpreted as ranging from normal to diminished protective sensation, with the average baseline score representing diminished light touch. A further search of the literature for normative data revealed that the average sensory thresholds of the current study are similar to the original normative study by Semmes et al. (1960) and more recent studies (Cuypers et al., 2010; Voerman, van Egmond, & Crul, 1999). Semmes, Weinstein et al. (1960) reported a mean sensory threshold of 3.18 $\log^{10}$ (range = 2.84-3.52) in 20 healthy, young participants. These results suggest that participants in the current study have normal sensory threshold, with a slightly wider range of scores potentially reflecting the wider age range. The wide range of scores combined with a small sample size may have made the detection of statistically significant changes difficult.

It is unlikely that the participants' baseline sensory thresholds contributed to the lack of change observed in the current study. Based on the lowest measurable sensory threshold score (1.65 $\log^{10}$) and the estimation of true change, calculated using TE (± 0.4 $\log^{10}$), a decrease in sensory threshold would have been able to be captured.

6.4.3 Measurement of sensory threshold

Other measures of sensory function may have captured change when SWM did not. SWM measure pressure threshold and the function of the sensory system, which includes, mechanoreceptors of the skin, large myelinated (Aβ) afferent fibers, peripheral nerve function, and the dorsal column medial leminiscal tract to the thalamus and primary somatosensory cortex (Johansson et al., 1980; Weinstein, 1993). Therefore, any changes occurring to different types of sensation and/or in other areas of the CNS may not be reflected in this measure. Measures of two point discrimination have demonstrated a decrease in threshold following a short period of PES (Schlieper & Dinse, 2011) and observed decreases in two point discrimination threshold following tactile co-activation have not been accompanied by a decrease in sensory threshold (Kalisch, Tegenthoff, & Dinse, 2008). Any changes in sensory function, as measured by two point discrimination, would not have been captured in the current study by the use of SWM.

Chapter 7: Conclusion

In healthy adults, 30 minutes of PES with directed or diverted attention did not result in an increase in corticomotor excitability, excitability of the primary somatosensory cortex or a decrease in sensory threshold. Stimulation parameters such as duration, frequency, pulse width and intensity and / or the combination of these parameters are likely to have contributed to the findings of the current study. It is clear from the current discussion that the optimal combination of stimulation parameters to increase cortical excitability and decrease sensory threshold in the shortest amount of time have not yet been determined. The majority of literature has used techniques that are unable to be replicated clinically and have used timeframes that would not be feasible in a clinical environment. PES has the potential to enhance rehabilitation interventions however there are a number of areas of future research that need to be addressed before it can be implemented clinically.

Chapter 8: Future research

A number of areas for future research have been indentified during the course of this study. These include:

1. Investigation of the effect of different stimulus intensities (above motor threshold, below motor threshold, sensory threshold, subsensory threshold) on corticomotor excitability, excitability of the primary somatosensory cortex and function, with other parameters standardised.

2. Investigation of the effect of different frequencies of stimulation (10, 20, 50, 100 Hz) at intensities above and below motor threshold on corticomotor excitability, excitability of the primary somatosensory cortex and function, with other parameters standardised.

3. Investigation of the effect of PES with directed and diverted attention on corticomotor excitability, excitability of the primary somatosensory cortex and function.

Once optimal PES parameters have been determined:

4. Investigation of the effect of repeated sessions of PES on corticomotor excitability, excitability of the primary somatosensory cortex and function.

5. Investigation of the effect of PES within clinical populations.

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Appendix A

Ethical approval

MEMORANDUM

Auckland University of Technology Ethics Committee (AUTEC)

To: Denise Taylor
From: **Madeline Banda** Executive Secretary, AUTEC
Date: 3 July 2009
Subject: Ethics Application Number 09/94 **The effect of sensory electrical stimulation on brain activity and hand sensation.**

Dear Denise

Thank you for providing written evidence as requested. I am pleased to advise that it satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC) at their meeting on 11 May 2009 and that I have approved your ethics application. This delegated approval is made in accordance with section 5.3.2.3 of AUTEC's *Applying for Ethics Approval: Guidelines and Procedures* and is subject to endorsement at AUTEC's meeting on 13 July 2009.

Your ethics application is approved for a period of three years until 2 July 2012.

I advise that as part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through *http://www.aut.ac.nz/about/ethics*. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 2 July 2012;
- A brief report on the status of the project using form EA3, which is available online through *http://www.aut.ac.nz/about/ethics*. This report is to be submitted either when the approval expires on 2 July 2012 or on completion of the project, whichever comes sooner;

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

Please note that AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to make the arrangements necessary to obtain this.

When communicating with us about this application, we ask that you use the application number and study title to enable us to provide you with prompt service. Should you have any further enquiries regarding this matter, you are welcome to contact Charles Grinter, Ethics Coordinator, by email at charles.grinter@aut.ac.nz or by telephone on 921 9999 at extension 8860.

On behalf of the AUTEC and myself, I wish you success with your research and look forward to reading about it in your reports.

Yours sincerely

Madeline Banda
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Nicola Towersley nicola.towersley@aut.ac.nz, Gwyn Lewis

Appendix B

Edinburgh Handedness Questionnaire

EDINBURGH HANDEDNESS QUESTIONNAIRE

Name ……..……..…

Date of Birth …… Gender: M / F

Please indicate your preference for the use of the left or right hand in the following tasks. If you have such a strong preference for one hand that you would never try to use the other hand unless forced to, place "++" in the column. If you would mostly use one hand but may sometimes use the other hand, place "+" in the column of the hand you would mostly use. If you would perform the task with either hand place "+" in both columns.

Some of the tasks require both hands. In these cases the part of the task, or object, for which hand preference is wanted is specified.

Please try to answer all of the questions. Only leave a blank if you have no experience of the task or object.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking match (match)		
10	Opening jar (lid)		
11	Which foot do you prefer to kick with?		
12	Which eye do you use when using only one?		

Total			

Please leave blank **EHQ = (R–L)/(R+L)**

Appendix C

Procedure for measuring sensory threshold

Standarised procedure: SWM sensory threshold testing

Set up	Seat participant in semi-reclined modified podiatry chair with pillow supporting head and a table, covered by a towel, supporting both arms. Check room temperature (20-24 ◦C) Place data collection sheet and testing filaments (A-H) on the table ready for use
Procedure explanation	*This test measures the sensation in your hand using these plastic filaments* (show thick filament). *For this research we are interested in testing the tip of your index finger on both hands. This procedure is safe and painless.* *We will need to repeat this test twice before the treatment and twice after the treatment.* *During this test you will be required to close your eyes. Different sized filaments will be pressed gently against the skin like this* (demonstrate). *When you feel that your index finger is being touched please say yes.*
Mark areas	*So that I test the same area on each index finger, can I mark your index finger tips with this marker pen?* Mark the apex of the arch of the fingerprint on each index finger.
Practice (eyes open)	Demonstrate the procedure with the participants eyes open.
Testing	*Please close your eyes and I will begin testing. Keep your eyes closed until I ask you to open them again.* *Please indicate by saying 'YES' when you feel that you are being touched.*
Procedure	Begin with the right index finger Begin with a noticeable stimulus. Decrease in a stepwise manner until the participant no longer perceives a stimulus (lower boundary) and then increase until the stimulus is perceived again (upper boundary) Apply filaments perpendicular to the skin to the point of bending Apply for 1 second, hold 1 second and release for 1 second Ensure random application times. Limit auditory cues If slippage or bouncing occurs: repeat the application Record the first and last filaments perceived on the data collection form

Appendix D

Advertisement

Volunteers required to participate in a study on the effects of sensory electrical stimulation on brain activity and hand sensation

WHO?
We would like people between the ages of **20 -70** to take part in this study

If you are interested and:
Do not have a neurological disorder
Do not have a pacemaker or epilepsy
Do not have a history of seizures
Do not have metal implants in the head or hand region (tooth fillings are fine)

WHERE?
The study will take place at AUT University, Akoranga Drive, Northcote

HOW LONG?
Your involvement will require approximately 1 hour on 6 separate days

For more information please call
Nicola Towersey
Ph 921 9999 x7641 (please leave a message)
nicola.towersey@aut.ac.nz

Appendix E

Information sheet

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Participant Information Sheet

Date Information Sheet Produced:

06 June 2009

Project Title

The effect of peripheral electrical stimulation on brain activity and hand sensation.

An Invitation

You are invited to take part in a research study that will explore the effect that peripheral electrical stimulation will have on brain activity and hand sensation. This supervised study is the work of a qualified physiotherapist as part of my Master's degree. You may be eligible for this study if you meet the following entry criteria:

- Are between the ages of 20-70
- Do not have any neurological disorders
- Do not have epilepsy, cardiac arrhythmia, history of seizures or, violent or recurring, headaches.
- Do not have a skull fracture or other known skull defects.
- Have not had a head injury or concussion within the last six months
- Do not have a pacemaker, intracardiac lines, artificial heart valve containing conductive material, and cranial-facial reconstruction or metal implants in the head or hand region.
- Are not taking any medications that lower seizure threshold

Your participation in this study is voluntary, and you may withdraw at any time without any adverse consequences

What is the purpose of this research?

The brain is capable of change or re-organisation. This occurs as you learn a new movement or following brain injury to re-learn movement. Sensation plays an important role in this process and recent studies have begun to show that peripheral electrical stimulation may positively influence re-organisation of the brain and improve function.

To date these studies have used laboratory techniques that are not readily available or practical in the rehabilitation setting. The purpose of this study is to examine peripheral electrical stimulation, using standard rehabilitation equipment and practical timeframes (30 minutes), on brain activity and hand sensation. This information is valuable as it will assist therapists when considering what rehabilitation strategies are best for improving rehabilitation outcomes following brain injury.

How was I chosen for this invitation?

Participation in this study is voluntary. If you wish to join this study, please contact:

Nicola Towersey (09) 921 9999 extension 7641 (do leave a message if unattended).

What will happen in this research?

When you ring, the researchers will discuss any questions or concerns you may have about participating in the study and check that you are eligible to participate in the study by asking you some questions. You will then be given a week to consider if you would like to take part. If you decide to participate, you will be

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sent an information sheet and an appointment will be arranged for you to attend the laboratory the following week.

When you arrive for your appointment, this sheet will be discussed with you to check that you understand the details and are happy to participate. You will be asked to sign a consent form and will be given a copy to keep. Next you will be asked to complete two questionnaires.

You will then be seated in a comfortable chair with your arm supported on a table. Electrodes will be attached to your wrist and thumb, for recording muscle signals and for stimulating the hand. At this stage you will be tested in one of two ways:

- Using a *Magnetic Stimulator Machine*, the researcher delivers small magnetic impulses onto your scalp. These pulses activate the motor pathways of the brain, which results in a small twitch in the thumb muscles. The electrodes on the thumb record this muscle activity, which tells us about the activity of the motor pathways of the brain. This procedure is safe and completely painless. The sensation of your thumb and index finger will also be tested using small plastic filaments. Different sized filaments will be pressed gently against the skin and you will be asked to identify when you feel indentation of the skin.

- Electrical stimulation will be delivered at the wrist and the researcher will record the activity of the sensory area of the brain via three electrodes on your head. This procedure is safe and painless.

Once these tests have been conducted, the researcher will use one of three therapies. All of these therapies involve the application of peripheral electrical stimulation for 30 minutes via two adhesive electrodes at the wrist. Different intensities of electrical stimulation are being tested and you may or may not feel a tingling sensation in your hand. It will not be painful. In addition during the therapy you will either be cued to count sounds that you hear from the computer or count the number of stimulations that you feel.

At this stage you will re-tested to record any change in brain activity or sensation in the hand immediately following peripheral sensory electrical stimulation and at two 5 minute intervals following the therapy.

There will be six sessions, at least 48hrs apart, and each lasting about one hour. You will receive one of the three therapies per session and will receive each therapy twice. Your commitment of six hours to this study may be challenging.

What are the discomforts and risks?

Some participants may find the time demands of this study onerous. If you wish to participate in this study you will be required to attend the laboratory for six, one hour sessions (six hours in total).

There is a small chance that the procedures being used in this study may induce anxiety in some people. This is unlikely however as we will ensure that you are fully informed about what to expect prior to any procedure and we will monitor how you are feeling throughout each procedure.

The Magnetic Stimulator is safe and completely painless, but does cause the muscle of the hand and sometimes face to twitch. This carries no risk. Also some people find the click noise associated with the magnetic stimulation annoying and some people experience a mild headache following magnetic stimulation due to face and neck muscle contraction.

The electrical nerve stimulator used for testing and for the therapy may cause a tingling sensation on the skin but is not painful. A small area of skin at the wrist may need to be shaved and wiped with an alcohol wipe before the electrodes are applied. This can cause a temporary stinging sensation and may cause mild skin reddening.

The manufacturers recommend that neither machine be used on people with epilepsy or pacemakers. It is recommended that individuals with a history of seizures or violent or recurring headaches, skull fracture or other known skull defects, history of a head injury or concussion within the last six months, intracardiac lines, artificial heart valve containing conductive material, and cranial-facial reconstruction or metal implants in the head region, except dental implants and some dentures or are taking any medications that lower seizure threshold do not have magnetic stimulation.

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Individuals with cardiac arrhythmia and metal implants in the hand region should not have electrical stimulation.

If you have any of the above criteria you will not be able to participate in this study.

How will these discomforts and risks be alleviated?

To alleviate any feelings of anxiety we will ensure that you are fully informed about what to expect prior to any procedure and will monitor how you are feeling throughout each procedure. You will be asked to inform the researcher if you feel any anxiety or discomfort and procedures can be terminated at anytime. You may withdraw from this study at any time without being disadvantaged and no reason needs to be given for withdrawing from the study.

The intensity of the magnetic stimulator will begin at a very low level, allowing time for you to get used to the muscle twitch sensation. You will be asked to inform the researcher if you feel any anxiety or discomfort, so that the stimulator intensity can be adjusted. Ear plugs will be offered to reduce the noise of the stimulation and mild analgesia will be available if you develop a headache. Stimulation can be terminated at anytime.

The intensity of the electrical stimulation will be set up for each individual so that the tingling sensation is comfortable. You will be asked to inform the researcher if you feel any anxiety or discomfort, so that the intensity can be adjusted.

To minimise skin reddening from the electrodes, new electrodes will be used on each occasion and aloe lotion will be available in the laboratory to use once electrodes have been removed.

What are the benefits?

There are no direct benefits to you. However your participation is helpful in furthering the knowledge in this area which may eventually improve the rehabilitation of brain injured adults. You will have the experience of participating in a modern research laboratory.

What compensation is available for injury or negligence?

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

How will my privacy be protected?

Your confidentiality will be maintained in the following ways. Results will be identified by a code number only. Researchers will only have access to coded data, which will exclude their knowing your identity. All results will be pooled, so no names or any material that could identify you will be published or presented. Consent forms are locked away in a separate location from the data, so no association can be made between the results and the consent forms. After six years, this data will be destroyed.

What are the costs of participating in this research?

The cost to you is your time. This study will involve approximately six, one hour sessions, excluding travel time to and from the laboratory at Akoranga Drive, Northcote. Travel vouchers will be provided to compensate for taxi or petrol costs incurred for travel to and from the Laboratory.

What opportunity do I have to consider this invitation?

You will have a week to consider whether to take part after you phone the researcher.

How do I agree to participate in this research?

On the day of the assessment the key points of this information sheet will be discussed by the researcher to ensure that you have clearly understood the information. You will then need to complete a consent form before the assessment begins.

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You may withdraw from this study at any time without being disadvantaged and no reason needs to be given for withdrawing from the study.

Will I receive feedback on the results of this research?

Yes. If you wish, a summary of the results will be sent to you when the study is completed. It is usual for there to be substantial delay between the time of your participation and the time of receiving these results. The results may be published in a journal and presented at a conference.

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

You are welcome to discuss this information with Nicola who will attempt to answer any questions you may have.

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, *Denise Taylor, denise.taylor@aut.ac.nz, (09) 921 9680*.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *madeline.banda@aut.ac.nz* , 921 9999 ext 8044.

Whom do I contact for further information about this research?

Researcher Contact Details:

Nicola Towersey (master's degree student). nicola.towersey@aut.ac.nz. Phone: 921 9999 ext. 7641

Project Supervisor Contact Details:

Dr Denise Taylor. denise.taylor@aut.ac.nz. Phone: 921 9680

Approved by the Auckland University of Technology Ethics Committee on 03/07/09, AUTEC Reference number 09/94.

Appendix F

Consent form

Consent Form

Project title: The effect of peripheral electrical stimulation on brain activity and hand sensation.

Project Supervisor: **Associate Professor Denise Taylor**

Dr Gwyn Lewis

Researcher: **Nicola Towersey**

- O I have read and understood the information provided about this research project in the Information Sheet dated 24th April 2009.
- O I have had an opportunity to ask questions and to have them answered.
- O I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- O I meet the age criteria of 20-70 years of age
- O I do not have a neurological disorder.
- O I am not suffering from epilepsy, have a history of seizures, head injury or concussion within the last six months, skull fracture or other known skull defects, history of violent or recurring headaches, or cardiac arrhythmia.
- O I do not have a cardiac pacemaker, intracardiac lines, artificial heart valve containing conductive material, cranial-facial reconstruction or metal implants in the head or hand region.
- O I am not taking any medications that lower seizure threshold
- O I agree to take part in this research.
- O I wish to receive a copy of the report from the research (please tick one): YesO NoO

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if you wish to receive a copy of the report):

……..

……..

……..

Date:

Approved by the Auckland University of Technology Ethics Committee on 03 07/09 AUTEC Reference number 09/94

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

Appendix G

Final consent form

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Participant Information Sheet

Date Information Sheet Produced:

06 June 2009

Project Title

The effect of peripheral electrical stimulation on brain activity and hand sensation.

Project

You participated in a research study that explored the effect of peripheral electrical stimulation on brain activity and hand sensation.

At the time of your participation in this study we informed you that different intensities of stimulation were being tested and that you may or may not feel a tingling sensation in your hand. However during two of the testing procedures the stimulation machine was actually turned off. This was an important part of the study as it enables us to be confident that any results in the study are actually due to the treatment and not just the application of the machine. There was no other feasible way that we could gain this information.

How do I agree to participate in this research?

Now that you are aware of the details of this study you have the opportunity to agree to participate or withdraw from the study without being disadvantaged. Please complete the following consent form to indicate your preference.

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

You are welcome to discuss this information with Nicola who will attempt to answer any questions you may have.

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, *Denise Taylor, denise.taylor@aut.ac.nz, (09) 921 9680*.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *madeline.banda@aut.ac.nz* , 921 9999 ext 8044.

Whom do I contact for further information about this research?

Researcher Contact Details:

Nicola Towersey (master's degree student). nicola.towersey@aut.ac.nz. Phone: 921 9999 ext. 7641

Project Supervisor Contact Details:

Dr Denise Taylor. denise.taylor@aut.ac.nz. Phone: 921 9680

Approved by the Auckland University of Technology Ethics Committee on 03/07/09 AUTEC Reference number 09/94

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Consent Form 2

Project title: The effect of peripheral electrical stimulation on brain activity and hand sensation.

Project Supervisor: **Associate Professor Denise Taylor**

Dr Gwyn Lewis

Researcher: **Nicola Towersey**

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 06 June 2009.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time, without being disadvantaged in any way.
- ○ I agree to take part in this research. (please tick one): Yes○ No○

Participant's signature: .....

Participant's name: .....

Date:

Approved by the Auckland University of Technology Ethics Committee on 03/07/09 AUTEC Reference number 09/94