exciteBCI: A neuromodulatory intervention for people with stroke

Optimising for translation into clinical practice

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Abstract

Stroke is the leading cause of long-term adult disability. People with stroke describe locomotor disability as a significant ongoing concern. Despite being the primary focus of physical rehabilitation, the overall amount of locomotor rehabilitation received is low. As a result, there is an urgent need for innovative approaches to locomotor rehabilitation. Endogenous paired associative stimulation (ePAS) is a neuromodulatory intervention that pairs electroencephalography (EEG) derived signals known as the movement-related cortical potential (MRCP) with electrical stimulation. In people with stroke, ePAS has been demonstrated to enhance neural plasticity and improve locomotion. However, people with stroke describe ePAS as time-consuming and unchallenging, and the optimal intervention parameters have yet to be determined. This thesis aimed to optimise the intervention delivery of exciteBCI, a portable medical wearable device in the prototype stage designed to deliver ePAS during locomotor rehabilitation. A pragmatist philosophical approach framed the research, and mixed methods were used to support intervention delivery optimisation from both a neurophysiological and clinical use perspective.

The first research objective was to optimise the stimulation parameters of the ePAS intervention. This objective was addressed using a systematic review (manuscript I) and a factorial study with repeated measures (manuscript II). The systematic review critically appraised the evidence for the efficacy of lower limb paired associative stimulation (PAS) and the optimal stimulation parameters. Findings revealed moderate-to-poor quality evidence to support that a single session of lower limb PAS can modulate corticomotor excitability in healthy people and people with stroke**.** Across experiments, intervention stimulation parameters were highly variable, limiting conclusions about optimal parameters. Subsequently, a factorial study (manuscript II) investigated ePAS intervention efficacy in healthy people when stimulation intensity and movement parameters were manipulated. ePAS interventions were significantly more effective at increasing corticomotor excitability compared to control interventions, except in the case of the low intensity-voluntary ePAS intervention. Findings also confirmed that stimulation intensity and movement type treatment parameters interact within ePAS interventions. However, substantial inter-individual variability in intervention responses were observed. This highlighted the possibility that inaccuracies in the manual feature extraction of MRCP signals obfuscate the timing of the pairings. In response, a reliability study (manuscript III) was undertaken to determine the intra- and inter-rater reliability of EEG experts'

identification of the peak negativity feature from averaged MRCPs obtained from healthy people and people with stroke. Findings demonstrated excellent intra- and inter-rater reliability for the voluntary movement condition and low to moderate intra- and inter-rater reliability for the imagined movement condition. Together, the findings from the neurophysiological studies strengthened the case for prioritising voluntary-based movements as part of the exciteBCI intervention design.

The second objective of this research was to optimise the usability and acceptability of the exciteBCI to support its clinical translation. Guided by the International Organization for Standardization (ISO) 9241-210:2019 standard, an iterative user-centred design approach supported by a qualitative descriptive methodology was undertaken (manuscript IV). People with stroke and physiotherapists participated in single session sprint cycles and sustained user testing where exciteBCI augmented locomotor rehabilitation. Findings revealed that users perceived exciteBCI to be an acceptable rehabilitation technology which could fit within a rehabilitation context and provided clear device requirements to guide future device development. More broadly, the study highlighted important understandings that inform the design and development of rehabilitation technologies.

This thesis demonstrates a rigorous approach to optimising the delivery and development of a complex rehabilitative technology. The research has made a significant contribution to the development of exciteBCI in preparation for evaluation of efficacy and implementation in clinical practice. This research illustrates the value of drawing on both neurophysiological and clinical knowledge in the development of new technologies and offers a framework for the development of complex rehabilitative technologies.

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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.

Signature Date: 19/05/2023

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Publications

Publications included in this thesis

Published peer-reviewed scientific journal articles

Chapter 4 **Alder G,** Signal N, Olsen S, Taylor D, A systematic review of Paired Associative Stimulation (PAS) to modulate lower limb corticomotor excitability: Implications for stimulation parameter selection and experimental design. *Front Neurosci.* 2019; 13:895. doi:10.3389/fnins.2019.00895	GA, DT, and NS conceptualised the study. GA performed the search strategy, extracted study data, and critically revised and wrote the manuscript with contributions from SO. GA and NS independently screened articles for eligibility and independently completed quality check lists for included articles. GA, NS, SO, and DT contributed to the interpretation of the results. NS edited the manuscript. NS and DT critically reviewed the manuscript. GA responded to the journal reviewer feedback and completed manuscript revisions. All authors read and agreed to the published version of the manuscript.
Chapter 5 **Alder G,** Signal N, Vandal AC, Olsen S, Jochumsen M, Niazi IK, Taylor D. Investigating the intervention parameters of endogenous Paired Associative Stimulation (ePAS). *Brain Sci.* 2021; 11:224. doi:10.3390/brainsci11020224	GA, DT, and NS conceptualised the study. GA, NS, ACV, and DT designed the methodology, and GA acquired ethical approval. GA, IKN, and MJ were responsible for investigation and data curation. Formal analysis was completed by ACV. GA, NS, ACV, and IKN carried out visualisation of the data. Supervision was provided by NS, IKN, ACV, and DT. GA prepared the original draft and GA, NS, and SO edited the manuscript. All authors critically reviewed the manuscript. GA responded to the journal reviewer feedback and completed manuscript revisions. All authors read and agreed to the published version of the manuscript.

Published peer-reviewed scientific journal articles

Chapter 6 **Alder G,** Signal N, U Rashid, Olsen S, Niazi I, Taylor D. Reliability of manual feature extraction methods in movement related cortical potential analysis. *Sensors.* 2020; 20(8): 2427. doi:10.3390/s20082427	GA, UR, NS, IKN, and DT conceptualised the study. GA, UR, NS, and DT designed the methodology, and GA acquired ethical approval. UR and GA were responsible for software development. GA led investigation and data curation. GA and UR performed the formal analysis and data visualisation was completed by GA, UR, NS, SO, IKN, and DT. DT, NS, and IKN provided supervision. GA prepared the original draft of the manuscript, and GA, NS, and SO edited the manuscript. All authors critically reviewed the manuscript. GA responded to the journal reviewer feedback and completed manuscript revisions. All authors read and agreed to the published version of the manuscript.

Submitted to peer-reviewed scientific journal

Chapter 8 **Alder G,** Taylor D, U Rashid, Olsen S, Brooks T, Terry G, Niazi I, Signal N. A BCI neuromodulatory device for stroke rehabilitation: An iterative user-centred approach to the design of rehabilitation technology. *JMIR Rehab Ass Tech. 2023*; 49702 (forthcoming/in press)	GA, NS, and DT conceptualised the study. GA, NS, DT, and GT designed the methodology, and DT and GA acquired ethical approval. NS, DT, UR, GA, SO, and IKN acquired funding, and GA performed project administration. GA, NS, TB, GT, UR, and SO contributed to data collection. UR and IKN were responsible for the technology. Data analysis was performed by GA and reviewed by NS and GT. Supervision was performed by NS and DT. The original draft was written by GA and NS, and edited by SO. All authors reviewed the submitted manuscript.

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Other related publications during candidature

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Niazi IK, Muhammad S, Rashid U, Amjad I, Olsen S, Haavik H, **Alder G,** Kumari N, Signal S, Taylor D, Farina D, Jochumsen M. Associative cue-based asynchronous brain-computer interfacing induces cortical plasticity in chronic stroke patients. *Ann Clin Transl Neurol.* 2022; 9(5): 722. doi:10.1002/acn3.51551

Olsen S, **Alder G,** Williams M, Chambers S, Jochumsen M, Signal N, Rashid U, Niazi IK, Taylor D. Electroencephalographic recording of the movement-related cortical potential in ecologically-valid movements: A scoping review. *Front Neurosci.* 2021; 15:721387. doi:10.3389/fnins.2021.721387

Olsen S, Signal N, Niazi IK, **Alder G**, Rashid U, Nedergaard R, Taylor D. Reliability of tibialis anterior muscle voluntary activation using the interpolated twitch technique and the central activation ratio in people with stroke. *Brain Sci.* 2021; 11(2):176. doi:10.3390/brainsci11020176

Olsen S, Signal N, Niazi IK, Rashid U, **Alder G**, Mawston G, Nedergaard R, Jochumsen M, Taylor D. Peripheral electrical stimulation paired with movement-related cortical potentials improves isometric muscle strength and voluntary activation following stroke. *Front Hum Neurosci.* 2020; 14:156. doi:10.3389/fnhum.2020.00156

Conference presentations

Olsen S, **Alder G,** Rashid U, Ghani U, Boulle N, Williams M, Chambers S, Jochumsen M, Signal N, Taylor D and Niazi IK Recording brain signals in real-world movements for enhanced rehabilitation. Te Tītoki Mataora Forum, NZ HealthTech Week; 2022; Auckland.

Alder G, Signal N, Olsen S, Taylor D. A systematic review of paired associative stimulation to modulate lower limb corticomotor excitability: Implications for stimulation parameter selection and experimental design. International Neuromodulation Society (INS) 14th world Congress; May 2019, Sydney.

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

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

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

Olsen S, Signal N, Niazi IK, Christensen T, **Alder G**, Jochumsen M, Taylor D. Exploring measures of gait variability following neuromodulation. A feasibility study in people with stroke. Poster presentation at the Minnesota Neuromodulation Symposium; April 2017; Minneapolis, USA, AND, poster presentation at Rehab Week Conference; July 2017; London.

Glossary of Terms

Locomotion

The ability to move from one place to another[1]. The terms locomotion, walking, gait, and mobility are frequently used interchangeably in the stroke rehabilitation literature. In this thesis, locomotion is referred to as a task-specific activity because it is guided by the individual's goal and the environment in which it occurs. As a result, locomotion can encompass a wide range of activities such as getting on and off a bed or chair, getting in and out of a car, climbing a flight of stairs, crossing the street, navigating obstacles or terrains, mobilising through crowded areas or when it is dark outside.

Endogenous Paired Associative Stimulation (ePAS)

A non-invasive neuromodulatory intervention that aims to induce neural plasticity by increasing corticomotor excitability of the target muscle. Typically, the intervention is delivered in a laboratory-based setting. ePAS delivers single pulses of peripheral electrical stimulation (PES) to a peripheral nerve to give rise to an afferent stimulus that is paired with an endogenous event-related potential derived from electroencephalography, known as the movement-related cortical potential (MRCP). The MRCP can be generated from voluntary or imagined movements. During the ePAS intervention the afferent stimulus from the PES is precisely timed to arrive in the motor cortex during the most negative point of the MRCP signal.

Brain computerised interface (BCI)

A system that interprets brain signals and sends specific commands to an external device to control an external activity[2].

exciteBCI

A portable medical wearable device in the prototype stage designed to deliver ePAS in a stroke rehabilitation context. exciteBCI utilises a Brain-Computer-Interface (BCI) in which the MRCP is extracted and paired with the afferent stimulus from peripheral electrical stimulation to deliver ePAS. It combines ePAS with locomotor task-specific exercises that are guided via a tablet device.

Abbreviations

AMT	Active motor threshold
CME	Corticomotor excitability
CPN	Common peroneal nerve
CS	Cosine similarity
BCI	Brain computer interface
dCPN	Deep branch of the common peroneal nerve
DF	Dorsiflexion
EEG	Electroencephalography
EMG	Electromyography
ERP	Event-related cortical potential
ePAS	Endogenous paired associative stimulation
HZ	Herts (Frequency)
ICC	Intraclass correlation coefficient
ISI	Interstimulus interval
ISO	International Organization for Standardization
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MEP	Motor evoked potential
MRC	Medical Research Council
MRCP	Movement-related cortical potential

ms	Millisecond
MTh	Motor threshold
μV	Microvolt
mV	Millivolt
MVC	Maximum voluntary contraction
NIBS	Non-invasive brain stimulation
NMDA	N-methyl-D-aspartate
PAS	Paired associative stimulation
PES	Peripheral electrical stimulation
PN	Peak negativity (of the MRCP)
rTMS	Repetitive transcranial magnetic stimulation
RMTh	Resting motor threshold
s	Second
S1	Primary somatosensory cortex
SEM	Standard error of the measurement
SD	Standard deviation
SEP	Sensory evoked potential
SOL	Soleus muscle
STDP	Spike-timing dependent plasticity
TA	Tibialis anterior muscle
TMS	Transcranial magnetic stimulation
UCD	User-centred design

Chapter 1. Introduction

1.1 Statement of the problem

A stroke is a neurological condition that results in an abrupt focal injury to the central nervous system caused by a blocked or leaking blood vessel[3]. Despite substantial spontaneous recovery, stroke remains the primary cause of long-term adult disability; impacting approximately 80 million individuals worldwide[4], with an estimated 113 million disability-adjusted life years lost each year[5]. Many people living with stroke have difficulty performing daily activities, which leads to changes in life roles, limited social engagement, lower health-related quality of life and, ultimately, a significant societal health burden[6,7]. Despite advances in stroke prevention and acute care, the incidence of stroke is predicted to climb by 40% in the next decade because of population growth and ageing[8]. Direct healthcare costs in New Zealand currently exceed NZ$700 million, with indirect costs estimated at NZ$3 billion[9]. The growing expense and burden of stroke highlights the pressing need for effective rehabilitation interventions to reduce disability and maximise independence and participation for people living with stroke.

Following a stroke, up to 80% of people experience deficits in locomotor-related abilities, which has one of the most significant effects on daily independence[10,11]. People with stroke cite locomotor deficits as one of the most burdensome limitations and unmet long-term needs after stroke[12]. Therefore, it is not surprising that people with stroke identify independence with locomotor-related activities as a primary goal during rehabilitation[13-16]. A significant proportion of physical rehabilitation is devoted to the treatment of locomotor disabilities[13,15,17,18]. Despite this intervention, up to 50% of people experience persistent locomotor disability after inpatient rehabilitation[19] and less than 20% achieve unrestricted community ambulation[20,21].

Current national and international evidence-based practice guidelines for people with stroke recommend that task-specific training in meaningful contexts should be a key component of locomotor rehabilitation[22-24]. In accordance with motor learning principles, it is recommended that these activities should be designed to encourage large volumes of specific, repetitive, intensive activity that are progressively challenging, tailored to the individual's goals, and supplemented with performance feedback[25-31].

Despite evidence that larger volumes of practice can reduce disability, and enhance independence after a stroke[25-27], observational studies show that the actual amount of active

rehabilitation received is extremely low[32-35]. In New Zealand, people with stroke spend as little as 30-minutes per day engaged in physiotherapy[34] and, on average, practice just five repetitions of sit-to-stand and between 202 and 560 steps during locomotor rehabilitation[36,37]. Outside formal rehabilitation sessions, patients are frequently alone and inactive[36,38] and fall far short of recommended daily physical activity levels. Once discharged into the community, people with stroke can wait 10-30 days to receive community rehabilitation and, on average, have just six community visits with a physiotherapist[8,39]. While people with stroke value physical rehabilitation, they describe rehabilitation dose and intensity to be insufficient and often not reflective of their personal goals[40]. They advocate for more intensive patient-centred rehabilitation and more opportunities to practice outside formal sessions[40]. Collectively, these findings highlight the shortcomings of existing service delivery models and health systems worldwide in providing enough intensive rehabilitation to reduce disability and improve independence following stroke. Given current and future resource constraints, as well as the predicted increase in stroke incidence over the next decade, creative rehabilitation solutions are desperately needed.

1.2 A potential solution

As understandings of neural plasticity and its role in motor recovery after stroke has evolved, non-invasive neuromodulatory interventions have been advocated as one potential solution to the rehabilitation shortcomings noted above. Non-invasive neuromodulatory interventions typically involve repeatedly applying a magnetic or electrical stimulus to the central and/or peripheral nervous system to induce neural plasticity that endures beyond the period of stimulation[41]. When combined with traditional locomotor rehabilitation, non-invasive neuromodulatory interventions have the potential to accelerate stroke recovery[42-45].

One non-invasive neuromodulatory technique that has been investigated in both healthy and neurological populations is Paired Associative Stimulation (PAS). PAS pairs a single pulse of electrical stimulation to a peripheral nerve with a single pulse of transcranial magnetic stimulation (TMS) over the corresponding motor cortex[46,47]. Repeated pairing of stimuli over an extended period can induce an increase or decrease in corticomotor excitability of the corticospinal pathway to the target muscle depending on the order and timing of the pairings[46,48]. However, because of safety considerations and low tolerance for TMS in people with stroke[49], and the need for expensive equipment and skilled operators, the use of TMS as the cortical input during the PAS intervention may limit the intervention's potential clinical utility[50].

Endogenous Paired Associative Stimulation (ePAS) is a non-invasive neuromodulatory intervention that is thought to have similar neurophysiological mechanistic underpinnings as PAS. In contrast to PAS, ePAS does not require TMS as the exogenous efferent stimuli. Instead, ePAS pairs a single pulse of electrical stimulation to a peripheral nerve with an endogenous event-related potential known as the movement-related cortical potential (MRCP). The MRCP is derived from surface electroencephalography (EEG) signals generated from voluntary or imagined movements[51,52]. Surface EEG is well tolerated and has no known contraindications, suggesting that it might be a more feasible option for stroke rehabilitation.

During the ePAS intervention the afferent stimulus from the PES is precisely timed with the most negative point of the MRCP signal to induce increased corticomotor excitability of the target muscle[53,54]. Modulation of corticomotor excitability has been demonstrated in both healthy participants[53-58] and people with stroke[59,60]. In addition, improvements in motor function and locomotion have been observed in people with stroke[59-61]. There is some evidence to support that ePAS can be delivered with various combinations of afferent stimulation (PES, muscle stimulation, passive robotic system) and endogenous motor activation (imagined or voluntary movement)[53,62,63]. The studies, however, lack systematic exploration. Given the potential of ePAS to promote neural plasticity after stroke, determining the optimal intervention parameters to maximise effect is a critical step prior to translation to clinical practice and is, therefore, addressed as part of this doctoral research.

The use of EEG as the efferent stimulus during the ePAS intervention has several potential advantages over the use of TMS in traditional PAS protocols. However, qualitative evidence suggests that when administered as a stand-alone intervention, ePAS is neither acceptable to people with stroke nor practical to apply in a clinical environment using laboratory equipment[64]. According to people with stroke, rehabilitation should include meaningful real-world activities that reflect personal goals that should be practiced with increasing intensities[40,64,65]. These perspectives have significant implications for optimising the delivering of ePAS in clinical practice and increasing the likelihood of long-term adoption. One option is to provide ePAS via a portable wearable device during meaningful real-world locomotor-related activities at increasing intensities. exciteBCI is a portable medical wearable device in the prototype stage. It is designed to deliver ePAS in a stroke rehabilitation context by utilising a Brain-Computer-Interface (BCI) in which the MRCP is extracted and paired with the afferent stimulus from the peripheral electrical stimulation.

exciteBCI combines ePAS with locomotor task-specific exercises that are delivered via a tablet device. exciteBCI embeds the principles of rehabilitation; maximum tolerated dose, progressive challenge, sufficient repetition, and a task-specific focus that strongly reflects locomotor-based goals that are important to the user. However, research has yet to explore device features, usability, and acceptability of exciteBCI from a user perspective. Therefore, understanding first-hand the perspectives and experiences of exciteBCI of people with stroke and physiotherapists is an essential next step to improve its translation into clinical practice and long-term adoption and is, therefore, addressed as part of this doctoral research.

1.3 Thesis aim and objectives

This doctoral thesis aimed to optimise the intervention delivery of exciteBCI, a neuromodulatory endogenous paired associative stimulation intervention for people with stroke from both a neurophysiological perspective and for clinical use. A pragmatist philosophical approach[66,67] guided this thesis, which utilised mixed methods to support intervention delivery optimisation.

The specific thesis objectives were to:

1. Optimise the stimulation parameters of the ePAS intervention by:

(i) Critically appraising the evidence for the efficacy of lower limb PAS and the optimal stimulation parameters for intervention delivery in healthy and stroke populations, to inform ePAS stimulation parameter selection and;

(ii) Investigating ePAS intervention efficacy when stimulation intensity and movement parameters are manipulated.

2. Optimise the usability and acceptability of the exciteBCI, a portable medical wearable device in the prototype stage, to support its translation to clinical practice by:

   (i) Identifying the exciteBCI device requirements from the perspective of people with stroke and physiotherapists and;

   (ii) Exploring people with stroke and physiotherapists' perceptions and experiences of the exciteBCI, and how well it fits with rehabilitation.

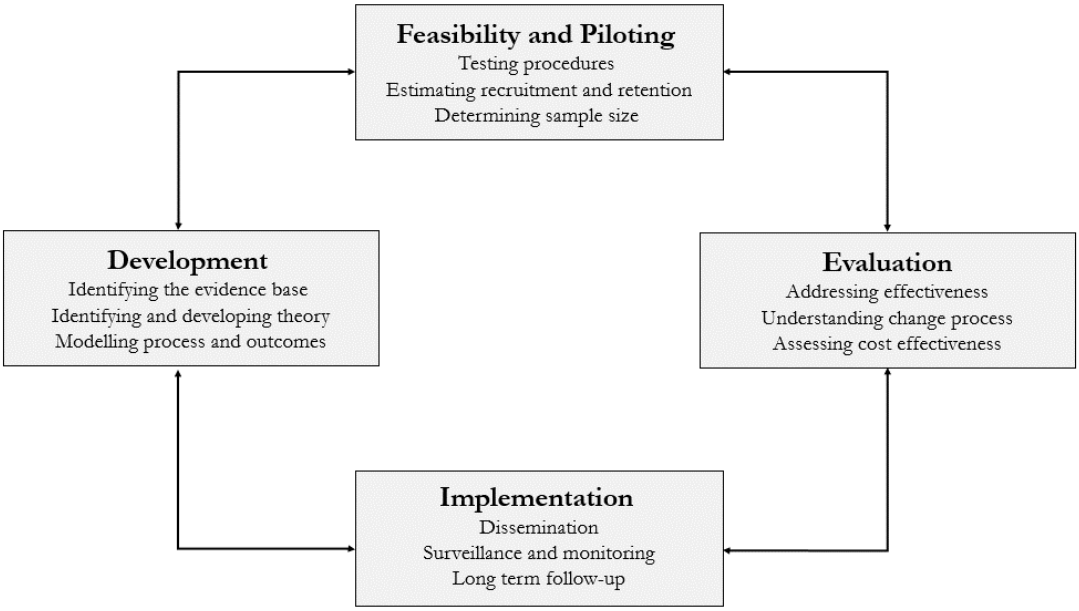
1.4 Methodological overview and supporting frameworks

A pragmatist epistemology was chosen to address the research aim and objectives of this doctoral thesis. Pragmatism is a problem-solving philosophy that seeks practical solutions to human problems[66,67]. The research outcomes are often more practical because pragmatic researchers view the research problem from more than one viewpoint and methodology, and frequently use mixed methods to better understand the problem[68]. This thesis sought to address the issue of optimising exciteBCI, a medical device that could deliver the neuromodulatory intervention ePAS and 'fit' in the context of stroke rehabilitation. Therefore, this doctoral thesis employed experimental and user-centred design (UCD) methods to support development and optimisation of exciteBCI a rehabilitation wearable device that would be suitable for translation into clinical practice.

This doctoral thesis was informed by the Medical Research Council (MRC) recommendations for complex interventions[69]. It is acknowledged that the development of locomotor-based interventions is complex due to the presence of multiple interacting components[69]. For example, locomotor-based rehabilitation must be tailored to the needs of an individual and the environment in which they are implemented, and the behaviours of those receiving or delivering the intervention will differ. The MRC is an iterative four-stage framework that guides the development and evaluation of complex interventions and includes, Development, Feasibility and Piloting, Evaluation, and Implementation. Figure 1.1 provides a schematic outline of the MRC framework.

While the exciteBCI intervention has a recognised scientific mechanistic underpinning, this thesis sought to optimise its delivery for people with stroke in accordance with evidence-based rehabilitation and task-specific training parameters and is sited in the Development, and Feasibility and Piloting stages of the MRC recommendations for complex interventions framework. Although the MRC recognises that user involvement is essential to ensure the acceptability of an intervention, it does not provide specific guidance in this regard. Therefore, this thesis also utilised UCD research principles to aid the Development, and Feasibility and Piloting stages of the exciteBCI, with the long-term aim of improving translation to clinical practice.

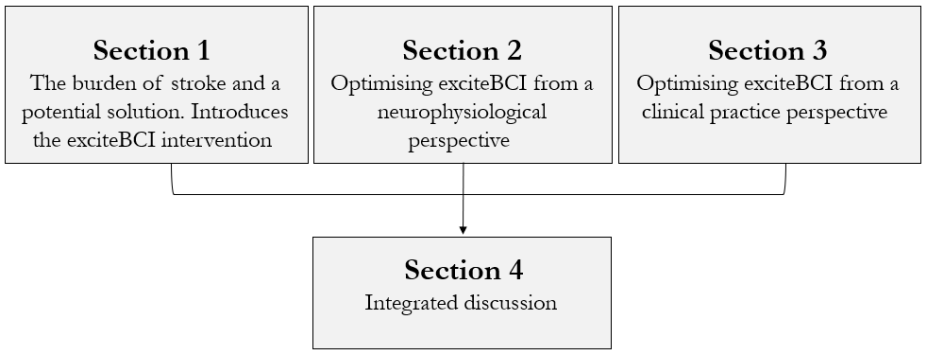
Figure 1.1 Key elements of the MRC framework for developing complex interventions



1.5 Structure of the thesis

This thesis is divided into four sections. Figure 1.2 provides a schematic representation of these sections.

Figure 1.2 Structure of the thesis



Section 1 introduces the problem, the burden of stroke, and a potential solution, exciteBCI, and corresponds to the development stage of the MRC framework.

- Chapter 2 presents a narrative literature review describing the impact of locomotor disability following stroke, neural plasticity and its role in motor learning in both the healthy and stroke brain, current evidence-based rehabilitation approaches for restoring locomotion, the perspectives of physical rehabilitation and rehabilitation technology in the opinion of people with stroke and rehabilitation clinicians, rehabilitation dosage and training parameters, neuromodulatory interventions and PAS.

- Chapter 3 introduces ePAS a non-invasive neuromodulatory intervention that has primarily been investigated in a research laboratory setting as a potential solution to reducing locomotor disability when targeting the paretic ankle dorsiflexors. The chapter describes how the ePAS intervention is typically delivered; its advantages compared to more traditional paired associative interventions; and a literature review outlining the current evidence base, its delivery optimisation to date, and its potential to be delivered during locomotor related activities. The chapter also provides a rationale for the optimisation and development of exciteBCI and the importance of considering it from both an experimental, clinical, and user design perspective.

Section 2 focuses on intervention optimisation at the neurophysiological level and relates to objective 1 of the thesis: *Optimise the stimulation parameters of the ePAS intervention*. It comprises of two chapters relating to objective 1(i) and 1(ii) respectively. Section 2 corresponds to the development stage of the MRC framework.

- Chapter 4 presents a published manuscript which addresses objective 1(i) of the thesis: *Critically appraising the evidence for the efficacy of lower limb PAS and the optimal stimulation parameters for intervention delivery in healthy and stroke populations, to inform ePAS stimulation parameter selection,* by undertaking a systematic review investigating the efficacy of PAS on lower limb corticomotor excitability in healthy and stroke populations and evaluating the stimulation parameters employed.

- Chapter 5 presents a published manuscript which addresses objective 1(ii) of the thesis: *Investigating ePAS intervention efficacy when stimulation intensity and movement parameters are manipulated,* by undertaking a factorial study design with repeated measures to investigate the interaction effects of ePAS intervention parameters stimulation intensity and movement type, and differentiate them from super-additive, additive, or sub-additive treatment effects in healthy participants.

The results of Chapter 5 highlighted a gap in the evidence base regarding the reliability of MRCP feature extraction screening as one potential source of variability in intervention delivery that would have an impact on the eventual translation to clinical practice. To addresses this gap a reliability study was undertaken in Chapter 6.

- Chapter 6 includes a published manuscript that examines the intra- and inter-rater reliability of EEG experts' identification of the peak negativity feature from averaged MRCPs obtained in healthy people and people with stroke.

Section 3 focuses on intervention optimisation for clinical practice and comprises a chapter relating to objective 2 of the thesis: *Optimise the usability and acceptability of the exciteBCI, a portable medical wearable device in the prototype stage, to support its translation to clinical practice,* and comprises of two chapters relating to objective 1(i) and 1(ii) respectively. Section 3 corresponds with the development and the feasibility and testing stages of the MRC framework.

- Chapter 7 focuses on objective 2(i) *Identifying the exciteBCI device requirements from the perspective of people with stroke and physiotherapists.* This chapter describes the concepts of usability and acceptability and their importance in the adoption and sustained use of rehabilitation technology. The chapter describes UCD as an approach to rehabilitation technology development and utilises the International Organization for Standardization (ISO) 9241-210:2019 standard[70] as a framework to support the UCD process and development of the exciteBCI intervention.

- Chapter 8 presents a submitted manuscript which addresses objective 2(i): *Identifying the exciteBCI device requirements from the perspective of people with stroke and physiotherapists* and objective 2(ii): *Exploring people with stroke and physiotherapists' perceptions and experiences of the exciteBCI and how well it fits with rehabilitation.* The method of this study is informed by UCD research and utilises an iterative usability testing approach to facilitate modifications to design features based on participant feedback. Data collection tools included video observations, 'think-aloud' and 'near live' protocols, semi-structured interviews, and clinical outcome measures.

Section 4 presents an integrated discussion, Chapter 9, which synthesises the findings and implications of this thesis, identifies the strengths and limitations of the research, and offers recommendations for future research.

1.6 Delimitations of the study

This doctoral thesis is part of a larger programme of ongoing research investigating the exciteBCI intervention, at Auckland University of Technology's Rehabilitation Innovation Centre. Therefore, it is important to state the boundaries of this doctoral thesis. This thesis does not address the following:

- The exciteBCI interventions paired associative stimulation component has the potential to be delivered online in real time by a brain computerised interface, enabling participants to self-pace their movements. This thesis investigates an offline version of

the ePAS and exciteBCI intervention in which participants follow a cue-based protocol and the timing of the pairing is finalised offline before the intervention is delivered. This decision was made due to the infancy of the online version of exciteBCI in people with stroke and the importance of optimising the intervention in a stepwise manner.

- exciteBCI has the potential to improve upper limb stroke rehabilitation and target other key muscle groups involved in locomotion. This thesis focuses on lower limb disability, specifically the dorsiflexor muscles and their role in locomotion.

- This thesis does not evaluate the efficacy of exciteBCI or cost effectiveness in people with stroke, nor does it evaluate the implementation into clinical practice.

SECTION ONE:

THE BURDEN OF STROKE AND A POTENTIAL SOLUTION

Chapter 2. Background

2.1 Prologue

This chapter describes the impact of stroke on locomotion. It then explores the evidence for, and limitations, of locomotor rehabilitation and non-invasive brain stimulation (NIBS) techniques as an adjunct to motor rehabilitation. Finally, an emphasis is placed on PAS, a NIBS technique based on Hebbian-associative plasticity principles. PAS serves as the mechanistic foundation for the neurormodulatory lab-based intervention ePAS and the clinical-based intervention exciteBCI that will be introduced in Chapter 3.

2.2 Stroke disability

Strokes can affect a variety of behavioural domains depending on the size and location of the lesion, including cognitive, sensory, perceptual, language, and emotional deficits. The most common deficits are contralateral motor impairments[71,72]. Neuromuscular control is altered when the motor cortex (M1), premotor cortex, or descending neural pathways are injured, and can lead to subsequent muscle weakness, changes in muscle tone, and abnormal patterns of muscle activation[73]. While spontaneous recovery occurs it is usually insufficient, and motor recovery rates vary from person to person[74]. While changes in muscle tone and abnormal patterns of muscle activation can affect locomotor disability, these impairments are not thought to respond to non-invasive neuromodulatory interventions, such as the exciteBCI intervention, and will thus not be discussed in this thesis.

Muscle weakness is defined as the failure to exert normal levels of force[75]. Evidence indicates that deficits in muscle strength and power of the lower limb is one of the most common impairments associated with hemiparetic locomotor disability and that the severity of muscle weakness correlates with the magnitude of locomotor disability[76]. Secondary changes due to early immobilisation and decreased physical activity have been reported 3-weeks post stroke[77-80]. Evidence indicates that these secondary changes exacerbate as stroke chronicity increases[81].

Achieving independent locomotion is the most commonly stated goal during stroke rehabilitation[13-16]. Initially, after a stroke about 50% of patients are non-ambulant, 12% require physical assistance, and 37% can ambulate independently[82]. On discharge, approximately 50% of people still experience persistent locomotor disability[19] and less than

20% of people with stroke achieve unrestricted community locomotion[20,21]. Locomotor capacity is a significant factor in determining whether a person with stroke is discharged home or admitted to residential or nursing home care[83]. Even for those who have been discharged, the actual amount of locomotor-related activity carried out at home and in the community is very limited, reducing the likelihood of returning to previous levels of participation[84,85].

The neural control of locomotion is complex and involves a variety of neural structures and pathways. Reciprocal locomotor rhythm is believed to be predominately controlled by spinal cord central pattern generators and the brainstem[86-88], but neuroscience evidence illustrates that neural circuity activated during steady state walking also includes the sensorimotor cortex, basal ganglia, cerebellum, limbic system, and peripheral sensory feedback[88-94]. While evidence suggests that the corticospinal pathway contributes little to the direct control of steady state walking, it plays a critical role in modulating locomotor control when the environment or behavioural goal demands increase in complexity[95-97]. Examples include changes in speed, terrain, and ambient demands; obstacle negotiation; and the addition of a secondary cognitive task[97].

Locomotor disability after stroke is characterised by abnormal kinematic and kinetic patterns, deviations in temporospatial gait parameters[82], and increased energy expenditure[98]. Deviations from normal gait variability (regularity and consistency of a step cycle) have also been reported in the stroke literature[99]. Neuroimaging and neurophysiological studies investigating lower limb impairment and locomotion disability post stroke reveal lesions to the corticospinal tract, internal capsule, superior longitudinal fasciculus, putamen, caudate, insula, pallidum, superior temporal gyrus, corona radiata, and white matter associated with the pedunculopontine nucleus[91]. Deficits in these brain areas have been associated with a deterioration in walking capacity (corticospinal tract, corona radiata, pedunculopontine nucleus, pallidum and putamen[100-105]) and walking speed (corticospinal tract, internal capsule, corona radiata, superior longitudinal fasciculus, external capsule and ipsilesional M1 connectivity, putamen, insula and basal ganglia[104,106-112]).

Drop foot, which is caused by a weakness of the dorsiflexor muscles and/or spasticity of the plantaflexor muscles, is one of the most significant contributors to locomotor disability[113]. Failure to sufficiently dorsiflex the ankle on the hemiparetic limb during swing phase can cause foot dragging or toe catching[113], a decrease in step and stride length[114], reduced cadence (steps per minute)[115], and a delayed or absent response to perturbations, leading to an increased risk of stumbling and falling[116]. Hemiparetic dorsiflexion strength is

an independent predictor of locomotor capacity[117], walking speed[118,119], and walking endurance[120]. This is not surprising given that the corticospinal connections to motor neurones of the tibialis anterior muscle are more prominent than those of any other lower limb muscle[121], confirming the critical function of ankle dorsiflexion in safe and efficient locomotion[122].

People with chronic stroke perceive ankle and foot impairments to greatly restrict community locomotion and heighten fear of falling[123]. Evidence also provides insight into important locomotor outcomes for people with stroke, revealing that while personal preferences vary, independent locomotion, as well as the ability to walk faster and for longer distances, maximises participation in the home and community settings and should be a central part of physical rehabilitation[124,125]. Collectively, these studies show that efficacious interventions to improve dorsiflexor muscle strength are needed to maximise locomotor-related recovery in persons who have had a stroke.

2.3 Neural plasticity

It is clear that the brain can reorganise and change as a result of experience and learning, and that this happens throughout the human lifespan[126-129]. This has informed understandings of the injured central nervous system and stroke recovery. Neural plasticity is broadly defined as the nervous system's ability to respond to intrinsic or extrinsic stimuli by remodelling its structure, function, and neural connections[128], and refers to a wide range of changes that occur at many levels of the nervous system's organisation. These may include modifications at a molecular, cellular, and synaptic level; structural and functional modifications within specific brain regions or neural networks; and behaviour modifications observed during motor skill or adaptability forms of learning, such as rehabilitation[130]. This section describes associative synaptic plasticity, a form of plasticity that occurs in motor cortical neurones (as well as many other brain areas) and is believed to be the mechanism underpinning the neuromodulatory lab-based intervention ePAS and the clinical-based intervention exciteBCI that will be introduced in Chapter 3.

Synaptic plasticity is coined as the cellular basis of learning and memory and produces lasting changes in synaptic efficacy[131,132]. As outlined by Donald Hebb's postulate of associative plasticity in 1949[133] synaptic efficacy is increased when a presynaptic neurone participates in the repetitive firing of a postsynaptic cell. This long-lasting increase in synaptic efficacy is referred to as long-term potentiation (LTP) and has also been demonstrated in animals and humans *in vitro*[134-136]. While Hebb did not describe the

mechanism by which synaptic efficacy is reduced, experimental studies show that if the presynaptic neurone is activated repeatedly after the post synaptic neurone, synaptic efficacy is reduced, and is termed long-term depression (LTD)[135,137]. Whether LTP or LTD takes place depends on the order and the precise temporal interval between the two stimuli and is known as spike-timing-dependent neural plasticity (STDP)[138-142]. STDP has been investigated non-invasively in the human motor cortex using PAS paradigms and are discussed further under section 2.9.

2.4 Current rehabilitation approaches for restoring walking

Stroke rehabilitation should be designed to achieve goals that are meaningful and functionally relevant to the needs of the individual[143]. As a result, task-specific training has emerged as a widely accepted treatment approach in stroke rehabilitation[72,144]. Task-specific training involves practising meaningful real-life tasks with the purpose of acquiring or requiring a skill to improve functional abilities[145]. Synonyms of task-specific training described in the stroke rehabilitation literature include repetitive task practice[28], task-related training[145], and task orientated therapy[146]. The underpinnings of task-specific training are drawn from the motor control, motor learning, and learning dependent neural plasticity evidence base[147,148]. To ensure learning occurs, task-specific training interventions include repetitive and intensive task practice that is context specific, progressively challenging, tailored to the individual's goals, and supplemented with positive feedback on task performance[128,148,149].

Neurophysiological and neuroimaging studies in people with stroke demonstrate that task-specific training can facilitate neural plasticity at a number of levels of the nervous system. These include immediate changes in corticomotor excitability, promotion of axonal and dendritic sprouting, neurogenesis, and increases in lower limb cortical representations[128,150-152]. When compared to motor impairment-based training, task-specific training induces long-lasting motor learning and associated cortical reorganisation[14,146,153,154]; therefore, reducing stroke disability and improving activities of daily living[72,144,149,155].

The stroke rehabilitation literature describes a variety of efficacious rehabilitation interventions than can improve locomotor-related outcomes after stroke. Interventions include circuit class training[29,156]; treadmill training (with or without body weight support)[30,31]; functional electrical stimulation[157-159]; and the less widely adopted evidence-based modalities such as robotics[159], virtual reality[160,161], and activity promotion wearables[162]. Circuit class training consisting of locomotor-related activities is strongly advocated by

practice guidelines for people with stroke, as is body weight support treadmill training when coupled with overground walking and balance training[22]. When considering the principles that underpin these efficacious interventions, many of them include the training parameters of task-specific training.

2.5 Training parameters

Task-specific training includes a number of modifiable training parameters that must be taken into account when designing locomotor-related interventions for stroke rehabilitation to optimise outcomes for people with stroke.

2.5.1 Salience and specificity

Rehabilitation should be intrinsically and extrinsically meaningful and relevant to the patient, and align with the their goals and needs[146,148,163,164]. Evidence indicates that salience, motivation, and attention are key contributors to modulating neural plasticity in both the healthy and stroke brain[146,165-168]. As independent locomotion is a key goal for people with stroke, motivation for practicing locomotor-related activities within rehabilitation is high[169].

Training effects of task practice are frequently confined to the task being trained and may not translate to tasks that are similar but not yet trained[170,171]. Therefore, the contextual and environmental demands specific to the task being trained should be incorporated into rehabilitation to maximise neural plasticity[152,172,173] and outcomes for people with stroke. In the context of locomotion, this may also include additional motor or cognitive tasks such as carrying shopping, walking while talking, or reading a map[97,174].

2.5.2 Dose

The term 'dose' lacks transparency in rehabilitation[25-27]. Most commonly it is operationalised as the *amount* of time spent in rehabilitation, although it has also been reported based on the *number* of repetitions[175]. Dose encompasses the session duration, which is generally quantified in minutes or hours[175]; the frequency of sessions per day or week[175]; and the programme length, which is a specified period of rehabilitation from start to finish, and is usually reported in weeks[28]. While the optimal dose of rehabilitation is unknown, evidence from systematic reviews and meta-analyses report that larger doses of rehabilitation result in modest reductions in locomotor-related disability and increased independence[25-27,156]. Accordingly, evidence-based practice guidelines for people with stroke, recommend that patients receive as much inpatient rehabilitation as feasibly

possible[22] and that outpatient or community rehabilitation should continue for up to two years as required[23,24]. These guidelines also recommend that patients experiencing locomotor difficulties should be given opportunities to participate in individually tailored walking practice as much as possible[28].

2.5.3 Intensity

Intensity is a complex variable and often confused with dose[25,176,177]. Intensity conveys how *hard* the person works and can relate to the metabolic cost, the work rate (physical or mental), and perceived effort during a specific activity or within a single rehabilitation session[176,178,179]. Evidence suggests that when intensity is manipulated, locomotor-related training performed at moderate to high intensities can improve outcomes in walking speed[180-184] and distance[182,184-186] compared to low-intensity training in people with stroke.

2.5.4 Task difficulty

Extensive practice of motor tasks can improve task performance but for retention and transfer of learning to occur repetition alone is insufficient[187,188]. For long lasting changes to ensue, evidence suggests that the level of task difficulty is an important consideration[172]. Practice should be designed to ensure just the right amount of challenge, not too easy nor too difficult[189,190]; and when the difficulty level is tailored to the individual, rather than having fixed levels of increased difficulty, motor learning is further enhanced[191]. Multiple variables can be used to modify the task difficulty. Examples include changing the practice structure of the task (part vs. whole task, constant vs. variable, blocked vs. random), the task complexity (speed, sensory input, secondary motor or cognitive task, level of physical assistance required), and feedback provision[172,192-194]. While there is evidence to indicate that increasing task difficulty can enhance locomotor related outcomes in people with stroke[184,195,196], it remains unclear what the optimal level of task difficulty is and how higher levels of task difficulty influence rates of learning and engagement in locomotor rehabilitation.

2.5.5 Extrinsic feedback

Motor learning literature in healthy populations indicates that both the type and timing of extrinsic feedback influences skill learning and retention[147,197]. Reinforcement of positive outcomes improves learning and limits decay after the learning has taken place[198]. In people with stroke, the optimal way in which to deliver feedback in a task-specific training context is unknown. Few studies have investigated single components of extrinsic feedback making

it challenging to understand what components have led to the improved outcomes reported[199]. Based on available evidence, motor learning in people with stroke can be enhanced with the provision of positive feedback[14] in the form of instructive explicit feedback[200,201] (feedback provided about the movement execution[202]), reinforcement reward-based feedback[200,203] (feedback provided about the outcome of the task[202]), and delivered in an averaged format which fades over time to avoid dependency[172,197,199].

2.6 Perspectives of physical rehabilitation; people with stroke

Clinical guidelines for stroke state unequivocally that stroke rehabilitation must be a person-centred, goal-oriented process that prioritises patients and their families[22-24]. As a result, it is critical to learn about their rehabilitation experiences and perspectives, and that their preferences are incorporated into the development of new rehabilitation interventions.

Luker and colleagues[40] conducted a systematic review of qualitative research studies that sought to understand the perceptions and experiences of people with stroke in physical rehabilitation. While participants clearly valued physical rehabilitation, all 32 studies included in the review highlighted unfavourable physical rehabilitation experiences. Participants described feeling bored, alone, frustrated, and disempowered; and that the amount of rehabilitation received was insufficient, with sessions seldom including meaningful practice that aligned with personal goals. Importantly, participants believed that more opportunities for activity and more intensive practice, both within and outside of physical rehabilitation sessions, would have a positive effect on their recovery.

Several studies have confirmed the acceptability of high-intensity task-specific locomotor-related training programmes for people in the subacute and chronic stages of stroke[65,204]. Higher intensity rehabilitation practice was found to be a facilitator rather than a deterrent to rehabilitation participation[65,204], and that 'working harder', which included both physical and mental effort, was directly related to the sense of success they gained from participating in the programme[65].

In light of these findings, future research on intervention development and implementation should prioritise the perspectives and experiences of people with stroke, as well as consider ways in which to maximise autonomy[205], rehabilitation dose, and intensity of practice within and outside of formal rehabilitation sessions.

2.7 Perspectives of rehabilitation technology

There is a rising interest in the development and application of rehabilitation technologies as one way to overcome the insufficient dose and intensity of conventional stroke healthcare treatment models and, in turn, help minimise stroke disability and increase independence[30,159,206]. According to qualitative research, both people with stroke and their clinicians see a variety of potential benefits to using rehabilitation technologies. These include opportunities to participate in higher volumes of rehabilitation, increased patient motivation, more opportunities for independent practice, improved clinician efficiency, and objective feedback on patient progress[207-210]. Yet, few rehabilitation technologies successfully translate into clinical practice[209,211]. Frequently reported barriers to the adoption of rehabilitation technology include cost, limited access, poor usability and utility, and the technology not meeting the needs and goals of its users[207,208,210,212-217]. By directly involving patients, clinicians, and other relevant stakeholders in the design, development, and implementation of rehabilitation technologies, it may be possible to reduce some of these known barriers and better support the adoption and long-term use of technologies[209].

2.8 Non-invasive brain stimulation for people with stroke

Neuromodulation utilises medical technology to modulate neural activity of the central and or peripheral nervous systems by administering electrical stimuli, magnetic stimuli, or chemical agents via implanted or non-implanted devices[218]. This section provides an overview of non-implantable devices, also known as non-invasive brain stimulation (NIBS) techniques, that target the motor system and have been investigated in people with stroke.

NIBS techniques have piqued interest as a potential adjunct to conventional stroke rehabilitation interventions because of their ability to modulate corticomotor excitability, neural connectivity, and interact directly with memory and learning mechanisms, potentially reducing stroke disability[42,43]. NIBS interventions typically apply magnetic or electrical stimulation over the skull to elicit neural activity in the underlying neurones of the central nervous system or to a peripheral nerve or muscle to elicit an afferent stimulus to modulate neural activity of the central nervous system[41]. Several NIBS techniques can be found in the stroke literature and include repetitive TMS (rTMS), Transcranial Direct Current Stimulation (tDCS), and PAS[219]. PAS has a particular relevance to the development of the neurormodulatory lab-based intervention ePAS and the clinical-based intervention exciteBCI and will be covered in the following section.

Much of the NIBS evidence base has focused on enhancing the response of the motor system[43]. This can be achieved by applying several different stimulation protocols. Firstly, excitatory protocols apply stimulation over the ipsilesional hemisphere to upregulate the corticomotor excitability of the ipsilesional M1[43,220]. Secondly, inhibitory protocols provide stimulation over the contralesional hemisphere. The purpose of this stimulation protocol is to reduce interhemispheric inhibition from the contralesional hemisphere and upregulate the corticomotor excitability of the ipsilesional M1, with the aim of improving the interhemispheric balance between both motor cortices[43,220]. However, recent research evidence suggests that interhemispheric inhibition imbalances occur primarily during the chronic stage of stroke, most likely due to compensatory mechanisms rather than the lesion itself[221], calling into question the suitability of inhibitory protocols in the acute and subacute stages of stroke recovery. Thirdly, coupling two different stimulation protocols in succession, for example, by applying an inhibitory stimulation protocol followed by an excitatory protocol over the ipsilesional M1, can also induce corticomotor excitability of the ipsilesional M1[222].

Studies have demonstrated that excitatory, inhibitory, and combined protocols can be applied when the participant is at rest, during muscle activity, or coupled with conventional stroke rehabilitation to heighten the effects of rehabilitation[42,43,122,220]. Stimulation may also be applied prior to a conventional rehabilitation intervention, as a priming intervention, or during a functional rehabilitation intervention such as treadmill training[42,43,122,220]. Two recent meta-analyses concluded that there is moderate evidence to indicate that NIBS interventions combined with conventional rehabilitation are either superior[44] or equally effective[45] at improving walking capacity[45] compared to sham interventions in people with stroke. Despite the rapid development of NIBS treatments and a wide range of stimulation regimens, the evidence for their effectiveness in reducing stroke disability has not translated into everyday clinical practice for people with stroke[220]. Predominately this can be attributed to the insufficient strength of available evidence. In addition, NIBS interventions require specialist equipment, regulatory approvals, and trained operators, further impeding their effective translation into clinical practice.

2.9 Paired associative stimulation

PAS is a laboratory-based NIBS intervention that has been investigated in both healthy and neurological populations[46,223-225]. PAS induces neural plasticity and is based on associative plasticity principles[46]. It serves as the mechanistic foundation for the neurormodulatory lab-

based intervention ePAS and the clinical-based intervention exciteBCI that will be introduced in Chapter 3.

PAS prototypically involves the pairing of a single pulse of electrical stimulation to a peripheral nerve with a single pulse of TMS over the corresponding M1[46]. When this pairing of stimuli is delivered over an extended period (approximately 100-200 pairings) corticomotor excitability of the corticospinal pathway to the target muscle can be increased or decreased. Whether the excitability of the cortical pathways is increased or decreased is thought to be dependent on the selected interstimulus interval (ISI) between the two stimuli. For example, when the afferent stimulus reaches M1 at the same time or just before the TMS stimulus, excitability is increased[46], often described as facilitatory or excitatory PAS. Alternatively, if the peripheral afferent stimulus reaches M1 after the TMS stimulus, excitability is decreased[48] and commonly described as inhibitory PAS. The effects following PAS are not only dependent on the timing of the two stimuli, but are specific to the target muscle, rapidly evolving, persist beyond cessation of the stimulation period, reversible, and require activation of N-methyl-D-aspartate receptors and the involvement of L-type voltage-gated Ca2+ channels[46,48]. As a result, PAS has been likened to associative LTP-like or LTD-like plasticity mechanisms that resemble STDP observed in animals[138-140], and humans *in vitro*[141,142]. Evidence indicates that after PAS, spinal and brainstem excitability remains unchanged, implying that the plasticity is likely cortical in origin. The exact timing and location of these plasticity mechanisms remain unknown[46,48,225].

While much of the PAS literature focuses on healthy populations and upper limb protocols, several recent narrative reviews propose the use of PAS for the lower limb as a promising intervention to promote motor recovery[220,223,225]. However, there has been no systematic review or meta-analysis to ascertain its effects in healthy or stroke populations. Both excitatory and inhibitory PAS protocols have been investigated in people with stroke and have successfully modulated corticomotor excitability when applied to a resting muscle of the hand or lower limb[226-231], or during a functional activity such as treadmill training[232]. Only one study has assessed the cumulative effects of PAS, demonstrating improvements in walking speed and stride length[233]. However, given this study was of poor-quality, cautious interpretation is recommended. (Refer to section 4.5.3 and Appendix A.1 for methodological quality assessment score).

2.10 Summary

Stroke is a significant cause of locomotor disability and can limit an individual's activity and participation in the home and the wider community. Locomotor disability is commonly caused by lesions to the motor cortices and descending neural pathways which can lead to a contralateral hemiparesis. The more severe the lower limb hemiparesis, the more severe the locomotor disability, with drop foot due to muscle weakness being a significant contributor.

Achieving independent locomotion is important for people with stroke, but the amount of rehabilitation received in clinical practice is limited. Non-invasive neuromodulatory interventions have been proposed as one potential rehabilitation adjunct to address these shortcomings due to their ability to enhance corticomotor excitability of the ipsilesional motor cortex and can be applied either prior to or during conventional rehabilitation.

PAS pairs a single pulse of electrical stimulation to a peripheral nerve with a single pulse of TMS over the corresponding motor cortex. The timing of the two stimuli determines whether the intervention enhances or reduces the corticospinal pathway's excitability to the target muscle. PAS, like many neuromodulatory interventions, has yet to be used in rehabilitation. Barriers to implementation are most likely related to feasibility concerns about the need for specialised equipment, trained operators, and the use of TMS as the cortical input, which limits the intervention's clinical utility.

Chapter 3. Endogenous Paired Associative Stimulation

3.1 Prologue

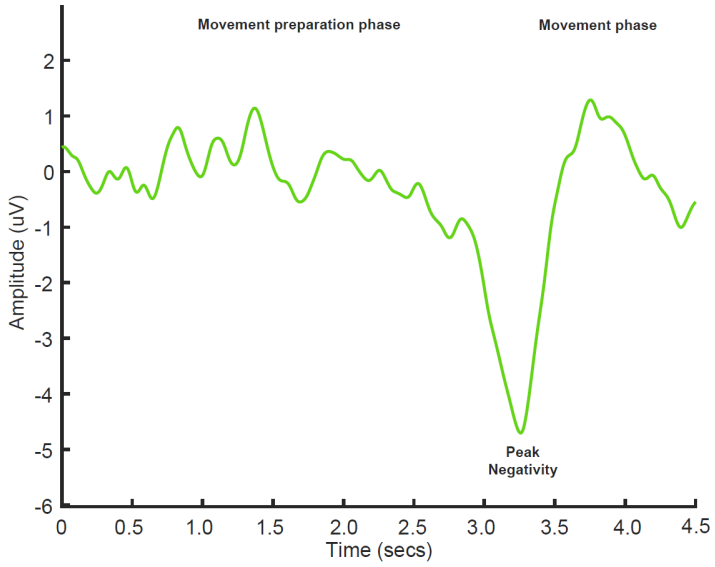
This chapter describes a laboratory-based non-invasive neuromodulatory intervention—ePAS—an intervention based on the underlying principles of Hebbian-associative plasticity, which hypothesises that activating neural cells simultaneously in a correlated manner leads to increased synaptic strengthening between those cells [133,234]. ePAS typically delivers single pulses of peripheral electrical stimulation to a peripheral nerve to give rise to an afferent stimulus that is paired with an endogenous event-related potential derived from EEG, known as the movement-related cortical potential generated from voluntary or imagined movements [53,54]. The chapter begins by introducing the movement-related cortical potential and the typical method of ePAS delivery, as well as its potential advantages over TMS-based paired associative interventions. Following that, a literature review outlines the existing evidence base for ePAS in healthy and stroke populations, intervention parameter optimisation to date, acceptability of the intervention in the opinion of people with stroke, and its potential to be administered during locomotor activities. Finally, this chapter provides a rationale for the development and optimisation of exciteBCI, a rehabilitation wearable device suitable for clinical use.

3.2 Movement-related cortical potentials

Cortical potentials associated with movement, perception, and cognition in the human brain are known as event-related potentials (ERPs) [235]. The movement-related cortical potential (MRCP) is a type of ERP that represents neural activity during movement preparation and execution and can be observed during EEG recordings [236]. This slow (≈0.5 Hz) negative potential is detectible during the preparation and execution of voluntary self-paced or cued movements and imagined movements [51,52]. The MRCP commences approximately 1.5 to 2 seconds prior to movement with a steeper negative slope approximately 500ms prior to its peak. This peak negative amplitude (–5 to –30 uV) is commonly observed just before movement onset and is referred to as the peak negativity (PN)[51,52]. The PN is followed by a positive shift which is thought to represent the feedback of movement control[51]. See Figure 3.1 for an example of the MRCP signal.

This thesis examines MRCPs generated from externally-cued movements (i.e., where there is a "Warning" and a "Go" cue), which is also termed a contingent negative variation[237]. To avoid ambiguity, the term MRCP will be used throughout this thesis.

Figure 3.1 The movement-related cortical potential (MRCP) and its relevant components



The initial shift in negativity of the signal is associated with movement preparation and the PN is associated with the execution of movement. The PN is followed by a positive shift which is thought to represent the feedback of movement control.

The MRCP is generated by a variety of cortical and subcortical neural substrates[51,52,236,238,239]. Research evidence suggests that the dorsal premotor cortex is more involved in the generation of externally-cued movements[240]. MRCPs display the greatest amplitude over Cz or CPz central scalp electrodes when recorded during ballistic voluntary or imagined ankle dorsiflexion movements[241] and these peak negativities are most likely generated by the bilateral supplementary motor regions and the contralateral motor cortex (M1)[242]. When compared to imagined movements, voluntary movements have greater amplitudes and their peak negativity is more easily identifiable[241,243].

Other variables that may impact the morphology of the MRCP include the speed or force necessary for the movement, attention to task, task difficulty, fatigue, the performer's level of motor skill, and the presence of neurological conditions[51,52,241,243-245].

3.3 ePAS a laboratory-based intervention

The ePAS intervention repeatedly pairs single pulses of peripheral electrical stimulation (PES) to a peripheral nerve at motor threshold with endogenous MRCPs derived from imagined or voluntary movement. It provides an alternative way of delivering the traditional PAS protocols previously described in Chapter 2 (see section 2.9). The use of an

endogenous efferent stimulus has several advantages over an exogenous stimulus such as TMS. TMS provides an artificial input to the brain which results in a firing of cortico-motor neurones in the area around the stimulation. TMS generates activation of numerous motor neurone pools simultaneously, including those innervating agonist and antagonist muscles[41]. Some muscles, such as those in the lower limb that are located deep in the interhemispheric fissure, can be difficult to stimulate using TMS[246]. Replacing the TMS with endogenous MRCP signals allows the cortical structures to be activated in a sequential manner which, unlike TMS, is representative of voluntary motor preparation and execution. TMS can be painful for certain individuals and is contraindicated for those who have epilepsy, a pacemaker, metal implants, skull abnormalities, or who use medicines such as neuroleptics, tricyclic antidepressants, or medications that reduce seizure thresholds[247]. This potentially excludes many people with stroke, particularly those with co-existing medical problems. When a motor evoked potential (MEP) in the target muscle cannot be elicited, TMS has limited utility. This frequently occurs in people with moderate to severe stroke due to damaged corticospinal tracts[248-250]. Surface EEG is painless and has no known contraindications for its use, and may lead to a more clinically viable intervention for people with stroke.

3.3.1 Standard ePAS protocol

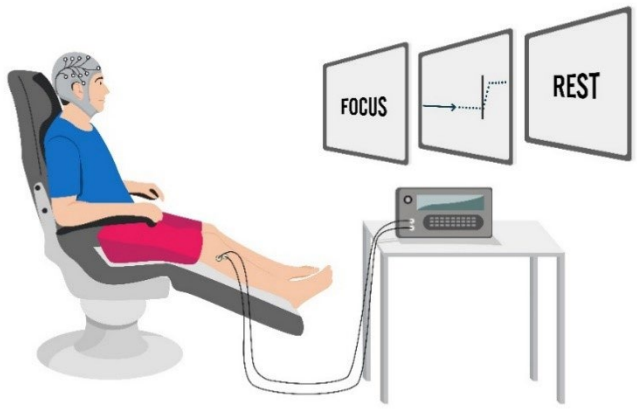
A baseline session is typically included in the standard ePAS protocol, during which EEG signals are recorded while the participant is seated and performs 50 repetitions of imagined or voluntary single joint movement in time with a visual cue displayed on a computer screen. The participant is guided through the planning and execution of the movement by a moving cursor. The visual cue prompts the participant to (1) focus on the computer screen; (2) prepare for the movement; (3) execute a ballistic (imagined or voluntary) movement, hold for approximately 1 second; and (4) rest.

To identify the peak negativity value, EEG signals are recorded from Ag–AgCl scalp electrodes located at FP1, F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4, according to the international 10–20 system. The right ear lobe is used as a reference and the system grounded at the nasion, and impedance is maintained below 5kΩ. The raw EEG signals are then imported into MATLAB software, where a second-order zero-phase Butterworth filter is used to reduce noise by band-pass filtering the channels (0.05-5 Hz). All channels, except FP1, are spatially filtered to correct for spatial blurring with a large Laplacian filter with Cz as the centre electrode to obtain a single virtual channel. The virtual channel is then divided into 50 epochs of 4.5 seconds each (3 seconds prior and 1.5 seconds after the

cue to move)[53,56,62,251]. Each of the 50 epochs is visually inspected and manually disregarded if there is no indication of a gradual negative shift before the cue or if FP1 electrooculographic activity exceeds 70 mV. The remaining epochs are then averaged, and the signal's most negative point is selected as the PN[53,57]. During the ePAS intervention participants follow the visual cue, and the afferent stimulus from the PES is precisely timed to arrive during the PN of the MRCP[53]. To account for the conduction time between the peripheral nerve and the M1, the PES is activated a predetermined number of milliseconds before the PN[53].

To deliver the ePAS intervention, the PES is delivered at motor threshold and the pairing of stimuli is repeated 50 times, taking approximately 15-minutes. As a result, ePAS increases corticomotor excitability of the corticospinal pathway to the target muscle[53,54]. While ePAS has the potential to target a wide range of muscle groups, the ankle dorsiflexors have so far received the most attention due to their critical role in locomotor recovery after stroke[122] (see Chapter 2, section 2.2). Figure 3.2 shows the ePAS intervention set-up when targeting the right ankle dorsiflexors.

Figure 3.2 ePAS intervention set-up



Participants observe the visual cue to prompt the timing of either voluntary or imagined dorsiflexion while receiving PES at motor threshold to the deep common peroneal nerve. The afferent stimulus from the PES is timed to arrive during the PN of the MRCP.

3.4 Intervention efficacy in healthy participants

Mrachacz-Kersting and colleagues[53] conducted the first experimental study to investigate the effects of the cue-based ePAS intervention on neural plasticity in healthy people. This

study manipulated the timing in which the afferent stimulus sent via the deep common peroneal nerve was paired with the MRCP during 50 repetitions of imagined ankle dorsiflexion movements. Nine participants performed a series of pre-post experiments consisting of a baseline EEG recording session and three single sessions, each separated by at least 48 hours. The afferent stimulus was timed to arrive (1) during the preparation phase of the MRCP, (2) during the PN of the MRCP (execution phase), and (3) after the PN of the MRCP. Cortico-motor excitability was assessed using single-pulse TMS during which the tibialis anterior muscle (TA) was at rest. TMS measurements were recorded immediately before and after each intervention. Mean peak-peak TA motor evoked potential (MEP) amplitudes were extracted for corticomotor excitability analysis.

The findings demonstrated that the timing of the afferent stimuli was critical for inducing corticomotor excitability. TA MEP amplitudes were only statistically significantly increased when the afferent stimuli arrived during the PN of the MRCP. No statistically significant changes in TA MEP amplitude were observed after the intervention when the afferent stimuli arrived before or after the execution phase (PN). The authors also investigated the effects on mean MEP amplitude after three separate control interventions, imagined movement only (n = 8), PES of the deep common peroneal nerve only (n = 4), and stimulation of the antagonist nerve (tibial nerve) (n = 9). No statistically significant differences were found. Finally, four participants that took part in the ePAS intervention were also assessed for changes in spinal excitability (H-reflex and F-waves) immediately before and after the intervention. Findings demonstrated that spinal measures remained unaltered, suggesting that the processes leading to the increase in corticomotor excitability likely occurs supraspinally and, as hypothesised, may target M1.

Later, in 2012, Niazi et al.[54] devised a template matching method to allow the initial negative phase of the MRCP to be detected online during a self-paced ePAS intervention using a BCI. The advantage of an online BCI is that the detection of the MRCP and the delivery of the PES triggered by the BCI can occur in real time, in a self-paced manner. This could improve the precision with which afferent stimuli are paired with MRCPs. Furthermore, the BCI could enable ePAS to be embedded within conventional rehabilitation activities potentially making it a more practical fit in clinical practice. In this pre-post study design MRCP's were detected online in eight healthy participants during 50 self-paced imagined ankle dorsiflexion movements, while the PES was delivered at motor threshold to the deep common peroneal nerve. To ascertain whether participants had performed self-paced imagined ankle dorsiflexion movements, a confirmation method was

employed. Participants were instructed to extend their left index finger promptly after receiving electrical stimulation if they had performed an imagined movement (true positive). Alternatively, participants were instructed to extend their right index finger if they had received the electrical stimulation but had not, in fact, performed an imagined movement (false negative). This continued until 50 true positives were completed. An additional four healthy participants participated in two separate control sessions: self-paced imagined movements only and PES of the deep common peroneal nerve only. Corticomotor excitability was assessed using single-pulse TMS immediately before and after each intervention.

The results revealed that the MRCPs were detected online with a true positive rate of 67±8% and false positive rate of 22±9%. A statistically significant increase in mean TA MEP amplitude occurred immediately after the BCI self-paced ePAS intervention compared to the control groups. Spinal excitability was also assessed and stretch reflexes remained unchanged after the intervention. However, this was only assessed in two participants.

Mrachacz-Kersting et al.[53] and Niazi et al.[54] demonstrated for the first time in healthy populations that an endogenous MRCP-driven cued-based offline or self-paced online neuromodulatory intervention can elicit neural plasticity. The neurophysiological underpinnings of ePAS appear to be similar to those of traditional PAS protocols in that the intervention effects are dependent on the timing of the two stimuli, specific to the target muscle, and rapidly evolving, akin to an LTP-like form of plasticity. The methodological quality of both studies, however, was lacking; sample size calculations, group randomisation, blinded assessors, and multiple comparison adjustments were not considered. Furthermore, the recruited participants were young, and not representative of the age group in which stroke is most prevalent. Consequently, these shortcomings reduce the level of certainty in the efficacy of ePAS and the neuroscientific underpinnings, necessitating additional rigorous research.

3.5 Duration of effect in healthy participants

One of the defining neurophysiological underpinnings of neuromodulation is that the effects of neural plasticity outlast the stimulation period, as evidenced in traditional PAS literature[223,225]. The ePAS intervention delivers 30 to 50 pairings and the intervention duration lasts between 10 and 15-minutes. While several ePAS studies have demonstrated that corticomotor excitability modulation outlasts stimulation duration, this has not been

tested beyond 30-minutes[57,62]. The duration of effect has significant implications for successful clinical implementation, especially if neuromodulation interventions are to be delivered prior to conventional rehabilitation interventions. Understanding the time course of plasticity effects may aid clinicians in determining how ePAS can be effectively incorporated into conventional stroke rehabilitation to maximise corticomotor excitability, optimise learning, and potentially improve the effects of conventional rehabilitation on stroke recovery. According to national and international stroke rehabilitation guidelines, daily physiotherapy sessions should last from 45 to 60-minutes[22,24,252]. As a result, determining whether the ePAS modulates corticomotor excitability for up to 60-minutes would be an appropriate time course to investigate.

Olsen et al.[56] specifically investigated the duration of the effects on corticomotor excitability after administering the cue-based ePAS intervention to healthy participants performing imagined movements up to 60-minutes. This pre-post repeated measures study found statistically significant increases in corticomotor excitability immediately after, 30, 45, and 60-minutes after the intervention and demonstrates that the increase in corticomotor excitability persists well beyond the period of stimulation. Future research should focus on the duration of effect of ePAS in people who have had a stroke, performing voluntary movement as well as how best to deliver it in conjunction with conventional stroke rehabilitation to maximise functional outcomes.

3.6 Modifications of ePAS intervention parameters in healthy participants

Several studies have modified the intervention parameters of the standard ePAS intervention to optimise its delivery. These modifications include various combinations of afferent stimulation (muscle-located PES, robotic-assisted passive movement) and motor activation (voluntary and imagined movement).

3.6.1 PES stimulation location

Jochumsen et al.[62] investigated whether pairing muscle-located PES or nerve-located PES with voluntary ankle dorsiflexion movements influenced the amount of corticomotor excitability of the TA muscle in healthy people (n = 12). This same-subject, repeated-measures crossover study compared four interventions: (1) voluntary ankle dorsiflexion paired with single pulses of nerve-located PES to the deep common personal nerve, (2) voluntary ankle dorsiflexion paired with a train of pulses of muscle-located PES to the TA

muscle, (3) voluntary ankle dorsiflexion only, and (4) muscle-located PES only. For interventions (1) and (2) the PES was timed to arrive in M1 during the cue to move as opposed to the PN of the MRCP. Jochumsen and colleagues[62] considered that healthy participants had the capacity to consistently time their movements with the cue, making the cue an estimate of the PN timing. Number of repetitions (n = 50) was dose matched across all interventions. Corticomotor excitability was measured immediately before, immediately after, and 30-minutes later.

The results showed a statistically significant increase in corticomotor excitability immediately after the intervention and 30-minutes after the pairing of muscle-located PES and voluntary ankle dorsiflexion movements, but no statistically significant effects for the control interventions (voluntary ankle dorsiflexion only and muscle-located PES only). There was also no statistically significant increase in corticomotor excitability after combining nerve-located PES with voluntary ankle dorsiflexion movements. This finding contrasts with previous ePAS research that delivered nerve-located PES to the deep common peripheral nerve during imagined ankle dorsiflexion movements[53,56,253]. One possible explanation for this disparity with previous work is that the current study paired the PES with the cue to move rather than the PN of the MRCP. As a result, pairings may have been timed incorrectly. The effect of afferent feedback on corticomotor excitability may be altered by adjusting PES stimulation parameters such as stimulation intensity[254] and frequency[255]. While both nerve-located and muscle-located ePAS interventions delivered the same intensity (motor threshold) the muscle-located pairings were delivered as a train of single pulses, implying that the duration of afferent input projected to the M1 would have been longer than the single pulse afferent input used in the nerve-located PES intervention, potentially reducing the number of incorrect timing of pairings. Higher PES intensities may provide larger increase in corticomotor excitability[254,256] although the optimal stimulation parameters delivered during ePAS have not been widely or systematically researched. Furthermore, while Jochumsen et al.[62] were the first to investigate the effects of pairing voluntary ankle dorsiflexion movements with PES on corticomotor excitability in healthy people (rather than imagined movements), no ePAS studies have compared the effects of endogenous motor activation (imagined versus voluntary movement) on modulating corticomotor excitability. This study demonstrated moderate methodological quality; however, the inclusion of a blinded assessor for corticomotor excitability measurements and statistical analysis would have improved methodological rigour.

3.6.2 Robotic devices

Several studies have investigated using an exoskeleton robotic system to facilitate passive movement of the ankle dorsiflexors instead of PES to elicit the afferent stimulus during a self-paced ePAS intervention[55,63,257]. Each of the three studies employed a same-subject, repeated-measures crossover design and recruited 9, 12, and 12 healthy participants respectively [55,63,257]. All three studies demonstrated that passive movement induced by the exoskeleton robotic system paired with self-paced imagined ankle dorsiflexion was just as effective at increasing corticomotor excitability as the standard self-paced ePAS intervention (PES to the deep common personal nerve[63,257] or TA muscle[55] for up to 30-minutes after the intervention). Jochumsen and colleagues[63] also found that PES and passive movement combined paired with self-paced imagined movement to be just as effective. In addition to the ePAS intervention, Xu et al.[257] confirmed no statistically significant changes in corticomotor excitability when participants performed imagined or passive movement only. These studies were of moderate methodological quality. Jochumsen and colleagues[63] should be commended for the robust reporting of all findings based on an *a priori* study design and statistical analysis plan.

This section provides moderate quality evidence that different intervention parameters can be modified to modulate corticomotor excitability in healthy participants, with effects akin to the standard ePAS intervention. Further research is needed to investigate intervention parameters more systematically and in people who have had a stroke in order to optimise clinical practice implementation. Capitalising on what is understood from the traditional PAS literature could benefit this process of optimisation from a neurophysiological perspective.

3.6.3 Real-time self-paced versus offline cue-based ePAS interventions in healthy participants

Mrachacz-Kersting et al.[57] and Jochumsen et al.[252] recently compared the effects of the offline cue-based ePAS intervention with the online BCI self-paced ePAS intervention (n = 10 and n = 15, respectively) in healthy people performing imagined movement. Both studies found that both the offline and online BCI ePAS interventions significantly increased corticomotor excitability 30-minutes after the intervention, but no statistically significant difference was found between the two interventions at this time point in either study. Jochumsen et al.[252] did, however, report an immediate increase in corticomotor excitability following both ePAS interventions. While both studies had similar BCI

performance results (true positive rate ~73% and ~75%, respectively), one possible reason for a difference in the immediate increases in corticomotor excitability between the studies could be the higher session dose (number of pairings and intervention duration). Jochumsen et al.[252] delivered 50 pairings (duration ~15-minutes), whereas Mrachacz-Kersting et al.[57] delivered 30 pairings (duration ~8-minutes). This is pure conjecture, and no studies have specifically compared the effects of session dose on corticomotor excitability, but this type of comparison warrants further investigation. Collectively, these studies support that both the offline and online BCI ePAS interventions modulate corticomotor excitability, lasting up to 30-minutes. Similar comparisons should be validated in people with stroke to ascertain optimal delivery prior to translation into clinical practice.

3.7 Intervention efficacy in people with stroke

Mrachacz-Kersting et al.[60] presented a double-blinded parallel controlled trial with repeated measures to investigate the cumulative effect of three sessions of the cue-based ePAS intervention and compared this to three sessions of a sham intervention in 22 people with chronic stroke. Participants receiving the ePAS intervention attempted 50 cued voluntary ankle dorsiflexion movements with the paretic limb while single pulses of PES were delivered to the deep common peroneal nerve, each timed to arrive during the PN of the MRCP. Participants receiving the sham intervention attempted 30-50 repetitions of the cued-based ankle dorsiflexion, but single pulses of PES were scheduled to randomly arrive before or after the PN of the MRCP. Measures of cortico-motor excitability using single pulse TMS were evaluated from the paretic TA muscle at rest at a variety of intensities (90, 100, 110, 120, and 130% resting motor threshold (RMTh)) and were recorded before, immediately after, and 30-minutes later. Mean peak-peak TA MEP amplitudes were extracted for corticomotor excitability analysis. In addition, the lower limb Fugel-Meyer scale, foot and hand tapping frequency, and walking speed were evaluated pre and immediately post the three sessions. Findings revealed a statistically significant increase in corticomotor excitability immediately after the ePAS intervention (130% RMTh) and 30-minutes after the intervention (90, 110, and 130% RMTh respectively). There were no statistically significant differences in corticomotor excitability across the three sessions nor were there any statistically significant effects for the sham intervention group. Statistically significant changes were also reported in the lower limb Fugel-Meyer scale, foot tapping frequency, and walking speed for the ePAS intervention but not the sham. While improvements in walking speed surpassed the standard error of the measure (0.04m/s)[258] clinically significant improvements were not obtained[259].

This was the first cue-based ePAS study to show statistically significant improvements in neurophysiological, motor impairment, and activity-based measures in people with chronic stroke. There were significant limitations to the study design which include the lack of a powered sample, the absence of randomisation, missing MEP data (n = 3) from the ePAS intervention group not accounted for in the statistical analysis, no follow-up measurements were undertaken, and a lack of group comparisons in the statistical analysis meant that the findings cannot suggest superiority of the ePAS group over the sham group. Furthermore, results may have been influenced by the fact that the ePAS and sham treatments were not dosage matched (more pairings were consistently delivered to the ePAS participants) and baseline mean walking speeds differed significantly between groups (ePAS participants 0.4 metres per second slower).

Later, Mrachacz-Kersting et al.[59] investigated the cumulative effects of ePAS in 24 subacute patients receiving inpatient rehabilitation. The study was a double-blinded parallel randomised controlled trial that compared effects of the cue-based ePAS intervention with a sham intervention. Participants received a total of 12 intervention sessions which were delivered 3 times per week over 4-weeks. Participants receiving the ePAS intervention attempted 30 cued voluntary ankle dorsiflexion movements with the paretic limb while single pulses of PES were delivered to the deep common peroneal nerve at motor threshold (MTh), each timed to arrive during the PN of the MRCP. Participants receiving the sham intervention were dose matched for number and timing of pairings but the single pulses of PES were delivered at an intensity below MTh (70% of MTh) with the assumption that this would result in no afferent stimuli reaching M1 during the PN of the MRCP.

Single pulse TMS was used to assess corticomotor excitability in the paretic TA muscle at rest at various intensities (90, 100, 110, 120, and 130% RMTh). Measurements were recorded before, immediately after, and 30-minutes after the intervention during sessions 1, 6, and 12. Mean peak-peak TA MEP amplitudes were processed for the corticomotor excitability analysis. Results demonstrated a statistically significant increase in corticomotor excitability immediately after the ePAS intervention and 30-minutes after the intervention, irrespective of measurement session and stimulation intensity. There were no statistically significant pre-post differences in corticomotor excitability for the sham intervention group. Clinical measures were evaluated pre and immediately post the 12 sessions. The lower limb Fugel-Meyer scale significantly improved for both the ePAS and the sham intervention groups, but neither were clinically significant. A between group comparison

produced a significant improvement for the ePAS intervention only. Both intervention groups improved their pre-post comfortable walking speed (10m walk test) and exceeded the minimal clinically important difference, but there was no statistically significant difference in improvement between the groups. In addition, both groups had statistically significant improvements in their pre-post scores for the Modified Rankin Scale and the Functional Ambulation Classification scale but no statistically significant pre-post difference in improvements between intervention groups were observed for either of these measures.

These findings contrast with those of Mrachacz-Kersting et al's[60] study in people with chronic stroke, which observed changes in functional locomotor outcomes for the ePAS intervention group but not the sham group. Several factors may have contributed to the differing outcomes observed in these studies. These include variations in the time since stroke onset (subacute vs. chronic), the specific type of sham intervention employed, whether the studies were dose-matched, the inclusion of additional rehabilitation, and differences in statistical analysis and methodological rigor.

Mrachacz-Kersting and colleagues' work[59,60] highlight the need for further investigation into the potential of ePAS to induce corticomotor excitability and improve motor disability in people with stroke. The fact that these studies included voluntary or attempted voluntary ankle dorsiflexion movement rather than imagined movements was a strength of this work. Imagined movements, in contrast to voluntary movements, do not provide internal feedback of performance, which is critical for motor learning[260]. Much of the research in the field of BCIs in healthy populations has utilised imagined movements as the input signal, asserting that the cortical activation is comparable to that of voluntary movements[261-263]. While there are some similarities in cortical activation between voluntary and imagined movements[264], imagined movements engage inhibitory networks to suppress voluntary movement production[265,266], as opposed to the recruitment of more complex cortical networks during the planning and execution of voluntary movement[267]. Research demonstrating lower levels of M1 activation during neuroimaging, decreased corticomotor excitability[268-273], and MRCPs with lower amplitudes[241,243] supports reports of imagined movements eliciting weaker activation of cortical neurones compared to voluntary movements. Aside from the distinctions between imagined and voluntary movements, there are reports that the capacity to conduct motor imagery is varied and typically reduced in people with stroke compared to healthy controls[274,275]. As a result, it seems reasonable to maximise the opportunity for recovery by utilising voluntary movements in patients who

can undertake the movement and consider the use of imagined movement in people who are unable to even partially complete the movement required.

A limitation of Mrachacz-Kersting and colleagues'[59,60] work was the methodological quality. Future studies should improve methodological rigour by being more explicit about randomisation procedures and defining a transparent statistical analysis plan *a priori* that avoids the use of multiple statistical tests, and instead considers the use of linear mixed regression modelling to maximise statistical efficiency and avoid potential type-I errors[276]. Furthermore, to avoid potential selection bias, an a priori statistical analysis plan should consider how they will address missing data. Future studies should also investigate whether improvements in activity are maintained by conducting follow-up assessments.

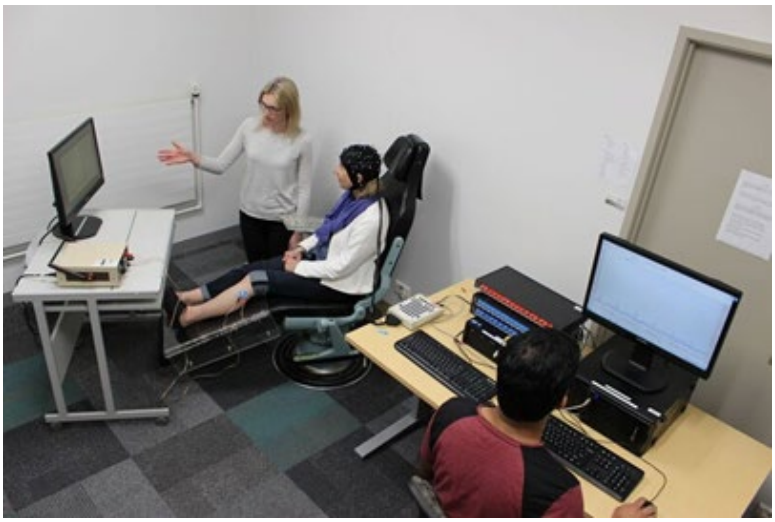
Finally, a comment on the applicability of Mrachacz-Kersting and colleagues'[59,60] findings to the wider stroke population. In section 3.3 various challenges associated with the use of TMS-related interventions were discussed, limiting their utility in people with stroke; these challenges also limit their utility as a measurement tool for corticomotor excitability. The fact that resting MEPs were elicited from the stroke participants within these studies suggests they presented with mild to motor lower limb motor disability indicating a potential selection bias within their sample. Therefore, future studies should aim to explore a more diverse sample, including persons with more profound motor impairment, to be more representative of the stroke population.

More recently, Olsen and colleagues[61] investigated alternative motor recovery measures to TMS to determine the efficacy of a single session of ePAS for stroke participants with a broader range of lower limb motor disability. They carried out a double blinded cross-over study with repeated-measures in people with chronic stroke (n = 15) presenting with mild to severe motor disability. The study compared a single session of ePAS during voluntary (or attempted voluntary) movement with a sham intervention (no PES). They reported a statistically significant increase in voluntary activation and isometric dorsiflexor muscle strength immediately after the ePAS intervention but not after the sham intervention. The observed increase in voluntary activation assumes a central mechanism for ePAS, complementing prior studies that have confirmed changes in corticomotor excitability in both healthy individuals[53,54,55,57,63,257,252] and people with stroke[59,60], while revealing no impact on spinal excitability[53,54]. This study encourages the exploration of alternative measures to TMS in future research and highlights the potential of ePAS to augment stroke rehabilitation for a broader range of lower limb motor disabilities.

3.8 ePAS intervention feasibility and acceptability in people with stroke

Chapter 2 emphasised the importance of user feedback in the development of complex rehabilitation interventions to optimise translation to clinical practice and better support long-term adoption. To date, few studies have considered user experience in the non-invasive neuromodulatory literature[277,278]. Olsen[64] recently investigated the feasibility and acceptability of the ePAS intervention in patients with chronic stroke. A double-blind parallel dose matched randomised controlled trial compared the effects of the cue-based ePAS intervention with a sham intervention (no PES). Participants attended 12 intervention sessions 3 times per week over 4-weeks. Semi-structured interviews were conducted with participants at the end of the 4-week period. The findings highlighted that as an intervention, ePAS delivered in this way was not acceptable to people with stroke and the intervention did not correspond with participants' prior experiences or perspectives of what physical rehabilitation entails. Participants indicated that the seated ePAS intervention was not physically challenging enough and that rehabilitation should involve hard physical work, the set-up time was too long, equipment was too cumbersome and, as a result, not very comfortable (see Figure 3.3 for ePAS set-up). These findings support the perspectives of physical rehabilitation in people with stroke in that rehabilitation should be meaningful, relate to real world activities that reflect personal aspirations and should be physically challenging[40,65] (see Chapter 2, section 2.7). These perspectives, taken together, have significant implications for the design and development of the ePAS intervention for it to be considered an acceptable "fit" for clinical practice.

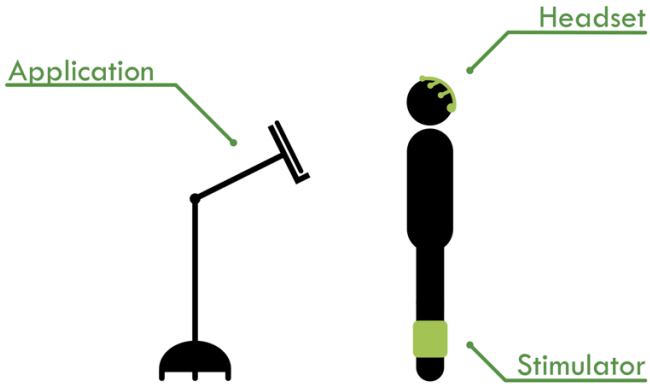
Figure 3.3 The ePAS intervention set-up that was not acceptable to people with stroke when delivered in this way, nor feasible for clinical practice



3.9 Embedding neuromodulation in rehabilitation

The benefits of task specific training to support neural plasticity and motor learning in stroke recovery have been previously outlined in Chapter 2 (section 2.5). While much of the evidence for neuromodulation interventions supports its use when the participant is relaxed or performing single joint movements while seated, there is a growing body of evidence to support its use during locomotor-related tasks[232,277,279-284]. Delivering ePAS during locomotor-related activities could improve the acceptability of the intervention by maximising time spent in meaningful rehabilitation and could provide opportunities for increased intensity and dose. Advances in EEG technology support the successful detection and classification of MRCPs associated with locomotor-related activities in both healthy people[285-291] and people with stroke[288,292,293]. Embedding neuromodulation in rehabilitation requires that the intervention and its associated equipment fits with clinical practice. To realise this, our research team set out to design and develop exciteBCI, a portable wearable BCI device that delivers ePAS in a stroke rehabilitation context utilising a UCD approach. The vision for this portable wearable device is displayed in Figure 3.4.

Figure 3.4 An illustration of the exciteBCI vision, which includes a portable wearable BCI device that delivers ePAS during locomotor-related activities



ExciteBCI consists of two wearable components: an EEG headset and a muscle stimulator for ePAS delivery, as well as a mobile application component to support ePAS delivery within locomotor rehabilitation.

3.10 Summary

There is moderate to poor evidence that ePAS studies have demonstrated increased corticomotor excitability after a single session in healthy populations performing imagined movements for up to 60-minutes[53-58]. Increased corticomotor excitability has also been shown after cumulative sessions in people with chronic and subacute stroke performing

attempting voluntary movements[59,60]. Taking into account the necessity for caution regarding methodological rigor the neuromodulatory effects of ePAS appear to be a) dependent on the timing of the pairing of the peak negativity of the MRCP and the afferent input specific to the target muscle and b) rapidly evolve and outlast the period of stimulation[53-60]. Alongside these corticomotor excitability changes, improvements in motor function[59,61] and locomotor abilities have also been observed in people with stroke[59,60].

Evidence suggests that various combinations of intervention parameters have been utilised across ePAS studies but lack systematic investigation and, to date, the optimal parameters are unknown. More research is required to thoroughly investigate intervention parameter selection prior to implementation into clinical practice.

The typical ePAS intervention is not acceptable in the opinion of people with stroke, nor is it practical to implement into a clinical context using laboratory equipment[64]. Delivering ePAS via a portable wearable BCI device during meaningful real-world locomotor-related activities could be one approach to achieving user acceptability and should be investigated with a UCD approach.

SECTION TWO:

INTERVENTION OPTIMISATION AT THE NEUROPHYSIOLOGICAL LEVEL

Chapter 4. A Systematic Review of Paired Associative Stimulation (PAS) to Modulate Lower Limb Corticomotor Excitability: Implications for Stimulation Parameter Selection and Experimental Design

4.1 Prologue

A small number of ePAS studies have investigated various intervention parameter combinations based on the type of afferent stimulation and endogenous motor activation, but a more systematic approach is needed to optimise the intervention. The neurophysiological mechanistic underpinnings of ePAS and exciteBCI are based on traditional PAS paradigms, therefore a critical review of the traditional PAS research evidence was conducted.

This published manuscript relates to the following thesis objective:

Objective 1: Optimise the stimulation parameters of the ePAS intervention by:

(i) Critically appraising the evidence for the efficacy of lower limb PAS and the optimal stimulation parameters for intervention delivery in healthy and stroke populations, to inform ePAS stimulation parameter selection.

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A Systematic Review of Paired Associative Stimulation (PAS) to Modulate Lower Limb Corticomotor Excitability: Implications for Stimulation Parameter Selection and Experimental Design

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4.2 Abstract

Non-invasive neuromodulatory interventions have the potential to influence neural plasticity and augment motor rehabilitation in people with stroke. Paired associative stimulation (PAS) involves the repeated pairing of single pulses of electrical stimulation to a peripheral nerve and single pulses of transcranial magnetic stimulation over the contralateral primary motor cortex. Efficacy of PAS in the lower limb of healthy and stroke populations has not been systematically appraised. Optimal protocols including stimulation parameter settings have yet to be determined. This systematic review (a) examines the efficacy of PAS on lower limb corticomotor excitability in healthy and stroke populations

and (b) evaluates the stimulation parameters employed. Five databases were searched for randomized, non-randomized, and pre-post experimental studies evaluating lower limb PAS in healthy and stroke populations. Two independent reviewers identified eligible studies and assessed methodological quality using a modified Downs and Blacks Tool and the TMS Checklist. Intervention stimulation parameters and TMS measurement details were also extracted and compared. Twelve articles, comprising 24 experiments, met the inclusion criteria. Four articles evaluated PAS in people with stroke. Following a single session of PAS, 21 experiments reported modulation of corticomotor excitability, lasting up to 60 min; however, the research lacked methodological rigor. Intervention stimulation parameters were highly variable across experiments, and whilst these appeared to influence efficacy, variations in the intervention and outcome assessment methods hindered the ability to draw conclusions about optimal parameters. Lower limb PAS research requires further investigation before considering its translation into clinical practice. Eight key recommendations serve as guide for enhancing future research in the field.

Keywords: paired associative stimulation, transcranial magnetic stimulation, cortical excitability, neuronal plasticity (MeSH), STDP, primary motor cortex, rehabilitation (MeSH), stroke (MeSH)

4.3 Introduction

Non-invasive neuromodulatory interventions such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and paired associative stimulation (PAS) have emerged in recent years in response to an increased understanding of neural plasticity as an adaptive process[219]. These interventions modulate the excitability of cortical and spinal neurones to enhance neural connectivity and learning[42]. Non-invasive neuromodulatory interventions are increasingly being investigated as methods to promote neural plasticity and functional motor recovery following acquired brain injury such as stroke[294]. This review focuses on lower limb PAS a neuromodulatory intervention that uses temporally paired transcranial magnetic stimulation (TMS) and peripheral electrical stimulation to modulate neural plasticity and is therefore distinct from other neuromodulatory interventions in its delivery method and likely mechanism of action. To date the evidence for this technique has not been systematically reviewed.

PAS typically involves the repeated pairing of single pulses of electrical stimulation to a peripheral nerve with single pulses of transcranial magnetic stimulation (TMS) over the corresponding primary motor cortex (M1)[46,295]. PAS results in a rapid change in

corticomotor excitability (CME) of the corticospinal pathway to the target muscle. This change in CME is believed to be dependent on the temporal pairing of the two stimuli in the M1, which can be altered by manipulating the interstimulus interval (ISI). When the peripheral afferent stimulus arrives in the M1 in synchrony with, or just prior to, the TMS stimulus, there is an increase in excitability of the targeted corticospinal pathway (facilitatory PAS); whereas, when the peripheral afferent stimulus arrives after the TMS stimulus, corticomotor inhibition is observed (inhibitory PAS[48]). PAS has been likened to the cellular learning process, spike-timing-dependent neural plasticity (STDP) observed in animals[138-140], and humans *in vitro*[141,142], where changes in the order and timing of pre- and post-synaptic stimuli determine whether there is an increase or decrease in synaptic efficacy[132]. Whilst stimulation parameters vary between studies, to date, optimization of PAS has primarily focused on the ISI; where the ISI is based on either the estimated conduction time from the peripheral nerve to the M1, or is individualized to the sensory evoked potential (SEP) or motor evoked potential (MEP) latency[48,279,296-299]. Less is known about the influence of other PAS parameters, such as stimulus intensity, stimulation frequency, or the optimal contraction state of the target muscle during stimulation.

PAS has been extensively investigated in the upper limb[223,225,300]; however there has been less focus on its effects in the lower limb. The neural mechanisms for the control of the lower limb differ from those in the upper limb and such differences in cortical and spinal circuity may alter the response to PAS[301-305]. For PAS to be considered as a therapeutic tool, particularly if walking is a primary focus of rehabilitation after stroke[13,15,16,306], its efficacy in the lower limb must be evaluated. In addition, the influence of various stimulation parameters on intervention efficacy must be considered.

Two narrative reviews have proposed that lower limb PAS is efficacious in healthy people and shows promise for promoting motor recovery in people with stroke [223,225], but to our knowledge there has been no systematic review to ascertain its effect on the lower limb in these populations. A systematic approach to evaluating the research evidence is essential when considering the translation of neuroscience research to clinical populations and clinical practice. In particular the rigor of the experimental method is paramount. Therefore, the primary aim of this systematic review was to determine the efficacy of PAS on lower limb CME in healthy and stroke populations, whilst explicitly critiquing the methodological quality of the research and the stimulation parameters utilized during PAS interventions.

4.4 Method

A systematic review of the literature was undertaken using the methodology defined by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement[307].

4.4.1 Search strategy

A literature search was carried out using the following electronic databases: EBSCO (CINAHL plus, MEDLINE, SPORTDiscus), Scopus, Web of Science (Neurosciences, Engineering Biomedical, and Rehabilitation) and Ovid (AMED). Search terms are presented in Table 4.1. Search terms were entered using truncation and wild card characters, and abbreviations were also included in the search. Additional citations were identified by hand searching reference lists of relevant studies, and through electronic searches of relevant author names.

Table 4.1 Search terms

	Healthy population	**Stroke population**
Participants		Stroke OR CVA OR cerebrovascular accident OR hemipleg* OR pares*
Intervention	pair* associat* stim* OR PAS OR dual stim*	
Outcomes	cortical excit*OR cortical motor excit* OR corticomotor excit* OR corticospinal excit* OR long term potentiation OR LTP OR LTP like OR spike timing dependent plast* OR STPD OR synapse specific assoc* plast*OR motor evoke* potential* OR MEP OR transcranial magnetic stimulation OR TMS	

A second search was performed including search terms related to stroke, to ensure relevant literature related to the stroke population had not been missed. Two independent reviewers (GA, NS) screened titles and abstracts, and where necessary, the full-text publication was reviewed for eligibility according to the criteria in Table 4.2. If there was any uncertainty about inclusion, a third reviewer (DT) was consulted until a consensus was reached. The independent reviewers were not blinded to the study authors, institutes, or journal titles. The literature search was last performed on the 10th of March 2019.

Table 4.2 Inclusion and exclusion criteria for selected studies

	Inclusion	Exclusion
Participants	Aged over 18 years. Either healthy or with a primary diagnosis of stroke with motor deficit in the affected lower limb (there were no restrictions on the type of stroke, lesion location, time since stroke, or severity of lower limb motor deficit).	Animal studies Participants experiencing neurological disorders other than stroke.
Intervention	Traditional lower limb PAS interventions, defined as the repeated pairing of pulses of peripheral electrical stimulation to a peripheral nerve with pulses of TMS over the contralateral primary motor cortex to induce excitation or inhibition.	PAS interventions targeting the spinal region, upper limb, both cerebral hemispheres, brain areas outside the primary motor cortex, or PAS combined with other neuromodulatory interventions.
Comparison	Either no intervention, sham intervention, or traditional lower limb PAS with different stimulation parameters.	
Outcomes	Corticomotor excitability as measured by motor evoked potential (MEP) amplitude, area, or stimulus response curves, induced with either single or paired pulse TMS to the primary motor cortex.	
Trial design	Randomised, non-randomised, and pre-post experimental studies.	Case reports.
Data reported	Original primary data collected pre- and post-intervention to establish the net effect of PAS.	
Type of publications	Full-text peer-reviewed journals, in English, between January 2000 and March 2019.	Review articles, conference proceedings, articles containing anecdotal descriptions, and expert opinions.

4.4.2 Data extraction

Details of the study design, sample size, participant characteristics, target muscle, stimulation parameters (ISI, number of pairings, frequency, intensity, pulse width, waveform, duration, dose, electrode location, resting, or active muscle state), outcome measurement technique (single pulse TMS, as a measure of CME, or paired pulse TMS, as a measure of intracortical excitability), and study findings, were extracted from the included studies.

4.4.3 Quality assessment

Methodological quality was assessed by two independent reviewers (GA, NS) using the modified Downs and Blacks quality checklist[308] and the TMS Quality Checklist[309]. Any disagreement was discussed with a third reviewer (DT) until consensus was achieved. All reviewers have experience in the application of TMS and experimental neurophysiological research methods in both healthy and stroke populations[56,62,252,310]. The modified Downs and Blacks quality checklist evaluates the methodological quality of randomized and non-randomized studies and is commonly used in rehabilitation systematic reviews[311-314]. It consists of 27 questions related to reporting, external validity, internal validity, and power. The TMS Quality Checklist is used to assess the methodological quality of studies that use TMS for outcome measurement. It considers 30 factors related to participant characteristics, experimental methodology, and analysis, and four factors related to paired-pulsed techniques. For each checklist, the scores were converted to percentages. Scores above 75% were deemed high quality, 50–75% moderate quality, and below 50% poor quality, as per previous publications that had utilized these checklist tools[315-317].

4.4.4 Data analysis

A descriptive analysis of the results was carried out with a focus on the effect of the intervention on CME, the stimulation parameters utilized, and the methodological rigor.

4.5 Results

4.5.1 Identification and selection of studies

After the removal of duplicates the electronic database literature search yielded 1,083 citations and a further two articles were identified from hand searching. After exclusion based on title and abstract, 33 articles were obtained for full-text review. Following the full-text review, 21 articles were excluded. A total of 12 articles, eight with healthy participants and four with participants with stroke, met the selection criteria and were included in the review. Where multiple experiments were presented in one article, all experiments were included that fulfilled the inclusion criteria. There were 24 independent experiments across the 12 articles. Figure 4.1 provides a flow chart that summarises the study selection process.

4.5.2 Description of included studies

Participants

A total of 150 healthy participants and 39 people with chronic stroke were included across the 12 articles. Healthy participants were younger than those with stroke (age range 19–68 years and 37–79 years, respectively). Male to female representation was similar across healthy studies (males n = 85, females n = 75), but there was a larger proportion of males in the stroke studies (males n = 26, females n = 13). Participants with stroke varied in lesion location and time since stroke (11 months to 33.1 years). Lesion side was comparable, with 21 participants with right hemiplegia and 18 with left hemiplegia.

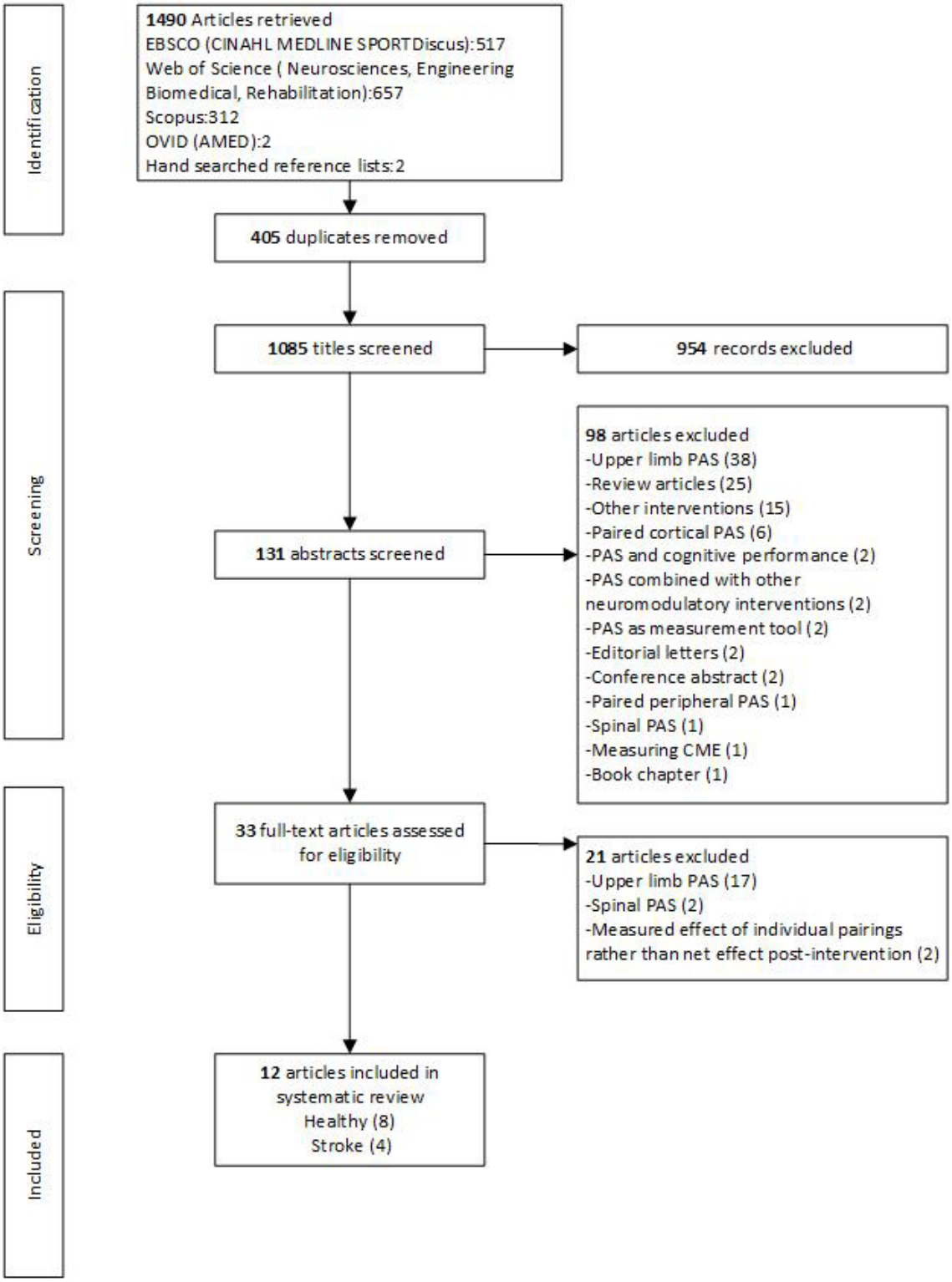
Study Designs

The experiments utilized pre-post, pre-post repeated measures, and same-subject repeated measures crossover study designs[229,230,232,233,279,280,296,297,299,318-320]. The experiments explored either the efficacy of a single PAS intervention, the efficacy of different types of single-session PAS interventions with varying stimulation parameters or made comparisons between PAS and other neuromodulatory interventions such as rTMS and tDCS. Only three articles compared PAS to a control intervention[279,280,296]. One article evaluated the cumulative effect of multiple sessions of PAS[233]. One article established the optimal ISI initially, and then went on to evaluate the repeatability of PAS using the chosen ISI[319]. See Table 4.3 for details of each experiment.

PAS Interventions

Among the 12 articles there were 20 experiments in healthy people (n = 136) and one experiment in people with stroke (n = 9) that investigated facilitatory PAS interventions; these targeted the corticospinal pathway of either the tibialis anterior muscle (TA)[233,279,280,296,297,318,320], the peroneous longus muscle (PL)[233], or the soleus muscle (SOL)[299,319]. The target muscle was either inactive[233,280,296,297,299,319,320], engaged in a voluntary contraction[296,299,318], or activated during treadmill walking[279,318]. Inhibitory PAS interventions were investigated in three experiments in healthy people (n = 50); two targeting the TA muscle during treadmill walking[279] and one targeting the SOL muscle during voluntary contraction[299]. Three experiments in people with stroke (n = 30) applied inhibitory PAS to the contralesional hemisphere to decrease asymmetrical inter-hemispheric inhibition; these targeted the non-paretic TA[230,232] or vastus medialis muscle (VM)[229]. Two of these experiments also included healthy controls (n = 21)[229,230].

Figure 4.1 PRISMA flowchart



Measurement Outcomes

All experiments measured CME with single pulse TMS[229,230,232,233,279,280,296,297,299,318-320]. Changes in TMS-induced MEP amplitude (or area) were expressed as either a relative percentage change (pre-intervention value normalised to 100%) and or an absolute mean change (mV). Some experiments also measured MEP amplitude stimulus response curves[299] or intracortical facilitation and inhibition[297]. TMS measurements were recorded from a target muscle in its resting state[233,296,297,299,319,320], during an active contraction[233,297,299,319], during treadmill walking[230,232,279,280,318], or whilst pedalling on a static cycle[229].

4.5.3 Methodological quality assessment

Refer to Table 4.3. for quality scores, and Supplementary Material for breakdown of scores (Appendix A.1, A.2, A.3). Assessors examining methodological quality demonstrated excellent pre consensus interrater reliability for both quality tools (Downs and Black $\varkappa$ = 0.896, TMS Quality checklist $\varkappa$ = 0.931). The Downs and Black quality checklist revealed that articles were of low to moderate quality (mean overall score 54%, SD 8%, range 38–64%). In general, authors failed to control for confounding variables, adverse events, external validity, blinding, selection bias, and power. The TMS Quality Checklist tool revealed an overall mean quality score of 66% (SD 9%; range 38–75%), with all but one article[233] being deemed moderate quality. For the majority of studies, the TMS method and analysis was well-described, but information about certain factors that can influence MEP measurement was lacking (medications, medical comorbidities, participation in repetitive motor activity, target muscle activity prior to TMS stimulation, and activity of surrounding muscles).

4.5.4 Intervention efficacy

Intervention efficacy was determined based on statistically significant changes in group mean MEP amplitude (or area) of the target muscle. Approximate changes (≈) have been interpreted from graphs where mean and variance estimates were not provided, and as such should be interpreted with caution. A summary of the main results can be found in Table 4.3.

Immediate Changes

Of the 12 experiments in healthy people that analyzed the immediate effects of facilitatory PAS, 10 reported statistically-significant increases in relative mean MEP amplitude

immediately post-intervention (range 19 to ≈180%[279,296,297,319,320]). Three experiments reported no statistically-significant differences[280,296,299]. An additional four experiments in healthy people recorded MEPs immediately following facilitatory PAS, but grouped the data with other post-intervention time-points[279,318]; (see duration of effect section below) or with inhibitory PAS data[279], or failed to report the primary outcome of MEP amplitude[318]. Most facilitatory PAS experiments (n = 16 of total 20) targeted the TA. The immediate relative effect was largest when PAS was delivered during a TA voluntary contraction using an ISI of 55ms or an optimized ISI based on individualized common peroneal nerve SEP latency (N34 peak), and when recording MEPs from the TA at rest[296,320]. For the SOL muscle, immediate relative increases in CME occurred when PAS was delivered to an inactive muscle and MEPs were recorded from the SOL at rest[319]. In contrast, facilitatory PAS delivered to the SOL muscle during a small voluntary contraction did not increase resting or active MEPs; however, when the authors undertook an additional unplanned analysis excluding non-responders (n = 4 out of 15), there was a significant increase in resting MEPs[299].

Four experiments analyzed the immediate effects of inhibitory PAS[230,279,299]. One additional healthy experiment studied inhibitory PAS, but as referred to above, grouped the effects of inhibitory and excitatory PAS together[279]. Across healthy participants, there were immediate relative decreases in CME when inhibitory PAS was applied to: the TA during treadmill walking[230,279], the SOL muscle during a small voluntary contraction[299], and the inactive vastus medialis muscle (VM)[229]. The three experiments involving participants with stroke applied inhibitory PAS to the unaffected hemisphere and inactive non-paretic target muscle and showed increased relative TA MEP amplitudes of the paretic TA (recorded during treadmill walking[230,232]), but no effect in the affected VM (recorded during pedalling on a static cycle[229]).

Duration of Effect

Thirteen experiments in healthy people reported the duration of effect following facilitatory PAS. Increases in CME were observed from 5 to 60 min post intervention and ranged from relative increases of 13 to ≈340%[279,280,296,297,299,319,320]. An additional four experiments collected MEPs at various post-intervention time-points but either: grouped all post-intervention time-points[274], combined results with inhibitory PAS experiments[279], didn't report the primary outcome[318], or only analyzed the time-point of maximum facilitation[318].

The largest MEP increases were observed at 30 min post-intervention when facilitatory PAS was delivered to the inactive TA, using an ISI of 55ms or individualized to SEP latency (N34), and MEPs were recorded from the TA at rest[296,320]. When PAS was delivered with low TMS (80% AMTh), increases in excitability were observed up to an hour post-intervention in both resting and active MEPs (≈85 and ≈25%, respectively[297]). Of the four facilitatory experiments that targeted the SOL muscle, increases in MEP amplitude were shown at 5, 15, and 30 min post-intervention[299,319]. MEP increases were largest 5 min post-intervention, using a PAS protocol applied to the inactive muscle with an ISI equal to "SEP latency (P32) + 18ms" (mean 50 ± 2ms) (mean increase 88%[319]). Based on these results, a later study set the ISI at 50ms and delivered PAS during a small plantar flexor contraction [5% maximum voluntary contraction (MVC)]; a facilitatory effect was measured 15 min post-intervention (mean increase 73%[299]).

With regards to inhibitory PAS, four experiments assessed the duration of effect at a range of time-points post-intervention and showed an inhibitory effect at 10–15 min post-intervention in healthy people[229,230,279,299] and 10–30 min post-intervention in people with stroke[229,230]. One additional experiment, with both healthy and stroke participants, investigated the effects of inhibitory PAS at 10 and 20 min post-intervention, but performed statistical analysis on only a combination of both time-points and the point of maximum modulation[232]. Another study combined results following inhibitory PAS with excitatory PAS[279]. Across the healthy experiments, small decreases in MEP amplitude were seen at 10 min following a PAS intervention delivered during treadmill walking[279], at 15 min following a PAS intervention delivered during a small plantar flexor contraction (this affected active but not resting MEPs[299]), and 10–15 min following a PAS intervention delivered to the inactive TA and VM[229,230]. In participants with stroke, inhibitory PAS applied to the unaffected hemisphere resulted in small increases in CME in the paretic TA 5–20 min post-intervention (recorded during treadmill walking[230,232]) but no excitation in the paretic VM 10–30 min post-intervention (recorded during pedalling[229]).

Effect of Multiple Sessions

When two facilitatory PAS interventions were delivered to healthy people at least 3 days apart, there were comparable increases in CME following each intervention, although cumulative effects were not explicitly explored[319]. The single study which has specifically explored the cumulative effects of PAS, delivered 20 interventions over 4-weeks to people with chronic stroke (n = 9) and reported no statistically significant group changes in either active or resting MEPs[233].

Control Experiments

Four healthy experiments compared PAS to a control intervention. Controlled interventions included PES only whilst sitting, TMS only whilst sitting[280], treadmill walking only, TMS while treadmill walking, PES while treadmill walking[279], and dorsiflexion only in sitting[296]. None of these significantly modulated CME ($p > 0.05$).

Table 4.3 Overview of the lower limb PAS studies included in the review

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Healthy Studies								
Stinear 2005								
Same-subject repeated-measures crossover	*n*=14 (24-58yr)	TA	2 PAS interventions, 7 days apart 1. PAS+ (late swing phase treadmill walking) 2. PAS- (late swing phase treadmill walking)	Post 0,10min Active (late swing phase) 1.0-1.5mV	1. ↑19% (and ↑23% MEP area) 2. ↓15% (and ↓12% MEP area)	10min 1. ↑21% (and ↑19% MEP area) 2. ↓18% (and ↓15% MEP area)	61	70
Same-subject repeated-measures crossover	*n*=4	TA	3 control conditions, 2 PAS interventions, two single sessions Control conditions given consecutively on treadmill (1. walk only, 2. PES + walk, 3. TMS + walk) followed by: 4. PAS+, or 5. PAS- (late swing phase treadmill walking). Repeated with either 4 or 5 in next session.	Post each condition and post 10min Active (late swing phase) 1.0-1.5mV	Controls 1,2,3: no difference *X:* 4.PAS+ and 5.PAS- results grouped: ↑14% from post-intervention walk measure (shows effect of PAS vs walking control)	*X:* 4.PAS+ and 5.PAS- grouped: 10min ↑10% from post-intervention walk measure		
Same-subject repeated-measures	*n*=4	TA	1 PAS intervention PAS+ with voluntary DF contraction	Post 0,10min Active (late swing phase), 1.0-1.5mV	Pooled time points: ↑23%			
Prior 2006								
Same-subject repeated-measures crossover	*n*=10 (20-30yr)	TA	3 PAS interventions PAS+ during treadmill walking 1. late swing phase 2. early swing phase 3. stance phase	Post 0,10,20,30min Active (late swing phase) 1.0 mV	1. Group findings not reported *X*: Re-grouped according to response *'Facilitators'* (n=5) pooled time points: ↑18% late swing (vs ↓4% early swing). Max time point: ↑30% ii). *'Inhibitors'* (n=5) pooled time points: ↓23% late swing (vs ↓1% early swing. Max time point: ↓30% late swing (vs ↑3% early swing). 2. and 3. No difference in group effect		46	68

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Same-subject repeated-measures crossover	*n*=5 (26-32yr)	TA	2 PAS interventions PAS+ during treadmill walking 1. late swing phase 2. mid swing phase	Post 0,10,20,30min. Active (late swing phase) 1.0 mV	1. Max time point ↑25% 2. Max time point ↓13%			
Jayaram 2007								
Same-subject repeated-measures crossover	*n*=13 (29-46yr)	TA	3 PAS interventions PAS+ during 1. sitting with high intensity TMS (120% AMth) 2. treadmill walking with high intensity TMS (120% AMth) 3. Sitting with low intensity TMS (100% AMth)	Post 0,5,10,15,20min Active (late swing phase) 1.0 mV	No difference	*Within group:* 1. 5min ↑12.8%, 15min ↑16.1% 2. No difference 3. No difference *Between group:* 1 > 3 5min (↑12.8% vs ↓6%) 10min (↑7.1% vs ↓7.9%) 15min (↑16.1% vs ↓2.5%) Max time point: (↑24% vs ↑7%) 2 > 3 5min (↑8.5% vs ↓6%)	50	68
Mrachacz-Kersting 2007								
Same-subject pre-post crossover	*n*=5	TA	7 PAS interventions PAS+ to inactive muscle with ISIs of 1. 20ms 2. 30ms 3. 40ms 4. 45ms 5. 50ms 6. 55ms 7. 60ms	Post 30min Resting 120% RMTh	Not tested	30 min 1. No difference 2. No difference 3. 40ms ≈↓20% 4. 45ms ≈↑135%, 5. 50ms ≈↑150%, 6. 55ms ≈↑340% 7. No difference	57	70

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Same-subject repeated-measures crossover	*n*=14	TA	2 PAS interventions, 1 control condition 1. PAS+ to inactive muscle (ISI 55ms) 2. PAS+ with voluntary DF contraction (ISI 55ms) 3. Voluntary DF only	Post 0min Resting 120% RMTh	1.No difference 2. pre 0.26±0.22mV post 0.50±0.39mV (-92%) 3. No difference	Not tested		
Same-subject repeated-measures crossover	*n*=5	TA	2 PAS interventions PAS+ with voluntary DF contraction (ISI 55ms) with 1. Moderate TMS intensity (120% RMTh) 2. Low TMS intensity (80-100% RMTh)	Post 0,15, 30min Resting 120% RMTh	1. ≈↑180% TMS 2. ≈↑175% TMS No between group differences	Not reported		
Same-subject repeated-measures	*n*=13	TA	1 PAS intervention PAS+ to inactive muscle (ISI = SEP 'N34' latency + 6ms)	Post 0, 30min Resting 120% RMTh	↑96%	30min ↑88%		
Pre-post	*n*=12	TA	1 PAS intervention PAS+ to inactive muscle (ISI = SEP 'N34' latency + 6ms)	Post 0 min Resting 120% RMTh	↑67% (n=5) ↑73% (n=7)	Not tested		

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Roy 2007								
Pre-post repeated-measures overlapping but different subjects	*n*=18 (each group *n*=8, except control *n*=5)	TA	6 PAS interventions, 1 control intervention PAS+ to inactive muscle ISIs adjusted based on MEP latency 1. -40ms (TMS precedes) 2. 0ms 3. 20ms 4. 35ms 5. 40ms 6. 60ms 7. control -170ms (TMS precedes)	Post 0,10,20,30, 60min a) Resting 300% PTh or 150% RMTh b) Active (10% MVC) 1.0mV	a) Resting MEPs 1. -40ms ↑≈65% 2-7. No difference b) Active MEPs 1-7. No difference	a) Resting MEPs 1. -40ms 10min ↑≈60%, 20min ↑≈55%, 60min ↑≈65% 2. 0ms 10min ↑≈25%, 20min ↑≈45%, 30min ↑≈67%, 60min ↑≈40% 3-7. No difference b) Active MEPs 1,2,5,6. No difference *Grouped resting and active MEPS* 1,2. No difference 3. 10-60min ↑(A&P) 4. 10-60min ↑ 5,6,7. No difference	39	69
Pre-post repeated-measures	*n*=8	TA	1 PAS intervention PAS+ to inactive muscle with low intensity TMS (80% AMTh)	Post 0,10,20,30, 60min a) Resting 300% PTh or 150% RMTh b) Active (10% MVC) 1.0mV	a) Resting MEPs No difference b) Active MEPs ↑≈35%	a) Resting MEPs 10min ↑≈ 30%, 20min ↑≈55%, 30min ↑≈70%, 60min ↑≈85% b) Active MEPs 0-60min ↑21%±16%, 10min ↑≈20%, 30min ↑≈25%		
Pre-post repeated-measures	*n*=8	TA	1 PAS intervention PAS+ to inactive muscle (ISI=20ms)	Post 15,30min Resting Paired pulse: conditioning 95% AMTh, test 0.3-0.6mV	Not tested	15min ↑41% SICI and ICF: no difference 30 min ↑37% SICI and ICF: No difference		

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Kumpulainen 2012								
Same-subject pre-post crossover	*n*=8 (22-28yr)	SOL	4 PAS interventions, 3 days apart PAS+ to inactive muscle with ISIs of SEP 'P32' latency plus either 1. 6ms 2. 12ms 3. 18ms 4. 24ms	Post 5min a) Resting b) Active (5% MVC) 120% RMTh	Not tested	5min a) Resting MEPs 1. ↓31±30% (ISI 38±2ms) 2. No difference 3. ↑88±105% (ISI 50±2ms) 4. No difference b) Active MEPs: 1-4 no difference	61	60
Pre-post repeated-measures	*n*=8 (20-24yr)	SOL	1 PAS intervention PAS+ to inactive muscle (ISI = SEP 'P32' latency + 18ms)	Post 0, 30min Resting a) 90,100,110,120,130, 140% RMTh b) mean of (a) above	a) stimulus response curve no change b)↑43±44%	30min a) stimulus response curve slope ↑73% b) ↑53±41%		
Same-subject pre-post	*n*=8 (23-27yr)	SOL	1 PAS intervention, repeated twice ≥3 days apart PAS+ to inactive muscle (ISI = SEP 'P32' latency + 18ms)	Post 5min a) Resting b) Active (5% MVC) 120% RMTh	Not tested	5min. a) Resting MEPs: ↑46±52%, ↑36±32% (session 1,2) b) Active MEPs: No difference		
Kumpulainen 2015								
Pre-post repeated-measures	*n*=30 (21-29yr	SOL	2 PAS interventions, 2 groups 1. PAS+ with voluntary PF contraction (ISI =50ms) (n=15) 2. PAS- with voluntary PF contraction (ISI =20ms) (n=15)	Post 0, 15min a) Resting 120% RMTh b) Active (20% MV) 120% AMTh c) Active (50% MVC) 120% AMTh	1. a) No difference (*X:* Grouped 11 responders ↑≈87%) b) No difference c) ↓9±12% 2. a) ↓27±32% b) ↓15±25% c) No difference	15min. 1. a) ↑73±123% b) No difference c) ↓8±14% 2. a) No difference (*X:* Grouped 12 responder's ↓≈43%) b) ↓9±18% c) No difference	61	65

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Mrachacz-Kersting 2017								
Same-subject repeated-measures crossover	*n*=11 (22-32yr)	TA	2 PAS interventions, 7 days apart PAS+ to inactive muscle (ISI=SEP 'N34' latency +6ms) 1.Biphasic TMS pulse 2. Monophasic TMS pulse	Post 0, 30min Resting 120% RMTh	1.pre 0.32±0.23mV post 0.43±0.24mV (↑74%) 2. pre 0.28±0.14mV post 0.44±0.22mV (↑83%) No between group differences	1. 30min 0.60±0.33mV (↑117%) 2. 30min 0.49±0.18mV (↑105%) No between group differences	57	74
Same-subject pre-post crossover	*n*=10 (22-28yr)	TA	2 PAS interventions, ≥7 days apart PAS+ to inactive muscle (ISI= ISI=SEP 'N34' latency +6ms 1. High intensity TMS (120% RMTh) 2. Low intensity TMS (95% AMTh)	Post 0, 30min Resting 120% RMTh	1.pre 0.37±0.26mV post 0.46±0.22mV (↑53%) 2. pre 0.39±0.29mV post 0.50±0.39 mV (↑55%) No between group differences	1. 30min 0.62±0.37mV (↑95%) 2. 30min 60±0.47mV (↑80%) No between group differences		
Stroke Studies								
Uy 2003								
Pre-post uncontrolled	*n*=9 (43-78yr)	TA and PL	1 PAS intervention PAS+ to inactive muscle (ISI=35ms) 20 sessions over 4 weeks	Post 4 weeks a) Resting 115% RMTh b) Active (5-10% MVC) 115% AMTh	Not tested	4 weeks No difference *X:* a) *n=5* ↑TA, n=3 ↑PL b) *n=3* ↑TA, n=5 ↑PL	38	38

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Jayaram 2008								
Pre-post repeated-measures	People with chronic stroke (*n*=10) (44-64yr)	TA	1 PAS intervention, 2 groups PAS- to inactive muscle (ISI=MEP latency minus 8ms) Stroke: Applied to contralesional hemisphere and non-paretic TA	Post 0,5,10,15min Active (late swing phase) 1.0mV	Paretic TA: ↑34% Non-paretic TA: No difference	Paretic TA: 5min ↑30%, 10min ↑20%, 15min ↑38% Pooled time points: ↑30% Non-paretic TA: No difference Pooled time points: ↓9%	64	75
	Age-matched healthy (*n*=10)		Healthy: Applied to dominant hemisphere and contralateral TA	Post 0,5,10,15min Active (late swing phase) 1.0mV	Non-stimulated TA: ↑18% Stimulated TA: No difference	Non-stimulated TA: 5min ↑32%, 10min ↑23%, 15min ↑34% Pooled time points: ↑26% Stimulated TA: 10min ↓15%, 15min ↓16% Pooled time points: ↓13%		
Jayaram 2009								
Same-subject repeated-measures crossover	People with chronic stroke (*n*=9) (45-66yr)	TA	3 interventions, 2 days apart 1. PAS- (late swing phase treadmill walking, ISI=MEP latency minus 8ms). Contralesional hemisphere and non-paretic TA 2. rTMS- contralesional 3. tDCS+ ipsilesional	Post 0,10, 20min TA: Active (late swing phase) 120% AMTh MH, VL and MG: Peak activation during gait cycle 120% AMTh	Non-stimulated: pooled time points TA ↑20%, MH VL MG no difference Stimulated limb: pooled time points MH ↓24%, TA VL MG No difference Non-stimulated: max time point TA ↑22%, MH VL MG No difference Stimulated limb: max time point MH ↓37%, TA VL MG No difference		56	73

Study design	Sample	Target muscle	Interventions	TMS measure (post intervention time points, muscle state, stimulation output)	Immediate effect on MEP amplitude (expressed as % change from pre-intervention)	Duration of effect on mean MEP amplitude (expressed as % change pre-intervention)	D&B QC score (%)	TMS QC score (%)
Rogers 2011								
Pre-post repeated-measures	People with chronic stroke (*n*=11) (37-79yr)	VM	1 PAS intervention, 2 groups Stroke: PAS- to inactive muscle, contralesional hemisphere and non-paretic VM	Post 0,10,20, 30min Active (mid VM burst on cycle ergometer), MEP size 2-3 times background EMG	Paretic VM: No difference Non-paretic VM: ↓	Paretic VM: No difference Non-Paretic VM: 10min ↓, 20min ↓, 30min ↓ Pooled time points: ↓21%.	58	65
	Healthy (*n*=11) (27-69yr)		Healthy: PAS- to inactive muscle, left hemisphere and right VM	Post 0,10,20, 30min Active (mid VM burst on cycle ergometer), MEP size 2-3 times background EMG	Non-stimulated: No difference Stimulated VM: ↓	Non-stimulated VM: 10, 20-30min No difference Stimulated VM: 10min↓ 20-30min No difference Pooled time points ↓15%		

vs = compared with another group for statistical significance; MEP value is expressed as relative % change from pre-intervention where 0% = no change; ≈ = approximated from graphs presented in article; ¯ = significantly decreased MEP (% or mV) alpha 0.05;- = significantly increased MEP (% or mV) alpha 0.05; Pooled time points = all post-intervention time points pooled for analysis; Max time point = time point with maximum facilitation used for analysis; X = unplanned analysis or unconventional analysis; TMS QC= TMS Quality Checklist; D&B QC= Modified Downs and Black Quality Checklist; PAS+ = facilitatory PAS; PAS- = inhibitory PAS; TA = tibialis anterior muscle; PL = peroneus longus muscle; SOL = soleus muscle; MG = medial gastrocnemius muscle; VM = vastus medialis muscle; VL = vastus lateralis muscle; MH = medial hamstrings muscle; CPN = common peroneal nerve; TN = tibial nerve; FN = femoral nerve; MEP = motor evoked potential; SEP = somatosensory evoked potential; TMS = transcranial magnetic stimulation; SICI = short interval intracortical inhibition; ICF = intracortical facilitation; RMTh = resting motor threshold; STh = sensory threshold; PTh = perceptual threshold; AMth = active motor threshold; MEPmax = maximum MEP amplitude; PES = peripheral electrical stimulation; DF = dorsiflexion, MVC = maximum voluntary contraction; ISI = inter stimulus interval (unless stated otherwise, peripheral electrical stimulation is delivered first); Rpm = revolutions per minute; rTMS = repetitive transcranial magnetic stimulation; TDCS = Transcranial direct current stimulation.

4.5.5 Stimulation parameters

PAS stimulation parameters varied across the experiments, including stimulation location, number of stimulation pairings, ISI, and the stimulation intensity, frequency, and waveform. A summary of the stimulation parameters employed in the experiments are presented in Table 4.4.

Stimulation Location and Application

The peripheral electrical stimulation component of the PAS targeted the TA muscle via the common peroneal nerve (CPN) in 19 experiments[230,232,233,279,280,296,297,318,320], the SOL muscle via the tibial nerve (TN) in four experiments[299,319], and the vastus medialis (VM) muscle via the femoral nerve (FN) in one experiment[229]. The TMS component of the PAS was delivered over the M1 at the optimal stimulation site for the target muscle, with the exception of 12 experiments that chose a site where MEP outcomes could be elicited from both the target muscle and its antagonist[296,320] and the contralateral side[232,279,318]. The type of TMS coil employed and its orientation was reported for all experiments. Eighteen applied a double-cone coil[229,230,232,279,280,296,297,318,320], four a batwing coil[299,319] and one experiment described an angled figure of eight coil[233]. Seventeen experiments reported the direction of the TMS current flow across the cortex, all of which reported a posterior-anterior current flow[229,230,280,296,318,320].

Dose: Number of Stimulation Pairings and Intervention Duration

Across the experiments, PAS interventions included 60–360 stimulation pairings lasting 4–30 min. Results varied across studies. To compare whether the number of stimulation pairings and duration of stimulation effected CME, one experiment recorded MEPs midway through, immediately following, and 30 min following a facilitatory PAS intervention[296]. After 180 pairings there was no statistically significant increase in resting MEP amplitude, but after 360 pairings a significant effect was observed, and this was maintained at 30 min post-intervention. In contrast, another experiment delivered a relatively short 5 min intervention, with 60 pairings (3 afferent stimuli to 1 TMS stimulation) and showed increases in resting MEP amplitudes of ≈30–85% from 10 to 60minutes post-intervention[297]. Across all experiments, those that delivered more stimulation pairings for longer periods to an inactive target muscle tended to yield greater

effects[296,297,299,319], than those which delivered fewer stimulation pairings for shorter periods to a muscle that was either inactive or engaged in treadmill walking[230,279,280,318].

Interstimulus Interval (ISI)

ISIs were estimated based on either MEP latencies[229,230,232,279,280,318] SEP latencies (either the N34 or P32 peaks[296,319,320]), or on findings from previous lower limb PAS experiments[296,297,299,319]. Across 18 experiments, facilitatory effects were seen when ISIs ranged from 33.5 to 56 ms for the TA[279,280,296,318,320] and 48–52 ms for the SOL[299,319]. In five experiments, inhibitory effects were seen when ISIs were in the range of 18–24 ms for the TA[230,232,279], 16–18 ms for the VM[229], and 20 ms for SOL[299]. The largest increases in CME were seen in the TA muscle with ISIs of 40–55 ms[320]. It should be noted that when ISIs were individualized to SEP latency, all participants demonstrated increased CME[296,320]. In contrast, one paper showed facilitatory effects with a wide range of ISIs (−40, 0, 20, and 35 ms) where the peripheral electrical stimulus (PES) was timed to arrive up to 90 ms after the TMS[297].

Stimulation Intensity

Across the experiments, a range of TMS intensities for the PAS interventions were described. The most common TMS intensity, used in 11 experiments, was 120% of resting motor threshold (RMTh) with an inactive[296,319,320], or slightly contracted[299] target muscle. Six experiments used a TMS intensity of 120% of active motor threshold (AMTh) during treadmill walking[232,279,318]. Other intensities can be seen in Table 4. Several experiments indicated that PAS yielded similar increases in CME when higher and lower TMS intensities were utilized (80–100% RMTh vs. 120% RMTh; 95% AMTh vs. 120% RMTh; 80% AMTh) and MEPS were recorded from a resting muscle[296,320] and a slighted contraction muscle[297]. However, when a lower TMS intensity (100% AMTh obtained during treadmill) applied in sitting was compared with higher intensities applied in sitting or during walking (120% AMTh obtained during treadmill walking), and MEPS were recorded during treadmill walking, results were significantly better with both high intensity TMS conditions[280].

The intensities of PES varied across the experiments and were calculated as proportions of either motor threshold (MTh), sensory threshold (STh), or perceptual threshold (PTh). When PAS was applied to the inactive muscle, intensities of peripheral stimulation included 100% MTh[233,296,320], 120% MTh[229,230,280], 150% MTh[319], and either 300% STh/PTh or 150% MTh[297]. When PAS was applied to the active muscle, PES intensities of 100% MTh[296] and

150% MTh[299] were used during a voluntary contraction, and 120% MTh was used during treadmill walking[232,279,280,318]. No studies provided a rationale for the PES intensity used, nor compared the effect of different intensities. There were no apparent differences between facilitatory and inhibitory PAS interventions, nor healthy or stroke experiments in relation to the PES intensity utilized.

Stimulation Frequency

The frequency at which each pair of PES and TMS were paired together was reported across the majority of experiments and ranged from 0.1 to 0.5 HZ[230,232,233,280,296,297,299,318-320]. Two studies also reported the frequency of PES because they matched multiple afferent stimuli with each TMS pulse[233,297]. Of these studies, one showed no significant change in resting or active MEPs following a 4-week intervention[233], whilst the other demonstrated an increase in both resting and active MEPs, lasting 60, and 30 min, respectively[297]. The literature did not allow a direct comparison of the effect of multiple vs. single afferent stimuli due to the variation in other intervention parameters across studies.

PES Pulse Width

Twenty-one experiments specified that the peripheral stimulation was delivered with a pulse width of 1 ms; however, justification for this was not provided. No experiments compared the effects of different pulse widths.

Pulse Waveform

Only six experiments with healthy people and one experiment with people with stroke documented the waveform of the TMS pulse; six utilized a monophasic pulse and two a biphasic pulse[232,299,319,320]. When PAS interventions with either mono- or bi-phasic waveforms were compared, both were equally effective[320]. With regards to the PES, waveform selection was not reported across any of the experiments.

Table 4.4 Overview of stimulation parameters employed across the included studies

Target muscle	Stimulus location	Muscle state during PAS intervention	ISI (ms)	TMS coil type, orientation and direction of induced current	TMS intensity	PES intensity	Number of stimulation pairings	Stimulation period (mins)	Frequency	Pulse width (ms)
Healthy Studies										
Stinear 2005										
TA	CPN	PAS+ - Active: treadmill walking - Active: with voluntary DF contraction	Individualized MEP latency +5ms	-Double-cone coil -Mid-sagittal plane ≈ 1cm anterior to the vertex -Direction of current: NR	120% AMTh	120% MTh	120	10	NR	NR
TA	CPN	PAS- -Active: treadmill walking	Individualized MEP latency -10ms		120% AMTh	120% MTh	120	10	NR	NR
Prior 2006										
TA	CPN	PAS+ Active: treadmill walking	Individualized MEP latency +5ms	-Double-cone coil -Mid-sagittal plane, coil intersection ≈ 2cm posterior to vertex -Posterior-anterior current	120% AMTh	120% MTh	120	10	0.2	1
Jayaram 2007										
TA	CPN	PAS+ Inactive muscle	MEP latency +5ms	-Double-cone coil -Mid-sagittal plane coil, intersection ≈ 2cm posterior to vertex -Posterior-anterior current	120% AMTh	120% MTh	120	4	0.5	1
TA	CPN	PAS+ Inactive muscle	MEP latency +5ms		100% AMTh	120% MTh	120	4	0.5	1
TA	CPN	PAS+ Active: treadmill walking	MEP latency +5ms		120% AMTh	120% MTh	120	4	0.5	1
Mrachacz-Kersting 2007										
TA	CPN	PAS+ Inactive muscle	20, 30, 40, 45, 50, 55, 60ms	-Double-cone coil - ≈2–3 cm anterior to the vertex -Posterior-anterior current	120% RMTh	100% MTh	360	30	0.2	1

Target muscle	Stimulus location	Muscle state during PAS intervention	ISI (ms)	TMS coil type, orientation and direction of induced current	TMS intensity	PES intensity	Number of stimulation pairings	Stimulation period (mins)	Frequency	Pulse width (ms)
TA	CPN	PAS+ -Inactive muscle -Active: 5-10% MVC	55ms		120% RMTh	100% MTh	360	30	0.2	1
TA	CPN	PAS+ Active: 5-10% MVC	55ms		DF matched reduced to 80-100% RMTh	100% MTh	360	30	0.2	1
TA	CPN	PAS+ Inactive muscle	Individualized SEP latency (N34) +6ms		120% RMTh	100% MTh	360	30	0.2	1
TA	CPN	PAS+ Inactive muscle	Individualized SEP latency (N34) +6ms		120% RMTh	100% MTh	360	30	0.2	1
Roy 2007										
TA	CPN	PAS+ Inactive muscle	MEP latency -70, -30, -10, +5, +30ms (afferent volley arrived 15-90ms post TMS)	-Double-cone coil - ≈1cm lateral and 1cm posterior to the vertex -Posterior-anterior current	MEPs 0.3–0.6 mV	300% PTh or 150% MTh	90	15	0.1	1
TA	CPN	PAS+ Inactive muscle	15–35ms		80% AMTh	300% STh	60	5	0.2 (X 3 stimuli at 100 Hz 10ms train)	1
TA	CPN	PAS+ Inactive muscle	20ms		MEPs 0.3–0.6 mV	300% PTh or 150% MTh)	90	15	0.1	1
Kumpulainen 2012										
SOL	TN	PAS+ Inactive muscle	Individualized SEP latency (P32) + 6, 12, 18, 24ms	-Double batwing coil -Optimally positioned, where SOL MEPs were greater/more consistent than MEPs of adjacent coordinates for a given stimulus intensity	120% RMTh	150% MTh	200	<20	0.2	NR
	TN	PAS+ Inactive muscle	Individualized SEP latency (P32) + 18ms	-Direction of current: NR	120% RMTh	150% MTh	200	<20	0.2	NR

Target muscle	Stimulus location	Muscle state during PAS intervention	ISI (ms)	TMS coil type, orientation and direction of induced current	TMS intensity	PES intensity	Number of stimulation pairings	Stimulation period (mins)	Frequency	Pulse width (ms)
	TN	PAS+ Inactive muscle	Individualized SEP latency (P32) + 18ms		120% RMTh	150% MTh	200	<20	0.2	NR
Kumpulainen 2015										
SOL	TN	PAS+ Active: 5% MVC	50ms	-Double batwing coil - ≈1 cm lateral and 1 cm posterior to the vertex	120% RMTh	150% MTh	200	17	0.2	NR
SOL	TN	PAS- Active: 5% MVC	20ms	-Direction of current: NR	120% RMTh	150% MTh	200	17	0.2	NR
Mrachacz-Kersting 2017										
TA	CPN	PAS+ Inactive muscle	Individualized SEP latency (N34) +6ms	-Double-cone coil - ≈1cm lateral and 1cm posterior to the vertex -Posterior-anterior current	120% RMTh	100% MTh	360	30	0.2 biphasic pulse	1
TA	CPN	PAS+ inactive muscle	Individualized SEP latency (N34) +6ms		120% RMTh	100% MTh	360	30	0.2 monophasic pulse	1
TA	CPN	PAS+ Inactive muscle	Individualized SEP latency (N34) +6ms		-95% AMTh -120% RMTh	100% MTh	360	30	0.2 biphasic pulse	1
Stroke studies										
Uy 2003										
TA/PN	CPN	PAS+ Inactive muscle	35ms	- Angled figure of eight coil - Region of the vertex -Direction of current: NR	100% MTh	100% MTh	180	30 4 weeks	0.1 (PES: 500ms train of 10Hz,)	1
Jayaram 2008										
TA	CPN	PAS- Inactive muscle	Individualized MEP latency -8ms	-Double-cone coil -Mid-sagittal plane coil, intersection ≈ 2cm posterior to vertex -Posterior-anterior current	120% AMTh	120% MTh	120	4	NR	1

Target muscle	Stimulus location	Muscle state during PAS intervention	ISI (ms)	TMS coil type, orientation and direction of induced current	TMS intensity	PES intensity	Number of stimulation pairings	Stimulation period (mins)	Frequency	Pulse width (ms)
Jayaram 2009										
TA	CPN	PAS- Active: treadmill walking	Individualized MEP latency -8ms	-Double-cone coil -Mid-sagittal plane coil, intersection ≈ 2cm posterior to vertex -Direction of current: NR	120% AMTh	120% MTh	120	4	0.2	1
Rogers 2011										
VM	FN	PAS- Inactive muscle	Individualized MEP latency -8ms	-Double-cone coil -Mid-sagittal plane coil, intersection ≈ 2cm posterior to vertex -Posterior-anterior current	Active (mid VM burst on cycle ergometer), MEP size 2-3x background EMG	120% MTh	120	≈11	0.5	NR

PAS+ = facilitatory PAS; PAS- = inhibitory PAS; TA = tibialis anterior muscle; PL = peroneus longus muscle; SOL = soleus muscle; MG = medial gastrocnemius muscle; VM = vastus medialis muscle; CPN = common peroneal nerve; TN = tibial nerve; FN = femoral nerve; MEP = motor evoked potential; SEP = somatosensory evoked potential; TMS = transcranial magnetic stimulation; AMth = active motor threshold; RMTh = resting motor threshold; MTh = motor threshold; STh = sensory threshold; PTh = perceptual threshold; MEPmax = maximum MEP amplitude; PES = peripheral electrical stimulation; DF = dorsiflexion, MVC = maximum voluntary contraction, ISI = inter stimulus interval (unless stated otherwise, peripheral electrical stimulation is delivered first); mV = millivolts; mins = minutes; secs = seconds; ms = milliseconds; Hz = hertz; ≈ = approximate time in minutes; NR = *not reported; ≈ approximately.*

4.6 Discussion

This systematic review examined the efficacy of PAS on lower limb CME in healthy and stroke populations, whilst explicitly considering the methodological quality of the research and the influence of stimulation parameters on the reported outcomes. Bearing in mind that the body of literature lacks methodological rigor and therefore may be subject to bias, the key finding supports the efficacy of a single session of lower limb PAS to modulate CME in healthy and stroke populations. An important limitation is the lack of studies that have investigated the effect of multiple sessions of PAS over time, as would commonly be done in a clinical setting. Whilst stimulation parameters appear important, the ability to draw robust conclusions about the selection of optimal parameters is hindered by: (1) limited systematic evaluation of stimulation parameter settings within and across experiments; (2) variability in the muscle state during PAS interventions; (3) inter-individual variability in the magnitude of response to the PAS interventions; and (4) variability in the muscle contraction state during CME measurement and the influence this has on the ability to elucidate an effect. We discuss the key findings below, whilst highlighting limitations in the evidence-base, and providing recommendations for future lower limb PAS research in healthy and stroke populations.

4.6.1 Methodological quality

Lower limb PAS interventions are part of an emergent field of neuromodulation research, which predominately consists of early exploratory work. The majority of studies included in this review were of moderate-to-poor quality (Downs and Black mean 54%, SD 8%, range 38-64%). Given the lack of methodological rigor in the research, care should be exercised when interpreting the findings in relation to both efficacy and optimal parameters. Study sample sizes were generally low, with only one study reporting a power calculation[279]. Aspects of external validity were poorly addressed with samples often not representative of the population. All studies scored poorly on aspects of internal validity; this frequently related to a failure to consider and report relevant covariates, and the absence of both randomization and blinding of participants and assessors.

4.6.2 Intervention efficacy of lower limb PAS in healthy people

The majority of studies in this review reported that a single session of facilitatory or inhibitory lower limb PAS resulted in an immediate change in CME in healthy participants[230,279,296,297,299,319,320]. Few studies compared PAS to a sham intervention within the same experimental design[279,296]. However, several reported separate experiments where

individual components of the intervention were evaluated in isolation[230,279,296]. Although these experiments support the argument that it is the pairing of the two stimuli in PAS that induces the effect, powered randomized controlled studies with a sham arm are required to rigorously evaluate this. Modulation of upper limb CME induced by PAS suggests a mechanism of action that is cortical in origin[46,321]. Given that the lower limb is more influenced by spinal input compared to the upper limb[301-303] it could be postulated that spinal mechanisms may contribute to changes in CME following lower limb PAS. However, several small lower limb PAS experiments indicated that spinal excitability measurements (H-reflex and F-waves) remained unchanged following PAS[296,297,299,319,320].

Some experiments supported the notion that the duration of effect may extend up to an hour following the intervention[297], although the magnitude of the effect, with respect to the post-intervention time-point, varied across studies[230,279,296,297,299,319,320]. Studies of both upper limb PAS, and other non-invasive neuromodulatory interventions, report changes in CME for up to 120 mins[300,322]. However, within lower limb PAS literature, the neuromodulatory effect has not been investigated beyond 60 min post-intervention. In a number of experiments included within this review, despite measuring CME at various post-intervention time-points, the authors only analysed and reported the time-point at which maximum facilitation occurred[232,318], or grouped the results across time-points[232,279]. In these instances, it is not possible to interpret the time-course of the effect.

4.6.3 Intervention efficacy of lower limb PAS in people with stroke

This review identified a small number of studies investigating lower limb PAS interventions in people with stroke[229,230,232,233]. No studies explored the effect of a single session of facilitatory lower limb PAS in people with stroke. One study[233] investigated the cumulative effects of 20 facilitatory PAS sessions delivered over 4-weeks; they evaluated CME, muscle strength, range of movement, and gait measurements, in nine people with chronic stroke. Measurements of CME and muscle strength remained unchanged, but there were statistically significant group improvements in a number of gait parameters (cadence, stride length, and heel-strike). However, given the poor quality of this study, its small sample size, and the absence of a control group, these results may be due to a practice effect and so cautious interpretation is advised.

Several authors assessed single-session inhibitory lower limb PAS interventions in people with stroke, to ascertain whether applying inhibitory PAS to the contralesional M1 and the unaffected lower limb would improve the balance of reciprocal interhemispheric

inhibition[229,230,232]. This model of rebalancing interhemispheric inhibition has been proposed as an important factor in post-stroke motor recovery[323], and therefore inhibiting contralesional M1 activity has been widely adopted in other neuromodulatory interventions[324]. Jayaram and Stinear applied inhibitory PAS to the contralesional hemisphere and demonstrated small increases in excitability of the corticospinal pathway to the paretic TA, lasting up to 20 min[230,232]. In contrast when a similar inhibitory PAS intervention was applied to the VM, outcomes were highly variable and there were no significant facilitatory effects in the ipsilesional corticospinal pathway[229]. Higher ipsilesional motor thresholds are often observed in people with stroke and MEP latencies can be prolonged due to damaged corticospinal tracts[248-250]. It has been asserted that this can cause difficulty estimating the ISI required for applying facilitatory PAS to the ipsilesional hemisphere, making application of inhibitory PAS to the contralesional hemisphere more feasible[232]. However, evidence from other non-invasive neuromodulatory interventions in people with stroke has shown mixed responses to inhibitory interventions applied to the contralesional M1[325,326]. The relevance of interhemispheric inhibition to lower limb movement is unclear[304,305] and its role in stroke recovery has been called into question in a recent meta-analysis, which showed insufficient evidence for interhemispheric imbalance after stroke[327]. This suggests that despite methodological challenges, future work should focus on facilitatory interventions delivered to ipsilesional M1.

4.6.4 Stimulation parameters

Numerous stimulation parameter settings were employed across the body of research, often in a non-systematic way, making it challenging to unpack how various stimulation parameters may influence the modulation of CME. Based on the depth and quality of the research, it is feasible to comment on the following parameters: ISI, TMS stimulation intensity, TMS coil type, TMS waveform, and the dose of treatment (number of stimulation parings and duration).

Dose: Number of Stimulation Pairings and Intervention Duration

Whilst there was a tendency for interventions with more stimulation pairings and longer durations to yield greater changes in CME in healthy people[232,296,297,299,319], the research was not systematic in nature, and methodological differences across studies made direct comparisons challenging. One poor-quality study reported a contrasting finding, demonstrating that a relatively short 5-minute intervention with only 60 pairings, increased

CME[297]. At this stage it is not possible to assert the optimal number of pairings or intervention duration, and further research is required.

Interstimulus Interval (ISI)

In facilitatory PAS interventions increases in CME were observed with a range of ISIs ranging from 33.5 to 56ms for TA[279,280,296,318,320] and 48–52ms for SOL[299,319]. Taking into account an average conduction time of 42–47ms from the peripheral nerve to the somatosensory cortex, plus a 10ms central processing delay[296,328], these ISI values result in the afferent volley arriving at M1 between 4ms before, and 23.5ms after, the TMS stimulation. This is a much larger window (27.5ms) than reported in upper limb facilitatory PAS interventions, where increases in CME are observed when the afferent volley arrives at the M1 either synchronously with, or just before, the TMS stimulation, within a narrower window (6ms[46,223]). That said, in the lower limb PAS literature, the largest increases in CME were observed when the afferent stimulus and TMS arrived at the M1 at approximately the same time[296]. Substantial CME modulation was also observed in two moderate-quality studies when the ISI was individualized to each participants SEP latency plus a central processing delay[296,320]. Although the magnitude of effect still varied across participants, these experiments demonstrated increases in CME in all participants. This contrasts with the upper limb literature which demonstrates conflicting results when ISIs were individualized based on either SEP latency alone[298], or SEP latency plus a central processing[298,329]. It is not clear whether these discrepancies between upper and lower limb PAS interventions are due to differences in interpretation of SEP latency, failure to account for central processing time[223], differences in connectivity between the sensory and motor cortices for the upper and lower limbs[330-333] or insufficient high quality evidence.

When inhibition of CME was the goal, the moderate-quality research supports using a shorter ISI (18–24ms[229,230,232,279,299]). These ISIs equate to the afferent volley arriving in the M1 28–39ms after the TMS stimulus, assuming a conduction time of 52–57ms. In contrast, one study used an ISI in this range, and reported an increase, rather than decrease, in CME; although this poor-quality study also reported facilitatory effects with ISIs of −40, 0, and 35ms[297], which contrasts with the other literature.

With ISIs in the middle range (34–40ms), the effects of PAS were more inconsistent, with moderate-quality experiments showing either excitation[279,280] or inhibition[296,319] and to poor-quality experiments demonstrated a mixture of excitation and inhibition across participants[233,318]. This variability in response may be related to inter-individual variability in

conduction times and the influence the task has on conduction-time estimates[334,335]. This might suggest that, within this ISI range, it is important to individualize ISIs using SEP latencies. However, as previously suggested, this individualized approach may be more difficult in people with stroke, where altered conduction and central processing times[248-250] can influence the ISI calculation. This may explain why Uy et al.[233] reported excitation in some participants with stroke but no group effect.

Whilst it is asserted that pairing of the afferent volley and the TMS occurs in the M1[46,48], the definitive timing and location remains unknown. However, the time-dependent nature of PAS resembles STDP observed in single neurones[138,142]. Whether through STDP or some other mechanism, the literature reviewed, along with findings from upper limb research[223,225,300], indicates that the effects of PAS resemble long-term potentiation (LTP) or long-term depression (LTD) plasticity[133] with most experiments showing a rapid, change in CME that persists beyond the period of stimulation.

TMS Intensity

Research which addressed the effect of the TMS intensity during facilitatory PAS interventions was conflicting. Two moderate-quality experiments[296,320] and one poor-quality experiment[297] demonstrated that increases in CME were achieved when both sub- and supra-threshold TMS stimulus intensities were utilized. In contrast, one moderate-quality experiment demonstrated that a very low intensity TMS stimulation was less effective than a higher intensity stimulation[280]; however the intensity of TMS stimulation (100% AMTh during treadmill walking), applied during the seated intervention, was substantially lower than that used in other studies. Subthreshold TMS intensities may improve the feasibility of PAS, however further work is required to determine the minimum intensity required to induce changes in CME and to verify whether higher intensity TMS stimulation confers greater benefit.

TMS Coil Type

Experiments consistently used either a double-cone or batwing TMS coil, and in those experiments that reported current direction, a posterior-anterior flow was selected. These angular coils were an appropriate choice as they create an electric field which extends to deeper cortical structures[336]. Coil type is an important consideration, particularly in lower limb PAS where the target M1 area is found deep within the interhemispheric fissure[337,246]. In addition, a number of other aspects of the TMS delivery method, such as coil location,

coil stability and the direction of the induced current may contribute to the efficacy of PAS and therefore should be considered in future research.

TMS Pulse Waveform

There is limited evidence with respect to the influence of TMS waveform on CME. One moderate-quality study inferred that the TMS waveform does not influence outcomes, as both monophasic and biphasic waveforms produced similar changes in CME[320]. However, the authors acknowledged that the findings across the two groups were not directly comparable, as one group evaluated CME with MEPs induced with monophasic TMS, and the other group induced MEPs with biphasic TMS. The potential for biphasic TMS to produce an enhanced effect is supported by work by Kammer et al.[338] and Sommer et al.[339], who showed that a biphasic waveform can stimulate neurones positioned in both AP and PA directions, resulting in stimulation of a more diverse collection of neurones, compared to a monophasic waveform. Thus, further research is required to systematically test the effect of different TMS waveforms during PAS in people with stroke.

4.6.5 Target muscle state during PAS Interventions

In addition to stimulation parameters, one aspect of the intervention that varied across the studies was the contraction-state of the target muscle. Moderate-quality studies showed that when facilitatory PAS was delivered to the inactive or minimally-active muscle, larger relative increases in CME were observed[296,299,319,320] than when delivered during a treadmill walking task[230,232,279,280,318]. One possible explanation for this is that during movement there is gating of somatosensory input, such that somatosensory evoked potentials are 30% smaller in walking than standing[334]. The low level of PES (120% MTh) utilized in the five studies that delivered PAS during treadmill walking[232,279,280] may not have been sufficient to adequately reach the M1, for pairing with TMS stimuli. This idea is supported by one moderate-quality cross-over experiment[280] where the same 13 participants received facilitatory PAS during (i) sitting, and (ii) walking, but only the sitting intervention resulted in increases in CME.

4.6.6 Variability in response to lower Limb PAS

Across the studies, contrasting results to lower limb PAS were evident within both healthy and stroke populations. Whilst the majority of experiments indicated a significant modulatory effect, several experiments indicated no overall change in CME from baseline[228,313,275,291,224,314] and in some cases modulation was in the opposite direction to what

would have been anticipated[274,313,292,224]. Responders and non-responders have been reported in other non-invasive brain stimulation research, whereby the anticipated change in MEP outcomes is reported to occur in only 39–53% of the participants[224,340,341]. Non-modifiable factors such as age[329,342,343], gender[344], cranial and cortical anatomy[224,340,345], genetic profile[346-349], and hormonal fluctuations[350-352], and modifiable factors such as time of day[353], attention to task[295], use of caffeine, alcohol and nicotine[354-356], medications[357], and motor activity prior, during or after the intervention[358-361], are all well known or hypothesized to influence an individual's response to neuromodulatory interventions. In order to strengthen our understanding of the variability in response to neuromodulatory interventions, it is essential that researchers control for modifiable factors within their study design, while considering non-modifiable factors as covariates when analyzing and interpreting results.

One moderate-quality study included in this review evaluated the repeatability of the response to PAS in healthy people[314], and demonstrated that whilst there was large inter-individual variability following facilitatory PAS (mean increase 46 ± 52%, n = 8), individuals demonstrated a repeatable response to the same PAS intervention delivered 3 days later (mean increase 36 ± 32%, ICC = 0.85). This finding contrasts with upper limb PAS studies, where the individual responses to PAS were highly variable between sessions[352,362]. Such variability within and between individuals emphasizes the need for caution when extrapolating findings.

4.6.7 TMS measurement considerations

Another explanation for the variability in results is the different methods employed for assessing CME across the studies. In general, PAS experiments which recorded resting MEPs showed larger relative changes in MEP amplitude[296,297,319,320]. In contrast, experiments which recorded MEPs during a functional task (treadmill walking) showed smaller relative changes in MEP amplitude[229,230,232,279,280,318]. However, it must be considered that during a functional task, small relative changes in MEPs represent larger absolute changes. In addition to recording MEPs in the resting muscle or during functional tasks, five experiments recorded active MEPs during a voluntary contraction (5–50% MVC)[233,297,299,319]. Only two of these experiments demonstrated significant changes in active MEP amplitudes[297,299], yet four of the five experiments demonstrated changes in resting MEPs[297,299,319]. This suggests that it may be more difficult to induce changes in active MEPs than resting MEPs. A possible explanation may relate to the different neurones being recruited during resting and active MEPs (low threshold vs. high threshold[41,363,364]), and the

task-specificity of cortical circuitry. For example, when PAS is delivered to an inactive muscle, and changes are seen in resting but not active MEPs[297,319], this may be because the changes in the specific circuitry involved were only measurable in the resting condition. However, this idea is contradicted by other results where PAS was delivered to an inactive target muscle and changes occurred in MEPs recorded during functional tasks[230,280].

Across the studies included in this review TMS checklist scores indicate moderate methodological quality (mean 66%, SD 9%, range 38–75%). Improvements in the methodological quality of TMS measurement may improve the ability to detect changes in response to the intervention. Whilst we have touched on the importance of reducing intra- and inter-individual variability by controlling for modifiable factors within study designs and addressing non-modifiable factors as covariates, future research should also consider methods to further minimize trial to trial MEP variability. This variability is believed to be linked to continuous fluctuation in cortical activity rather than noise in the signal[365]. One way to potentially minimize this variability in TMS measurement is by delivering real time electroencephalogram (EEG) triggered TMS. Synchronising each TMS pulse with specific sensorimotor oscillatory phases in alpha bands of EEG signals enables consistency in the delivery of the stimulus, and in turn reduces variability in trial-to-trial MEPs[366,367]. This method may provide a more comprehensive understanding of the effect of the intervention on CME.

The use of resting MEPs as an outcome measure likely creates a selection bias by favouring people with stroke with less severe impairment. Future research should aim to investigate a more heterogeneous sample, inclusive of people with moderate to severe disability, which would be more reflective of the population of interest. TMS measurements during a voluntary contraction, or functional activity such as treadmill walking, may be best suited to this patient population. Furthermore, whilst studies which investigate CME provide insight into the neurophysiological effects of PAS, we cannot extrapolate this effect to behavioral changes such as improved motor performance. Therefore, it is essential to consider pertinent behavioral measurement tools that can ascertain the cumulative effects of lower limb PAS on motor performance in patient populations, before considering the translation of lower limb PAS into clinical practice.

4.6.8 Strengths and limitations

This is the first systematic review to determine the efficacy of PAS on lower limb CME in healthy and stroke populations. In doing so, the review provides a detailed synthesis of the

literature by explicitly considering the influence of stimulation parameter selection and methodological quality of the research.

There are a number of limitations to this review. Firstly, whilst a comprehensive set of search terms were predefined and piloted to ensure maximal retrieval, pertinent literature may have been overlooked. It is possible that publication bias may account for some of the effects reported. Secondly, it was not possible to obtain all outcome data and their variance estimates, requiring changes in CME to be interpreted from graphical representations. These approximations may have resulted in inaccuracy. Thirdly, this review does not include a meta-analysis; until the body of evidence grows in methodological rigor, it is not possible to combine studies statistically. Future robust randomized controlled trials are required to confirm the efficacy of lower limb PAS on CME in healthy and stroke populations, and to determine the influence of stimulation parameter selection.

4.6.9 Future recommendations

The studies reviewed provide moderate-to-poor quality evidence that a single session of lower limb PAS can modulate CME in healthy and stroke populations for up to an hour. There is insufficient evidence for the optimal stimulation parameter settings. In order to advance our understanding of the therapeutic value of lower limb PAS interventions in stroke rehabilitation, future research should:

1. Improve methodological rigor by making comparisons with a control group, performing power calculations, reducing selection bias, blinding participants and assessors, and controlling for confounding variables.

2. Take a systematic approach to testing the efficacy of different PAS stimulation parameters: ISI; number of pairings; pairing frequency; TMS intensity and waveform; PES frequency and pulse width; electrode location; and the target muscle state.

3. Consider individualizing ISIs based on SEP latencies, as per evidence from moderate quality studies[296,320].

4. Consider how the muscle contraction state during MEP measurement influences the ability to detect a significant effect, and consider testing MEPs under multiple conditions (resting, active, and functional muscle states).

5. Explicitly report methods to control confounding variables during CME measurement and undertake measurement procedures according to best practice[41,309].

6. Include behavioral measures (i.e., motor performance) and consider investigating the cumulative effects of PAS in patient populations.

7. Define a statistical analysis plan a priori and ensure that all results are presented. Report whether absolute and relative changes in CME are used for statistical analysis. To facilitate the synthesis of studies, raw data should be presented. Clearly identify any secondary exploratory analyzes.

8. Measure CME at multiple post-intervention time points but avoid analyzing multiple time points together. This will facilitate our understanding about the time-course of neuromodulatory effects. From a neurorehabilitation perspective, this knowledge will allow researchers and clinicians to consider how PAS might be best integrated with standard rehabilitation to take advantage of the window of excitation.

4.7 Conclusion

This systematic review critically assessed the efficacy of PAS on lower limb CME in healthy and stroke populations, whilst explicitly considering methodological rigor and stimulation parameter selection. Findings from this review suggest lower limb PAS requires further investigation before considering its translation into stroke rehabilitation. There is moderate-to-poor quality evidence to support the efficacy of a single session of lower limb PAS to modulate CME in healthy and stroke populations. Stimulation parameter selection appears to influence efficacy, but robust conclusions are hindered by a lack of high-quality studies that systematically compare different PAS-delivery methods employed across studies. To advance our understanding in the field, we propose eight key recommendations for the design of future research.

4.8 Ethics statement

Ethical approval and consent were obtained in all the individual studies that were included in this review.

4.9 Author contributions

GA, DT, and NS conceptualized the study. GA performed the search strategy, extracted study data, and critically revised and wrote the manuscript with contributions from SO. GA and NS independently screened articles for eligibility and independently completed quality check lists for included articles. GA, NS, SO, and DT contributed to the

interpretation of the results, read and approved the final manuscript. NS edited the manuscript. NS and DT carried out a critical revision of the manuscript.

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4.11 Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.12 Acknowledgements

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The double lines represent the end of the published manuscript.

4.13 Summary

The findings of this systematic review identified evidence of moderate-to-poor quality that a single session of lower limb PAS modulates corticomotor excitability in healthy and stroke populations. While the selection of intervention stimulation parameters appears to influence efficacy, the stimulation parameters used across experiments varied significantly, and few studies systematically compared stimulation parameters within experiments. The ISI was the stimulation parameter that received the greatest attention. Individualising ISIs based on SEP latencies may enhance corticomotor excitability, according to research of moderate quality. However, in a clinical setting, this method is likely impractical for determining the optimal ISI for the exciteBCI intervention[64].

Chapter 5. Investigating the Intervention Parameters of Endogenous Paired Associative Stimulation (ePAS)

5.1 Prologue

Based on the narrative and systematic reviews presented in Chapters 2 and 3 respectively, it was determined that there is limited evidence to inform the selection of exciteBCI intervention parameters. This chapter presents the findings from a factorial study design which investigated the interaction effects of ePAS intervention parameters, stimulation intensity and movement type.

This published manuscript relates to the following thesis objective:

Objective 1: Optimise the stimulation parameters of the ePAS intervention by:

(ii) Investigating ePAS intervention efficacy when stimulation intensity and movement parameters are manipulated.

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Minor formatting adjustments have been made to the published manuscript to ensure uniformity throughout the thesis. Supplementary materials associated with this publication can be found in Appendix B. These include TMS checklist scores, a detailed account of the statistical analysis plan, and all primary and secondary results tables.

Link to the original publication https://www.mdpi.com/2076-3425/11/2/224/htm

Investigating the intervention parameters of endogenous paired associative stimulation (ePAS)

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5.2 Abstract

Advances in our understanding of neural plasticity have prompted the emergence of neuromodulatory interventions, which modulate corticomotor excitability (CME) and hold potential for accelerating stroke recovery. Endogenous paired associative stimulation (ePAS) involves the repeated pairing of a single pulse of peripheral electrical stimulation

(PES) with endogenous movement-related cortical potentials (MRCPs), which are derived from electroencephalography. However, little is known about the optimal parameters for its delivery. A factorial design with repeated measures delivered four different versions of ePAS, in which PES intensities and movement type were manipulated. Linear mixed models were employed to assess interaction effects between PES intensity (suprathreshold (Hi) and motor threshold (Lo)) and movement type (Voluntary and Imagined) on CME. ePAS interventions significantly increased CME compared to control interventions, except in the case of Lo-Voluntary ePAS. There was an overall main effect for the Hi-Voluntary ePAS intervention immediately post-intervention ($p = 0.002$), with a sub-additive interaction effect at 30 min' post-intervention ($p = 0.042$). Hi-Imagined and Lo-Imagined ePAS significantly increased CME for 30 min post-intervention ($p = 0.038$ and $p = 0.043$ respectively). The effects of the two PES intensities were not significantly different. CME was significantly greater after performing imagined movements, compared to voluntary movements, with motor threshold PES (Lo) 15 min post-intervention ($p = 0.012$). This study supports previous research investigating Lo-Imagined ePAS and extends those findings by illustrating that ePAS interventions that deliver suprathreshold intensities during voluntary or imagined movements (Hi-Voluntary and Hi-Imagined) also increase CME. Importantly, our findings indicate that stimulation intensity and movement type interact in ePAS interventions. Factorial designs are an efficient way to explore the effects of manipulating the parameters of neuromodulatory interventions. Further research is required to ensure that these parameters are appropriately refined to maximise intervention efficacy for people with stroke and to support translation into clinical practice.

Keywords: Paired associative stimulation; movement related cortical potential; neuromodulation; neural plasticity; rehabilitation (MeSH); stroke (MeSH); factorial design; linear mixed regression

5.3 Introduction

Advances in our understanding of neural plasticity have prompted the emergence of non-invasive neuromodulatory interventions[43]. These interventions have the potential to facilitate adaptive neural plasticity in partially disrupted neural networks and promote motor recovery following neurological injury such as stroke[368]. Paired associative stimulation (PAS) is an example of a non-invasive neuromodulatory intervention that is based on the principles of Hebbian-associative plasticity[133,234]. PAS involves the repeated temporal pairing of two stimuli, usually a single pulse of electrical stimulation to a peripheral nerve with a single pulse of transcranial magnetic stimulation (TMS) over the

contralateral primary motor cortex (M1)[46]. PAS induces a rapid change in corticomotor excitability (CME) of the corticomotor projections from the M1 to the target muscle. The inter-stimulus interval (ISI) of the paired stimuli influences whether CME is increased or decreased[46,48]. (For reviews see[223,225,369]). The literature has proposed that these effects resemble spike-timing-dependent neural plasticity[138-142].

In contrast to PAS, endogenous paired associative stimulation (ePAS) is an intervention that substitutes the exogenous TMS stimulation with an endogenous movement-related signal. This endogenous signal is derived from electroencephalography (EEG) and is known as the movement-related cortical potential (MRCP). The MRCP is a slow negative potential observed during the preparation and execution of both imagined and voluntary movements[51,52]. The MRCP commences approximately 1.5–2 s prior to and peaks around the onset of movement[51,52]. When the MRCP is produced in response to externally-cued movements (i.e., where there are two contingent cues, a "Warning" and a "Go" cue), it is also referred to as the contingent negative variation (CNV) [237]. Multiple cortical and subcortical neural substrates give rise to the generation of the MRCP; these include the supplementary motor area, cingulate motor areas, premotor cortex, prefrontal cortex, primary motor cortex, primary somatosensory cortex, thalamus, basal ganglia, and cerebellum[51,52,236,238,239]. Whilst the MRCP neural substrates are similar for the generation of externally-cued and self-paced movements, the literature suggests that the dorsal premotor cortex plays a critical role in externally-cued movements compared to those that are self-paced[240].

Typically, ePAS involves the repeated pairing of a single pulse of electrical stimulation to a peripheral nerve with the MRCP, such that the peripheral afferent stimulus arrives during the peak negativity (PN) of the MRCP[53,54]. Like PAS, there is some suggestion that the neuromodulatory effects of ePAS are dependent on the ISI, because CME is increased when the peripheral afferent stimulus is hypothesised to arrive in the M1 during the PN of the MRCP[53]. A single session of ePAS has been shown to increase CME for up to 60 min post-intervention in healthy participants performing imagined movement[53-58] and up to 30 min post-intervention in people with subacute[59] and chronic stroke[60] attempting voluntary movement. Improvements in motor function[59,61] and locomotor abilities have also been noted following ePAS interventions in people with chronic stroke[60].

Previous research has shown that ePAS can be delivered with various combinations of afferent stimulation (peripheral nerve stimulation, muscle stimulation, robotic-assisted passive movement) and endogenous motor activation (imagined or voluntary movement).

To date, there has been little systematic exploration of the most effective method of delivering ePAS[53,62,63,251]. Given its potential to promote neural plasticity following stroke, identifying the most effective way in which to deliver the ePAS intervention is an important step prior to its translation into clinical populations and implementation in clinical practice.

Two intervention parameters that may influence the effectiveness of ePAS are (1) the peripheral electrical stimulation (PES) intensity and (2) the movement type: voluntary or imagined. With regards to PES intensity, research to date has delivered ePAS with the electrical stimulation set to motor threshold[53-56,59,251] or at 110% of the motor threshold[58]. However, neuroimaging and neurophysiological research that has investigated PES alone suggests that stimulation delivered above motor threshold (suprathreshold) is more likely to result in increased CME, compared with stimulation delivered at or below the motor threshold[254,256,370,371]. Therefore, it seems reasonable to investigate whether ePAS is more effective when delivered using suprathreshold PES compared to motor threshold PES. With regards to movement type, ePAS research in healthy participants has largely utilised an MRCP derived from imagined movement as the endogenous signal[53-57,251]. Whilst there are similarities in cortical activation between voluntary and imagined movement[264], voluntary movement calls upon more complex cortical networks[267], whereas imagined movement engages inhibitory networks to prevent the occurrence of voluntary movement[265,266]. Imagined movements generate lower levels of cortical activation compared to voluntary movements, as evidenced by MRCPs with lower amplitudes[241,243], lower levels of M1 activation on neuroimaging, and reduced CME[268-273]. When considering translation into clinical populations, it is also worth noting that motor imagery skills are often limited in people with stroke[265]. Furthermore, unlike voluntary movements, imagined movements do not provide internal feedback on performance, which is crucial for motor learning[260]. In light of this literature, it is vital to investigate whether ePAS delivered during voluntary movement yields larger increases in CME than ePAS delivered during imagined movements.

When exploring the effect of manipulating both PES intensity and movement type, it is important to consider their interaction. The literature indicates that greater increases in CME are seen when PAS or PES is combined with voluntary movement rather than with no movement[296,371-373]. Additionally, PES or PAS combined with voluntary movement is more effective than voluntary movement alone[372-374]. This suggests that the two parameters (electrical stimulation and movement type) may interact with one another to produce an

enhanced or additive effect on CME. This might indicate that during ePAS, manipulating either PES intensity or movement type could individually influence intervention efficacy, and that manipulating both parameters together may produce an even greater effect. If the combined effect of suprathreshold PES + voluntary movement is greater than the addition of the two individual effects alone, this would be considered 'super-additive'. It is possible that the delivery of ePAS using suprathreshold stimulation and voluntary movement might yield a super-additive effect.

The primary aim of this study was to investigate whether ePAS delivered using single pulses of suprathreshold PES, paired with MRCPs produced during voluntary ankle dorsiflexion movements, would yield a super-additive increase in CME in healthy adults, and whether this effect would be maintained for 45 min post-intervention. The secondary aims of this study were to investigate whether (a) ePAS using suprathreshold PES paired with voluntary dorsiflexion movement would yield the greatest effect on CME compared to all other interventions, (b) ePAS interventions that delivered suprathreshold PES intensities would yield greater effects on CME than those that delivered motor threshold PES or did not deliver PES (control), and (c) ePAS interventions that involved voluntary dorsiflexion movements would yield greater effects on CME than those involving imagined movements.

5.4 Method

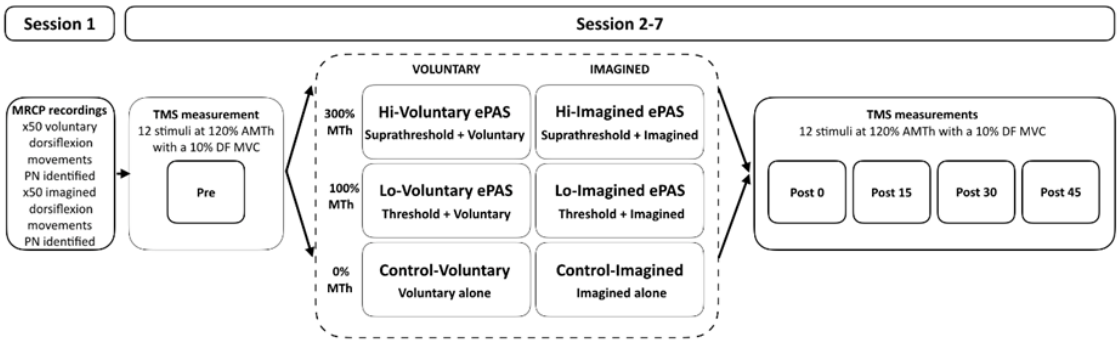
5.4.1 Study design

This study employed a factorial design comprising six interventions with repeated measures (refer to Figure 5.1). Factorial designs provide an efficient method to investigate the interaction effects of treatment parameters (in this case stimulation intensity and movement type) and differentiate them from super-additive, additive or sub-additive treatment effects[375]. A super-additive effect indicates that the combination is greater than the additive effects of the two treatment parameters alone. A sub-additive effect indicates that the combination is less than the additive effects of the two treatment parameters alone.

Participants completed a baseline testing session where their MRCP was recorded during both voluntary and imagined ankle dorsiflexion movements. This was followed by six intervention sessions, which were completed in a randomised order and separated by at least 48-hours. Randomisation was restricted so that no two sequences were identical. Interventions included (1) Hi-Voluntary ePAS: suprathreshold PES and voluntary dorsiflexion (2) Hi-Imagined ePAS: suprathreshold PES and imagined dorsiflexion (3) Lo-

Voluntary ePAS: motor threshold PES and voluntary dorsiflexion (4) Lo-Imagined ePAS: motor threshold PES and imagined dorsiflexion (5) Control-Voluntary: voluntary dorsiflexion alone and (6) Control-Imagined: imagined dorsiflexion alone. TMS-derived measures of CME were recorded using single pulse TMS immediately before and at 0, 15, 30 and 45-minutes following each intervention by a blinded assessor.

Figure 5.1 Schematic illustration of the factorial study design with six intervention conditions



MRCP, movement-related cortical potential; DF, dorsiflexor; PN, peak negativity; TMS; transcranial magnetic stimulation; AMTh, active motor threshold; MTh motor threshold; MVC, maximum voluntary contraction.

5.4.2 Sample size calculation

The study was powered to detect a super-additive effect size of 130μV, corresponding to a Cohen's effect size of 0.55 for the primary hypothesis. Simulations were predicated on the most relevant available literature[296], where TMS-derived measurements were recorded from a resting muscle and expressed as mean motor evoked potential (MEP) amplitudes. Simulations assumed a within-participant correlation ranging between 0.35 and 0.85, and a standard deviation (SD) at baseline of 0.23. To achieve statistical power of 80%, 25 participants were required to participate in all six interventions.

5.4.3 Participants

Healthy adults aged over 18 years with no known neurological conditions volunteered for the study. Participants were excluded if they were taking medications that may have affected central nervous system excitability. Prior to the study, all participants completed a TMS screening eligibility questionnaire[49] and provided written consent. Participants were asked to abstain from strenuous exercise and caffeine consumption prior to data collection. The study was approved by the Auckland University of Technology Ethics Committee

(15/270) and took place at the Health and Rehabilitation Research Institute at Auckland University of Technology, Auckland, New Zealand.

5.4.4 Experimental set-up and procedures

Session 1

MRCP recordings

During session 1, MRCPs were derived from the EEG recorded during 50 repetitions of visually-cued voluntary ankle dorsiflexion movement and 50 repetitions of visually-cued imagined ankle dorsiflexion movement. The order of these two recordings was pseudo-randomised and separated by a 10-minute rest period. Participants were seated with approximately 100° of hip flexion and the legs supported in 25° knee flexion with the ankles in a relaxed, slightly plantarflexed position. A 40 channel EEG cap (Quik-cap, Ag/AgCl electrodes Compumedics, Neuroscan, Dresden, Germany) was positioned with the CZ electrode positioned halfway between the nasion and the inion, and halfway between each tragus. A sterile blunt needle was used to lightly abrade the scalp and administer conductive gel to the FP1, F3, FZ, F4, C3, CZ, C4, P3, PZ, P4 electrodes (according to the international 10-20 system). A reference electrode was positioned over the mastoid process and a ground electrode on the forehead. Impedance of less than 5kΩ was maintained.

Participants were familiarised with the visual cue displayed on a computer monitor that was customised in MATLAB software 7.13 (MathWorks, Inc., Natick, MA, USA, 2010). The visual cue prompted participants to; (1) focus on the screen, (2) prepare for the ankle movement by watching a moving cursor, (3) execute either a ballistic voluntary or imagined dorsiflexion movement with their right ankle at a specified time-point and hold for 1 second, and (4) rest. The length of focus and rest periods varied (2-3 seconds and 6-8 seconds respectively). Participants completed two sets of 25 repetitions for both voluntary and imagined movement conditions, while continuous EEG was recorded via a 40-channel EEG amplifier (NuAmps, Compumedics Neuroscan, Dresden, Germany) and sampled at 500 Hz with 32-bit accuracy (SCAN software, Compumedics Neuroscan, Dresden, Germany).

MRCP feature extraction

Continuous EEG signals were imported into MATLAB software 8.5 (MathWorks, Inc., Natick, MA, USA), where individual EEG channels were band-pass filtered from 0.05 to 5Hz with a second order zero-phase Butterworth filter. All channels excluding FP1 were spatially filtered using a large Laplacian filter to acquire a single virtual channel with CZ as the centre electrode[376]. The virtual channel was separated into 50, 4.5 second epochs (3 seconds before the cue to move and 1.5 seconds after)[53,56,62,251]. Each of the 50 epochs were visually inspected and manually rejected if there was no evidence of a progressive negative shift preceding the cue or if FP1 electrooculographic activity surpassed 70mV[53,56]. The remaining epochs were averaged, and the most negative point of the signal was selected as the PN.

Sessions 2-7

Each session was conducted at a similar time of day and sessions were separated by a minimum of 48 hours. Participants adopted the same seated position as described in session one. The six different interventions were dose matched (number of repetitions n = 50) and lasted approximately 15-minutes. Participants followed the same visual cue described in session 1.

Outcome measure - corticomotor excitability (CME)

The primary outcome measure was TMS-induced motor evoked potentials (MEPs) of the tibialis anterior (TA) muscle; this was assessed with single pulse TMS during a 10% maximal voluntary contraction (MVC) of the dorsiflexor muscles to provide an indication of CME[41]. MEPs were recorded pre-intervention, and at 0, 15, 30 and 45-minutes post intervention. TMS procedures were replicated at each of the six sessions as per the International Federation of Clinical Neurophysiology (IFCN) guidelines[41].

For recording MEPs, electromyography (EMG) surface electrodes (Blue sensor N, Ambu, Ballerup, Denmark) were placed over the muscle belly of the right TA muscle and a reference electrode over the right tibia based on SENIAM guidelines[377]. Prior to EMG electrode placement, the skin was shaved, abraded, and cleaned with alcohol to reduce impedance. If impedance exceeded 5kΩ, skin preparation and electrode placement was repeated.

Prior to CME measurements, each participant's dorsiflexor MVC was established. Fastening belts were secured around the right foot and ankle and both hips to maintain a stable position. Participants were instructed to dorsiflex their right ankle as hard as possible for 3-5 seconds and were provided with loud vocal encouragement and continuous visual feedback via an oscilloscope (TDS014B, Tektronix, New Zealand). Participants performed three MVC contractions, each followed by a 2-minute rest. Isometric dorsiflexion force data was collected using a single axis load cell (Model PTASP6-E, Precision Transducers Limited, New Zealand, capacity 300kg and error <0.02%), sampled at 100Hz via a data acquisition board (Micro 1401, CED, Cambridge, UK) and processed using Signal software (CED, Cambridge, UK). The MVC was established by measuring the peak amplitude of the largest of the three trials and deducting the mean baseline value recorded at rest[310]. A 10% MVC value was then calculated. This level of contraction was used during TMS measurements based on its sensitivity to changes in motor-evoked potential (MEP) amplitude[378].

For the application of TMS, participants wore a fitted cap with 1 × 1cm gridlines relative to the vertex. Single pulse TMS was administered with a Magstim 200 using a monophasic pulse and posterior-anterior current flow[41] via a double cone coil (10cm outer diameter per wing, Magstim Company Limited, Dyfed, UK), as per recommendations for lower limb M1 stimulation [246]. Initially the junction of the coil was positioned approximately 0.5-1cm lateral to CZ[248,379]. Stimulation intensity was initially delivered at 30% of the stimulator output and increased in increments of 5%. The coil position was systematically adjusted to determine the 'hotspot' which was defined as the location where the largest TA MEP was induced at the lowest stimulation intensity. Grid references for the hotspot were recorded to maintain accurate positioning of the coil in subsequent applications. Participants were then required to generate a 10% dorsiflexor MVC that matched a visual target on an oscilloscope, during which the active motor threshold (AMT) was established; the AMT was defined as the lowest stimulus intensity required to produce a minimum of five TA MEPs out of ten stimuli with peak-peak amplitudes of >100μV[41]. At each measurement time-point, 12 single pulse TMS stimuli were delivered at 120% of AMT during a 10% MVC. Stimuli were delivered every 6-8 seconds and participants were encouraged to focus their attention on the oscilloscope target. TA EMG data were amplified to 1000 Hz (AMT-8, Bortec Biomedical, Canada), and sampled at 2000 Hz via a data acquisition board (Micro 1401, CED, UK) and Signal software (CED, Cambridge, UK). The methodological quality of the TMS measurement procedures for this study were evaluated in accordance with the TMS Quality Checklist [60] and are reported in supplementary material (see Appendix B.5).

ePAS interventions

The peripheral electrical stimulation (DS7A, Digitimer Limited, Hertfordshire, UK) was applied via two additional surface electrodes (Blue sensor N, Ambu, Ballerup, Denmark) that were positioned on the skin over the right deep common peroneal nerve (dCPN), approximately 2-4cm anteriorly and inferiorly to the head of fibula, with the cathode placed proximally. The optimal stimulation location was determined by palpating for TA tendon movement without the presence of palpable synergistic and antagonistic activity[56,62,251]. Once the optimal location was identified, the motor threshold (MTh) was determined: this was defined as the lowest stimulation intensity (mA) required to elicit a palpable flicker in the TA tendon[56,62].

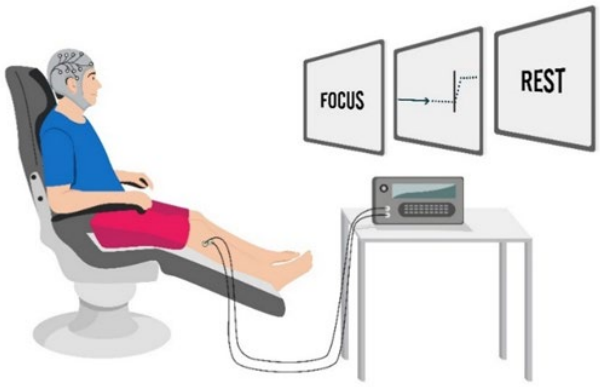
The level of suprathreshold PES intensity was established from pilot work. It was deemed important to select a tolerable PES intensity to minimise antidromic effects that could negatively influence the intervention[380]. A visual analogue scale (VAS) was utilised to rate discomfort of various PES intensities and piloting indicated that an intensity of 300% MTh did not exceed a rating of 5/10 (n = 5, mean intensity 33mA, mean VAS 4/10). Of the four ePAS interventions, two interventions Hi-Voluntary and Hi-Imagined delivered a PES intensity at 300% of MTh to elicit a substantial TA muscle contraction. The other two interventions Lo-Voluntary and Lo-Imagined delivered a PES intensity at 100% of MTh to elicit a palpable flicker in the TA tendon (see Figure 5.2).

During the delivery of ePAS, participants completed 50 repetitions of either voluntary or imagined movement, while 50 single pulses (1ms) of PES were delivered to the dCPN. Each 1ms PES pulse was delivered 50ms prior to the PN of the participant's average MRCP for the corresponding movement condition. The 50ms represents the average conduction time from the dCPN to the M1[53].

Control interventions

For the two control interventions (Control-Voluntary and Control-Imagined), participants performed either 50 visually-cued voluntary dorsiflexion movements, or 50 visually-cued imagined dorsiflexion movements, of the right ankle. Sham PES was delivered concurrently (set to 0% MTh). An illustration of the laboratory set-up is displayed in Figure 5.2.

Figure 5.2 Intervention set-up



Participants observed the visual cue to prompt the timing of either voluntary or imagined dorsiflexion whilst receiving either suprathreshold (300%) stimulation, motor threshold stimulation (100%), or no stimulation (0%) to the right deep common peroneal nerve.

5.4.5 Data processing and analysis

TA EMG data was processed using Signal software (CED, Cambridge, UK). A predefined processing criterion was established to address contaminated EMG responses at each of the measurement time-points and is provided in supplementary material (see Appendix B.6). Less than 5% of the EMG data was discarded. CME outcomes were processed using a customised script developed in MATLAB 2015a to identify four MEP parameters: (1) absolute MEP amplitude (μV); (2) absolute MEP area (μV/ms); (3) relative MEP amplitude (% change) and; (4) relative MEP area (% change). The decision to investigate MEP area was based on literature that suggests it may be more sensitive to changes due to the polyphasic nature of MEPs in the lower limb[381,382]. The decision to investigate both absolute and relative MEP data was consistent with a number of previous neuromodulation studies[58,369]. Absolute MEP amplitude values were established by extracting the peak-peak amplitude of each individual MEP observation. Absolute MEP area values were established by measuring the area of rectified EMG activity of each individual MEP for 30ms, starting 2ms before its onset. MEP onset was defined as the first point where EMG activity exceeded 2 standard deviations of mean background EMG activity for more than 2ms on an averaged waveform for each measurement time-point. The background area was established by rectifying individual EMG signals and calculating the area of a 70ms window that terminated 2ms prior to the stimulation artefact. Individual MEP amplitudes and areas were used for the absolute MEP statistical analysis. For the

relative MEP analysis, the individual MEP amplitudes and areas were averaged, to give a mean MEP for each participant at each time point. Relative MEP amplitude and MEP area % change values were calculated as follows [(post-pre)/pre] x100.

5.4.6 Statistical analysis

A detailed account of the pre-specified statistical analysis plan is provided in the supplementary material (see Appendix B.7). The inferential framework selected for the primary and secondary analysis was linear mixed regression modelling, which provides greater statistical efficiency and minimises the risk of type-I error compared to a repeated measures ANOVA[276]. The large size of the data sets (>7800 individual MEP observations in the absolute MEP data and >580 observations in the relative MEP data) renders concerns of non-normality of the residuals secondary, in spite of the dependence between the observations, if we extend the arguments of Lumley and colleagues regarding linear regression to linear mixed regression[383]. Analyses were carried out using package *lme4*[384] in R (R Core Team) and SAS/STAT™ software. A blind review was carried out to identify covariates for adjustment and the covariance structure of potential models. Baseline covariates MVC and AMTh were tested for adjustment in the models (using blinded treatment codes to adjust for treatment) and using a 5% significance threshold to decide on inclusion. Absolute and relative pre-intervention MEP amplitude and MEP area values were also tested in the same manner. The blind model selection was based on Akaike's information criterion[385]. An assessment of residual covariance structure and heteroscedasticity across the blind intervention groups in the retained models was also carried out. Missing data was assumed to be missing at random, under this assumption the linear mixed regression analysis adequately allayed selection bias from missing data[386]. The actual models retained for the analysis were the versions of the blind models with an interaction term between movement type and stimulation intensity to address the primary hypothesis. For the analysis of absolute datasets, the model was identical for both MEP amplitude and MEP area data. A decision was made *a priori* to refrain from applying corrections of adjustment for multiplicity due to the explanatory nature of this study[387]. Type III errors for terms and interactions were obtained against a null hypothesis that set to zero all higher-order interactions involving the target term or interaction. Mean MEP effect sizes (μV and μV/ms); and 95% confidence intervals were also calculated. Means and standard deviations are reported as mean ± SD for participant characteristics, MRCP data and PES intensities. Processing and analysis of relative MEP data are reported in supplementary material (see Appendix B.7).

5.5 Results

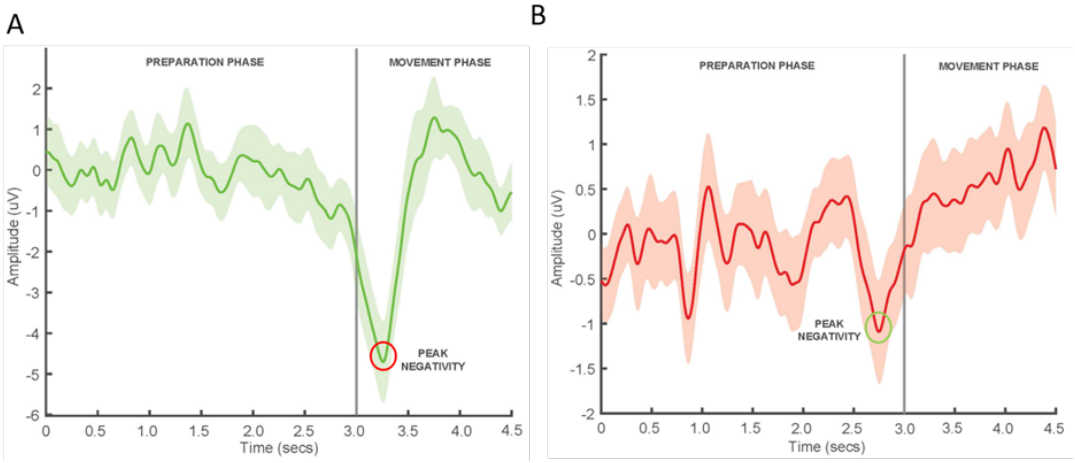
5.5.1 Patient characteristics

The mean age of the 25 participants was 28 ± 7 years (range 19–52), and 15 participants were female. Three potential participants were excluded from the study, one due to a recent skull fracture and two due to routinely taking medication that may have altered excitability of the central nervous system.

5.5.2 MRCP

During the processing of the 50 MRCP epochs, on average, 5 ± 2 and 9 ± 6 epochs, for voluntary and imagined movement conditions, respectively, were manually rejected due to eye blinks or artefacts. The timing of the PN of the averaged MRCP occurred at a mean of 13 ± 67 ms after the cue in the voluntary movement condition and 4 ± 155 ms after the cue in the imagined condition. Figure 5.3 provides examples of averaged MRCPs with 95% confidence intervals obtained from an individual performing voluntary ankle dorsiflexion (A) and imagined movement ankle dorsiflexion (B).

Figure 5.3 Average MRCPs with 95% confidence intervals obtained from one participant (A) performing voluntary ankle dorsiflexion and (B) performing imagined ankle dorsiflexion



The vertical line at the 3-second mark corresponds with the visual cue to move.

5.5.3 PES intensities (mA)

The dCPN PES was delivered at the following intensities during each of the four ePAS interventions: Hi-Voluntary 37 ± 18 mA, Hi-Imagined 33 ± 16 mA, Lo-Voluntary 14 ± 8 mA, and Lo-Imagined 11 ± 4 mA.

5.5.4 Baseline corticomotor excitability (CME)

Baseline raw MEP values for absolute MEP amplitude and MEP area are reported in Table 5.1.

Table 5.1 Baseline raw MEP values for absolute MEP amplitude and MEP area

	MEP amplitude (μV)	**MEP area (μV/ms)**
Mean	1730	7.2
Within SD	1060	4.6
Between SD	839	3.8

5.5.5 Study findings

Due to the explanatory nature of this study a large number of results were generated from the models. Within this paper we present the key findings, all other results are provided in the supplementary material (see Appendix B.8). The results for baseline covariates, model interactions and main effects for absolute MEP amplitude and absolute MEP area are provided in Table 5.2.

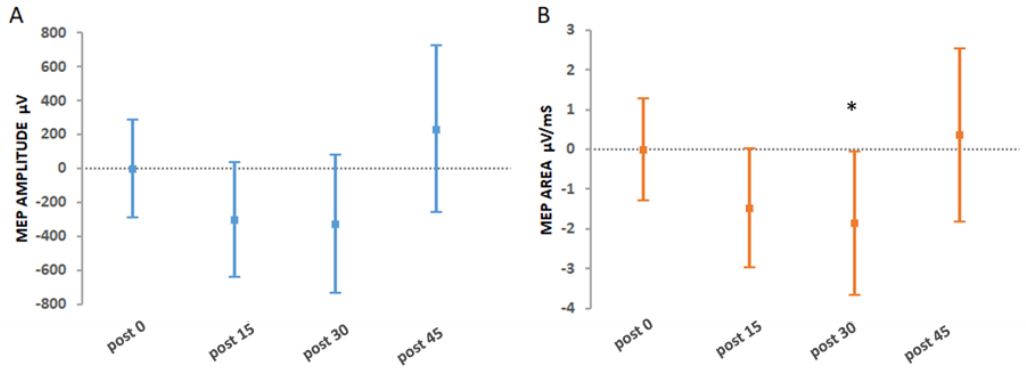
Table 5.2 Observed significance of baseline covariates, main and interaction effect estimates absolute MEP amplitude and MEP area

		MEP amplitude (μV)	*MEP area (μV/ms)*
	Numerator *df*	***P* value**	***P* value**
Baseline covariates			
AMTh	1	0.0001*	0.0001*
MVC	1	0.06	0.04*
Main effects and interactions			
Stimulation intensity	16	<0.00005*	<0.00005*
Movement type	12	0.002*	0.001*
Time	18	0.009*	0.0004*
Stimulation intensity x Movement type	8	0.0005*	0.0001*
Stimulation intensity x Time	12	0.002*	<0.00005*
Movement type x Time	9	0.001	0.002*
Stimulation intensity x Movement type x Time	6	0.0004*	0.0003*
Hi-Voluntary intervention			
Super/sub-additivity of suprathreshold stimulation overall, voluntary vs. imagined	8	0.0005*	0.0001*
Super/sub-additivity of suprathreshold stimulation vs. no stimulation and voluntary vs. imagined	4	0.0001*	<0.00005*
Super/sub-additivity of suprathreshold stimulation vs. threshold and voluntary vs. imagined	4	0.139	0.108
Lo-Voluntary intervention			
Super/sub-additivity of threshold stimulation vs. no stimulation and voluntary vs. imagined	4	0.0013*	0.0004*

Primary findings

The primary aim was to investigate whether Hi-Voluntary would yield a super-additive increase in CME, which was maintained for 45 min post-intervention. Table 5.2 presents the interactions for the effects of Hi-Voluntary whereby the statistical model with the interaction term (super- or sub-additivity) was compared to the statistical model with no interaction (additivity) for the levels of stimulation intensity and movement type. Figure 5.4 displays the results of the primary analysis for absolute MEP amplitude (μV) and absolute MEP area (μV/ms) at each post time-point.

Figure 5.4 (A) MEP amplitude and (B) MEP area adjusted estimates for the primary analysis investigating super- or sub-additivity effects for the Hi-Voluntary intervention at each post-intervention time-point



Error bars depict 95% CIs. * indicates significant effects (p <0.05).

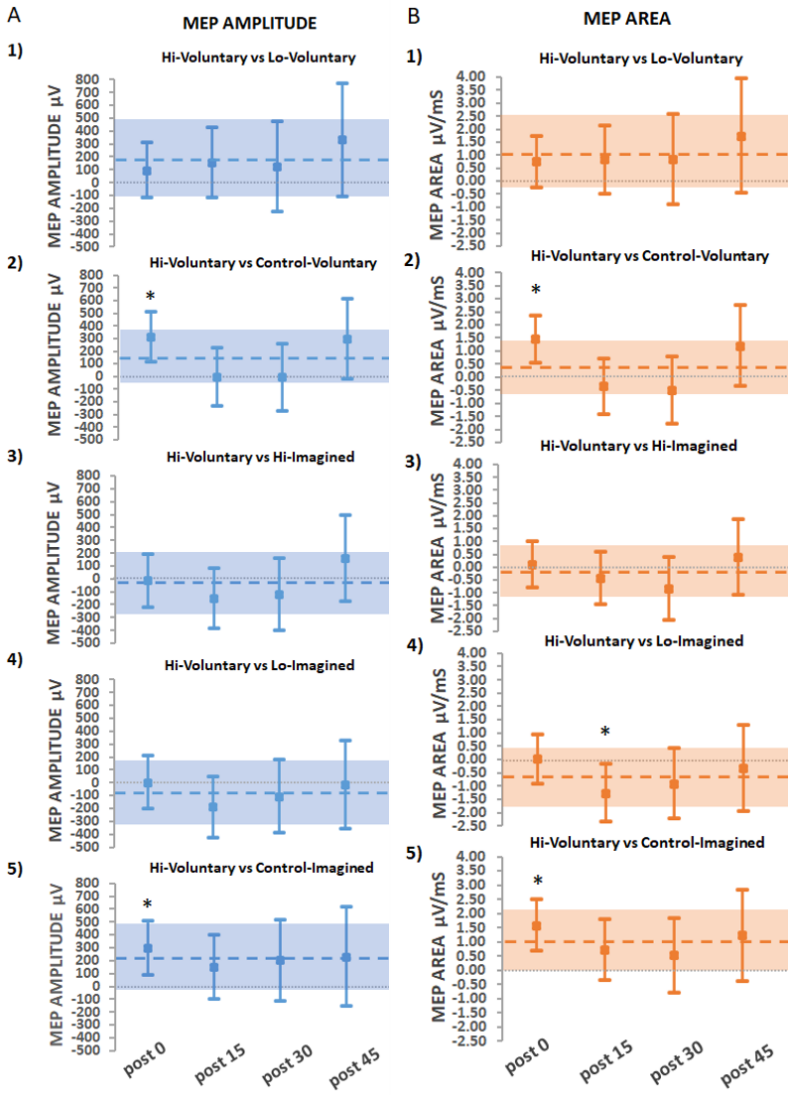
For the Hi-Voluntary intervention, the analysis revealed an interaction between suprathreshold stimulation intensity versus no stimulation and voluntary versus imagined movement for both absolute MEP amplitude (p = 0.0001) and MEP area (p < 0.00005). The analysis did not reveal a super-additive effect. However, a significant sub-additive effect was observed for absolute MEP area 30 min post-intervention (−1.87 µV/ms 95% CI [−3.68, −0.06], p = 0.042). There was no significant interaction for suprathreshold stimulation versus threshold stimulation and voluntary versus imagined movement for absolute MEP amplitude (p = 0.139) and MEP area (p = 0.108).

An unplanned post hoc analysis investigated whether Lo-Voluntary also had a sub-additive effect on CME. This analysis confirmed a significant interaction between threshold stimulation intensity (100% MTh) versus no stimulation (0% MTh) and voluntary versus imagined movement for absolute MEP amplitude (p = 0.0013) and MEP area (p = 0.0004). A significant sub-additive effect occurred at 15 min post-intervention for the absolute MEP amplitude (−505.6 µV 95% CI [−871.4, −139.8], p = 0.006) and MEP area (−3.21.6 µV/ms 95% CI [−4.9, −1.48], p = 0.0003). This sub-additive effect extended to 30 min post-intervention for absolute MEP area (−2.79 µV/ms 95% CI [−5.01, −0.57], p = 0.014).

Secondary findings: the effects of Hi-Voluntary compared to all other interventions

A secondary aim of the study investigated whether ePAS using suprathreshold PES paired with voluntary dorsiflexion movement (Hi-Voluntary) would yield the greatest increase in CME compared to all other interventions. These comparisons are illustrated in Figure 5.5 for absolute MEP amplitude (µV) and Figure 5.5 for absolute MEP area (µV/ms).

Figure 5.5 Estimated adjusted effect differences in absolute units between Hi-Voluntary and each intervention on (A) MEP amplitude and (B) MEP area, at each post-intervention time point and averaged over time



Error bars depict 95% CIs. Dashed lines depict averaged over time estimates with a shaded bar for 95% CIs. * indicates significant effects (p <0.05).

Absolute MEP amplitudes were significantly greater for Hi-Voluntary compared to Control-Voluntary immediately post-intervention (311 µV 95% CI [109, 511.8], p = 0.002) and when compared to Control-Imagined immediately post-intervention (295.5 µV 95% CI [87.37, 503.6], p = 0.005). Comparisons for Hi-Voluntary with each of the other ePAS interventions (Lo-Voluntary, Hi-Imagined, and Lo-Imagined) were non-significant at all time-points (p > 0.1 in all comparisons).

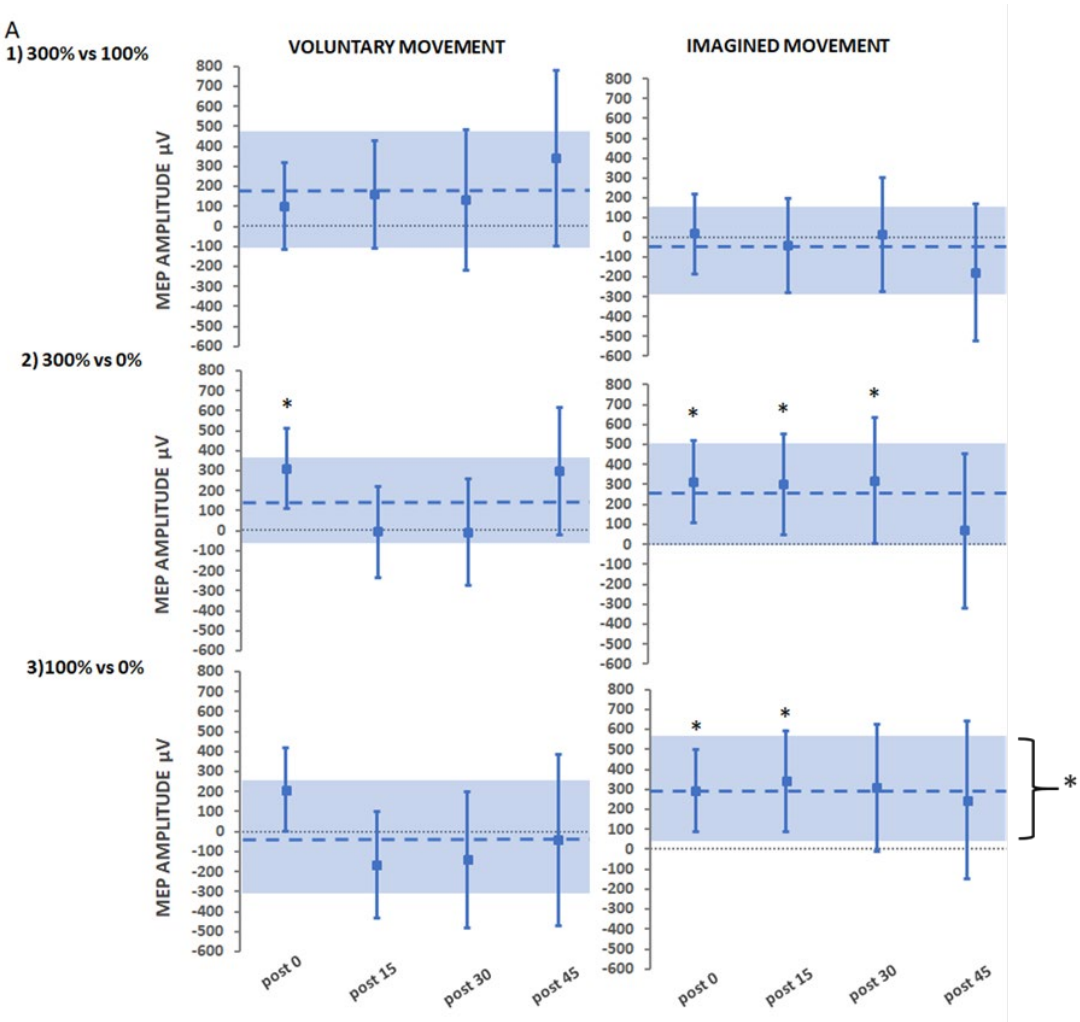
Results for absolute MEP area replicated those of absolute MEP amplitude, except in the case of Hi-Voluntary compared to Lo-Imagined, where a greater significant effect was

observed at 15 min post-intervention for the Lo-Imagined intervention (−1.28 μV/ms 95% CI [−2,37, −0.19], p = 0.021).

Secondary findings: stimulation intensity

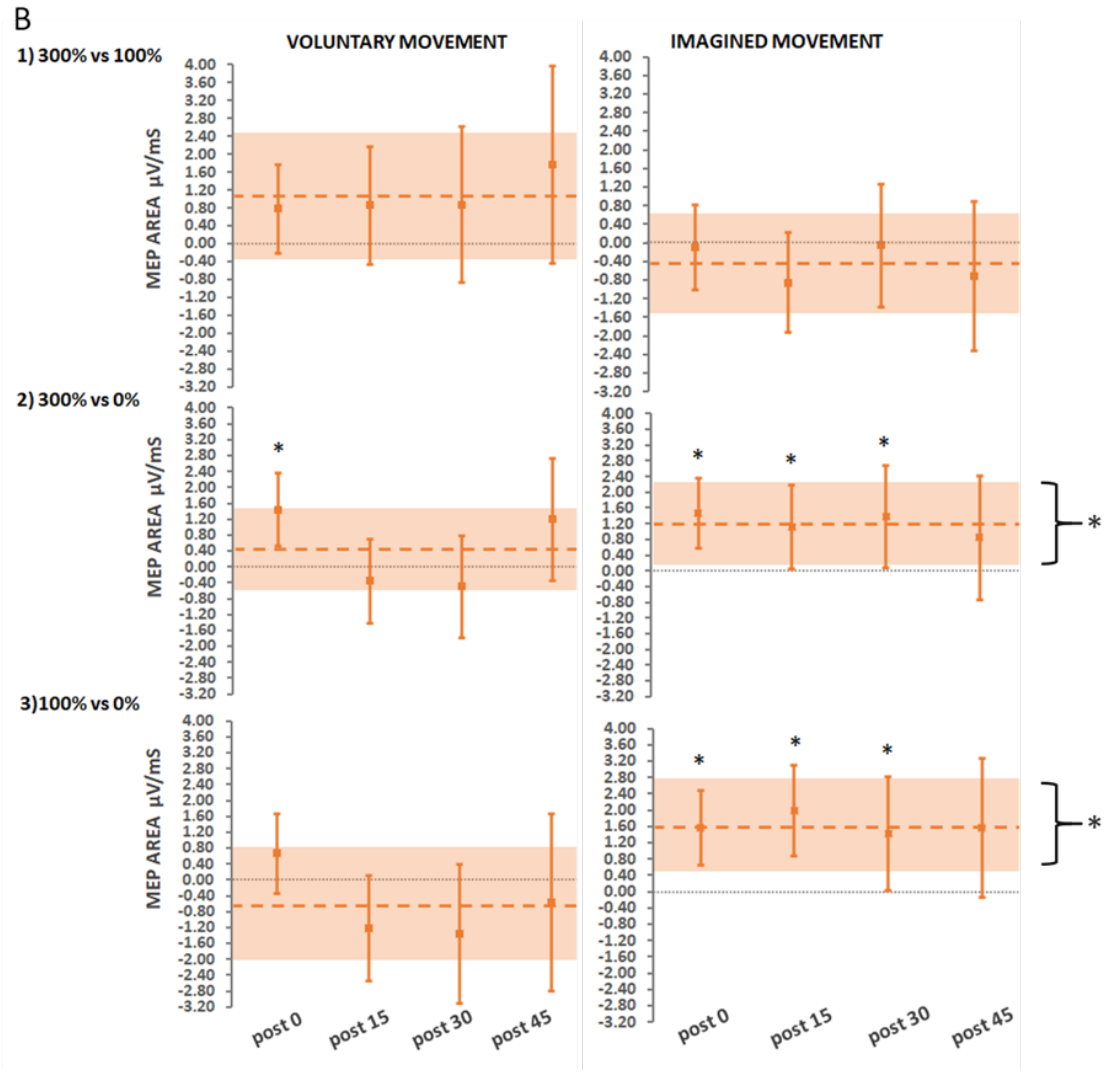
A further secondary aim of the study was to investigate whether treatment interventions that delivered suprathreshold PES intensities (Hi-Voluntary, Hi-Imagined) would yield greater increases in CME than those that delivered threshold intensities (Lo-Voluntary, Lo-Imagined) and no stimulation (Control-Voluntary, Control-Imagined). These comparisons are illustrated in Figure 5.6A for absolute MEP amplitude (μV) and Figure 5.6B for absolute MEP area (μV/ms).

Figure 5.6A Estimated adjusted effect differences between stimulation intensity levels delivered during voluntary movement and imagined movement on (A) MEP amplitude at each post-intervention time-point and averaged over time



Error bars depict 95% CIs. Dashed lines depict averaged over time estimates with a shaded bar for 95% CIs. * indicates significant effects (p <0.05).

Figure 5.6B Estimated adjusted effect differences between stimulation intensity levels delivered during voluntary movement and imagined movement on (B) MEP area, at each post-intervention time-point and averaged over time



Error bars depict 95% CIs. Dashed lines depict averaged over time estimates with a shaded bar for 95% CIs. * indicates significant effects ($p < 0.05$).

Suprathreshold stimulation (Hi) vs. threshold stimulation (Lo)

Comparisons for ePAS interventions delivered with suprathreshold compared to threshold stimulation for either voluntary or imagined movement conditions (Hi-Voluntary vs. Lo-Voluntary, Hi-Imagined vs. Lo-Imagined) were not significant for absolute MEP amplitude or MEP area ($p > 0.1$ in all comparisons).

Suprathreshold stimulation vs. no stimulation

Comparisons determined that absolute MEP amplitudes were significantly greater for Hi-Voluntary compared to Control-Voluntary immediately post-intervention only (311 μV 95% CI [109, 511.8], $p = 0.002$). For the imagined movement interventions, absolute MEP amplitudes were significantly greater for Hi-Imagined compared to Control-Imagined immediately (312 μV 95% CI [105.2, 518.8], $p = 0.003$), 15 min (299 μV 95% CI [47.35, 551.2], $p = 0.020$) and 30 min post-intervention (319 μV 95% CI [5.58,632.4], $p = 0.046$). Results for absolute MEP area replicated those of absolute MEP amplitude, except in the case of the averaged over time comparison that determined a significantly greater increase for Hi-Imagined compared to Control-Imagined (1.2 μV/ms 95% CI [0.14, 2.58], $p = 0.026$).

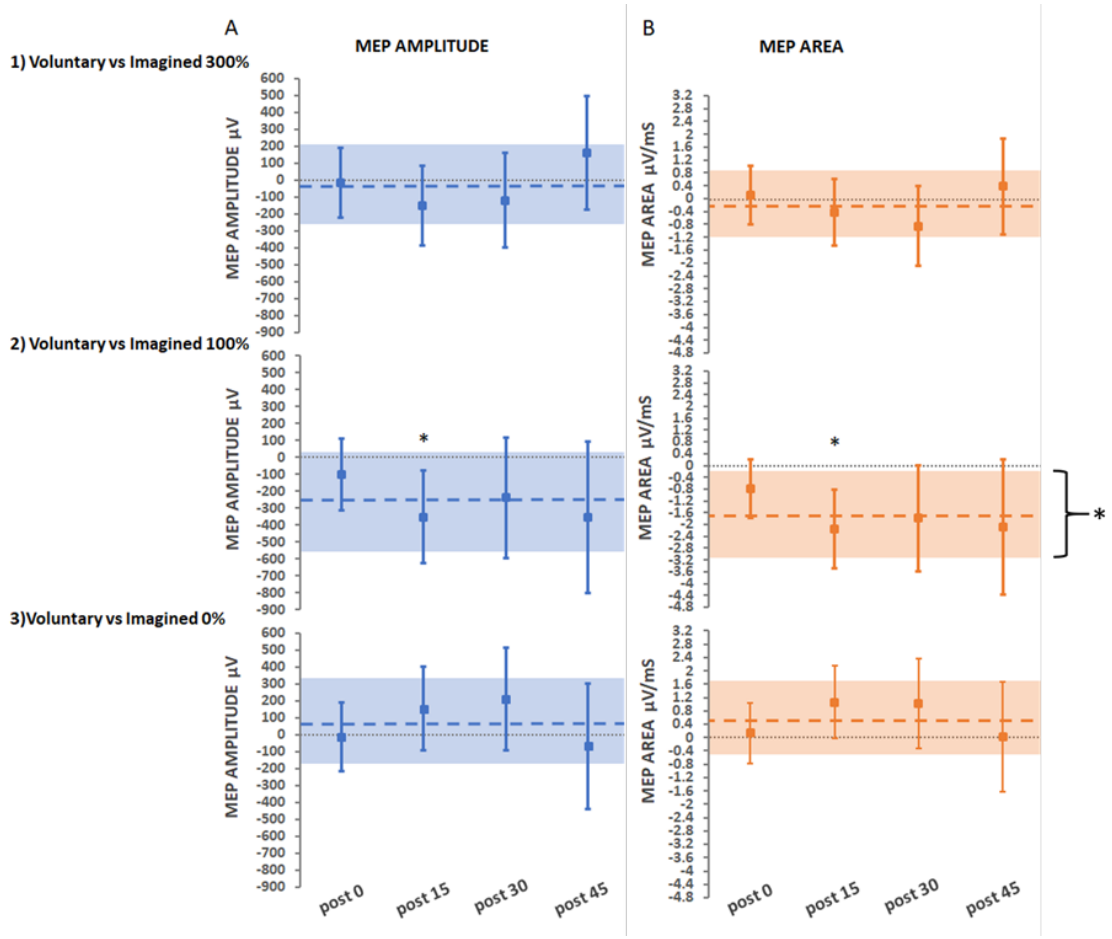
Threshold stimulation vs. no stimulation

There were no significant differences in absolute MEP amplitude for any of the comparisons made for Lo-Voluntary and Control-Voluntary ($p > 0.05$ in all comparisons). However, for Lo-Imagined, there were significant increases in absolute MEP amplitude when compared to Control-Imagined immediately post-intervention (295 μV 95% CI [89.6, 500.7], $p = 0.004$), 15 min post-intervention (339.9 μV 95% CI [86.28, 593.6], $p = 0.009$), and averaged over time (297 μV 95% CI [36.3, 558], $p = 0.026$). The results for absolute MEP area replicated those of absolute MEP amplitude, except in the 30 min post-intervention time-point comparison that revealed a significantly greater increase for Lo-Imagined compared to Control-Imagined (1.4 μV/ms 95% CI [0.03, 2.81], $p = 0.043$).

Secondary findings: movement type

The secondary aim was to investigate whether treatment interventions that involved voluntary dorsiflexion movement (Hi-Voluntary, Lo-Voluntary, Control-Voluntary) would yield greater increases in CME than treatment interventions that involved imagined movements (Hi-Imagined, Lo-Imagined, Control-Imagined). Comparisons made between voluntary and imagined movement at different intensities of stimulation are illustrated in Figure 5.7 for absolute MEP amplitude (μV) and absolute MEP area (μV/ms).

Figure 5.7 Estimated adjusted effect differences between voluntary and imagined movement at each stimulation intensity level on (A) MEP amplitude and (B) MEP area, at each post-intervention time-point and averaged over time



Error bars depict 95% CIs. Dashed lines depict averaged over time estimates with a shaded bar for 95% CIs. * indicates significant effects (p <0.05)

Voluntary vs. imagined movement at suprathreshold stimulation

Comparisons for the Hi-Voluntary and Hi-Imagined interventions were non-significant for absolute MEP amplitude and MEP area ($p > 0.1$ in all comparisons).

Voluntary vs. imagined movement at threshold stimulation

Comparisons determined that absolute MEP amplitude was significantly greater for Lo-Imagined compared with Lo-Voluntary at 15 min post-intervention only (−352 µV 95% CI [−626.2, −78.29], $p = 0.012$). The results for absolute MEP area replicated those of absolute MEP amplitude, except in the case of the averaged over time comparison that determined a significantly greater increase for Lo-Imagined compared to Lo-Voluntary (−1.7 µV/ms 95% CI [−3.18, −0.22], $p = 0.025$).

Voluntary vs. imagined movement with no stimulation

Comparisons for the Control-Voluntary and Control-Imagined interventions were non-significant for absolute MEP amplitude and MEP area ($p > 0.05$ in all comparisons).

5.6 Discussion

This ePAS study is the first to systematically unpack the effect of manipulating the parameters of stimulation intensity and movement type in an effort to enhance intervention efficacy prior to translation to clinical populations and implementation in rehabilitation practice. To support the discussion of the results, we first provide an overview of the main effects of the four ePAS interventions investigated and then focus on the primary hypothesis exploring the interaction effects of Hi-Voluntary ePAS. Following this, the interpretation of the interaction effects is supported by systematically exploring the effects of the two intervention parameters within the factorial design: PES intensity and movement type.

5.6.1 ePAS intervention efficacy

The ePAS interventions Hi-Voluntary, Hi-Imagined, and Lo-Imagined were all significantly more effective at increasing CME than their respective control interventions. These findings are in keeping with previous research investigations of Lo-Imagined ePAS interventions in healthy people[53-58]. This study extends those findings by demonstrating that Hi-Imagined and Hi-Voluntary ePAS interventions are also effective at increasing CME in healthy people. However, Lo-Voluntary ePAS was not more effective at increasing CME than Control-Voluntary. This finding is in contrast with a previous study that assessed the effect of a Lo-Voluntary intervention delivered just above the motor threshold (110% MTh)[58]. In that study, the intervention effects were not significantly different from the Control-Voluntary intervention immediately post-intervention, but they were significantly increased at 30 min post-intervention[58]. It is notable in our findings that the duration of the effect differed across ePAS interventions. In both the Hi-Imagined and Lo-Imagined interventions, an increase in CME was seen for up to 30 min post-intervention, whereas in the Hi-Voluntary intervention, the effect did not last beyond the immediate post-intervention time point. Previous research in Lo-Imagined ePAS interventions reported durations of effects lasting between 30 and 60 min post-intervention for both absolute and relative MEP amplitude data when recorded from a resting muscle[55-57,63]. Explanation for the differences between the four ePAS interventions in both the magnitude and duration of

effects are explored below through the interpretation of these findings in relation to both movement type and stimulation intensity.

5.6.2 Hi-Voluntary ePAS

The primary objective of this study was to investigate whether an ePAS intervention that paired suprathreshold PES with the MRCP during voluntary movement (Hi-Voluntary) would yield a super-additive increase in CME of the TA muscle in healthy adults for up to 45 min post-intervention. Our findings did not confirm this hypothesis. The MEP area analysis did reveal a significant interaction between stimulation intensity and movement type, illustrating a *sub-additive* effect at 30 min post-intervention. This finding suggests that the combination of suprathreshold stimulation and voluntary movement (Hi-Voluntary) produced a smaller increase in CME than the sum of these two parameters. Given that CME was significantly greater following Hi-Voluntary than following Control-Voluntary, it can be asserted that while the Hi-Voluntary intervention loses some of the effect of stimulation intensity and voluntary movement when paired, the intervention is more effective at increasing CME than performing voluntary movement alone (Control-Voluntary). A potential explanation for why we did not find a super-additive effect for the Hi-Voluntary intervention could be that the intervention parameters require further refinement and optimisation. Further work is required to fully elucidate the mechanisms of action of this intervention.

5.6.3 Stimulation intensity

For the secondary analyses of the factor 'stimulation intensity', it was hypothesised that interventions that delivered suprathreshold stimulation (Hi-Voluntary, Hi-Imagined) would yield greater increases in CME than those that delivered threshold PES (Lo-Voluntary, Lo-Imagined) or no stimulation (Control-Voluntary, Control-Imagined). This hypothesis was not supported, as there was no difference between suprathreshold and threshold stimulation. However, there were differences between stimulation (Hi-Voluntary, Hi-Imagined, Lo-Imagined) and no stimulation (Control-Voluntary, Control-Imagined).

The post hoc analysis investigating the interaction effect of the Lo-Voluntary intervention revealed that, akin to Hi-Voluntary, Lo-Voluntary had a *sub-additive* effect at some time-points post-intervention. It is notable that the magnitude of the sub-additive effect was greater for the Lo-Voluntary intervention than for the Hi-Voluntary intervention. In voluntary movement conditions, the low-intensity afferent volley generated in the Lo-

Voluntary intervention may be subsumed by the endogenous motor cortex activation generated during the preparation and execution of voluntary movement. Jochumsen and colleagues[62] showed that the pairing of motor threshold nerve stimulation with the MRCPs from voluntary movement (Lo-Voluntary) was no more effective at increasing CME in healthy people than either voluntary movement or PES alone. Their findings showed that to be effective, the voluntary movement needed to be paired with muscle stimulation delivered at motor threshold[62]; muscle stimulation may have produced a larger afferent volley, less likely to be subsumed by endogenous M1 activity. These findings might reflect the differences in the stimulation frequency, current density, and motor unit recruitment observed when stimulating muscle versus a nerve[62,255,388,389] and warrant further investigation into the PES intensity applied during ePAS interventions.

In contrast to our findings in healthy people, Lo-Voluntary ePAS applied to people with stroke has been shown to be more effective than attempted voluntary movement alone for increasing CME[59,60] and muscle strength[61]. Many people with stroke have lower levels of motor cortex activation[248-250], which might be less likely to subsume the afferent stimulation. However, studies investigating the effects of PES alone in people with stroke have reported that higher intensities of stimulation are more effective at increasing CME, reducing impairment, and improving function[390-392]. The ePAS intervention has not yet been applied at stimulation intensities greater than the motor threshold in people with stroke. It is possible that, if well tolerated, higher PES intensities may be required to maximise the effects of ePAS in people with stroke.

5.6.4 Movement type

For the secondary analyses of the factor of 'movement type', it was hypothesised that interventions that involved voluntary movement (Hi-Voluntary, Lo-Voluntary, Control-Voluntary) would yield greater increases in CME than imagined movements (Hi-Imagined, Lo-Imagined, Control-Imagined). Our findings did not support this hypothesis, demonstrating no difference in CME between voluntary and imagined movement conditions except for the Lo-Imagined intervention. When compared to the Lo-Voluntary intervention, Lo-Imagined yielded larger effects at 15 min post-intervention (MEP amplitude and MEP area) and when all time-points were averaged (MEP area). The effect of the Lo-Imagined intervention has been demonstrated in previous ePAS studies in healthy people[53-58]. This may be linked to the concept of subsumed afferent input discussed above.

In this study, we used the same ISI across all participants for each of the four ePAS interventions[53]. It is possible that the optimal temporal pairing between PES and cortical activity, and thus the ISI, differs between imagined and voluntary movement. Imagined movement involves motor preparation and activation of M1, but the final command to activate the descending corticospinal neurones is inhibited[265]. Thus, the timing at which the afferent volley arrives at M1 may interact differently with facilitatory and inhibitory networks in voluntary versus imagined movement. The ISI is known to be critical in determining whether PAS paradigms result in an increase or decrease in CME[46-48]. A recent systematic review that examined the efficacy of PAS on lower limb CME and the influence of stimulation parameters found that increases in CME were largest when selecting an ISI of 40–55 ms or an optimised ISI based on the individualised somatosensory evoked potential latency[369]. However, little prior work has been done to inform the optimisation of the ISI during ePAS[53], and no studies have investigated the optimal ISI during voluntary movement ePAS conditions. Future ePAS research should therefore investigate the optimal ISI for both the individual and the movement type.

A final consideration for the delivery of ePAS using either voluntary or imagined movement is its potential application to stroke rehabilitation. Whilst the imagined movement condition was more effective when the PES was delivered at the motor threshold (Lo-Imagined), we have previously acknowledged the potential benefits of giving higher intensity stimulation to people with stroke, and in this study, the combination of higher intensity stimulation with voluntary movement (Hi-Voluntary) produced significant effects. In addition, people with stroke might have difficulty performing motor imagery due to cortical damage[274], and voluntary movement has the additional benefit of providing internal feedback on performance, which is essential for motor learning[260]. Thus, from a clinical perspective, there are a number of potential benefits of delivering ePAS during voluntary movement, but further research is required to compare the effects of various combinations of stimulation intensity and movement type in people with stroke.

5.6.5 Strength and limitations

To our knowledge, this is the first study to begin to unpack the effects of different intervention parameters of a neuromodulatory intervention using a factorial design. The findings of this study are strengthened by the use of a sound *a priori* statistical analysis plan, including the consideration of baseline covariates that might introduce variability in the data, and an analysis of both MEP amplitude and area and measures of change (absolute and relative). A number of considerations are required when interpreting the results.

First, the study was powered to detect changes in MEP amplitude, not MEP area, yet some findings were only observed in MEP area data. Our choice of MEP amplitude as a primary outcome measure was driven by the availability of data for the sample size calculation[53]. However, MEP area was considered an important outcome, as evidence suggests it may be more sensitive to changes due to the polyphasic nature of MEPs in the lower limb[381,393].

Second, whilst the sample size was powered to detect a super-additive effect corresponding to a Cohen's effect size of 0.55, our data featured a much larger between-participant standard deviation at the pre-intervention time-point than the work used to power this study[296], resulting in an effect size of just 0.15. It is possible that this large variability was related to the use of active MEP measurements[394] in our study, in contrast to the resting MEPs used in the study that informed the sample size calculation[53]. MEPs are difficult and sometimes impossible to elicit in the resting muscle of people with stroke[248-250], and therefore, we chose to record active MEPs in our study. This would enable replication of this study in the stroke population and minimise selection bias in future work. In our study, the magnitude of change in active MEPs may have been smaller than the measurement error, hindering the ability to see interaction effects. We have provided between-participant standard deviations for active MEP amplitude and active MEP area measures, which can be used to inform future calculations of standardised effect sizes.

Third, whilst we made every effort to ensure high methodological quality during TMS measurement procedures (see Supplementary Material: TMS Quality Checklist in Appendix B.5) the use of a standard hand-held TMS coil could reduce the ability to reliably locate the M1 representation of interest[395]. The use of neuronavigation systems with neuroimaging to track the coil and head position during TMS measurement procedures has demonstrated improved spatial accuracy of cortical localisation[396,397], decreased variability in trial-to-trial MEPs[398], and more timely TMS procedures[399] compared to the standard hand-held coil method. Therefore, if available, the use of neuronavigation should be considered to strengthen the methodological quality of TMS measurement procedures.

Fourth, the method used in this study to identify the timing of the peak negativity involved an offline manual method, where the MRCP data were averaged from pre-recorded voluntary and imagined movements. This method has been used extensively in the literature to determine the timing of the temporal pairing in efficacious ePAS interventions[53,55-61,63,252]. However, if the temporal pairing is a key factor that dictates the success of the ePAS intervention, the use of online detection for each MRCP trial could

improve the accuracy of individual pairings in real time and maximise the effects of the intervention[54,57,252].

Finally, a factorial design enables the researcher to evaluate multiple intervention parameters and identify potential interactions between these parameters whilst maintaining statistical efficiency[375]. However, for pragmatic reasons, we did not include control conditions of suprathreshold stimulation only (Hi) and threshold stimulation only (Lo) in the factorial design. Whilst a number of previous ePAS[53,54,63], PAS[280,296], and PES[372] studies have failed to show any effects of stimulation alone, this decision limited our ability to fully unpack the effect of the different intervention parameters.

5.6.6 Future recommendations

In order to advance our understanding of the optimal delivery of ePAS, we recommend that future research consider the following:

- Factorial designs should be used to explore the interaction effects of different intervention parameters in neuromodulatory interventions; parameters could include stimulation intensity, movement type, ISI, and the number of stimuli.

- To support translation into clinical practice, this work and similar factorial designs should be undertaken in people with stroke. These studies should not only explore the neurophysiological effects of the intervention but also assess changes in impairment and functional outcomes.

- Using TMS measurements from both resting and active muscle would allow comparison to previous work and enable the researcher to consider the impact of measurement error on the findings.

- The baseline covariates AMTh and MVC were considered and suitably adjusted for in the factorial models for the primary analysis of this study. Future research should also consider interactions with baseline covariates as part of a pre-planned blind model selection process. This may shed light on how baseline covariates modulate responses to neuromodulatory interventions.

5.7 Conclusion

Factorial designs are an efficient way to explore the effects of manipulating the parameters of neuromodulatory interventions. The present study systematically unpacked the effect of

manipulating PES intensity and movement type in ePAS interventions. Our findings make several contributions to the current evidence. First, the findings are consistent with previous research investigations that support the excitatory effect of Lo-Imagined ePAS interventions on CME in healthy people. Second, this study extends those findings by demonstrating that delivering suprathreshold PES stimulation intensities during both Hi-Imagined and Hi-Voluntary ePAS interventions is also effective. Third, our findings indicate an interaction effect between intervention parameters; this effect was sub-additive for Hi-Voluntary and Hi-Imagined ePAS interventions. From a clinical perspective, we have discussed the potential benefits of delivering Hi-Voluntary ePAS. However, to support translation into clinical practice, further research is necessary to evaluate the efficacy of different configurations of stimulation intensity and movement type in people with stroke. Further factorial study designs should be considered to determine the most effective ePAS intervention parameters for people with stroke.

5.8 Author contributions

Conceptualisation, GA, NS, and DT; Methodology, GA, NS, ACV, and DT; Investigation and data curation, GA, IKN, and MJ; Formal analysis, ACV; Visualisation, GA, NS, ACV, and IKN; Supervision, NS, IKN, ACV, and DT; Prepared original draft, GA; Edited manuscript, GA, NS, and SO.; All authors critically reviewed the manuscript; All authors read and agreed to the published version of the manuscript.

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5.10 Conflict of interest statement

The authors declare no conflict of interest.

5.11 Acknowledgements

We gratefully acknowledge the time given to this study by the research participants. Without their willingness this work would not have been possible. We would also like to acknowledge Hui Hiang Abraham-Lek and Thomas Christensen for their assistance with data collection.

5.12 Summary

While the findings of this study were somewhat unexpected and did not support the initial hypotheses, they highlighted that there was considerable inter-individual variability in intervention response. The possibility that inaccuracies in the estimation of the PN of the averaged MRCP might contribute to inter-individual variability in intervention response and its implications for intervention optimisation were raised. Olsen's ePAS feasibility study in people with chronic stroke, conducted concurrently with this study, raised similar issues[64]. This led us to consider undertaking further research into the reliability of the manual screening method used to determine the MRCP's PN and this work is addressed in the following chapter.

Chapter 6. Intra-and Inter-rater Reliability of Manual Feature Extraction Methods in Movement Related Cortical Potential Analysis

6.1 Prologue

Chapter 5 called for an investigation into the reliability of the manual MRCP processing method used to determine the peak negativity of the MRCP that is used to inform the timing of the ePAS intervention. At this point of the doctoral journey an additional thesis objective was introduced.

This published manuscript relates to the following thesis objective:

- Determine the intra-rater and inter-rater reliability of EEG experts' identification of the peak negativity feature from averaged MRCPs obtained from healthy people and people with stroke.

Publication citation

Alder G, Signal N, Rashid U, Olsen S, Niazi I.K and Taylor D (2021). Intra- and inter-rater reliability of manual feature extraction methods in movement related cortical potential analysis. Sensors 2020, 20(8),2427; https://doi.org/10.3390/s20082427

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Cite Score 6.4

Minor formatting adjustments have been made to the published manuscript to ensure uniformity throughout the thesis. Supplementary materials associated with this publication can be found in Appendix C. These include figures to support the primary findings and a detailed account of the statistical analysis plan for the secondary analysis on epoch selection.

Link to the original publication

https://www.mdpi.com/1424-8220/20/8/2427/htm

Intra- and inter-rater reliability of manual feature extraction methods in movement related cortical potential analysis

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6.2 Abstract

Event related potentials (ERPs) provide insight into the neural activity generated in response to motor, sensory and cognitive processes. Despite the increasing use of ERP data in clinical research little is known about the reliability of human manual ERP labelling methods. Intra-rater and inter-rater reliability were evaluated in five electroencephalography (EEG) experts who labelled the peak negativity of averaged movement related cortical potentials (MRCPs) derived from thirty datasets. Each dataset contained 50 MRCP epochs from healthy people performing cued voluntary or imagined movement, or people with stroke performing cued voluntary movement. Reliability was

assessed using the intraclass correlation coefficient and standard error of measurement. Excellent intra- and inter-rater reliability was demonstrated in the voluntary movement conditions in healthy people and people with stroke. In comparison reliability in the imagined condition was low to moderate. Post-hoc secondary epoch analysis revealed that the morphology of the signal contributed to the consistency of epoch inclusion; potentially explaining the differences in reliability seen across conditions. Findings from this study may inform future research focused on developing automated labelling methods for ERP feature extraction and call to the wider community of researchers interested in utilizing ERPs as a measure of neurophysiological change or in the delivery of EEG-driven interventions.

Keywords: electroencephalography (EEG) processing; event related potential (ERP); movement related cortical potential (MRCP); stroke; intra-rater reliability; inter-rater reliability

6.3 Introduction

Surface electroencephalography (EEG) has been widely used to study electrophysiological activity within the cortex[400]. A common approach is to record event-related potentials (ERPs), which are often recorded following the presentation of a sensory stimulus, and are characterised by a range of waveforms of varying latencies and amplitudes which are time-locked to specific sensory, motor, or cognitive events[235]. ERPs have considerable epoch-to-epoch variability, due to random noise and artefacts[401]. To account for this, ERPs are often processed by averaging a number of epochs (between 50 and 200)[244,401-403]. To ensure each single epoch contains an ERP, and not an artefact, each epoch is visually inspected prior to averaging, then the average ERP is visually inspected, and relevant features of the waveform manually labelled[53,402-405]. This process of visually inspecting and manually labelling ERP data is common practice[53,402-405] but little is known about its reliability.

In the field of diagnostics, the inter-rater reliability of visual-inspection methods for identifying abnormal activity in continuous EEG data have shown only fair to moderate reliability[406-408]. The few studies which have investigated the inter-rater reliability of visual inspection and manual labelling have demonstrated moderate to excellent inter-rater reliability using a range of statistical methods across a variety of ERP waveforms[409,410]. No studies were identified which evaluated intra-rater reliability. Those studies comparing the reliability of human experts with that of algorithms suggest that better agreement is seen between humans, than between algorithms, or between humans and algorithms[409,410]. Given

the growing use of EEG data within research settings, for both outcome measurements[409] and the delivery of EEG-driven interventions[244,411,412], it is important to assess the reliability of manual ERP labelling methods, prior to establishing effective algorithms that can automatically carry out this process.

An example of a context which requires reliable labelling of ERPs is in the delivery of an endogenous paired associative stimulation (ePAS) intervention, a non-invasive neuromodulatory intervention that has been shown to modulate corticomotor excitability in healthy people[53,55,56,413] and people with stroke[59,60]. Based on traditional paired associative stimulation (PAS)[223,225,369], ePAS involves the delivery of 50 single pulses of peripheral electrical stimulation, each paired with an endogenous ERP signal known as the movement related cortical potential (MRCP)[53,55,56,59,60]. The MRCP is observed as an individual prepares and executes a voluntary or imagined movement[51,52] and is characterised by a slow (≈0.5 Hz) negative potential which begins approximately 1.5 to 2 s prior to movement and peaks around the onset of movement (amplitude –5 to –30 uV)[51,52]. When the MRCP is generated during externally-cued movements (i.e., where there is a "Warning" and a "Go" cue), it is also known as a contingent negative variation[237].

The neuroplastic effects of ePAS rely on accurately timing the peripheral electrical stimulation so that the afferent volley arrives in the primary motor cortex (M1) at the most negative point of the MRCP (peak negativity; PN)[53]. This timing is achieved by triggering the peripheral electrical stimulation at a set number of milliseconds before the PN of the MRCP to account for the conduction time between the peripheral nerve and the M1[53]. However, the neuromodulatory effects of ePAS present considerable between-participant variability[55,56,59,60,413]. For example, Olsen et al.[56] showed increases in corticomotor excitability ranging from 4%–396% (n = 10). While large between-participant variability has been documented in response to other neuromodulatory interventions[224,329,341,346,347,352,414,415] it is important to identify sources of variability that can be controlled[341] such as inconsistencies in the intervention delivery method[341,352,414]. One factor that may contribute to the variable response following ePAS, is inaccurate estimation of the PN of the averaged MRCP[53]. This currently involves visual inspection of 50 pre-recorded epochs, exclusion of epochs that lack the expected MRCP characteristics, and then labelling of the PN from the averaged MRCP. Any variability in this process will alter the PN value, which is used to time the peripheral electrical stimulation in the subsequent ePAS intervention potentially influencing efficacy[53]. The primary aim of this study was to examine the intra-rater and

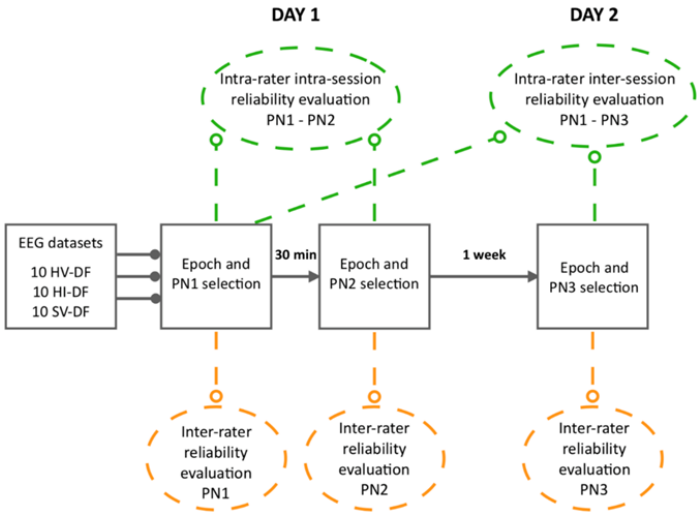
inter-rater reliability of EEG experts' identification of the PN timing from averaged MRCPs derived from healthy people and people with stroke.

6.4 Method

6.4.1 Study design

This reliability study utilized a repeated-measures design (refer to Figure 6.1). Five EEG experts participated in three separate MRCP evaluation sessions: sessions 1 and 2 were conducted on the first day with a 30-min break in-between, and session 3 was conducted seven days later. Intra-rater reliability for each expert was assessed within (intra-session) and across evaluation sessions (inter-session). Inter-rater reliability across experts was assessed within each of the three evaluation sessions. At each session, experts examined the same 30 EEG datasets including three different conditions: (1) healthy participants performing 50 voluntary ankle dorsiflexion movements (10 datasets); (2) healthy participants performing 50 imagined ankle dorsiflexion movements (10 datasets); and (3) participants with stroke performing 50 voluntary ankle dorsiflexion movements (10 datasets). Each dataset contained 50 epochs, relating to 50 repetitions of movement. The experts visually examined each epoch using a custom-built graphical user interface tool developed in MATLAB 2016a and manually excluded epochs they considered not representative of the expected MRCP characteristics. The included epochs within each dataset were then averaged to produce an average MRCP and experts were required to manually label the peak negativity (PN).

Figure 6.1 An overview of the study design



The three conditions and the 10 datasets within a condition were pseudo-randomized for each expert at each separate evaluation session. Epochs within a single dataset remained in the order in which they were recorded. HV-DF = healthy voluntary dorsiflexion; HI-DF = healthy imagined dorsiflexion; SV-DF = stroke voluntary dorsiflexion. PN1 = evaluation session 1 day 1; PN2 = evaluation session 2 day 1; PN3 = evaluation session 3 day 2.

6.4.2 Participants

EEG experts were required to have had at least one years' experience working with MRCP signals and the ePAS intervention protocol. EEG data were collected from 20 healthy participants and five participants with stroke as part of two independent ePAS studies. The criteria for inclusion of healthy participants were related to age (>18 years) and the absence of neurological conditions. Participants with stroke were included if they had experienced a single stroke at least six months previously, had a hemiparesis impacting their walking ability, and a gait speed of 0.5–1.2 m per second. Participants with stroke were excluded if they had contra-indications to transcranial magnetic stimulation (this related to the ePAS outcome measures), or cognitive, perceptual or communications impairments. Study participant characteristics are reported in Table 6.1. Healthy participants completed a single MRCP recording session of either visually-cued voluntary dorsiflexion movements (n = 10) or visually-cued imagined dorsiflexion movements (n = 10). Participants with stroke (n = 5) participated in two identical MRCP recording sessions at least three days apart and performed visually-cued voluntary dorsiflexion movements (10 datasets).

Table 6.1 Characteristics of study participants: healthy participants and participants with stroke

	Healthy Participants	**Participants with Stroke**
Mean age (years)	28.6 (21–52)	67 (57–78)
Gender (males: females)	8:12	2:3
Lesion		
-Hemisphere (right: left)		3:2
-Type (ischemic: haemorrhagic)		4:1
Mean time since stroke (years)		7 (1–17)
Mean gait speed (m/s)		0.4 (0.2–0.75)

m/s = metres per second. Bracketed age and m/s data represent ranges.

6.4.3 Ethical procedures

EEG experts came from two institutions, the Health and Rehabilitation Research Institute at Auckland University of Technology, Auckland, New Zealand, and the Centre of Sensory-Motor Interaction, Department of Health Science and Technology Alborg University, Denmark. Ethical approval for the two studies from which the data was drawn received ethical approval from the Auckland University of Technology Ethics Committee (AUTEC 15/270 and 14/255). All participants provided written and informed consent prior to participation.

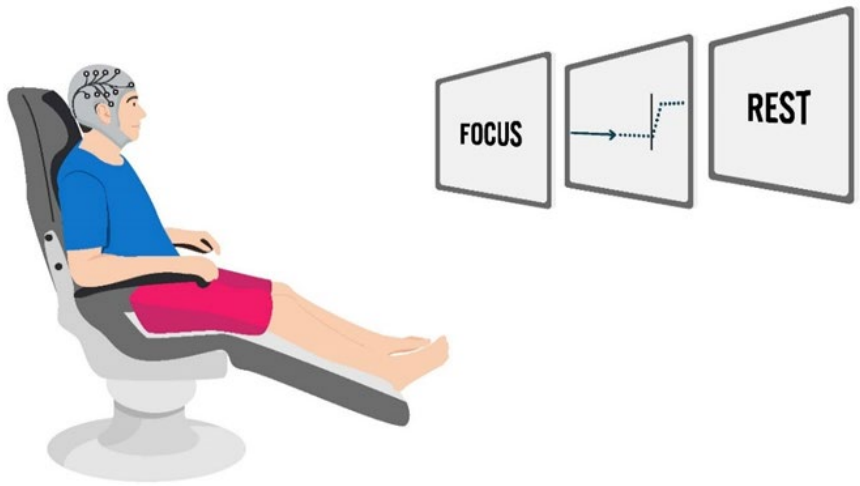
6.4.4 Experimental procedures

Externally-cued movement paradigm

Healthy participants and participants with stroke were seated in a chair with approximately 90–100° hip flexion, 25° knee flexion and the ankles in a relaxed slightly plantarflexed position. Participants were orientated to a visual cue on the computer monitor (MATLAB, MathWorks, Inc., Natick, MA, USA, 2011). The visual cue consisted of four different phases that guided participants to (1) focus on the screen, (2) prepare for the movement, (3) execute the ballistic (voluntary or imagined) movement to achieve a fully-dorsiflexed position and hold it for approximately 1 s and then (4) rest. A moving cursor guided the participant through the preparation and execution of movement. The length of focus and rest times varied per repetition (2–3 s and 6–8 s, respectively). Continuous EEG recordings were collected during two sets of 25 repetitions of ankle dorsiflexion movement (voluntary or imagined). Participants with stroke performed the voluntary dorsiflexion to the best of their movement ability, and within their maximal available active dorsiflexion range of

motion, which was limited for some participants. An illustration of the laboratory set-up is displayed in Figure 6.2.

Figure 6.2 An illustration of the set-up for continuous electroencephalography (EEG) recordings where a participant executes either voluntary or imagined ballistic dorsiflexion movements in time with a visual cue displayed on a computer monitor



EEG data acquisition

A 40 channel EEG Quik-Cap (Compumedics Neuroscan, Dresden, Germany) was fastened below the chin of participants with the Cz electrode positioned midway between the nasion and the inion (sagittal plane), and midway between each tragus (coronal plane). Skin was lightly abraded using a sterile blunt needle. Conductive gel was inserted into 12 electrodes, FP1, F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4, according to the international 10–20 system, as well as a reference electrode on the right mastoid and a ground electrode on the right forehead (Ag/AgCl electrodes, Compumedics, Neuroscan). Impedance remained below 5 kΩ. EEG signals were digitised via a 40-channel EEG amplifier (NuAmps, Compumedics Neuroscan, Dresden, Germany) with a sampling rate of 500 Hz, 32 bits accuracy and recorded in SCAN software (Compumedics Neuroscan, Dresden, Germany).

EEG data processing

Continuous EEG signals for each movement condition were imported into MATLAB 2015a. Each channel was band-pass filtered from 0.05 to 5 Hz (second-order zero-phase Butterworth filter). All channels except FP1 were spatially-filtered with a large Laplacian filter

with Cz as the centre electrode, to obtain a single virtual channel. The virtual channel was separated into 50, 4.5 s epochs (3 s preceding the cue to move and 1.5 s post)[53,56,62,251].

MRCP evaluation by EEG experts

Experts evaluated all 30 datasets independently of one another using the customised user interface (MATLAB, MathWorks, Inc., Natick, MA, USA, 2011). Randomization of datasets was performed in MATLAB 2016a using the ***randperm*** function with randomization configuration set to ***shuffle***. This meant that the current time was used as a seed for the random number generator. Conditions, and the 10 datasets within a condition, were randomized for each expert and each separate evaluation session. Epochs within a single dataset remained in the order in which they were recorded from the study participant to reflect normal collection procedures. For each dataset, experts were provided with the following information: the movement type (voluntary or imagined dorsiflexion); the participant population (healthy people or people with stroke); the onset of the 'cue to move' within the epochs (at the 1500 samples mark); and the methods by which the EEG data had been recorded and filtered (see EEG Data Processing section). Experts were required to visually inspect each of the 50 epochs presented in each dataset and accept or reject epochs based on whether they determined the signal represented an MRCP in view of the information provided. The included epochs within a single dataset were then averaged and presented to the expert as an average MRCP signal. Experts were then required to manually label the PN from the average MRCP signal using the mouse pointer. Experts were instructed to evaluate each dataset as quickly and as accurately as possible.

6.4.5 Statistical analysis

Primary analysis: average MRCP PN labelling

PN values for each condition within each of the three evaluation sessions were entered into SPSS software package version 24 for analysis. PN data were deemed to be normally distributed based on histogram visual analysis and the Shapiro–Wilks test. Relative reliability for average PN values for each condition was assessed using intraclass correlation coefficient (ICC) estimates. The ICC is a unitless measure that compares the between-participant variance to the total variance[416] which includes between-participant variance and error variance. In this case the error variance represents expert variance, either the variance between experts (inter-rater reliability) or within one expert across two sessions (intra-rater reliability). ICC estimates and their 95% confidence intervals were calculated based on a

single measures, absolute agreement, 2-way random-effects model which accounts for both systematic and random error[416,417]. ICC values are bound from 0 to 1, where values closer to 1 indicate stronger reliability. The following criteria were used to interpret ICC values and their 95% confidence intervals: >0.8 excellent; 0.6–0.8 good; 0.4–0.6 moderate; <0.4 poor[418]. Absolute reliability was assessed using the standard error of the measurement (SEM), which provides an index of reliability in the same unit as the measurement of interest[419], which in the case of PN values, is milliseconds. Unlike the ICC, the efficiency of the SEM is not susceptible to small between-participant variations and quantifies how much the absolute values differ from the 'true' value[416]. The smaller the SEM, the greater the reliability. The following equation was used: SEM = √MSE, where MSE represents the mean sum of squares for the error term from the ANOVA[416]. SEM means and standard deviations are reported as mean ± SD for intra- and inter-rater reliability for each condition.

Secondary analysis: epoch selection

We conducted a post hoc secondary analysis to explore factors that may influence the manual selection of epochs by experts. We investigated the influence of two factors on the ability of experts to provide the same response for inclusion of epochs: (1) the morphology of the signal and (2) the experience of the EEG expert. Epoch selection was defined as *'matched'* if an expert chose to *accept* an epoch for inclusion at two different evaluation sessions (intra-rater: evaluation sessions 1 and 2 and 1 and 3) or if all five experts *accepted* the same epoch in a single evaluation session (inter-rater: evaluation sessions 1, 2 and 3). The morphology of the epochs was quantified using the cosine similarity index. This was defined as the similarity of a single epoch from a participant compared to the average of all 50 epochs from the same participant, which was considered a representation of the expected MRCP characteristics[420],

$$\text{Cosine similarity index} = \frac{u.v}{||u|| \times ||v||}$$

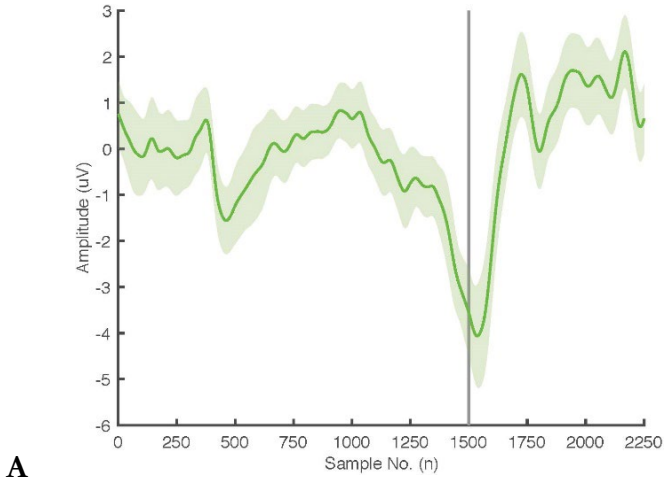
where u and v are vectors, u is the average MRCP of all 50 epochs from a participant and v is a single epoch from the same participant. '.' represents the dot product between the two vectors and ‖.‖ represents the L2 norm of a vector. The self-reported experience of experts working with MRCP signals was quantified in years. A linear mixed-effects model was set up to evaluate the variance of cosine similarity across conditions. In the case of significant findings for cosine similarity across conditions, pairwise *t*-tests using Tukey's method were

performed and presented with cosine similarity means and standard deviations as mean ± SD for each condition. Logistic mixed-effects models were set up to fit linear trends between the log odds for getting a matched epoch, cosine similarity and expert experience. The log odds were transformed to the corresponding linear scale and presented as the probability of getting a matched epoch. For each condition effect sizes were reported along with their 95% confidence intervals. All models were set up in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and fitted using lme4 package version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and fitted using lme4 package version 1.1-17[421]. For each condition the significance level was set to $p < 0.05$. The statistical models set up to test these secondary hypotheses can be found in Supplementary Materials (see Appendix C.4).

6.5 Results

The five EEG experts had a mean of 4.7 years of experience (range 1.5–8 years) working with MRCP signals and the ePAS intervention. Figure 6.3 presents examples of MRCP averages with 95% confidence intervals representing the filtered epochs of one participant from each condition.

Figure 6.3 Movement related cortical potential (MRCP) averages with 95% confidence intervals obtained from averaging filtered epochs



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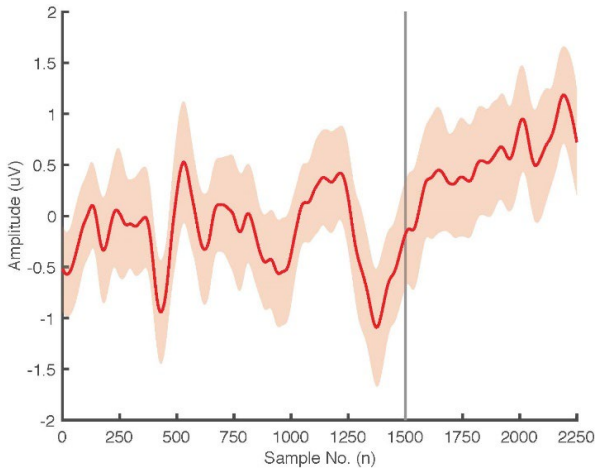

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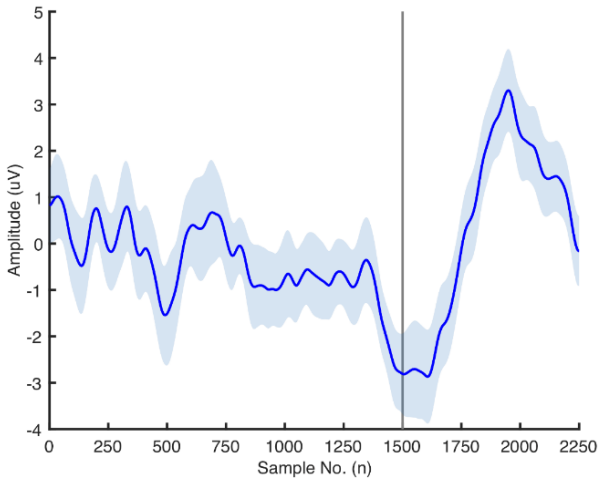


C

(A) a healthy participant performing voluntary dorsiflexion, (B) a healthy participant performing imagined dorsiflexion, and (C) a participant with stroke performing voluntary dorsiflexion. Sample number 1500 corresponds to the onset of the cue to move.

6.5.1 Primary findings: average MRCP PN labelling

Intra-rater reliability (intra- and inter-session)

Intra-session and inter-session relative (ICCs and 95% confidence intervals (CIs)) and absolute (SEMs) reliability values for each condition are presented in Table 6.2.

Table 6.2 Intra-rater reliability measures (intra-session and inter-session) of the labelled average MRCP PN for each of the three conditions

	Healthy Voluntary DF		Healthy Imagined DF		Stroke Voluntary DF	
	ICC	**SEM**	**ICC**	**SEM**	**ICC**	**SEM**
Intra-session Reliability: PN1 and PN2						
E1	1.00 (0.99–1.00)	7.7	0.61 (0.34–0.89)	155.54	0.84 (0.46–0.96)	78.14
E2	0.99 (0.97–0.99)	18.9	0.90 (0.67–0.97)	63.55	0.91 (0.70–0.98)	46.98
E3	0.90 (0.67–0.97)	72.6	0.75 (0.30–0.93)	75.42	0.93 (0.75–0.98)	27.43
E4	1.00 (0.99–1.00)	6.99	0.63 (0.09–0.89)	120.38	1.00 (0.99–1.00)	3.84
E5	1.00 (0.99–1.00)	5.06	0.63 (0.06–0.89)	180.21	0.95 (0.80–0.99)	37.9
Inter-session Reliability: PN1 and PN3						
E1	0.99 (0.95–1.00)	19.61	0.55 (-0.03–0.86)	184.61	0.90 (0.65–0.98)	57.47
E2	0.98 (0.93–0.97)	30.56	0.76 (0.28–0.93)	115.10	0.94 (0.77–0.98)	41.22
E3	0.98 (0.93–1.00)	32.61	0.48 (-0.09–0.83)	116.01	0.85 (0.50–0.96)	55.81
E4	0.95 (0.83–0.99)	52.76	0.05 (-0.60–0.64)	279.2	0.80 (0.42–0.95)	72.81
E5	1.00 (0.98–1.00)	15.32	0.68 (0.10–0.91)	193.39	0.83 (0.46–0.96)	65.91

Intraclass correlation coefficients (ICCs) with lower and upper 95% confidence intervals and standard error of the measurements (SEMs) in milliseconds for each EEG expert. E = EEG expert number; DF = dorsiflexion; PN = peak negativity; PN1 = evaluation session 1; PN2 = evaluation session 2; PN3 = evaluation session 3.

Relative reliability

Intra-session intra-rater relative reliability (sessions 1 and 2) was excellent across all experts in the voluntary movement conditions in both healthy people and people with stroke (ICCs >0.90 and ICCs >0.84, respectively), with adequately restricted 95% CIs. For the imagined movement condition in healthy people, intra-session reliability within four experts was in the good range (ICCs 0.61–0.75) but had wide confidence intervals with the lower bound CIs extending into the poor range, and one expert was excellent (ICC = 0.90), with moderately-wide CIs.

Inter-session intra-rater reliability (sessions 1 and 3) across experts was excellent in the voluntary movement conditions in both healthy people and people with stroke (ICCs >0.95 and ICCs >0.80, respectively), with narrower CIs for the voluntary movement

condition in healthy people. ICCs for healthy imagined movement were good for four experts (ICCs 0.48–0.76), and poor for one expert (ICC = 0.05). For three out of the five experts, the lower bound CIs of the ICCs extended below 0 demonstrating very poor relative reliability.

Absolute reliability

The intra-session intra-rater SEMs (sessions 1 and 2) for the voluntary movement conditions in both healthy people and people with stroke were fairly small across the five experts (22 ± 26 ms and 39 ± 24 ms, respectively), compared to the larger errors observed for the imagined movement condition in healthy people (119 ± 49 ms). A similar pattern across conditions was observed in the inter-session intra-rater SEMs (sessions 1 and 3), where SEMs for the voluntary movement conditions in both healthy people and people with stroke remained fairly small across experts (30 ± 15 ms and 59 ± 11 ms, respectively), but the imagined movement condition in healthy people produced a much larger measurement error (178 ± 66 ms).

Inter-rater reliability

Inter-rater relative (ICCs and 95% CIs) and absolute (SEMs) reliability values for each of the three conditions, appraised at each evaluation session, are presented in Table 6.3.

Table 6.3 Inter-rater reliability measures of labelled average MRCP PNs for each of the three conditions

	Inter-rater reliability: PN1, PN2, PN3					
	Healthy Voluntary DF		**Healthy Imagined DF**		**Stroke Voluntary DF**	
	ICC	**SEM**	**ICC**	**SEM**	**ICC**	**SEM**
PN1	0.99 (0.97–1.00)	26.13	0.40 (0.14–0.74)	187.89	0.84 (0.67–0.95)	58.71
PN2	0.95 (0.88–0.98)	51.15	0.76 (0.53–0.92)	104.81	0.88 (0.74–0.96)	62.12
PN3	0.97 (0.92–0.99)	39.75	0.2 (0.00–0.60)	246.51	0.78 (0.67–0.87)	79.17

Intraclass correlation coefficients (ICCs) with lower and upper 95% confidence intervals and standard error of the measurements (SEMs) in milliseconds. PN = peak negativity; PN1 = evaluation session 1; PN2 = evaluation session 2; PN3 = evaluation session 3; DF = dorsiflexion.

Relative reliability

Inter-rater relative reliability within all three evaluation sessions was excellent for the voluntary movement condition in healthy people (ICCs > 0.95, with narrow 95% CIs). Similar results were observed in the voluntary movement condition in people with stroke (sessions 1 and 2) with the first two sessions in the excellent range (ICC > 0.84) and the third session almost excellent (ICC = 0.78), but with somewhat wider confidence intervals. Results for inter-rater reliability for the imagined movement condition in healthy people

had much lower agreement, with ICC values ranging from poor to good across the three evaluation sessions with wide confidence intervals. Exemplar figures demonstrating substantial agreements and disagreements of PN labelling across the five experts for two different datasets can be found in the Supplementary Materials (Appendix C.3).

Absolute reliability

Inter-rater SEMs across evaluation sessions for the voluntary movement conditions in both healthy people and people with stroke were akin to those reported for intra-rater inter-session reliability (40 ± 39 ms and 79 ± 67 ms, respectively), and the imagined movement condition in healthy people demonstrated very large SEMs (247 ± 180 ms).

6.5.2 Secondary findings: epoch selection

Cosine similarity across conditions

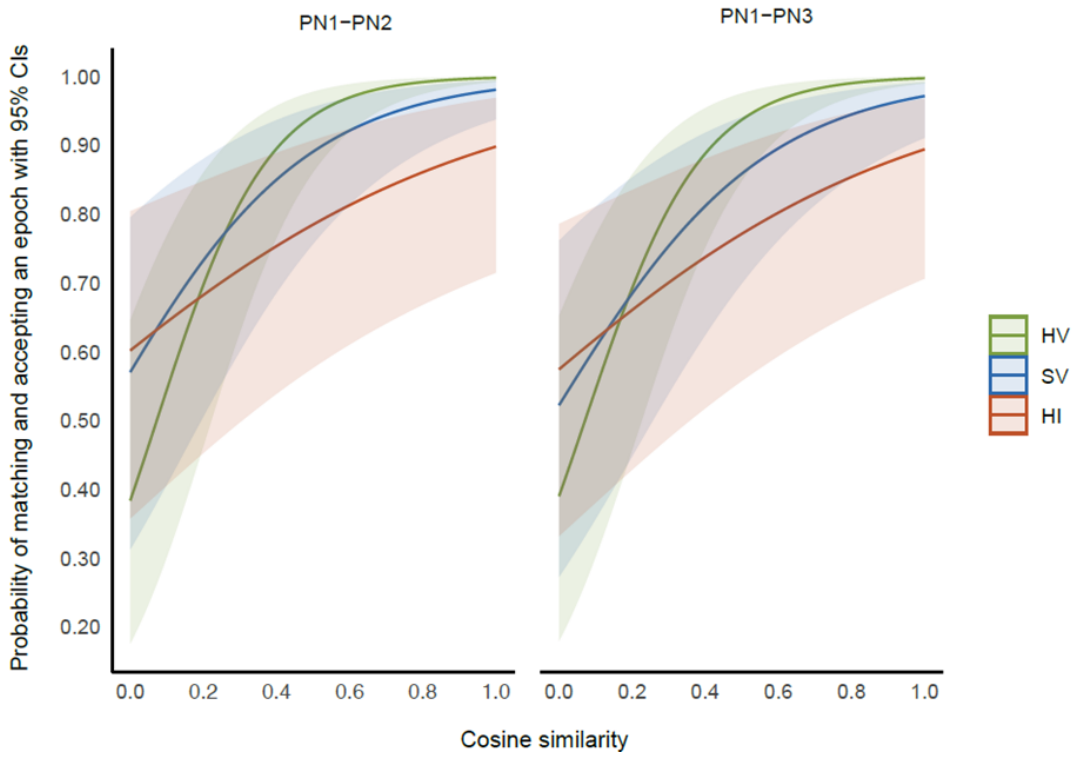
The linear mixed-effects model revealed a significant difference in the cosine similarity index score across conditions ($\chi 2$ [2] = 28.67, $p < 0.0021$). Pairwise comparisons determined that cosine similarity index was significantly greater (t [27] = 4.32, $p < 0.0005$) in the voluntary movement in healthy people (0.39 ± 0.18) compared to the imagined movement in healthy people (0.27 ± 0.19) and significantly greater (t [27] = –4.89, $p < 0.0001$) in the voluntary movement in people with stroke (0.41 ± 0.18) compared to the imagined movement condition in healthy people (0.27 ± 0.19). There was no statistically significant difference in cosine similarity between voluntary movement conditions in people with stroke and healthy people (t [27] = –0.57, $p < 0.0005$).

Intra-rater reliability (intra- and inter-session)

Results from the logistic mixed-effects model revealed a statistically significant interaction effect of cosine similarity and condition ($\chi 2$ [2] = 29.02, $p < 0.0001$) on the ability of experts to give matched responses. Linear log trends representing the association between cosine similarity (CS) and the log odds of epochs being matched were largest in the healthy voluntary movement condition (CS trend 6.41, 95% CI 5.17–7.65, $z = 10.14$, $p < 0.0001$). This indicates that for the voluntary movement condition in healthy people, for each unit increase in the cosine similarity index score, the log odds of getting a matched epoch increased by 6.41 times. This was followed by the voluntary movement condition in people with stroke (CS trend 3.58, 95% CI 2.38–4.67, $z = 6.07$, $p < 0.0001$) and imagined movement condition in healthy people (CS trend 1.80, 95% CI 0.73–2.86, $z = 3.32$, $p < 0.0009$). Figure 6.4 presents a graph demonstrating the relationship between the probability

of experts obtaining a matched epoch and cosine similarity with 95% confidence intervals in each condition for intra-session (PN1 and PN2) and inter-session (PN1 and PN3) evaluations.

Figure 6.4 The relationship between the probability of experts obtaining a matched epoch and the cosine similarity



Data for each movement condition are presented (healthy voluntary (HV), stroke voluntary (SV), healthy imagined (HI)) with their 95% confidence intervals at intra-session (PN1 and PN2) and inter-session (PN1 and PN3) evaluations.

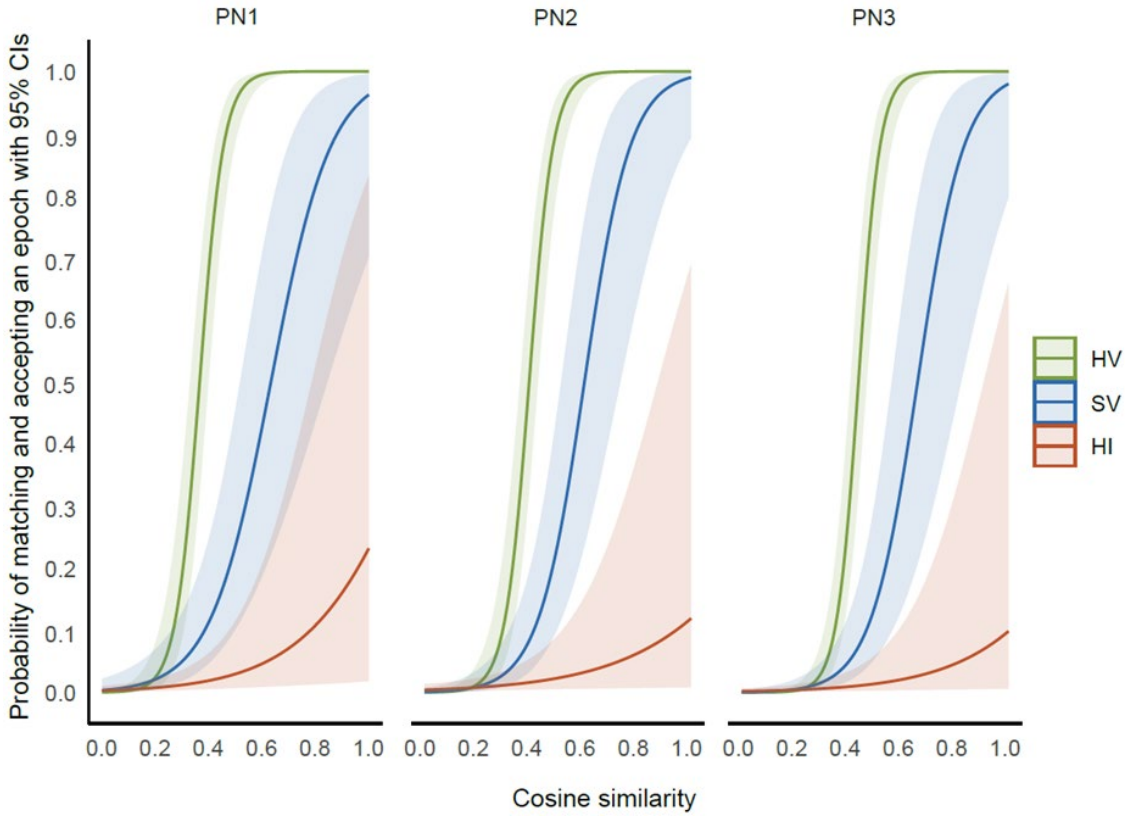
Results from the logistic mixed-effects model also revealed a statistically significant interaction effect of expert experience and condition (χ^2 [2] = 60.5743, $p < 0.0001$) but within each condition the log trend was non-significant (voluntary movement condition in healthy people, trend 0.23, CI −0.09–0.5, z = 1.37, p = 0.1708; imagined movement condition in healthy people trend 0.15, CI −0.18–0.47, z = 0.86, p = 0.3884; voluntary movement condition in people with stroke, trend 0.13, CI −0.01–0.64 z = 1.89, p = 0.0580).

Inter-rater reliability

Results from the logistic mixed-effects model revealed a significant interaction effect of cosine similarity and condition (χ^2 [2] = 30.74, $p < 0.0001$). There were no other statistically

significant interaction effects ($p < 0.05$). Linear log trends representing the association between cosine similarity (CS) and the log odds of getting a matched epoch were largest in the voluntary movement condition in healthy people (CS trend 23.00, 95% CI 18.04–27.97, $\tilde{\chi} = 9.08$, $p < 0.0001$) indicating that for a unit increase in the CS index score the log odds of getting a matched epoch increased by 23 times. This was followed by the voluntary movement condition in people with stroke (CS trend 10.60, 95% CI 6.95–14.26, $\tilde{\chi} = 5.69$, $p < 0.0001$) and the imagined movement condition in healthy people (CS trend 4.04, 95% CI 1.14–6.94, $\tilde{\chi} = 2.72$, $p = 0.0064$). Figure 6.5 presents a graph demonstrating the relationship between the probability of all five experts obtaining a matched epoch and cosine similarity with 95% confidence intervals for each condition at each of the three evaluation sessions.

Figure 6.5 Relationship between the probability of experts obtaining a matched epoch and the cosine similarity data for each movement condition



Movement conditions presented (healthy voluntary (HV), stroke voluntary (SV), healthy imagined (HI)) with their 95% confidence intervals at each of the three evaluation sessions.

6.6 Discussion

This study is the first to our knowledge to assess the inter- and intra-rater (intra-session and inter-session) reliability of the manual labelling process used to determine the PN of the averaged MRCP. The main finding was that intra- and inter-rater reliability of the PN value were much higher in the voluntary movement conditions in both healthy people and people with stroke, than in the imagined movement condition in healthy people. ICC values for all voluntary movement conditions were excellent (ICC >0.8), except in the case of inter-rater reliability in the third session (PN3) in people with stroke, which approached excellent (ICC 0.78). When comparing the voluntary movement conditions in healthy people and people with stroke, the 95% confidence intervals for relative and absolute intra- and inter-rater reliability were consistently wider in the stroke group. This larger measurement error in the stroke data could be influenced by differences in the MRCP signals that are observed in people with stroke compared to healthy people, such as longer latencies and smaller amplitudes[243]. Differences in the MRCP signal may have also influenced the poorer reliability observed in the imagined movement condition in healthy people. While similar cortical regions are activated during imagined and voluntary movements[264,422-424], there is a lower level of excitation during imagined movements[272,273] as demonstrated by MRCPs with lower amplitudes and less defined peak negativities[241,243]. The possibility that differences in the morphology of the MRCP signals influences the reliability of the PN was explored in our secondary analysis.

The secondary analysis revealed a strong relationship between the cosine similarity and the probability of agreement in accepting epochs within and between experts. The cosine similarity reflects the similarity between the morphology of an MRCP epoch and the morphology of the average of all 50 epochs. The lower cosine similarity in imagined movement in healthy people, and to a lesser extent voluntary movement in people with stroke, suggests that the morphology of the MRCP changes from epoch to epoch to a greater extent in these conditions. Conditions with higher cosine similarity also had higher ICCs, for example, the voluntary movement condition in healthy people had the highest cosine similarity and the highest ICCs, whereas the imagined movement condition in healthy people had the lowest cosine similarity and the lowest ICCs. Collectively, these findings suggest that the morphology of the signal contributed to the consistency of epoch inclusion and may explain the differences in reliability for each movement condition observed in the primary analysis.

Our secondary intra-rater analysis also revealed a statistically significant interaction effect of expert experience with condition, on the ability of experts to give matched responses. However, within each condition this influence was found to be statistically non-significant. This may be because the study was not powered to detect an association between experience and ability to match epochs but suggests that further consideration should be given to experience, particularly when processing imagined movement data or data from people with neurological pathologies such as stroke. It is notable that in the imagined movement condition in healthy people, there appeared to be a within-session training effect. For example, the inter-rater reliability at the first session was poor (PN1 ICC = 0.40) but improved in the second session 30 min later (PN2 ICC = 0.76), and then decreased again in the third session one week later (PN3 ICC = 0.20). For intra-rater reliability of the imagined movement condition, ICCs were higher for within-session comparisons, which took place 30 min apart (ICC ranges 0.61–0.9), than the between-session comparisons, which took place one week apart (ICCs ranges 0.05–0.76). This possible training effect for evaluations that took place within 30 min of each other, could be due to several factors including: (1) the consistent order of presentation of epochs within each dataset at each session (only the conditions and datasets were randomized) and (2) experts had a longer exposure time to the datasets on day 1 with two evaluation sessions compared to one evaluation session a week later. Future work could assess whether evaluating an imagined movement dataset more than once improves reliability when manually labelling MRCP data.

The findings from this study suggest that the large measurement error observed in the manual labelling process of average MRCP PNs in the imagined movement condition in healthy people may contribute to the high between-participant variation observed in response to the ePAS intervention when delivered during imagined movements. If the timing of the pairings is a critical component to the success of the ePAS intervention, we propose that imagined movements may not be the most appropriate choice of movement condition. This illustrates the importance of considering reliability and measurement error in ERPs for both outcome measurements and the delivery of EEG-driven interventions.

6.7 Methodological limitations

The generalizability of these results is subject to certain limitations. The EEG experts were from two academic centres and may not be representative of the EEG expert community working with ERPs. Expertise may influence the ability to match epochs and hence reliability, therefore the findings of this study may be less applicable to novice researchers

who are processing ERP data. Intra- and inter-rater reliability for the voluntary movement condition in people with stroke was predominantly excellent (ICC > 0.8), but the smaller sample of people with chronic stroke may reduce the generalizability of these findings to the wider stroke population, as ICCs can be impacted by smaller samples where there is small between-participant variability[416,419]. Finally, this study examined the reliability of experts evaluating the same MRCP datasets on multiple occasions and not the test-rest reliability of different MRCP datasets collected from the same participants. While these study findings may be useful when considering the reliability of ERP data, they should be replicated in other lower or upper limb muscle groups, recorded on two or more occasions from the same participants or in other ERPs.

6.8 Future recommendations

Future reliability studies should include experts from the wider ERP community and compare novice and expert evaluations. Future research should replicate the findings in a larger and more diverse sample of people with stroke and in other muscle groups, particularly if ePAS is seen as a potentially clinically viable neuromodulatory intervention for people with more acute stroke.

The results of this study may interest a wider community of researchers utilizing features of MRCPs during self-paced or cued paradigms to measure neurophysiological changes associated with motor performance and motor learning[425-435]. These results may also inform research into the development of automated labelling methods that can extract key features of ERPs. Rashid and colleagues[420] recently developed an automated method to identify MRCP features and highlighted the need for a reliable gold standard to which automated algorithms can be compared[436,437]. The present study is the first step towards providing reliable data for the comparison of manual labelling methods by EEG experts, with automated algorithms.

6.9 Conclusion

This study assessed the intra-rater and inter-rater reliability of EEG experts' identification of the peak negativity (PN) feature from averaged movement related cortical potentials (MRCPs) obtained from healthy people and people with stroke. We found excellent inter- and intra-rater (intra-session and inter-session) reliability for the voluntary movement condition in both healthy people and people with stroke. In comparison, intra-rater and inter-rater reliability in the imagined movement condition in healthy people was low to moderate. Our secondary post hoc epoch analysis revealed that the morphology of MRCP

signals influences the consistency of manual selection of epochs for inclusion within and between EEG experts. When the morphology of an MRCP epoch had greater similarity to the morphology of its average the probability of either a single expert or a group of experts selecting the same epochs for inclusion was much higher. Conditions with higher morphology similarity also had higher ICC values; for example, the voluntary movement condition in healthy people had the greatest morphology similarity and the highest ICCs, whereas the imagined movement condition in healthy people had the lowest morphology similarity and the lowest ICCs. The results from this study have implications for researchers evaluating MRCP data and potentially for those working with other ERP signals. This research may also provide a gold standard for the development of automated labelling methods of ERP features, as well as guidance for researchers who are using MRCPs as a neurophysiological measure of motor performance and motor learning in healthy and neurological populations.

6.10 Author contributions

Conceptualization, GA, UR, NS, IKN, and DT; methodology, GA, UR, NS, and DT; software development, UR and GA; investigation and data curation, GA; formal analysis, GA and UR; visualization, GA, UR, NS, SO, IKN, and DT; supervision, DT, NS, and IKN; prepared original draft, GA; edited manuscript, GA, NS, and SO; All authors critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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6.12 Conflict of interest statement

The authors declare no conflict of interest.

6.13 Acknowledgements

We gratefully acknowledge the time given to this study by the research participants. Without their willingness this work would not have been possible.

6.14 Summary

The findings from this study demonstrated that EEG experts identify the PN of averaged MRCPs in voluntary movement conditions in both healthy and people with stroke with excellent reliability. In contrast, in the imagined movement condition in heathy people, low to moderate inter- and intra-rater reliability was demonstrated. These findings have implications for the exciteBCI intervention's optimisation. Given that the timing of the pairings (interstimulus interval) is likely critical to the efficacy of the intervention, selecting a movement type with a lower measurement error (based on PN identification) is essential. Therefore, these findings strengthen the case for prioritising voluntary-based movements as part of the exciteBCI intervention design. This decision is further supported by experimental evidence (see Chapter 5, section 5.6.4) pertaining to the advantages of engaging in voluntary movement to support motor learning in people with stroke and is more closely tied to clinical practice.

SECTION THREE:

OPTIMISATION FOR CLINICAL USE THROUGH USER-CENTRED DESIGN

Chapter 7. A User-centred Design Approach to the Development of exciteBCI

7.1 Prologue

In Chapter 2, it was proposed that rehabilitation technologies could provide potential solutions for increasing the dose and intensity of locomotor-related rehabilitation for people with stroke (refer to section 2.8). It provided an overview of the known barriers and facilitators to the adoption and sustained use of rehabilitation technology as perceived by people with stroke and rehabilitation clinicians (refer to section 2.7). Chapter 3 indicated that ePAS in its current format is not an acceptable rehabilitation solution in the opinion of people with stroke, nor is it feasible to apply it in a clinical setting using laboratory equipment[64] (refer to section 3.8). In parallel to focusing on the optimisation of the intervention at the neurophysiological level, it is essential to consider how the intervention fits with clinical practice. One approach to achieving this could be to deliver ePAS via a portable wearable BCI device during meaningful real-world locomotor-related activities.

This current chapter primarily focuses on the following thesis objective:

Objective 2: Optimise the usability and acceptability of the exciteBCI, a portable medical wearable device in the prototype stage, to support its translation to clinical practice by:

(i) Identifying the exciteBCI device requirements from the perspective of people with stroke and physiotherapists

This chapter begins by defining usability and acceptability and their relevance to the adoption and sustained use of rehabilitation technology. This is followed by a brief description of UCD and the benefits of such an approach to the development and optimisation of complex interventions such as rehabilitation technology. Next the chapter introduces the ISO 9241-210:2019 standard[70] as a framework to support the UCD development process. Each stage of the ISO 9241-210:2019 standard[70] is then discussed in relation to the design and development process of exciteBCI. The chapter also discusses how the research team engaged in this process in the context of a national wearable technology competition called the C-Prize Challenge.

7.2 Usability and acceptability

Successful adoption and sustained use of rehabilitative technologies are intrinsically tied to the usability and acceptability of the technology[438-441]. A healthcare intervention that employs technology that has research evidence to support improved outcomes for its users but has low usability and acceptability risks poor uptake. This, in turn, is likely to risk reducing the intervention efficacy[442,443].

While it is acknowledged that there is a wealth of literature exploring the concepts of 'usability' and 'acceptability,' the definitions provided below are specifically recognised within the health technology literature and were used to support thesis objective 2[444]. Usability describes the "extent to which a system, product, or service can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use" (p. 3)[70]. Nielsen's usability model expands on this definition by outlining five usability attributes:

(1) Learnability - the system or device should be easy to learn

(2) Efficiency - the system should be easy to navigate, and tasks can be completed in a timely manner

(3) Memorability - the system should be easy to remember and easy to re-establish

(4) Errors - the system should have a low error rate and if errors occur, they should be easy to fix

(5) Satisfaction - the system should be pleasant and comfortable to use[445].

While the concept of acceptability is less well articulated in the health technology literature, acceptability can be defined as, "a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" (p. 4)[439]. Taking a UCD approach throughout the design and development life cycle can enhance usability and acceptability, increase the likelihood of successful adoption, and reduce the risk of technology abandonment prior to implementation in clinical practice[446,447].

7.3 User-centred design

UCD has been described as both a philosophy and a collection of methods drawn from human–computer interaction, design and human centred design research[448,449]. UCD emerged in the field of human-computer interaction in the 1970s and 1980s, where development processes focused on achieving a high level of usability in interactive system interfaces[450]. Products were frequently designed using requirement mapping and task analysis activities, and were tested against usability evaluation metrics and application standards[451]. The emphasis of UCD was revised in the 1990s in response to influences from design research methodologies that valued users' needs and encouraged users to participate actively in an iterative development process[452]. Users were no longer viewed solely as informants, but as bearers of experience[450]. As a result, a variety of design-based methods including user personas, storyboarding, early and rapid prototyping, observation analysis, and usability testing were implemented[451]. In recent decades, UCD has also incorporated concepts from both participatory and co-design, which commonly take a more problem-driven approach[448].

The evolution of UCD and its application in the development of medical devices such as rehabilitation technologies is supported by the ISO 9241-210:2010 standard[70] . The ISO provides a comprehensive framework of the activities to be undertaken when following a UCD approach. The standard emphasises that UCD approaches should engage users and relevant stakeholders in an iterative design and evaluation process through the entire project life cycle to produce a solution that prioritises the needs, characteristics, and tasks of the intended users[70]. Applying UCD principles early in the development of rehabilitation technology can help a development team characterise and investigate how their target users behave; better understand user requirements[450]; and identify and resolve potential usability, acceptability, and functionality issues[453-456]. Involving users from the beginning often minimises the need for design changes later in the development process[457] and significantly reduces development time and costs[458]. Despite this, the use of UCD in the development of rehabilitation technologies is rare[459]. This could be due to a failure to recognise the significance of usability testing, limited expertise or experience in the application of UCD, failure to report how UCD principles have been incorporated into the technology development, limited time and resources, or rehabilitation technology designs being based on requirements that developers prioritise over those of potential users[453,460]. The following section provides an overview of the UCD approach that was used to develop exciteBCI in accordance with the ISO 9241-210:2019 standard[70].

[redacted]

[redacted]

[redacted]

7.5 Summary

Optimising usability and acceptability of rehabilitation technologies to support their translation into clinical practice can maximise adoption and sustained use of the technology, and may contribute to better outcomes for people with stroke. This chapter has outlined the development of the exciteBCI rehabilitation technology in accordance with the UCD process described by the ISO 9241-210:2019 standard. This included the three initial stages of the process (1) understanding and specifying the context of use; (2) specifying user requirements; and (3) exploring design solutions through ideation, iterative prototyping, and testing activities and feedback from users and stakeholders. The following chapter presents the next stage of this process.

Chapter 8. A BCI Neuromodulatory Device for Stroke Rehabilitation: An Iterative User-centred Design Approach

8.1 Prologue

This chapter describes the exciteBCI UCD evaluation process, which involved usability testing with people with stroke and physiotherapists and corresponds to Stage 4 of the ISO 9241-210:2019 standard[70].

This submitted manuscript relates to the following thesis objective:

Objective 2: Optimise the usability and acceptability of the exciteBCI, a portable medical wearable device in the prototype stage, to support its translation to clinical practice by:

(i) Identifying the exciteBCI device requirements from the perspective of people with stroke and physiotherapists and;
(ii) Exploring people with stroke and physiotherapists' perceptions and experiences of the exciteBCI, and how well it fits with rehabilitation.

Minor formatting adjustments have been made to the submitted manuscript to ensure uniformity throughout the thesis. Associated supplementary materials can be found in Appendix E. These include the semi-structured interview frameworks.

A BCI neuromodulatory device for stroke rehabilitation: An iterative user-centred approach

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8.2 Abstract

Background: Rehabilitation technologies for people with stroke are rapidly evolving. These technologies have the potential to support higher volumes of rehabilitation to improve outcomes for people with stroke. Despite growing evidence of their efficacy, there is a lack of uptake and sustained use in stroke rehabilitation, and a call for user-centred design approaches during technology design and development. This paper focuses on a novel rehabilitation technology called exciteBCI, a complex neuromodulatory wearable technology in the prototype stage that augments locomotor rehabilitation for people with stroke. exciteBCI consists of a brain computer interface, a muscle electrical stimulator, and a mobile application.

Objective: This study presents the evaluation phase of an iterative user-centred design approach supported by a qualitative descriptive methodology that sought to i) explore users' perspectives and experiences of exciteBCI, and how well it fits with rehabilitation and ii) facilitate modifications to exciteBCI design features.

Methods: Iterative usability evaluation of exciteBCI was completed in two phases. Phase one consisted of three sprint cycles made up of single usability sessions with people with stroke (n = 4) and physiotherapists (n = 4). During their interactions with exciteBCI, participants used a 'think-aloud' approach followed by a semi-structured interview. At the end of each sprint cycle, device requirements were gathered, and the device was modified in preparation for the next cycle. Phase two focused on a 'near-live' approach in which two people with stroke and one physiotherapist participated in a 3-week programme of rehabilitation augmented by exciteBCI (n = 3). Participants completed a semi-structured interview at the end of the programme. Data were analysed from both phases using conventional content analysis.

Results: Overall, participants perceived and experienced exciteBCI positively, whilst providing guidance for iterative changes. Five interrelated themes were identified from the data: 1) 'This is rehab' illustrated that participants viewed exciteBCI as having a good fit with rehabilitation practice 2) 'Getting the most out of rehab' highlighted that exciteBCI was perceived as a means to enhance rehabilitation through increased engagement and challenge, 3) 'It is a tool not a therapist', revealed views that the technology could either enhance or disrupt the therapeutic relationship; 4) 'Weighing up the benefits versus the burden', and 5) 'Don't make me look different' emphasized important design considerations related to device setup, utilization and its social acceptability.

Conclusions: The study offers several important findings which inform the design and implementation of rehabilitation technologies. These included: 1) the design of rehabilitation technology should support and enhance the therapeutic relationship between the patient and therapist; 2) social acceptability is a design priority in rehabilitation technology but its importance varies dependent on the use context; and 3) there is value in employing design research methods which support understanding usability in the context of sustained use.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12617001527358

Keywords: User-centred design; Stroke; Rehabilitation technology; Wearable technology; Brain Computer Interface; BCI; Mobile Application; Think-aloud, Near Live; Semi structured interviews

8.3 Introduction

Stroke is a major health, socioeconomic, and financial burden that affects over 12 million people annually worldwide[474]. Despite advances in stroke prevention, the incidence of stroke is anticipated to rise due to population growth and ageing[475]. Following a stroke, up to 80% of people experience difficulty with locomotion[10,11]. Locomotion refers to the ability to move from one place to another[1] and encompasses a wide range of activities such as getting on and off a chair, walking indoors, climbing stairs, and navigating obstacles, terrains, and environments. While most people with stroke regain some ability to walk unassisted, less than 20% achieve unrestricted community locomotion[20,21]. Rehabilitation can reduce locomotor disability following stroke, particularly when delivered in large volumes[25-31], yet observational studies confirm the amount of rehabilitation received is limited, translating into poorer outcomes for people with stroke and consequent life-long disability[32-37]. Thus, innovative approaches to stroke rehabilitation are needed.

The last two decades have seen the rapid development of rehabilitation technologies such as robotics, virtual reality, neuromodulation devices, activity monitors, and mobile applications designed to augment rehabilitation after stroke. While there is evidence that these technologies can increase the amount of rehabilitation a person with stroke receives and improve outcomes[30,31,157-162], user adoption and sustained use of such technologies remains low[215,476-481]. The disconnect between initial efficacy and clinical translation likely relates to the usability of these technologies and their acceptability to users[209,482]. As a result, there has been a call for increased application of user-centred design approaches in the development of rehabilitation technologies[209,483,484]. Adopting user-centred design approaches can support the development of usable and acceptable technologies by prioritising the user's needs, involving users and relevant stakeholders throughout the project life cycle, and modifying the design of the technology based on iterative user-centred evaluation[70,453].

Non-invasive neuromodulatory interventions are one rehabilitation technology with potential to maximise rehabilitation outcomes and reduce physical disability. Typically, these interventions involve repeated magnetic or electrical stimulation to the central and/or peripheral nervous systems in order to induce neural plasticity[41]. Non-invasive

neuromodulatory interventions that target movement control have the potential to accelerate stroke recovery when combined with traditional rehabilitation[42-45]. However, such interventions often rely on complex medical devices and user interfaces operated by expert operators and lack usability and acceptability. To maximise the potential for successful implementation in rehabilitation practice, the research and development of non-invasive neuromodulatory technologies must include a user-centred approach[485,] In this paper, we present a complex neuromodulatory rehabilitation technology (exciteBCI) and its evaluation in a user-centred design research process.

8.3.1 exciteBCI

exciteBCI is a prototype, portable, medical wearable device designed to deliver neuromodulation during locomotor rehabilitation for people with stroke. The device uses a brain-computer-interface (BCI) in which a specific electroencephalography (EEG) signal, that reflects the person's intention to move, is extracted and paired with the afferent stimulus from peripheral electrical stimulation[53,54]. The electrical stimulation is timed to precisely coincide with the EEG signal in the motor cortex to induce neural plasticity[53,54].

exciteBCI evolved from an endeavour to translate a neuromodulatory intervention that had been tested in healthy and stroke populations in a clinical research laboratory setting[53,54,56,58,61,63,252,486,487], into a rehabilitation device suitable for the stroke rehabilitation context. Prior feasibility work found that the neuromodulatory intervention, when delivered during simple ankle movements while seated, was not acceptable to people with stroke and was not feasible for rehabilitation[64]. The equipment was deemed cumbersome and uncomfortable, the setup time excessive, and the movement tasks were considered meaningless and boring by people with stroke. Given that qualitative evidence indicates that rehabilitation should be centred around meaningful real-world activities that reflect the person's aspirations, and should be practised at progressively higher intensities[40,65], these perspectives have important ramifications for the implementation of the intervention in clinical practice and ensuring sustained use.

The iterative user-centred design process for developing exciteBCI has been guided by the International Organization for Standardization (ISO) 9241-210:2010 standard[70] and was driven by a transdisciplinary team comprised of physiotherapists, biomedical engineers, product designers, user experience and user interface designers, and a lived experience researcher. Initial work involved the following three phases (1) Understanding and specifying the context of use, (2) Identifying user requirements, and (3) Iteratively

developing design solutions[488]. This paper reports the fourth stage of ISO 9241-210:2010 standard[70]: (4) Evaluating the design. The aims of the research were to: i) explore users' perspectives and experiences of exciteBCI and how well it fits with rehabilitation, and ii) facilitate modifications to exciteBCI design features.

8.4 Method

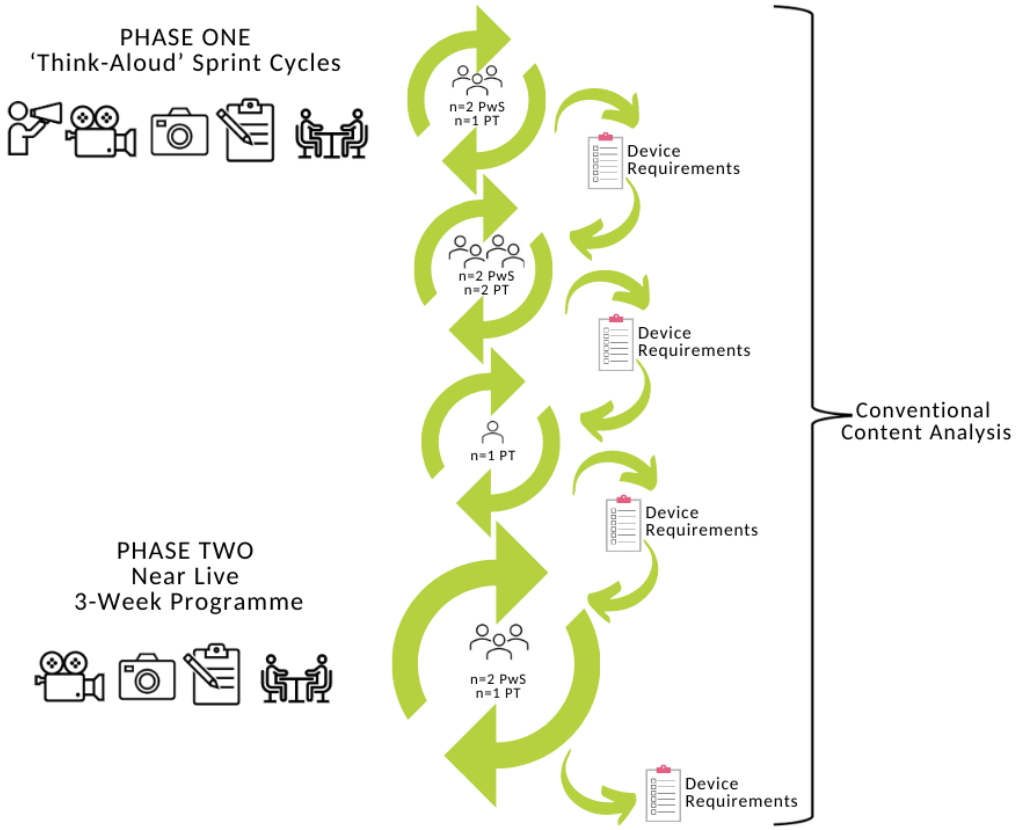
8.4.1 Study design

The evaluation phase of an iterative user-centred design approach supported by a qualitative descriptive methodology was used to address the aims of this study. In this study, users were people who had experienced a stroke and physiotherapists working in stroke rehabilitation. The study consisted of two phases. In phase one, a series of usability testing sprint cycles were conducted[489]. In phase two, a 'near-live'[490] testing approach was used in which two participants with stroke and a physiotherapist undertook a 3-week intervention of locomotor rehabilitation augmented by exciteBCI (see Figure 8.1).

8.4.2 Ethical Considerations

The study was approved by the New Zealand Health and Disability Ethics Committee (17/NTA/177) and locality authorisation was endorsed by the Auckland University of Technology Ethics Committee (17/373). Prior to the study all participants provided written informed consent. The privacy and confidentiality of participants was protected by secure storage of all data and deidentification of data where feasible. Participants received a NZD $40 gift voucher for each session they attended in acknowledgement of their contribution.

Figure 8.1 Overview of study design, data collection procedures, and data analysis

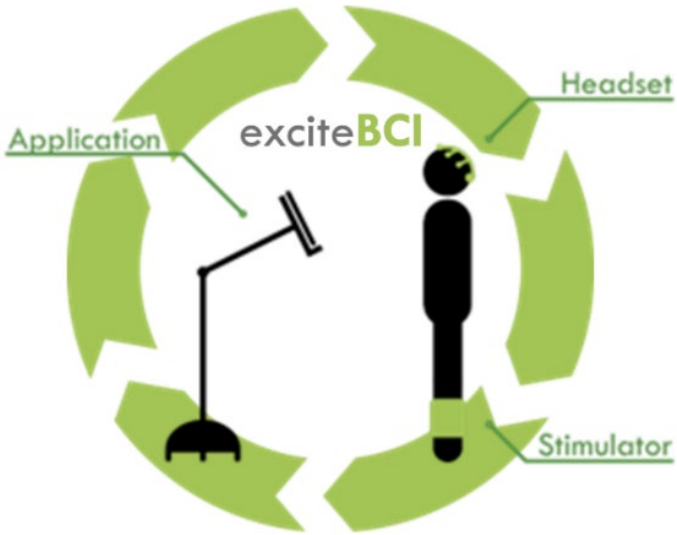


PwS; people with stroke, PT; physiotherapist.

8.4.3 exciteBCI prototype

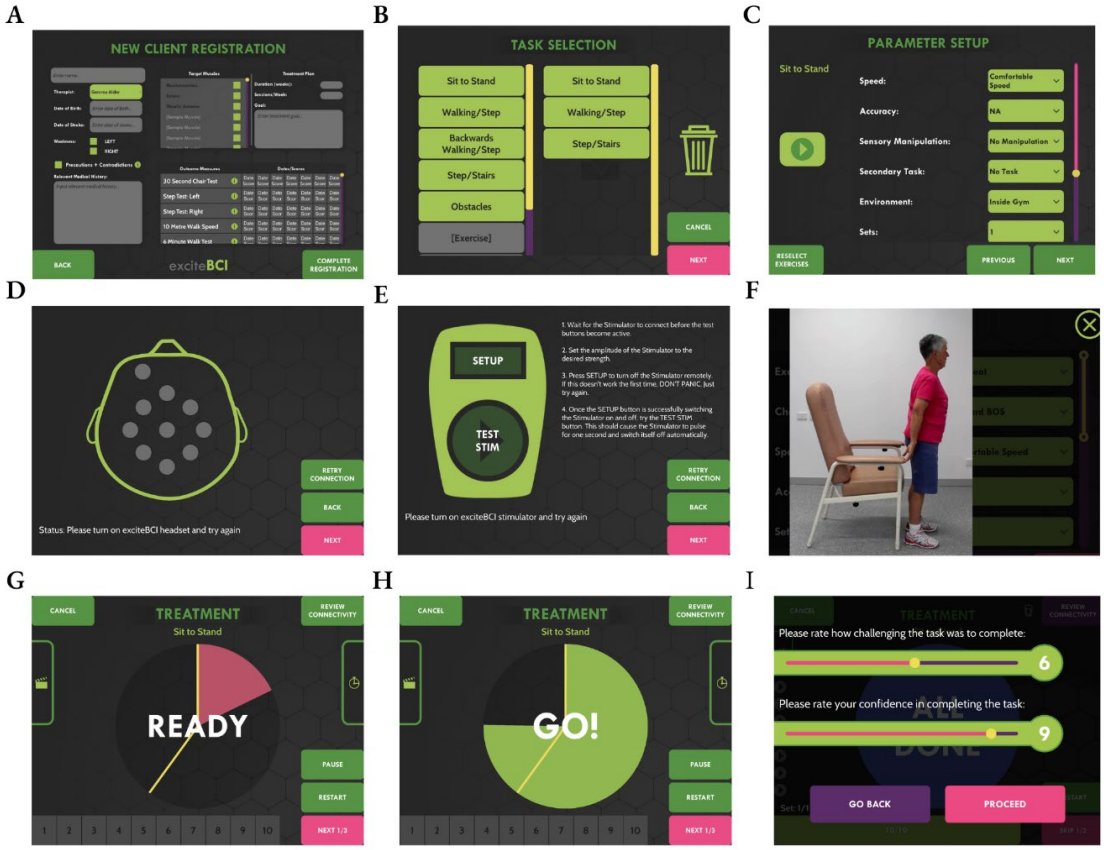
The exciteBCI prototype evaluated in this research is intended for clinical use, in collaboration with a qualified physiotherapist in an inpatient, outpatient, or community setting. exciteBCI has three components—two wearable components including an EEG headset and a muscle stimulator; and a third component, a mobile application. The three components communicate wirelessly (See Figure 8.2).

Figure 8.2 The exciteBCI consists of three components; an EEG headset, a muscle stimulator, and a mobile application, each of which communicates wirelessly



The EEG headset included nine gel electrodes capable of recording brain activity that was used to predict when the person with stroke was going to move. The muscle stimulator (NeuroTrac® Rehab, Auckland, New Zealand) was housed within a neoprene sleeve and worn during rehabilitation tasks to deliver electrical stimulation to a lower limb muscle. The muscle stimulator delivered the afferent stimulus which was paired with EEG brain activity to induce neural plasticity. The exciteBCI App was designed to support the delivery of the intervention. It included locomotor tasks cued with an audio-visual prompt. The locomotor tasks could be selected, and the task parameters such as number of repetitions, movement speed, and rest time manipulated to create an individualised locomotor rehabilitation programme. See Figure 8.3 for example screen shots from the exciteBCI App interface prototype v3.3. This version of the App was presented to participants during the first sprint cycle of phase one.

Figure 8.3 Example screenshots from the exciteBCI App interface prototype v3.3



(A) Registering a new patient, (B) the task selection suite where the patient and therapist select tasks that align with the patient's goals, (C) the parameters that can be manipulated for each task by the therapist to ensure an optimal level of task difficulty, (D) checking the impedance levels of the EEG headset, (E) the muscle stimulator is connected to the App and stimulation amplitude saved, (F), the patient watches a video on how to perform the task, (G-H) the timing signal (auditory-visual cue) to get ready and execute the task, (I) the patient completes the task difficulty and confidence ratings at the end of the task set.

8.4.4 Participants

People diagnosed with a stroke at least 6-months prior who presented with some restriction of the foot and ankle movement limiting locomotor function were recruited. People with English language limitations, cognitive, perceptual, and/or communication impairments, who were unable to engage in the research process even with support of a family member or a health professional, were excluded. New Zealand registered physiotherapists with at least 5-years professional experience in the field of neurological rehabilitation were recruited.

Networking with local healthcare and rehabilitation providers, and community advertising, was employed to recruit a convenience sample of participants. Prior to participating in the study all participants provided written informed consent.

8.4.5 Procedures and data collection

Phase one: think-aloud sprint cycles

People with stroke (n = 4) and physiotherapists (n = 4) participated in a single 1-hour usability testing session where they interacted with the exciteBCI prototype using a 'think-aloud' approach[491] followed by a semi-structured interview[492] (refer to Figure 8.1). At the end of each sprint cycle, user device requirements were compiled, and changes were made to the user interface and device before the next sprint cycle began. Participants were asked to use a 'think-aloud' process by verbalising their thoughts, observations, and opinions while interacting with the exciteBCI prototype in a planned series of activities (see Table 8.1). The researcher's interactions were kept to a minimum to support participants to fully engage in the 'think-aloud' process, but, when necessary, the researcher prompted the participant with phrases like "tell me what you're thinking now." Video and audio recordings, photographs, and researcher observations (TB, SO, UR) were used to capture the think-aloud process. Semi-structured interviews were conducted by two experienced researchers (GA, NS). The interviews were audio recorded and focused on participants experiences and opinions of the device, functionality, design features, and suggested improvements. See Appendix E.5 for phase one indicative interview questions. Consecutive participants participated in the sprint cycles until no new insights or changes to the exciteBCI device's design features were provided[493,494].

Phase two: 'near-live' programme of rehabilitation

A 'near-live' testing approach[490] was carried out in which two people with stroke engaged in a 3-week programme of locomotor rehabilitation augmented by exciteBCI (Soft Headset v2, App v3.6, Electrical Stimulator v.3). Eight 1-hour rehabilitation sessions took place in an outpatient clinical setting supervised by a New Zealand registered physiotherapist with 10-years of clinical experience in stroke rehabilitation (GA). Prior to the rehabilitation sessions, participants attended an initial assessment and planning session to establish locomotor-related goals and completed clinical outcome measures. Clinical measures included the 30-second Chair Stand test; 10-metre walk test; 6-minute walk test; four step square test; and lower limb muscle strength testing of the ankle dorsiflexors, ankle plantar

flexors, knee extensors, and hip flexors using a hand-held dynamometer[495]. Clinical measures were collected again at the end of the rehabilitation programme.

The rehabilitation programme was based on current evidence-based practice as recommended in the National and International Clinical Guidelines for Stroke[22-24] and included goal-oriented task-specific training of locomotor-related skills that were deemed important to the participant. The physiotherapist prescribed three to four different tasks from the suite of tasks within the tablet-based exciteBCI App per session. Informed by the principles of motor learning[172] the rehabilitation tasks were progressed over the programme based on the participant's rating of perceived difficulty for each task using a numerical visual analogue scale (VAS). Task parameters were manipulated, or new tasks were prescribed, to achieve a challenge point of 6-8 out of 10 on the task difficulty VAS scale for each task[65]. Participants completed between 30 and 100 repetitions of each task during the 1-hour session. The participant used the exciteBCI throughout the rehabilitation programme, which delivered electrical stimulation to the tibialis anterior muscle to coincide with the person's intended movement. Approximately 10-minutes of the 1-hour session was attributed to the donning and doffing of the equipment.

All rehabilitation sessions were video recorded and researcher observation notes (NS, TB) of the participant interactions with the exciteBCI prototype and photographs were taken at each session. Following completion of the rehabilitation programme, the participants with stroke and the physiotherapist (GA) took part in separate semi-structured interviews. Interviews were conducted by two experienced researchers (GT, SM) who were not involved in the development of exciteBCI. The interview focused on participant opinions and experiences of using the device within a rehabilitation context and included specific questions in response to video observations of the rehabilitation programme. All interviews were audio recorded. See Appendix E.6 for phase two indicative interview questions.

Table 8.1 Examples of activities used in phase one sprint cycles to facilitate the 'think-aloud' process

Physiotherapists	People with Stroke
1. Use the tablet to complete the initial client registration (10-15min).	
2. Use the tablet to design a task-specific training programme for a client (10-15min).	
3. Follow the instructions to set-up the headset (10-15min).	
4. Follow the instructions to set-up the electrical stimulation and place electrodes on the tibialis anterior muscle (10-15min).	
5. Calibrate the system - complete the task-specific training while the headset records your model's brain signals (10-20min).	1. Now you are set-up, follow the cue on the tablet to perform the exercises and we will record your brain signals (20-30min).
6. Complete task-specific training while your model receives the paired intervention (5-10min).	2. Follow the cue on the tablet screen to complete the exercises while receiving the neuromodulatory intervention (20-30min).
7. Remove the headset and electrical stimulation device (5-10min).	3. Please rate how difficult it was to perform that task and how confident you felt performing the task (5-10min).
	4. Donning and doffing of equipment (10-15min)

Since the time spent on each activity varied across participants, a time range (minutes) is listed against each activity. Similarly, the number of task-specific training exercises and associated repetitions varied across participants (2-4 exercises 20-80 repetitions per exercise). For the physiotherapist session the model was a member of the researcher team.

8.4.6 Data analysis

'Think-aloud' and interview data were transcribed verbatim. The transcripts and written observation notes were imported into NVivo 12 computer software package[496]. Data

analysis was undertaken in two stages. In the first stage, transcripts and videos were descriptively analysed by the primary researcher (GA) to identify user interface and device requirements within each sprint cycle. This analysis was then discussed with the team to inform the development of the device prior to the next cycle. This analysis also served as a familiarisation for the second stage of analysis.

The second stage of analysis focused on addressing the aim, to explore users' perspectives and experiences of exciteBCI, and how well it fits with rehabilitation. This stage used a modified version of conventional content analysis[497] and analysed data from both phases of the study. Conventional content analysis allows the researcher to immerse themselves in the data to acquire an accurate description of what participants experienced and understood about the topic at hand[492]. The data were coded inductively by the primary researcher (GA) at the sentence or phrase level, and a semantic coding framework was iteratively developed during the data analysis process[498]. Several activities were employed to enhance the understanding of code relationships, such as continuous comparisons within and between codes and data sources, as well as the practice of memoing to capture initial insights about the data and potential interactions among codes[499]. The coded data iteratively informed the development of categories. Categories and representative coded data were visually represented using a mind map in MIRO Application (miro.com) to support the development of themes. The coded data, categories, and prototype themes were reviewed by and discussed with two researchers (NS and GT) in a series of analysis meetings to ensure consistency of interpretation.

8.5 Results

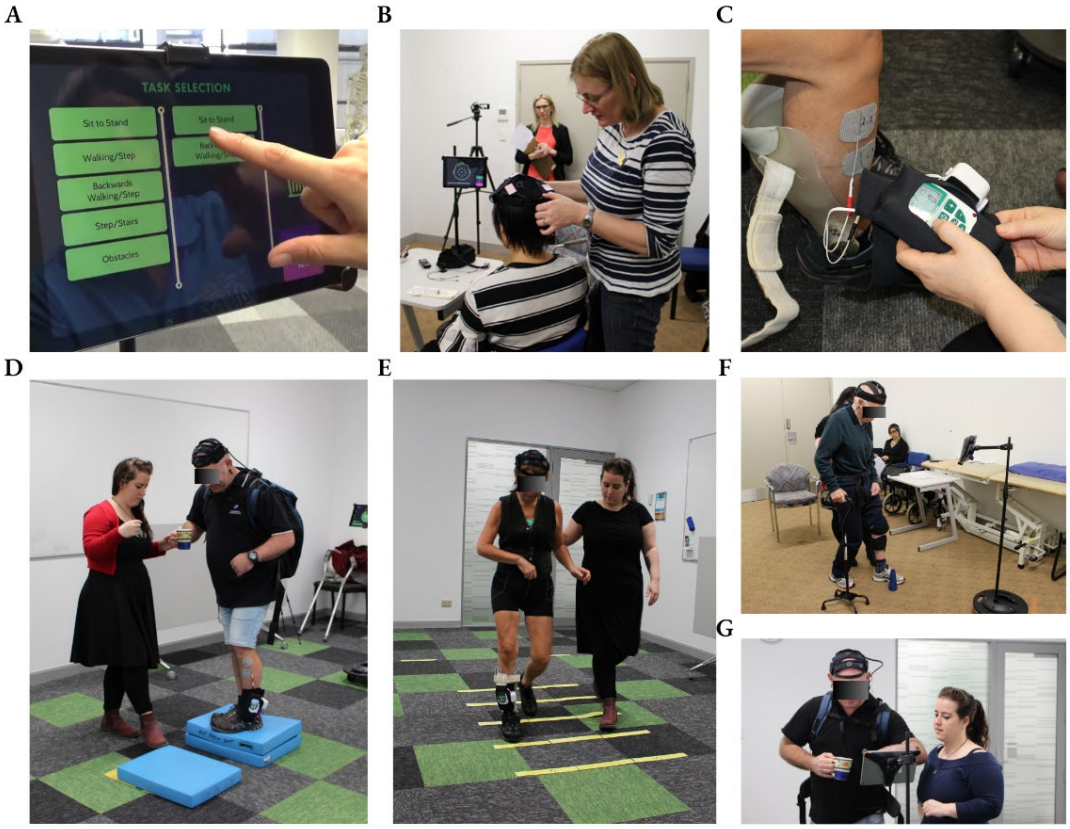
Eleven people participated in the study with no adverse events reported. Table 8.2 presents the demographic and clinical characteristics of participants and Figure 8.4 displays photographs of participants interacting with the device in phases one and two of usability testing. In the interests of intellectual property protection, the iterative device requirements to the user interface and the device are not presented in this paper.

Table 8.2 Participant characteristics

Demographic characteristic	Category	n
People with Stroke ($n = 6$)		
Type of stroke	Ischemic: Haemorrhagic	3:3
Lesion location (hemisphere)	Right: Left	4:2
Mean time since stroke	7 (2-19) years	-
Types of impairments	Motor	6
(n >6 due to some participants	Sensory	4
presenting with multiple impairments)	Perceptual	2
	Cognition	2
	Communication	1
Functional ambulation category scores[461]		
Non-functional walker (unable to walk)	0	0
Dependent walker requires continues manual contact	1	0
Dependent walker requires intermittent manual contact	2	1
Dependent walker requires verbal supervision/guiding	3	1
Independent walker on level surfaces only	4	3
Independent walker on any surface	5	1
Prior experience of technology components		
FES (n >6 due to experience in more than one category)	Clinical	4
	Research	3
	No experience	1
BCI	Clinical	0
	Research	3
	No experience	3
Mobile Application-based interventions	Clinical	0
	Research	0
	No experience	6
Gender	Female	3
	Male	3
Ethnicity	New Zealander	3
	European	2
	Asian	1
Age	<45 years	1
	45-65 years	2
	>65years	3
Physiotherapists ($n = 5$)		
Years qualified as a physiotherapist	5-10	1
	10-20	3
	>20	1
Highest qualification	Bachelor of Science	4
	Masters	1
Years of clinical experience in stroke rehabilitation	5-10	3
	10-20	1
	>20	1
Prior experience of technology components		
Years experience using FES	2-12	5
Years experience using BCI	3 (research context)	1(GA)
*Years experience using Mobile Applications for rehabilitation**	3-10 years	5
Gender	Female	5
Ethnicity	New Zealander	3
	European	2

BCI; Brain-computered interface, FES; functional electrical stimulation, GA; Primary author. * Video mobile applications to capture patients' performance and /or exercise provision mobile applications.

Figure 8.4 Photographs of participants from phase one sprint cycles and phase two 'near-live' 3-week programme interacting with the exciteBCI device

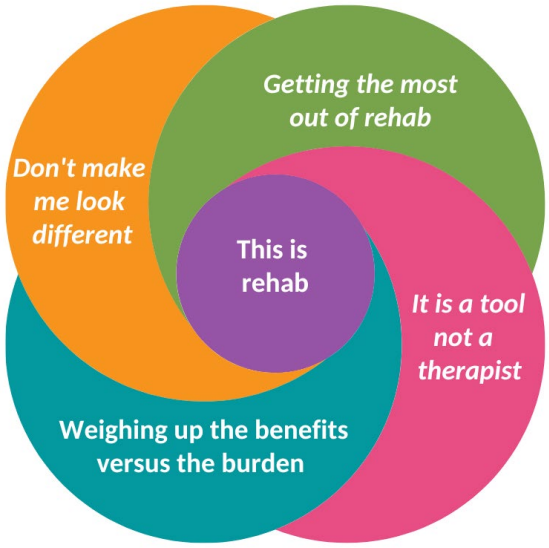


(A) A participant with stroke and physiotherapist work in partnership to select task-specific training exercises in the exciteBCI App, (B) A physiotherapist participant setting up the EEG headset, (C) A physiotherapist setting up the muscle stimulator on a participant with stroke, (D-F) Participants with stroke engaging in locomotor rehabilitation whilst wearing the exciteBCI device and receiving the neuromodulatory intervention with the physiotherapist, (G) A participant with stroke using the App rating scale of perceived rehabilitation task difficulty to inform the physiotherapist about the challenge-point of the task.

Overall, the findings showed that both participants with stroke and physiotherapists had positive perceptions and experiences of the exciteBCI intervention and could see it being used in a rehabilitation context. Five themes were generated from the data and are presented in Figure 8.5. Central was the theme 1) This is rehab, which interacted and was

influenced by the themes 2) Getting the most out of rehab, 3) It is a tool not a therapist, 4) Weighing up the benefits versus the burden, and 5) Don't make me look different. Illustrative quotes that corroborate the data have been selected for thematic representation, and pseudonyms have been used.

Figure 8.5 The relationship of themes associated with the users' perceptions and experiences of exciteBCI, and how well it fits with rehabilitation



8.5.1 Theme 1: This is rehab

At the core of the findings was the theme, 'This is Rehab'. Despite being a novel technology incorporating a BCI and App, both physiotherapists and people with stroke identified that the exciteBCI was clearly a rehabilitative tool suitable for supporting and augmenting rehabilitation practice.

> *At first, I thought, it's not a new treatment […] we're doing something that's extra, but it's basically just facilitating what we're doing anyway. (Sarah, Physiotherapist, Sprint Cycle 2)*

> *For clinical use, the intervention worked brilliantly. (Anni, Age 58, PwS, 3-week programme)*

Many expressed surprise at how congruent the technology was with their own clinical practice and their understanding of rehabilitation principles. This congruence appeared to enhance perceptions of usability and acceptability. They readily identified the ways in which the technology could be integrated into current rehabilitation practice.

> *It doesn't seem to be over complicated, and once you use it on a daily basis more or less it's actually not that difficult. (Zoe, Physiotherapist, Sprint Cycle 2)*

Participants were easily able to understand the purpose and mechanism of the intervention. Physiotherapist participants drew on their understanding of functional electrical stimulation (FES), a modality commonly used in clinical practice, in understanding the physiological underpinnings of the paired neuromodulatory intervention. They identified that the exciteBCI device could offer benefits over FES, particularly in relation to the way the person's own brain signals are used to drive the delivery of electrical simulation and suggested that this would enhance outcomes from rehabilitation.

> *With an external stimulus like the FES hand switch, I need to try and time it right. So, it's not that, it's not inconvenient it's just […] makes more sense to take the relationship internally rather than externally. It's the patients driving it […] And I think that will facilitate learning more. (Sarah, Physiotherapist, Sprint Cycle 2)*

Physiotherapists described how the exciteBCI App would support them to deliver effective rehabilitation by supporting their clinical reasoning process, enabling specificity in the design of rehabilitation programmes and promoting efficiency. They particularly valued the way the exciteBCI App aided them to think about different aspects of task specific training. However, they also consistently emphasised the importance of being able to tailor rehabilitation to the individual. This prompted them to describe additional App features which might support further personalisation.

> *What this shows [points to video playing task], it's the goal of doing it perfectly well, but it might not look like that for them [the client]. Would be great if the actual client performing the task can be videotaped as well. (Sarah, Physiotherapist Sprint Cycle 2)*

> *Shopping bags, washing basket so they are the things that we would [..] quite commonly do, but […] when I choose secondary tasks, I often choose things that I know this patient is going to do and relates to their goals […] so a customize option is essential (Zoe, Physiotherapist Sprint Cycle 2)*

Attention to an efficient workflow, minimising duplication of information being entered, and system interoperability were also priorities for physiotherapists. They particularly valued how the exciteBCI App could support efficient and comprehensive clinical record keeping and support handover between therapists.

> *I would think about a lot of these different parameters, but I might not be as explicit about them in my notetaking […] this is way more thorough […] structured […] easy to follow, easy to pick up on for next time […] and so much quicker. (Megan, Physiotherapist, Sprint Cycle 1)*

Physiotherapists identified the challenge associated with the use of clinical terminology and language, calling for App features, such as icons and pop-up definitions, which would support users to have a clear understanding of key terms.

> *Accuracy? so I've got large target, small target, wide path, small path […] so path I presume means width? […] I think photos or icons is a really good thing to just clarify stuff- probably more than words. (Megan, Physiotherapist, Sprint Cycle 1)*

Most also described the need for prior hands-on training opportunities led by an experienced clinical expert, specifically addressing the rehabilitation approach, device setup, and troubleshooting. This was deemed essential to support the successful uptake of the technology into rehabilitation. Additionally, they recommended incorporating training and troubleshooting videos directly into the App.

8.5.2 Theme 2: Getting the most out of rehab

People with stroke and physiotherapists described the ways in which the exciteBCI, and in particular the App, could support people with stroke to engage in more intensive and challenging rehabilitation at higher doses. Participants valued the way the exciteBCI supported people with stroke to work hard. This was achieved in multiple ways. Firstly, the App enabled physiotherapists to design specific and challenging rehabilitation programmes for patients.

> *It just was a really nice, structured way of […] finding that sweet spot to maintain challenge but for the participants to feel they are making progress and all that hard work is paying off. (Gemma, Physiotherapist, 3-week programme)*

Secondly, the task difficulty rating scales supported both people with stroke and physiotherapists to judge the challenge of each task and served as a prompt to work on more challenging tasks.

> *[…] and the rating scale is really helpful too. You have a bit more about what's challenging for them and what's not. Gives you a better starting point. (Zoe, Physiotherapist, Sprint Cycle 2)*

Thirdly, the audio-visual cue that prompted the onset of movement compelled people with stroke to remain focused. By setting the time of task practice, limiting the amount of rest, and promoting attention on the task, large volumes of rehabilitation were achieved.

> *[…] I think the way that the system has been constructed is quite focus oriented…It's actually keeping the time […] you get so much more in [the session]. (Anni, Age 58, PwS, 3-week programme)*

Together, these factors supported people with stroke to work at intensities and volumes beyond what they normally would achieve during rehabilitation. This supported substantial gains in balance and walking and, in turn, built self-efficacy.

I felt a sense of achievement you know, and that's what's important, I'm still making progress. (Jake, Age 44, PwS, 3-week programme)

These findings illustrate that both people with stroke and physiotherapists discovered a number of features within the App which support fundamental rehabilitation principles.

8.5.3 Theme 3: It is a tool, not a therapist

Participants with stroke emphasised that developing a trusted relationship with their therapist was fundamental to their rehabilitative journey. They discussed the ways in which the App might support or disrupt this relationship. Participants in phase one raised the possibility that the App could disrupt the therapeutic relationship.

[…] Physically having the device and therapist there complicates the relationship…so the therapist really needs to make sure their cues show engagement and interest […] there is a risk here. (Thonia, Lived experience researcher)

While those that participated in the 3-week programme did not highlight the same concern, all participants stressed that the App was a therapeutic tool which should not be viewed as a substitute for the therapist.

[…] if you feel I handed over the therapy session to this [App] and I've cognitively left the building, then that is disastrous, to our relationship and their treatment. If I'm not engaged, why would they want to be. (Jude, Physiotherapist, Sprint Cycle 3)

Most participants indicated that they would be happy to use the App independently; however, the majority indicated a preference for using the device with the physiotherapist present. They described how the physiotherapist offered guidance and feedback about their performance and progress.

So, if I'm not doing a sit to stand correctly [points at App] then who is going to correct me? [...] I like the feedback from the therapist, because at some point the quality of the movement does matter. (Lilly, Age 64, PwS, Sprint cycle 1)

Participants also described how the physiotherapist motivated them to work harder by encouraging them to do their best work while also understanding their personal limits in a way that the App could not.

The physiotherapist can push you further. They can see that you can be pushed extra. Which is important […] people get tired, aagh and ready to give up, whereas the therapist goes another 10-minutes. Helps you squeeze out that last little bit. (Bob, Age 84, PwS, Sprint cycle 1)

Consequently, some participants felt that the exciteBCI either should not or could not be used without the support of a physiotherapist. These findings illustrate that attention to the

impact of the technology on the therapeutic relationship during both design and implementation of rehabilitation technology is essential.

8.5.4 Theme 4: Weighing up the benefits versus the burden

While both people with stroke and physiotherapist participants saw the benefits and potential of exciteBCI, they also called for "real world evidence" of effect, research-based evidence, or endorsement from a trusted source.

> *[…] If I knew it was going to bring about a speedier recovery, I would be more likely to use it. (James, Age 74, PwS Sprint cycle 2)*

> *If my physio turned up with it, I wouldn't mind at all. (Jenny, Age 67, PwS, Sprint cycle 2)*

Those who engaged in the 3-week programme drew on their own experiences of the intervention to generate "real-world evidence".

> *When we visited French festival, I was helped up onto the raised platform advertising electric cars […] Renault Twizy. I don't think I was pressing down on my husband's hand as much, on 'reaching' up, and managed to squeeze myself into the car-space for a photo or two, […] great! Extending my reach, even just a wee bit, was brilliant. (Anni, Age 58, PwS, 3-week programme)*

Physiotherapists described how they would consider cost, client suitability, set-up time, workflow, and clinical effectiveness when deciding on whether to adopt the exciteBCI intervention.

> *I would need to know it was going to make a really big difference to invest in purchasing it and have a fair amount of clients I could use it with. […] it's difficult without actually using it in clinical practice as to know sort of who would really benefit. (Megan, Physiotherapist, Sprint Cycle 1)*

While participants with stroke called for the device to be integrated into their rehabilitation as early after stroke as possible, some physiotherapists saw a tension between the set-up time of both the headset and the App and the decision to implement the device in different clinical contexts.

> *I don't think [..] you'd use it on an acute ward […] I think it takes too much time [....] based on how much time […] physios have based in my experience […] I just think time and all the equipment there and everything else that goes on. I don't, can't see it working. In a rehab ward maybe. Definitely outpatients. (Jude, Physiotherapist Sprint Cycle 3)*

When discussing use of the device in the home, participants with stroke and physiotherapists from phase one (single session) viewed the headset as a potential barrier to

adopting the device. This was mainly due to the perceived difficulty of setting it up independently for those with upper limb disability, and the need for gel to be inserted into the EEG electrodes while wearing the headset. The set-up of the electrical stimulator and App were not viewed in the same light. While the people with stroke who participated in the 3-week programme expressed similar concerns, they were eager to offer suggestions to also make it a viable option for independent use.

8.5.5 Theme *5*: Don't make me look different

Almost all participants emphasised how the social acceptability of the device would influence their desire to use it. The need for a socially acceptable device design was less important in a clinical setting or at home than if the device was being used in a public or social context.

> *It's [the headset] not for glamour it's for results […] it's the job it's doing, reading the brain. Glamour doesn't matter, does it? If there's certain areas of the brain it can read, it's got to work. It doesn't matter what it looks like […] not whilst you're doing rehab. You're there for the rehab. (Lilly, Age 64, PwS, Sprint cycle 1)*

Never-the-less, most participants called for a device which did not draw attention to themselves or their disability.

> *Many people find it difficult to approach you, when you walk differently, or they treat you differently […] So, you can understand why I would value a design that doesn't make me look even more different than I already do. (Jenny, Age 67, PwS, Sprint cycle 2)*

Participants posited that what constitutes a socially acceptable device might also vary depending on a person's gender, age, and culture. The length of time since their stroke diagnosis and how much rehabilitation was prioritised in their daily lives also appeared to influence the participants' perspectives of whether they would consider using the wearable device in their daily lives.

> *Initially I would [during inpatient rehab] […] you're ready to take anything that you think will help but what shifts the balance of that is I think it's about - I'm more progressed now and more - I want people to see me where I'm at now. (James, Age 74, PwS, Sprint cycle 2)*

Concerns about the social acceptability of the device largely pertained to the aesthetics of the headset and the EEG gel. The current headset design was viewed as unacceptable for wearing out in public where social perceptions play a role. Minimising and concealing the device with clothing or incorporating it into something that looked familiar and fits with everyday life, such as a hat or headphones, was seen as an important future design

consideration. Participants from phase one perceived there to be no issue with the use of EEG gel in a rehabilitation environment. While participants in the 3-week programme described the inconvenience of repeated gel use and its impact outside of the rehabilitation context, they perceived the benefits they experienced from the intervention outweighed this inconvenience. In contrast, participants perceived the electrical stimulator to be more acceptable. It was noted that the electrical stimulator and its neoprene housing resembled sports braces which were considered socially acceptable and in common use.

8.6 Discussion

This study applied a user-centred design approach to explore the perspectives and experiences of people with stroke and physiotherapists when engaging with exciteBCI rehabilitation technology and how well it fits within a stroke rehabilitation context. The results support the acceptability of the exciteBCI intervention and its 'fit' with clinical practice, and will inform the requirements for future device development. The findings have also provided key insights which can inform the design and implementation of rehabilitation technologies more broadly.

8.6.1 Technology and the therapeutic relationship

This research highlights the importance of considering the impact of technology on the therapeutic relationship between patients and therapists. The therapeutic relationship refers to the relational process that takes place during clinical interactions. It is considered a critical aspect of rehabilitation by both patients and therapists[500-502]. Qualitative research in neurorehabilitation indicates that positive therapeutic relationships are pivotal in supporting patient engagement, positive patient experiences, and in enhancing patient outcomes[503,504]. The "It is a tool, not a therapist" theme identified that both people with stroke and physiotherapists who participated in the phase one single usability sessions cautioned that the exciteBCI App could be disruptive to the therapeutic relationship. Similar concerns have been raised in other health technology domains citing disruptions of the therapeutic relationship as a potential barrier to technology adoption[505-508]. In contrast, in the current study, participants that used the exciteBCI App over multiple sessions in phase two, highlighted how the technology could be successfully integrated into clinical interactions to support and enhance the therapeutic relationship. Participants described how utilising the rating scales within the exciteBCI App facilitated a shared understanding of the rehabilitative challenge, allowing the person with stroke to take control of their rehabilitation and identifying opportunities for progressing rehabilitation challenge in

collaboration with the physiotherapist. However, this required the physiotherapist and the person with stroke to be mindful of the role of the technology, its value and limitations, and to use it purposefully and appropriately.

The current findings combined with previous literature emphasise how crucial it is to take the patient, therapist, and technology triad into account when designing and implementing rehabilitation technology. While research in telehealth has attended to the influence of technology on the therapeutic relationship over time and its implications for usability [509-511], the same attention has not been given to the development of rehabilitation technology devices. Understanding the influence of the technology on clinical interactions and workflow, and the ways in which these change over time is critical. Being attuned to the impact rehabilitation technologies have on therapeutic relationships requires a deep understanding of the role of the therapist and patient, and the rationale for the technology. This knowledge should be applied in two ways: (1) designers and developers should explicitly consider how the design of the technology can support and strengthen the therapeutic relationship, and (2) therapists and healthcare educators should consider how rehabilitation technologies can be used to support person-centred rehabilitation ensuring that the therapeutic relationship is preserved and developed throughout the rehabilitation process.

8.6.2 Considerations for social acceptability in rehabilitation technology design

The findings from the "Don't make me look different" theme clearly articulate that people with stroke place weight on the aesthetics and social acceptability of a rehabilitation technology device when considering whether to use it. Social acceptability may be particularly important in the design of head mounted wearable devices[512-514]. This is an important finding given that social acceptability is often a lesser priority in the rehabilitation technology development process. Defining the target user population and understanding their device requirements early in the design and development process may resolve acceptability issues and minimise the need for significant design changes later in the process[457]. This approach has the potential to not only mitigate issues of acceptability and usability, but reduce the impact on development time and costs, while simultaneously increasing the chances of successful adoption and sustained use of the technology[458,485]. Importantly, our study findings indicate that the need for a socially acceptable device design is dependent on the context in which the technology is to be used. Therefore, device developers should be cognisant of the use context when prioritising social

acceptability. Given the shift in rehabilitation services to the community[515] and supported self-management programmes[516], social acceptability for both users and bystanders[512,514] is likely to be a pivotal consideration in the design of rehabilitation technologies in the future.

8.6.3 User testing in a sustained way

User-centred design approaches are increasingly being encouraged to inform health technology design and development[459,485]. Yet much of the methodological literature describes single session usability evaluation, where novice users' perceptions and experiences of the technology inform the next iteration[517]. While this approach can highlight "entry-level" usability issues or novice user frustrations that can often be quick fixes, it is unlikely to identify fundamental usability and acceptability issues, or the sources of frustrations that could be barriers to sustained use of the technology[489,517]. This is an important limitation when employing user-centred design methods for the development of rehabilitation technologies which are intended for sustained use. To ensure that we captured design requirements which support both adoption and sustained use of the exciteBCI technology, in addition to the iterative single usability evaluation sessions, we conducted 'near-live' usability testing over a 3-week period. This approach allowed us to investigate the technology's 'fit' with a programme of rehabilitation. Users' long-term experiences, and the ways in which the device's usability and acceptability evolved over time were elucidated.

An important finding was that users' perspectives and usability priorities shifted with sustained use of the exciteBCI technology. Long-term users were less concerned with the technology's practicalities, such as the ease of setting up the exciteBCI App and headset. While these inconveniences were noted, they were apparently offset by the benefits users experienced from the intervention itself. It appeared that from engaging in sustained use, they obtained the "real-world evidence" in support of the technology which was desired by participants in phase one. Long-term users also did not highlight that the technology might disrupt the therapeutic relationship. Instead, they were more focused on the pleasure they had from "getting the most out of rehab", the increase in self-efficacy they experienced, and the gains they made when the technology augmented the rehabilitation process. Similar findings have been reported in the literature. When meaningful connections are formed with a technology over time, the pleasure derived from its use acquires more weight, and practical limitations become less significant[518]. A single session usability assessment may not always foresee future satisfaction with the technology since it may be evaluating expectations rather than user experience[519]. In the context of this study, it is critical to

remember that the user experience includes not only the technology itself, but also the experience gained from participating in the rehabilitation process, and that this experience occurs within the context of a therapeutic relationship. As a result, explicitly designing the technology to support both meaningful rehabilitation and best practice from the physiotherapist to establish and nurture a therapeutic relationship is paramount.

Our findings in relation to the sustained use of exciteBCI technology also provide important guidance for its eventual implementation in clinical practice. Current models for implementing rehabilitation technologies often rely on an instructional booklet and/or training and accreditation package, usually provided by the manufacturer of the technology. Whilst these strategies are likely to support the adoption of a rehabilitation technology, they are less likely to support sustained use. Implementation science literature emphasises the importance of strategies such as identifying factors and barriers to sustained use, the use of clinical champions on site, and the use of behaviour change strategies to ensure therapists are supported in practice change[520-522].

8.6.4 Limitations of the study

This study took a rigorous approach to qualitative research; however, it is important to acknowledge that we used a convenience sampling method in this study, all participants were in the chronic stage of stroke (2-19 years since stroke onset) and the physiotherapists worked in an outpatient rehabilitation or community setting. While participants reflected on prior lived experiences of inpatient rehabilitation closer to the onset of their stroke, when their stroke symptoms were more severe, or when physiotherapists worked in an inpatient setting, future user testing should include participants who are currently undergoing or providing inpatient rehabilitation. This will determine if their experiences align with or differ from the device features described in this study and help to understand how well it fits in an inpatient rehabilitation setting. In Phase One, while the physiotherapists had extensive experience with the patient cohort and their associated clinical presentation, the model utilized during the usability evaluation was not an individual with stroke. This may have influenced the resulting usability findings. Only one physiotherapist (GA) participated in the 'near-live' 3-week programme. Future research should explore usability testing over longer periods of time with a range of different users. Another potential limitation of the study design was that it did not capture the initial expectations of phase two long-term users. Therefore, we were unable to interpret how their initial expectations may have shaped their experiences of using exciteBCI and whether their expectations were confirmed or disregarded at the end of the programme.

8.7 Conclusion

This study presented an iterative user-centred design approach supported by a qualitative descriptive methodology exploring users' perspectives and experiences of exciteBCI, a complex neuromodulatory rehabilitative technology designed to augment locomotor rehabilitation for people with stroke. The five interrelated themes generated from the analysis revealed that overall exciteBCI was perceived and experienced positively by people with stroke and physiotherapists, and viewed as technology that could be implemented into a rehabilitation context. The findings provide important insights pertinent to the broader field of rehabilitation technology's design, implementation, and sustained use. Notably, these findings highlight that rehabilitation technology design should: 1) consider ways to support and enhance the therapeutic relationship, 2) recognize that social acceptability is a design imperative, but its significance varies depending on the use context, and 3) that there is merit in employing research design methods that explore device usability within the context of sustained use.

8.8 Author contributions

GA, NS, and DT conceptualised the study. GA, NS, DT, and GT designed the methodology, and DT and GA acquired ethical approval. NS, DT, UR, GA, SO, and IKN acquired funding, and GA performed project administration. GA, NS, TB, GT, UR, and SO contributed to data collection. UR and IKN were responsible for the technology. Data analysis was performed by GA and reviewed by NS and GT. Supervision was performed by NS and DT. The original draft was written by GA and NS, and edited by SO. All authors reviewed the submitted manuscript.

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8.10 Data availability

The data sets generated during and/or analyzed during this study are not publicly available due to the requirements of ethical approval which do not permit data sharing. Data may be obtained from the corresponding author upon reasonable request, with the approval of the relevant ethics committee.

8.11 Conflict of interest statement

None to declare.

8.12 Acknowledgements

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8.13 Additional content

There are several supporting documents that were not included in the submitted manuscript that relate to the design and development of exciteBCI (Appendices E.8-E.9) and clinical findings (Appendices E.10-E.11). These include:

Appendix E.8 – A summary of phase one (single session) iterative device requirements applied to the exciteBCI and those compiled at the end of phase two 'near-live' 3-week rehabilitation programme that will inform future iterations of exciteBCI.

Appendix E.9. – A walkthrough of the most recent exciteBCI App screens. This version of the device is currently being used in a clinical dose-escalation trial that seeks to identify the optimal exciteBCI intervention rehabilitation dose to improve outcomes for people with stroke.

Appendix E.10 – A detailed session-by-session programme description extracted from the exciteBCI App of one participant's 3-week rehabilitation programme augmented by the exciteBCI device.

Appendix E.11 – A summary of the pre and post clinical measurement findings for the two participants with stroke that participated in the 3-week rehabilitation programme augmented by the exciteBCI device.

8.14 Summary

This chapter has presented the exciteBCI user-centred design evaluation process in correspondence with Stage 4 of the ISO 9241-210:2019 standard[70]. Device requirements

were addressed iteratively throughout the evaluation process and, therefore, repeatedly cycled back through Stages 2, 3, and 4 of the ISO 9241-210:2019 standard[70]. Device requirements from the second phase of 'near-live' usability testing will guide exciteBCI's future design and implementation decisions in a rehabilitation context. Overall, these findings provide evidence for the optimisation of the exciteBCI from a clinical perspective and inform the direction for future research.

SECTION FOUR:

INTERGRATED DISCUSSION

Chapter 9. Integrated Discussion

9.1 Prologue

This chapter provides an overview of the main findings of this research in relation to the thesis aim and objectives and considers the optimisation of the exciteBCI intervention from a neurophysiological and clinical standpoint. Following that, the chapter discusses the key strengths and limitations of the thesis before summarising future research directions.

9.2 Introduction

This doctoral thesis sought to optimise the intervention delivery of exciteBCI, a complex neuromodulatory intervention for people with stroke by:

1. Optimising the stimulation parameters of the ePAS intervention and;

2. Optimising the usability and acceptability of the exciteBCI, a portable medical wearable device in the prototype stage, to support its translation to clinical practice.

The objectives of the thesis were successfully achieved by conducting a comprehensive body of research that was framed within a pragmatist approach that enabled these objectives to be investigated from a neurophysiological and clinical perspective. These are discussed in section 9.3 and 9.4 respectively. The thesis was guided by the MRC recommendations for complex interventions[69] and UCD principles outlined in the ISO 9241-210:2010 standard[70]. Studies included a narrative review, a systematic review, a factorial study with repeated measures, a reliability study, and a UCD study. The research presented in this thesis advances understanding of key considerations in optimising the exciteBCI intervention for people with stroke and makes a significant contribution in the neurophysiological and clinical domains. The findings will support future research into neuromodulatory-based interventions and the design and development of rehabilitation technologies.

9.3 Neurophysiological optimisation

9.3.1 Unpacking the evidence to inform neurophysiological optimisation

The neuromodulatory intervention, ePAS, commonly administered in a laboratory setting, was introduced in Chapter 3. A narrative review of the ePAS evidence revealed that few studies had examined the effects of stimulation parameter selection on intervention outcomes, necessitating a more systematic investigation to optimise intervention delivery. In response, Chapter 4 *systematically reviewed the evidence for the efficacy of lower limb PAS and the optimal stimulation parameters for intervention delivery in healthy people and people with stroke to inform which ePAS stimulation parameters to optimise*[369].

This systematic review was the first of its kind to be published in the PAS literature, building upon previous narrative reviews. It expanded the understanding of the efficacy of lower limb PAS in healthy and stroke populations[223,225]. It was achieved by systematically evaluating intervention efficacy, providing a thorough review of the stimulation parameters used, and a robust critique of the methodological quality of the evidence-base. The systematic review found that;

(i) There was moderate-to-poor quality evidence to support that a single session of lower limb PAS can modulate corticomotor excitability in healthy people and people with stroke.

(ii) **Stimulation parameter selection may impact intervention efficacy.** However, the scarcity of high-quality studies that systematically compared different PAS-delivery methods within and across studies prevented definitive conclusions from being drawn.

A significant strength of this review was the provision of eight key recommendations for future research to improve the methodological rigour of PAS studies (see Chapter 4, section 4.6.9). If these recommendations are followed and the methodological rigour of PAS studies is improved, evidence from these studies could then be synthesised in a meta-analysis. This would support a better understanding of whether the therapeutic benefits of PAS for people with stroke are sufficient to warrant its translation to clinical practice. However, unlike ePAS, the acceptability and feasibility of PAS in the context of stroke rehabilitation has yet to be investigated.

9.3.2 Investigating the effect of manipulating stimulation parameters

The findings of the systematic review also guided methodological decisions in the investigation of ePAS intervention efficacy (Chapter 5). As findings from Chapters 3 (narrative review) and Chapter 4 (systematic review) concluded there was limited available evidence to guide which ePAS stimulation parameters to optimise, the pragmatic decision was made in Chapter 5 to *investigate ePAS intervention efficacy when stimulation intensity and movement parameters were manipulated*. Subsequently six of the methodological recommendations drawn from the systematic review (Chapter 4, section 4.6.9) using a factorial study design with repeated measures in healthy people[486] were followed. The benefit of using this type of design was that it allowed the research team to unpack the interaction effects of the two treatment parameters and distinguish between super-additive, additive, and sub-additive treatment effects. To our knowledge, this is an approach that has not previously been used in the field of neuromodulatory research. Additional strengths of the methodological approach used in this study were discussed in Chapter 5 (section 5.6.5).

There were several key findings from the factorial study;

(i) **In general, ePAS interventions were significantly more effective at increasing corticomotor excitability compared to control interventions.** These findings complemented prior evidence for the efficacy of low intensity imagined ePAS interventions in healthy people while expanding on the available evidence by demonstrating that both high intensity voluntary and imagined ePAS interventions increased corticomotor excitability in healthy people. However, this study also revealed that low intensity voluntary ePAS intervention was not more efficacious than the voluntary control intervention.

(ii) **That stimulation intensity and movement type parameters interact within ePAS interventions.** These interactions were sub-additive for the high intensity voluntary and imagined ePAS interventions. Interestingly, the sub-additive effect of low intensity voluntary ePAS intervention was more pronounced. This led us to speculate that the low intensity afferent volley produced in the low intensity voluntary ePAS intervention may have been subsumed by the endogenous motor cortex activation associated with planning and executing a voluntary movement.

The findings of both the systematic review and the factorial study brought to light an intriguing issue pertaining to the interpretation of the neurophysiological findings and the clinical optimisation of the intervention. This issue concerned the *state* of muscle

contraction during motor evoked potential (MEP) measurement before and after the intervention and how the muscle contraction state might affect researchers' ability to distinguish a significant intervention effect on corticomotor excitability (see Chapter 4, section 4.6.7 and Chapter 5, section 5.6.5). While the findings from the systematic review recommended recording MEPs under multiple muscle conditions (i.e., resting, active, and functional muscle states) (see Chapter 4, section 4.6.9), we elected to record MEPs from an active muscle in the factorial study. This was for two reasons. First, because the intention was to replicate this work in people with stroke and compare it to the findings of the factorial study. Using active MEPs was likely to reduce participant selection bias as resting MEPs are often difficult to elicit in people with more severe motor impairment[248-250]. Second, the pragmatic decision to keep time requirements of the protocol to a minimum for study participants. While these decisions were valid, also recording resting MEPs may have offered more insights into the efficacy of stimulation intensity and movement type, and their interactions. Despite this potential measurement limitation, the robust methodological approach and the future recommendations from both the systematic review and the factorial study could have a significant impact on the wider field of neuromodulation research.

9.3.3 Considering the reliability of the MRCP PN feature extraction

In interpreting the findings of the factorial study, substantial inter-individual variability in the intervention response was identified. This, together with similar concerns observed in concurrent ePAS feasibility work in people with stroke[64], raised the possibility that inaccuracies in the estimation of the PN of the averaged MRCP may have contributed to the inter-individual variability observed. This important finding was brought to light by the methodological rigour used in the factorial study that may have not otherwise been identified, and is pivotal in interpreting the findings of ePAS neurophysiological research. We therefore introduced a new thesis objective in Chapter 6 to *determine the intra-rater and inter-rater reliability of EEG experts' identification of the peak negativity feature from averaged movement related cortical potentials obtained from healthy people and people with stroke.* This reliability study[523] revealed that;

(i) EEG experts demonstrated excellent reliability when identifying the PN of averaged MRCPs in voluntary movement conditions in both healthy and people with stroke.

(ii) The imagined movement condition in healthy people, revealed low to moderate inter- and intra-rater reliability.

(iii) **The morphology of MRCP signals influences the consistency with which epochs are manually selected for inclusion within and between EEG experts.** When an MRCP epoch's morphology and that of its average were more similar, there was a much higher likelihood that one expert or a group of experts would choose the same epochs for inclusion.

These findings further supported the rationale for prioritising voluntary movements as part of the exciteBCI intervention design. These reliability findings will also aid parallel research focused on algorithm refinement and device development which aims to develop an online, real-time version of the exciteBCI intervention neuromodulation component.

When it came to investigating the intervention parameter *movement type*, the factorial study and the reliability study were somewhat contradictory. The factorial study showed that imagined ePAS interventions increased corticomotor excitability for up to 30-minutes after the intervention, and that the low intensity imagined ePAS interventions were more effective at increasing corticomotor excitability than the low intensity voluntary ePAS intervention. However, despite using the same raw EEG data from the factorial study, the reliability study revealed low to moderate inter- and intra-rater reliability for identifying the PN from averaged MRCPs in the imagined movement condition. Given the poor to moderate reliability in identifying the PN in imagined MRCPs, these findings could suggest that the requirement for close temporal pairing in imagined ePAS interventions may be less stringent than previously thought.

One could speculate that this relates to the morphology of the MRCP. MRCPs derived from imagined movement tend to have lower amplitudes and less defined peak negativities compared to MRCPs derived from voluntary movement[241,243]. This is thought to be due to lower cortical activation during imagined movement[272,273] and the absence of sensorimotor afferent feedback. Therefore, the window of effect, and thus the ISI range, may be wider in imagined movement than voluntary movement, where the latter are characterised by MRCPs with larger amplitudes and defined peak negativities. Understanding the relationship between the reliability of the MRCP, the movement type, and the size of the window (the ISI range) in which the neurophysiological effect of the ePAS intervention may occur is a key consideration for the design and implementation of the exciteBCI device and should be explored in subsequent neurophysiological studies to optimise the delivery of the exciteBCI intervention.

9.4 Clinical optimisation

This thesis clearly demonstrates that while optimising the intervention at the neurophysiological level is important, understanding how well the intervention fits with clinical practice is also critical. According to the ePAS narrative review in Chapter 3, people with stroke reported that the ePAS intervention in its current delivery format was not an acceptable rehabilitation intervention, nor was its application feasible in a clinical setting using laboratory equipment[64]. To address these concerns, the possibility of delivering ePAS via a portable wearable BCI device during meaningful real-world locomotor-related activities as a potential solution was explored. This was achieved by adopting an iterative UCD approach. The design and development of exciteBCI was guided by the 4-stages of the ISO 9241-210:2019 standard[70].

9.4.1 Defining the purpose of the device and device requirements

Chapter 7 *identified the exciteBCI device requirements from the perspectives of people with stroke and physiotherapists* and successfully followed stages 1-3 of the ISO 9241-210:2019 standard[70] to (1) understand and specify exciteBCI's use context; (2) specify user requirements; and (3) explore design solutions through ideation, iterative prototyping, testing activities, and feedback from users and stakeholders. The user requirements for the exciteBCI were generated from a variety of sources to identify device requirements which are both evidence-based and user-informed (see Chapter 7, section 7.4.2). The addition of focus groups in the initial phase of specifying user requirements may have provided a more in-depth understanding of the users' needs and could have further strengthened the UCD process[524]. Nevertheless, the approach translated into the exciteBCI team defining clear device requirements including that exciteBCI should;

(i) Deliver ePAS during meaningful locomotor-related tasks that are personalised to the user's goals
(ii) Provide opportunities for higher doses of intensive practice that are progressively more challenging
(iii) Be strongly underpinned by evidence
(iv) Fit within the context of rehabilitation and be easy to use and reliable.

9.4.2 Investigating the acceptability and usability of the device

Chapter 8 centred on the usability evaluation of exciteBCI and corresponded to stage 4 of the ISO 9241-210:2019 standard[70]. It explored people with stroke and physiotherapists'

perceptions and experiences of the exciteBCI and how well it fits with rehabilitation, and collated and iteratively responded to exciteBCI device user requirements based on user evaluation. Using a series of usability testing sprint cycles and a 'near-live' 3-week locomotor rehabilitation programme augmented by exciteBCI, a rigorous and thorough evaluation of the exciteBCI prototype was conducted. The findings of this study revealed that;

(i) **Overall people with stroke and physiotherapists perceived that exciteBCI is an acceptable rehabilitation technology which could fit within a rehabilitation context.** A number of themes were generated from the data and included (1) This is rehab, (2) Getting the most out of rehab, (3) It is a tool not a therapist, (4) Weighing up the benefits versus the burden, and (5) Don't make me look different.

(ii) **This study also contributed understandings which inform the design and development of rehabilitation technologies more broadly including (1) the importance of designing rehabilitation technologies which support and enhance the therapeutic relationship and (2) that the importance of social acceptability as a design priority in rehabilitation technology varies dependent on the user context**.

(iii) **Importantly, this study also highlighted research methodologies which can support the design of technologies which fit with clinical practice. The importance of exploring usability in a sustained way was emphasised.** This approach enabled the researchers to understand how users' priorities can shift over time. Something that might have gone unnoticed if the research team had taken the more common approach to usability testing, which involves novice users and only a single session evaluation[517].

In Chapter 7, the research team documented both the broader purpose of the exciteBCI rehabilitation technology and the specific device requirements (see sections 7.4.1 and 7.4.2 respectively). At the culmination of the clinical optimisation focus (Chapter 8) of the thesis, the research has provided the foundational work required to address the four goals specified and has refined the detailed device requirements for exciteBCI. These findings provide a clear framework for the next phase of the research which is highlighted in the future direction section below (see section 9.7).

9.5 Strengths of the thesis

There are several key strengths in this body of work which are evident across the breadth of thesis. These include adopting a pragmatist approach, the use of supporting frameworks, theoretical underpinnings, and research rigour.

9.5.1 A pragmatist approach

A key strength of the thesis is its foundation in a pragmatist paradigm. By taking a pragmatist approach to addressing the aim and objectives of this doctoral thesis the research team were able to draw upon different research methods to address the concept of optimisation broadly, and to utilise a range of research methods to address neurophysiological and clinical optimisation specifically. The benefit of addressing both neurophysiological and clinical optimisation in parallel is that the generation of new knowledge iteratively informed the optimisation of the exciteBCI intervention and the device development. For example, the decision to investigate the efficacy of the ePAS intervention in both voluntary and imaginary movement conditions was motivated by clinical understandings of how the intervention could be implemented in stroke rehabilitation. Similarly, neurophysiological understandings derived from the MRCP reliability findings drove the decision to prioritise voluntary-based movements in the exciteBCI intervention design. The pragmatic approach was also enabled by a breadth of expertise and knowledge to inform the work. This is evident in the transdisciplinary nature of the research team, the involvement of a lived experience researcher in the team, and the emphasis on valuing the knowledge and expertise of both physiotherapists and people with stroke. Whilst both clinical and neurophysiological questions remain (see section 9.7), the use of a pragmatic approach was critical to generating and drawing together different bodies of knowledge to inform the design and development of the exciteBCI technology.

9.5.2 Supporting frameworks

The development and the evaluation process for optimising the delivery of the exciteBCI intervention for people with stroke was guided by the MRC framework for complex interventions[69] and the ISO 9241-210:2019 standard[70]. Adopting these established frameworks enabled the researchers to explicitly position the work with respect to device and complex intervention development and evaluation. The research presented in Chapters 2-8 was clearly situated within the MRC framework. Optimising the intervention delivery from a neurophysiological perspective was grounded in the Development stage, whilst the clinical optimisation spanned the Development and Feasibility and Testing stages of the

MRC framework. Chapters 7-8 were further situated in the ISO 9241-210:2019 standards[70] iterative process. Following the ISO 9241-210:2019 standard provided an appreciation for the importance of user involvement in the early stages of design and development of rehabilitation technology. Rehabilitation technologies, such as virtual reality and robotics, have been criticised for moving too quickly to evaluation of clinical efficacy using clinical trials[525]. In this research, the use of the ISO 9241-210:2019 standard[70] supported the research team to attend to users' perspectives to inform the design of the technology before exploring efficacy. Collectively, the use of these frameworks allowed the research team to leverage the pragmatic approach and a range of research methods to advance understandings of a complex technology in a complex clinical context.

9.5.3 Theoretical underpinnings

The research methods, intervention, and technology development that was undertaken in this thesis explicitly drew upon substantive evidence-based bodies of knowledge related to neuroscience and rehabilitation to inform the generation of new knowledge. For example, when deciding which ePAS intervention parameters to focus on for neurophysiological optimisation, the research team leveraged understandings from the neuroscience and motor learning literature[128,130,147,172]. The approach to clinical optimisation drew on evidence pertaining to rehabilitation including principles of motor learning, task-specific training, and person-centred rehabilitation[25,26,40,143,144,172,504]. The success of this is evidenced in the qualitative findings presented in Chapter 8 (see section 8.5). The "*This is rehab"* theme described how physiotherapists saw congruence between their own clinical practice and knowledge of rehabilitation principles and the exciteBCI technology. Similarly, the "*Getting the most out of Rehab*" theme described the ways in which people with stroke and physiotherapists experienced exciteBCI as a technology that could provide more intensive and challenging rehabilitation, at higher doses. This deliberate approach to leverage existing bodies of knowledge to support the development of a rehabilitative technology is reflected in the research teams' progress toward a device ready for evaluation of efficacy and implementation in clinical practice.

9.5.4 Research rigour

A fundamental strength of this thesis was the rigour applied throughout the research process. This was deemed essential to support both neurophysiological and clinical optimisation perspectives and a mixed method research approach. Examples of robust research designs and methods are evident in numerous sections of this thesis (Chapters 4-

8) and sections 9.3 and 9.4 of this integrated discussion chapter. Several specific examples include; (1) following the PRISMA guidelines for executing the systematic review and reporting study findings (Chapter 4); (2) utilising quality assessment tools like the Downs and Black (Appendix A.1) and the TMS Checklist (Appendix A.3 and Appendix B.5); (3) the use of a factorial design to unpack a complex research question pertaining to the efficacy of intervention parameters stimulation and their interactions (Chapter 5, section 5.4.1), which was supported by a sound pre-specified data processing and analysis plan (Chapter 5, sections 5.4.5, 5.4.6 and Appendix B.7); and (4) and in the evaluation stage of the UCD process utilising both single session and repeated (3-week programme) usability testing sessions in the study design to explore both the adoption and long-term use of the exciteBCI technology (Chapter 8, section 8.4.4).

From a qualitative research perspective, rigour signifies the process of establishing trust and confidence in the research findings[526]. This was demonstrated through purposeful peer review to enhance data collection and analysis processes, and the meticulous and continual application of researcher reflexivity[527]. Whilst the primary researcher (GA) was also the treating physiotherapist in the 3-week rehabilitation programme augmented by the exciteBCI, several strategies were put in place to ensure space was given for the participants' voices. This included the participants with stroke and the physiotherapist (GA) being interviewed by two experienced researchers (GT and SM) who were not involved in the development of the exciteBCI. During the data analysis phase, transcripts were thoroughly reviewed, and regular critical discussion meetings were held between GA, NS, and GT to support the development of categories and themes.

Using robust research methods throughout the thesis was critical in unravelling some of the complexities of intervention optimisation and aided the research team in having a clear understanding of the findings from one study to inform subsequent work, even when they used different research methods.

9.6 Limitations of the thesis

The limitations of each study have previously been discussed in their respective chapters and reference has also been made to specific limitations of the research in sections 9.3 and 9.4 of this integrated discussion chapter. More broadly, it is important to recognise that the optimisation of the intervention delivery of exciteBCI and the design and development of the exciteBCI device are incomplete. The external validity of the research findings is limited by a number of factors; (1) The participants were not fully representative of the

target population identified for exciteBCI and (2) the context in which the research was conducted was limited to a laboratory setting (Chapters 4-6) and an outpatient clinical setting (Chapters 7-8). The acceptability of exciteBCI and its device requirements may differ when other users and clinical contexts are considered. While this thesis has successfully tackled complex neurophysiological and clinical questions, there remain a number of unanswered questions that need to be addressed prior to moving into the Evaluation and Implementation stages of the MRC framework[69]. These are specifically outlined in the future directions section below.

9.7 Future directions

This research has supported a move towards an intervention that is more acceptable to people with stroke and physiotherapists in a rehabilitation context. While there are several important neurophysiological questions to be addressed in the future, these should be investigated using the exciteBCI wearable device and correspond to the Development stage of the MRC framework[69]. They include;

- Investigating the reliability of the online BCI system to detect and classify the MRCP in locomotor-related tasks. Findings from the scoping review that collated research evidence investigating the MRCP in ecological valid movement tasks revealed that the MRCP could be identified and classified during locomotor-related tasks in healthy and stroke populations[528]. Future studies should ascertain whether this can be reliably achieved in people with stroke, performing locomotor-related tasks in a clinical setting using the exciteBCI wearable.

- Investigating the optimal interstimulus interval (ISI) for the temporal pairing between the afferent peripheral electrical stimulus and the cortical activity when people with stroke are performing locomotor-related tasks using an online BCI system. This could be explored using a factorial study design.

- Investigating how increasing task complexity of locomotor-related tasks in people with stroke influences the latency and amplitude of the MRCP. To date, this has mostly been explored in healthy populations with little focus in neurological populations[528]. Most studies indicated that as complexity increases so does the amplitude of the MRCP[528]. Differences in MRCP characteristics across different locomotor-related tasks has implications for the timing of neuromodulation component of the exciteBCI intervention.

- exciteBCI research to date has focused on the ankle dorsiflexors. It would be important to explore other lower limb muscles that could be targeted during the intervention and that relate specifically to the functional tasks being trained. Understanding whether paired neuromodulation could be applied to more than one muscle group (i.e., dorsiflexors and hamstrings) to support better congruency with relevant locomotor-related tasks is also warranted.

Prior to the evaluating the efficacy of the exciteBCI there are a number of clinical related matters to address which correspond to the Feasibility and Piloting stage of the MRC framework[69]. These include;

- Developing an EGG headset which meets device usability and social acceptability requirements. To alleviate the inconvenience of EEG gel use, designers should prioritise the development of a headset that uses dry electrodes and that the user can don, doff, and operate independently with one hand. This could entail designing a wearable that can be concealed or better integrated into familiar garments.

- Future exciteBCI App development needs to consider embedding feedback and reward for both the person with stroke and the physiotherapist to optimise user experience. For example, the number of successful paired stimulations the patient had received or notifications regarding loss of system connectivity, as well as patient dashboards where visual summaries of patient progress can be monitored. For reward this could include gamification options.

- Additional exciteBCI sustained usability testing evaluations where users' initial expectations are captured at the beginning and then reviewed at the end of the rehabilitation programme is required to better understand whether expectations and user requirements shift or are maintained across a programme of rehabilitation. This should be completed with a diverse sample including novice and expert physiotherapists working in stroke rehabilitation from different clinical settings (inpatient, outpatient, and community), and where acuity and or severity for people with stroke is more pronounced.

- Development of training modules to support therapists to set-up and implement the exciteBCI technology into clinical practice with an emphasis on how best to

support the therapeutic relationship between clinician and patient and how to design and deliver effective task-specific training.

- Define the optimal exciteBCI intervention dose to improve outcomes for people with stroke. Currently the research team are undertaking a dose-escalation study to ascertain the maximum tolerable rehabilitation dose of the exciteBCI intervention.

- Findings from the dosage study will inform the rehabilitation dose provided in future efficacy-based clinical trials. Two potential clinical trial study designs include an intention and dose matched controlled trial where the comparator is task-specific training or a pragmatic trial where the comparator is usual care.

Finally, while the research team may be some time away from carrying out the implementation phase of the research, in line with recommendations from the recently updated MRC framework[529] the team will continue to consider potential facilitators and barriers to implementation of the exciteBCI. Identifying relevant implementation strategies during the earlier phases of the MRC framework may increase the chances of developing an intervention that can be successfully adopted and maintained in a real world setting[529].

9.8 Conclusion

This thesis utilised a pragmatist approach to optimising the delivery of exciteBCI, a complex neuromodulatory intervention aimed at improving locomotor-related abilities in people with stroke, in preparation for its translation into clinical practice. Optimisation was addressed from a neurophysiological and clinical perspective utilising mixed methods. Studies included a narrative review, a systematic review, a factorial study with repeated measures, a reliability study, and a user-centred design study. The neurophysiological evidence generated in this thesis provides further support for the value of ePAS in enhancing neural plasticity in people with stroke and provides guidance for continued optimisation of intervention parameters. The user-centred design study illustrated that exciteBCI is a suitable vehicle for the clinical translation of the ePAS intervention which is both acceptable and fits with clinical practice. The research has emphasised the importance of having a thorough understanding of the proposed intervention's neurophysiological effects, the people who will employ the technology, and the context in which it will be used. This thesis has demonstrated a rigorous approach to the development of a complex rehabilitative technology which has important lessons that advance understandings of what is important in the design of rehabilitation technologies.

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Appendices

Appendix A: Supplementary documents for Chapter 4

Relates to the following publication:

Alder G, Signal N, Olsen S and Taylor D (2019) A Systematic Review of Paired Associative Stimulation (PAS) to Modulate Lower Limb Corticomotor Excitability: Implications for Stimulation Parameter Selection and Experimental Design. Front. Neurosci.13:895. doi: 10.3389/fnins.2019.00895. The supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.00895/full#supplementary-material

A.1 Modified Downs and Black scores

	Reporting										External validity			Internal validity (bias)							Internal validity (confounding)							Power	Total	%
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27			
Healthy Studies																														
Stinear 2005	1	1	1	1	1	1	0	0	1	1	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	1	17	61
Prior 2006	1	1	1	1	0	0	1	0	1	1	0	0	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	13	46
Jayaram 2007	1	1	1	1	0	1	0	0	1	1	0	0	1	0	0	1	0	1	1	1	1	0	1	0	0	0	0	14	50
Mrachacz-Kersting 2007	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	0	1	1	0	1	0	0	1	0	16	57
Roy 2007	1	1	1	1	0	0	0	0	1	0	0	0	1	0	0	1	0	1	0	1	1	0	0	0	0	1	0	11	39
Kumpulainen 2012	1	1	1	1	1	1	1	0	1	0	0	0	1	0	0	1	1	1	1	1	1	0	1	0	0	1	0	17	61
Kumpulainen 2015	1	1	1	1	1	1	1	0	1	0	0	0	1	1	0	1	1	1	1	1	1	0	0	0	0	1	0	17	61
Mrachacz-Kersting 2017	1	1	1	1	1	0	1	0	1	1	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	0	16	57
Stroke Studies																														
Uy 2003	1	1	1	1	0	1	0	0	0	0	0	0	1	NA	0	1	1	0	NA	1	0	0	NA	NA	0	0	0	9	38
Jayaram 2008	1	1	1	1	1	1	1	0	1	1	0	0	1	NA	0	1	1	1	1	1	0	0	NA	NA	0	1	0	16	64
Jayaram 2009	1	1	1	1	1	1	1	0	1	1	0	0	1	NA	0	1	0	1	1	1	0	0	1	0	0	0	0	15	56
Rogers 2011	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	0	0	NA	NA	0	1	0	15	58

For questions 1-4 and 6-27, a score of 1 = no. For question 5, a score of 1 = partially answered and a score of 2 = yes. For questions 1-10, a score of 0 = no. For questions 11-27, a score of 0 = no or not able to be determined, N/A = not applicable.

A.2 Copy of Modified Downs and Black scoring system[308]

Item	Criteria	Possible Answer
Reporting		
1	Is the hypothesis/aim/objective of the study clearly described?	Yes = 1 No = 0
2	Are the main outcomes to be measured clearly described in the introduction or methods section? If the main outcomes are first mentioned in the results section, the question should be answered no.	Yes = 1 No = 0
3	Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.	Yes = 2 Partially = 1 No = 0
6	Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes = 1 No = 0
External validity		
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to determine = 0
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to determine = 0

Item	Criteria	Possible Answer
Internal validity - bias		
14	Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes = 1 No = 0 Unable to determine = 0
16	If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to determine = 0
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to determine = 0
18	Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
19	Was compliance with the intervention/s reliable? Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
20	Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - confounding (selection bias)		
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.	Yes = 1 No = 0 Unable to determine = 0
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0

Item	Criteria	Possible Answer
23	Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.	Yes = 1 No = 0 Unable to determine = 0
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All nonrandomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 Unable to determine = 0
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 Unable to determine = 0
26	Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
Power		
27	*Was there a power calculation undertaken or an adequate explanation of why sample size was chosen?	Yes = 1 No = 0

A.3 TMS Quality Checklist scores

	Healthy Studies																Stroke Studies							
	Stinear (2005)		Prior (2006)		Jayaram (2007)		Mrachaz-resting (2007)		Roy (2007)		Kumpula-inen (2012)		Kumpula-inen (2015)		Mrachaz-Kresting (2017)		Uy (2003)		Jayaram (2008)		Jayaram (2009)		Rogers (2011)	
	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C
Participant factors																								
Age of participants	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1
Gender of participants	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA	1	NA
Handedness / Footedness of participants	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	0	0	0	0
Participants prescribed medication	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Use of CNS active drugs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Presence of neurological/psychiatric disorders in healthy participants	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	NA	NA	1	1	NA	NA	1	1
Any medical conditions	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
History of specific repetitive motor activity	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Methodological factors																								
Position and contact of EMG electrodes	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	1
Amount of relaxation/contraction of target muscles	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Prior motor activity of the muscles to be tested	1	1	1	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Level of relaxation of muscles other than those being tested	NA	1	NA	1	NA	0	NA	1	NA	1	NA	1	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0
Coil type (size and geometry)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Coil orientation	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	1	1	1	1	1	1
Direction of induced current in the brain	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	1	1	1	1	1	1
Coil location and stability (with or without neuro-navigation system)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1

	Healthy Studies																Stroke Studies							
	Stinear (2005)		Prior (2006)		Jayaram (2007)		Mrachaz-Kresting (2007)		Roy (2007)		Kumpula-inen (2012)		Kumpula-inen (2015)		Mrachaz-Kresting (2017)		Uy (2003)		Jayaram (2008)		Jayaram (2009)		Rogers (2011)	
	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C
Type of stimulator used (e.g. brand)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stimulation intensity	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pulse shape (monophasic or biphasic)	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0
Determination of optimal hotspot	1	0	0	0	0	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0
The time between MEP trials	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	1	1	1	1	1	1
Time between days of testing	1	1	1	1	1	1	1	1	1	1	1	1	NA	NA	1	1	1	1	NA	NA	1	1	NA	NA
Subject attention (level of arousal) during testing	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	0	0	1	1	1	1	0	0
Method of determining threshold (active/resting)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1
Number of MEP measures made	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Paired pulse only																								
Intensity of test pulse	NA	NA	NA	NA	NA	NA	NA	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Intensity of conditioning pulse	NA	NA	NA	NA	NA	NA	NA	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Inter-stimulus interval	NA	NA	NA	NA	NA	NA	NA	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Analytical factors																								
Method of determining MEP size during analysis	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Size of unconditioned MEP	NA	NA	NA	NA	NA	NA	NA	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Totals	18	17	17	17	18	16	18	17	21	19	15	15	16	15	19	18	10	8	19	17	18	17	16	15
% Score	72	68	68	68	72	64	72	68	72	66	60	60	67	63	76	72	42	33	79	71	75	71	67	63
Overall % Score	**70**		**68**		**68**		**70**		**69**		**60**		**65**		**74**		**38**		**75**		**73**		**65**	

Appendix B: Supplementary documents for Chapter 5

Relates to the following publication:

Alder G, Signal N, Vandal AC, Olsen S, Jochumsen M, Niazi IK and Taylor D (2021) Investigating the Intervention Parameters of Endogenous Paired Associative Stimulation (ePAS). Brain Sci. *11*, 224. doi: 10.3390/brainsci11020224

B.1 Ethical approval

B.2 Participant information sheet

B.3 Transcranial Magnetic Stimulation (TMS) safety checklist

B.4 Consent form

The following supplementary material for this article can also be found online at **https://www.mdpi.com/2076-3425/11/2/224/s1**

B.5 TMS Quality Checklist scores

B.6 Predefined TA EMG processing criteria

B.7 Statistical analysis plan

B.8 Additional results

B.1 Ethical approval

AUTEC Secretariat

Auckland University of Technology
D-89, WA505F Level 5 WA Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

25 August 2015

Denise Taylor
Faculty of Health and Environmental Sciences

Dear Denise

Re Ethics Application: **15/270 The Aalborg Brain Computer Interface: Optimising the delivery of stimulation parameters for the BCI-MRCP driven PAS protocol for people with stroke.**

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

Your ethics application has been approved for three years until 24 August 2018.

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

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 24 August 2018;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 24 August 2018 or on completion of the project.

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

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

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

All the very best with your research,

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

Cc: Gemma Alder galder@aut.ac.nz, Nada Signal; Imran Khan Niazi; Nicola Towersey

B.2 Participant information sheet

Participant Information Sheet

Date Information Sheet Produced: 16th November 2015

A comparison of intensity stimulation parameters to enhance cortico-motor excitability during the Aalborg Brain Computer Interface (BCI) protocol in healthy individuals.

An Invitation

Kia ora, talofa lava and hello, my name is Gemma Alder and I am a PhD student at AUT. You are invited to take part in a study aiming to explore the effects of a new rehabilitation approach to improve walking after stroke.

Please remember that:

- Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study.
- If you do agree to take part you are free to withdraw at any time, without having to give a reason.

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

What is the purpose of this research?

Recent rehabilitation research has begun exploring whether Brain Computer Interface (BCI) devices have potential to improve rehabilitation for people following stroke. The purpose of this study is to optimise the delivery of the Aalborg (BCI) intervention in order to improve its future use for people with stroke.

Brain computer interface's (BCI's) interpret brain signals, allowing specific commands from the brain to be sent to an external device.

The Aalborg BCI interprets brain signals whilst participants move their foot and uses these signals to trigger electrical stimulation of the leg muscles. Repeated stimulation has been shown to increase brain activity which may help people with stroke improve their walking ability.

However, it's not yet clear what the optimal stimulation parameters are and whether the intensity of electrical muscle stimulation influences the amount and duration of brain activity increase.

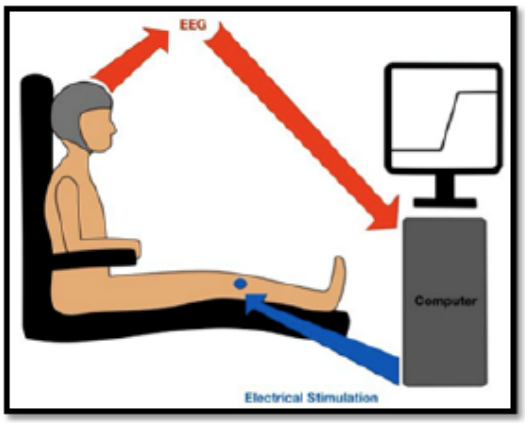

Figure 1. The intervention

This research project aims to measure the effects of various intensities of electrical muscle stimulation to the leg muscles during the intervention on brain activity in healthy adults and to evaluate whether this has an effect on the duration of increased brain activity following the intervention.

These findings would inform the researchers whether the 'intensity of stimulation' is an important parameter to consider when applying the Aalborg BCI intervention in future research projects that intend to recruit participants who have had a stroke. The findings of this project will also be written up as part of a PhD project.

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

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

You will have made contact with myself and your participation in this study is voluntary. You may be eligible for this study if you meet the following entry criteria:

- Aged over 18 years,
- Do not have any neurological disorders,
- Do not have epilepsy, cardiac arrhythmia, history of seizures,
- 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.

We will be recruiting 17 people to participate in the study.

What will happen in this research?

You will be contacted by us to make an appointment to attend the laboratory at the Health & Rehabilitation Research Institute, AUT North Campus, Akoranga Drive, Northcote. The study involves participating in seven sessions, at least 48 hours apart. The sessions involve recording your brain activity using a technique called Transcranial Magnetic Stimulation (TMS).

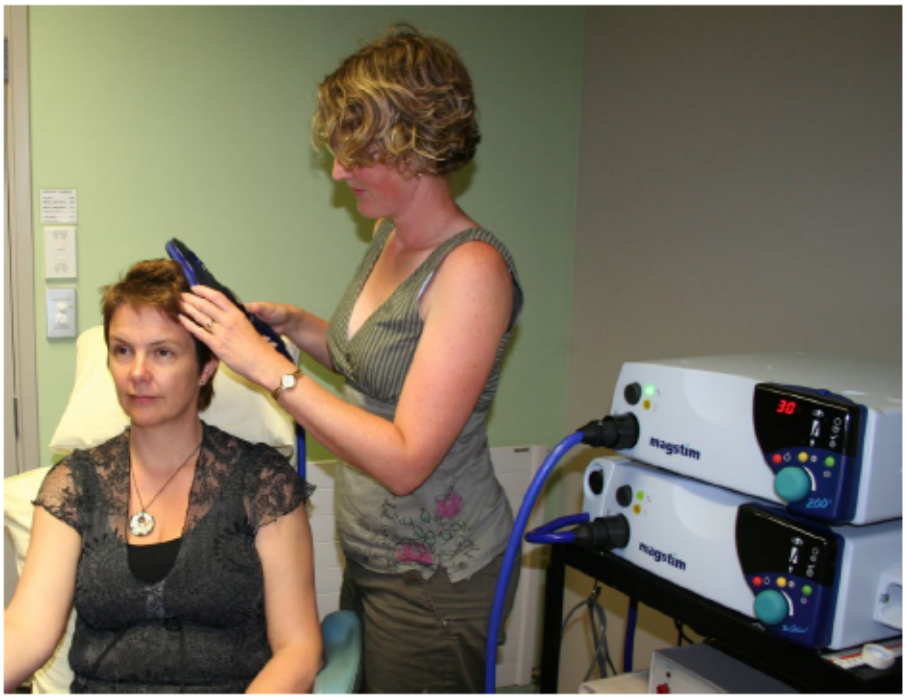

Figure 2. Testing brain activity using the TMS machine

This is a safe and painless technique that involves the researcher delivering small magnetic pulses to your head. These pulses activate nerve cells in your brain, resulting in a twitch in your leg muscles. Some people cannot have TMS either because there is a slight increased risk of seizure with it or because its effects are not known in that group. If you are interested in taking part in the study, we will use a TMS Safety questionnaire to ensure its okay for you to be included in the study.

Using this technique will help us to understand how the level of activity in your brain relates to the muscles in your leg before taking part in the treatment.

Once we have recorded your baseline brain activity, we would then like to invite you back to take part in a further six separate sessions of the Aalborg BCI.

Each intervention will last approximately 15 minutes and vary slightly. You will be asked to imagine or lift your foot in time with a prompt on the computer screen. The level of electrical stimulation applied to your leg muscle during the intervention will be varied. This will cause a twitching of your leg muscle but should not be painful.

Figure 3. EEG Cap to record your brain activity.

This is an Electroencephalography (EEG) cap similar to that used in this research project. It has electrodes attached to it to record your brain activity during the intervention. Conductive gel is placed in each of the electrodes allowing a good EEG signal to be detected by the computer.

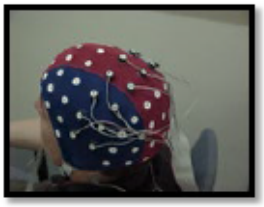

Figure 4. Stimulating electrodes

These are similar to the electrodes that will be used on your leg to provide the electrical stimulation, which will cause a muscle twitch in your leg.

Measuring the intervention:

TMS will be used to measure your brain activity before, immediate after and at 15, 30, and 45 minutes following the intervention.

The remaining six sessions are anticipated to last approximately 1 hour and 15 minutes. The total time required from you as a potential participant would be up to 9 hours over 6 separate sessions.

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

There is a small chance that the procedures being used in this study may make some people anxious. We will minimise this chance by making sure you are fully informed about what to expect prior to any procedure. We will monitor how you are feeling throughout each procedure, and you are able to stop the session at any stage.

TMS is safe and painless but does cause the muscle in your leg and sometimes face to twitch. This carries no risk. Also, some people find the clicking 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 intensity of the magnetic stimulator will begin at a very low level, allowing participants time to get used to the muscle twitches sensations, and ear plugs will be offered.

The electrical nerve stimulation used during the intervention may cause a tingling sensation in the leg, but it should not be painful. The intensity will start at a low level for you to get used to any tingling sensations.

Small areas of skin on the leg will need to be shaved, lightly, exfoliated and wiped with alcohol wipe before the electrodes can be applied. This can cause a temporary stinging sensation and may cause minor, temporary skin reddening. Aloe Vera lotion will be offered as required.

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

Epilepsy, pacemaker, history of seizures, violent or recurrent headaches, skull fracture or other skull defect, head injury or concussion in the last 6 months, conductive or metal implants (except dental implants), seizure lowering medications, or cardiac arrhythmia.

What are the benefits?

There are no direct benefits to you. However, by taking part in this study you are acting, as co-researcher and your contribution will help to develop a new rehabilitation programme for people with stroke. You will also have the experience of participating in a modern research laboratory project.

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 ten years, this data will be destroyed.

What are the costs of participating in this research?

The cost to you is your time. This would be a total of approximately 9 hours over 6 separate sessions, excluding your travel time. Travel vouchers will be provided on each visit to compensate for your time and to assist with travel costs incurred for traveling to and from the laboratory.

What opportunity do I have to consider this invitation?

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

How do I agree to participate in this research?

You can contact us on the details below if you wish to take part in the study. You will need to undergo a brief screening assessment and complete a consent form before participating in the research study.

Will I receive feedback on the results of this research?

Yes. If you wish, a copy of your results and a short summary of the overall findings 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.

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

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

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

Whom do I contact for further information about this research?

Researcher Contact Details:

Primary Researcher: Gemma Alder

Health & Rehabilitation Research Institute

AUT University

Private Bag 92006

Auckland 1142

921 9999 ext. 8935

galder@aut.ac.nz

Project Supervisor Contact Details:

Project Supervisor Dr Denise Taylor

Health & Rehabilitation Research Institute

AUT University

Private Bag 92006

Auckland 1142

921 9680

Denise.taylor@aut.ac.nz

Approved by the Auckland University of Technology Ethics Committee Reference number 15/270.

B.3 Transcranial Magnetic Stimulation (TMS) safety checklist

Participant Safety Checklist for using Transcranial Magnetic Stimulation

Volunteer Name:_____

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

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

Checklist completed by: _____

Signature: _____

Date: _____

B.4 Consent form

Consent Form

A comparison of intensity stimulation parameters to enhance cortico-motor excitability during the Aalborg Brain Computer Interface (BCI) protocol in healthy individuals.

Project Supervisor: ***Associate Professor Denise Taylor***

Researchers: ***Gemma Alder, Dr Nada Signal, Dr Imran Khan Niazi, Dr Mads Jochumsen, Nicola Towersey.***

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 25 August 2015.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ 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.
- ○ I have had the medical risks associated with this research project explained to me
- ○ I am aware of the reasons for potential exclusion from participation in this study
- ○ To the best of my knowledge I am not suffering from any contraindication to the use of Transcranial Magnetic Stimulation as outlined by the researcher.
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes ○ No ○

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if appropriate):

.....

.....

.....

Date:

Approved by the Auckland University of Technology Ethics Committee on 25 August 2015 AUTEC Reference number 15/270

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

B.5 TMS Quality Checklist scores

	Reported	Controlled
Participant factors		
Age of participants	1	1
Gender of participants	1	NA
Handedness / Footedness of participants	1	1
Participants prescribed medication	1	1
Use of CNS active drugs	1	1
Presence of neurological/psychiatric disorders in healthy participants	1	1
Any medical conditions	1	1
History of specific repetitive motor activity	0	0
Methodological factors		
Position and contact of EMG electrodes	1	1
Amount of relaxation/contraction of target muscles	1	1
Prior motor activity of the muscles to be tested	1	1
Level of relaxation of muscles other than those being tested	NA	0
Coil type (size and geometry)	1	1
Coil orientation	1	1
Direction of induced current in the brain	1	1
Coil location and stability (with or without neuro-navigation system)	1	1
Type of stimulator used (e.g. brand)	1	1
Stimulation intensity	1	1
Pulse shape (monophasic or biphasic)	1	1
Determination of optimal hotspot	1	1
The time between MEP trials	1	1
Time between days of testing	1	1
Subject attention (level of arousal) during testing	1	1
Method of determining threshold (active/resting)	1	1
Number of MEP measures made	1	1
Paired pulse only		
Intensity of test pulse	NA	NA
Intensity of conditioning pulse	NA	NA
Inter-stimulus interval	NA	NA
Analytical factors		
Method of determining MEP size during analysis	1	1
Size of unconditioned MEP	NA	NA
Totals	24	23
% Score	96%	92%
Overall % Score	**94%**	

1= yes, 0= no, NA= non aplicable.

B.6 Predefined TA EMG processing criteria

1 The first EMG responses was removed from each time point due to participants often being startled from the sensation and/ or anticipation of the first TMS pulse.
2 EMG responses were removed if there was no stimulation artefact visually present corresponding to the TMS trigger.
3 EMG responses will be removed if silent EMG or excessively large / erratic voluntary muscle activity was present within the 70ms preceding the stimulation artefact or if during data collection the participant was not at their 10% force line when the TMS pulse was triggered.

B.7 Statistical analysis plan

1. Analysis sets and datasets

Missingness at random assumption

It is assumed that missing data are missing at random (MAR). The planned linear mixed effects analysis will adequately account for missing data under this assumption [Carpenter 2007].

Data sets

There will be two data sets used in the analysis. One will be the absolute data set, consisting of the absolute values of the outcome's pre-intervention, immediately post-intervention, and at 15, 30 and 45-minutes post-intervention (normally, 5 time-points). All measurements at all time-points will be retained. The second one will be called the relative data set and will consist in the relative change from the pre-intervention measure immediately post-intervention and at 15, 30 and 45-minutes post-intervention. These relative changes will be computed from the mean of the measurements at each time point, and a weight corresponding to the number of observations retained post-intervention to compute the mean at each post-intervention time point. The relative change was calculated as follows (post-pre)/pre x100.

2. Study outcomes and baseline covariates

Cortico-motor excitability (CME) outcomes

CME outcomes are measured pre-intervention, and at 0, 15, 30 and 45-minutes post-intervention. They consist of:

(1) Absolute MEP amplitude values

(2) Absolute MEP area values

(3) MEP Amplitude % change values

(4) MEP Area % change values

Baseline covariates

The covariates collected pre-intervention consist of maximum voluntary contraction (MVC) and active motor threshold percentage (AMT). These covariates have been tested for

adjustment in the models during a blind review (using the blinded treatment codes to adjust for treatment), using a 5% significance threshold to decide on inclusion. Pre-intervention MEP Amplitude and MEP area values have also been tested in the same manner.

3. Structure of analyses

Notes on the data

We distinguish between Blind Intervention and Blind Intervention Group, in the absolute data only.

Blind Intervention takes on values "None", "A"," B", "C", "D", "E", "F", with "None" applying in all pre-intervention observations. It is used to define fixed effects.

Blind Intervention Group takes on values "A", "B", "C", "D", "E", "F" and refers to the intervention applied in a whole session, including the pre-intervention measurements. It is used to define random effects.

Only the Blind Intervention Group is used in the relative data, as the pre-intervention observations are not included in the analyses.

Inferential framework

The inferential framework selected is linear mixed modelling. The large size of the data sets (over 7300 observations in the absolute data and over 580 observations in the relative data) render concerns of non-normality of the residuals secondary, in spite of the dependence between the observations, if we extend the arguments of Lumley and colleagues [383] regarding linear regression to linear mixed regression. Analyses were carried out using package *lme4* [384] in *R (*R Core Team 2018) *and SAS/STAT™ software.*

Blinded selection of model

During the blind review, the model to be used will be selected from amongst 144 models (absolute data) or 288 models (relative data) defined with the core elements listed below. A final assessment of residual covariance structure and heteroscedasticity across the Blind Intervention Groups in the retained model will be carried out.

Core covariate:

-Blind Intervention: None, A, B, C, D, E, F (None is applied to the pre-intervention data)

Core random effects:

-Participant random intercept: P01, ,P025

-Participant and Blind Intervention Group interaction random intercept: P01*A, P01*B, etc.

The model also involves the following alternative components.

Alternative covariates:

(1) Time point: either time as a factor (PRE, POST0, POST15, POST30, POST45), time as continuous (PRE=0, POST45=4), or time as continuous as well as its square

(2) Time point and Blind Intervention interaction: either none, or in interaction with time as a factor, or in interaction with time as a continuous covariate

(Note: For covariates only, we do not mix categorical and continuous in the same model)

(3) MVC: Present or not

(4) AMT: Present or not

(5) Baseline MEP value: Present or not (relative data only)

(6) Order of the intervention in the cross-over: Present or not

Alternative random effects

(7) Participant random slope for time as continuous: Present or not

(8) Participant and Blind Intervention Group interaction random slope for time as continuous: Present (only if 7. is present) or not

Notes:

Time was taken as continuous in random effect regardless of fixed effects. Model selection was automated up to selection of items 1 to 8 with the use of package *lme4* [384] in *R* (R Core Team, 2018). Further covariance investigation was carried out using PROC MIXED, part of the SAS/STAT software. In case item 7 was retained, alternative formulations for the variance structure were investigated (*R*-side covariance structure), with time as a continuous index and instances of participant-interventions as subject. These covariance structures were:

-compound symmetry

-heterogeneous compound symmetry

-autoregressive of order 1

-autoregressive moving average of order (1, 1)

-spatial exponential

-spatial Gaussian

-spatial power covariance's.

In all cases, heterogeneity of the variance parameters by treatment group was investigated, always using AIC as a criterion. Under failure to converge, the model was deemed inadequate without further investigation.

Retained models

Absolute data

The final model was selected based on Akaike's information criterion and corresponded to the following model for both MEP Amplitude and MEP Area.

Retained fixed effects:

-Blind Intervention

-Time as a factor

-Blind Intervention in interaction with time

-AMT

-MVC

Retained random effects:

-Participant random intercept

-Participant in interaction with Blind Intervention Group random intercept and random time slope

Other variance parameters:

-Variances were found to be heterogeneous across Blind Treatment Groups.

Relative data

The final model for the relative data was selected based on Akaike's information criterion and corresponded to the following model for both relative MEP Amplitude and MEP Area.

Retained fixed effects:

-Blind Intervention

-Absolute baseline value

Retained random effects:

-Participant random intercept

-Autoregressive moving average of order 1,1, with continuous time as the index and participant-time as the subject

Other variance parameters:

-Variance parameters were found to be heterogeneous across Blind Treatment Groups.

Primary analysis

Translation to unblinded model

The actual model retained for the primary analysis is the factorial version of the retained model. Movement type takes on the values "None", "Real", "Imagined"; Intensity takes on the values "NA", "0%", "100%", "300%". The values "None" for Movement type and "NA" for intensity only apply in the Pre-intervention phase, for Tx equal to "None".

Absolute data

Retained fixed effects:

-Movement type

-Intensity

-Time as a factor

-Movement type in interaction with time

-Intensity in interaction with time

-Three-way interaction of Movement type, Intensity and time

--AMT

MVC

Retained random effects:

-Participant random intercept

Other variance parameters:

-Participant in interaction with Blind Intervention Group random intercept and random time slope. -Heterogeneous variances across interventions.

Relative data

Retained fixed effects:

-Movement type

-Intensity

-Movement type in interaction with intensity

-Baseline absolute value

Retained random effects:

-Participant random intercept

Other variance parameters:

-Auto-regressive moving average of order 1, in the measurement time ordering, with participant-intervention as the subject; heterogeneous variance parameters across interventions.

B.8 Additional results

B.8a Estimated adjusted Super/sub-additive effects in absolute units of stimulation intensity levels (vs no stimulation) and Voluntary movement (vs Imagined movement) on MEP amplitude and MEP area, at each post-baseline time point

	Adjusted estimate MEP Amplitude μV Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Area μV/ms Δ (95% CIs)**	**p-value**
Primary analysis: Super/sub-additivity, Intensity suprathreshold vs no stimulation and real vs imaginary movement				
POST0	-1.2 (-289.2,86.8)	0.99	-0.02 (-1.31,1.26)	0.97
POST15	-305.3 (-643,32.34)	0.076	-1.49 (-2.99,0.011)	0.051
POST30	-327.9 (-735.7,79.83)	0.11	-1.87 (-3.68,-0.06)	**0.042***
POST45	229.7 (-262.9,722.3)	0.35	0.355 (-1.83,2.53)	0.74
Super/sub-additivity, Intensity threshold vs no stimulation and real vs imaginary movement				
POST0	-85.64 (-378.9,207.6)	0.56	-0.91 (-2.25,0.438)	0.18
POST15	-505.6 (-871.4,-139.8)	**0.006***	-3.21 (-4.9,-1.48)	**0.0003***
POST30	-448.1 (-909.8,13.68)	0.05	-2.79 (-5.01,-0.57)	**0.014***
POST45	-287.3 (-860.3,285.7)	0.32	-2.13 (-4.91,0.645)	0.13

*⊿: Difference; Significant effects (p <0.05) are in bold text with **

B.8b Estimated adjusted effect differences in absolute units between Hi-Voluntary and each intervention on MEP amplitude and MEP area, at each post-baseline time point and averaged over time

	Adjusted estimate MEP Amplitude μV Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Area μV/ms Δ (95% CIs)**	**p-value**
Hi-Voluntary vs Lo-Voluntary				
POST0	101 (-114.1,316.8)	0.35	0.78 (-0.22,1.778)	0.12
POST15	160 (-111.8,431)	0.24	0.863 (-0.45,2.177)	0.19
POST30	132 (-218.3,481.8)	0.45	0.869 (-0.87,2.607)	0.32
POST45	339 (-100.6,778.2)	0.12	1.767 (-0.44-3,975)	0.11
Averaged over time	183 (-104.8,470.5)	0.20	1.07 (-0.36,2.503)	0.13
Hi-Voluntary vs Control-Voluntary				
POST0	311 (109,511.8)	**0.002***	1.443 (0.527,2.359)	**0.002***
POST15	-6 (-232.9,220.9)	0.95	-0.36 (-1.42,0.703)	0.50
POST30	-9 (-275.2,257.3)	0.94	-0.5 (-1.78,0.783)	0.44
POST45	298 (-18.7,614.2)	0.06	1.195 (-0.35,2.744)	0.12
Averaged over time	148 (-67.37,364.1)	0.17	0.445 (-0.6,1.489)	0.39
Hi-Voluntary vs Hi-Imagined				
POST0	-16.58 (-222.7,189.5)	0.87	0.112 (-0.8,1.026)	0.81
POST15	-151.9 (-386.5,82.69	0.20	-0.43 (-1.47,0.609	0.41
POST30	-119.9 (-399.6,159.9)	0.39	-0.85 (-2.09,0.384)	0.17
POST45	160.1 (-174.8,495)	0.34	0.384 (-1.1,1.865)	0.60
Averaged over time	-32.07 (-260.3,196.1)	0.78	0.2 (-1.21,0.812)	0.69
Hi-Voluntary vs Lo-Imagined				
POST0	0.341 (-204.4,205.1)	0.99	0.011 (-0.91,0.93)	0.98
POST15	-192.6 (-429,43.82)	0.10	-1.28 (-2.37,-0.19)	**0.021***
POST30	-108.3 (-394.5,178)	0.45	-0.91 (-2.25,0.433)	0.18
POST45	-18.15 (-363,326.7)	0.91	-0.34 (-1.97,1.294)	0.68
Averaged over time	-79.67 (-313.1,153.8)	0.49	-0.63 (-1.72,0.466)	0.25
Hi-Voluntary vs Control-Imagined				
POST0	295.5 (87.37,503.6)	**0.005***	1.579 (0.667,2.492)	**0.000***
POST15	147.3 (-103.5,398.2)	0.24	0.7 (-0.37,1.775)	0.20
POST30	199.1 (-114,512.2)	0.20	0.517 (-0.8,1.836)	0.43
POST45	228 (-156.8,612.8)	0.23	1.224 (-0.38,2.829)	0.13
Averaged over time	217.5 (-38.85,473.8)	0.094	1.005 (-0.07,2.082)	0.066

⊿: Difference; Significant effects (p <0.05) are in bold text with

B.8c Estimated adjusted effect differences in absolute units between stimulation intensity levels delivered during voluntary movement and imagined movement on MEP amplitude, at each post-baseline time-point and averaged over time

	Adjusted estimate MEP Amplitude μV Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Amplitude μV Δ (95% CIs)**	**p-value**
Voluntary			**Imagined**	
300% vs 100%				
POST0	101 (-114.1,316.8)	0.35	16.92 (-186.7-220.5)	0.87
POST15	160 (-111.8,431)	0.24	-40.68 (-278.4-197.1)	0.73
POST30	132 (-218.3,481.8)	0.45	11.6 (-275.2-298.4)	0.93
POST45	339 (-100.6,778.2)	0.12	-178.2 (-524-167.5)	0.30
Averaged over time	183 (-104.8,470.5)	0.20	-47.6 (-281.1-185.9)	0.68
300% vs 0%				
POST0	311 (109,511.8)	**0.002***	312 (105.2-518.8)	**0.003***
POST15	-6 (-232.9,220.9)	0.95	299.3 (47.35-551.2)	**0.020***
POST30	-9 (-275.2,257.3)	0.94	319 (5.587-632.4)	**0.046***
POST45	298 (-18.7,614.2)	0.06	67.97 (-317.5-453.4)	0.72
Averaged over time	148 (-67.37,364.1)	0.17	249.6 (-6.64-505.8)	0.056
100% vs 0%				
POST0	210 (-0.14,419.1)	0.050	295.1 (89.58,500.7)	**0.004***
POST15	-166 (-431.9,100.5)	0.21	339.9 (86.28,593.6)	**0.009***
POST30	-141 (-480.9,199.6)	0.41	307.4 (-11.79,626.5)	0.058
POST45	-41 (-468.1,385.9)	0.84	246.2 (-147.8,640.2)	0.21
Averaged over time	-35 (-312.9,243.9)	0.80	297.2 (36.28,558)	**0.026***

*Δ: Difference; Significant effects (p <0.05) are in bold text with **

B.8d Estimated adjusted effect differences in absolute units between stimulation intensity levels delivered during voluntary movement and imagined movement on MEP area, at each post-baseline time-point and averaged over time

	Adjusted estimate MEP Area μV/ms Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Area μV/ms Δ (95% CIs)**	**p-value**
Voluntary			**Imagined**	
300% vs 100%				
POST0	0.78 (-0.22,1.778)	0.12	-0.1 (-1.01,0.812)	0.82
POST15	0.863 (-0.45,2.177)	0.19	-0.85 (-1.93,0.228)	0.12
POST30	0.869 (-0.87,2.607)	0.32	-0.05 (-1.37,1.265)	0.936
POST45	1.767 (-0.44,3.975)	0.11	-0.72 (-2.32,0.881)	0.37
Averaged over time	1.07 (-0.36,2.503)	0.13	-0.43 (-1.51,0.643)	0.42
300% vs 0%				
POST0	1.443 (0.527,2.359)	**0.002***	1.468 (0.566,2.369)	**0.001***
POST15	-0.36 (-1.42,0.703)	0.50	1.13 (0.063,2.197)	**0.038***
POST30	-0.5 (-1.78,0.783)	0.44	1.371 (0.074,2.668)	**0.038***
POST45	1.195 (-0.35,2.744)	0.12	0.84 (-0.73-2,414)	0.28
Averaged over time	0.445 (-0.6,1.489)	0.39	1.202 (0.146,2.258)	**0.026***
100% vs 0%				
POST0	0.663 (-0.33,1.654)	0.18	1.568 (0.65,2.479)	**0.000***
POST15	-1.22 (-2.55,0.104)	0.070	1.982 (0.86,3.096)	**0.000***
POST30	-1.37 (-3.12,0.385)	0.12	1.424 (0.03,2.817)	**0.043***
POST45	-0.57 (-2.8,1.659)	0.60	1.56 (-0.15,3.274)	0.073
Averaged over time	-0.63 (-2.07,0.818)	0.38	1.634 (0.49,2.771)	**0.005***

⊿: Difference; Significant effects (p <0.05) are in bold text with

B.8e Estimated adjusted effect differences in absolute units between voluntary and imagined movement at each stimulation intensity level on MEP amplitude and MEP area, at each post-baseline time-point and averaged over time

	Adjusted estimate MEP Amplitude μV Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Area μV/ms Δ (95% CIs)**	**p-value**
Voluntary vs Imagined 300%				
POST0	-16.58 (-222.7,189.5)	0.87	0.112 (-0.81.026)	0.81
POST15	-151.9 (-386.5,82.69	0.20	-0.43 (-1.47,0.609	0.41
POST30	-119.9 (-399.6,159.9)	0.39	-0.85 (-2.09,0.384)	0.17
POST45	160.1 (-174.8,495)	0.34	0.384 (-1.1,1.865)	0.60
Averaged over time	-32.07 (-260.3,196.1)	0.78	-0.2 (-1.21,0.812)	0.69
Voluntary vs Imagined 100%				
POST0	-101 (-313.9,111.9)	0.35	-0.77 (-1.76,0.227)	0.12
POST15	-352.2 (-626.2,-78.29)	**0.012***	-2.15 (-3.49,-0.8)	**0.002***
POST30	-240 (-595.3,115.4)	0.18	-1.78 (-3.57,0.017)	0.052
POST45	-356.9 (-804.2,90.31)	0.11	-2.1 (-4.39,0.181)	0.070
Averaged over time	-262.5 (-554.1,28.99)	0.076	-1.7 (-3.18,-0.22)	**0.025***
Voluntary vs Imagined 0%				
POST0	-15.38 (-217.7,186.9)	0.88	0.137 (-0.77,1.041)	0.76
POST15	153.4 (-91.9,398.7)	0.21	1.06 (-0.03,2.152)	0.056
POST30	208.1 (-93.97,510.1)	0.17	1.016 (-0.32,2.356)	0.13
POST45	-69.65 (-440,300.7)	0.70	0.029 (-1.61,1.667)	0.97
Averaged over time	69.11 (-176.8,315)	0.57	0.561 (-0.53,1.652)	0.30

*∠1: Difference; Significant effects (p <0.05) are in bold text with **

B.8f Observed significance of estimated baseline covariate, main and interaction effects for Relative MEP amplitude and MEP area

	Numerator *df*	**Relative MEP Amplitude (%) p- value**	**Relative MEP Area (%) p-value**
Baseline absolute value	1	**0.004***	**0.002***
Movement type	3	0.71	0.46
Stimulation intensity	4	0.17	0.12
Simulation intensity x Movement type	2	0.50	0.28

*Significant effects (p <0.05) are in bold text with **

B.8g Estimated adjusted extra-additive effects in percentage points from baseline of stimulation intensity levels (vs no stimulation) and Voluntary movement (vs Imagined movement) on MEP amplitude and MEP area

Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	**p-value**	**Adjusted estimate MEP Area – pct pt Δ (95% CIs)**	**p-value**
Super/sub-additivity, Intensity suprathreshold vs no stimulation and real vs imaginary movement			
-1.30 (-24.7,22.15)	0.91	-3.7 (-27.5,20.1)	0.76
Super/sub-additivity, Intensity threshold vs no stimulation and real vs imaginary movement			
-11.4 (-31.1,8.3)	0.25	-16.4 (-37.1,4.3)	0.12

*pct pt ⊿: percentage point difference; Significant effects (p <0.05) are in bold text with **

B.8h Estimated adjusted effect differences in percentage points from baseline between Hi-Voluntary and each intervention on the MEP amplitude and MEP area

Contrast	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value	Adjusted estimate MEP Area – pct pt Δ (95% CIs)	p-value
Hi-Voluntary vs Lo-Voluntary	13.3 (-7.2,33.8)	0.20	13.3 (-6.1,32.7)	0.17
Hi-Voluntary vs Control-Voluntary	13.4 (-5.7,32.4)	0.16	12.2 (-7.0,31.4)	0.20
Hi-Voluntary vs Hi-Imagined	2.8 (-17.6,23.2)	0.78	1.4 (-18.4,21.3)	0.89
Hi-Voluntary vs Lo-Imagined	6.0 (-15.0,27.1)	0.56	2.0 (-19.1,23.2)	0.85
Hi-Voluntary vs Control-Imagined	17.5 (-2.6,37.6)	0.086	17.3 (-2.6,37.2)	0.087

*pct pt ⊿: percentage point difference; Significant effects (p <0.05) are in bold text with **

B.8i Estimated adjusted effect differences in percentage points from baseline between stimulation intensity levels delivered during voluntary movement and imagined movement on MEP amplitude

	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value
	Voluntary		**Imagined**	
300% vs 100%	13.3 (-7.2,33.8)	0.20	3.2 (-12.3,18.7)	0.68
300% vs 0%	13.4 (-5.7,32.4)	0.16	14.7 (0.4,29.0)	**0.044***
100% vs 0%	0.1 (-12.6,12.8)	0.99	11.5 (-3.8,26.8)	0.14

*pct pt ⊿: percentage point difference; Significant effects (p <0.05) are in bold text with **

B.8j Estimated adjusted effect differences in percentage points from baseline between stimulation intensity levels delivered during voluntary movement and imagined movement on MEP area

Contrast	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value	Adjusted estimate MEP Area – pct pt Δ (95% CIs)	p-value
Hi-Voluntary vs Lo-Voluntary	13.3 (-7.2,33.8)	0.20	13.3 (-6.1,32.7)	0.17
Hi-Voluntary vs Control-Voluntary	13.4 (-5.7,32.4)	0.16	12.2 (-7.0,31.4)	0.20
Hi-Voluntary vs Hi-Imagined	2.8 (-17.6,23.2)	0.78	1.4 (-18.4,21.3)	0.89
Hi-Voluntary vs Lo-Imagined	6.0 (-15.0,27.1)	0.56	2.0 (-19.1,23.2)	0.85
Hi-Voluntary vs Control-Imagined	17.5 (-2.6,37.6)	0.086	17.3 (-2.6,37.2)	0.087

*pct pt ⊿: percentage point difference; Significant effects (p <0.05) are in bold text with **

B.8k Estimated adjusted effect differences in percentage points from baseline between movement types at each stimulation intensity level on MEP amplitude and MEP area

	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value	Adjusted estimate MEP Amplitude – pct pt Δ (95% CIs)	p-value
	Voluntary		**Imagined**	
300% vs 100%	13.3 (-7.2,33.8)	0.20	3.2 (-12.3,18.7)	0.68
300% vs 0%	13.4 (-5.7,32.4)	0.16	14.7 (0.4,29.0)	**0.044***
100% vs 0%	0.1 (-12.6,12.8)	0.99	11.5 (-3.8,26.8)	0.14

*pct pt ⊿: percentage point difference; Significant effects (p <0.05) are in bold text with **

Appendix C: Supplementary documents for Chapter 6

Relates to the following publication:

Alder G, Signal N, U Rashid, Olsen S, Niazi I and Taylor D. (2020) Reliability of Manual Feature Extraction Methods in Movement Related Cortical Potential Analysis. Sensors, 20 (8), 2427. doi: 10.3390/s20082427.

C.1 Ethical approval amendment

C.2 Consent from

The supplementary material for this article can also be found online at:

https://www.mdpi.com/1424-8220/20/8/2427/s1

C.3 Examples of averaged healthy MRCP data

C.4 Statistical analysis plan for secondary analysis: epoch selection

C.1 Ethical approval amendment

AUTEC Secretariat

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T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

10 March 2017

Denise Taylor
Faculty of Health and Environmental Sciences
Dear Denise

Re: Ethics Application: **14/255 A Brain Computer Interface (BCI) driven Paired Associative Stimulation (PAS) protocol: A rehabilitation intervention for people with stroke.**

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

The amendment to data analysis protocols is approved.

I remind you that as part of the ethics approval process, you are required to submit the following to the Auckland University of Technology Ethics Committee (AUTEC):

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 12 November 2017;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 12 November 2017 or on completion of the project.

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

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

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

All the very best with your research,

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

C.2 Consent from

Consent Form

AUT UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Project title: **Intra- and inter-rater reliability of manual processing methods of feature extraction from movement related cortical potentials in healthy people and people with stroke**

Project Supervisor: ***Associate Professor Denise Taylor***
Researchers: ***Gemma Alder, Dr Nada Signal, Dr Imran Khan Niazi***

- 14/255 The Aalborg BCI: a MRCP driven PAS protocol for people with stroke.
- 15/270 The Aalborg Brain Computer Interface: Optimising the delivery of stimulation parameters for the BCI-MRCP driven PAS protocol for people with stroke.

- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ 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.
- ○ I am aware of the reasons for potential exclusion from participation in this study
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes ○ No ○

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if appropriate):

.....

.....

.....

Date:

***Approved by the Auckland University of Technology Ethics Committee on 10th March 2017 AUTEC Reference number* 14/255 and 15/270**

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

C.3 Examples of averaged healthy MRCP data

The top graph in the below figure presents an imagined movement dataset where substantial disagreement between experts' average MRCP PN labelling was evident (SD = 51 samples). The bottom graph in Figure S1 presents a different imagined movement dataset where there was substantial agreement between experts' average MRCP PN labelling (SD = 5 samples).

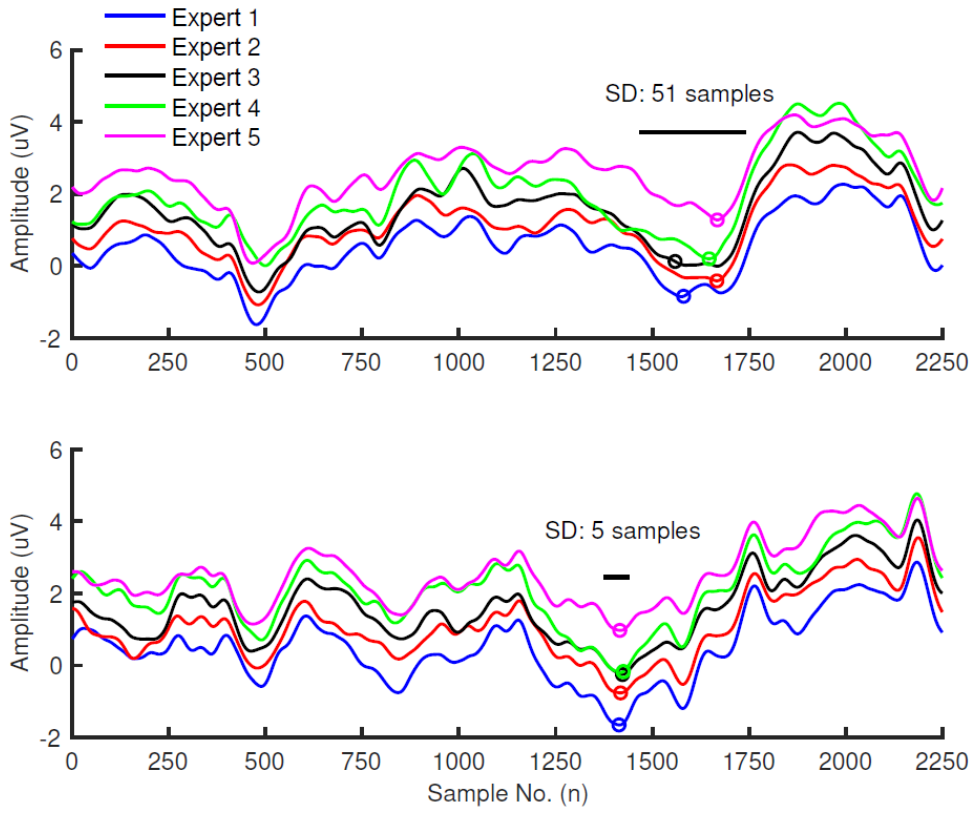


Figure. Averaged MRCPs from two example healthy participants performing imaginary movements. Five MRCP averages (different colors) were produced from the same dataset according to each expert's included epochs. MRCP averages were offset for visual clarity (expert 1 = 0.5 uV,expert 2 = 1 uV, expert 3 = 1.5 uV, expert 4 = 2 uV, expert 5 = 2.5 uV). Sample number '1500' corresponds to the onset of the cue to move. Each expert's manually-labelled PN is circled. SD = standard deviation of samples across the five experts.

C.4 Statistical analysis plan for secondary analysis: Epoch selection

We investigated the influence of two factors: (1) morphology of the signal and (2) experience of an EEG expert on the ability of experts to provide the same response for inclusion of epochs. Epoch selection was defined as 'matched' if an expert chose to accept an epoch for inclusion at two different evaluation sessions (intra-rater: evaluation sessions 1 and 2 and 1 and 3) or if all five experts accepted the same epoch in a single evaluation session (inter-rater: evaluation sessions 1, 2 and 3).

Hypotheses:

We tested the following secondary null hypotheses:

(i) There is no relationship between the morphology of the epoch and the ability of an expert to accept the same epochs for inclusion across two evaluation sessions (intra-rater: evaluation sessions 1 and 2 and 1 and 3).

(ii) There is no relationship between the experience of an expert and their ability to accept the same epochs for inclusion across evaluation sessions (intra-rater: evaluation sessions 1 and 2 and 1 and 3).

(iii) There is no relationship between the morphology of the epoch and the ability of all experts to accept the same epochs for inclusion in a single evaluation session (inter-rater: evaluation sessions 1, 2 and 3).

Quantifying variables:

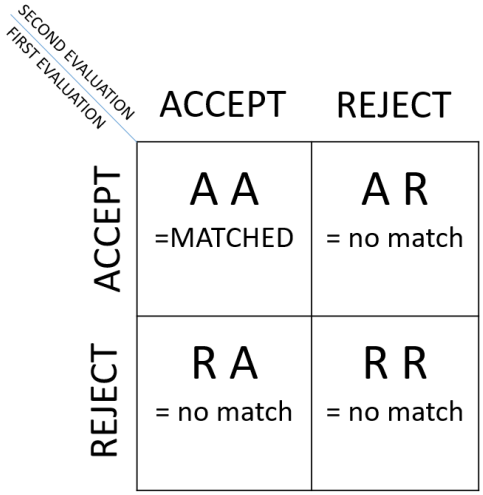
The morphology of the epochs was quantified using the cosine similarity index. This was defined as the similarity of a single epoch from a participant compared to the average MRCP of all 50 epochs of the same participant, which was considered a representation of the expected MRCP characteristics. The cosine similarity index within each condition was computed as follows[420]:

$$\text{Cosine similarity index} = \frac{\mathbf{u}.\mathbf{v}}{||\mathbf{u}||\ x\ ||v||}$$

where u and v are vectors, u is the average MRCP of all 50 epochs from a participant and v is a single epoch from the same participant. '.' represents the dot product between the two vectors and ‖.‖ represents the L2 norm of a vector. The self-reported experience of experts working with MRCP signals was quantified in years. We quantified 'matched' and 'no match'

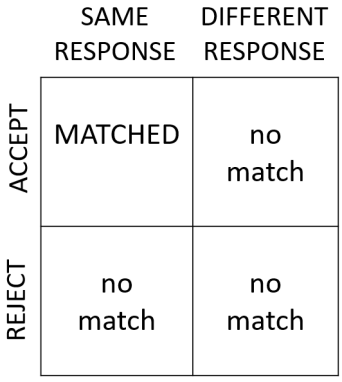
as binominal categorical variables. For the intra-rater analysis, we assigned matched when a single expert accepted the same epoch at both evaluation time points (i.e., evaluation sessions 1 and 2 (intra-session) or evaluation sessions 1 and 3 (inter-session)) and assigned no match when there was a mismatch in their epoch choice or both epochs were rejected. All possibilities for a given epoch are presented in the below Figure.

Figure. Intra-rater analysis (intra-session and intersession). Possible options for an epoch match or no match by a single expert at two different time points. A = accepted; R = rejected.



For the inter-rater analysis we assigned matched when all five experts accepted the same epoch at a single evaluation session (i.e., session 1, 2 or 3) and assigned no match in all other cases. For example, if four experts rejected an epoch and one expert accepted the epoch, we assigned a no match, or if all five experts rejected the epoch, we also assigned a no match. The possibilities for a given epoch are presented in the below Figure.

Figure. Inter-rater analysis. Possible options for an epoch match or no match across the five experts within a single evaluation session.



Intra-rater and inter-rater statistical models

Logistic mixed-effects models were set up in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and fitted using lme4 package version 1.1-17 [421]. For each condition

the significance level was set to $p < 0.05$. Car package version 3.0-0 [63] provided analysis of deviance tables for each of the models using the Anova function. Main effects and interactions were reported using Type III Wald Chi-squared tests. In the case of interactions, linear trends for cosine similarity and expert experience were obtained with emmeans package version 1.3.4[437].

Intra-rater (intra- and inter-session) statistical model

Relates to hypotheses (i) and (ii)

To assess the influence of the morphology of epochs and expert experience on expert's ability to match epochs for inclusion at evaluation sessions 1 and 2 and 1 and 3 we used a logistic mixed-effects binominal regression model with a logit link. Conditions, participants, single epochs, experts and time were entered as nominal categorical variables. Time had two levels: the first corresponding to epoch matches from evaluation session 1 and 2 and the second corresponding to epoch matches from evaluation sessions 1 and 3. Cosine similarity index and expert experience were entered as continuous variables. Cosine similarity index, time, expert experience and condition were treated as fixed effects. Participants, epochs nested under participants and experts were treated as random intercept effects.

$$\text{Matched\_status} \sim (\text{cosine\_similarity} \times \text{time} + \text{expert experience}) \times \text{condition} + (1|\ \text{participant/epoch}) + (1|\ \text{expert})$$

Inter-rater statistical model

Relates to hypothesis (iii)

To assess the influence of morphology on all five of the expert's ability to match epochs for inclusion at the same evaluation session we used a logistic mixed-effects binominal regression model with a logit link. Condition, participants, single epochs and time were entered as nominal categorical variables. Time had three levels each corresponding to epoch matches from evaluation sessions 1, 2 and 3. Cosine similarity index was entered as a

continuous variable. Condition and time were treated as fixed effects. Participants and epochs nested under participants were treated as random intercept effects.

$$\text{Matched\_status} \sim \text{cosine\_similarity} \times \text{time} \times \text{condition} + (1| \text{participant/epoch})$$

Cosine similarity statistical model

To assess cosine similarity across conditions a linear mixed-effects model with Gaussian family and an identify link was also set up in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and fitted using lme4 package version 1.1-17 [421]. For each condition the significance level was set to $p < 0.05$. In the case of significant findings for cosine similarity across conditions, pairwise t-tests using Tukey's method were performed and presented with cosine similarity means and standard deviations as mean ± SD for each condition. Condition and epoch were entered as categorical variables and cosine similarity index as a continuous variable. Condition and epochs were treated as fixed effects. The cosine similarity of each study participant was modelled with a random intercept.

$$\text{cosine similarity} \sim \text{condition} \times \text{epoch} + (1| \text{participant}) \text{ pt.}$$

Appendix D: Supplementary documents for Chapter 7

JOURNAL ENTRY: 22 AUG

Image: Testing usability of our exciteBCI system using role play in the clinical environment. Mock up paper apps and a music stand as an iPad holder!

Gemma Alder: Our system, exciteBCI, is a portable, wearable rehabilitation device that can modulate changes in brain nerve activity to promote recovery in patients who have suffered a stroke. In the last two weeks, we've been particularly focused on finalising the details of our project plan, and in completing our Health and Disability Ethics application for usability testing of the system.

Team members are working well together, and we are making progress on all fronts. Everyone is buzzing from the input and the connections made at Bootcamp 1, and we've injected this new knowledge into the project as it moves forwards. The value of early prototyping is a case in point– expect to see a lot from us in the way of roleplay and paper app mock ups, through to digital models and 3D printing.

One thing we're keen to explore in the coming weeks is the question of the 'social acceptability' of wearables – it's becoming more and more apparent to us that rather than there being a single solution, it depends entirely on who you are and what your situation is, so we'll certainly be taking more input from end-users on that.

JOURNAL ENTRY: 5 SEPT

Image: Denise and Imran problem-solving through some issues with the stimulator electronics

Gemma Alder: The past couple of weeks have seen the team working hard and getting the individual sub-assemblies built and up and working. The three main components of the system are all working now; the next stage is to get them all talking to each other, as we start our first clinical trials in only three weeks – no pressure!

The clinicians have been working closely with an advisor - who has had a stroke - to look at the user experience, usability, and social acceptability of the system. They have been feeding this information back to the designers and engineers in real-time during this sprint phase to completion of version 1 of the prototype.

The C-Prize competition has certainly put a lot of pressure on the team, but we are all loving the progress that we are making and the contribution the process is making to our research, work, and professional experience.

The next couple of weeks will see us getting the first version prototype complete and ready for the clinical trials – they will be focused on usability and the user experience for both the patient and the clinician.

JOURNAL ENTRY:20 SEPT

IMAGE: Iterative prototyping in progress!

Gemma Alder: It has been a busy two weeks, with more iterative prototyping and a strong focus on testing the communication between the various components of the wearable system. We are pleased to say that so far this has been a real success!!

We also welcomed Scott Brebner - a software designer and developer – to the team. He is already hard at work creating the user interface for our clinician portal app and is particularly focused on utilising the feedback from our physical therapist. Scott will also be working closely with Usman who has been putting some serious hours into the backend development of the app and into ensuring successful Bluetooth communication between the three components of our product.

The first version prototype is just about complete, and it will mark the beginning of our usability and acceptability trial, scheduled to kick off later this month. In the meantime, there will be some role-play workshops to get us prepped. The team is really looking forward to optimising the future versions of the prototype based on user experience feedback from people with stroke and clinicians.

JOURNAL ENTRY: 1 OCT

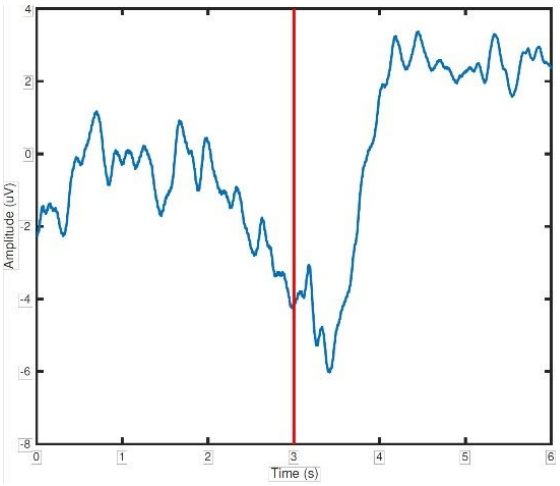


IMAGE: A successful EEG recording and workshopping the app

Denise Taylor: It's all go for us – we're just need the final ethical approval letter and then we are all go on the usability trials. We also have a working prototype that needs only a bit of fine-tuning to optimise triggering exciteBCI via the app. We expect to complete this in the next week.

The headset design is coming along nicely, we have 3-D printed a number of prototypes and have consulted clinicians and our stroke advisor about the fit, appearance and acceptability. We have trialled various versions of the headset and are beginning to get a clear understanding of how to produce a stable, comfortable EEG headset that works reliably and is acceptable to clinicians and patients alike.

The role-playing workshops with people with stroke and clinicians have really enabled us to understand potential barriers and facilitators to using the exciteBCI in clinical practice. Importantly too, it is helping to ensure that we design the exciteBCI to fit well with clinical practice, both now and into the future.

JOURNAL ENTRY: 12 OCT

IMAGE: Denise and Usman are all smiles at the Team Rehabilitation Innovation C-Prize video update.

Gemma Alder: It's been another busy couple of weeks for team Rehabilitation Innovation, leading up to Bootcamp #2. We have continued to prepare for the clinical trials and develop our device by utilising ongoing feedback from clinicians and our stroke advisor. So far, the response to exciteBCI has been very positive, and the valuable opinions from our potential users continues to drive our development process and fuel the fire in our bellies.

One of our current prototype challenges is producing headsets that fit a wider range of head sizes. The headset needs to be fit for comfort and functionality, as the user will be exercising whilst the headset collects brain signal data. One of the technical constraints identified by the usability testing is the material properties of the current headset prototype. We intend to explore softer materials and slightly different mechanisms to secure the headset over the coming weeks. We look forward to getting more feedback on this from our potential users during the clinical trials.

We also had a visit from the C-Prize film crew last week for a video update on our C-Prize journey. This was a fantastic opportunity to voice our passion for developing exciteBCI, highlight our achievements so far and identify future challenges. But also, to reflect on how far we have come in the last 13 weeks. This really gave our team a boost and was a great way to complement our journal entries.

JOURNAL ENTRY: 27 OCT

IMAGE: The excitement leading up to the finals has got all a little too much from our engineer Imran

Gemma Alder: It's less than 4 weeks to go until the C-Prize finals, and the excitement is building here at team Rehabilitation Innovation. Bootcamp #2 really got us in the right frame of mind for the finals. Highlights for the team were interacting more with the finalists, hearing about their awesome progress and chatting with Laurie Winkless from Callaghan. She had some really useful tips with regards to presenting our idea to journalists and the general public. She emphasised the importance of the team conveying a shared clear and consistent message and being able to do pitch this in under a minute. We had a practice run and got some great feedback.

The last few weeks have seen us making some really positive steps forwards in terms of our working prototype, in particular our headset and experimenting with new materials has been a real success! The app is receiving a daily makeover based on user feedback, and it's really starting to take shape. We have also been busy developing a library of exercises for the app and Thonia (our stroke advisor) has been testing out the exercises to ensure client challenge and engagement. So far, she has given us the thumbs up.

We are also thrilled to say we received the golden ticket from the Ethics Committee, so exciteBCI usability trials commence this week! The team are buzzing for this opportunity to hear more from potential real users and utilise their feedback to modify the device to improve its usability and acceptability to clinicians and people with stroke.

JOURNAL ENTRY: 12 NOV

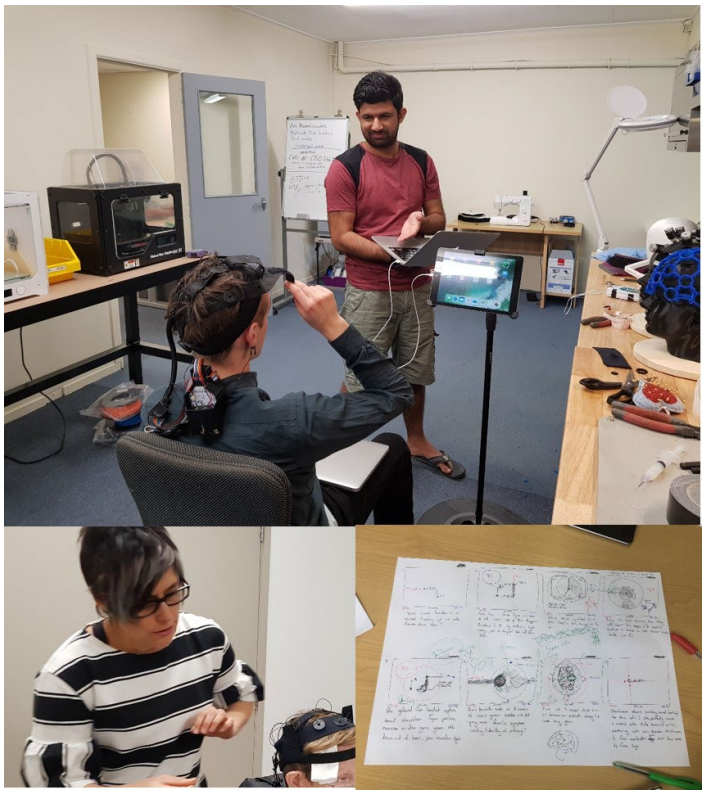


IMAGE: Usman and Scott work out issues with headset connectivity and the App; Nada in another round of usability testing; and planning out the presentation

Denise Taylor: CRAZY is the only word for it. The countdown is on, nerves are fraying, 3-D printers are whirring, usability studies are sprinting along... can we just push it a wee bit further?? A large focus of our work has been around usability testing and iterating the designs. There is nothing quite as informative as trying it out for real! Both our patient and therapist users have provided outstanding feedback on the system, so we feel we are getting close to a system that works for the patients and has a good fit with clinical practice.

Nada, Gemma and Sharon have been going flat-out with the usability studies, challenging Usman, Imran, Richard, Faisal and Scott to update their work faster than the speed of light. We have learnt a valuable lesson, though – changing too many things at one time can lead to catastrophe... Our working version of exciteBCI briefly plummeted to near-disaster! So, we are being smarter about taking careful step changes, even if travelling at high speed.

Planning for the final presentation to the judges is in full swing. We are struggling through how to pitch it, what to put in and what to leave out, we have covered so much ground in the last few months. So, gotta go, usability is calling!

D.2 Rehabilitation Innovation exciteBCI C-Prize Diary

Appendix D.2 is embargoed till 14 November 2026

Appendix E: Supplementary documents for Chapter 8

Relates to the following submitted manuscript:

Alder G, Signal N, U Rashid, Olsen S, Brooks T, Terry G, Niazi I and Taylor D. An iterative user-centered approach to the design of rehabilitation technology: A wearable BCI neuromodulatory device for stroke rehabilitation.

E.1 HDEC ethical approval

E.2 AUTEC locality approval

E.3 Participant information sheet and consent form: people with stroke

E.4 Participant information sheet and consent form: physiotherapist

E.5 Phase one sprint cycles: semi-structured interview framework

E.6 Phase two 'near-live' programme of rehabilitation: semi-structured interview frameworks

E.7 Headset concept and prototype iterations

E.8 exciteBCI device requirements collated from phases one sprint cycles of the user-centered design evaluation process

E.9 exciteBCI mobile App screens: most current version post evaluation

E.10 Phase two 'near-live' programme of rehabilitation: an outline of a participant's 3-week programme augmented by the exciteBCI device prototype

E.11 Clinical outcome measurement scores for the two participants that completed phase two 'near-live' 3-week programme of rehabilitation augmented by the exciteBCI prototype

E.1 HDEC ethical approval

Health and Disability Ethics Committees

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

0800 4 ETHICS
hdecs@moh.govt.nz

24 October 2017

Dr Denise Taylor
Health & Rehabilitation Research Institute
Faculty of Health and Environmental Sciences
AUT University
Northcote 0627

Dear Dr Taylor

Re:	**Ethics ref:**	**17/NTA/177**
	Study title:	Use of exciteBCI for technology-assisted stroke rehabilitation: Usability and acceptability

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

Conditions of HDEC approval

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

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
2. Before the study commences at *any* locality in New Zealand, it must be registered in a clinical trials registry. This should be a WHO-approved (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au). However https://clinicaltrials.gov/ is acceptable provided registration occurs prior to the study commencing at *any* locality in New Zealand.
3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

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

Your **next progress report** is due by **23 October 2018.**

Participant access to ACC

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

—

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

Yours sincerely,

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

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

E.2 AUTEC locality approval

AUTEC Secretariat

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

1 November 2017

Denise Taylor
Faculty of Health and Environmental Sciences

Dear Denise

Re Ethics Application: **17/373 Use of exciteBCI for technology assisted stroke rehabilitation: Usability and acceptability**

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

Note: The insurance should be trial specific not general liability.

Your ethics application has been approved for three years until 1 November 2020.

Standard Conditions of Approval

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

Please quote the application number and title on all future correspondence related to this project.

AUTEC grants ethical approval only. If you require management approval for access for your research from another institution or organisation then you are responsible for obtaining it. You are reminded that it is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard.

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

Yours sincerely,

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

Cc: galder@aut.ac.nz; nada.signal@aut.ac.nz; solsen@aut.ac.nz; usman.rashid@aut.ac.nz

E.3 Participant information sheet and consent form: people with stroke

Participant Information Sheet

Study title:	*The exciteBCI: usability study of a rehabilitation device for people with stroke*	
Locality:	**AUT University, Northcote**	Ethics committee ref.:17/NTA/177
Lead investigator:	**Prof Denise Taylor**	Contact phone number: 09 921 9680

Kia ora, Talofa lava, and Hello.

You are invited to take part in a study on the usability of the exciteBCI. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

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

This document is 7 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

We are a team of researchers from AUT University and Exsurgo Rehabilitation and we are developing an intervention aimed to improve outcomes for people with stroke. In laboratory-based studies this intervention has been shown to increase activation of motor cortical brain cells associated with movement and promote recovery of leg function after stroke.
We are making a smaller, lighter, portable version of the laboratory device which can be used in clinical settings and want to observe physiotherapists and people with stroke while they use the device, and then interview them to find out what they think about the exciteBCI and how it could be made better. We will use these findings to modify the device to improve its usability and acceptability to clinicians and people with stroke.

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Locality:	**AUT University, Northcote**	Ethics committee ref.:17/NTA/177
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WHAT IS THE EXCITEBCI?

The exciteBCI is a wearable rehabilitation device made up of three components; 1) an electroencephalography (EEG) headset, 2) an electrical muscle stimulator and 3) a tablet-based exercise App that is used to control the exciteBCI. The EEG headset is placed on the head and collects brain wave activity. The electrical muscle stimulator is similar to those used in routine clinical practice and is placed over a selected muscle in the lower leg. The exciteBCI will be controlled by the App to identify a particular brain wave and time the electrical muscle stimulation. The App allows the therapist to vary the exciteBCI parameters, select exercises and give feedback on performance according to the needs of the person with stroke.

The study is funded in part by AUT University, the MedTech Centre of Research Excellence (PhD studentship) and Callaghan Innovation (C-Prize finalist money). This study has ethical approval from the Health and Disability Ethics Committee.

If you have questions about the study please contact:

Gemma Alder, AUT University: Tel: 09 921 9999 ext 7815
email: gemma.alder@aut.ac.nz
Denise Taylor, AUT University: Tel: 09 921 9680
email: denise.taylor@aut.ac.nz

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

Who is being invited to participate in this research?

We are interested in inviting people with stroke and physiotherapists to take part in this study.

Person with stroke inclusion criteria

- Stroke was more than 6 months ago
- Some limitation in movement of the foot and ankle that impacts locomotor function
- Sufficient English language and communication skills to hold a conversation

Physiotherapist inclusion criteria

- New Zealand registered physiotherapist
- At least 5 years of professional experience in neurological rehabilitation

As a stroke participant what will I be asked to do?

Single session

The study would involve attending one 90-minute session at AUT Northshore We will observe you using the exciteBCI and interview you afterwards to gain your feedback. We are interested in how easy to use the device is and how it works as an addition to standard physiotherapy. All participants will be given the device to use and will be video and audio recorded while using the device and asked to 'think out loud' (saying what you are thinking when using the device). A physiotherapist with experience of using the device will set you up with it. The researchers will write down notes during the session. Then you will be interviewed and audio recorded on what you thought about using the exciteBCI. The audio recording will be listened too and transcribed word for word by a researcher and you will be sent the transcript of your session for verification. The first two participants with stroke will use a nonworking version of the exciteBCI and so will not experience the muscle stimulation, instead we will be interested in what you think about the device, how it looks, how easy it is

to fit and how you feel about it. The next 6 participants will have a working version that delivers the electrical stimulation.

Short clinical intervention
Two participants with stroke will have the opportunity to also volunteer for a longer intervention with a working exciteBCI device where we are interested in how it operates in a real clinical environment and what changes to your locomotor skills, if any, we see over that time. A registered physiotherapist who has experience working with exciteBCI will deliver the intervention. The intervention consists of standard physiotherapy exercises that are tailored for your needs during which you will wear the exciteBCI. Before and after the intervention standard clinical measures of walking, balance and strength will be taken. This will involve attending nine one-hour sessions at AUT Northshore over a three-week period. A short semi-structured interview will be completed after the intervention to understand what it was like to receive the exciteBCI intervention as a part of your physiotherapy intervention. The interview is anticipated to last approximately 60-90minutes.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Possible risks to participation in this study
The exciteBCI delivers an electrical stimulus to a muscle in your lower leg. The device used to do this is the same as one routinely used in clinical practice. As with any muscle stimulation there is a risk that you won't like the stimulus and find it uncomfortable. If this is the case, we can reduce the amount of stimulus or stop the stimulator altogether for the remainder of your session. There is a small risk that the sticky substance on the electrode will irritate your skin, if you have a skin reaction to wearing standard Elastoplast this will be more likely. If your skin becomes itchy, we can remove the electrodes.
For the two stroke participants early in the study who will have a nonworking prototype these risks will not be present.
There is a small risk that the EEG headset will be uncomfortable or cause a headache. If this is the case it will be removed and a softer research EEG cap will be used instead or the session can be stopped by the participant. This set up does involve touching the participants head, an area considered 'tapu' by Maori. To ensure that Tikanga Maori is respected, the researcher will always ask for consent before touching the participant's head.

Possible benefits to participation in this study
Single session
There is some indication for the stroke participants that a single session using this intervention can have a transitory effect on movement, but this is unlikely to be sustained. However, by taking part in this study you are acting as a co-researcher and your contributions may help with the development of a rehabilitation device that we hope will improve lower limb function for people with stroke.

Short clinical intervention
The stroke participants who volunteer for the 3-week intervention period may demonstrate improved lower limb function.

WHO PAYS FOR THE STUDY?

There are no direct costs to participants. Participants will contribute their time. A $40 taxi or petrol voucher will be provided for each return trip to help cover travel expenses to AUT University.

WHAT IF SOMETHING GOES WRONG?

If you were injured as a result of treatment given as part of this study, which is unlikely, you **won't** be eligible for compensation from ACC. However, compensation would be available from the study's sponsor, AUT University, in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided.

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

WHAT ARE MY RIGHTS?

Participation is voluntary

Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. Participation will render no or limited therapeutic benefits and the device will not be available once the study has ended. You are able to withdraw from the study at any time. If you choose to withdraw from the study, we will continue to use the data collected from you up to the point of your withdrawal. This is to ensure that all opinions, both positive and negative, are represented in the data collected. You can request to see any data collected during your session.

This research may inform the development of a rehabilitation technology intended for commercialisation. Your participation in this study does not mean you have any claim on intellectual property rights for the exciteBCI device.

Privacy and confidentiality

Identification numbers will be assigned and used to refer to all data associated with you. Any identifying features will be removed from reported data unless your expressed permission is given. Personal information will be kept in files and folders separated from data files. Only people who are involved in the research project will have access to personal information and data.

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

What happens to the data?

The video and audio data will be destroyed at the end of the study. Other data will be kept for a period of 10 years in a locked storage facility and then destroyed.

What use will we make of the data?

We will use the data to help us improve the design of the exciteBCI with the hope that in the future it will become a device that is available for people to purchase (expected timeframe: up to 5 years).

WHO PAYS FOR THE STUDY?

There are no direct costs to participants. Participants will contribute their time. A $40 taxi or petrol voucher will be provided for each return trip to help cover travel expenses to AUT University.

WHAT IF SOMETHING GOES WRONG?

If you were injured as a result of treatment given as part of this study, which is unlikely, you **won't** be eligible for compensation from ACC. However, compensation would be available from the study's sponsor, AUT University, in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided.

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

WHAT ARE MY RIGHTS?

Participation is voluntary

Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. Participation will render no or limited therapeutic benefits and the device will not be available once the study has ended. You are able to withdraw from the study at any time. If you choose to withdraw from the study, we will continue to use the data collected from you up to the point of your withdrawal. This is to ensure that all opinions, both positive and negative, are represented in the data collected. You can request to see any data collected during your session.

This research may inform the development of a rehabilitation technology intended for commercialisation. Your participation in this study does not mean you have any claim on intellectual property rights for the exciteBCI device.

Privacy and confidentiality

Identification numbers will be assigned and used to refer to all data associated with you. Any identifying features will be removed from reported data unless your expressed permission is given. Personal information will be kept in files and folders separated from data files. Only people who are involved in the research project will have access to personal information and data.

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

What happens to the data?

The video and audio data will be destroyed at the end of the study. Other data will be kept for a period of 10 years in a locked storage facility and then destroyed.

What use will we make of the data?

We will use the data to help us improve the design of the exciteBCI with the hope that in the future it will become a device that is available for people to purchase (expected timeframe: up to 5 years).

We will present the results of the data at rehabilitation research and medical technology related conferences and publish the findings in a peer reviewed journal (expected timeframe: up to two years).

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

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

Nada Signal
09 921 9999
Nada.signal@aut.ac.nz

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

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

For Maori health support please contact :

He Kamaka Walora
Waitemata District Health Board
09 486 8324 ext 3553
Auckland District Health Board
09 307 4949 ext 29400

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

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

Consent Form

Please tick to indicate you consent to the following

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

E.4 Participant information sheet and consent form: physiotherapist

Participant Information Sheet (Therapist)

Study title:	*The exciteBCI: usability study of a rehabilitation device for people with stroke*	
Locality:	**AUT University, Northcote**	Ethics committee ref.:17/NTA/177
Lead investigator:	**Prof Denise Taylor**	Contact phone number: 09 921 9680

Kia ora, Talofa lava, and Hello.

You are invited to take part in a study on the usability of the exciteBCI. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, or friends. Feel free to do this.

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

This document is 6 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

We are a team of researchers from AUT University and Exsurgo Rehabilitation and we are developing an intervention aimed at improving walking ability in people with stroke. The intervention has been tested previously and shown to be safe and effective when delivered using laboratory-based equipment.
We are making a smaller, lighter, portable version of the laboratory device, which can be used in clinical settings and want to observe people with stroke and therapists while they use the device, and then interview them to find out what they think about the exciteBCI and how it could be made better. We will use these findings to modify the device to improve its usability and acceptability to clinicians and people with stroke.

WHAT IS THE EXCITEBCI?

The exciteBCI is a wearable rehabilitation device made up of three components; 1) an electroencephalography (EEG) headset, 2) an electrical muscle stimulator and 3) a tablet-based exercise App that is used to control the exciteBCI. The EEG headset is placed on the head and collects brain wave activity. The electrical muscle stimulator is similar to those used in routine clinical practice and is placed over a selected muscle in the lower leg. The exciteBCI will be controlled by the App to identify a particular brain wave and time the electrical muscle stimulation. The App allows the therapist to vary the exciteBCI parameters, select exercises and give feedback on performance according to the needs of the person with stroke.

The study is funded in part by AUT University, the MedTech Centre of Research Excellence (PhD studentship) and Callaghan Innovation (C-Prize finalist money). This study has ethical approval from the Health and Disability Ethics Committee.

If you have questions about the study please contact:

Gemma Alder, AUT University: Tel: 09 921 9999 ext 7815
email: gemma.alder@aut.ac.nz
Denise Taylor, AUT University: Tel: 09 921 9680
email: denise.taylor@aut.ac.nz

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

Who is being invited to participate in this research?

We are interested in inviting physiotherapists to take part in this study.

Inclusion criteria

- New Zealand registered physiotherapist
- At least 5 years of professional experience in neurological rehabilitation

Person with stroke inclusion criteria

- Stroke was more than 6 months ago
- Some limitation in movement of the foot and ankle that impacts locomotor function
- Sufficient English language and communication skills to hold a conversation

As a physiotherapist participant what will I be asked to do?

The study would involve attending one 90-minute session at AUT Northshore. We will observe you interacting with the exciteBCI, putting it on one of our researchers, turning it on and setting a programme, then taking it off again and asked to 'think out loud' (saying what you are thinking when using the device). We will interview you afterwards to gain your feedback. Before using the device, you will be asked a few questions about your approach to stroke rehabilitation. You will be video and audio recorded during the session. The researchers will write down notes during the session. The audio recording will be listened too and transcribed word for word by a researcher and you will be sent the transcript of your session for verification. We are interested in your opinions and hope that they will influence the next prototype of the exciteBCI.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Possible risks to participation in this study
The exciteBCI delivers an electrical stimulus to a muscle in the lower leg. The device used to do this is the NeuroTrac Rehab, which is routinely used in clinical practice.

The setup of this device involves touching the head, an area considered 'tapu' by Maori. To ensure that Tikanga Maori is respected, consent to touch one's head will always be sought.

Possible benefits to participation in this study
Physiotherapists will be exposed to a new device and will increase their knowledge of new and upcoming rehabilitation technologies.

WHO PAYS FOR THE STUDY?

There are no direct costs to participants. Participants will contribute their time. A $40 taxi or petrol voucher will be provided for each return trip to help cover travel expenses to AUT University.

WHAT IF SOMETHING GOES WRONG?

If you were injured as a result of treatment given as part of this study, which is unlikely, you **won't** be eligible for compensation from ACC. However, compensation would be available from the study's sponsor, AUT University, in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided.

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

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Participation is voluntary
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If you choose to withdraw from the study, we will continue to use the data collected from you up to the point of your withdrawal. This is to ensure that all opinions, both positive and negative, are represented in the data collected. You can request to see any data collected during your session.

This research may inform the development of a rehabilitation technology intended for commercialisation. Your participation in this study does not mean you have any claim on intellectual property rights for the exciteBCI device.

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Consent Form

Please tick to indicate you consent to the following		
I have read or have had read to me in my first language, and I understand the Participant Information Sheet.		
I have been given sufficient time to consider whether or not to participate in this study.		
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time.		
I consent to the research staff collecting and processing my information.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw will continue to be processed.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I understand the compensation provisions in case of injury during the study.		
I know who to contact if I have any questions about the study in general.		
I understand that I have no ownership of intellectual property arising from this study.		
I understand my responsibilities as a study participant.		
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

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

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

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

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

Researcher's name: _____

Signature: _____ Date: _____

E.5 Phase one sprint cycles: semi-structured interview framework

- Can you describe your thoughts about the exciteBCI? likes/dislikes

- Can you please tell me about… (Mobile App, Headset, Stimulator)

  - Aesthetics
  - Comfort and fit
  - Support
  - Suitability – during exercise
  - Content
  - Ability to follow onscreen instructions
  - Screen readability
  - Understandability
  - Linking devices effectiveness
  - Workflow
  - Practicality
  - Physical issues

- What improvements would you suggest?

- Was there anything you were looking for on the device or the App that you couldn't find?

- Can you describe how easy the exciteBCI and app have been to use from your perspective?

- How would you envisage the exciteBCI being used?

- Who do you think the exciteBCI would be suitable for?

- What contexts (inpatient, outpatient, residential care, community, home, rural settings) would you imagine using this device?

- Would a person using the exciteBCI need a support person to set-up and use the device, or could they manage it independently?

- How well does the exciteBCI align with your thoughts on rehabilitation?

E.6 Phase two 'near-live' programme of rehabilitation: semi-structured interview frameworks

Framework for Participants with Stoke

"I understand that you have been involved in a research project that is looking at the usability and acceptability of a device called exciteBCI as part of a 3-week rehabilitation programme. I would like to ask you some questions, discuss your personal experience and perceptions of using the exciteBCI device. The purpose of this interview is to understand what people with stroke think about exciteBCI and how it might be improved in preparation for translation into rehabilitation".

General:

- Can you tell me about your overall impressions of exciteBCI?
- What have you liked / disliked about your experience using exciteBCI?
  (Suitability of the exercises, support, effectiveness, using technology, therapist, ability to follow app instructions, the visual and auditory cue, the rating scales, physical issues, electrical stimulation sensation…)
- How was the exciteBCI device and programme similar or different from your past experiences of rehabilitation?
- I understand that before you started the treatment sessions you discussed with your physiotherapist (Gemma) what you wanted the rehabilitation sessions to focus on. How well did the sessions meet your needs/ expectations?
- Often rehabilitation involves a person with stroke working directly with a physiotherapist, with not a lot of equipment or gadgets. What was it like to have a device, mobile app and a cue used in rehabilitation?
  (Supports or hinders engagement / ability to be seen as an individual /perception of therapist 'expertise….)
- How has the exciteBCI rehabilitation programme impacted /affected you?
  - If positive, what was it about the exciteBCI device and programme that made it positive? (Why does it work?)
  - If negative, what was it about the exciteBCI device and programme that made it negative? (Why doesn't it work?)

What exciteBCI does and its components:

"I would like to focus a little more on the actual device and its different components. "I understand there are three main components a headset, a muscle electrical stimulator and an exercise mobile app"

- Can you tell me a bit about your understanding of how the exciteBCI device works?
  (Components – headset, app with personalised exercises, it pairs the brain (EEG) signal with the muscle stimulation to strengthen the pathways to the muscle)

Headset

- Can you please tell me about what it was like setting up and wearing the headset?
  (Tell me about…Comfort, fit, weight, suitability during exercises, the use of the gel on your head, dealing with dried gel in the hair post sessions was this a burden or not?)

- Do you have any suggestions on how the headset could be improved?

Electrical stimulator unit, electrodes, neoprene sleeve

- Can you please tell me about your experience of using the muscle electrical stimulator on your leg muscle?
  (Tell me about…comfort, fit, weight, suitability during exercises, stimulus sensation during set-up and during exercise could they feel it, was it distracting)

- Do you have any suggestions on how the electrical stimulator could be improved?

MobileApp

- Can you please tell me about what it was like using the exercise app?
  (Tell me about…, screen readability, ability to follow onscreen instructions, exercise availability)

Visual Auditory cue: (show picture)

- Tell me what it was like to follow the ready/ go cue?
  (Timing movement with the cue challenging or not. If that depends, what did it depend on?)

- Did you tend to pay more attention to the sound of the cue, the visual representation or both?

- Why do you think you were more focused on the sound / visual part of the cue?

- What was it like following the cue on the app and performing the exercises at the same time?

- Do you have any suggestions on how the cue could be improved?

Rating scales: (show picture)

"I understand that once you completed a set of exercises you were asked to rate the exercises".

- Can you tell me about your experience using these rating scales?
  (Ease of use, confusion around meaning?)
- What were you considering when you were rating difficulty of the task?
  (Did it relate to just the physical task or concentrating on the task/ cognitive component)
- What were you considering when you were rating your confidence to perform the task?
  (Whether you completed it, how it made you feel pleased, nervous etc.)
- How did it feel rating the exercise after completing every set of reps?
- Do you have any suggestions on how the rating scales could be improved?

Technical difficulties with device

- I understand that there were some technical difficulties with the device during your sessions. How did this impact your experience?
- Did these technical difficulties impact the ability of the therapist to carry out your rehabilitation programme?

Suitability

- Who do you think the exciteBCI would be suitable for?
- Who is the exciteBCI not suitable for?
- Would a person using the exciteBCI need someone assisting or supervising to set-up and use the device, or could they manage it independently? How could this be improved?
- How long did the exciteBCI system take to set-up? Was this acceptable to you?

Future use

- Would you consider using the exciteBCI device in the future? If so, why? If not, why not?

"I don't have any further questions is there anything else you would to tell me about your experience?"

Framework for Physiotherapy Participants

"I understand that you have been involved in a research project that is looking at the usability and acceptability of a device called exciteBCI as part of a 3-week physiotherapy rehabilitation programme". I would like to ask you some questions, discuss your personal experience and perceptions of using the exciteBCI device. The purpose of this interview is to understand what therapists think about exciteBCI and how it might be improved in preparation for translation into rehabilitation".

General:

- Can you tell me about your overall impressions of exciteBCI?

- What have you liked / disliked about your experience using exciteBCI?
  (Ability to follow app instructions, the visual and auditory cue and the rating scales, physical issues, suitability of exercises, support, effectiveness)
- How was the exciteBCI device and programme similar or different from your past experiences of your rehabilitation practice?

- How well did the exciteBCI meet your needs/ expectations of a rehabilitation technology?

- Often rehabilitation involves a person with stroke working directly with a physiotherapist, with not a lot of equipment or gadgets. What was it like to have a device, mobile app and a cue used in rehabilitation?
  (Supports or hinders engagement / ability to be seen as an individual / therapeutic relationship /perception of therapist 'expertise….)

- How do you think the exciteBCI affected the participants?
  - Did the effect of the programme vary? Did some participants benefit more or less?

  - If positive, what was it about the exciteBCI device and programme that made it positive? (Why does it work?)

  - If negative, what was it about the exciteBCI device and programme that made it negative? (Why doesn't it work?)

- Do you think that the effort that the participants put into the programme was worth the benefits they got out of it? Why was it worth the effort? Why wasn't it worth the effort?

- Are there any ideas or concepts from the rehabilitation programme you will integrate into your clinical practice?

What the exciteBCI device does and its components

"I would like to focus a little more on the actual device and its different components. "I understand there are three main components a headset, a muscle electrical stimulator and an exercise mobile app"

- Can you tell me a bit about your understanding of how the exciteBCI device works?
  (Components – headset, app with personalised exercises, it pairs the brain (EEG) signal with the muscle stimulation to strengthen the pathways to the muscle)

Headset

- Can you please tell me about what it was like setting up the headset?
  (Tell me about…Comfort, fit, weight, suitability during exercises, the use of the GEL, connectivity?)
- Do you have any suggestions on how the headset could be improved?

Electrical stimulator unit, electrodes, neoprene sleeve

- Can you please tell me about your experience of using the muscle electrical stimulator during rehab?

- Do you have any suggestions on how the electrical stimulator could be improved?

App

- Can you please tell me about what it was like using the exercise app?
  (Tell me about screen readability, ability to follow on screen instruction, exercise availability, training parameters, customisability etc…)

Visual Auditory cue: (show picture)

- Tell me what it was like to use the ready/ go cue?

- Did patients tend to pay more attention to the sound of the cue, the visual representation or both?

- Why do you think they were more focused on the sound / visual part of the cue?

- Do you have any suggestions on how the cue could be improved?

Rating scales: (show picture)

"I understand that once they completed a set of exercises participants were asked to rate the exercises".

- Can you tell me about your experience using these rating scales? (Ease of use, confusion around meaning?)
- What were participants considering when they were rating difficulty of the task?
  (Did it relate to just the physical task or concentrating on the task/ cognitive component)
- What were participants considering when they were rating your confidence to perform the task?
  (Whether they completed it, how it made them feel pleased, nervous etc.)
- What were you considering when they were rating difficulty of the task?
  (Did it relate to just the physical task or concentrating on the task/ cognitive component)
- How did it feel progressing the task difficulty of the exercisses based on these ratings?
- Do you have any suggestions on how the rating scales could be improved?

Technical difficulties with device

- I understand that there were some technical difficulties with the device during your sessions. How did this impact your experience?

Suitability

- Who do you think the exciteBCI would be suitable for?
- Who is the exciteBCI not suitable for?
- Would a person using the exciteBCI need someone assisting or supervising to set-up and use the device, or could they manage it independently? How could this be improved?
- How long did the exciteBCI system take to set-up? Was this acceptable to you?

Future use

- Would you consider using the exciteBCI device in the future? If so, why? If not, why not?

"I don't have any further questions is there anything else you would to tell me about your experience?"

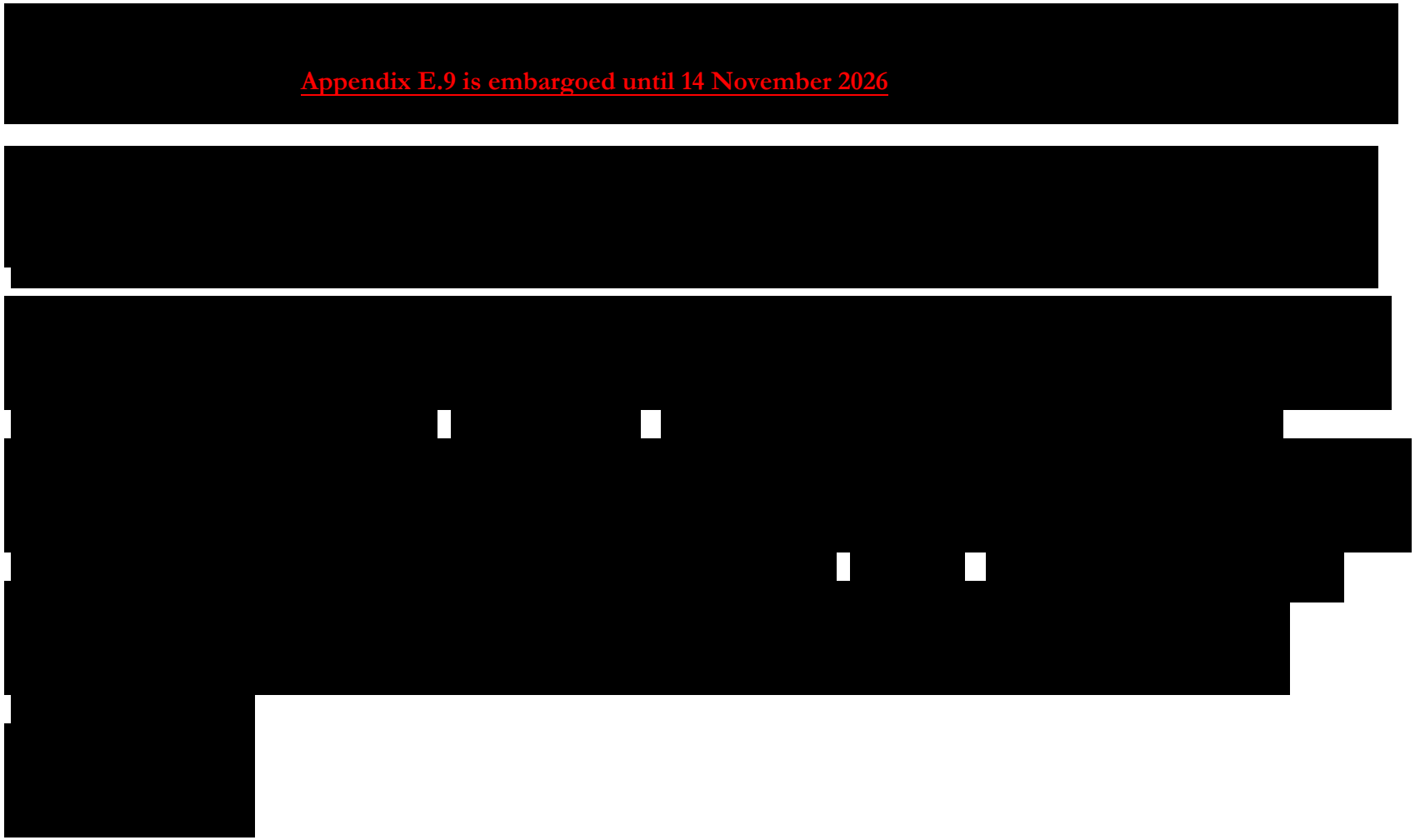
E.7 Headset concept and prototype iterations

Appendix E.7 is embargoed until 14 November 2026

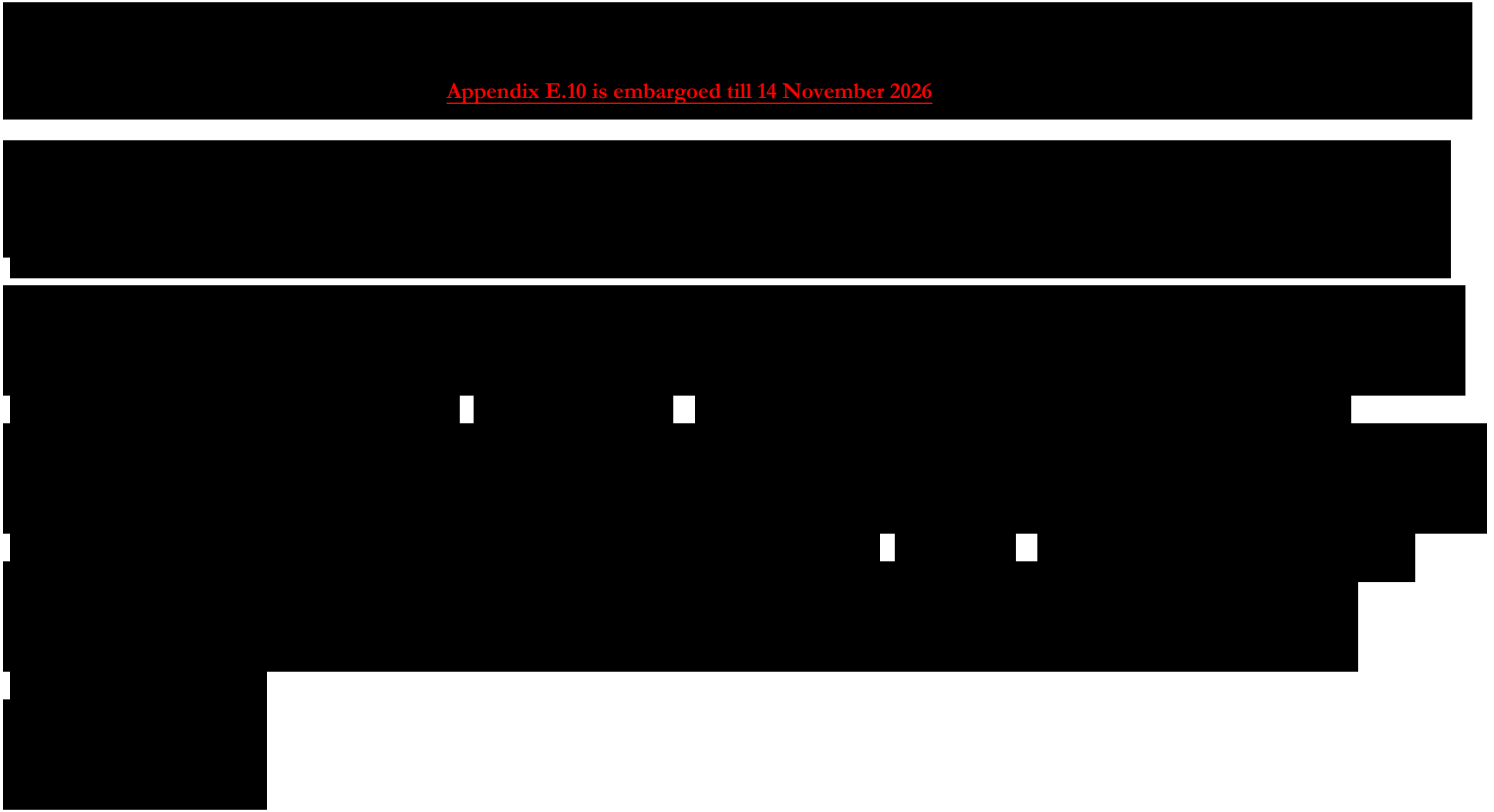
E.8 exciteBCI device requirements collated from phases one and two of the user-centered design evaluation process

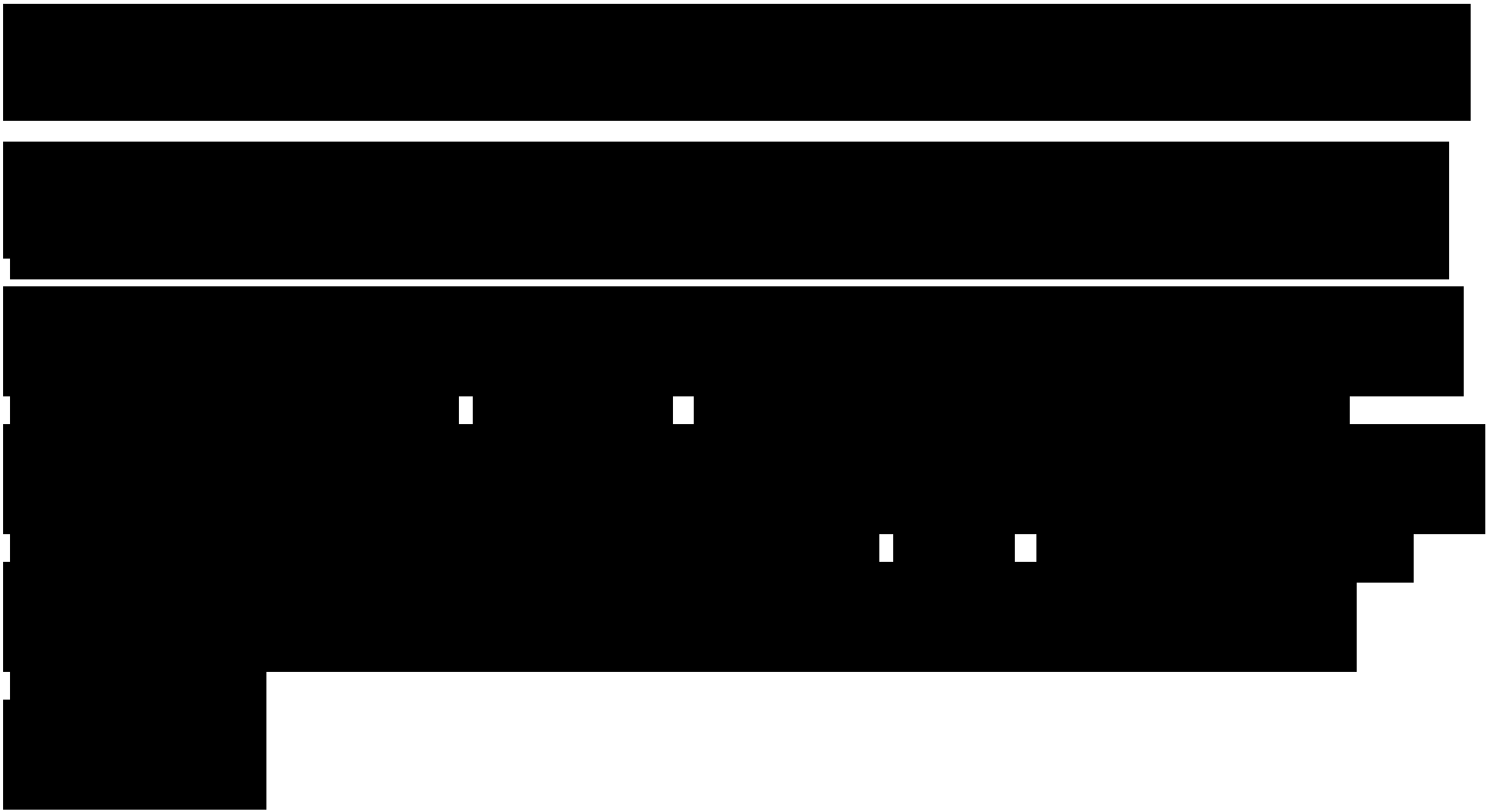
Appendix E.8 is embargoed until 14 November 2026

E.9 exciteBCI Mobile App Screens: most current version post evaluation



E.10 Phase Two 'near-live' programme of rehabilitation: an outline of a participant's 3-week programme augmented by the exciteBCI device prototype





E.11 Clinical outcome measurement scores for the two participants that completed phase two 'near-live' 3-week programme of rehabilitation augmented by the exciteBCI prototype.