ASSESSING THE POSSIBILITY OF A 4 WEEK BCI REHABILITATION INTERVENTION ON STROKE PATIENTS

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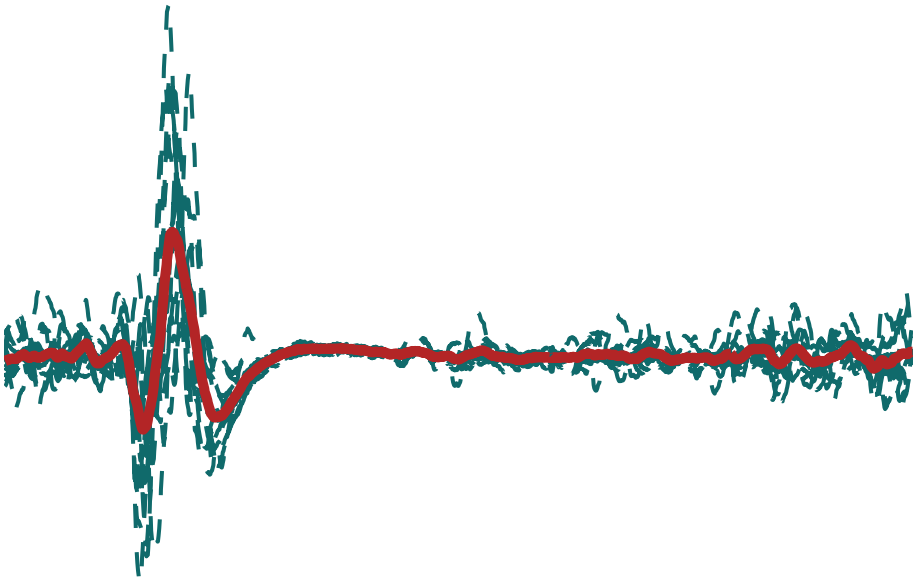

Master's Thesis - Biomedical Engineering & Informatics
Department of Health Science and Technology
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June 3rd, 2015

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Title:
Assessing the Possibility of a 4 Week BCI Rehabilitation Intervention on Stroke Patients

Theme:
Master's Thesis: Sensory-motor control and rehabilitation systems

Project period:
Spring 2015

Project group:
15gr1079

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No. of Pages: 87

No. of Appendix Pages: 18

Total no. of pages: 105

Completed: 3rd June, 2015

Abstract:

Stroke is the main cause of disabilities in adults. More efficient tools and rehabilitation methods for patients with limited recovery potential are needed. Research has found potential in using brain-computer interface driven paired associative stimulation (BCI PAS), to enhance corticospinal excitability of Tibialis Anterior. However, BCI PAS has yet to be applied to stroke patients and functional outcome assessed over several weeks of intervention.
In this study, a research design was developed that tested BCI PAS on a single stroke patient, while a separate experiment investigated retention of corticospinal excitability changes induced by BCI PAS, on 10 healthy subjects.
Results proved that it was possible to assess corticospinal excitability and functional changes in a stroke patient over a 4 week intervention phase, using TMS in two conditions and 3D gait analysis. Increased corticospinal excitability in healthy subjects was maintained 45 minutes after an intervention, suggesting that BCI PAS has a potential application as priming before physiotherapy.

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Titel:
Evaluering af Muligheden for en 4 Ugers BCI Rehabiliterings Behandling af Slagtilfælde Patienter

Tema:
Kandidat Speciale: Sensory-motor control and rehabilitation systems

Projekt periode:
Forår 2015

Projekt gruppe:
15gr1079

Forfatter:
Thomas Momme Christensen

Vejleder:
Ernest N. Kamavuako

Sidetal: 87

Appendiks sider: 18

Total sider: 105

Afsluttet: 3. juni 2015

Dansk Synopsis:

Slagtilfælde er den primære årsag til bevægelseshandicap i industrilandene. Rehabilitering af slagtilfælde patienter er en seriøs udfordring for sundhedssektoren, hvor nye og mere effektive værktøjer og rehabiliteringsmetoder er nødvendigt. Forskning har fundet potentiale i en relativ ny metode til neurorehabilitering. Metoden gør brug af et brain-computer interface der kan måle bevægelses intentioner og forberedelse, vha. bevægelses-relaterede kortikale potentialer. Disse signaler kan også måles i slagtilfælde patienter. Studier på raske forsøgspersoner har vist at hjerne excitabilitet kan øges, ved at give perifær nervestimulation på et bestemt tidspunkt, i den kortikale bevægelses forberedelse. Det er dog endnu ikke blevet undersøgt hvorvidt behandlingen kan føre til funktionelle forbedringer i patienter, når den gives over en længere behandlingsperiode.

I dette projekt blev et forsøgsdesign udviklet, til at undersøge effekten af en 4 ugers behandling af patienter. Forsøgsdesignet blev testet på en enkelt slagtilfælde patient. Derudover blev et separat forsøg udført på 10 raske forsøgspersoner, der skulle undersøge hvor lang tid ændringer i hjerne excitabilitet bevares efter en behandling. Formålet med dette var at undersøge potentielle implementerings muligheder i klinikken.

Forsøgene viste at det er muligt at gennemføre et 4 ugers behandlings forsøg med denne metode. Det var muligt at undersøge ændringer i hjerne excitabilitet og bevægelsesfunktion, ved brug af to måder at anvende transcranial magnetic stimulation (TMS) på, samt 3D ganganalyse. Forsøget på raske forsøgspersoner viste at behandlingen førte til en stor øgelse af hjerne excitabilitet efter en behandling. Denne stigning var bevaret 45 minutter efter behandlingen. Resultatet af dette forsøg betyder at behandlings metoden potentielt kan have en anvendelse som priming før traditionel fysioterapeutisk behandling.

ACKNOWLEDGEMENTS

Throughout this project carried out in New Zealand (Auckland University of Technology), assistance and guidance was given by a group of people that I would like to acknowledge to show my appreciation. Sharon Olsen, a physiotherapist and research officer, participated in the setting up and collection of data from the experiments, was refered to as Investigator 2 in this project. Dr. Denise Taylor, Dr. Nada Signal and Dr. Imran Khan Niazi for the additional supervision, with the challenges, and hosting BCI group meetings for sharing of knowledge. Also, a special thanks to research officer, Yanto Naude, for his supervision and training in operating the motion capture system, placement of markers and technical support.

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ACRONYMS

AAU	Aalborg University
ADL	Activities of daily living
CIMT	Constraint induced movement therapy
CPN	Common peroneal nerve
EMG	Electromyography
FMA	Fugl-Meyer Assessment
BCI	Brain-computer interface
MRCP	Movement-related cortical potential
MEP	Motor evoked potential
MVC	Maximum voluntary contraction
PN	Peak negativity
PAS	Paired associative stimulation
TMS	Transcranial magnetic stimulation
TA	Tibialis anterior
RHS	Right heel strike
LTO	Left toe off
LHS	Left heel strike
RTO	Right toe off

INTRODUCTION

Stroke is the third most common cause of death in developed countries. It is the main cause of disability in adults hence causing a major impact on patients, their relatives and economically on the society, [Duncan et al., 2005; Hankey et al., 2000; Langhorne et al., 2011,0]. Due to demographic changes with an increasing population of elderly, stroke is considered likely to be responsible for even greater death and disability in the future, [Wolf et al., 1991]. Great efforts are made in optimising and finding more effective rehabilitation strategies so as to enhance the recovery process, working towards improving the functional outcomes, thus contributing to patient satisfaction and reduce long-term care expenditures, [Duncan et al., 2005].

A novel method for neurorehabilitation has been explored in recent research. The method uses a brain-computer interface (BCI) to help temporally pair the cognitive process of movement intent with a timed sensory feedback, e.g. from peripheral electrical stimulation. This method has shown that it can induce neural plasticity, and is based on the theories of synaptic plasticity, postulated by Donald w. Hebb, [Daly and Wolpaw, 2008; Grosse-Wentrup et al., 2011; Hebb, 1949]. It is a further development of traditional paired associative stimulation (PAS) therapy.

The novel rehabilitation stragedy involving motor intention drived PAS by use of a BCI, will in this report be refered to as a 'BCI PAS protocol'.

PAS is a rehabilitation technique involving TMS of the motor cortex while providing peripheral electrical stimulation, to facilitate neuroplastic changes.

Induction of neural plasticity has been measured with the application of transcranial magnetic stimulation (TMS) to the motor cortex with measurement of motor evoked potentials (MEP). When recorded pre and post an intervention, MEPs from TMS can reveal changes in corticospinal excitability. Corticospinal excitability has been found to be an indicator of motor impairment in stroke patients and increases with motor learning, [Pascual-Leone et al., 1995; Perez et al., 2004]. However, the relationship between stroke patients' motor impairment, e.g. reduced corticospinal excitability, and their function, is still an unexplored area, [Langhorne et al., 2011]. There is also limited evidence showing functional benefit for patients from these impairment-focused rehabilitation methods. In contrast strong evidence shows that task-oriented therapies can improve patients' recovery of functions and indepence in activities of daily living (ADL), [Langhorne et al., 2011]. This is a challenge for a BCI PAS protocol as it is currently tested at a motor impairment-based level, where it can increase the cortical excitability of a target muscle, [Daly and Wolpaw, 2008; Grosse-Wentrup et al., 2011; Xu et al., 2014]. However, a BCI PAS protocol can potentially also be applied in a task-oriented way with variability in movement types and tasks, in an attempt to improve functional outcome, [Xu et al., 2014].

The review of Grosse-Wentrup et al. [2011] revealed that as of now, most of the studies utilising BCI assisted neuro rehabilitation, have been performed only on healthy subjects and for shorter periods of time. A few studies have analysed changes in corticospinal excitability from pairing motor intention with sensory feedback from passive movement, [Buch et al., 2008; Ramos-Murguialday et al., 2013]. No studies have according to the author's current knowledge, tested the therapeutic outcome of a BCI PAS protocol

on stroke patients. It is of interest to know whether changes found in corticospinal excitability translates to functional improvements in a stroke population, and what outcome measures can be used to assess these functional abilities, [Grosse-Wentrup et al., 2011].

This initiates the following questions that will be further analysed from a review of litterature:

- *What are the major challenges for adopting a BCI PAS protocol in a clinical setting on stroke patients?*
- *What outcomes have been observed in such or similar studies?*
- *What outcome measures are appropriate to identify functional improvements after a BCI rehabilitation program?*

Part I

PROBLEM ANALYSIS

In the problem analysis, the ultimate goal is to arrive at a relevant research question, based on analysing literature resolving the questions as specified in the introduction. First a section will look into stroke, to establish insight into consequences of the condition, how it is rehabilitated and the recovery of patients is evaluated. Then a section describing the BCI PAS protocol and how it can be applied to stroke patients and the challenges in archieving that. In this section it will also be assessed which measures of functional improvement have successfully been used in previous studies of effects of BCI neuromodulation techniques.

1 STROKE

1.1 OVERVIEW OF STROKE

Stroke is defined as a neurological deficit of cardiovascular cause, and a disturbance of blood supply to the brain that can lead to degradation of brain cells and loss of brain function, [WHO, 1975]. It is a serious health-care problem that is common and disabling, [Duncan et al., 2005; Langhorne et al., 2011]. Stroke is so common that it is the third most common cause of death in developed countries, with a mortality rate of approximately 30 %, during the first six months of disease, [Hankey et al., 2000]. As most patients will survive a stroke, the greatest health effect will normally be caused by the long-term consequences for the patient and his/her family, [Langhorne et al., 2011]. Stroke patients suffer from physical and mental impairments, such as motor control, speech and language, vision, sensation, and cognition, [Langhorne et al., 2011].
Motor impairment that is the most common impairment from stroke and affects about 80% of patients, can be seen as a limitation of function or loss of control, [Langhorne et al., 2009]. As strokes often occours in arteries supplying brain areas responsible for control and initiation of movement, such as the middle cerebral artery, a stroke typically affects the motor control of the face, arm, and leg of one side of the body. The consequences of these motor control impairments can be seen as sensorimotor deficiencies, balance disorders, abnormal muscle tone and decreased range of motion. This leads to gait abnormalities, disability and handicap, [Langhorne et al., 2011; Wikström et al., 2014]. Rehabilitation of stroke subjects is therefore a huge task for health care, where it's main focus is to aid in the recovery of impairment and regaining of lost function, [Langhorne et al., 2009].

1.2 REHABILITATION OF STROKE PATIENTS

Recovery after stroke is heterogenous, and long-term effects depends on several variables such as size and site of the stroke lesion, dysfunctions, complications, concurrent diseases, and by the extent of motivation and spontaneous recovery. After each stroke incident, a spontaneus recovery happens where restoration of the functionality of the damaged neural tissue takes place, as well as a substitution process of reorganisation of partly spared neural tissue to obtain and relearn functions of damaged sites, and compensation [Fjaertoft and Indredavik, 2007; Langhorne et al., 2011]. The magnitude of spontaneous recovery after stroke, is illustrated in figure 1. Despite the heterogeneity of stroke recovery, the process of regaining daily function and activities is somewhat predictable in the first days after stroke, [Langhorne et al., 2011].

Rehabilitation of stroke begins during acute hospitalisation and the sub-acute phase, when the diagnosis of stroke is confirmed and the patient is stable. The most important goal at this stage is to prevent a recurrent stroke, mobilise the patient, and encourage

resumption of self-care activities, [Duncan et al., 2005]. Thereafter, the focus of care progresses to assessment and recovery of any residual physical and cognitive deficits, as well as compensation for residual impairment, in the transitional and adaptation phases, [Duncan et al., 2005; Langhorne et al., 2002]. The following list is an overall structure for a stroke recovery process, a more detailed illustration can be seen on figure 1.

- Acute phase: 0-24 hours
- Sub-acute phase: 1 day - 3 weeks
- Transitional phase: 3 weeks - 3 months
- Adaptation phase: >3 months

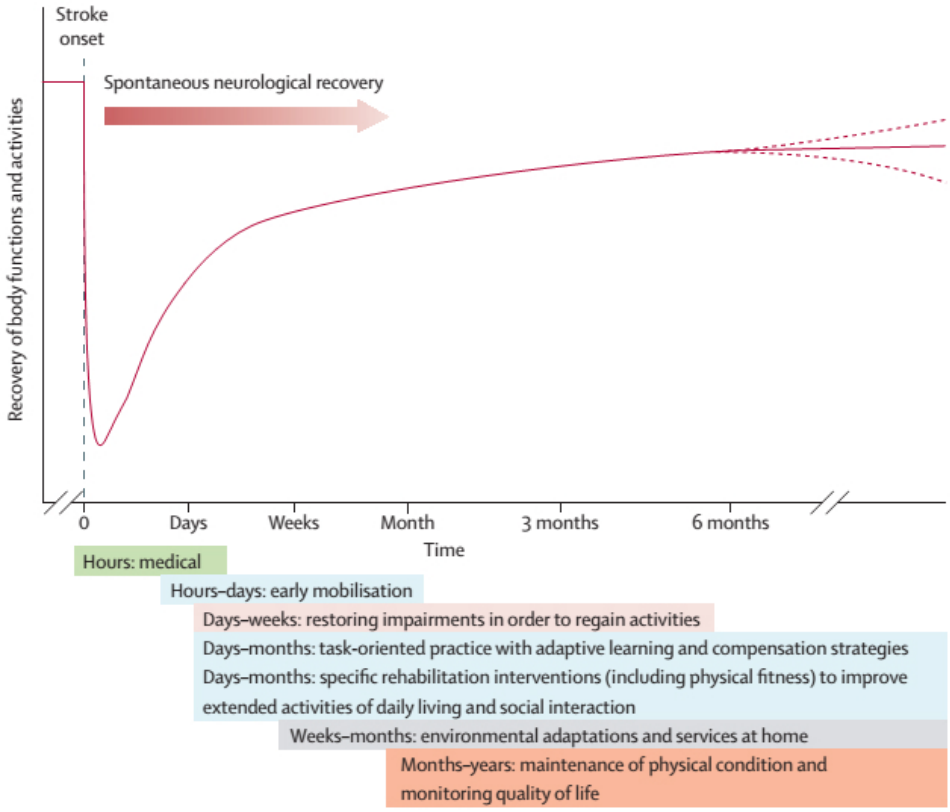

Figure 1: Illustration of the process of recovery of body functions after a stroke, visualising the spontaneous neurological recovery and with a timeframe for events in the recovery, [Langhorne et al., 2011]

Better outcomes have been achieved when post-acute stroke patients have received a coordinated, multidisciplinary evaluation and intervention. The patient should receive care from a variety of treatment diciplines, from a multidiciplinary team, [Duncan et al., 2005; Foundation, 2010].

Guidelines help decide whether a patient should receive rehabilitation. Rehabilitation services should be provided to a patient if his functional status poststroke is lower than his functional status pre stroke, and if there is a potential for recovery. This potential can be estimated by a National Institutes of Health Stroke Scale obtained during the

Figure 2: Illustration of the problem solving process used in rehabilitation to reduce disability and handicap in stroke patients

first week after an acute ischemic stroke. This scale can help a prediction of which patients that are more likely to have a good outcome from rehabilitation, [Duncan et al., 2005]. Stroke patients with severe complications or who are very dependent in activities of daily living, with poor prognosis for recovery of functionality, would not qualify for rehabilitation, [Duncan et al., 2005].

1.2.1 *Rehabilitational strategies*

There has not been found sufficient evidence for neurologic recovery leading to functional improvements, using impairment-based therapies. However, strong evidence suggests that task-oriented rehabilitation is effective in recovery of functionality, [Langhorne et al., 2011]. This means that functional recovery seem to be achieved through the mechanisms of adaptation, compensation and cortical reorganisation, [Langhorne et al., 2011].
However, it has been found that motor-skills learned in one training session generalise poorly to natural tasks that are not directly trained. Task-variability has been identified as being of importance in training, as it besides making training resemble everyday tasks more, also has a positive effect on retention of motor-skills, [Kitago and Krakauer, 2013; Langhorne et al., 2011; Xu et al., 2014]. The number of repetitions of tasks and rest periods has also been found to be important in training, [Kitago and Krakauer, 2013; Langhorne et al., 2011; Pollock et al., 2014]. These are some of the mechanisms implemented in traditional rehabilitation methods, and they are derived from motor learning theory.
The Cochrane review of different rehabilitation approaches for recovery of function and mobility after stroke Pollock et al. [2014] found that rehabilitation has a significant beneficial effect on functional recovery after stroke, for independence in ADL. A dose of 30 to 60 minutes of training per day, 5 to 7 days per week, was found to be effective, and no difference in effectiveness was found between the studied rehabilitational strategies.

Impairment-based therapy focuses on recovery of specific motor impairments such as e.g. muscle strenght or stamina. Task-oriented rehabilitation focuses on recovery of functional abilities such as standing, walking, grasping etc.

Rehabilitation of stroke patients is a multidiciplinary challenge, and conventional physiotherapy can consists of methods such as constraint induced movement therapy (CIMT),

biofeedback, virtual reality and functional electrical stimulation, [Duncan et al., 2005; Foundation, 2010]. The national stroke foundation of Australia, [Foundation, 2010], has carried out a set of guidelines for physiotherapists in stroke rehabilitation. Some suggestions are as follows:

- As much as possible practice should be provided withing the first six months after stroke, with a minimum of one hour active practice per day.
- Patients should be encouraged by staff members, with the help of their family and/or friends if appropriate to continue to practice skills they learn in therapy sessions throughout the remainder of the day.
- Upper limb training should commence early and CIMT is one approach that may be useful within the first week after stroke.
- For people with reduced strength the following techniques can be used, progressive resistance exercises, electrical stimulation, electromyographic (EMG) biofeedback in conjunction with conventional therapy
- People with difficulty in standing up from a chair should practice this, feedback can be used.
- Tailored, repetitive practice of walking (or components of walking) as much as possible. The following interventions can be used in addition: Cueing of cadence, mechanically-assisted gait, joint position biofeedback, virtual reality training.
- Ankle-foot orthoses can be used for people with persistent drop foot

1.2.2 *Scales and Assessments used for Evaluation of Stroke Patients*

Different scales are used for assessment of stroke patients. These are usually applied pre, during and post interventions, to evaluate patients' progress in recovery. They can also be used as admission and discharge criterias and assessment tools. An overview of the different scales often used are shown in table 1, [Pollock et al., 2014].

Primary outcomes
1. Independence in activities of daily living scales • Barthel Activities of Daily Living Index • Functional Indepdence Measure • Modified Ramkin Scale • Katz Index of Activities of Daily Living • Rehabilitation Activities Profile 2. Motor Function Scales • Motor Assessment Scale (MAS) • Fugl-Meyer Assessment (FMA) (lower limb section) • Rivermead Mobility Index • Rivermead Motor Assessment
Secondary
1. Balance (Berg Balance Scale) 2. Gait Velocity 3. Length of Stay

Table 1: List of scales and measures used for evaluation of stroke patients in rehabilitation, Pollock et al. [2014].

The independence in activities of daily living scales are evaluating a persons disability, as well as the of stroke rehabilitation is ultimately to be able to improve a patient's score in these. Whereas the motor function scales are assessing functionality on a lower level, e.g. the ability to get from supine position to sitting, and the amount of assistance requirred, or the ability to feel sensations of touch under the sole of the foot. The items listed as secondary outcomes, are more specific assessments or individual measures.

2 BCI PAS FOR INDUCTION OF NEUROPLASTICITY

2.1 OVERVIEW OF THE DEVELOPMENT TOWARDS AN EFFECTIVE NEUROREHABILITATION PROTOCOL

This section serves as an introduction to the mechanisms behind neurorehabilitation and an overview of the research done in developing the BCI PAS protocol. First the concept of PAS and results facilitating it will be explained, then focus will be on the BCI PAS protocol and preliminary results obtained from testing on healthy subjects.

Through a long series of studies, PAS has been showed to be able to induce neuroplasticity, [Chen and Udupa, 2009; Stefan et al., 2000; Wolters et al., 2003,0]. PAS is a technique using repetitive low-frequency single pulse electrical stimulation of a nerve or motor point of a muscle, followed by a TMS pulse delivered over the motor cortex, causing the depolarisation of postsynaptic neurons, [Chen and Udupa, 2009]. PAS is based on the principles of Hebbian's theory of spike-timing dependent plasticity, where inputs are timed to arrive at a neuron at the same time, [Chen and Udupa, 2009; Hebb, 1949]. This is recognised as inducing a form of synaptic plasticity known as long-term potentiation (LTP), [Stefan et al., 2000,0].

As was mentioned in the introduction, a BCI PAS protocol, which is a novel method for neurorehabilitation, has been studied in recent research and is developed based on the above findings. The method utilises motor imagination or actual motor execution to depolarise the cortical motor neurons, instead of the TMS stimulation, [Daly and Wolpaw, 2008; Grosse-Wentrup et al., 2011]. For PAS therapy, it has been found that a disinhibition of the motor cortex during stimulation have resulted in increased induction of LTP, and that voluntary contraction or motor imagination can cause this transient disinhibition, [Khaslavskaia and Sinkjaer, 2005; Mrachacz-Kersting et al., 2007,0]. In order to ensure the correct temporal pairing of the cortical motor drive with the electrical feedback, BCI setups have been used to detect movement intent. Motor execution and motor imagination both produce a slow cortical potential referred to as a movement related cortical potential (MRCP). This signal can be observed and detected from analysis of EEG recordings over the motor cortex, [Birbaumer et al., 1990; Jochumsen et al., 2013; Lakie, 2004; Niazi et al., 2011,0,0; Xu et al., 2014]. In the BCI PAS protocol, MRCPs are used to control the timing of the peripheral electrical stimulation. Another advantage of pairing the peripheral electrical stimulation with voluntary movement intent, over the use of TMS of the motor cortex, is that the natural pathways are employed and in the natural sequence. Furthermore it might not be possible with TMS to only stimulate the area of interest. The study of Mrachacz-Kersting et al. [2012] showed that pairing of motor intention with sensory feedback led to significant increases in corticospinal

excitability in the cortical projection to the tibialis anterior (TA), and not to the antagonist muscle, demonstrating the specificity of the BCI PAS protocol. The proposed method for rehabilitation of stroke patients also has perspectives for integrating task variability into the training, so as to increase the outcome, as motor learning theory suggests, [Kitago and Krakauer, 2013; Langhorne et al., 2011; Mrachacz-Kersting et al., 2012; Xu et al., 2014]. This could be made possible as the progress made in detecting different movement types from motor imagination, [Gu et al., 2009; Jochumsen et al., 2013; Niazi et al., 2011], opens up for practising different movement types in the training.

Most of the research with the BCI PAS type of rehabilitation paradigm, have focused on recovery of motor control of hand and arm movements such as reaching and grasping, or lower extremity functions such as lifting the foot, [Ramos-Murguialday et al., 2013; Xu et al., 2014]. Recovery of ankle dorsiflexion control is a key goal to improve ambulation, [Zhang et al., 2013], and studies have shown the ability of the BCI PAS protocol to induce plasticity in the form of changes in corticospinal excitability of the TA muscle, [Mrachacz-Kersting et al., 2012; Xu et al., 2014].

The following section will assess challenges in testing and adjusting the BCI PAS protocol to stroke patients.

2.2 APPLICATION ON STROKE PATIENTS

The aim of the research done on the BCI PAS protocol, is to move it from the laboratory and into clinical settings, to assist in rehabilitation of e.g. stroke patients.
A few studies have been carried out testing movement intention paired with sensory feedback on stroke patients. One of these is the study of Ramos-Murguialday et al. [2013]. They evaluated the efficacy of a four-week daily BCI training with an orthoses, driving motions of a weakened arm, to facilitate effects of physiotherapy in patients with severe paresis. They found that a contingent online orthosis and BCI training adjuvant to physioteraphy, results in more prominent improvement in FMA, than a control BCI intervention together with physiotherapy. This was tested in chronic stroke patients without residual movement ability of the affected hand. This means that proprioceptive feedback that is associated with control of ipsilesional sensorimotor rythms can prime and enhance the effects of physiotherapy on motor recovery, [Ramos-Murguialday et al., 2013].

The rehabilitation strategy applied in Ramos-Murguialday et al. [2013] is similar to the mentioned BCI PAS, in pairing voluntarily driven cortical potentials with sensory feedback. It is different in the way that it uses sensorimotor rythms and not MRCPs as the control signal, and that it provides proprioceptive feedback from passive movement and not electrical stimulation as in the BCI PAS protocol.

In order to employ a BCI PAS protocol on stroke patients, it is required that the timing of their cortical process of preparing and planning movements, can be identified, as it can for healthy subjects. This has been the focus of a few studies. By use of MRCPs it has been possible to online detect movement execution in stroke patients with promising results. Although a lower detection accuracy is found, compared to that of healthy subjects, [Niazi et al., 2011; Xu et al., 2014]. It should be noted though that some stroke patients would have impaired motor imagination abilities, as a consequence to damage to brain regions responsible for planning of movement, [de Vries and Mulder, 2007; Jackson et al., 2001; Yilmaz et al., 2013]. But for the patients able to perform motor imagination but with limited motor function, could make rehabilitation possible, [Mihara et al., 2013]. Ramos-Murguialday et al. [2013] found out that severely weakened

stroke patients included in their study, were still able to perfom motor imagination and attempting hand movement. They underlined that motor imagination and intent-to-move rehabilitation strategies have been reported useful in patients with mild to moderate motor deficits, [Ramos-Murguialday et al., 2013].

MEPs from TMS are routinely used in rehabilitation research to investigate changes in neural plasticity after rehabilitation interventions, [Cacchio et al., 2011; Forrester et al., 2008]. However when a MEP cannot be be elicited in the target muscle, as it frequently occurs in people with moderate to severe stroke, it is of limited value as a tool. A solution to this problem is to prime the corticospinal tract by a contraction of the target muscle during TMS. To control this measurement, force output can be measured with a level of MVC as a target. Studies have shown that MEPs during a low level of maximum voluntary contraction (MVC) are less variable than MEPs obtained at rest, for healthy subjects, [Darling et al., 2006; Van Hedel et al., 2007]. People with stroke however, have difficulty maintaining a consistent level of contraction, which can be an explanation for the increased variability seen in MEPs during low level MVC, [Butler et al., 2005; Cacchio et al., 2011; Canning et al., 2000; Wheaton et al., 2009]. The study of Van Hedel et al. [2007] states that variance in MEPs might be less during functional muscle contraction. This means that reliability of TMS to assess changes in plasticity in stroke patients is still a relatively unexplored area and studies have been using different paremeters of TMS.

A challenge for moving from healthy subjects to randomised controlled trials on stroke patients is study designs, [Grosse-Wentrup et al., 2011]. It is not ethical acceptable to withhold established treatments, [Grosse-Wentrup et al., 2011]. This means that only stroke patients not anymore receiving traditional therapy can be included in the BCI PAS study. This limits the likelyhood of success with a rehabilitation intervention, as the potential for recovery after a stroke, decreases with time, [Grosse-Wentrup et al., 2011]. Another option for studies that want to assess rehabilitation methods, is to test the effect of the intervention together with traditional physiotherapy, [Grosse-Wentrup et al., 2011]. Such as it was done in the study Ramos-Murguialday et al. [2013]. In addition to ethical challenges of experimenting on stroke patients, is health issues and contraindications for interventions. The use of TMS, being it as part of a traditional PAS protocol, or as a method of assessment of corticospinal exitabilily, involves some safety concerns and ethical considerations, [Rossi et al., 2009]. Application of TMS has a low probability of causing seizures, transient headaches, hearing impairment, interference with implanted devices, in certain subject groups, [Rossi et al., 2009]. This can be limiting in studies involving stroke patients. Some of the contraindications for the use of TMS are personal history of epilepsy, implanted devices, vascular or methabolic brain lesions, administration of seizure threshold lowering drugs, and severe heart diseases, [Rossi et al., 2009]. The use of TMS can therefore be a challenging factor for studies, as some stroke patients might be excluded. TMS studies are therefore often carried out on healthy subjects, but due to differences in extraneous variables between healthy subjects and stroke patients, results should be analysed with caution, [Ridding and Ziemann, 2010]. Variables such as attentional focus, age, and acticity/exercise level, could influence the potential for induction of plasticity, [Ridding and Ziemann, 2010]. Subject sample characteristics is therefore a critical point in the current neurorehabilitation research. Due to health issues

and resource-intensive research protocols, convenience samples of stroke patients are easily skewed towards subgroups, meaning that the samples are not representative of a whole population, [Wikström et al., 2014]. It is therefore suggested that more research should be carried out on stroke patients, [Wikström et al., 2014; Xu et al., 2014]. In the study of [Xu et al., 2014] it is specifically suggested that studies with greater subject samples and interventions applied over longer time, should be carried out in the future. This in order to analyse the retention of the neuroplastic changes seen, over time.

2.3 MEASURING TIBIALIS ANTERIOR MOTOR CONTROL AND FUNCTION IN STROKE PATIENTS

The selection of outcome measures is a critical element in the design and execution of a therapeutic clinical trial, Sullivan et al. [2011]. Different measures have been used to assess recovery of motor impairment and function from rehabilitation strategies, and their effectivity and reliablity depends on the context they are utilised in. An aim for future BCI PAS studies is to test on stroke populations, and evaluate functional outcomes of the protocols, [Grosse-Wentrup et al., 2011; Langhorne et al., 2011; Xu et al., 2014]. Measures previously used for neuro rehabilitation protocols will be assessed below.

TMS induced MEPs has primarily been used as outcome measure in BCI PAS protocols, [Grosse-Wentrup et al., 2011]. The BCI PAS protocol has already shown that it can increase the corticospinal excitability of the TA, [Mrachacz-Kersting et al., 2012; Xu et al., 2014]. Increases found in corticospinal excitability have been correlated with recovery from motor impairment, but not with recovery of functional locomotor skills [Hendricks et al., 2003; Piron et al., 2005]. However neural plasticity in response to locomotor rehabilitation have shown improvements in corticospinal excitability of lower limb muscles following rehabilitation. This was both when TMS was obtained during an isometric contraction and at rest, [Forrester et al., 2006; Yen et al., 2008].

In the study of Ramos-Murguialday et al. [2013], upper limb functionality was assessed before and after a BCI neurofeedback protocol, applied every day for four weeks (see section 2.2). However for lower limbs, similar studies are yet to be carried out. The functional outcome measure used was the upper limb part of the FMA scale. In section 1.2.2 table 1 the FMA scale and other scales were introduced. The FMA motor score for upper limbs is a clinical measure, indicative of corticospinal tract integrity and potential for motor recovery after stroke, [Stinear et al., 2007]. The FMA scale is one of the most widely recognised and clinically relevant measures of body function impairment after stroke. The motor domain of the FMA scale has proven reliability and validity in assessing motor impairment level over a stroke recovery course, Sullivan et al. [2011] The FMA scale also includes measures for lower limb function that could be relevant for assessment of individual lower limb rehabilitation. Such as hip, knee and ankle, flexion and extension ability, Sullivan et al. [2011].
Another scale using measures involving TA motor control is the MAS. The MAS includes assessment of functionality such as balance and e.g. independence in getting from supine to sitting position. Of measures from MAS possibly involving TA motor control are walking and stepping tests. Of other individual measures important in the assessment of stroke

recovery is walking speed and muscle strength, Duncan et al. [2005]; Pollock et al. [2014].

Another approach, that has been limited in it's use for assessing outcomes of interventions on stroke patients, is the analysis of patterns in gait data collected via a 3D motion capture setup, [Wikström et al., 2014]. Gait analysis has primarily been used for diagnosing gait abnormalities and for planning and assessing interventions to improve gait, in patients with cerebral palsy, [Wikström et al., 2014]. Observational gait analysis has been identified as an inadequate method for the evaluation of gait abnormalities, while the study by Fuller et al. [2002] suggests that instrumented gait analysis can contribute to the assessment of ankle and foot deformity in stroke patients. Whereas scales used for motor function assessment can be insensitive to minor changes, instrumented gait analysis might be able to detect these and provide good reliability between sessions, [Boudarham et al., 2013; Collins et al., 2009; McGinley et al., 2009; Schwartz et al., 2004]. A study of hemiplegic gait found alterations in spatiotemporal and kinematic parameters, [Olney et al., 1994]. Of the kinematic parameters especially the sagittal plane showed alterations, [Olney et al., 1994].

Observational gait analysis is the visual assessment of gait by specialists. Instrumented gait analysis utilises motion capture systems to analyse based on quantitative data

AIM

3

Stroke, the main cause of disabilities in adults, is causing long-term consequences for the patient and society. More efficient tools, and methods of rehabilitation for patients currently with limited recovery potential are needed. Recent research has found potential in BCI PAS neurorehabilitation, where increased corticospinal excitability has been reported as results. The method has primarily been tested on healthy subjects. Only a few studies have been performed on stroke patients, but using slightly different paradigms. One of these showed that it was possible to improve functional abilities in stroke patients, when used as priming before physiotherapy. In order to move forward, several reviews suggest that controlled trials on stroke populations should be carried out testing the outcome of the BCI PAS method. They suggest that the intervention period should be of several weeks, and more functional measures should be included, to evaluate if the effect of the method could be of clinical relevance. However, performing BCI PAS experiments on stroke patients are complicated by contraindications to TMS, ethical study design challenges, and variability in neurophysiologic outcome measures due to the heterogeneity of strokes. In clinical trials on outcomes of treatments, different functional scales and subscales of these, have been used to evaluate if changes are of clinical relevance. A tool that has been identified as useful in assessing recovery of locomotor abilities is 3D gait analysis.

The aim of the current study was to set up a study design for a future clinical trial and test its feasibility and effectiveness on stroke patients. The study should investigate the effect of BCI PAS on neurophysiologic and functional recovery of lower extremity, in stroke patients.
A study design was created where the BCI PAS intervention was given 3 times a week for 4 weeks, with neurophysiologic and functional measures obtained before, during and after the intervention phase. The measures used to assess functional recovery was individual measures from acknowledged clinical scales, involving TA motor function. Futhermore 3D gait analysis was used to collect kinematic data, with the purpose of investigating and potentially identifying biomechanic parameters revealing relevant changes. The neurophysiologic measures of interest was MEPs of TMS to assess changes in neuroplasticity. Two different conditions of TMS were used in the assessment. TMS while performing a small contraction of TA and TMS during the functional task of stepping up.

As research indicate that priming before physiotherapy might be a possible application for BCI PAS in the clinic, it was also important to investigate how long time, changes in corticospinal excitability lasts, following a session of BCI PAS training.
Therefore an initial study was carried out on healthy subjects investigating the retention period of neurophysiologic changes.

RESEARCH QUESTIONS

The current study aimed at answering the following research questions:

- *How is the retention of potential changes in corticospinal excitability from the proposed BCI PAS protocol, assessed by TMS elicited MEPs?*

- *How can a 4 week BCI PAS training paradigm be set up to assess neurophysiologic and functional recovery in stroke patients, using acknowledged functional measures, 3D gait analysis and TMS elicited MEPs?*

Part II

METHOD

In the method, the aim will be assessed and a strategy of answering it will be prepared. The method will describe the experimental designs developed, explain which settings and equipment was used and how data analysis was carried out. The aim consisted of two parts, and two experiments were carried out to answer them. These two experiments will have there own separate chapters, both for experimental design and data analysis.

METHOD OVERVIEW

Based on the topics covered in the introduction, i.e the consequences of a stroke, rehabilitation, techniques for assessing recovery and previous success with a BCI PAS paradigm on stroke patients, the aims and research questions were formulated. The aim of this research project was to develop an experimental design for testing the feasibility and effect of a BCI PAS intervention on stroke patients. Furthermore it was of interest to investigate, whether the intervention could have an application as priming before physiotherapy, by assessing the retention of changes. In order to answer this, experiments were carried out. Two individual experiments, with some common parts, were designed. Data was collected and processed, and ultimately results analysed and evaluated, based on the individual aims. This process is illustrated on figure 3.

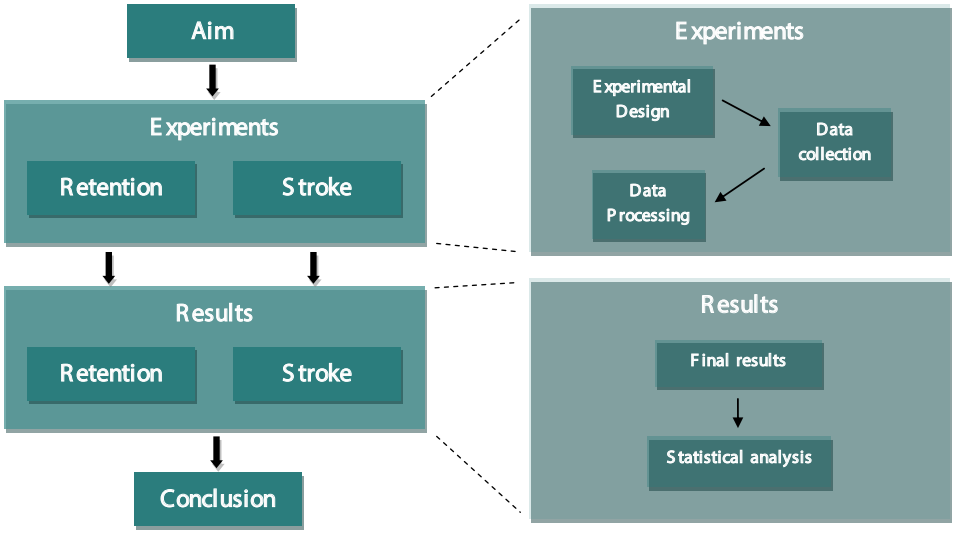

Figure 3: Overview of the path from the aim with the research questions to results that can be used to answer the questions. As two experiments were carried out to answer the aim, the experiment box contains the two experiments, refered to as 'Retention' and 'Stroke'. The components of the experimental phase for each of the two experiments are illustrated in the experiment box to the right. Each experiment involved experimental design, data collection and dataprocessing. The dataprocessing revealed final results for each experiment and statistical analysis was done for both. Finally the results of each experiment were evaluated and synthesised in a conclusion.

The experiment was part of a larger study carried out in collaboration with a research group at *Health & Rehabilitation Research Institute, Auckland University of Technology, Auckland, NZ* and the experiments were done at their facilities.
The experimental design was therefore a result of the aim of this current project fitted into the larger scope of the research group, exploring the feasibility of a 4 week BCI PAS clinical trial on stroke patients. For both experiments ethical approvals were obtained

from the Auckland University of Technology Ethics Committee.

One of the things of interest was to investigate the retention of neurophysiological changes due to a BCI PAS protocol, and the experimental setup developed to answer this aim is covered in the first part of the method. This experiment will be refered to as the 'Retention' study.
The main goal of the project was designing an experimental design for assessing the effectiveness of the BCI PAS training on recovery of lower extremity function in stroke patients. This experiment will be explained in the second part of the method and referred to as the 'Stroke' study. As some of the elements in the two experimental designs will be identical, these elements will be reported in the Retention Study only. In the stroke experiment elements will refer to the retention experiment if they are identical to elements described there.

4 RETENTION STUDY: EXPERIMENTAL DESIGN

With the purpose of investigating the potential of the BCI PAS protocol being used for priming of the corticospinal tract before physiotherapy, the following research question was asked:

How is the retention of potential changes in corticospinal excitability from the proposed BCI PAS protocol, assessed by TMS elicited MEPs?

In designing an experiment to provide an answer to this, decisions were taken that influenced the design and methods used. This experiment and the stroke experiment target lower extremity rehabilitation with the focus on the TA muscle. The BCI PAS intervention was tested using 50 electrical stimulations at the common peroneal nerve (CPN) paired with motor imagination, as this dosage was used in Mrachacz-Kersting et al. [2012]. To find the optimal timing for pairing motor imagination and electrical stimulation, an initial motor imagination task was carried out, where slow cortical potentials were recorded through EEG and analysed. TMS was applied to the contralateral motor cortex of the right leg while MEPs from the TA was acquired through EMG recordings. This was done prior to the intervention, immediately after the intervention, 30 min, 45 min, and 60 min after the intervention.

4.1 EXPERIMENTAL UNITS

Subjects were both reqruited internally and externally of the institute, and the communication channel was either per phone, email or in person. An information sheet about the purpose and description of the experimental procedure and potential risks were given, together with an informed consent form (see appendix B). Subjects were screened for their eligibility, meeting inclusion criteria and excluded based on exclusion criteria. Inclusion and exclusion criteria can be seen in table 2. Exclusion criteria was mainly influenced by the vast contraindications of TMS. A separate participant safety checklist (see appendix B) was used for TMS contraindications. 8 subjects were in total excluded in the screening process. 10 healthy subjects (7 males and 3 females) with a mean age of 33.7 years (SD = 12 years) were reqruited for this study, who passed all of the inclusion and exclusion criteria.

4.2 EXPERIMENTAL TYPE AND STRUCTURE

The study was structured as an exploratory analysis of data from an open trial, non-randomised repeated measures design, with time after the intervention as the independent variable and corticospinal excitability as the dependent variable. The corticospinal

Inclusion Criteria	Exclusion Criteria
Adults, generally healthy, comfortable with the idea of TMS, profiency with communication, cognition and perception	Disability or medical condition affecting lower limb strength, cardiac conditions, hypertension, uncontrolled metabolic disorders, active acute infection, musculoskeletal pain in lower limb, major depression, other neurological pathologies

Table 2: Inclusion and Exclusion criteria

excitability variable is estimated by TMS elicited MEPs. The experiment was not controlled, as a controlled study already had been carried out previously, testing the individual effects of motor imagination, imagination + tibial nerve stimulation, and watching the cue, [Mrachacz-Kersting et al., 2012]. The findings in that study was that neither of those controls resulted in significant increases in corticospinal excitability, [Mrachacz-Kersting et al., 2012].
The repeated measures design allows statistical inference to be made with fewer subjects, by reducing the effects of extraneous variables. Identified variables potentially of influence in this experiment are listed in table 3.

Type of variable	Experimental variables
Dependent	MEPs
Independent	Time after intervention (post, post30, post45 and post60), timing of sensory feedback
Intervening	Muscle fatique, attention, motivation
Extraneous	Gender, age, and education

Table 3: Experimental variables catagorised in dependent, independent, intervening and extraneous variables.

The experiment consisted of 3 different modules; an initial measurement to collect a timing to be used for the intervention (refered to as a 'MRCP session'), a measurement of corticospinal excitability (refered to as a 'TMS session'), and the motor imagination driven PAS intervention (refered to as 'BCI intervention').

4.3 EXPERIMENTAL MODULES

The experiment was carried out in a neurophysiologic laboratory at Auckland University of Technology. The test subject was during the whole experiment seated in steady adjustable chair, while the 3 different types of experiment modules were carried out.

4.3.1 *MRCP session*

The purpose of this session was to find the timing for the electrical stimulation needed for the intervention. Studies have found that sensory feedback arriving at the sensory motor cortex at the time of peak negativity (PN) of the MRCP, in a cued motor imagination task, have lead to increases in corticospinal excitability, [Mrachacz-Kersting et al., 2012]. Mrachacz-Kersting et al. [2012] showed that the timing of PN in a cued motor imagination task does not change significantly over time. Therefore an average timing from 50 imagined ankle dorsiflexions were calculated, and used for the intervention session. This meant that the intervention procedure could be simplified, as MRCP recordings could be carried out on another day and that online detection of PN with an additional training period, was not needed.

MRCPs are slow cortical potentials that can be extracted from EEG recordings, when a person cognitively prepares for a movement. As the target muscle in this rehabilitation paradigm was TA (innervated during ankle dorsiflexion), a setup with 9 EEG electrodes centered around the CZ position in a 10-20 system was of interest. A NuAmps 40 Channel EEG cap was used and the 9 electrodes being recorded from were F3, F4, FZ, C3, C4, CZ, P3, P4, PZ. A frontal electrode was used as GND, and the bony surface behind the right earlobe was used as reference by a Ag/AgCl electrode. All impedances were ensured to be below $5k\Omega$. The electrodes were monopolar and connected to a NuAmps Digital Amplifier Model 7181 where data was sampled by 500 Hz and analog to digitally converted with a resolution of 32 bit. The NuAmps amplifier was connected to a Windows PC running a version of NuAmps Scan Express, acquiring data.

On another screen, an animation with cues to focus, anticipate and execute the movement intent were given, controlled via a MATLAB program. A trigger from the MATLAB program was sent to the NuAmps EEG amplifier, indicating the times of movement initiation in the visual cue. The experimental setup for a MRCP session is shown on figure 4

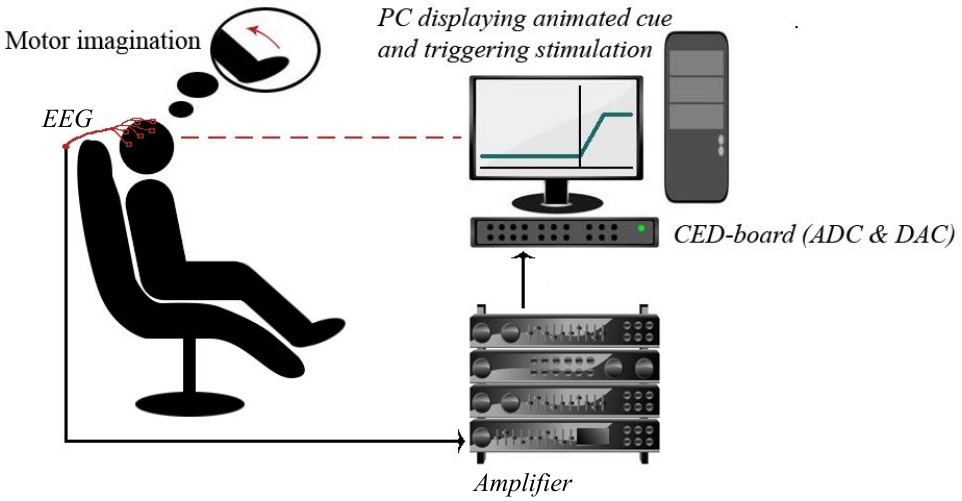

Figure 4: Experimental setup of the MRCP session.

Identification of Peak Negativity

At the end of the MRCP session, the EEG data collected from the 50 imagined ankle dorsiflexions were processed offline. The 9 EEG channels were 0.05 Hz to 5 Hz bandpass filtered using a Butterworth 2nd order infinite impulse response filter applied in MATLAB in both directions to cancel out delays due to filtering. A virtual channel was then created based on the 9 channels, by using a large laplacian filter centered around CZ. The purpose of this was to optain a better resolution at the electrode most proximal to the motor cortex innervating the TA muscle, which was CZ. A laplacian filter works as a highpass filter, and in this application substracts $1/8$ of each channel around CZ, from CZ. A grand average of the 50 epochs was then made, based on the time-locking event which was the movement initiation point, that was acquired as a trigger from the computer running the cue program. An example of a characteristic grand average MRCP from motor imagination can be seen in figure 5.

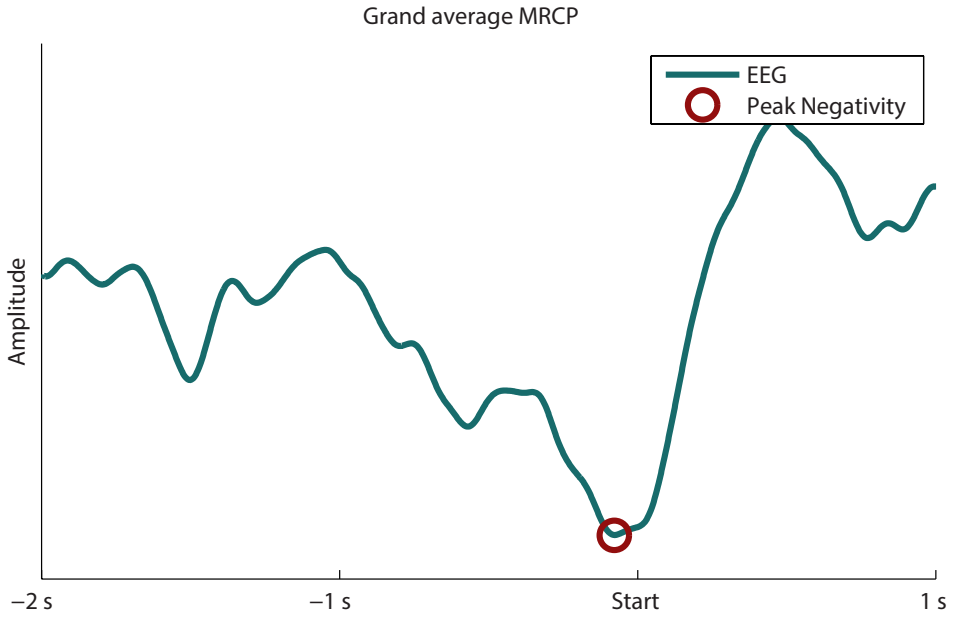

Figure 5: Example of a grand average MRCP of 35 trials from a healthy subject. The red circle in the figure marks the point of peak negativity. 'Start' marks the time where the subject is instructed by the cue to start motor imagination.

As it can be difficult to time the imagination of a dorsiflexion with the given cue, and also as EEG signals easily are infected by artifacts from more powerful signal sources such as EMG, some EEG epochs would not have a shape similar to a MRCP. If the grand average of all 50 repetitions therefore did not result in a characteristic MRCP shape, with PN clearly defined within 200 ms on each side of the movement onset cue, individual epochs were visually inspected. Based on the visual inspection, epochs was rejected, if they were contained EMG artifacts or had no clear identifiable PN. Finally the timing of PN related to the movement initiation cue was extracted.

4.3.2 *TMS session*

TMS sessions were used to estimate the corticospinal excitability of a subject. 15 repetitions of single pulse, posterior to anterior TMS at 120 % of the stimulation resting threshold intensity were given by a *Magstim*^{200}, through a double cone coil. The stimulation resting threshold intensity was defined as the intensity that gives an MEP in 6 out of 12 stimulations, with a minimum peak-to-peak amplitude of 50 μV. Hotspotting and identification of the resting threshold intensity was done initially. MEPs were obtained via monopolar surface Ag/AgCl electrodes, placed on TA in accordance to the SENIAM project (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles). The skin below electrodes was prepared by shaving, abrasion and cleaning with alcohol pads, in order to reduce the electrical resistance of the skin. Electrode impedances were ensured to be below $5k\Omega$. EMG data was acquired by a CED Power1401 board, with a sample rate of 5000 Hz, a gain of 1000 V/V and lowpass filtered with a cut-off frequency of 1000 Hz.
The experimental setup for a TMS session is shown on figure 6.

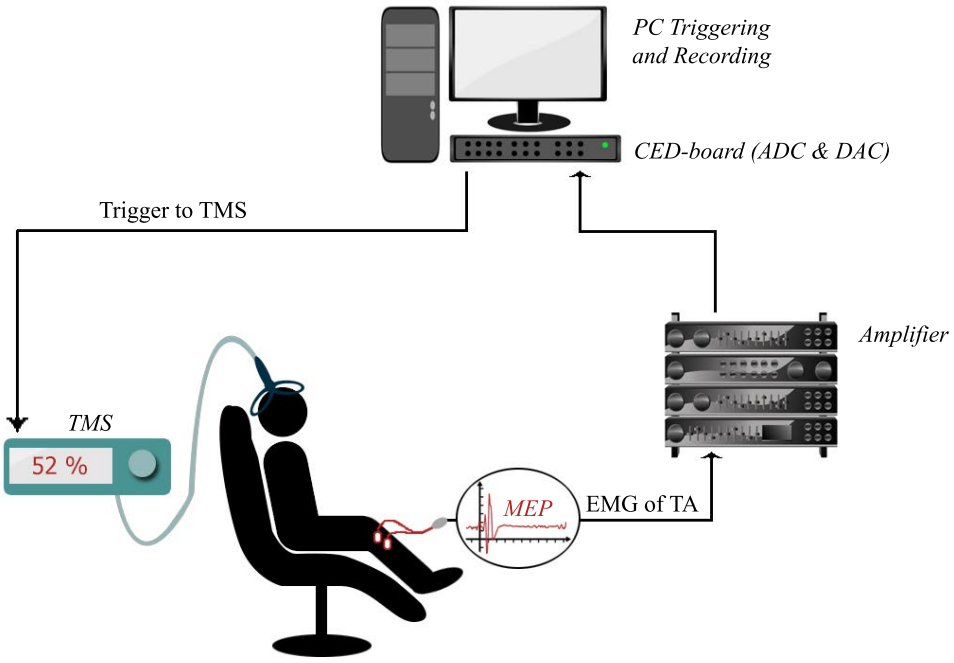

Figure 6: Experimental setup of the TMS session in the Retention study.

4.3.3 *BCI intervention*

For the intervention 50 movement cues were given on a screen and the subject was instructed to perform motor imaginations of ankle dorsiflexions. The timing of PN found in the MRCP session was used in this session, to trigger a stimulater (Digitimer Stimulator DS7AH) via the CED board. The stimulater was configured to deliver a 1 ms single pulse

stimulation to the deeper branch of CPN, innervating the TA muscle. The stimulation intensity was set above motor threshold and below pain threshold, detected by a palpable twitch in the TA tendon at the ankle joint and a confirmation of no perception of pain from the test subject. A MATLAB program was configured to deliver the pulse at 50 ms (sensory delay) + 5 ms (cortical computational delay) + the individual PN latency from the MRCP session, before the timing of movement initiation onset in the cue. The experimental setup for a BCI intervention session is shown on figure 7.

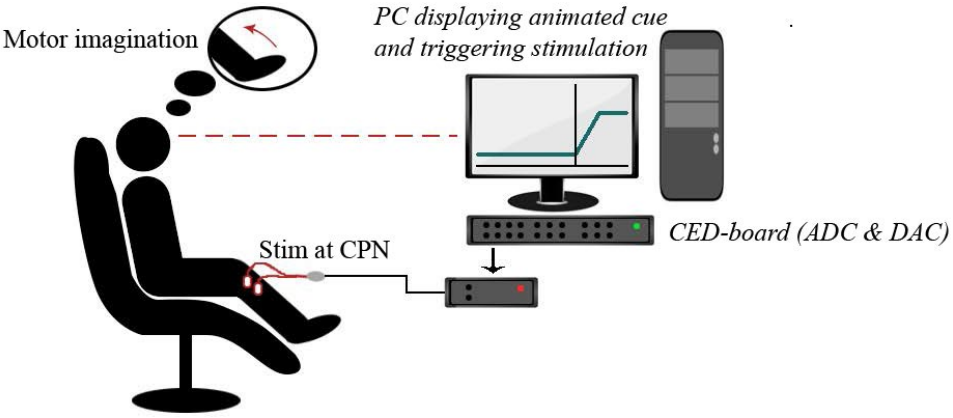

Figure 7: Experimental setup of the BCI intervention session.

5 RETENTION STUDY: DATA ANALYSIS

Data analysis of this experiment consisted of peak-to-peak analysis of MEPs. Then averaging of these peak-to-peak amplitudes from each subject Pre, Post, Post30, Post45, and Post60, and then statistical analysis to see if the experiment revealed significant differences.

5.1 MEP PEAK-TO-PEAK ANALYSIS

A window was used after the TMS stimulation artifact to locate the maximum peak-to-peak MEP amplitude from EMG, for each of the 15 stimulations. An average of these 15 maximum peak-to-peak amplitudes were created for each TMS session, for each subject.

5.2 STATISTICAL ANALYSIS

For statistical analysis the software IBM SPSS Statistics was used. Each of the dependent measures Pre, Post, Post30, Post45 and Post60 were tested for normality using the Shapiro-Wilk test. A repeated measures one-way ANOVA was used to analyse the effect of the time factor. This was choosen as ANOVA is a robust analysis and despite an assumption of normality, can handle minor deviations.
Another assumption of ANOVA is sphericity, meaning that the variances and covariances of the different times should be similar. Mauchly's test of sphericity was used. If the null-hypothesis of sphericity would be rejected, which is a typical phenomenon with real data, it would be corrected for by adjusting the degrees of freedom, using the Greenhouse-Geisser correction. The effect of the time factor would then be analysed in the ANOVA, with post-hoc tests investigating potentially significant changes between times, in case of a significant time factor.

6 STROKE STUDY: EXPERIMENTAL DESIGN

The goal of this second experiment was investigating the feasibility of designing an experiment for assessing the effectiveness of the BCI PAS protocol, on recovery of lower extremity function in stroke patients. Initially the scope of the experiment was also to estimate an effect of the intervention based on a sample of subjects, but due to exclusion of stroke subjects and the fixed time frame for the project, the scope changed to testing the experimental design and intervention on a single stroke patient. The experiment was designed to be performed on 20 stroke patients and will be continued after the end of this current project. As mentioned in chapter ii the study was done in collaboration with a research group at Auckland University of Technology. Setup of the experiment and data collection was done in conjunction with a physiotherapist and research officer, refered to as investigator 2. Throughout the experiments, check sheets were used to systemise the experimental process and to standardise the experiment for each subject by recording subject specific configurations. In the beginning of each session, potential changes to medicine, intake of caffeine or medical issues were recorded. An example of a check sheet covering two experimental sessions can be seen in Appendix B.

6.1 EXPERIMENTAL TYPE AND STRUCTURE

The study was structured as a double-blinded randomised controlled trial with a repeated measures design. It was decided that subjects should be blinded and use an active control group to avoid placebo effects. Investigator 2 was also blinded, making the full scope experiment double-blinded, to avoid investigator bias, [Besen and Gan, 2014]. Blinding was carried in the way that the subject was told they would receive one out of two interventions but not which. The two types of interventions were: A high intensity intervention or a low intensity intervention of the BCI PAS. The difference between high and low intensity was that the peripheral electrical stimulation would only be activated in the high intensity intervention. For the low intensity intervention no stimulation would be given in the BCI PAS intervention, but the rest of the protocol would be identical. The control was thereby an active control. Randomisation would be used to divide subjects into two groups of equal size. Due to only one subject in the current study, the study type carried out was in the shape of a exploratory case study with blinding and a repeated measures design. Evaluation of the effect of the intervention based on this current study, would therefore be limited by only being based on one subject, with no control.

The repeated measures design was important, as it allows statistical inference to be made with fewer subjects, by reducing the effects of extraneous variables. Identified variables potentially of influence in this experiment are listed in table 4.

Type of variable	Experimental variables
Dependent	MEPs
Independent	Time after intervention (post, post30, post45 and post60), timing of sensory feedback
Intervening	Muscle fatique, attention, motivation
Extraneous	Gender, age, and education

Table 4: Experimental variables catagorised in dependent, independent, intervening and extraneous variables.

The experiment consisted of a 4 week intervention period, preceeded by 2 sessions of pre measures to establish a baseline in the repeated measures. After the 4 week intervention period 2 sessions of measures were used as post measures. During the 4 week intervention phase, measures were taken before and after the first intervention each week. This was to identify within session effects, that might not be stored to be seen in the post measures after the 4 weeks. The structure of this study on stroke patients can be seen on figure 8.

Phase	Session	Day	Duration
Pre-Intervention	Screening, Consent, TMS screen (check for MEP), Clinical Evaluation (-7 days)	Pre-intervention Week – Monday/Wed	2 hours
	MRCP , TMS (static and stepping) (-3 days)	Friday	2 hours
Intervention	MRCP + TMS + Intervention 1 + TMS	**Week 1** - Monday	3 hours
	Intervention 2	Wednesday	1 hour
	Intervention 3	Friday	1 hour
	MRCP + TMS + Intervention 4 + TMS	**Week 2** - Monday	3 hours
	Intervention 5	Wednesday	1 hour
	Intervention 6	Friday	1 hour
	MRCP + TMS + Intervention 7 + TMS	**Week 3** - Monday	3 hours
	Intervention 8	Wednesday	1 hour
	Intervention 9	Friday	1 hour
	MRCP + TMS + Intervention 10 + TMS	**Week 4** - Monday	3 hours
	Intervention 11	Wednesday	1 hour
	Intervention 12	Friday	3 hours
Post-Intervention	MRCP + TMS	Monday	2 hours
	Clinical Evaluation (+3 to +5 days)	Wednesday	1 hour
	Clinical Evaluation speed only (+10 day)	Monday	1 hour

Figure 8: Overview of the experimental structure. The experiment consists of the phases, Pre-Intervention, Intervention and Post-Intervention. Each session is carried out on the day showed in the 'Day' column, where the weeks are also specified.

6.2 EXPERIMENTAL UNITS

Chronic stroke patients were the test subjects for this experiment. As the study was carried out at the research institute for health and rehabilitation, contacts to current and previous patients at the clinic were used. Besides that, different local stroke societies were informed about the study and helped advertising it.
Screening of participants was done in several steps, initially per phone or email, to ensure that general inclusion criteria were met. An information sheet about the purpose and description of the experimental procedure and potential risks were given, together with an informed consent form (see appendix B). Subjects were screened for their eligibility, meeting inclusion criteria and excluded based on exclusion criteria. Inclusion and exclusion criteria can be seen in table 5. Exclusion criteria were mainly influenced by the contraindications of TMS and cardiac diseases. A separate participant safety checklist (see appendix B) was used for TMS contraindications. 3 stroke patients were excluded from the experiment due to factors such as deterioration of general health, TMS contraindications and uncomfort of receiving TMS. One stroke patient was included as a subject and the characteristics are as follows: 75 years of age, male, 5 years post left ischaemic stroke, suffering from right hemiplegia but able to walk 10 m in a slow pace.

Inclusion Criteria	Exclusion Criteria
Older than 18 years, had a stroke $>$ 6 months ago, able to walk 10m, willing to participate in the 6 required weeks, comfortable with the idea of TMS, profiency with communication, cognition and perception	Disability or medical condition affecting lower limb strength, cardiac conditions, hypertension, uncontrolled metabolic disorders, active acute infection, musculoskeletal pain in lower limb, major depression, other neurological pathologies

Table 5: Inclusion and Exclusion criteria of the Stroke study

6.3 NEUROPHYSIOLOGICAL AND FUNCTIONAL MEASURES

As figure 8 reveals, the experiment involved a group of measures to assess the effect of the BCI PAS intervention applied on stroke patients, 3 times a week for 4 weeks. In the pre-intervention week the subject had his final screening in person and a group of measures assessing the subject's initial functional level, including 3D gait analysis. In the 4 week intervention phase the subject received the BCI PAS intervention. Neurophysiologic measures were made before and after the first intervention in a week. After the 4 weeks of intervention was the post-intervention phase, consisting of clinical evaluation of functional measures and gait analysis. The study consists of the following assessments and experimental modules that will be further described:

- Clinical evaluation
- Walking and stepping test
- 3D gait analysis

- MRCP
- TMS
  - Static
  - Dynamic
- BCI PAS intervention

6.4 EXPERIMENTAL MODULES

The experiment was carried out in a gait analysis laboratory at Auckland University of Technology, with power grid running at 50Hz. During the experiments, Investigator 2, who was a trained physiotherapist, used her professional skills in instructing, guiding and supporting the patient through the measures and intervention.
In the next part the content of the different experimental modules will be described. The MRCP session was set up and carried out similar to what was done in the Retention study. For description refer to 4.3.1. A difference was though that in this experiment, the stroke patients were not supposed to imagine movements, but attempt them. The BCI PAS intervention was also similar to the one from used in the Retention study (see 4.3.3) but likewise also differed in the type of movement intent. The stroke subjects were instructed to attempt actual ankle dorsiflexions in the intervention. MRCP's were recorded the first day in each intervention week with the purpose of extracting a peak-negativity value to use in the BCI PAS intervention that week, but also to use the MRCP as a measure. Studies have found the time of peak negativity in relation to a given cue, not to change over time, but the onset of the negative slope can change, [Yilmaz et al., 2013]. In stroke patients it has been found that the onset of the negative slope can change due to neuroplastic changes, [Yilmaz et al., 2013], why this measure was included. However in this current project this feature was not further analysed.

6.4.1 *Clinical evaluation and 3D motion analysis*

The purpose of the clinical evaluation was to assess functional abilities before and after the 4 week intervention phase. The clinical measures used were based on the analysis of measures used in stroke rehabiltation. Out of a group of several potential measures, and scales such as MAS or the FMA scale, used in the upper extremity study, [Ramos-Murguialday et al., 2013], a few were selected. The measures selected are assessing functional abilities and focusses on tasks where TA is involved. The selected tests are listed below:

- Gait speed in 10 m normal walking test (walking aids allowed)
- Gait speed in 10 m fast walking test (walking aids allowed)
- Number of steps in 15 s, left leg (walking aids not allowed)
- Number of steps in 15 s, right leg (walking aids not allowed)
- 3D motion analysis of gait

- 3D motion analysis of stepping with impaired leg

Gait speed in 10 m walking tests are common in the assessment of function and independence in stroke patients. For the assessment of gait speed in normal and fast walking, two lines were marked on the floor indicating the 10 m walking path, and the patient was instructed to walk between the lines, with walking aids if needed. The middle 6 meters were used for calculating the average walking speeds. The test was repeated 3 times.
The step test consisted of timed 7.5 cm stepping up tasks for both the affected and unaffected leg without walking aids. The number of repetitions executed in 15 seconds was recorded. The step test was applied as it was a measure that could be taken in less than 5 minutes in an already extensive protocol, has shown good test-retest reliability and is responsive to changes during recovery of stroke, [Mercer et al., 2009].

3D motion analysis was done with the subject performing two tasks, normal walking and stepping with the impaired leg. During the two tasks, locations of reflective markers positioned on body landmarks, ground reaction forces, and EMG from the TA and Soleus were acquired. For the motion analysis a Qualisys Motion Capture system was used with 9 Oqus500 IR cameras and passive retroreflective markers. Two forceplates in the floor were used in conjunction with the motion capture system. EMG was captured using wireless EMG preamplifiers from Noraxon USA, and a Noraxon USA TeleMyo DTS Desk Receiver for sampling.

6.4.1.1 *Setup of 3D motion capture protocol*

Before every motion capture session, the motion capture system was calibrated to ensure a high precision of locating reflective marker positions ($< 0.7mm$ error). The location of the area of the two forceplates were also captured and saved in the settings. A handheld trigger was used to initiate the synchronised recording of 3D motion, ground reaction forces, and EMG

Reflective markers were placed on anatomical landmarks according to the Helen Hayes marker set model, showed in figure 9. The Helen Hayes market set model covers lower extremity and has been used with success in other studies and in the Gait Analysis Clinic at Auckland University of Technology, for gait analysis of kids with cerebral palsy, [Boudarham et al., 2013].

The anatomical landmarks used for the markers with references to the numbers on figure 9 are listed below:

1. Right Acromion Process
2. Left Acromion Process
3. T2
4. Sternal Notch
5. Mid PSIS

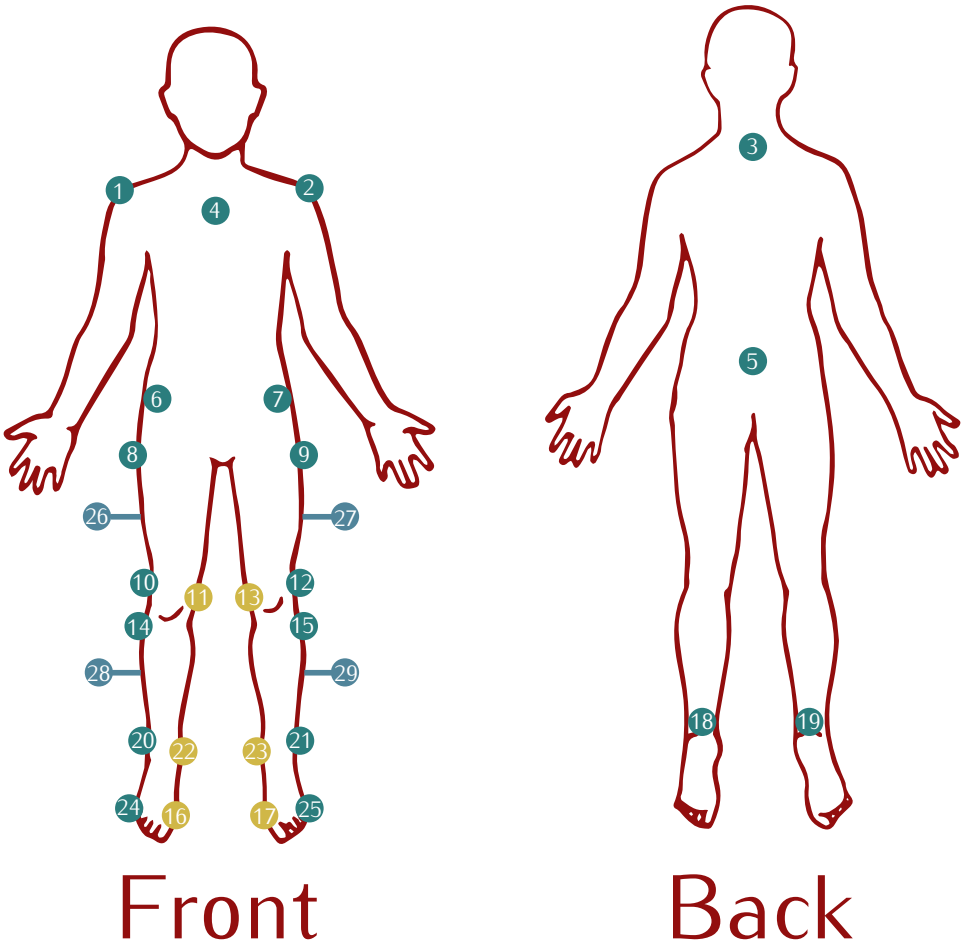

Figure 9: Illustration of the used Helen Hayes marker set model. The yellow markers are removed after the static measurement.

6. Right ASIS
7. Left ASIS
8. Right trochanter
9. Left trochanter
10. Right lateral femoral epicondyle notch
11. Right medial femoral epicondyle notch
12. Left lateral femoral epicondyle notch
13. Left medial femoral epicondyle notch
14. Right fibula head
15. Left fibula head
16. Right 1st metatarsal head
17. Left 1st metatarsal head

18. Left calcaneous
19. Right calcaneous
20. Right lateral malleoli
21. Left lateral malleoli
22. Left medial malleoli
23. Right medial malleoli
24. Right 5th metatarsal head
25. Left 5th metatarsal head
26. Right femoral wand
27. Left femoral wand
28. Right tibial wand
29. Left tibial wand

Supervision and training in the correct placement of markers was given by Research Officer & Physiotherapist Yanto Naude, Auckland University of Technology, who has several years of experience in gait analysis of cerebral palsy patients. The precise placement of markers was of importance, as small deviations could lead to errors in computation of angles.

First a static 3 s measurement was made, where the subject was instructed on standing still in a neutral posture. The static measurement would be used to create a model of the body in the post processing phase. Markers 11, 13, 16, 17, 22 an 23 were then removed, as their positions could be approximated from the remaining markers based on the static model. Removal of these markers allows the subject to move more freely and natural.

Then the patient was supposed to perform the walking test. The patient was instructed to walk normally between two lines, with the forceplates in the center of the path. Data was recorded every time the patient walked within the center 5 m, where the cameras would have the best chance of seeing all of the markers. The goal was to obtain minimum 10 complete gait cycles of data. The first 3 walks were excluded from analysis due to recommendations from the study of Boudarham et al. [2013], who showed that hemiplegic patients can walk cautiously in gait trials in such a degree that it can affect measures.

The last motion capture test was a stepping test. The subject was instructed to stand with one foot on each force plate. A 18 cm step (standard step height) was placed in front of subject. The subject steps weak leg up onto step, rests for one second, then returns to normal stance. This was repeated 10 times and recorded in one trial. The purpose of this test was to specificly examine the ankle dorsiflexion dynamics and compensation of other segments during the task. The results of this measure was however not evaluated in the current project.

Figure 10: Illustrations of setup of markers and wireless EMG

6.4.2 *TMS under static and dynamic conditions*

Studies have shown that MEPs during a low level of MVC are less variable than MEPs obtained at rest [Darling et al., 2006; Van Hedel et al., 2007]. TMS was therefore used with a small contraction of TA, and an active motor threshold to decide the stimulus intensity. 10 % of MVC was used as a level of contraction. This measure was refered to as TMS during a static condition.
TMS was also used during a dynamic condition, which was a stepping up task. This was decided as Van Hedel et al. [2007] states that MEPs during functional muscle contractions have less variabillity than during a static contraction, in stroke patients. This theory was supported by the study of Signal [2014], where reliability was established for TMS elicited MEPs during treadmill walking in stroke patients. Based on this it was decided to measure MEPs under the dynamic condition of a stepping task. Stepping is an elementary functional task and depends primarily on an ability to balance and lift the stepping foot up, and innervates TA. Peak-to-peak amplitudes of MEPs would be used as a feature.

6.4.2.1 *Static TMS*

MEPs were measured during 10 % MVC of the TA. The subject was placed in a steady adjustable chair, with the impaired foot-ankle joint strapped to a mechanical device with a build in force transducer. The force transducer was connected to a CED board and directly to an oscilloscope that was placed in front of the subject for visual feedback

of the force level. The same TMS and EMG equipment was used as in the Retention study on healthy subjects (see 4.3.2).

First hotspotting was done, to find a location of the TMS coil that would result in distinctive MEPs recorded by surface EMG at the TA muscle. The subject was wearing a cap with pieces of velcro, for attachment of the coil, and a grid to locate the position of the coil. When the location was found, the placement of the coil was recorded.

The subject was then instructed to perform 3 MVCs with a rest period of 2 minutes between. The maximum peak-to-peak amplitude of these 3 MVCs was found and recorded together with a baseline amplitude. MVC values of 8 %, 10 %, and 12 % were calculated. The 8 and 12 % MVC with the added baseline value, were used to setup an interval in the program Signal, that would send a trigger to activate the TMS device. A horisontal cursor was placed on the oscilloscope at the value of 10 % MVC plus baseline, to make the subject able to produce a controlled amount of force, that would enter the defined interval for activating a TMS stimulation.

Then the coil was placed again in the position on the cap that was found during hotspotting, and Signal was configured to trigger the TMS every time force level entered the defined interval, but with a minimum of 6 seconds between triggers. The subject was instructed to monitor the oscilloscope, while slowly building up a contraction of the TA, until the force level raised to the 10 % MVC cursor, triggering a TMS pulse, and then instructed to relax. This was done with different stimulation intensities until a stimulation intensity was found that resulted in 5 out of 10 MEPs with a minimum peak-to-peak amplitude of $50\mu V$. This intensity was used as the active motor threshold. 120 % of the active motor threshold intensity was then finally used for 15 recorded stimulations, triggered by the 8 to 12 % MVC output. The experimental setup for a static TMS session is shown on figure 11.

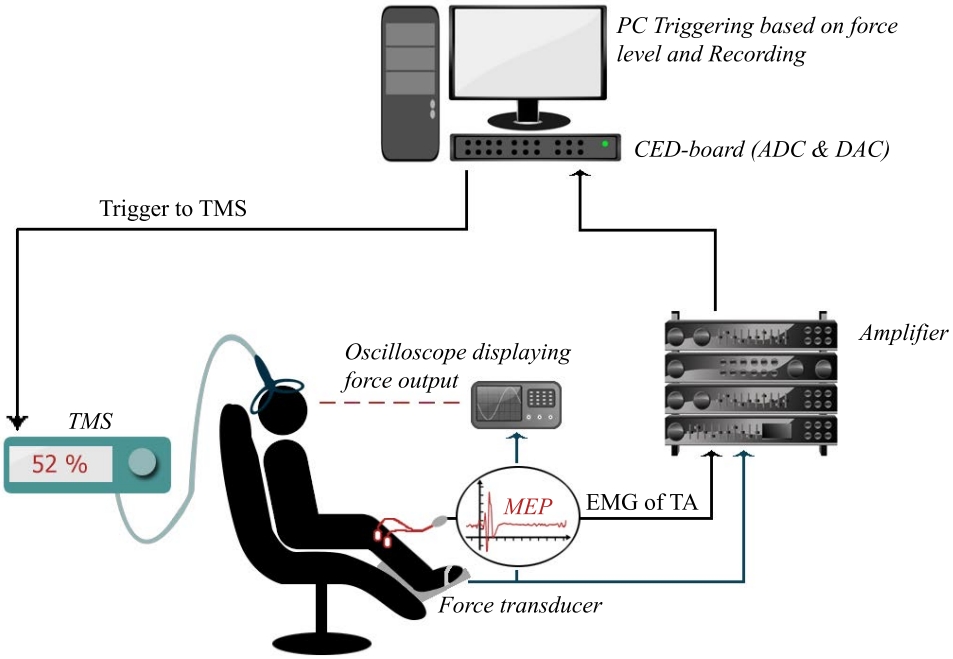

Figure 11: Experimental setup of the static TMS session.

6.4.2.2 *Dynamic TMS*

MEPs were recording during a dynamic stepping task. The purpose was to stimulate the motor cortex during the functional task of stepping up with the impaired leg. Stepping up involves a contraction of the TA muscle, to lift the foot by a rotation in the ankle joint. A standard step size of 17 cm was used and the subject was placed with the toes 10 cm from the step. Completion of the task requires a considerate lift of the foot, to not collide with the step. The goal was to stimulate during the stepping up at the timepoint of largest burst of EMG activity. This measure was carried out after the static TMS measure, and hotspotting and identification of the active motor threshold were thereby already done. But in order to be able to stimulate at a specific event measured by EMG, during stepping up, a configuration experiment was performed.

Configuration experiment

An analog footswitch was adhered using strapping tape to the lateral surface of the sole of the shoe or foot, on the heel of the affected leg. EMG was recorded from the TA muscle. The subject was then instructed to perform 8 stepping up movements, spaced with a few seconds between. A stepping up movement consisted of a step up with the affected leg, holding the weight on the unaffected leg, waiting a few seconds and then stepping down again. Based on the footswitch and EMG data from this recording, an average latency from the time of heel lift off to maximum EMG burst, was calculated.

Computing TA EMG burst after step up latency

Directly after the configuration experiment, the recorded data was loaded in a MATLAB script. The steps in this script are described here.

To investigate the footswitch signal and EMG data, they were plotted together and

a power spectrum analysis of the recorded EMG data was made. This can be seen on figure 12.

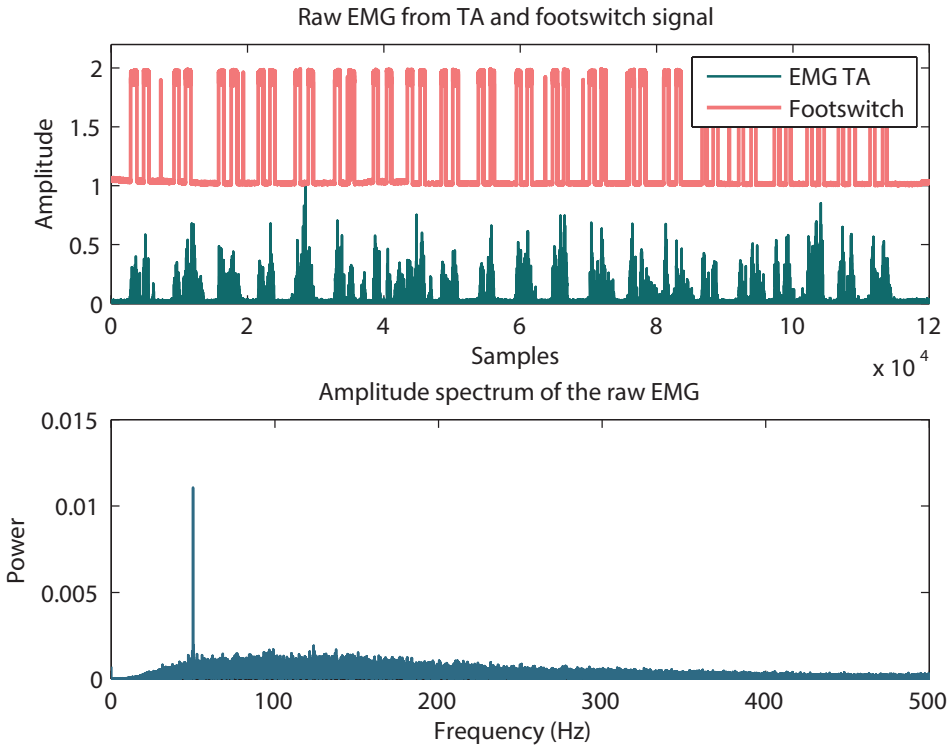

Figure 12: The top plot shows the recorded raw EMG and footswitch signals. The bottom plot shows the power spectrum of the EMG data.

From this visualisation it was apparent that a large amount of 50 Hz noise was captured. A 4th order Butterworth infinite impulse response band-stop filter, with cut-off frequencies 49 and 51 Hz, was applied to attenuate the 50 Hz noise. The filter was applied in both directions to cancel out filtering induced delays. Then a bandpass filter of similar type and cut-off frequencies 20 and 500 Hz was applied. The lower and upper bands were set based on the recommendations defined in De Luca [1997], stating that the main contributions to EMG are located between 20 and 500 Hz. Figure 12 reveals that the footswitch in stepping has been switching on and off, both during lift and landing but also during stance. As the purpose of the script was to effectively return a footlift-to-EMG-burst-latency, such inconsistency in the measure was an obstacle in the automation process. A few techniques were therefore used to preprocess the footswitch signal. These were thresholding and use of characteristics of timeframes for the relevant events, lifting, landing and time between steps, to ignore unrelevant changes in the signal. The result of filtering EMG data and reconstructing the footswitch signal can be seen on figure 13.

An interface for manually selecting step cycles were created, as some stroke patients would have difficulty performing steps and some epochs might need to be excluded from the calculations. A windowed RMS of the filtered EMG signal was computed, and then a maximum RMS value was found between each pair of identified stepping ups and downs. RMS value of the signal was used as a feature, as it indicates amplitude of the voluntarily elicited EMG signal, [De Luca, 1997]. Finally an average timing of maximum

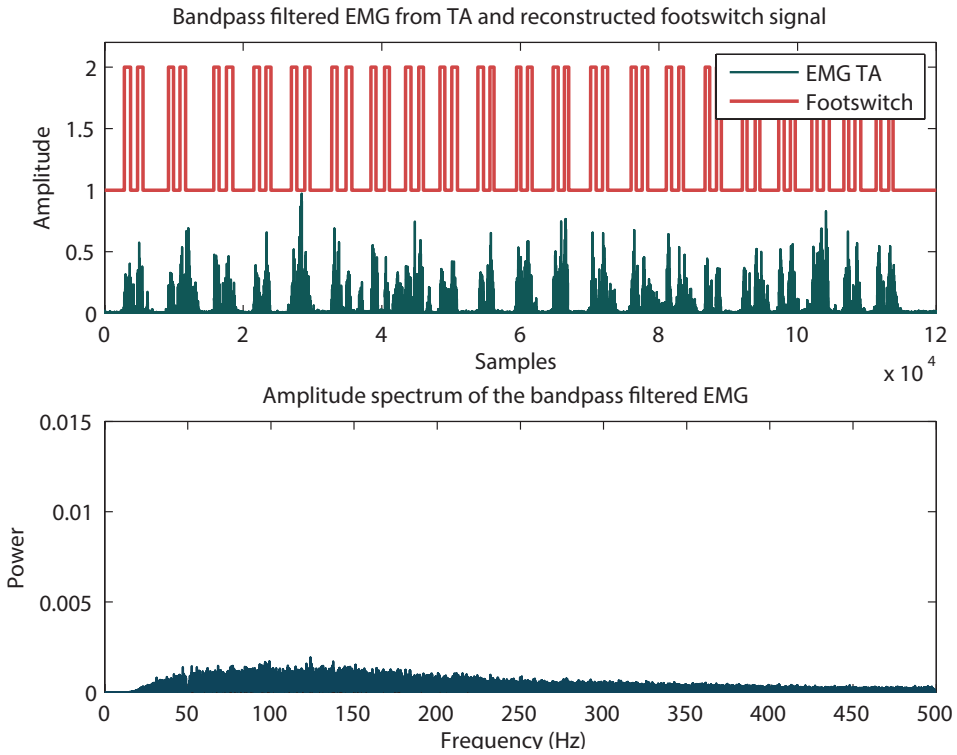

Figure 13: EMG and footswitch signals after respective filtering and reconstruction of them.

RMS value after lift off of the foot was calculated of the selected step cycles. Figure 14 shows the steps in finding the latency value.

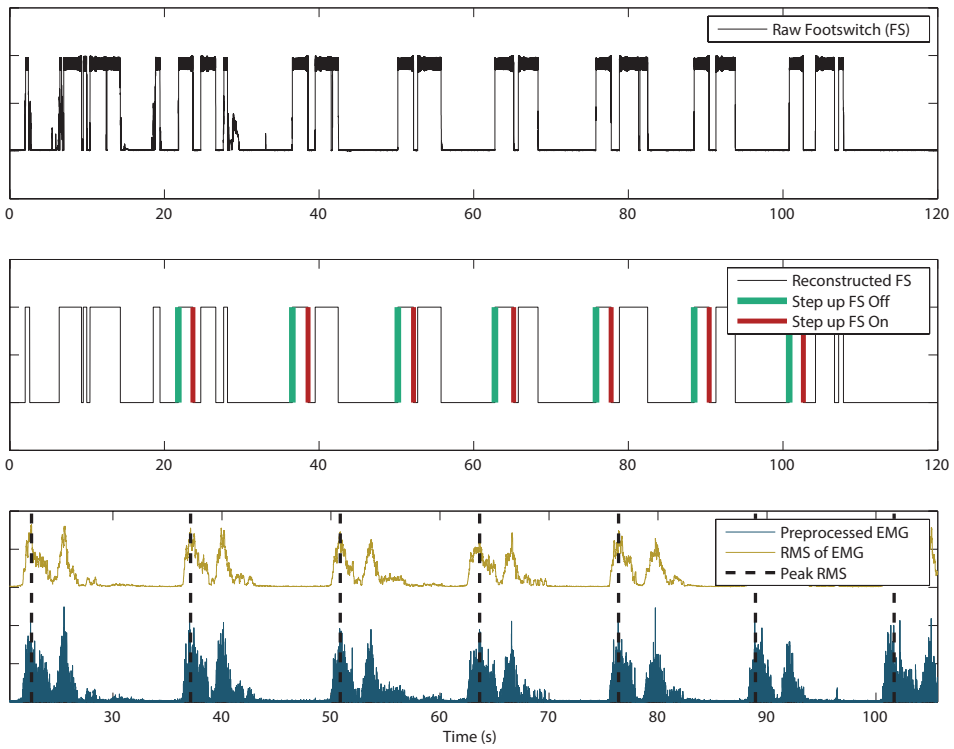

Figure 14: Plots illustrating the process of identifying step up phases, and maximum RMS value withing each stepping up phase. The top plot shows the raw footswitch signal, with noise in the form of unwanted small activations of the switch. The middle plot shows the reconstructed footswitch signal, with the beginning and end of the stepping up phases marked with green and red lines. Only the stepping up phases in the user selected time intervals will be marked. The bottom plot shows the filtered EMG signal and the result of the windowed RMS of the EMG signal. Based on the beginnings and ends of the stepping up phases, the maximum windowed RMS values are identifyed.

Recording MEPs from dynamic TMS

For the recording of 15 MEPs during the stepping task, the same stepping up routine was instructed to the subject, as during the configuration experiment. However this time the TMS would be activated by the footswitch plus a delay which was the latency computed in the configuration experiment. The program Signal was configured with the footswitch as a sweep trigger, and after the delay send a trigger to the TMS device. For safety reasons the subject was wearing a harness fastened to a rail under the ceiling. The TMS coil was put on the head of the subject and the weight of the cable was hold by an elastic rubber band attached to the rail. The subject was then instructed to perform 15 repetitions of stepping up, while EMG from TA was being recorded. The setup can be seen on figure 15.

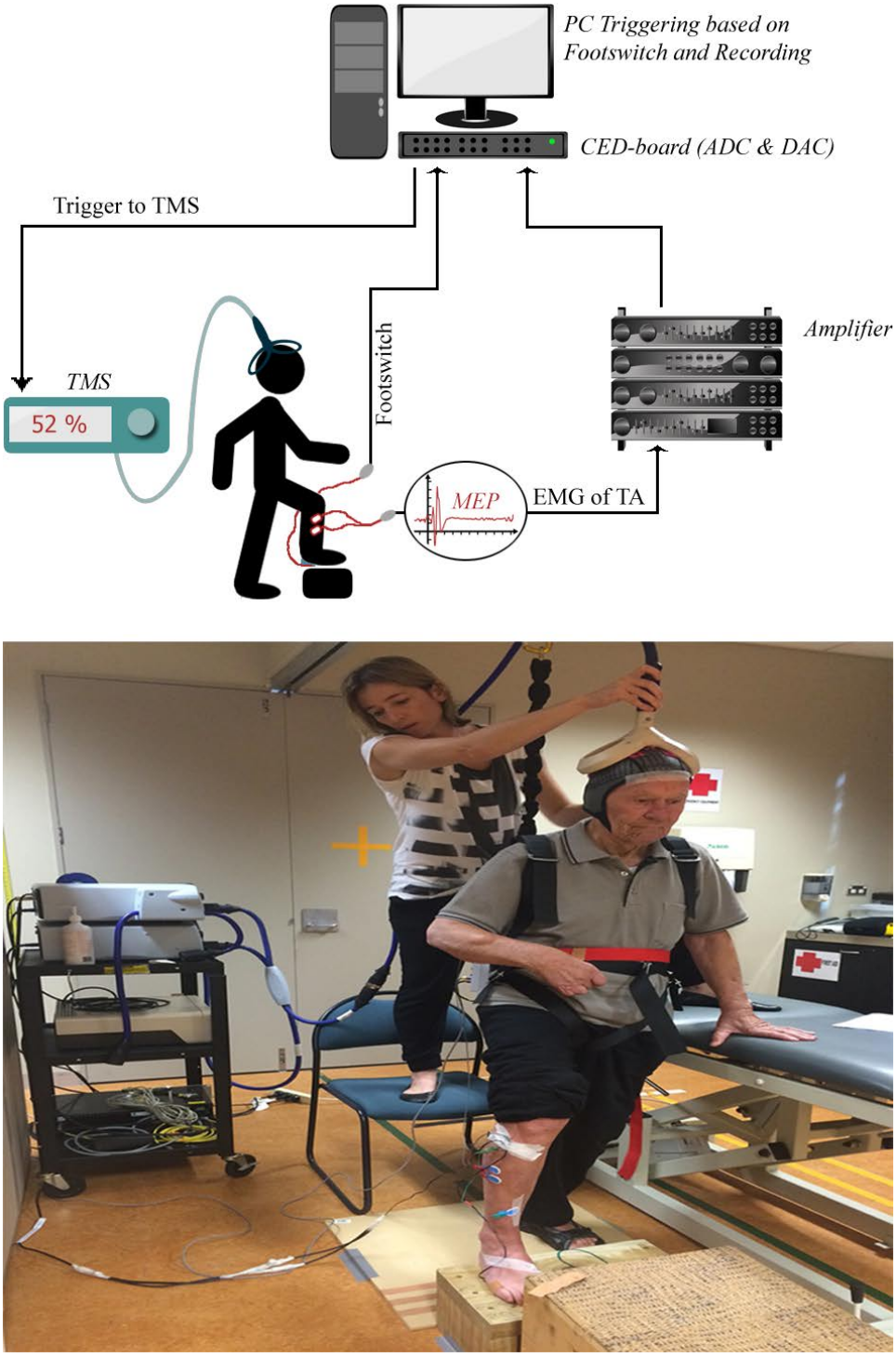

Figure 15: Illustration and picture of the experimental setup of the dynamic TMS session.

7 STROKE STUDY: DATA ANALYSIS

In order to analyse the collected data, features of interest needed to be extracted. From the TMS experiments MEPs were identified and then peak-to-peak amplitudes were extracted. Motion data captured via the motion capture system was preprocessed and kinematic features extracted.
As just a single subject was tested on in this experiment during the timeframe of the current project, descriptive statistics would only be used and no inferential statistics will be performed.

7.1 ANALYSIS OF 3D MOTION DATA

Collected motion data was processed in Qualisys Track Manager, where markers were labelled for all timeframes. If markers disappeared for short intervals due to being blocked from the cameras, the gaps was filled by a polynomial gap fill function in Qualisys Track Manager. Motion capture data was then exported from Qualisys Track Manager and opened by Visual3D. In Visual3D the static posture recording was used to create a gait body model from. The model was created based on the instructions in Visual3D's tutorial, [C-Motion, 2013]. The model consisted of segments such as thigh, foot, pelvis etc, that were defined by markers. Figure 16a shows the constructed 3D body model.

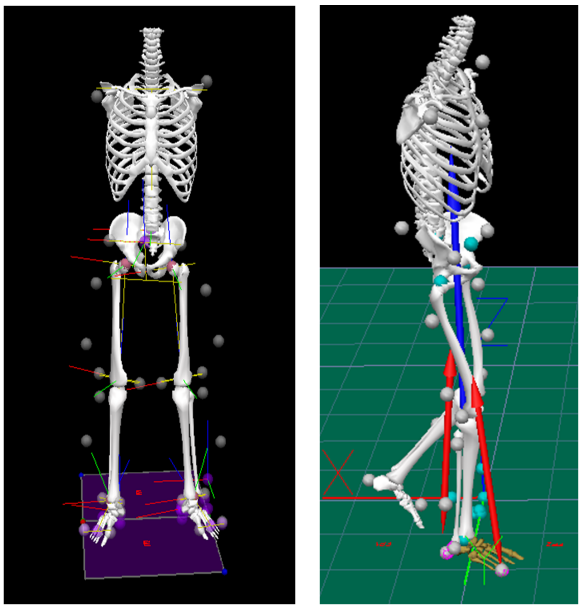

Figure 16: a) Picture of 3D body constructed from 3D marker data. b) Picture of posture during the identification of gait cycle events. The timeframe the picture was taken from shows a 'left toe off' event.

Once the model was created, a template was saved to use for the other files. The height and weight of the subject were inserted into the model. Then the model was applied to the files containing gait data constituting 10 gait cycles in total. The gait cycle events 'right heel strike' (RHS), 'left toe off' (LTO), 'left heel strike' (LHS) and 'right toe off' (RTO) were manually identified in the gait data files with the purpose of extracting specific gait event related measures. The recorded ground reaction forces were used in the identification of gait cycle events. Figure 16b shows a walking posture during the identification of gait cycle events. The events were then used to divide each marker trajectory into two sets of 10 individual gait cycles, LHS to LHS and RHS to RHS. For each marker an average was created of the 10 individual gait cycles, to obtain the average movement of each marker. The average was smoothed with a 5 Hz low pass filter, to leave out fine-scale structures. The applied 3D body model in Visual3D made it finally possible to extract gait features such as step length, stance/swing ratio, ankle rotation etc.

Features were plotted as functions of the normalised gait cycle from 0 to 100 %. Figure 17 shows some preliminary results of the Pre measure from the stroke subject. The knee flexion/extension and ankle plantarflexion/dorsiflexion angles are plottet for left side (unaffected) in green, and right side (affected) in red. A database containing gait data from 100 healthy subjects collected at Auckland University of Technology were plotted in the background to assess how gait of stroke patients deviate from gait of healthy people. The figure reveals as expected that for the unaffected side, the same shape of the movement is seen, although with a lower amplitude and timing. While for the affected side there is almost no movement of the ankle and knee joint, compared to the healthy data. This preliminary analysis showed that these two angles seemed influenced by the lower limb motor impairment of the stroke subject.

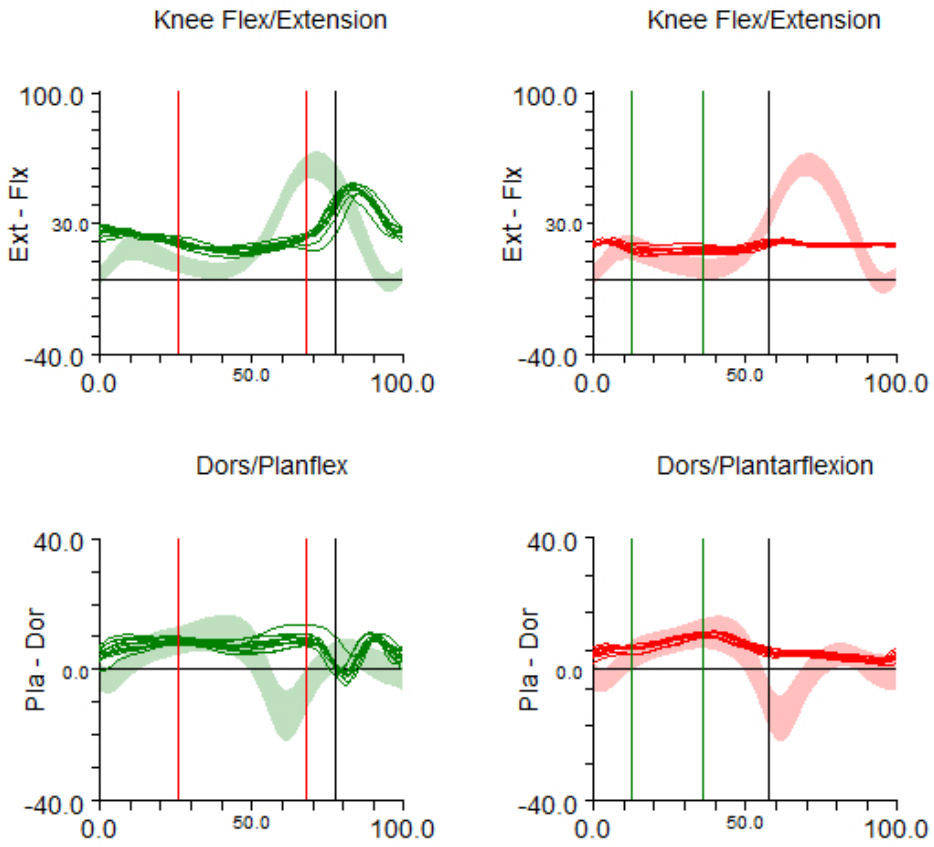

Figure 17: Preliminary results from the Pre gait analysis session of single stroke subject. Knee flexion/extension and ankle plantarflexion/dorsiflexion angles are plottet for left side (unaffected) in green, and right side (affected) in red. On the x-axes is the normalised gait cycle in percent. Normative data from 100 healthy subjects are plottet in the background of each of the 4 plots. Point 0.0 on the x-axis is the time of the heel strike of the respective body sides. The 3 vertical lines indicates contralateral toe off, contralateral heel strike and ipsilateral toe off.

Based on this ankle and knee rotation in the saggital plane were further analysed. On figure 18 ankle dorsiflexion/plantarflexion angle before the intervention, is plotted as a function of the normalised gait. The gait cycle events RHS, LTO, LHS and RTO are marked for both the left (unaffected) and right (affected) side. Two features were extracted for each side. The first feature was the range of motion between the 'toe off' and 'heel strike' events of the ipsilateral side. This span is marked by the dotted lines in green and red for the respective sides. The second feature was the maximum dorsiflexion increase. This was defined as the angle increment from the lowest angle of dorsiflexion after the ipsilateral 'toe off' event to the the maximum angle before the ipsilateral 'heel strike' event. This span is marked by two black dots for both left and right side.

The first feature will be refered to as 'ankleRangeOfMotion'. The second feature will be refered to as 'dorsiflexionIncrease'.

7.2 MEP PEAK-TO-PEAK AMPLITUDE EXTRACTION

During acquisition of TMS elicited MEP data, trials affected by errors, e.g. missing TMS stimulation, were tagged and excluded from analysis. This meant that up to 15

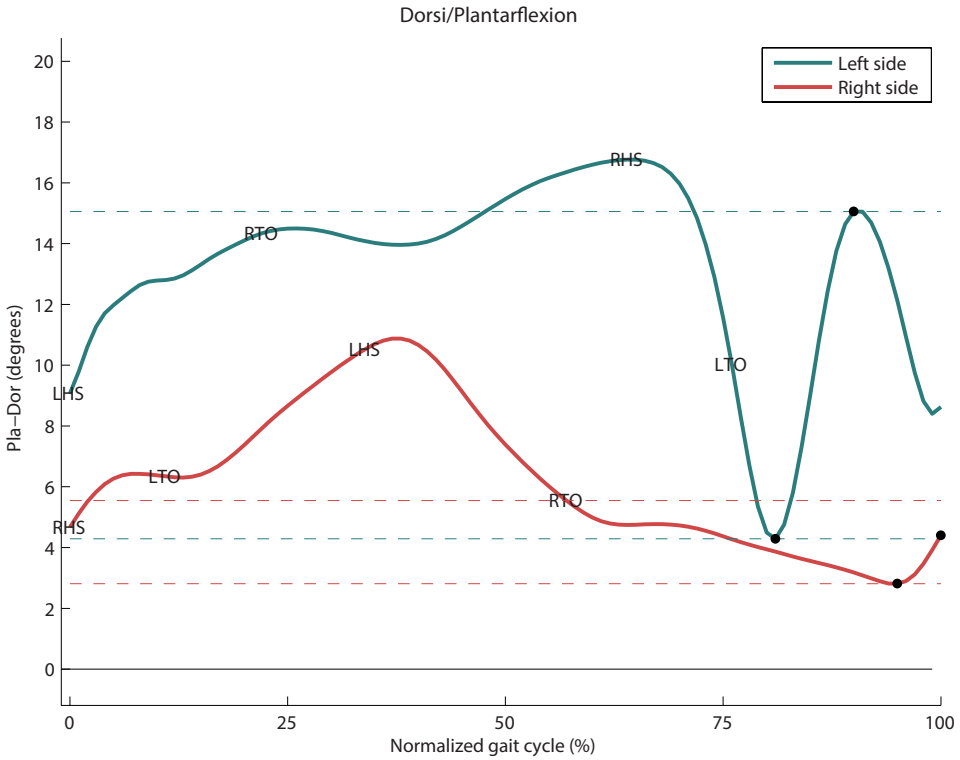

Figure 18: Plot of saggital dorsiflexion/plantarflexion angle from left and right side during an average gait cycle. Gait cycle events are marked by text tags. The feature 'ankleRangeOfMotion' is marked by the range of the dotted lines and the feature 'dorsiflexionIncrease' is marked by the range of the black dots.

trials were analysed for each TMS measure per session. For localisation of the maximum peak-to-peak amplitude of MEPs from the static and dynamic TMS measures, a window of 50 ms, starting 30 ms after the stimulation, was used. An average of up to 15 trials were created for each TMS measure.

Part III

RESULTS

After the collection, postprocessing and analysis, data will finally be presented in this part. With regards to the method, this part will first contain a chapter for the retention experiment and then one for the stroke experiment.

RETENTION STUDY: RESULTS

8

In this chapter results of the retention experiment will be presented. 10 healthy subjects completed the experiment with 15 TMS induced MEPs measured before the BCI PAS intervention and repeated 4 times after. The average MEP for each measurement time was calculated for each subject and visualised as boxplots on figure 19, to show the dispersion of the data.

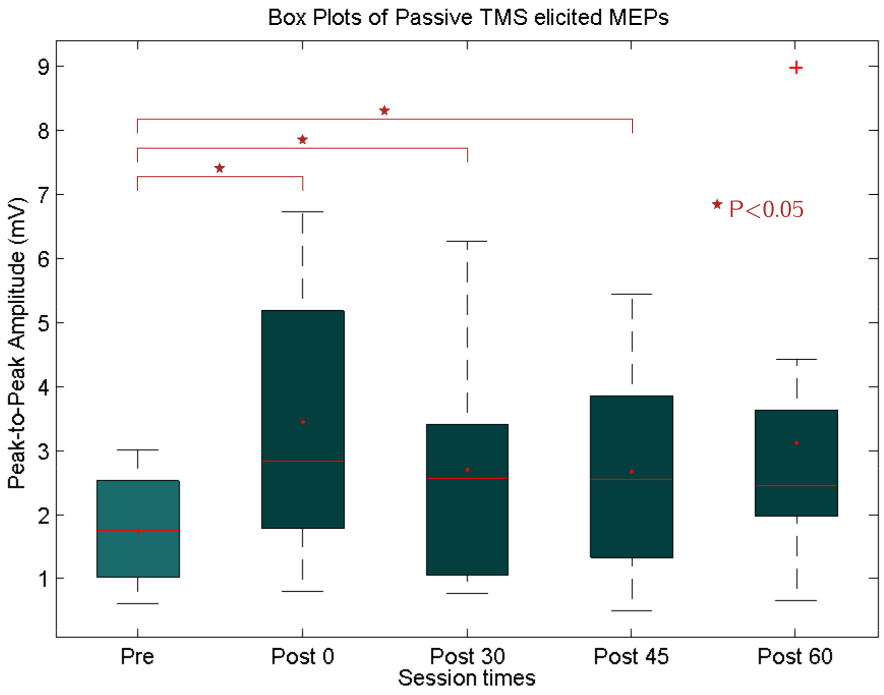

Figure 19: Boxplots of MEP peak-to-peak amplitude averages for each subject, for the 5 measurement times. Red horisontal lines are medians and the red dots are means. Significant differences from the Pre measurement are marked with stars.

For each boxplot, the red horisontal line is the median, the edges of the box are the first and third quartiles, the whiskers extend to 1.5 times the interquartile range from the box limits, and outliers are plotted individually if they are further away. The boxplots show variation between subject means which was also supported by calculated coefficients of variation which were 0.47, 0.63, 0.63, 0.58 and 0.74 for Pre to Post 60. The boxplots for Post 0, Post 30 and Post 45 showed medians above the interquartile range of the Pre measurement, which could indicate potentially significant increases in MEP peak-to-peak amplitudes. The amount of changes of the means from the Pre measurement to the 4 post measures is visualised in figure 20. The changes are shown in percentages from the Pre measure.

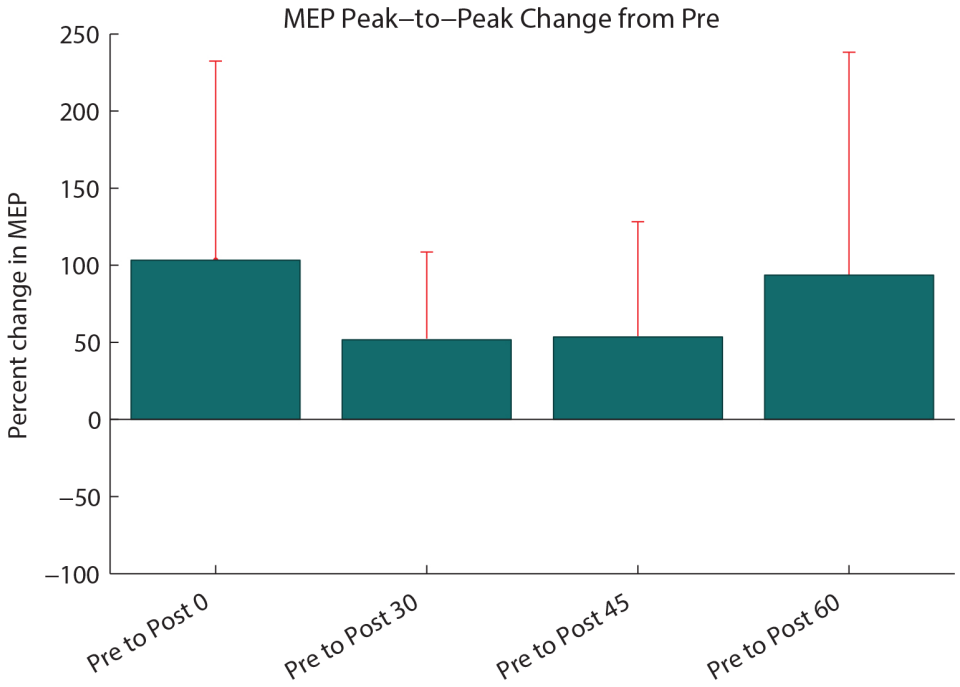

Figure 20: Barchart of the average percentage of MEP peak-to-peak amplitude change from the Pre measurement. The red errorbars demonstrate 1 standard deviation.

Figure 20 show that all the means of the post measurements increased after the interventions, with large standard deviations. The subject's means of the 4 post measures increased 103 %, 52 %, 53 % and 94 %.

For statistical analysis the software IBM SPSS Statistics was used. Each of the dependent measures Pre, Post, Post30, Post45 and Post60 were tested for normality. The Shapiro-Wilk test of normality revealed for Pre, Post, Post30, Post45 and Post60, the respective P-values: 0.731, 0.309, 0.339, 0.929 and 0.013. This means that all of the measurement times had normal distributions, except for Post60 where the null-hypothesis of normal distribution was rejected. Greenhouse-Geisser correction was used to due to non-sphericity, based on Mauchly's test of sphericity. Differences between the pre and post measures were analysed by a repeated measures one-way ANOVA statistics with a significance level of 0.05. The test of within-subjects effect of the time variable showed significance ($F_{2.39,21.51} = 4.26$, $P = 0.022$). As the P-value was significant and the main interest was to assess changes from the Pre measure, pairwise comparisons of the Pre measure and individual post measures were made. Post hoc tests revealed that the intervention elicited significant increases in MEP amplitudes for Post 0 (0.169 ± 0.062 mV, $P = 0.022$), Post 30 (0.095 ± 0.037 mV, $P = 0.029$) and Post 45 (0.092 ± 0.037 mV, $P = 0.033$). The change from Pre to Post 60 was not significant (0.137 ± 0.070 mV, $P = 0.081$).

STROKE STUDY: RESULTS

9

In this chapter results of the stroke experiment will be presented. A single stroke patient completed the experiment in the timeframe of this project. A range of different measures were used to assess the effect of the BCI PAS protocol. These measures were TMS elicited MEPs, clinical measures and instrumented gait analysis derived parameters.

9.1 TMS INDUCED MEPS UNDER STATIC AND DYNAMIC CONDITIONS

TMS was used during a static and dynamic condition. MEPs were captured and peak-to-peak amplitudes were extracted, with the aim of assessing changes in corticospinal excitability.

9.1.1 *Introducing measured MEPs*

Representative plots were created showcasing some of the collected data.

Figure 21 shows data collected during a static TMS measure. The top row shows two single MEPs recorded during a static TMS session. Both MEPs contains a spike located around 50 ms after the TMS pulse given at 0 ms, followed by a silent period. Left in the bottom row all MEPs from that session are plotted and an average line is illustrated. From this plot it can be seen that MEPs are accurately time locked to the eliciting TMS pulse. The plot in the right bottom corner shows force outputs for the session, from the TMS pulse at 0 ms to 80 ms. The force was generated by 10 % of MVC of the ankle joint. Black lines indicate the target force output range which was $10\% \pm 2\%$ and the mean of the trials is shown as a red line. As it can be seen, single trials in this session had a force level outside the target region. Across every session and all subject, the force level at the time of the TMS pulse was $12.65\% \pm 1.38\%$ of MVC.

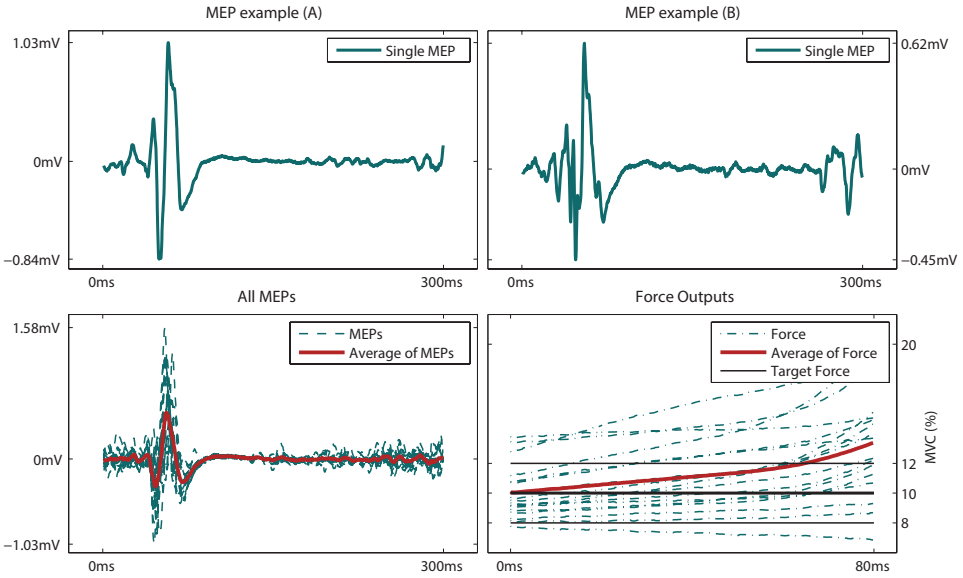

Figure 21: Data collected during a static TMS session. The top row shows two single MEPs. The bottom left plot shows all the MEPs from the session with a red average line drawn. The bottom right plot show force outputs during the session. A red average line is shown and the target region of $10\% \pm 2\%$ MVC is marked by black lines.

A result of peak-to-peak detection is shown on data, collected during a dynamic TMS session, on figure 22. The first two rows show single MEPs. The red circles mark the detected maximum and minimum amplitude. The third plot shows all the MEPs from the session and an average of them.

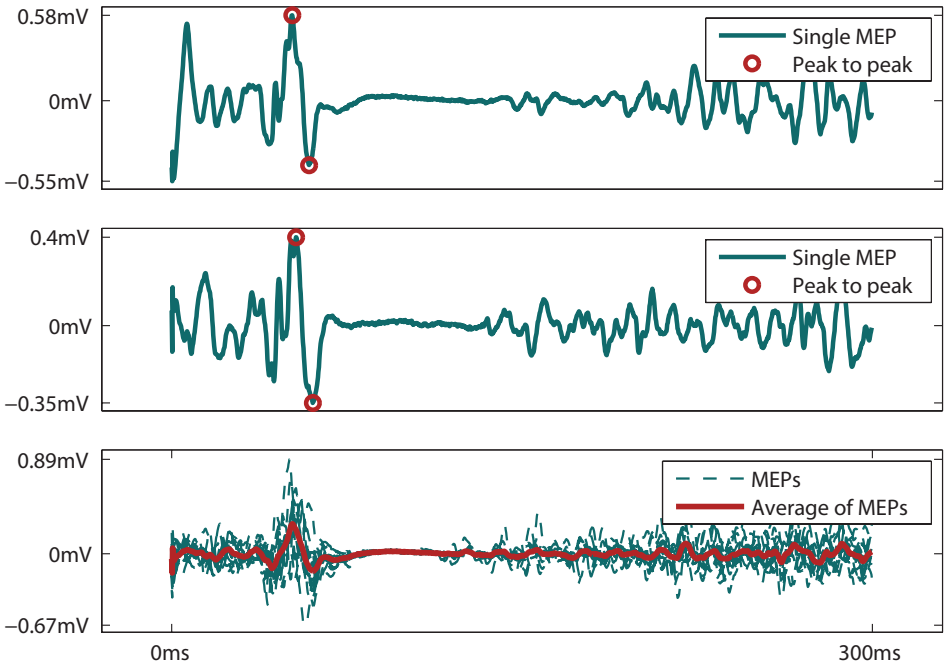

Figure 22: Data collected during a dynamic TMS session, with peak-to-peak amplitudes detected. The two first rows show single MEPs, with red circles marking the peak-to-peak amplitude. The bottom row shows all the MEPs plotted together and a red line illustrating an average of them.

9.1.2 *MEP peak-to-peak amplitudes during Static and Dynamic TMS*

TMS was applied and 14 peak-to-peak amplitudes were extracted from 6 sessions; Pre, Week 1, Week 2, Week 3, Week 4 and Post. This was done for both static and dynamic TMS. The obtained peak-to-peak amplitudes will be shown and analysed below, first those obtained from the static condition and then those from the dynamic condition. The results are showed as boxplots where the red horisontal line is the median, the edges of the box are the first and third quartiles, the whiskers extend to 1.5 times the interquartile range from the box limits. Outliers are plotted as red crosses individually if they are further away. Mean values are plotted with a red dot. During the 4 intervention week sessions, a baseline measure was taken before the intervention and a post measure after the intervention, to assess changes within session. The baseline and post measure from these intervention weeks are grouped together.
For both the static and dynamic TMS measure, coefficient of variance values were calculated for each of the 10 TMS measurement times, and averaged. The average coefficient of variance for TMS during the static measure was 0.48, and 0.27 for the dynamic.

Figure 23 show boxplots of the MEP peak-to-peak amplitude elicited by TMS during the static condition of a 10 % of MVC ankle dorsiflexion. The figure reveals a great difference between the Pre Week and the other measure times, as the Pre Week MEP amplitudes are approximately 3 times larger. The force output for this session was on average 15.45 % of MVC. The rest of the boxplots are looking relatively similar, with no visual change in median or mean over the 4 weeks of interventions. Small negative changes in MEP sizes from baseline to post measure, can be seen withing the sessions

Week 2 and Week 4. Generally it can be seen that except for the Pre measure, then the MEP amplitudes within a measure are with a relatively low spread and only a few outliers.

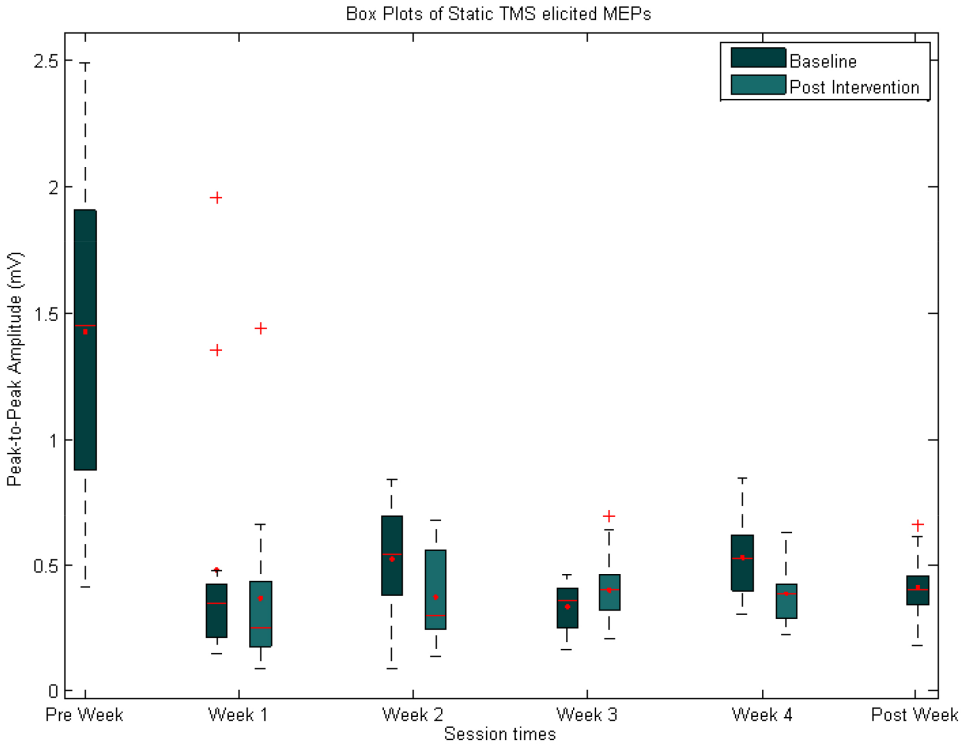

Figure 23: Boxplots of MEP peak-to-peak amplitudes elicited by TMS while performing 10 % MVC ankle dorsiflexion. The edges of the boxes are the first and third quartiles, the whiskers extend to 1.5 times the interquartile range from the box limits and outliers are plotted as red crosses individually if they are further away. Medians are marked by red horisontal lines and means are marked by red dots. MEPs were measured in the week before the interventions started (Pre Week), in the start of each intervention week (Week 1-4) and the week after the intervention weeks (Post Week). During the intervention week, pre and post measures were taken.

Figure 24 shows boxplots of the MEP peak-to-amplitude elicited by TMS during the dynamic condition of a stepping task. A negative difference can be seen from the Pre measure to the Post measure with no overlap of the interquartile ranges. Withing sessions no major changes but a good similarity can be seen except for Week 4, where a 20 % decrease in mean was seen from Baseline to Post. As for static TMS, the MEP amplitudes within a measure are with a relatively low spread and only a few outliers.

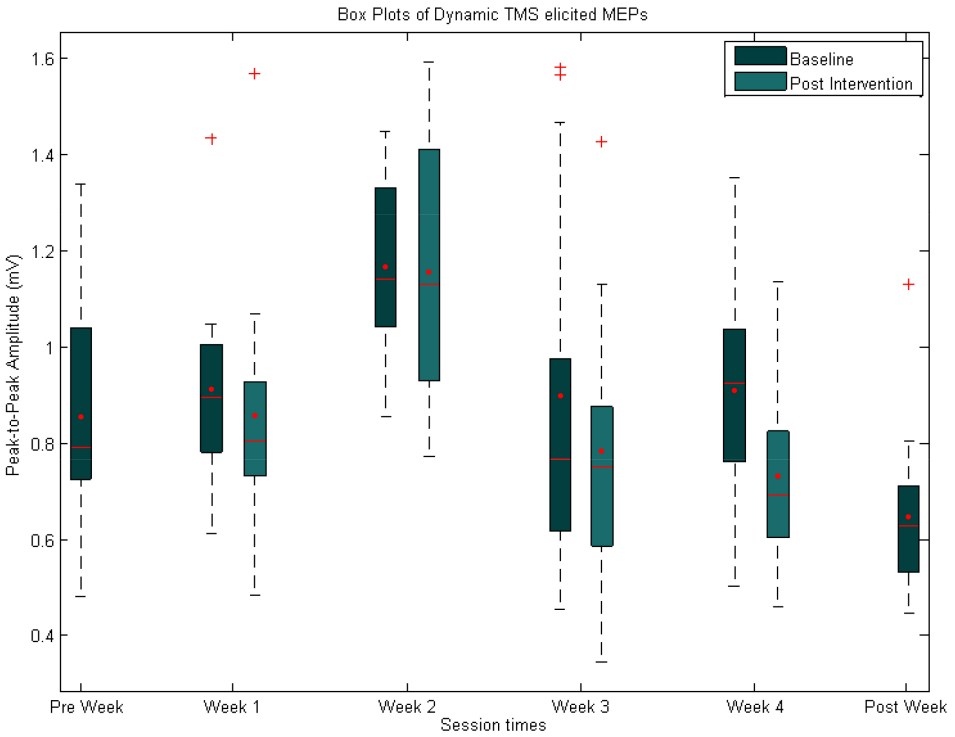

Figure 24: Boxplots of MEP peak-to-peak amplitudes elicited by TMS during the dynamic condition of stepping up. The edges of the boxes are the first and third quartiles, the whiskers extend to 1.5 times the interquartile range from the box limits and outliers are plotted as red crosses individually if they are further away. Medians are marked by red horisontal lines and means are marked by red dots. MEPs were measured in the week before the interventions started ('Pre Week'), in the start of each intervention week ('Week 1-4') and the week after the intervention weeks ('Post Week'). During the intervention week, pre and post measures were taken.

9.2 CLINICAL MEASURES

Clinical functional measures were collected with the aim of assessing changes in functional abilities after the intervention. These were MVC, 6 m comfortable walking speed, 6 m fast walk and a step test. These tests, except for MVCs, were carried out the week before the 4 intervention weeks and 3 days and 10 days after the 4 intervention weeks. MVCs were collected before the 4 weeks of interventions and in the beginning of each intervention week. Figure 25 shows the results of the clinical measures.

	Increase from Pre (%)				
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Post**
Maximum voluntary contraction (V)	19.811	17.925	144.811	55.189	5.189

	Gait speed (m/s)				
	Measure1	**Measure2**	**Measure3**	***MEAN***	***STD***
6m walk **comfortable** Pre	0.348	0.340	0.350	***0.346***	***0.006***
6m walk **comfortable** Post +3 days	0.310	0.310	0.298	***0.306***	***0.007***
6m walk **comfortable** Post +10 days	0.339	0.329	0.328	***0.332***	***0.006***
6m walk **fast** Pre	0.354	0.371	0.380	***0.368***	***0.014***
6m walk **fast** +3days	0.350	0.343	0.345	***0.346***	***0.004***
6m walk **fast** +10days	0.358	0.341	0.338	***0.346***	***0.011***

	Steps completed in 15 s	
	Affected leg	Unaffected leg
Step test Pre	0	0
Step test +3days	0	1
Step test +10days	0	2

Figure 25: These tables show the results of the clinical TA motor function related measures.

The MVCs showed no clear tendency of increasing or decreasing by time. Comparing the Pre to the Post value an increase of 5.2 % were found, but with a standard deviation of 56.9 % points.

The 3 measures of comfortable and fast walking speed for the Pre, Post 3 days and Post 10 days, showed low standard deviations. No major changes in walking speeds were found between the three measurement times.

The results from the stepping test showed that the subject was not able to perform a step up without aid either by the affected leg or unaffected leg in the pre measure. In the Post 3 days measure the subject was able to perform 1 step up of the affected leg and in the Post 10 days measure the subject performed 2 step ups of the affected leg.

9.3 PARAMETERS FROM 3D GAIT ANALYSIS

A 3D motion capture system was used to collect gait data. Markers on body landmarks were tracked while the subject performed normal walking and stepping. A model consisting of body segments was generated and kinematic data was extracted. Only the data from the walking trials was included in this report, and gait features was selected dependent on their relevance to TA motor function. Movement of the ankle and knee joint was further analysed. The measures were collected before the 4 weeks of interventions and after, to assess changes. 10 to 13 gait cycles were collected for each side in the Pre and Post measurement, and averaged for the respective sides.

In Appendix A, section A.1 spatiotemporal gait parameters from the Pre and Post measurements are showed. Step length for the affected and unaffected side was 0.28 m and 0.16 m in Pre, and 0.27 m and 0.14 m for Post. This means that the step length ratio moved from 1.75 in Pre to 1.93 Post. The $affected/unaffected$ ratio of $SwingTime/StanceTime$ in the gait cycle was in Pre 2.48 and 2.64 in Post mean-

ing that the *SwingTime*/*StanceTime* assymmetri between the left and right side increased. The double limb support time Pre to Post changed from 0.47 s to 0.46 s, right initial double limb support time changed from 0.17 s to 0.13 s and right terminal double limb support time changed from 0.30 s to 0.33 s.

9.3.1 *Further analysis of specific individual gait parameters*

The three specific gait parameters that were further analysed were ankleRangeOfMotion, dorsiflexionIncrease and kneeRangeOfMotion during the swing phase in the gait cycle. The results can be seen in Appendix A, section A.2, where data from 10 gait cycles, for each parameter, each side, Pre and Post intervention phase are shown. The mean values from these tables are extracted and compared between Pre and Post for each side and shown on figure 26. The results show for the unaffected side no major change in ankleRangeOfMotion or dorsiflexionIncrease, but a decrease in kneeRangeOfMotion of 14.74 degrees (38.4 %) from Pre to Post with low coefficients of variance (0.06 and 0.15). For the affected side, positive changes were seen for ankleRangeOfMotion and dorsiflexionIncrease from Pre to Post. AnkleRangeOfMotion increased by 1.07 degrees (32.6 %) and a dorsiflexionIncrease by 2.34 degrees (131.5 %). KneeRangeOfMotion decreased by 1.81 degrees (29.7 %). The coefficients of variance for the affected side were all below 0.23, except for the Pre measure of dorsiflexionIncrease which was relatively high (0.71).

Summary of Kinematic Gait Angles (degrees)

	Left			Right		
	Pre	Post	Difference	Pre	Post	Difference
Ankle Range of Motion	11.03	11.82	0.79	3.28	4.35	1.07
Dorsiflexion Increase	10.94	11.40	0.46	1.78	4.12	2.34
Knee Range of Motion	38.37	23.63	-14.74	6.10	4.29	-1.81

Figure 26: Summary of the kinematic gait parameters ankleRangeOfMotion, dorsiflexionIncrease and kneeRangeOfMotion located in Appendix A, section A.2. The figure contains a summary of the mean values from left and right side, pre and post intervention and differences between them.

Part IV

SYNTHESIS

In this part, results gathered from the two individual experiments will be evaluated. The aim of the synthesis is to summarise and interpret the findings, discuss methodological advantages and disadvantages, future work and implications.

DISCUSSION

10

10.1 SUMMARY OF FINDINGS

This project aimed to set up a study able to assess neurophysiologic and functional changes, from a BCI PAS protocol applied for 4 weeks, on a stroke population. Furthermore it of interest to find out how long time after an intervention, potential changes can be expected to last. This was in order to investigate the clinical relevance of the outcome of the used technique and to be able to advice on future implications, such as priming before physiotherapy.

The results of the retention study showed a significant increase in corticospinal excitability directly after the intervention, 30 minutes and 45 minutes after. These results suggest that the BCI PAS intervention could be a tool for priming of the corticospinal tract before a session of physiotherapy, which is important for implications.
It was possible to set up and design a BCI PAS protocol with 4 weeks of interventions, for assessment of neurophysiologic and functional changes and test it on a stroke patient. The results are based on a single subject and should therefore not be generalized much upon. However the tendencies found from the measures, and their usefullness in assessing the intended neurophysiologic and functional states, will be evaluated.
The results of the stroke study showed no consistent neurophysiologic changes measured by corticospinal excitability projection to the TA. A tendency towards improvement in some of the TA dependent functional measures was found, such as stepping ability and gait kinematics. 3D gait analysis showed to be a valuable tool in assessing the impact of functional changes on specific gait related parameters. The most prominent change in gait parameters was a 131.5 % increase in foot lift, of the affected side during the swing phase. The proposed method of examining corticospinal excitability during stepping up, showed lower variance in trials than when corticospinal excitability was measured during a contraction of 10 % MVC, supporting previous findings.
These inpretations, the implications and limitations of this project and future work, will be assessed in the following sections.

10.2 INTERPRETATIONS OF NEUROPHYSIOLOGIC AND FUNCTIONAL FINDINGS

As it only was possible to get one stroke patient through the BCI PAS experiment during the timeframe of the current project, no inferential statistics was made. It means that generalisation of results can not be made, but only tendencies can be described, the measure itself evaluated, and future directions for studies can be suggested. In this section findings and interpretation of these from the neurophysiologic and functional measures, will be made.

10.2.1 *Neurophysiologic Measures*

Excitability of the corticospinal tract to the TA muscle was quantified during a static and dynamic task by use of MEP ilicited by TMS.
There is reason to believe that the 'Pre Week' measurements during the static TMS measure, figure 23, was affected by errors. The 'Pre Week' had peak-to-peak amplitudes approximately 3 times larger than the other measurement times, which could be explained by the higher level of contraction found during this measure, which was 15.45 % of MVC opposed to 12.35 % on average on the other measurement times. Due to this, the baseline measure from 'Week 1' was used instead of the 'Pre Week' measure, when assessing changes pre to post intervention phase. Problems with controlling MVC will be discussed in section 10.3.
The results indicate no consistent changes from the 'Pre Week' to the 'Post Week', or 'Pre' to 'Post' within invervention sessions. This was not in accordance with what was found in the carried out retention experiment, or in a previous study testing the same BCI PAS intervention on healthy subjects, [Mrachacz-Kersting et al., 2012]. In that study significant increases in corticospinal excitability were found, [Mrachacz-Kersting et al., 2012]. Various reasons could explain why no change in corticospinal excitability was found in the tested patient of the current study. The patient could have been a non-responder due to a high age and potential inability to keep a high attentional level, as these factors influence potential for induction of plasticity, [Ridding and Ziemann, 2010]. The amount of correctly paired electrical stimulations could also have been too low, as the value of PN was seen changing from 150 ms before the cue to 150 ms after the cue, during the weeks.
The current study showed that it was possible to measure MEPs during a stepping task for a stroke patient. The dynamic TMS measure showed a low (0.27) coefficient of variance compared to the static TMS measure (0.48). This result is in accordance with other studies investigating the reliability of MEPs measured during a functional task, [Signal, 2014; Van Hedel et al., 2007].

10.2.2 *Functional Measures*

Functional changes over the course of the experiment were assessed with clinical functional measures, 3D gait analysis and MVCs. The clinical measures consisted of standardised tests for gait speed and stepping ability. The clinical measures for gait speed during comfortable and fast walking reavealed no major changes from 'Pre' to 'Post 3 days' and 'Post 10 days'. The results of the step test showed improvement in steps performed in 15 seconds of the paretic leg, from 'Pre' (0 steps) to 'Post 3 days' (1 step) and 'Post 10 days' (2 steps). This change in step test score could be a result of improvement in lower extremity motor control and flexion, [Mercer et al., 2009].

The 3D gait analysis made it possible to analyse a large group of spatiotemporal and kinematic parameters. A few of these parameters more closely related to TA motor control were selected for further analysis. Spatiotemporal parameters has been most oftenly used in the clinic to evaluate gait of stroke patients. The study of [Patterson et al., 2010] investigated gait symmetry of healthy subjects and chronic stroke patients. Upper boundary values for different spatiotemporal parameters of 81 healthy subjects

were found, with a 95 % confidence interval, and mean values of these parameters for 161 stroke patients were defined. Comparing these values to those obtained from the 3D gait analysis in this study, it can be seen that the gait of the tested stroke patient would be more similar to the gait of the stroke group in the mentioned study. The mean $SwingTime/StanceTime$ ratio for the stroke group in Patterson et al. [2010] was 1.34 ± 0.43, while the upper 95 % confidence interval for the healthy group was 1.11. The $SwingTime/StanceTime$ ratio found in this current study was 2.48 Pre and 2.64 Post, meaning that a major asymmetry was present for the subject, even compared to other stroke patients, and that this asymmetry did not improve after the BCI PAS protocol. The same was apparant for the step lenght symmetry between affected and unaffected leg which was measured to be 1.75 in Pre and 1.93 Post. The average step length asymmetry for stroke patients was in the study of Patterson et al. [2010] 1.12 ± 0.16. The double support time ratio was for the test subject in the current study found to change from 1.76 Pre to 1.94 Post, also indicating increasing asymmetry in the gait cycle. Summarising the results of these spatiotemporal parameters it can be seen that an inceasing asymmetry was found in the gait after the 4 weeks intervention phase. The $SwingTime/StanceTime$ parameter, gait speed and step length are closely related, while double support time is not related to other parameters and may provide unique gait information, [Patterson et al., 2010].

Of the kinematic parameteres, only parameters from the sagittal plane were evaluated. This was because the results showed great variations from the affected to unaffected side in this plane, and as the rotation of the ankle that TA is involved in, operates in that plane. The sagittal plane was also found in the study of Olney et al. [1994] to be the plane which contains most of the deviations found in hemiplegic gait. The sagittal kinematic parameters analysed further were ankle rotation and knee rotation. Would any changes be found in ankle rotation due to increased TA motor control, it could influence the knee rotation, as toe clearence often is reduced during swing in hemiplegic gait. Two features of the sagittal ankle rotation were extracted and compared Pre to Post, ankleRangeOfMotion and dorsiflexionIncrease. AnkleRangeOfMotion was defined as the total range of motion of the ankle joint from the ipsilateral 'toe off' event. DorsiflexionIncrease was defined as the maximum dorsiflexion, after the maximum point of plantarflexion after ipsilateral 'toe off'. For the affected side ankleRangeOfMotion increased by 1.07 degrees (32.6 %) and dorsiflexionIncrease increased by 2.34 degrees (131.5 %), indicating a better ability of dorsiflexing after toe off of the affected side. KneeRangeOfMotion was the knee equivalent of the ankleRangeOfMotion. This feature decreased by 1.81 degrees (29.7 %) for the affected leg Pre to Post, which could coincide with the small decrease measured in swing time of the affected leg.

MVCs were measured in the pre intervention week, at the beginning of the 4 intervention weeks and in the post intervention week. An increase of 19.8 % was seen from the 'Pre' measurement to 'Week 1'. No intervention had been performed between these measurements why the increase questions the reliability of MVC as a functional measure in this experiment. A consistent tendency of change due to interventions could not be seen.

10.3 METHODOLOGICAL CONSIDERATIONS AND FUTURE WORK

Tendencies of functional changes were found, but as it was only 1 subject and as no control had been performed, it can not be said whether those changes are due to the intervention, variability in measures or uncontrolled variables. One of those variables is motor skill training during the protocol, such as walking tests, stepping tests, and ankle dorsiflexions during the BCI interventions. A control group is therefore needed to account for these variables. The choice of control group is especially important for studies investigating neuroplastic changes, as this is influenced by various factors such as motor skill training and subject characteristics, [Ridding and Ziemann, 2010], [Pascual-Leone et al., 1995]. The study of Ramos-Murguialday et al. [2013] found promising functional improvements, from a BCI neuromodulation protocol pairing sensory rhythm desynchronisation with passive arm and hand movements from an orthosis. However the control group used, received randomly timed feedback from the orthosis, which could result in long term depression, [Wolters et al., 2003]. With the proposed double-blinded randomized controlled trial carried out on 20 stroke patients, of which 10 would be placebo-controls, it would be possible to isolate the effect of the intervention, [Castro, 2007]. The developed experimental protocol makes it possible to keep subjects blinded and make the only difference between the groups be whether they receive timed electrical stimulation or no stimulation.

A limitation in the experimental protocol important to consider, is the deviations found in the level of MVC during the static TMS measure. The aim was to have the subject hold an isometric contraction of 10 % MVC. Due to technical problems with the hardware and software used to control triggering of the TMS pulse, the force level deviated from trial to trial and was not as controlled as intended. This means that the results of the static TMS measure would be affected by this. TMS during an isometric 10 % MVC has been found to be a reliable measure in healthy people, with low measurement standard errors, making it a good measure to assess changes due to interventions, [Cacchio et al., 2011]. The intra-session test-retest reliability, of MEP amplitude in the paretic side in stroke patients, has been found to be good, [Signal, 2014]. However for inter-session the reliability has been found to be poor, [Signal, 2014], [Cacchio et al., 2011], [Wheaton et al., 2009]. An alternative to using TMS while performing an isometric contraction, could be the use of TMS during a functional task such as stepping, as was used in this current study. Future studies investigating the test–retest reliability of this measure is important for understanding if measured changes could be induced by the treatment or are due to variability in the measure. Good inter-session test-retest reliability has however been found for MEP amplitudes obtained during threadmill walking, [Signal, 2014]. If this can be confirmed by future studies, then the proposed protocol in this project could be simplified and shortened. To assess changes within intervention sessions, TMS while performing an isometric contraction could be used. TMS in a stepping or walking task could be used to assess changes between sessions.

10.4 IMPLICATIONS

This project proves that an experiment can be designed for assessing neurophysiologic and functional changes from a BCI PAS protocol on stroke patients. The project showed that a chronic stroke patient can be physically and mentally able to go through a 7 week experimental protocol, with sessions varying in duration from 25 minutes to 3 hours and requiring physical activity and mental focus. The used reseach design makes it possible to control the experiment with an active control group, so that the effect of the intervention can be isolated more. Another part of the project showed that 50 trials of the BCI PAS protocol, lead to significant increases in corticospinal excitability directly after the intervention, 30 minutes and 45 minutes after. This suggests that a future application for the BCI PAS therapy in the clinic could be as a priming intervention to increase corticomotor excitability prior to physiotherapy, which has been a success with a similar protocol, [Ramos-Murguialday et al., 2013]. Priming techniques that so far have been investigated include repetitive TMS, transcranial-direct-current-stimulation and motor imagery, [de Vries and Mulder, 2007; Jackson et al., 2001; Stinear et al., 2008; Woldag et al., 2006]. Using the BCI PAS protocol for priming would mean an alternative to TMS, which is a technique that can not safely be applied to every stroke patient, [Rossi et al., 2009]. The possibility of using the BCI PAS protocol as priming in an intervention with traditionel physiotherapy, means that future trials can use the 'best-available-therapy', in form of physiotherapy, as a control group. This would mean avoiding ethical concerns of not providing treatment, and opportunity for providing evidence of efficacy over an existing treatment, [Castro, 2007].

11 CONCLUSION

The aim of the this current project was to set up a study design for a future clinical trial of BCI PAS, testing its feasibility and effectiveness on lower extremity recovery of stroke patients. More specifically it was of interest to answer the following two research questions:

How can a 4 week BCI PAS training paradigm be set up to assess neurophysiologic and functional recovery in stroke patients, using acknowledged functional measures, 3D gait analysis and TMS elicited MEPs?

How is the retention of potential changes in corticospinal excitability from the proposed BCI PAS protocol?

This current project proposed a study design of a double-blinded randomised controlled trial, and tested it on a single stroke patient, in the form of a case study. The project showed that a chronic stroke patient can succesfully go through a 7 week experimental protocol, without any physical or mental limitations. Neurophysiologic recovery was assessed using TMS while holding a low level contraction. TMS was also tested in a stepping task and revealed that it potentially could be more reliable in assessing changes between sessions. 3D gait analysis proved to be a measure able to assess locomotor recovery in a stroke patient.
The results showed no consistent neurophysiologic changes, but an indication of improvement was found in stepping ability and gait kinematics. However, as the protocol was tested on just a single stroke patient, further research is needed.

Investigation of retention revealed a significant increase in corticospinal excitability, directly after the intervention consisting of 50 pairings of motor imagination with electrical stimulation at CPN. This positive effect was still significant 45 minutes after the intervention. These results suggest that a future application of the BCI PAS intervention could be as a priming intervention prior to physiotherapy, if the same results are found in a stroke population.

Part V

APPENDIX

APPENDIX A – ADDITIONAL RESULTS

A.1 SPATIOTEMPORAL GAIT PARAMETERS

Figure 27 and 28 shows different spatiotemporal gait measures, for Pre and Post respectively.

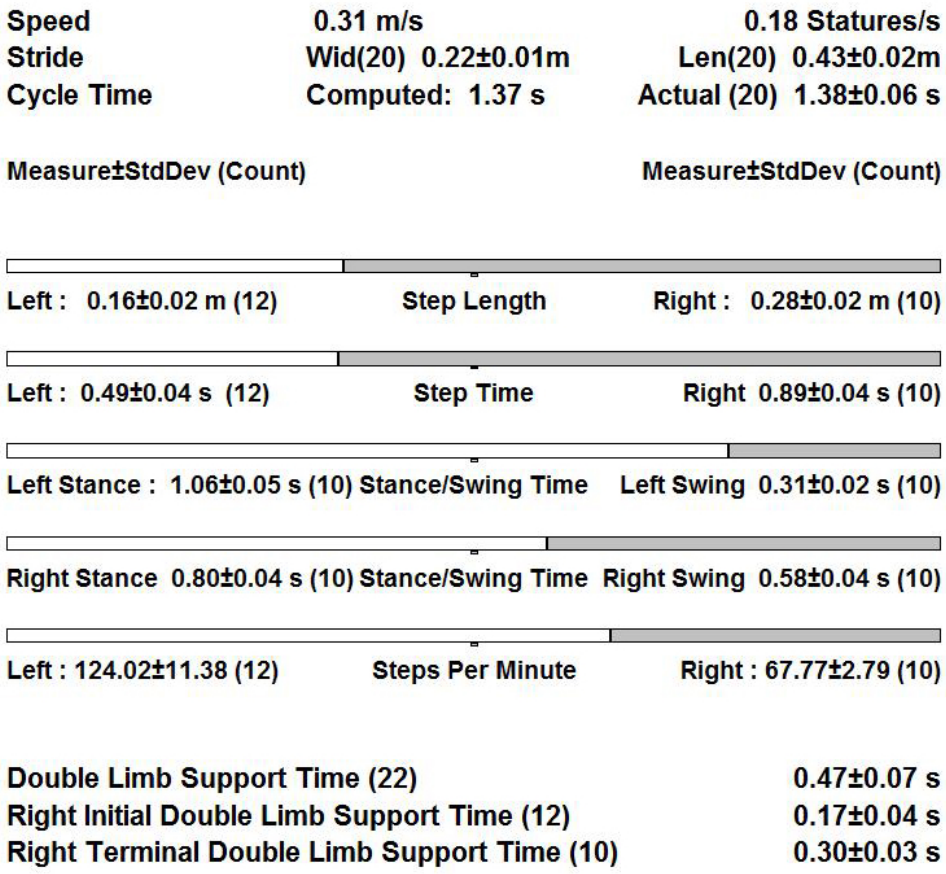

Figure 27: Pre intervention weeks spatiotemporal gait measures.

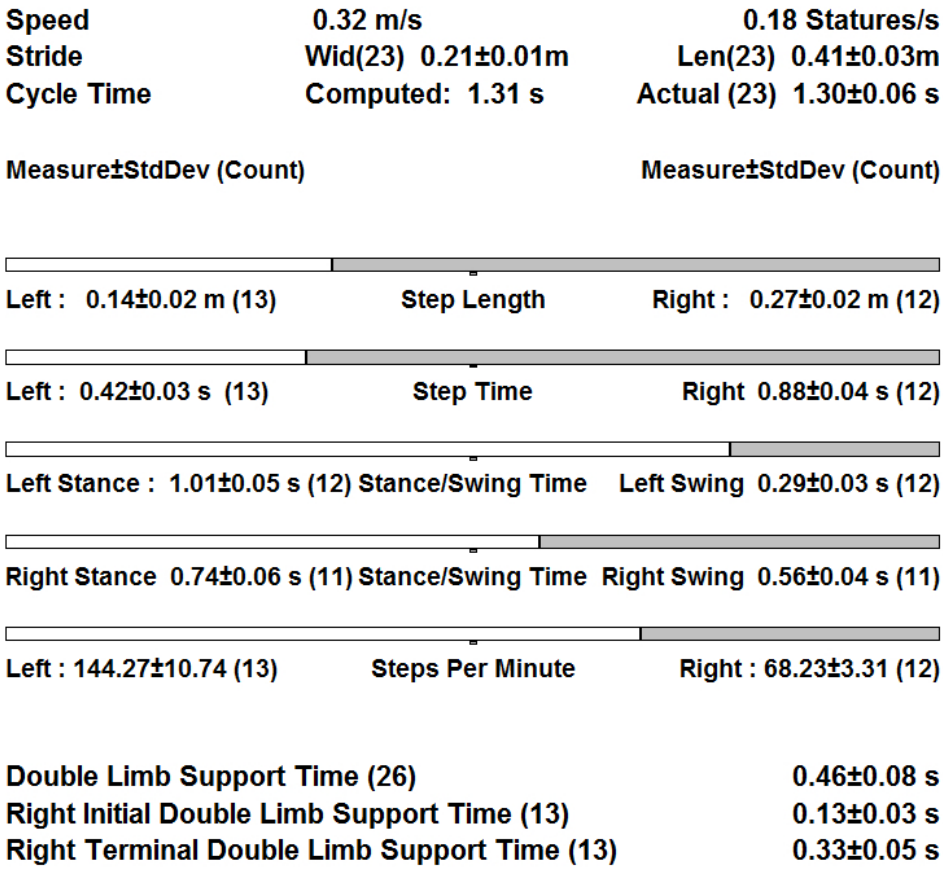

Figure 28: Post intervention weeks spatiotemporal gait measures

A.2 SELECTED KINEMATIC GAIT PARAMETERS

Figure 29 and 30 shows 'ankleRangeOfMotion' from 10 gait cycles for Pre and Post respectively.

ankleRangeOfMotion Pre left	min	max	diff
1.00	5.62	14.69	9.07
2.00	3.11	14.31	11.19
3.00	3.24	15.80	12.56
4.00	4.76	14.88	10.12
5.00	8.66	15.19	6.53
6.00	5.11	15.91	10.80
7.00	3.04	16.84	13.80
8.00	3.38	16.64	13.27
9.00	1.63	14.13	12.50
10.00	3.47	13.90	10.43
		mean	11.03
		std	2.17
		CoF	0.20

ankleRangeOfMotion Pre right	min	max	diff
1.00	3.60	7.07	3.47
2.00	3.23	6.59	3.36
3.00	2.89	5.90	3.01
4.00	2.98	5.70	2.72
5.00	2.49	5.54	3.05
6.00	2.62	6.81	4.19
7.00	2.99	5.10	2.10
8.00	1.11	5.35	4.25
9.00	2.67	5.20	2.53
10.00	1.75	5.90	4.15
		mean	3.28
		std	0.74
		CoF	0.23

Figure 29: AnkleRangeOfMotion angle from 10 gait cycles of the Pre measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

ankleRangeOfMotion Post left	min	max	diff
1.00	-0.53	9.08	9.61
2.00	-3.40	10.77	14.16
3.00	-4.60	10.51	15.11
4.00	-2.29	10.75	13.04
5.00	4.33	13.73	9.40
6.00	-0.47	9.83	10.30
7.00	-1.86	10.89	12.75
8.00	0.40	11.40	11.00
9.00	-1.48	10.08	11.56
10.00	-1.82	9.47	11.29
		mean	11.82
		std	1.91
		CoF	0.16

ankleRangeOfMotion Post right	min	max	diff
1.00	-1.24	3.00	4.24
2.00	-1.73	2.45	4.19
3.00	-1.14	2.13	3.27
4.00	-1.59	3.58	5.18
5.00	-1.17	2.58	3.75
6.00	-2.35	2.51	4.86
7.00	-1.13	3.29	4.42
8.00	-1.60	4.10	5.70
9.00	-2.08	1.44	3.52
10.00	-2.40	2.00	4.40
		mean	4.35
		std	0.75
		CoF	0.17

Figure 30: AnkleRangeOfMotion angle from 10 gait cycles of the Post measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

Figure 31 and 32 shows 'dorsiflexionIncrease' from 10 gait cycles for Pre and Post respectively.

dorsiflexionIncrease Pre left	min	max	diff
1.00	5.62	14.69	9.07
2.00	3.11	14.31	11.19
3.00	3.24	15.80	12.56
4.00	4.76	14.03	9.28
5.00	8.66	15.19	6.53
6.00	5.11	15.91	10.80
7.00	3.04	16.84	13.80
8.00	3.38	16.64	13.27
9.00	1.63	14.13	12.50
10.00	3.47	13.90	10.43
		mean	10.94
		std	2.23
		CoF	0.20

dorsiflexionIncrease Pre right	min	max	diff
1.00	3.60	4.58	0.98
2.00	3.23	3.93	0.70
3.00	2.89	3.82	0.93
4.00	2.98	5.70	2.72
5.00	2.49	3.50	1.01
6.00	2.62	6.81	4.19
7.00	2.99	3.72	0.72
8.00	1.11	2.01	0.90
9.00	2.67	5.04	2.37
10.00	1.75	4.99	3.23
		mean	1.78
		std	1.25
		CoF	0.71

Figure 31: DorsiflexionIncrease angle from 10 gait cycles of the Pre measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

dorsiflexionIncrease Post left	min	max	diff
1.00	-0.53	8.84	9.37
2.00	-3.40	10.77	14.16
3.00	-4.60	10.51	15.11
4.00	-2.29	10.14	12.43
5.00	4.33	10.40	6.07
6.00	-0.47	9.83	10.30
7.00	-1.86	10.89	12.75
8.00	0.40	11.40	11.00
9.00	-1.48	10.08	11.56
10.00	-1.82	9.47	11.29
		mean	11.40
		std	2.54
		CoF	0.22

dorsiflexionIncrease Post right	min	max	diff
1.00	-1.24	3.00	4.24
2.00	-1.73	2.45	4.19
3.00	-1.14	1.31	2.45
4.00	-1.59	2.72	4.31
5.00	-1.17	2.58	3.75
6.00	-2.35	2.51	4.86
7.00	-1.13	3.29	4.42
8.00	-1.60	4.10	5.70
9.00	-2.08	0.78	2.86
10.00	-2.40	2.00	4.40
		mean	4.12
		std	0.93
		CoF	0.23

Figure 32: DorsiflexionIncrease angle from 10 gait cycles of the Post measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

Figure 33 and 34 shows 'kneeRangeOfMotion' from 10 gait cycles for Pre and Post respectively.

kneeRangeOfMotion
Pre left

	min	max	diff
1.00	13.31	54.56	41.24
2.00	13.78	54.75	40.97
3.00	13.51	54.02	40.50
4.00	16.26	53.43	37.17
5.00	15.46	52.20	36.74
6.00	11.95	52.44	40.49
7.00	14.21	52.23	38.02
8.00	17.76	53.05	35.29
9.00	17.96	54.32	36.36
10.00	15.85	52.71	36.86
		mean	38.37
		std	2.21
		CoF	0.06

kneeRangeOfMotion
Pre right

	min	max	diff
1.00	13.58	20.05	6.47
2.00	15.95	21.81	5.86
3.00	15.19	21.03	5.84
4.00	13.21	20.15	6.94
5.00	15.17	20.72	5.55
6.00	12.59	19.88	7.29
7.00	13.94	20.64	6.70
8.00	15.87	21.91	6.03
9.00	15.53	21.01	5.48
10.00	16.98	21.83	4.85
		mean	6.10
		std	0.75
		CoF	0.12

Figure 33: KneeRangeOfMotion angle from 10 gait cycles of the Pre measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

kneeRangeOfMotion
Post left

	min	max	diff
1.00	28.26	49.31	21.05
2.00	28.19	50.78	22.59
3.00	22.61	51.61	29.00
4.00	20.40	49.42	29.02
5.00	22.55	45.86	23.31
6.00	28.33	45.36	17.03
7.00	22.67	47.01	24.33
8.00	25.05	49.15	24.10
9.00	26.77	50.41	23.64
10.00	25.67	47.90	22.23
		mean	23.63
		std	3.53
		CoF	0.15

kneeRangeOfMotion
Post right

	min	max	diff
1.00	17.08	22.76	5.68
2.00	17.23	21.08	3.85
3.00	18.12	22.50	4.38
4.00	20.41	24.29	3.88
5.00	17.04	20.95	3.91
6.00	16.44	20.38	3.94
7.00	17.70	21.42	3.71
8.00	17.50	21.74	4.23
9.00	15.95	21.03	5.08
10.00	17.24	21.43	4.19
		mean	4.29
		std	0.63
		CoF	0.15

Figure 34: KneeRangeOfMotion angle from 10 gait cycles of the Post measurement. The left table contains the values for the left side and the right table contains values for the right side. Mean values, standard deviations and coefficients of variance are calculated to assess variabilities across measures, taking the means into consideration.

APPENDIX B – DATA COLLECTION RELATED DOCUMENTS

B

Consent Form

AUT UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Project title: ***The Aalborg Brain Computer Interface: A rehabilitation strategy for people with stroke***

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

Participant's signature: .....

Participant's name: .....

Participant's Contact Details (if appropriate):

.....

.....

.....

Date:

Approved by the Auckland University of Technology Ethics

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

This version was last edited on 17 February 2015

Participant Safety Checklist for using Transcranial Magnetic Stimulation

Volunteer Name:_____

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

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

Medications checked for seizure threshold lowering effect? Yes / No

Checklist completed by: _____

Signature: _____

AUT
UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Date: _____

Participant Identifier	

AALBORG BCI STUDY – STROKE – PRE INTERVENTION WEEK

Arrival Time:

Has screening sheet been completed? *Y / N*

Has TMS screening been completed? *Y / N*

Has consent form been signed? *Y / N*

Wearing appropriate clothing? *Y / N*

Sex	*M F (circle)*
Date of Birth	
Ethnicity	
Date of Stroke	
Type of Stroke (if known)	
Side of Hemiplegia	*Left Right (circle)*
Medical Conditions:	
Medications and Dose:	
Cautions and Contraindications:	
Other Therapy/Relevant activities:	

Completed By:	Date:

Participant Identifier	

PRE-INTERVENTION DAY 1

TMS SCREENING

Start time:	
Set up tibialis anterior blue electrodes (x3)	
Can MEP be visualised in tibialis anterior?	*Y / N. If Yes, then proceed. Remove electrodes.*

PHYSICAL FUNCTION TESTS

Comfortable Paced 10m walk *(Record middle 6m of 10m. No markers/electrodes. Aids ok).*	*1. .* *(Rest 1 min)* *2. .* *(Rest 1 min)* *3. .*	*Comments:* *?aids* *Average = m/s*
Fast Paced 10m walk *(Record middle 6m of 10m. No markers/electrodes. Aids ok).*	*1. .* *(Rest 1 min)* *2. .* *(Rest 1 min)* *3. .*	*Comments:* *?aids* *Average= m/s*
Step Test *(No aids)*	*L= reps in 15s* *R = reps in 15s*	*Comments:*

Completed By:	Date:

Participant Identifier	

3D ANALYSIS

Room and the two forceplates calibrated?	*Y / N*	*std of wand length:*
Markers and EMG electrodes placed? *Unit number R Tib Ant:* *Unit number R Soleus:* *Unit number L Tib Ant:* *Unit number L Soleus:*	*Y / N*	 *R Tib ant - imp:* *R Soleus - imp:* *L Tib ant – imp:* *L Soleus – imp:*
5 sec Static recording?	*Y / N*	*File:* **Sub _pre2_static**
3D gait analysis *(Need 10 good hits on force plate, 5 on each leg. Aids ok).*	*R :* *L :* *D:*	*File:* **Sub _pre2_3dgait**
3D stepping analysis *(Start on force plate. Step weak leg up and down onto 19cm step. No aids).*	*Recorded ascent 10 times on affected leg only:* *Y / N* *R / L*	*File:* **Sub _pre2_3dstep** **Sub _pre2_3dstep**
Finish Time:		

Completed By:	Date:

Participant Identifier	

PRE INTERVENTION WEEK – DAY 2

Arrival time:	
Coffee? Exercise?	
Any new medical issues or medication changes?	

MAXIMAL VOLUNTARY CONTRACTION (MVC)

Configuration File	**mvc_1_collection**	
File name	**Sub _pre2_mvc**	
Which hole is being used to attach force plate?		
Oscilloscope – size of each MVC	*1.* *2.* *3.*	*10% value of largest:* *Placed horizontal cursor at 10% line on oscilloscope?* *Y / N*
Recorded 3 MVC's?	*Y / N*	*Time finished:*
Highest Tibialis anterior MVC *(for largest MVC)*	*Amp:*	*Base:* *(weight of foot lowers starting point)*
Calculated 10% MVC		

Completed By:	Date:

Participant Identifier	

MRCP RECORDING

Configuration Files:	*EEG (Scan):* **bci** *BCI (Matlab):* **bci_chiropractic** *EMG (Signal):*	
EMG Tibialis anterior	*Impedance <5 ohms Y / N* *Check EMG working?* *Check recording? Y/N*	**File:** **Sub _pre2_emgtibant**
Set up EEG cap. Distance nasion to cap =	*Has 20 minutes passed before starting EEG? Y / N*	
EEG Impedances all below 10%?	*Y / N*	
MRCP recorded?	*Start time:* *Y / N* *Finish time:*	**File:** **Sub _pre2_mrcp**
Timing of peak negativity		

TMS STATIC & DYNAMIC

Hotspot	File:		
Cap Location: *(Ensure midline/symmetrical)*	*Grid Reference of centre of head/ Cz:*	*Letter*	*Number*
	Distance cap to nasion:	*cm*	
	Taped down?	*Y / N*	

Find hotspot: *(Site where MEP is produced with lowest intensity. Do during rest if possible).*	*Grid References:*	*Letter*	*Number*
	X on Front of Coil		
	X on Back of Coil		

Completed By:	Date:

Participant Identifier	

Reset Baseline	
New Baseline:	
10% MVC + Base:	
8% MVC + Base:	
12% MVC + Base:	
Adjusted oscilloscope?	Y / N

Active Motor Threshold	*Configuration File:* **mvc_2_stim**	
When within 5% of AMT, reset baseline:	*New Baseline*	
	8% MVC + Base:	
	12% MVC + Base:	
	Adjusted oscilloscope?	Y / N
Active Motor threshold: (with 10% MVC). *(5/10 discernable and at or above 50mV)*	*%*	
Calculated 120% active motor threshold:	*%*	

Completed By:	**Date:**

Participant Identifier	

Static TMS (with 10% MVC)		*Configuration File:* **mvc_2_stim**					
Recorded MEP's x 15? *(approx 8 seconds between pulses?)*		*Y / N* *Y / N*			*Time started:* *File:* **Sub _pre2_tms_static**		
1		*6*		*11*		*16*	
2		*7*		*12*		*17*	
3		*8*		*13*		*18*	
4		*9*		*14*		*19*	
5		*10*		*15*		*20*	
10 good MEP's ? Y / N							

Dynamic TMS (stepping)	*Configuration File:*	
Foot switch in place? *Wood on ground to reduce noise?* *Toes on which line?*	*On Shoe / Foot (circle)* *Y / N*	*Instructions: Ready, Steady (and) Step, Wait.*
Timing	*Tempo or or 1 word/sec (circle)*	
Weightbearing used during stepping	*None /Finger tips /Full hand* *Height of plinth:* *(floor to lower edge of horizontal bar)* *Edge green line to plinth:*	*Which side?* *Comments:*

Completed By:	**Date:**

Participant Identifier	

EMG tibialis anterior recorded during 10 steps? (over 2 mins)	*Y / N*	*Mean timing of EMG burst:*
TMS start time: *Recorded 15 MEPS's during stepping?*	*Y / N*	*File:* **Sub _pre2_tms_dynamic**

1		*6*		*11*		*16*	
2		*7*		*12*		*17*	
3		*8*		*13*		*18*	
4		*9*		*14*		*19*	
5		*10*		*15*		*20*	

10 good MEP's? Y / N *Comments:*	*Finish Time:*

Completed By:	Date:

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