The University Of Sheffield.

INVESTIGATION OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION WITH A SPECIFIC FOCUS ON THE TREATMENT OF OVERACTIVE BLADDER

By

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Abstract

This thesis investigates transcutaneous electrical nerve stimulation (TENS), and in particular its role in the treatment of overactive bladder (OAB), which has been of interest for several decades. A standardization and an evaluation of various TENS parameters of stimuli would be beneficial to optimize the techniques used and to achieve the maximal effectiveness. Previously, Hoffman reflex (H reflex) inhibition was interpreted as a surrogate measure of bladder afferent nerve activity, and thus showed a potential to be useful for such evaluations. However, an influence of other factors, such as pelvic floor muscle contraction on this H reflex inhibition makes this surrogate measure unsuitable.

In general TENS techniques are usually implemented in the patient's treatment pathway as secondary treatment options. This is presumably due to a lack of effectiveness. Therefore a thought was given to enhance the effectiveness of the stimuli by producing a larger sensory input with a spatial temporal pattern. This lead to a development of a novel 'Sensory Barrage Stimulation', as introduced in this thesis. The technique showed promising effectiveness in comparison to a conventional type of TENS in the patients with elbow spasticity.

Other researcher groups have tried to enhance the effectiveness by stimulating deep nerve structures (usually only targetable by implanted devices) using non/invasive transcutaneous stimulation and a specific waveform. However the "Transdermal Amplitude Modulated Signal" waveform introduced for the treatment of OAB symptoms, which claimed to pass through the skin more easily did not appear to be any different to a conventional stimuli and thus it is not of benefit for the routine clinical practice.

Specifically, on the treatment for OAB syndrome symptoms, the most promising seems to be the Posterior Tibial Nerve Stimulation (PTNS) applied near the ankle. A well-established form of PTNS, which uses a needle to stimulate the nerve have disadvantages of being invasive and expensive due to the patient's clinical sessions. The transcutaneous form of PTNS was investigated here in a home based randomized pilot trial of idiopathic overactive bladder patients. A promising effect indicates that there might be patients who can benefit from this type of non-invasive and low cost approach of PTNS. Additionally a numerical modelling of both types of PTNS showed that both techniques achieve a stimulation comparable in a way of physiological effects. Thus suggesting the evidence of percutaneous form of PTNS is plausible to be present in the transcutaneous form.

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Sensory Barrage Stimulation is a concept of novel stimulation approach that was developed and tested in two consequent studies and formed a part of my thesis. Collaboration in these studies deserves an acknowledgement and thank you to Dr Siva

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Contents

List of publications arising from this work

M. Slovak, C. R. Chapple, A. T. Barker. Non-invasive transcutaneous electrical stimulation in the treatment of overactive bladder. Asian Journal of Urology 2015; 2:92-101. DOI: 10.1016/j.ajur.2015.04.013

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C. J. Hillary, M. Slovak, A. McCarthy, H. Hashim, C.R. Chapple. Recent developments in technology for the assessment and management of incontinence. Journal of Medical Engineering & Technology. Journal of Medical Engineering & Technology, 2015; 39(7): 434-440. DOI: 10.3109/03091902.2015.1088008

M. Slovak, J. Chindo, M. Reeves, B. Heller, A. T. Barker, S. Nair. Sensory Barrage Stimulation in the treatment of elbow spasticity: a cross over double blind randomized pilot trial. Neuromodulation. 2016; 19:220-226. DOI: 10.1111/ner.12383

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M. Slovak, A. T. Barker, C. R. Chapple. The assessment of a novel Transdermal Amplitude Modulated Signal (TAMS) for the treatment of overactive bladder syndrome. European Urology Supplements .03/2013; 12(1):e403-e404. DOI: 10.1016/S1569-9056(13)60888-X

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M. Slovak, C. Hillary, N. Osman, C. R. Chapple, A. T. Barker, Home based therapeutic application of non-invasive posterior tibial nerve stimulation in the treatment of overactive bladder symptoms: a pilot clinical trial, International Continence Society 2015, Montreal, Canada. Neurourology and urodynamics. Volume 34:S3, page S229

M. Slovak, J. Chindo, M. Reeves, B. Heller, A. T. Barker, S. Nair. Sensory Barrage Stimulation in the treatment of elbow spasticity: a cross over double blind randomized pilot trial. Technology for the Future: Proceedings of the Fifth Conference of the UK and Ireland Chapter of the International Functional Electrical Stimulation Society, Sheffield, UK, 8th – 9th May 2015 DOI: 10.13140/RG.2.1.3077.5528

List of presentations arising from this work

Transcutaneous Electrical Nerve Stimulation for the treatment of overactive bladder Young Urology meeting Bristol 2012, 7th to 8th May 2012

Transcutaneous Electrical Nerve Stimulation for the treatment of overactive bladder, EU Marie Curie People 2012 Conference, Cyprus, 5th to 6th November 2012

The assessment of a novel Transdermal Amplitude Modulated Signal (TAMS) for the treatment of overactive bladder syndrome, EAU Milan 2013, 15th to 19th March 2013

Transcutaneous Electrical Nerve Stimulation for the treatment of overactive bladder, Incontinence: The Engineering Challenge IX, London, 5th to 6th November 2013

Transcutaneous Electrical Nerve Stimulation for the treatment of overactive bladder, Medical School research Meeting, Sheffield 17th to 18th June 2013

Home based therapeutic application of non-invasive posterior tibial nerve stimulation in the treatment of overactive bladder, Sheffield IFESSUKI Conference 8th and 9th May 2015

Sensory Barrage Stimulation: a crossover double blind randomized pilot trial on patients with elbow spasticity, Sheffield IFESSUKI Conference 8th and 9th May 2015

Can H Reflex be a suitable surrogate measure of bladder afferent activity?, International Continence Society 2015, Montreal, 6th to 9th October 2015

Home based therapeutic application of non-invasive posterior tibial nerve stimulation in the treatment of overactive bladder symptoms: a pilot clinical trial, International Continence Society 2015, Montreal, 6th to 9th October 2015

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List of abbreviations

ADM	Abductor Digiti Minimi
AUC	Area Under the Curve
BM	Baseline Measurement
BoNT/A	Botulinum toxin type injection
BP	Blood Pressure
BTM	Baseline Test Mean
DO	Detrusor Overactivity
DH	Detrusor Hyperreflexia
DP	Detrusor Pressure
DC	Deep Cough
DPCN	Dorsal penile/clitoral nerve
EMG	Electromyography
FIDC	First Involuntary Detrusor Contraction
FDV	First Desire to void
FDTD	Finite Difference Time Domain
FEM	Finite Element Method
FES	Functional Electrical Stimulation
FSF	First Sensation of bladder Filling
FRA	First Reversal Angel
Hmax	H Reflex - maximum amplitude
HRV	Heart Rate Variability
HRQL	Heath-Related Quality of Life impact
IC	Interstitial cystitis
ICIQ	International Consultation on Incontinence Questionnaire
ICS	International Continence Society
IDO	Idiopathic Detrusor Overactivity
IVD	Irritative Voiding Dysfunction
ISCR	Integration area of Skin Conductance Responses
LC	Light cough
LUTS	Lower Urinary tract Symptoms
IPFM	Isolated Pelvic Floor Muscle
NICE	National Institute for Health and Care Excellence
NMES	Neuromuscular Electrical Stimulation
nSCR	Number of Skin Conductance Responses
MAS	Modified Ashworth Scale
MAP	Mean Arterial Pressure
MCC	Maximum Cystometry Capacity
MDP	Maximum Detrusor Pressure
MPFM	Maximal Pelvic Floor Muscle contraction
MRC	Medical research Council
MVFR	Maximum Velocity to First Reversal
ME	Multi-infarct Encephalopathy
Mmax	M wave maximum amplitude
MS	Multiple Sclerosis

Mtran	Maximum gradient of transcutaneous
Mperc	Maximum gradient of percutaneous
NDO	Neurogenic Detrusor Overactivity
NHS	National Health Service
OAB	Overactive bladder
PD	Parkinson's diseases
PDS	Participant DataSet
PEC	Perfect Electrical Conductor
PEE	Power of Elbow Extension
PEF	Power of Elbow Flexion
PESTOB	Peripheral Electrical Stimulation for the Treatment of Overactive Bladder
PFM	Pelvic Floor Muscle
PMNS	Patient-Managed Neuromodulation System
PPBC	Patient Perception of Bladder Condition
PPCBC	Patient Perception of Change in their Bladder Condition
PTN	Posterior Tibial Nerve
PTNS	Posterior Tibial Nerve Stimulation
SANS	Stoller Afferent Nerve Stimulation
SAT	Saturated Fat
SB	Symptoms Bother
SBS	Sensory Barrage Stimulation
SD	Standard Deviation
SEM	Standard Error of Mean
SU	Sensory urgency
SCI	Spinal Cord Injury
SDV	Strong Desire to Void
TAMS	Transdermal Amplitude Modulated Signal
TC	Test condition
TCM	Test Condition Measurement
TD	Test Dataset
TENS	Transcutaneous Electrical Nerve Stimulation
TPTNS	Transcutaneous Posterior Tibial Nerve Stimulation
UUI	Urge Urinary Incontinence
VAL	Valsalva manoeuvre
VAS	Visual Analogue Scale

Chapter 1 **Introduction**

The work in this chapter has been published in:

M. Slovak, C. R. Chapple, A. T. Barker. Non-invasive transcutaneous electrical stimulation in the treatment of overactive bladder. Asian Journal of Urology 2015; 2:92-101. DOI: 10.1016/j.ajur.2015.04.013

1.1. **General introduction & terminology**

We all drink fluid. As we drink the body expels waste and excess fluid in the form of urine, which is temporarily stored in the bladder. Most people do not consider the physiological and neurophysiological process that are involved in the sensation which leads them (at a socially acceptable time) to visit a toilet. However, for a significant proportion of the population, the signals and sensations prompting them to go are different. They have urgency (a sudden compelling desire to pass urine) which is a pivotal symptom of what is known as overactive bladder (OAB) syndrome.

OAB is a set of symptoms, which patients experience during the storage phase of a micturition cycle. Urgency, present in majority of the patients, is usually accompanied by frequency (the patient passes urine at short intervals during the day) and often by a nocturia (the patient has to wake up one or more time at night to pass urine) (Abrams et al., 2002). One third of patients experience urinary incontinence (any involuntary leakage of urine) (Chapple et al., 2005). The term “urgency incontinence”, “urge incontinence” or “wet OAB” are often used in the literature for this group of patients. The standardization of terminology by the International Continence Society (Abrams et al., 2002) suggests the additional use of the terms ‘urge syndrome’ or ‘urgency-frequency syndrome’. However, it is important to differentiate between urge, a normal sensation of the desire to void, and urgency, a pathological abnormal sensation of OAB syndrome (Chapple et al., 2005).

OAB syndrome has a great impact on patients’ quality of life. There are over 5 million people (19%) in the UK over the age of 40 for whom quality of life is affected by the symptoms of overactive bladder (Milsom et al., 2001). The first-line treatment is bladder training or fluid intake management (National Institute for Clinical Excellence, 2015). Alternatively, medication may be advised and usually start with various antimuscarinics agents. However, nearly half of these patients discontinue therapy due to lack of efficacy in reducing the symptoms or side effects, such as dry mouth or constipation (Benner et al., 2010). Recently a new class of drug Mirabegron, a ß3-adrenoceptor agonist has been introduced into the clinical practise with promising efficacy and good tolerability (Vij and Drake, 2015).

It is important to investigate alternative therapies which may offer a different or additional treatment pathway and which may have a substantial impact on patients' quality of life. One such alternative therapy is electrical stimulation, which has been used for the treatment of various lower urinary tract symptoms for several decades. Except the examples included further in this thesis, Sacral Anterior Root Stimulation has been intended to be used to improve micturition (Brindley et al., 1986) and formed a precursor for today widely available Sacral Neuromodulation.

1.2. **Basis of electrical stimulation**

The term 'electrical stimulation' is used to refer to stimulation of nerves and/or their respective muscles for therapeutic, diagnostic or research purposes (Reilly, 2011).

Stimulation can be delivered to the body in a variety of ways. These include non-invasive (transcutaneous techniques), where electrodes are placed on the surface of the skin, the use of probes inserted into body orifices (semi-invasive), and to more invasive stimulation approaches using needles to penetrate the tissue (percutaneous techniques) or long-term implantation of electrodes. The technology of electrical stimulation presented in this thesis is mainly focused on non-invasive techniques due to their advantages of being more patient-acceptable, non-invasive and of potentially low cost.

Electrical stimulation using surface electrodes is usually referred to as transcutaneous electrical nerve stimulation (TENS). This term is often used in conjunction to describe a widely-used therapy for pain relief; however the terminology can be used to describe any application of electrical stimulation delivered using surface electrodes. TENS is commonly applied via self-adhesive hydrogel surface electrodes with the stimulation being generated by small, hand-held, battery-operated and relatively inexpensive devices which are widely available to the general public. Usually, the stimulus intensity is set below the level which causes muscle to contract, in contrast to neuromuscular electrical stimulation (NMES) and functional electrical stimulation (FES) where motor level stimulation is used. The suggested mode of action is not fully understood but the gate-control mechanism is often proposed for pain management (Melzack and Wall, 1965).

A schematic diagram of electrical stimulation of a nerve, applied using two surface electrodes on the skin is shown in Figure 1.1. A voltage applied between these two electrodes causes current to flow into the tissue. The conventional direction of the current

flow is from the positive to the negative electrode. Most of the current flows just below the skin, however some will penetrate deeper into the tissue, enter the nerve fibre and change the nerve membrane voltage. When nerve membrane threshold voltage has exceeded an action potential is created and thus causes stimulation. This action potential travels along the nerve fibre in both directions.

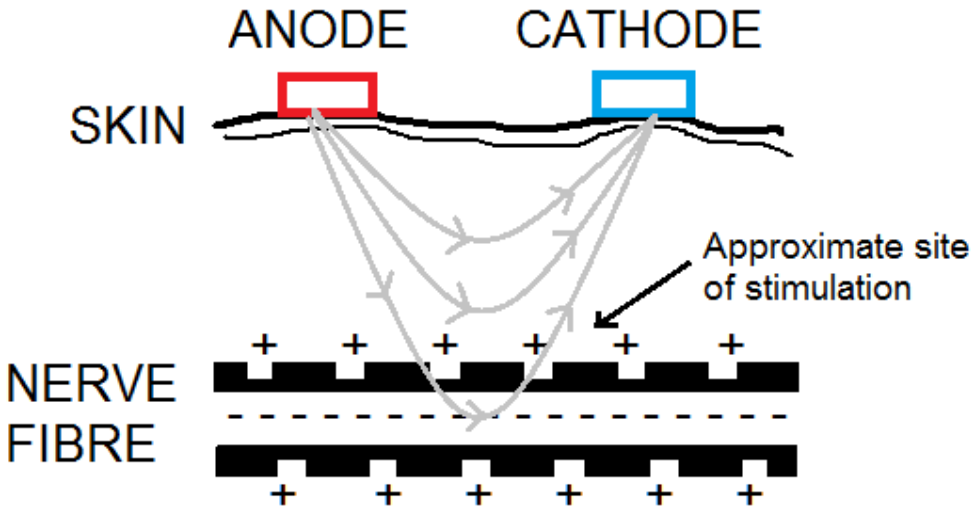


Figure 1.1 A diagram of electrical nerve stimulation

Electrical stimulation is often perceived as an alternative therapy option to conventional therapies (e.g. drug medication) and offered as a secondary treatment pathway. It is used frequently when standard therapy cannot be tolerated or is not effective. This secondary role is primarily due to the lack of comprehensive clinical trials evaluating its efficacy. Clinical guidelines currently therefore only recommend its utilisation within certain constraints; however, given the increasing body of evidence to support it, there may be a significant opportunity to bring benefit to a greater number of patients and their families in the future using this technology.

1.3. What do we already know about electrical stimulation as a treatment for the symptoms of overactive bladder?

Studies of electrical stimulation to treat symptoms of OAB can be divided into four main groups, based on their stimulation technique:

- Percutaneous stimulation using needle electrodes. The needle is usually inserted near the posterior tibial nerve (PTN) 5 cm proximally from the medial malleolus. In

commercial use, this is known as Stoller Afferent Nerve Stimulation (SANS) technique (Stoller, 1999), which has been improved from the original method by McGuire (McGuire et al., 1983a).

- Anal, penile or vaginal stimulation. This technique can use surface electrodes or particular semi-invasive electrodes to stimulate specifically localised areas (Bristow et al., 1996).

- Implanted stimulation devices. These devices usually consist of an implanted stimulator and implanted electrodes placed near a nerve root in the spinal cord, coupled with an external control device. The most common approach is known in the literature as sacral neuromodulation (Siddiqui et al., 2010). The well-established Finetech-Bridley Sacral Anterior Root Stimulator (Brindley, 1994), an electrical stimulator of sacral roots for emptying the bladder, formed a precursor to today's widely used sacral neuromodulation (Schmidt et al., 1999, Tanagho, 1993). The S2-S4 nerve roots provide the principle motor supply to the bladder. The S3 root mainly innervates the detrusor muscle and is the main target of sacral neuromodulation

- Transcutaneous electrical nerve stimulation. This uses surface electrodes at various stimulation sites on the body.

As stated previously, the work in this thesis focuses on transcutaneous electrical nerve stimulation. The primary reason for focussing on this modality is that it has a number of practical advantages in its delivery. The method is completely non-invasive. Surface electrodes, connected to a battery-operated low-cost stimulator, are applied to an appropriate site of the body. The stimulators are simple to operate. Inexpensive hydrogel-based electrodes and batteries are the only on-going treatment costs. TENS treatment itself should not require regular patient visits to clinics and is usually self-administered at home, which is convenient for the patient. In general there are minimal or no side effects from TENS, although sometimes redness or skin irritation may occur around the electrodes. This usually resolves once the stimulation session is finished. TENS has been used for pain control but its use in the treatment of OAB or in lower urinary tract diseases is less well established.

1.3.1. **Review of TENS for the treatment of OAB**

The literature review in this section will focus on TENS techniques where the electrical stimuli is passed through the intact skin. Other minimally invasive electrical stimulation techniques such as anal, vaginal stimulation plugs (Bristow et al., 1996, Tellenbach et al., 2012), percutaneous stimulation (needle is inserted near a targeted nerve) or implanted stimulation devices are beyond the scope of this review and thesis (Tanagho, 1993, Schmidt et al., 1999). In particular, plugs are often refused by the patient because of embarrassment and a sense of uncleanliness (Yokozuka et al., 2004).

The studies identified in this review can be subdivided into categories according to the site of stimulation used. A summary follows, with a particular focus on stimulation site, stimuli parameters, neural structures thought to be targeted, and the clinical and urodynamic outcomes achieved.

1.3.1.1. **Sacral site**

In 1996, Hasan et al. (Hasan et al., 1996) compared S3 neuromodulation using implanted devices with TENS applied over the perianal region (S2 – S3 dermatomes). Improvement in more than 50% of idiopathic detrusor overactivity (IDO) patients suggested the potential of using TENS at a sacral site.

In a study by Walsh et al., one week of continuous stimulation for 12 hours per day at S3 dermatomes significantly improved both frequency and nocturia. However only 3/32 patients continued with the therapy, and only on an intermittent basis, for up to 6 months of follow up (Walsh et al., 1999). The authors did not evaluate whether the patients found using TENS for 12 hours a day to be inconvenient and whether this may have led to discontinuation of therapy.

Following this study, an urodynamically assessed group of 33 patients with detrusor overactivity (DO) and symptoms of OAB reported similar effects for self-administered stimulation over the sacral site twice a day when compared to oxybutynin in a 14 week crossover trial (6w + 2w washout + 6w) (Soomro et al., 2001). The stimulation group also reported far fewer side effects in comparison to oxybutynin. The authors non-specifically documented some degree of difficulty in applying the stimulation in 30% of patients. This might reflect the inconvenience and difficulty of placing electrodes over the S2-S3 dermatomes or the length of the daily treatment session (up to 6 hours).

A heterogeneous group of neurogenic patients with urinary symptoms were investigated in a non-randomized trial using a TENS stimulator with electrodes placed above the natal cleft twice a day in a home setting (Skeil and Thorpe, 2001). 19/44 patients decided to keep the stimulator after this trial, consistent with the beneficial treatment effect size reported although no data is available on their subsequent usage of it.

Another small trial of 18 patients (7 neurogenic bladder, 5 overactive bladder, 6 nocturia) reported improvement in 10/18 patients after one month of stimulation over the posterior sacral foramina (Yokozuka et al., 2004). The authors suggested that this type of therapy causes less discomfort then vaginal or anal plug stimulation. However, this might partly be explained by their additional comment that in some cases, the intensity was not set to a high enough level to produce significant effects in all of the patients.

In addition to this up to date literature, a commercially available system VERV^{TM} Patient-Managed Neuromodulation System (PMNS, Ethicon Endosurgery Inc.) (Monga et al., 2011a) has been launched into the clinical practise in 2012. The system used so called Transdermal Amplitude Modulated Signal (TAMS) and claimed to stimulate deep nerve structures on the sacral site. However, subsequently this system was withdrawn and evaluation of TAMS waveform in this regards is discussed in Chapter 4.

1.3.1.2. **Posterior tibial nerve stimulation (PTNS)**

The posterior tibial nerve (PTN) is a branch of the tibial mixed nerve containing L5-S3 fibres, originating from the same spinal segments (S2-S4) as the parasympathetic innervations of the bladder (Figure 1.2).

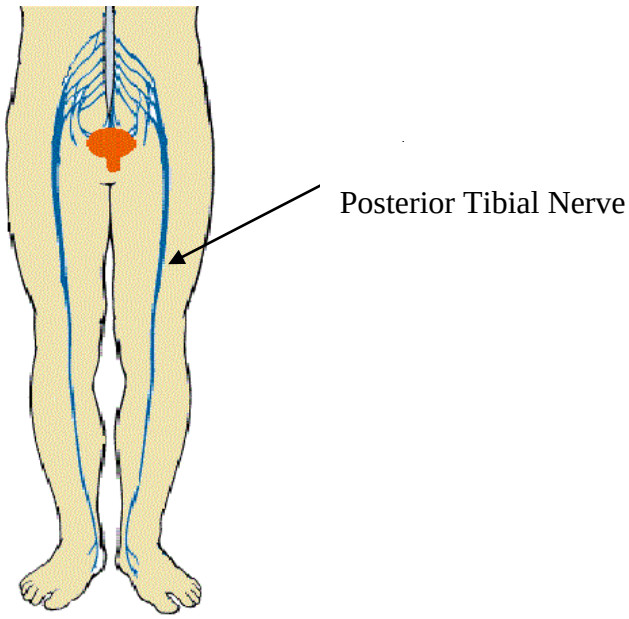


Figure 1.2 The posterior tibial nerve originates from the same spinal segments as the parasympathetic innervations of the bladder

McGuire et al. first used peripheral electrical stimulation to stimulate the PTN (McGuire et al., 1983b) in OAB patients. In this initial study a positive electrode was placed over the common peroneal or PTN and a ground electrode was placed over the contralateral equivalent site. They reported positive results in 8/11 DO patients who became dry after the treatment and in 7 neurogenic disease patients (Multiple Sclerosis MS, Spinal Cord Injury SCI) of which 5 became dry or improved. Sixteen years later, the Stoller Afferent Nerve Stimulator (SANS) was introduced, using a 34-gauge needle electrode inserted into the same place as used in electro acupuncture (the so-called SP6 point – 5 cm above the medial malleolus), with a surface electrode placed behind the medial malleolus. This position differed from the original description by McGuire et al., however further studies of either percutaneous or transcutaneous posterior tibial nerve stimulation have used electrodes placed on the same area as the SANS (Stoller, 1999). Currently a commercial device Urgent-PC (Uroplasty, Inc.) which uses the percutaneous technique is available. Usually 12 sessions of the percutaneous posterior tibial nerve stimulation, at weekly intervals, are used and a large randomized placebo controlled trial showed significant improvement in overall overactive bladder symptoms (60/110) compare to sham (23/110) (Peters et al., 2010). It was shown that Posterior Tibial Nerve Stimulation (PTNS) responders can benefit from the therapy over 12 additional months of regular PTNS sessions (MacDiarmid et al., 2010). The exact mechanism of PTNS remains unclear and further multidisciplinary studies are needed to clarify this. Based on these studies

Transcutanoeus Posterior Tibial Nerve Stimulation (TPTNS) has been investigated as a non-invasive alternative approach.

The clinical effects of TPTNS and oxybutynin, assessed by questionnaires, were reported in 5/9 women with overactive bladder, although more robust assessment tools and known pathology of the patients would be desirable in this study (Svihra et al., 2002). A significant improvement in elderly women with urgency urinary incontinence (Schreiner et al., 2010) was reported after 12 weeks of once a week stimulation in combination with Kegel exercises and bladder training. However this improvement was not superior to those patients with no stimulation. A self-administrated TPTNS non-randomized study where remarkably 83% MS patients reported clinical improvement in urgency (de Seze et al., 2011) also confirmed patients' acceptance of this therapy for use at home. In similar home based study later (Ammi et al., 2014) also reported positive response in anticholinergic refractory overactive bladder patients. In a separate placebo controlled trial, 37 women with symptoms of idiopathic OAB were randomized into a treatment or to a sham group with electrodes on the same site, but with no stimulus applied (Bellette et al., 2009). Urinary frequency significantly improved both in the treatment group ($p=0.002$) and in the sham group ($p=0.025$). Statistical significance between these groups was not achieved but this might be explained by unequal micturition episodes in the baseline (13.88 vs 11.35 per day) (Bellette et al., 2009), pointing to the desirability of stratifying the patient groups based on micturition frequency. Another placebo control trial was conducted in residential care home setting (Booth et al., 2013). Although the participants were only assessed by questionnaires urinary symptoms (frequency) improved significantly more in compare to sham stimulation (electrodes placed on the lateral side of the ankle and stimulation current reduced to 2 mA – this is likely to be below the sensation level).

In comparision to percutaneous PTNS, transcutaneous PTNS has the advantage of being completely non-invasive and can be self-administered by patients at home, which greatly lowers the overall cost of treatment. Stimulation can be delivered using a conventional TENS machine (Figure 1.3). Although two small placebo controlled trials have been conducted (Bellette et al., 2009, Booth et al., 2013), there is a need for more placebo controlled studies. In addition, its longevity of therapeutic action remains unknown.

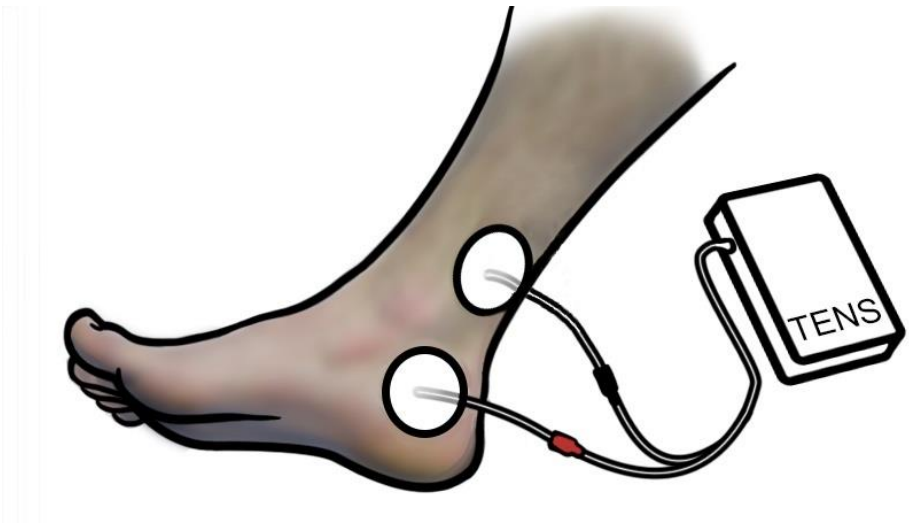


Figure 1.3 Transcutaneous Posterior Tibial Nerve Stimulation can be applied using a conventional TENS machine

The National Institute for Clinical Excellence (NICE) currently does not recommend percutaneous tibial nerve stimulation for the treatment of OAB symptoms unless there has been a multidisciplinary discussion, failure of conservative management including OAB drugs, and the patient does not want botulinum toxin or percutaneous sacral nerve stimulation (National Institute for Clinical Excellence, 2013). Further, the transcutaneous form of PTNS should not be offered, because there is insufficient evidence for it to be recommended.

1.3.1.3. **Other site of stimulation**

One of the first techniques for the treatment of lower urinary tract storage dysfunction stimulated the suprapubic region in patients with painful bladder syndrome (Fall et al., 1980, Fall, 1987). This method was used to relieve abdominal pain, similarly to the principle of TENS when used for the relief of pain. Subsequently these patients also experienced reduced urinary frequency (Fall, 1987). Two later studies documented an improvement in urodynamic parameters in patients with detrusor overactivity, sensory urgency or neurogenic problems. However, based on the literature, the efficacy of stimulation of a suprapubic site in patients with OAB symptoms is unproven (Bower et al., 1998, Radziszewski et al., 2009).

Another reported approach has used stimulation of the thigh muscle in spinal cord injury patients to relieve spasticity. In some of these cases, this has led to improvements in urgency incontinence (Shindo N, 1987) as well as an increase in the maximum

cystometric capacity (MCC) and reduced maximum detrusor pressure (MDP) (Okada et al., 1998, Wheeler et al., 1986). Further to this 6/19 patients reported clinical improvement in urinary incontinence and frequency extending out to 3 months after treatment (Okada et al., 1998).

Based on this literature overall, and the (at best) limited evidence for stimulation at other sites, the most promising transcutaneous electrical stimulation technique appears to be either sacral stimulation or PTNS as they either directly or indirectly target the S3 spinal cord root.

1.3.1.4. **Are acute effects of stimulation of clinical significance?**

An obvious approach to answer this question would be to assess the effectiveness of electrical stimulation in suppressing detrusor overactivity, as it presents in many patients with OAB symptoms (Wyndaele et al., 2004). This has led researchers to investigate the acute effects of electrical stimulation during an urodynamic study. These studies are summarised in Table 1.1.

In total, 146 patients with IDO, sensory urgency, or (DO) secondary to neurogenic diseases, showed improvements in MCC ($p=0.0009$) compared to controls (without stimulation) when stimulation was applied over the S3 dermatomes (Walsh et al., 2001). Similarly effects were demonstrated by (Hasan et al., 1996). However, comparison of suprapubic, sacral and sham stimulation by Bower et al. (Bower et al., 1998) did not clearly demonstrate these immediate effects on MCC. The authors concluded that the observed improvement in first desire to void (FDV) in DO patients may not be functionally important, although a significant reduction in maximum detrusor pressure may suggest potential efficacy in DO. Another approach used conditional stimulation (stimulation only turned on when a certain detrusor pressure was increased) to supress bladder contractions in 12 MS patients with neurogenic detrusor overactivity (NDO) at a sacral site (Fjorback et al., 2007a) and in 8 MS patients at the PTN (Fjorback et al., 2007b) using a needle electrode. However none of these patients had a positive response, in contrast to dorsal penile stimulation in which 10/12 patients were able to suppress detrusor contraction (Fjorback et al., 2007a). The dorsal penile nerve is a division of the pudendal nerve and similar effects of electrical stimulation have been shown when stimulating the pudendal nerve both in human studies (Spinelli et al., 2005, Vodusek, 1986) and in cat animal models (Tai et al., 2011, Tai et al., 2012). This nerve is a deep

nerve in the pelvic region. Although it has been suggested that it could be targeted using surface electrodes and a specific stimulation waveform (Tai et al., 2011, Tai et al., 2012) the exact mechanism by which this waveform would be more effective needs to be explored further.

Similarly inconsistent effects have been reported in acute TPTNS studies, although Amarenco et al. reported positive results in half of the neurogenic disease (MS, SCI, Parkinson's disease) patients he studied (Amarenco et al., 2003). These patients showed a 50% improvement in volume at the first detrusor contraction and/or MCC of more than 50% of the baseline value. A previous urodynamic study showed no significant differences in any of the urodynamic parameters in 36 detrusor overactivity patients (Hasan et al., 1996). These differing result might arguably be due to the different pathologies of the patient groups.

Neither of the two approaches to the investigation of acute effects, at either stimulation site, has clearly and robustly demonstrated effectiveness. Nevertheless, the balance of the literature indicates that patients may benefit from neuromodulation effects which could result from repeated stimulation sessions rather than a single application. In addition, de Seze et al. concluded that repeat treatment may be effective even in patients who did not respond to an acute sessions of TPTNS applied during urodynamic testing (de Seze et al., 2011).

Table 1.1 Literature reviewing the acute urodynamic effects of TENS

Study	Diagnosis	No. Pts	Site	Stimulus pulse parameters			Study details	Urodynamic outcome
				Frequency	Pulse width	Intensity		
(Hasan et al., 1996)	IDI	36	PTN Suprapubic	50 Hz	200 µs	Tickling sensation	Part of a large study	No significant difference in any of the parameters
		59	S2-S3 T12 (sham) Control	50 Hz	200 µs	Tickling sensation	3 groups, sham, control	MCC significantly improved in S2-S3 stimulation in compare to sham and control
(Bower et al., 1998)	DO, sensory urgency (SU)	79	Sacral	10 Hz	200 µs	Max. tolerable sensation	3 groups, sham	↑ Max DP and FDV
			Suprapubic	150 Hz	200 µs			↑ Max. DP and FDV
			Sham		no stimulation			↑ MCC in sensory urgency pts.
(Walsh et al., 2001)	IDI, SU, DH (SCI, MS)	146	Perianal dermatomes	10 Hz	200 µs	-	Control group	FDV (p=0.002) and Max CC. (p=0.0009) improved in compare to control
(Amarenco et al., 2003)	MS, SCI, PD, IDI	44	PTN	10 Hz	200 µs	Below motor response	Acute effect	48% (21/44) increased volume at FIDC, 34% (15/44) increased MCC
(Fjorback et al., 2007a)	MS	12	Sacral	20 Hz	500 µs	50-60 mA	Conditional stimulation	0/12 were able to supressed detrusor contraction
			DPCN	20 Hz	500 µs	50-60 mA		10/12 were able to supressed detrusor contraction

Abbreviations: DH – detrusor hyperreflexia, DO – detrusor overactivity, DP – detrusor pressure, DPCN – dorsal penile/clitoral nerve, FDV – first desire to void, FIDC – first involuntary detrusor contraction, IDI – Idiopathic detrusor instability, MCC – maximum of cystometry capacity, MS – multiple sclerosis, PD – Parkinson's diseases, PTN – posterior tibial nerve, SCI – spinal cord injury, SU – sensory urgency

1.3.2. **Which stimulation parameters?**

The literature on the stimulation parameters used is summarised in Tables 1.1 (acute urodynamic effects) and Table 1.2 (clinical and urodynamic effect of long-term applications). The location of electrodes and range of stimulus parameters are likely to be critical factors in all forms of stimulation. Relevant stimulus parameters include pulse width; pulse repetition frequency; burst length (if applicable) and stimulus intensity. In some studies the technical description of the stimuli used does not give all of these details.

To achieve sacral stimulation, Yokozuka et al. (Yokozuka et al., 2004) instructed patients to put surface electrodes on the posterior sacral foramen and to increase stimulation intensity until an anal contraction could be felt. They speculated that, in cases where there was no improvement, electrodes were not placed in the correct position or the intensity was not high enough due to associated discomfort. There is support for this in the results of Takahashi et al. (Takahashi, 2001) where slight changes in electrode location produced considerable apparent changes in urethral pressure response (Yokozuka et al., 2004). The sacral stimulation studies reported to date usually have electrodes positioned at the sacral foramina or on the buttocks overlying the S2 and S3 dermatomes. The precise positioning of electrodes on sacral sites varies between studies, presumably because the location of the sacral dermatomes is uncertain (Lee et al., 2008, Greenberg, 2003).

The intensity of the stimulation current was usually set to the maximum tolerable, dictated by pain threshold. In other studies, patients were instructed to set an intensity that produced only a tickling sensation (Hasan et al., 1996, Skeil and Thorpe, 2001, Soomro et al., 2001). Nerve trunks (roots) in these areas are located deep within foramina and it is unlikely that these were being directly stimulated at the stimulus intensity level being used by the latter studies. However, cutaneous nerves within the dermatomes are easy to stimulate and hence superficial sensory fibre stimulation, which may lead to both direct and indirect modulation of spinal cord reflex mechanisms, may explain the reported effects. Furthermore, the intensity which produces anal sphincter contraction (Yokozuka et al., 2004) involves the stimulation of motor nerves thus activating different mechanisms and indeed may cause significant discomfort to patients. The clarification of the exact site of stimulation and of the intensity required needs to be addressed in future work. Based on this evidence available it is not possible to conclude which stimulation

parameters are best for use in sacral stimulation. The original description of PTNS by McGuire et al. (McGuire et al., 1983b) has not been repeated in terms of the location of electrodes. Most studies place electrodes near the medial malleolus, where the PTN is relatively superficial. It is uncertain as to which leg the electrodes need to be placed on for optimal response, and whether this matters; some authors placed electrode on the left leg (Svihra et al., 2002, Amarenco et al., 2003, Bellette et al., 2009), while others on the right leg (Fjorback et al., 2007b, Schreiner et al., 2010, de Seze et al., 2011). It may also be more effective to place the electrodes bilaterally although no studies have yet looked at this. In describing the setting of current intensity, some of the studies reported motor responses during stimulation (Schreiner et al., 2010, Svihra et al., 2002). In other studies, the stimulation intensity was set either just below the motor threshold (Amarenco et al., 2003) or just above the perception threshold (de Seze et al., 2011).

The study reporting the most promising therapeutic results is that of de Seze et al. (de Seze et al., 2011), which reported PTNS to be successful for OAB symptoms in MS patients. Stimulation intensity in this study was set just around the perception threshold and patients did not report motor responses as a consequence of the stimulation. Hence only sensory fibres or cutaneous nerves overlying the PTN are likely to have been stimulated, which suggests this may be sufficient for the treatment of OAB rather than direct stimulation of PTN trunk itself. If the treatment is self-administered, it is likely that the patient would prefer lower stimulation levels, which may then lead to stimulation of only cutaneous nerves rather than the posterior tibial nerve itself.

Probably the biggest potential for widespread use is in transcutaneous techniques, which because of their non-invasive nature might be applied by patients in their own home environment and lower the related cost of the treatment. Dorsal penile / clitoral nerve (DPCN) stimulation using surface electrodes was investigated in several studies (Dalmose et al., 2003, Fjorback et al., 2006, Opisso et al., 2011), but there is not a great interest in these techniques, mainly because of inconvenience caused to patients (Opisso et al., 2008). Hence this stimulation site was not discussed in this review.

Table 1.2 Literature reviewing the clinical and urodynamic effects of TENS during long term applications

Study	Diagnosis/ patients characteristics	No. Pts	Site	Stimulus pulse parameters			Scheme of treatment	Clinical improvement (% of patients)	Urodynamic assessment
				Frequency	Pulse duration	Intensity			
(McGuire et al., 1983b)	MS, SCI, detrusor instability, IC	22	PTN/common peroneal nerve	-	-	-	-	80% became dry or improved after the treatment	-
(Hasan et al., 1996)	IDO	59	S2-S3 dermatomes, perianal	50 Hz	200 μs	Tickling sensation	2-4w, 2 groups	69% Urge incontinence, 73% enuresis, 37% urinary frequency (all defined as 50% benefit)	MCC. voided volume, no. of unstable contractions ($p>0.05$)
(Okada et al., 1998)	DH, IDI	19	Thigh region	30 Hz, pattern	200 μs	Max. below pain	2w, 1/d 20 min	32% clinical improvement in urinary incontinence and frequency.	11/ 19 patients MCC increase of more than 50%.
(Walsh et al., 1999)	Refractory IVD	32	S3 dermatomes	10 Hz	200 μs	-	1w, 1/d, 12h a day	76% in frequency, 56% reduction in nocturia, urgency symptom score on VAS not significantly improved	-
(Skeil and Thorpe, 2001)	Neurological	34	Sacral dermatomes	20 Hz	200 μs	Comfortable level	6w, 2/day 90 min	Significant improvement in incontinence episodes and frequency	Not significantly changed
(Soomro et al., 2001)	IDI	43	S3 dermatomes	20 Hz	200 μs	Tickling sensation	6w/up to 360 min daily crossover	56% (24/43) improved by more than 25% in number of daily voids	Not significantly changed in the stimulation study arm.
(Svihra et al., 2002)	OAB	28	PTN	1 Hz	100 μs	70% of motor response	5ses,1/w 30 min. 3 groups control	56% (5/9) patients in questionnaires score, control group no sign diff.	-

Table 1.2 (continue) Literature reviewing the clinical and urodynamic effects of TENS during long term applications

Study	Diagnosis/ patients characteristics	No. Pts	Site	Stimulus pulse parameters			Scheme of treatment	Clinical improvement (% of patients)	Urodynamic assessment
				Frequency	Pulse duration	Intensity			
(Yokozuka et al., 2004)	Neurogenic, unstable bladder, nocturia	18	Sacral S2-S4 dermatomes	20 Hz 10s on 5s off	300 µs	Anal sphincter contr.	4w, 2/day,15 min	55% improved in UUI and frequency	44% increased MCC. and inhibited contraction
(Bellette et al., 2009)	Non neurogenic OAB, women	37	PTN	-	-	-	8ses,2/w, sham group	Frequency and urgency improved significantly in both groups.	-
(Schreiner et al., 2010)	UUI, elderly women	51	PTN	10 Hz	200 µs	Some motor response	12ses, 1/w, 30min, control	UUI improved significantly in 76% vs. 26.9% patients in the control group	-
(de Seze et al., 2011)	MS	70	PTN	10 Hz	200 µs	Below motor response	3m, 1/day, 20min	83.3% (58/70) improved in urgency based on warning time, the urgency MHU subscale and frequency	Only % of classified overactive detrusor patients decreased significantly by 13%.
(Booth et al., 2013)	Bladder/Bowel dysfunction, elderly	30	PTN	10 Hz	200 µs	Comfort level	12 ses., 2/w, 30min., sham group	Frequency: 74% vs. 42% Urgency: 74% vs. 31% Incontinence: 47% vs.15%	-
(Ammi et al., 2014)	OAB	43	PTN	10 Hz	-	Comfort level	1 month, daily 20 min.	Bladder capacity and urgency scale improved significantly	

Abbreviations: DH – detrusor hyperreflexia, DP – detrusor pressure, IC – interstitial cystitis, IDI – Idiopathic detrusor instability, IVD – irritative voiding dysfunction, MCC – maximum of cystometry capacity, MS – multiple sclerosis, OAB – overactive bladder, PD – Parkinson's diseases, PTN – posterior tibial nerve, SCI – spinal cord injury, SU – sensory urgency, UUI – urge urinary incontinence

1.3.3. **Review conclusions**

The choice of stimulation parameters, the location of the TENS in the treatment of OAB symptoms, the outcome measures used and the underlying conditions and symptoms studied are very diverse in the literature to date. There is little long-term follow-up data published in the literature and hence the treatment regimen to produce ongoing benefits is unclear.

The current consensus is that the most promising site of stimulation is the stimulation of S3 area of the spinal cord over the sacral region or over the posterior tibial nerve, but it is not clear which approach to stimulus delivery is the most effective. Little is known about the underlying mechanisms of action and which exact structures need to be stimulated.

However there is tantalising evidence for the efficacy of the transcutaneous stimulation approach, although further large placebo controlled studies are required to provide a robust evidence base. The standardisation of future trial methodology is important to allow comparisons to be made between studies and stimulation protocols.

1.4. **Outline of the thesis**

As concluded in the literature review, there is some evidence of efficacy in the treatment of OAB with a transcutaneous stimulation approach. Standardisation of methodology in this area will be important in helping to define the best way to deliver the stimuli, using which parameters (such as frequency, pulse width, treatment duration, number of treatment sessions etc.), at which sites and with which intensity setting. Ideally methods to evaluate this multi-dimensional parameter space would be quick and straightforward because of the large number of combinations which need to be considered. However in a condition such as overactive bladder, the clinical improvement of urgency, frequency and urgency incontinence reported using various outcome measures will probably occur only over several days or longer, thus making an evaluation of multiple options a lengthy process. In addition, a large number of patients would be required to evaluate all possible stimuli settings, which is not practical and is beyond the scope of this work.

Therefore this thesis took an alternative route by initially trying to identify a surrogate measure for the effectiveness of the stimuli. It was hoped that finding such a measure would decrease the time needed to evaluate the stimuli options. Following this, an

evaluation using a clinical trial with identified stimuli parameters by such a surrogate measure would take a place. A further literature review identified several candidates for this measure, of which the most promising seemed to be the magnitude of the H reflex. However, piloting showed a large influence of other factors which made this potential surrogate measure unreliable and not suitable for this purpose.

The evidence of the TENS effects in OAB treatment remains limited. Despite the lack of clarity with regard to the stimulus parameters, it has been hypothesized that the lack of great effect may be due to a decrease in response following repeated exposure to the same stimulus. Therefore a stimulus methodology which produces more variable stimulation, both temporally and spatially, was investigated. At the same time it has been hypothesised that the effects might be also enhanced if a large surface area sensory stimulation input is produced. Therefore a novel form of stimulation called "Sensory Barrage Stimulation" was developed. In order to deliver this type of stimulation the existing ShefStim, 64-programmable stimulator (previously developed in the Department of Medical Physics, Sheffield) was modified.

For the first hypothesis of this novel concept of stimulation, a study investigating habituation effects was conducted. Although the results of this study did not clearly demonstrate habituation effects, importantly for further studies, the sensations produced by SBS were distinguishable. This allowed producing a sensation which mimics various subject recognisable sensations. Subsequently a stroking sensation pattern was developed and a pilot trial was conducted on patients with elbow spasticity, where stroking is used as a part of rehabilitation. This sensation in combination with larger sensory stimulation input produced by Sensory Barrage Stimulation demonstrated the feasibility of this approach and indicated that in comparison to a conventional TENS stimuli this might be more effective.

Other research groups have tried to enhance the effectiveness by stimulating deep nerve structures (usually only targetable by implanted devices) using non/invasive transcutaneous stimulation with a specific electrical waveform. However the "Transdermal Amplitude Modulated Signal" waveform introduced for the treatment of overactive bladder symptoms, which claimed to pass through the skin more easily did not appear to be any different to a conventional stimuli as tested in this thesis.

Further on in this thesis and as a major area of interest in the investigation of non-invasive electrical stimulation for the treatment of overactive bladder symptoms an investigation of posterior tibial nerve stimulation was carried out. Two approaches for stimulating the posterior tibial nerve were identified. The percutaneous approach is more established in the literature and in current clinical practice, but it is invasive and expensive. On the other hand the non-invasive approach of transcutaneous PTNS seems to be more readily deliverable, particularly in a home setting, although there is a lack of evidence of efficacy. Thus, the aim of this work was to study the field distributions of both methods in order to compare these two types of stimulation and to investigate whether evidence for the percutaneous form of PTNS thus might be applicable to the transcutaneous form.

Further, a pilot clinical trial exploring the effects of home-based application of posterior tibial nerve stimulation in comparison to sham stimulation was conducted. Although the effects reported in the trial seem to be small, they are comparable to the results obtained in the recent clinical trials for the treatment of overactive bladder symptoms using drug therapies. Additionally the trial patients studied here were refractory to various drug therapies and there are benefits of this modality as mentioned previously (can be done by patients at home, no side effects, low cost).

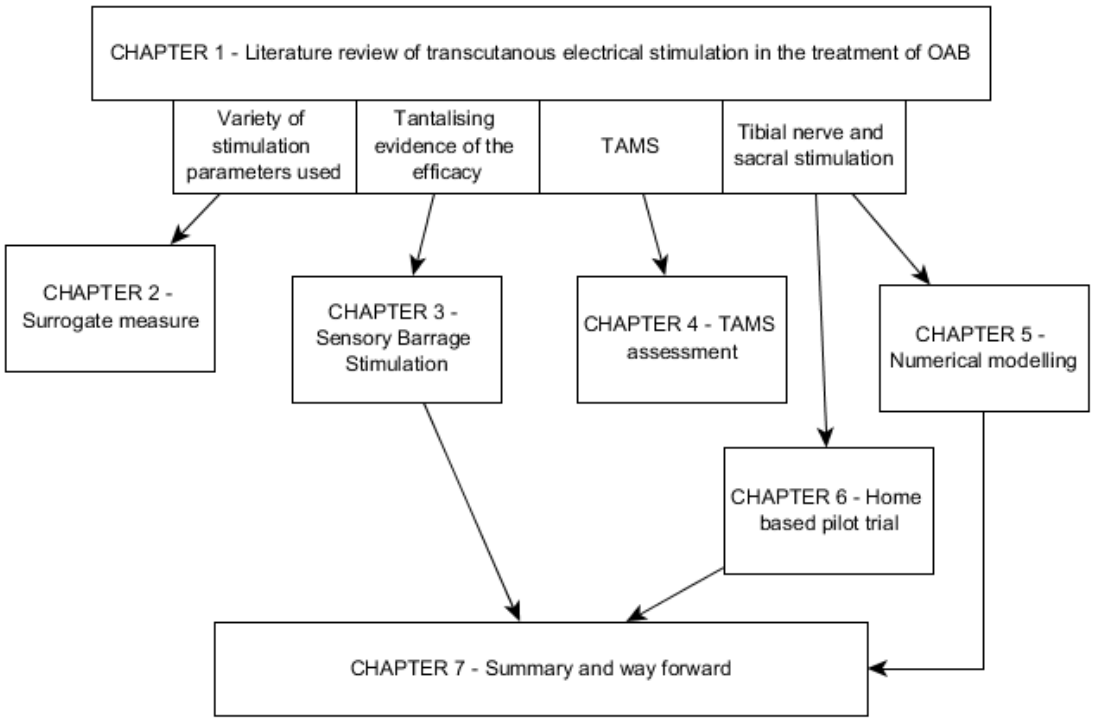


Figure 1.4 Outline of the thesis

1.4.1. **Summary of the main hypotheses**

- Is H reflex a suitable surrogate measure of bladder nerve activity?
- Is it feasible to produce larger and more "salient" sensory stimulation using a multichannel stimulation approach? Can this be a more effective type of stimulation in comparison to conventional single channel stimulation?
- Does the TAMS waveform pass through the skin more easily when compared to a conventional stimulation waveform?
- What stimulation current is needed in order to produce the same physiological effect obtained with percutaneous stimulation when the transcutaneous form of PTNS is used?
- Should self-administer home based transcutaneous PTNS be considered for further, larger, studies and subsequent deployment into clinical practice?

Chapter 2 **Potential surrogate measures for overactive bladder symptoms**

2.1. **Introduction**

The literature review in Chapter 1 has identified the potential of using transcutaneous electrical stimulation techniques for the treatment of OAB. However, there are some uncertainties in the optimal parameters of stimuli that should be used. The frequency and pulse width settings vary across the literature in both sacral and PTN stimulation techniques. Some studies used parameters based on the previous literature without primary evidence of their efficacy and without direct comparison to other possible settings. Uncertainties in the description of the intensity setting may have an impact on treatment effect. Different intensity settings may stimulate various types and depths of nerve structures (cutaneous, sensory or motor nerve fibres for example) and may produce different effects. The sacral site stimulation used in some studies also requires clarification in terms of the exact position of electrodes.

In addition to changes in the basic stimuli parameters, stimuli might also be delivered in bursts/trains of pulses. Furthermore, there is also the potential to produce more variable stimulation using a multichannel stimulation technique as discussed in Chapter 3. This technique can produce variable patterns of stimuli, but can also target a larger area of the tissue at the same time. This may hypothetically enhance the effect of stimulation.

Thus there are large numbers of possible stimuli parameters and protocol modifications, which may potentially improve the treatment of OAB. It would be desirable to investigate this spectrum of variables and determine what impact they have on the treatment effect.

Ideally the evaluation of these different variables should be quick and straightforward, and this is a challenge. The metrics of OAB symptoms such as frequency, urgency or number of incontinence episodes change over several days and thus making the evaluation of multiple options a lengthy process. An alternative approach is to find a surrogate measure for the effectiveness of the stimuli. A suitable surrogate measure could decrease the time of evaluation for the variables involved.

Any surrogate measure should ideally be easy to acquire, and preferably be useable in normal subjects to aid the collection of initial data. Although further clinical investigation will be required, this would allow a hypothesis relating to the optimal parameters to be formed.

Urgency, the pivotal symptom of overactive bladder syndrome is difficult to measure objectively. The majority of the clinical guidelines regard urinary diaries as the best and most essential tool for assessing the symptoms of overactive bladder (Chapple, 2014). However, urinary diaries still rely on patients understanding their importance and compliance with completing them. Therefore there has been research interest in using biomarkers as a measure of normal and pathological processes. In particular, increased Nerve Growth Factor in urine has shown some promise, but many criteria for a robust biomarker still need to be evaluated (Seth et al., 2013, Agilli et al., 2015). Bladder wall thickness is another potential biomarker, but also with contradictory results across studies (Cruz, 2012). Overactive bladder symptoms are complex and a single biomarker may not be sufficiently sensitive or selective. Additionally, for the purpose of this project, biomarkers might not provide easily detectable surrogate measures of different stimuli parameters in healthy volunteers. Hence different options for surrogate measure are explored here.

The lower urinary tract is closely coupled with the sympathetic and parasympathetic nerves of the autonomic nerve system. Heart rate variability (HRV) is frequently used as a measure of autonomic nervous system balance. Some studies suggest alternation of HRV related to bladder sensations (Ben-Dror et al., 2012, Mehnert et al., 2009). However, the autonomic nervous system balance measured by HRV is unlikely to be specific enough for bladder activity and OAB symptoms as it can be readily affected by emotional arousal or anxiety often also presented in patients with lower urinary tract symptoms. Instead, attempts have been made to find a surrogate measure linked with urgency, the pivotal symptom of overactive bladder.

Urgency is defined by the International Continence Society (ICS) as a sudden desire to pass urine, which is difficult to defer. The causal mechanism of this bothersome symptom remains unclear, but one possibility is that the urgency is caused by alterations in bladder afferent nerve activity. Based on this assumption the sympathetic skin response was studied as a potential way of objectively assessing sensory bladder function in healthy volunteers (Reitz et al., 2003), but further investigation in overactive bladder patients is needed. Another, potentially more attractive approach for investigating bladder nerve activity has been identified as H reflex calf muscle measurements (Conte et al., 2011). H reflex changes were presented as a putative measure of bladder nerve activity and were

shown to be modulated by treatment with Botulinum toxin A injections into the neurogenic overactive detrusor. This therefore has potential as a surrogate measure for this project and has been investigated further in the remainder of this chapter.

2.2. **H Reflex of the soleus muscle**

The Hoffman Reflex (or H reflex) has been investigated for several decades as a research and clinical tool. It has some similarity to stretch reflexes (e.g. knee jerk reflex), in which a muscle spindle of the quadriceps muscle is stretched and a signal travels to spinal cord via Ia nerve fibres. These afferent fibres activate efferent fibres (Alpha motor fibres) at the synapses and a signal travels back to the quadriceps muscle. Subsequently this signal contracts the quadriceps muscle spindles and causes a swing movement (stretch reflex).

The H reflex differs in terms of how the afferent signal is triggered. The signal is activated by using electrical stimulation of the sensory nerve fibres in the popliteal fossa and a reflex activates the soleus muscle, as in the knee jerk reflex (Edgoldbe, 2013) (Figure 2.1). The Electromyography (EMG) activity of the calf muscle group is recorded and H Reflex peak to peak amplitude measured.

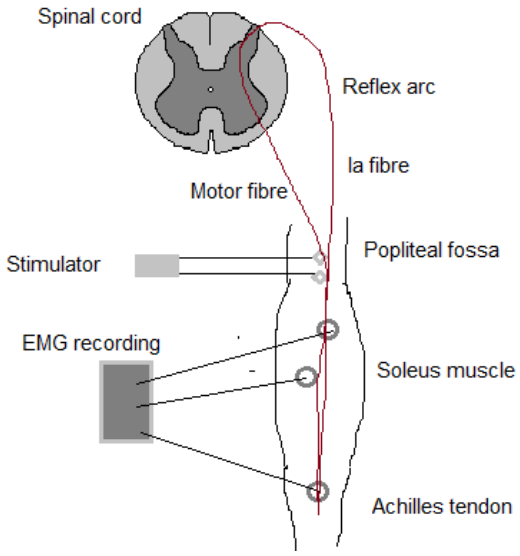


Figure 2.1 H Reflex pathway. Stimulation electrodes are placed in the popliteal fossa and active recording electrode on the belly of soleus muscle, with reference electrode on Achilles tendon.

If the strength of the stimulus is large enough to stimulate the motor fibres, then a direct motor contraction of the soleus muscles is produced (Figure 2.2, M wave). The

amplitudes of these two responses are dependent on the strength of the stimuli and are characterised by a recruitment curve (Figure 2.3). Clinically, the H reflex is used mainly for the evaluation of the calf muscle, where changes in bilateral responses may be an early sign of spinal stenosis (Palmieri et al., 2004).

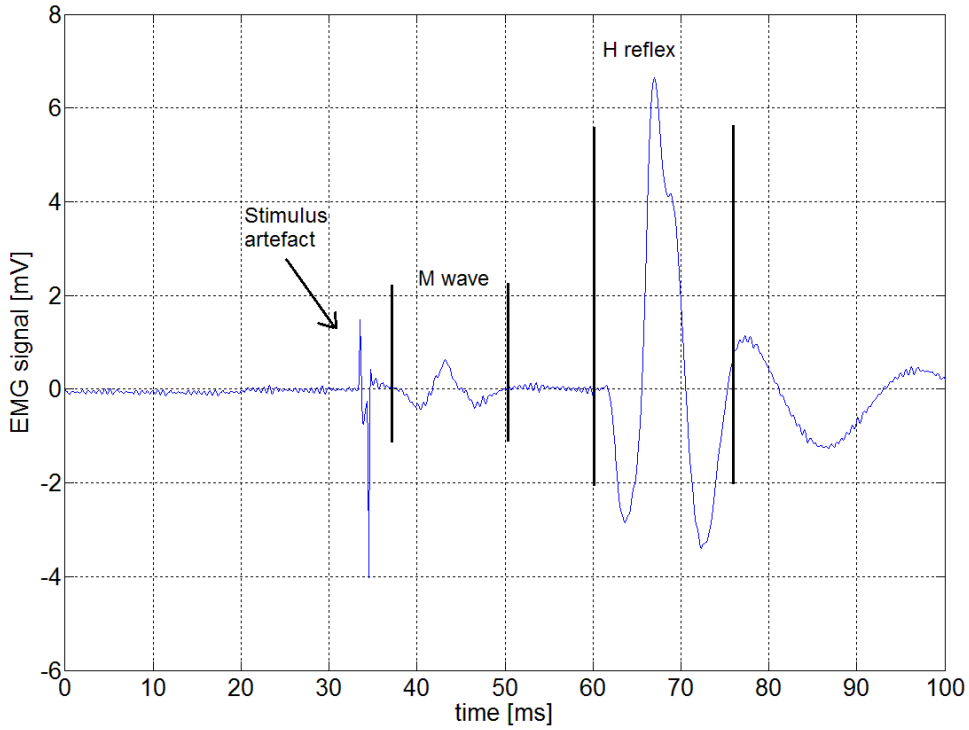


Figure 2.2 Typical normal EMG response at the soleus muscle

2.2.1. **H-reflex recruitment curve**

H reflex responses are activated at a relatively low intensity of stimulation. With increasing intensity of stimulation, more afferent fibres are activated and therefore produce a greater H reflex response (Figure 2.3). At the same time the direct stimulation of motor fibres produces the M wave signal. The H reflex magnitude reaches its maximum (H_{max}) at approximately 20% of the maximum of the motor response (M_{max}) stimulation intensity level. Further increases in intensity gradually decrease the H reflex magnitude until it completely ceases. This H reflex inhibition is due to antidromic collisions. An antidromic volley (electrical activity traveling in the opposite to normal direction) in a motor fibre collides with orthodromic activity (electrical activity travelling in the normal direction) activated as the H reflex (Palmieri et al., 2004).

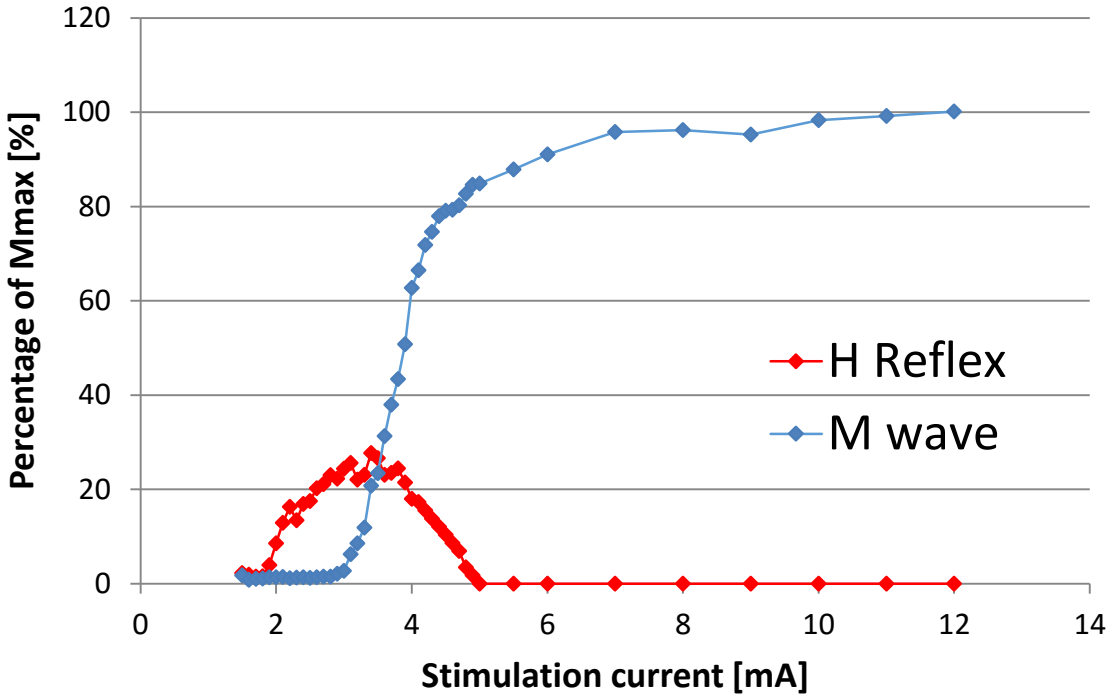


Figure 2.3 Recruitment curve as a percentage of M_{max} in one normal subject

2.2.2. **H Reflex changes during bladder filling**

Inghililleri et al. explored changes in the H reflex magnitude during bladder filling in normal subjects, spinal cord injury (SCI) patients and in multi-infarct encephalopathy (ME) patients (Inghilleri et al., 2001). The H reflex pk-pk magnitude evoked by stimulation in the popliteal fossa was measured with an empty bladder, at a medium bladder filling, at the maximum bladder filling and 10 minutes after voiding. A significant decrease in H reflex magnitude was observed in normal subjects and in ME patients at the maximum bladder fullness. However, in SCI patients the H reflex magnitude slightly (but not significantly) increased. After the voiding phase the H reflex size returned to the baseline value in all subjects. In 2002, Carbone et al. expanded their study to a group of non-neurogenic and neurogenic OAB and underactive bladder patients with similar results (Carbone et al., 2002). H reflex magnitude decreased at maximum bladder filling in normal subjects and non-neurogenic OAB patients. In contrast, neurogenic OAB patients (spinal cord injury) showed an increase in H reflex amplitude. It has been suggested that H reflex magnitude decrease is caused by an activation of spinal interneurons of bladder afferent input, which may change the level of spinal motorneurone excitability (Carbone et al., 2002). They suggested these findings may

help to determine the pathogenesis of voiding dysfunctions. The same researchers showed that H reflex inhibition at maximum bladder filling is supressed after itravesical Botulinum toxin type injection (BoNT/A) in Parkinson's disease patients (Conte et al., 2011). This is consistent with BoNT/A injected into the detrusor muscle modulating bladder afferent activity. These finding thus may have potentials for a surrogate measure of overactive bladder symptoms as needed in this thesis.

For the purpose of this work it was necessary to confirm the observations obtained by Conte et al. in a healthy subject. In addition it is important to consider other confounding factors, which may influence H reflex amplitude (Mai and Pedersen, 1976, McNulty et al., 2008, Sibley et al., 2007).

2.3. **Pilot trial**

Based on the literature discussed above, a pilot trial was carried out to investigate the H reflex magnitude changes in relation to bladder afferent nerve activity. Urodynamic cystometry evaluation is an invasive procedure and would not be practical for this work as a direct measure of bladder filling, therefore natural bladder filling via slightly enhanced water intake was used. A disadvantage of this approach is the relatively prolonged time required for the experiment.

Measurements of the H reflex in the soleus muscle has been described elsewhere (Knikou, 2008) however, more importantly, the problems of long term monitoring of the H reflex needs to be addressed. The angle of the hip is reported to be critical for H reflex recording (Conte et al., 2011, Knikou and Rymer, 2002) and initial pilot data showed that slight changes in the position of the leg caused a significant change in H reflex amplitude. Additionally, change in back posture may cause a stretch in the hamstring muscle tissue and cause a change in the position of the stimulation electrodes relative to the targeted structures. Therefore it is important to keep the position of both the electrodes and the body constant throughout the experiment. Interestingly it has been shown that M_{max} and H_{max} typically decrease during a long-term experiment (Crone et al., 1999), which might influence the overall findings for the purpose of this trial. However, such a decrease was not confirmed by McNulty et al. in whose study stable maximum amplitudes were obtained during 100 minutes measurements (McNulty et al., 2012). Additionally, the

study by (Crone et al., 1999) could have shown the decrease related to the bladder fullness, because the participants might not have been specifically instructed to empty their bladders before the H reflex measurements.

The H reflex amplitude is relatively sensitive to various other factors, such as anxiety (Sibley et al., 2007), alertness (Hodes, 1967), eye closure (Kameyama et al., 1989), turning of the head (Kameyama et al., 1989), previous muscle activity (Knikou, 2008) and so on. Therefore the participant must limit any movements and be as relaxed as possible.

Consecutive H reflex measurements are known to produce a progressive inhibition in H reflex magnitude, therefore inter-stimulus intervals of 10 seconds are recommended to suppress this inhibition (Aymard et al., 2000).

The time of the experiment was estimated to be 2 hours, therefore an automatic system to acquire the data was developed.

2.3.1. **Recording system**

To monitor the H reflex signal in an extended (as longer in duration) study ideally requires an automated process to simplify operator involvement and to consistently and objectively acquire data. The system is required to incorporate two essential functions:

- Deliver stimuli to generate the H reflex signal at predefined intervals.
- Record and automatically measure the signal H reflex magnitude.

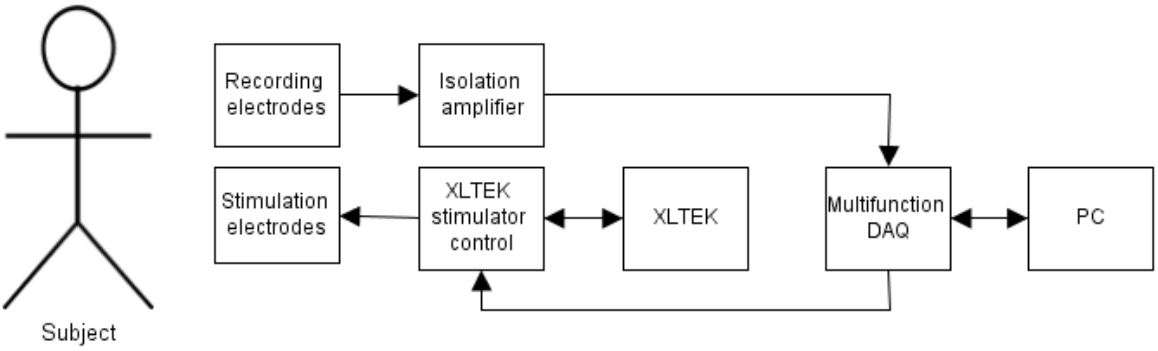


Figure 2.4 A purposed designed automatic measurement system

There are two signal flows in this system (Figure 2.4). These are a delivery of the stimuli through stimulation electrodes and a recording of the H reflex using the recording electrodes. Both parts are controlled by a computer running a LabView (National Instruments Ltd, UK) purpose-written application by Martin Slovak. This application synchronises the stimulator and measurement of the H reflex at a predefined interval. The measurement of M wave and H reflex magnitudes are made automatically by the software and saved along with the time of the measurement to a csv. file. The signal captured had similar latencies and thus allow to capture magnitude of M wave and H reflex (Figure 2.2) in predefined intervals.

The isolation amplifier (CED 1902, Cambridge Electronic Design, UK) feeds the EMG signal to the A/D converter of a Multifunction data acquisition unit (NI DAQpad-6015, National Instruments, Hungary). The digitised signal is then acquired using the LabView application and visualised on a laptop or PC screen.

The stimulation is delivered using an inbuilt constant current stimulator of the EMG Xltek system (XLTEK Neuromax 1004, Canada). A hardware interface unit was designed and constructed to enable the stimulator intensity and timing to be controlled by the LabView application and synchronised with the EMG measurement.

2.3.2. **Position of leg and M wave monitoring**

From the initial piloting it was observed that it is not critical at what angle the leg is kept, as long as the position is constant during the whole experiment. A convenient position of approximately 120° at hip, 30° at knee and 120° at foot was chosen and kept at this angle throughout the experiment in order to suppress any changes due to leg position. The participant's foot was supported by a footrest. To ensure that the same fibres are recruited in each of the measures, the M wave was monitored throughout the experiment and the stimulation intensity level adjusted if the M wave was significantly changed. The stimuli intensity was set to produce a small (compared to the supra-maximal response) M wave response of typically 1 mV. A stimulation interval of 10 s between recordings and a pulse width of 1 ms were adopted from methodology of (Carbone et al., 2002).

2.4. **Pilot trial results**

The pilot trial was carried out on a single healthy subject to test the feasibility of the protocol. During the first stage the stability of the measurements was recorded with an empty bladder over a duration of 90 minutes in a single experiment (Section 2.4.1). Following this recording, a natural bladder filling was evoked by an increased fluid intake (Section 2.4.2). At this stage it was observed that the H reflex was decreasing.

The bladder volumes have not been measured in this experiment, because an ultrasound bladder scan would require the subject to be in supine position and thus complicate the H reflex protocol measurements. Instead the subject recorded the perceived sensation according to the standardise terminology used for filling cystometry (Abrams et al., 2002).

All Figures in the following sections use the same legend – blue circles are single H reflex pk-pk amplitudes, green circles are single M wave pk-pk amplitudes, and a red line denotes the changes of H reflexes in 30 seconds intervals.

2.4.1. **Stability of H reflex magnitude measurement (empty bladder)**

To investigate the changes of H reflex magnitude with time measurements of H reflex with an empty bladder were recorded for approximately 90 minutes (Figure 2.5). This showed that the magnitude of H reflex does seem to be relatively stable. The unpaired Student's T-test showed no significant difference ($p = 0.344$) between the means of the first 30 minutes (mean = 6.79 mV, SEM = 0.11 mV, n = 180) and the last 30 minutes (mean = 6.65 mV, SEM = 0.10 mV, n = 180).

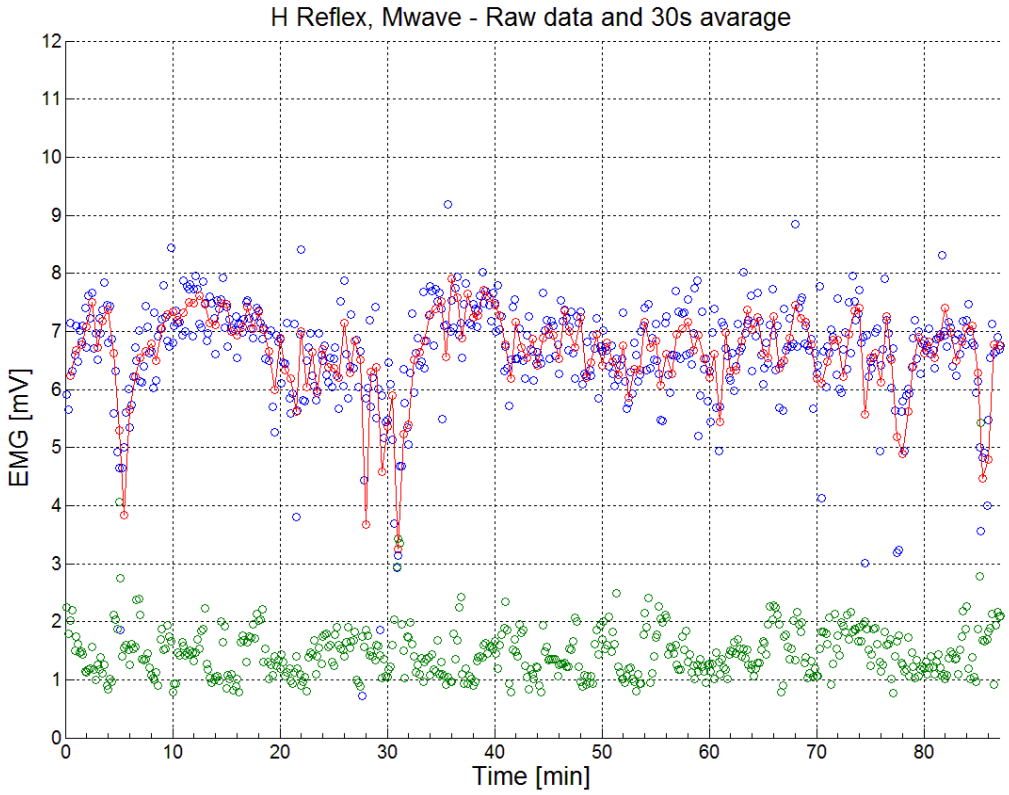


Figure 2.5 Example of stability of H Reflex measurement over 90min period. Green points – M wave pk-pk, Blue points – H reflex pk-pk, red line – changes of H reflex in 30s intervals

Two significant decreases at 5 minutes and 30 minutes, were caused by an involuntary movement or contractions of the leg muscles. Other obvious decreases at 28. minutes 78. minutes min and 85. minutes were unknown origin, however it is likely that they were related to involuntary movements.

2.4.2. **H reflex during bladder filling**

The H reflex magnitude gradually decreased during natural bladder filling and this decrease correlated with the sensation of bladder filling (Figure 2.6).

The regular water intake of 250 ml every 5 minutes started immediately after the start of recording and altogether 1.5 l of water was drunk. The first sensation of bladder filling (FSF) appeared at 40 minutes. The first desire to void (FDV) was sensed at 53 minutes, and a strong desire to void (SDV) was sensed from 67. minute. The maximum sensation occurred at approximately 88 to 90 minutes. Despite the fact that the sensation could be suppressed, this was considered as the maximum (MAX) and the subject went to the toilet

to void, with the electrodes still attached to their leg. The recording started again after the voiding at 93. minute and continued for another 30 minutes.

The baseline data were considered as the first 20 minutes (water intake should have had no effect as yet on the bladder fullness), followed by periods of sensation (FSF, FDV, SDV, MAX). Each sensation interval contained the measurement data until the next level of sensation (Table 2.1). A one-way ANOVA – Dunnett's multiple comparisons showed a significant difference between the baseline as a control and all period groups (including after the voiding period). There was no significant change between the first 10 minutes of baseline data in compare to the second 10 minutes of baseline ($p = 0.760$).

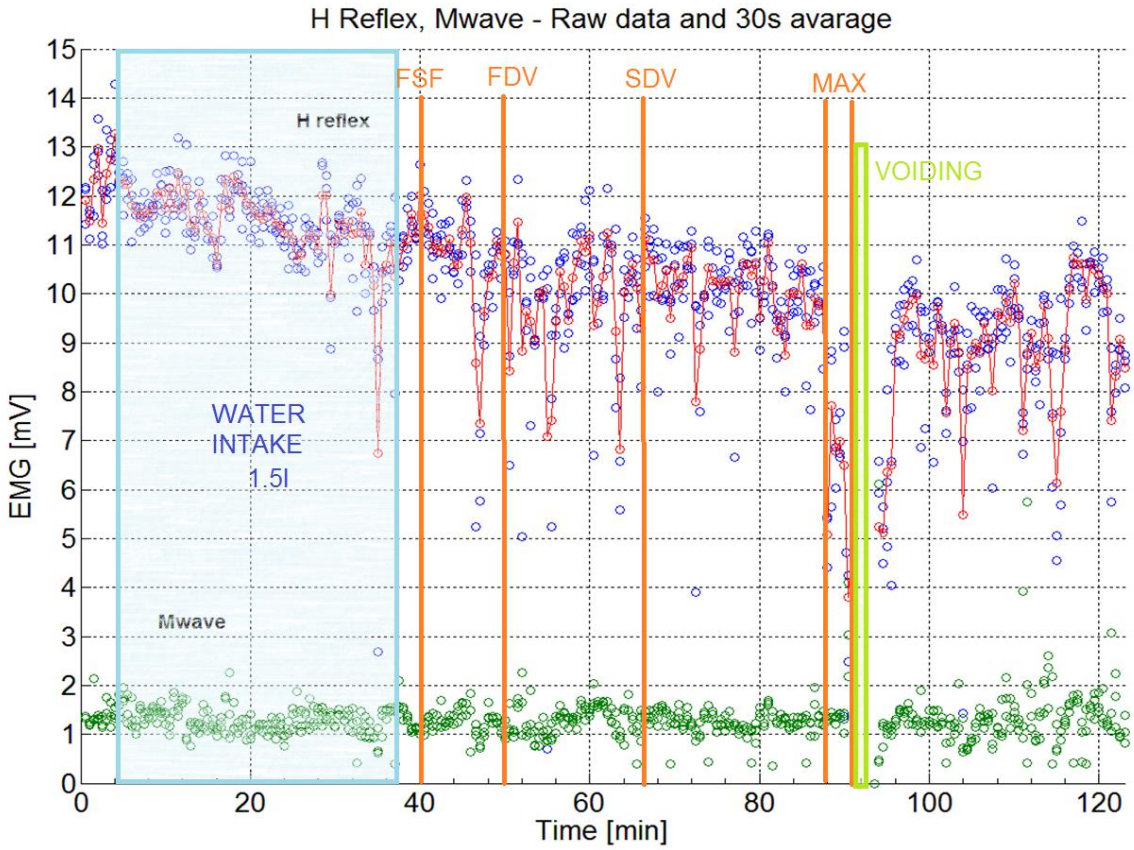


Figure 2.6 An example of individual H reflex (blue circles) and M wave (green circles) recordings during nature bladder filling.

Table 2.1 H Reflex pk-pk [mV] amplitude group data and mean change from baseline

	Baseline 0-10min	Baseline 10-20min	FSF 40-53min	FDV 53-67min	SDV 67-88min	MAX 88-90min	After 93-123min
Mean	12.1	11.8	10.6	9.8	9.9	6.7	8.8
SEM	0.08	0.08	0.2	0.2	0.1	0.6	0.1
n	60	60	61	102	125	13	178
95% CI	11.9-12.2	11.6-11.9	10.3-10.9	9.5-10.2	9.7-10.1	5.4-8.1	8.6-9.1
Change from baseline 0-10 min							
Mean		0.3	1.4	2.2	2.1	5.3	3.2
SEM		0.2	0.2	0.2	0.2	0.4	0.2
95% CI		-0.4 to 0.9	0.8 to 2.1	1.6 to 2.8	1.6 to 2.7	4.2 to 6.3	2.7 to 3.7
P values		0.760	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Although the experiment was interrupted at the maximum sensation, it has been noted that if this urge sensation can be suppressed then there is a return of the H reflex inhibition as well as the sensation.

This experiment was repeated three times on different days on the same subject and it was noted that the H reflex magnitude decrease might be related to a gradual increased activity of the pelvic floor muscle (PFM) during bladder filling. As it is pointed out above it was noted especially towards the end of the bladder filling cycle, when the bladder was full, and a more frequent and intense intensity of desire to void occurred. Therefore the following experiments investigated the influence of voluntary PFM contraction and cough, as an involuntary activation of PFM.

2.4.3. **Effect of Pelvic floor muscles / sphincter contractions and cough on H reflex**

In a further single experiment (Figure 2.7 and 2.8) H reflex baseline values were recorded for 3 minutes, then in a random order, voluntary contractions of the pelvic floor muscles/sphincters or cough was performed. Transcutaneous Posterior Tibial Nerve Stimulation (TPTNS) was applied as a feasibility test of practicality to use the H reflex as a surrogate measure of different stimulation settings simultaneously with voluntary contractions of the pelvic floor muscles/sphincters. The TPTNS (10 Hz, 200 μs pulse width, intensity below the motor contraction of toes) was applied using a TENS stimulator (TENStem Eco Basic, SchwaMedico, Germany) and surface electrodes (50x50 mm, Stimex, France) were placed below and above medial malleolus. There was a subjective observational feeling that PTNS may help to contract the PFM. The mean baseline value was 15.5 mV (SEM = 0.1 mV, calculated from first 3 minutes of the recording). Mean

contraction 10.9 mV (SEM = 0.2 mV) and mean contraction PTNS 10.9 mV (SEM = 0.3 mV) showed a significant difference (one-way ANOVA) to baseline, however these were not significantly different to each other nor to the mean of cough, 8.45 mV (SEM = 0.2 mV).

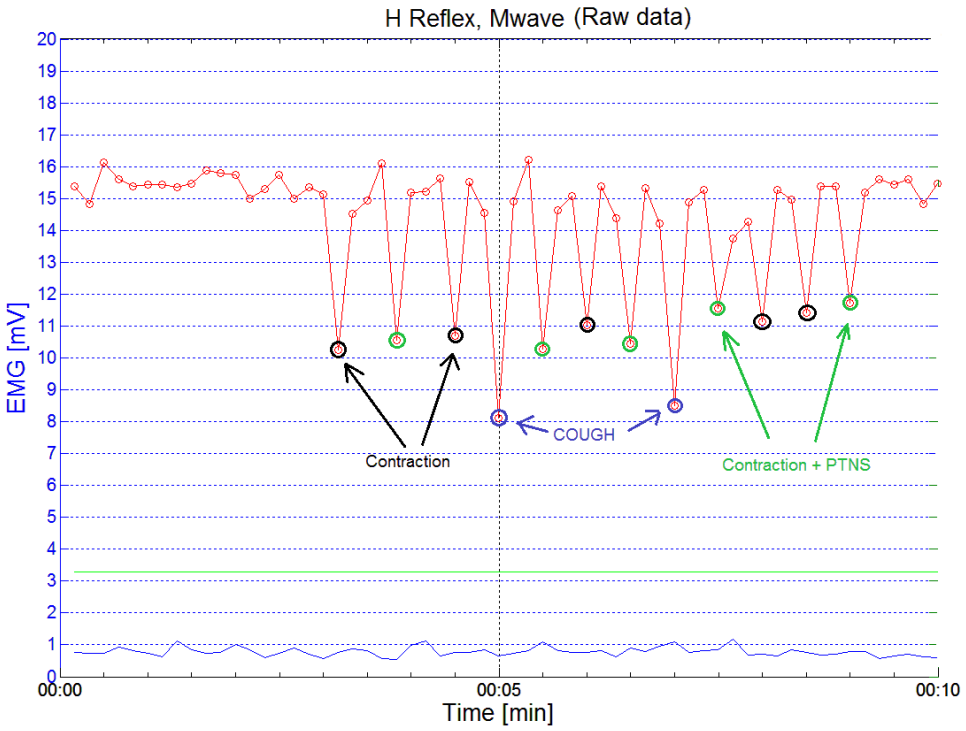


Figure 2.7 Inhibition of H reflex by cough and by contractions of pelvic floor muscles. Black - Contractions, Green - Contractions + PTNS, Blue - cough

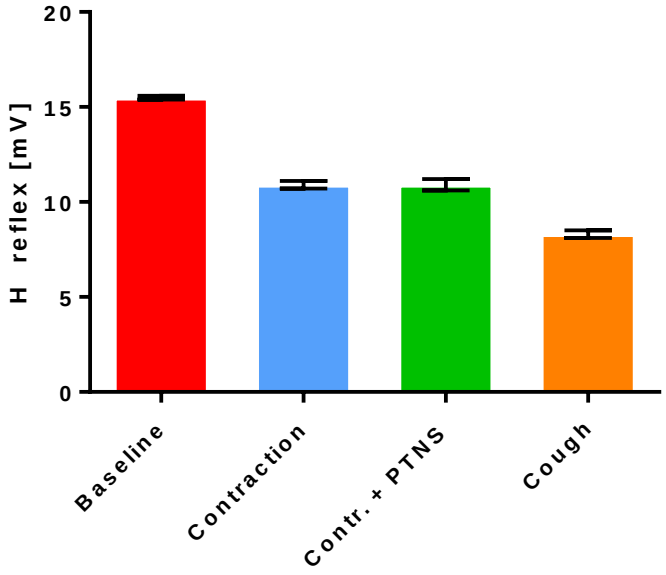


Figure 2.8 Effect of different actions on H reflex, mean ± SEM

2.5. **Discussion of the pilot experiments**

H Reflex inhibition during the bladder filling has been interpreted as an action of bladder afferent activity (Conte et al., 2011). This could make it a useful surrogate measure for the evaluation of different stimulation parameters in both normal subjects and patients. The pilot experiments demonstrated that the H reflex significantly decreases during natural bladder filling. However, such a decrease might not be caused only by the bladder afferent activity as originally suggested.

During bladder filling a gradual increase in the contraction of the external urethral sphincter and pelvic floor muscles is presented. The experiment involving contractions of PFM and cough (a cough causes reflex contraction of PFM to suppress leakage due to an increase of intra-abdominal pressure) demonstrated that the H reflex is significantly decreased by these interventions and therefore may be significant confounding factors. In addition, the H reflex amplitude might be influenced by various processes including discomfort or alertness. Sibley et al. 2007 identified decreases in H reflex amplitude due to anxiety (Sibley et al., 2007), which might slightly correlate with anxiety about leaking at the end bladder filling, hence the decrease during bladder filling.

This initial experiment has shown that H reflex amplitude might be sensitive to PFM or sphincters and therefore might not be an ideal surrogate measure of bladder afferent

activity. Transcutaneous PTNS applied during PFM contraction did not have an influence on the H reflex magnitude when compare to PFM contraction alone.

These initial experiments do not favour H reflexes as surrogate measure. However, the absence of other obvious candidates justified the study of these confounding factors in a larger group of healthy volunteers before any conclusion can be made. Therefore further investigations were carried out.

2.6. **Healthy volunteer study – is H reflex inhibition related to PFM?**

The pilot observations have been made on a single subject, therefore to assess if there is a significant influence of pelvic floor muscles on the H reflex magnitude, a group of healthy volunteers was studied. Similarly, Mai and Pedersen asked medical students to contract their sphincter during the H reflex measurement and a significant decrease in amplitude of H reflex was observed (Mai and Pedersen, 1976).

During the bladder filling cycle the bladder increases its volume and the bladder wall stretches. This causes an activation of stretch receptors in the bladder wall and increases the bladder afferent activity. The parasympathetic innervation of the detrusor is inhibited and the pelvic floor muscle group along with the urethral sphincter are activated to prevent the bladder from an involuntary emptying (Fowler et al., 2008). The aim of this study is to determine if H reflex inhibition mechanism is entirely due to the bladder nerve activity (Pathway 1, Figure 2.9) or if there might be an additive influence of PFM (Pathway 2, Figure 2.9). The study will not be able to determine if H reflex is a combination of these two pathways. However it will be able to determine if the pathway 2 exists and determine if the H reflex should be considered to be use as a surrogate measure.

External input for the activation of PFM might be voluntary or involuntary, of which the latter usually relates to an increase in the intra-abdominal pressure.

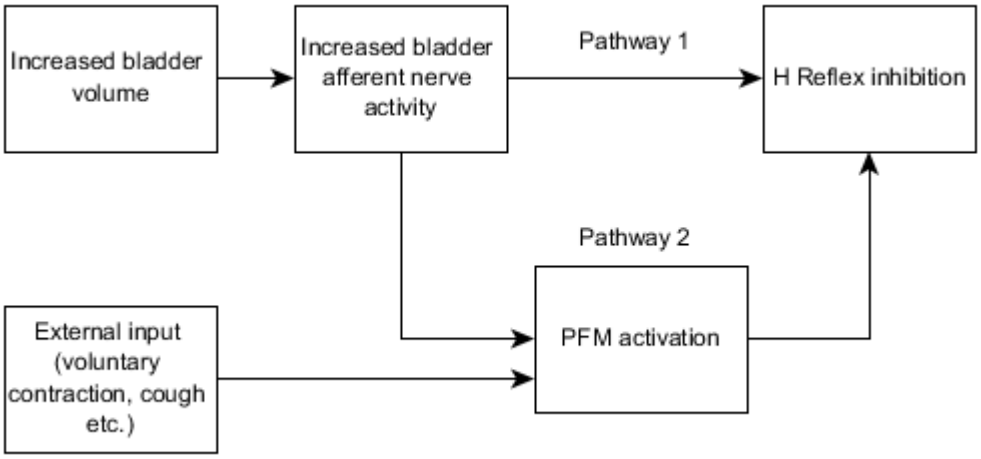


Figure 2.9 Possible pathways underlying the H reflex inhibition

2.6.1. **Materials and methods of the study**

The study was approved by the University of Sheffield ethics committee and the experiments were carried out at the Clinical Research Facility, Royal Hallamshire Hospital, Sheffield (Appendix A).

2.6.1.1. **Participants**

Potential participants were approached via the University email advertisement or directly by Martin Slovak. They were provided with an information sheet about the study. If they decided to participate, a study visit was arranged. As part of the study visit all the participants were checked against the inclusion and exclusion criteria (Appendix B) and signed the informed consent form.

2.6.1.2. **H reflex measurement**

The H reflex measurement system used in the piloting was used for the study (Section 2.3.1). A pair of stimulation electrodes was placed behind the knee at the popliteal fossa. The reference recording electrode was placed at the distal site of the achilles tendon. The active recording electrode was placed approximately half the distance between the reference electrode and the stimulation electrodes on the medial gastrocnemius muscle. The stimulating and recording electrodes were 3 cm^2 "duck-foot" shaped standard neurology electrodes (70010-K/C/12, Neuroline 700, Ambu, Malaysia). A 4x5 cm oval

shaped ground electrode (019-400500, CareFusion, USA) was placed between the stimulation electrodes and the active recording electrode.

One milliseconds, rectangular, constant current stimulation pulses of an intensity generating an M wave of around 1 mV and producing a clearly recognisable H reflex were delivered every ten seconds. To set achieve this optimal level of stimulation intensity, the stimulation electrode might have been slightly repositioned.

2.6.1.3. **Test process**

The participants were instructed about each of the test conditions (below) and asked to empty their bladder before the electrodes were placed on the skin. The participant sat on a comfortable adjustable chair with their knee flexed 30 degrees from full extension and the ankle kept approximately at a right angle to the lower leg, rested against a foot support.

Only the participant and the experimenter were present in the room to keep any distractions to a minimum. The participants were asked to relax, keep the leg in a stable position and to focus on the experiment throughout.

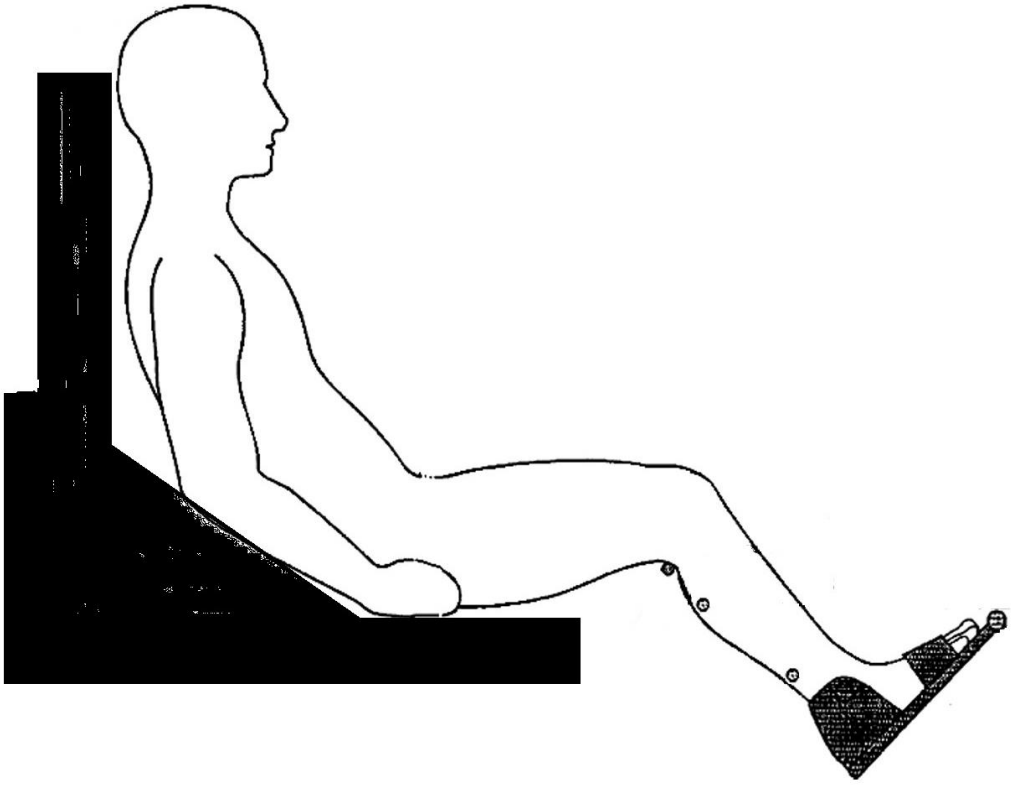


Figure 2.10 Participant's position on the adjustable chair during the H reflex recording

2.6.1.4. **Test conditions**

The test conditions were chosen to activate PFM either voluntarily or involuntarily. The voluntary activation was achieved using two types of exercise:

Isolated Pelvic Floor Muscle contraction (IPFM) – for this exercise, the following description from an advisory leaflet was used (Bladder and Bowel Foundation, 2008) .

"Sit comfortably with your knees slightly apart. Now imagine that you are trying to stop yourself passing wind from the bowel. To do this you must squeeze the muscles around the back passage. Try squeezing and lifting that muscle as if you really do have wind. You should be able to feel the muscle move. Your buttocks and legs should not move at all. You should be aware of the skin around the back passage tightening and being pulled up and away from your chair. Really try to feel this squeezing and lifting."

It was emphasised to the participants that they should try to avoid contractions of abdominal and buttocks muscles.

Maximal Pelvic Floor Muscle contraction (MPFM) – the same instructions as for the IPFM were provided, however this time the participants were asked to produce maximal contraction and were allowed to contract buttocks and/or abdominal muscles.

The involuntary pelvic floor muscle exercises consisted of:

Light cough (LC) – this was described as a gentle, light cough.

Deep cough (DC) – this was described as the strongest maximal cough that the participant is able to produce.

Valsalva Manoeuvre (VM) – the participant was asked to pinch their nose and perform a maximal attempt to forcibly exhale against the closed nose and mouth. This manoeuver should cause a modest activation of PFM (Thompson et al., 2006), although this was not assessed objectively in any of the test conditions.

2.6.1.5. **Test procedure**

All the measurements of H reflex and M wave and full EMG waveforms were recorded consecutively every 10 seconds and saved in the file. Each of the test conditions was

performed five times, in a randomized order. Five consecutive data measurements prior to each of the test conditions were used to calculate baseline values of H reflex. The participants were warned what the next required contraction type would be in advance. Five seconds before the measurement was trigged, the investigator counted down the time to ensure synchronisation between the test condition and the measurement. The experimenter recorded the time of each test and the next test condition was performed after another five baseline data measurements.

2.6.1.6. **Data analyses**

The complete data set for each of the participant consisted of 25 tests. To ensure brevity of the analyses, the following glossary of the terms used has been created.

Glossary of the terms used:

Participant Dataset (PDS) – each dataset consisted of 25 Test Datasets (TD). This is because each of the five test conditions was repeated five times.

Test dataset (TD) – these are data of one test (Table 2.2). The dataset consisted of the five baseline measurements (BM) and one test condition measurement (TCM).

Table 2.2 Example of the test data for one participant at one test condition

BM_1	BM_2	BM_3	BM_4	BM_5	$TCM_{IPFM,1}$
9.35 mV	8.06 mV	7.77 mV	5.8 mV	8.12 mV	4.28 mV

Baseline Measurement (BM_i)– the H reflex magnitude at the baseline measurement i (e.g. BM_1, BM_2, BM_3, BM_4, BM_5)

i – the ordinal number of the baseline measurement for a particular N and TC

Test Condition Measurement ($TCM_{TC,j}$) – the H reflex magnitude for a specified TC (e.g. $TCM_{IMPFM,1}$ – TCM at Isolated Pelvic Floor Muscle test condition, test one)

j – the ordinal number of the particular test for TC

Test Condition (TC) – the type of the test condition as defined in Section 2.6.1.4

Baseline Test Mean (BTM) - mean of the five baseline measurements prior to each of the test conditions.

Single change – this is a percentage change in the magnitude of H reflex for a test measurement from the baseline test mean.

Mean change – mean of the single changes for a particular TC

$$BTM_{TC,N} = \frac{\sum_{j=1}^{j=5} BM_{TC,N,j}}{j_{MAX}} \quad (2.1)$$

$$Single\ Change_{TC,N} = \frac{TCM_{TC,N}}{BTM_{TC,N}} \times 100 \quad (2.2)$$

$$Mean\ change_{TC} = \frac{\sum_{N=1}^{N=5} Single\ Change_{TC,N}}{N_{max}} \quad (2.3)$$

j_{MAX} – number of the baseline values measured, default five values

N_{max} – number of the tests for each test condition

The primary outcome measure was the mean change of the H reflex from the baseline for each test. The Wilcoxon test was used to compare the mean of BTM with TCM.

The single change was expressed as percentual change of test condition measurement (TCM) with baseline test mean (BTM) of the same test. This normalised value is a result of one test. The mean of five tests for each of the conditions was taken for each participant and compared to the control values of 100% (no change) using Wilcoxon tests.

Two way ANOVA test with Sidak's multiple comparison with post hoc analyses was used to compare the magnitude values of H reflex of mean BTM values with TM for each test condition and participant. The result of each multiple comparison was indicated as

Increase – post hoc significant difference and increase from BM (>100% of baseline)

Decrease – post hoc significant difference and decrease from BM (<100% of baseline)

No statistically significant difference was considered as *no change*.

2.6.2. **Results**

A total of 13 participants were recruited and finished fully the study protocol. Out of 325 total tests, 319 tests were analysed. Six tests from five participants have not been included into analyses due to a technical fault in the data collection.

2.6.2.1. **Demographics**

The participants consisted of five males and eight females. The majority of the participants were native English speakers, however, four participants had English as their second language. The demographic data of the group are summarised in the Table 2.3.

Table 2.3 Demographic data

Pt no.	Sex	Age	Body mass index
1	M	24	23.0
2	F	31	20.8
3	F	47	26.7
4	M	37	28.1
5	M	64	26.6
6	F	25	21.5
7	F	23	20.4
8	F	31	18.3
9	M	45	30.4
10	F	24	19.1
11	F	31	22.5
12	M	28	21.1
13	F	27	19.0
Mean (SD)		33.6 (11.9)	22.9 (3.9)

2.6.2.2. **Change of the H reflex magnitude**

The primary outcome (the mean change of H reflex amplitude during each of the test conditions) is summarised in Table 2.4. Statistically significant decrease in the H reflex amplitude were obtained in MPFM ($p = 0.0479$) and DC ($p = 0.0034$) with LC approaching significance ($p = 0.0681$).

Table 2.4 H reflex amplitude change

	H reflex amplitude pk-pk [mV]				
	IPFM	**MPFM**	**LC**	**DC**	**VAL**
Baseline					
Mean (SD)	6.2 (3.3)	6.0 (3.1)	6.1 (3.2)	6.3 (3.2)	6.2 (3.2)
Range	2.5 to 11.4	2.2 to 11.3	2.2 to 11.5	2.2 to 11.5	2.1 to 11.5
Test					
Mean (SD)	6.2 (2.9)	4.2 (2.6)	5.1 (2.9)	4.0 (3.0)	6.5 (3.2)
Range	1.1 to 11.4	1.0 to 8.9	2.2 to 10.6	0.5 to 9.4	2.5 to 11.5
Change					
Mean (SD)	-0.008 (1.4)	-1.8 (2.7)	-1.0 (1.7)	-2.3 (2.7)	0.3 (1.3)
Range	-2.5 to 2.4	-7.2 to 1.6	-4.9 to 0.9	-9.7 to 1.0	-2.1 to 2.4
CI 95%	-0.8 to 0.8	-3.4 to -0.2	-2.1 to 0.02	-4.0 to -0.6	-0.5 to 1.2
P value	P > 0.999	P = 0.0479	P = 0.0681	P = 0.0034	P = 0.273

* IPFM- isolated pelvic floor muscle contraction, MPFM - maximum pelvic floor muscle contraction, VAL - Valsalva manoeuvre, LC - light/gentle cough, DC - deep/strong cough

Table 2.5 and Figure 2.11 summarise the H reflex amplitude changes expressed as a change from the baseline in the mean of the five tests in each participant. Confidence interval of 95% indicates significant changes again in MPFM and DC.

Table 2.5 H reflex amplitude change from the baseline

	H reflex amplitude (% baseline)				
	IPFM	**MPFM**	**LC**	**DC**	**VAL**
Mean ± SD	106.8 ± 35.3	75.6 ± 37.4	88.2 ± 27.9	64.9 ± 35.5	112.4 ± 34.5
Range	49 - 176	26 – 142	33 - 130	5 - 120	60 - 194
CI 95%	85.4 - 128.1	53.0 - 98.3	71.3 - 105.0	43.4 - 86.36	91.5 - 133.2

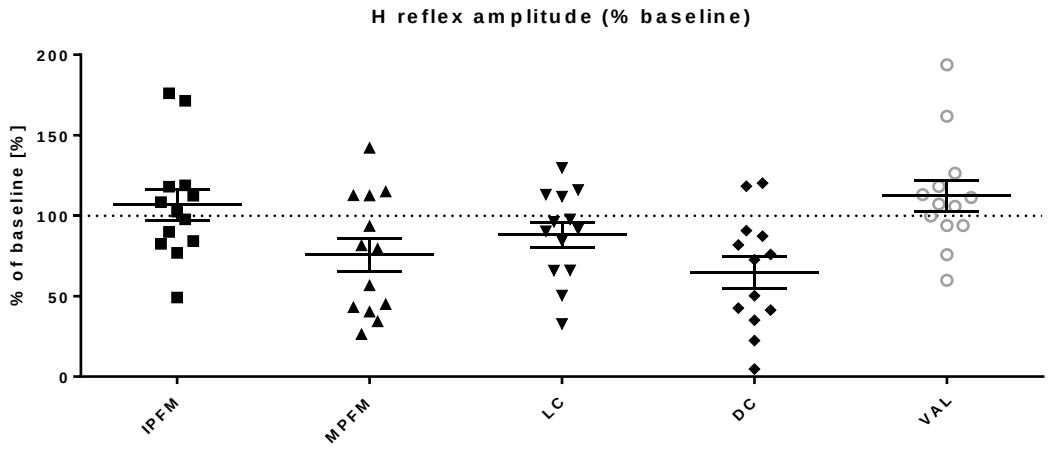


Figure 2.11 H reflex amplitude change in each of the participant

2.6.2.3. **Analyses of individual participant responses**

It has been noted that, in some participant, H reflex magnitude slightly increased rather than decreased and in some participant did not change significantly. A typical significant decrease is shown on Figure 2.12 (Participant #6, DC). A typical significant increase, which by its size was not as dramatic is shown on Figure 2.13 (Participant #11, MPFM). Therefore further analyses has evaluated the number of participants with a trend towards decreasing the H reflex magnitude and number of participants with a trend towards increasing. The trend of change is defined in the methodology (Section 2.6.1.6) as a significant change using Two way ANOVA test with Sidak's multiple comparison (Table 2.6)

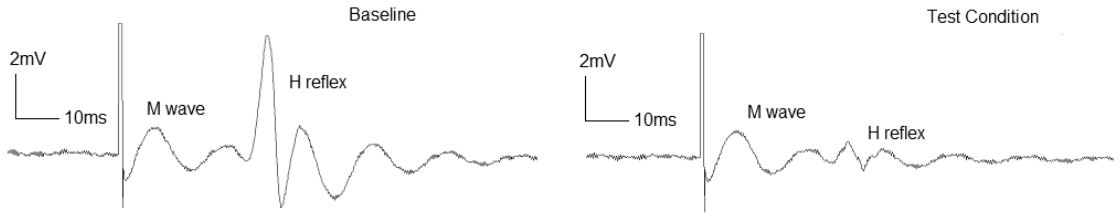


Figure 2.12 A typical decrease of H reflex magnitude during a test condition exercise

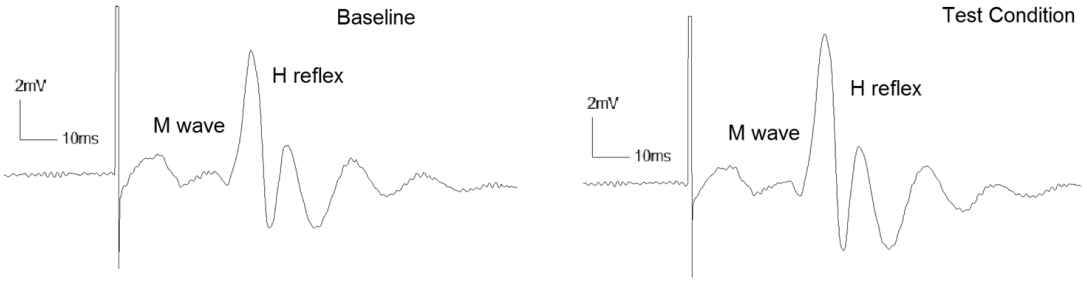


Figure 2.13 A typical slight increase of H reflex magnitude during a test condition exercise

Table 2.6 Summary of statistically significant changes of H reflex in each of the participant

Participant	Trend of change in the H reflex magnitude				
	IPFM	MPFM	LC	DC	VAL
1	-	Decrease	Decrease	Decrease	Decrease
2	-	-	-	-	-
3	-	Decrease	-	Decrease	-
4	-	-	-	-	-
5	-	-	-	-	-
6	-	Decrease	Decrease	Decrease	Decrease
7	Decrease	Decrease	-	Decrease	-
8	Increase	-	-	-	Increase
9	-	Decrease	-	-	-
10	Decrease	Decrease	Decrease	Decrease	Increase
11	Increase	Increase	-	-	Increase
12	-	Decrease	-	-	-
13	-	-	Decrease	Decrease	-
Decrease	2	7	4	6	2
Increase	2	1	0	0	3
No change	9	5	9	7	8

The participants #1, #3, #6, #7, #9, #10, #12 and #13 had a trend towards decreasing the H reflex magnitude during the test conditions exercises, whereas participants #8 and #11 has a trend to increase it. However these observations were not been observed in all of the test conditions. Participants #2, #4 and #5 did not show a significant difference during the test conditions in comparison to baseline in any of the test conditions exercises. These inconsistences are difficult to explain, but could be caused by the participant's insufficient activation of PFM. The level of PFM activation was not objectively assessed and relied on the subject compliance. The differences in the trend could be caused by natural variance across the population.

2.6.3. **Further analyses of the data**

Significant decrease of the H reflex magnitude during activation of pelvic floor muscles has been observed only during MPFM and DC (Table 2.4). As mentioned above it has been noted that, in some participant, H reflex magnitude slightly increased rather than decreased. At the same this changes have not been observed in all of the exercises, raw data for each participant are shown in Appendix C. Figure 2.14 shows a typical raw data set (for the Participant #1).

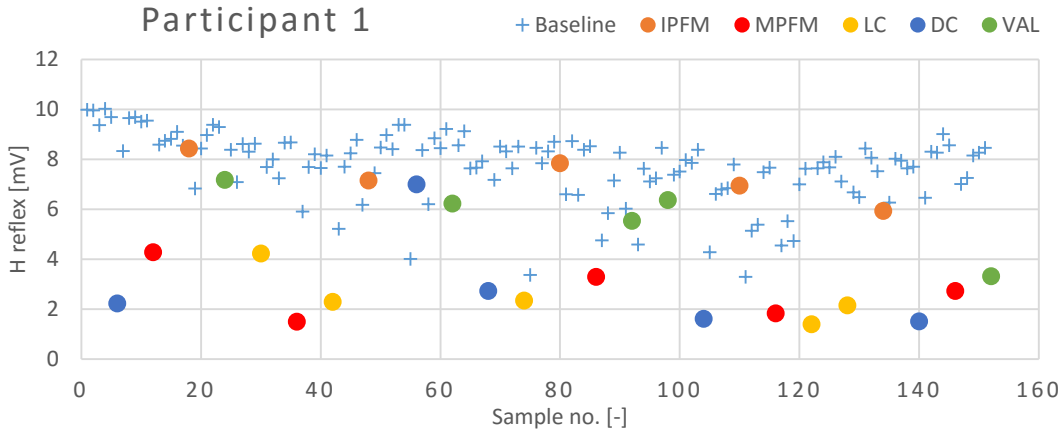


Figure 2.14 Typical dataset obtained during the experiment

The analyses up-to this point only considered the mean of each test condition. However, if the aim of this study remains to investigate H reflex variability, as opposed to movement in one direction, during PFM activation, then a different analysis is needed.

Therefore, further analyses will investigate the variation of the H reflex magnitude in each test condition, compared to the baseline values obtained without an activation of PFM. To do this the baseline variation has been compared with that of the test variation.

2.6.3.1. **Coefficient of variation**

The coefficient of variation (Wikipedia, 2016) from a sample of the data is calculated as:

$$C_v = \left(1 + \frac{1}{4 * N}\right) \times \frac{\sigma}{\mu} \tag{2.4}$$

Where,

N – Number of samples

μ - Sample mean

σ – Sample standard deviation

2.6.3.2. **Does the H reflex magnitude variation change during the exercise?**

To answer this question the variation of baseline sample is compared to the variation of the baseline and test data combined. In other words, the analyses should look for a difference if one measurement in the baseline data collection is replaced with a test condition. As there are five baseline measurement and one test condition per group, the coefficient of variation would be relatively insensitive to the contribution of the test condition if all measurements in the group are combined. Instead, a novel test in which a comparison of a pair of baseline measurements with a pair of baseline measurement and test condition measurement has been developed

The "Baseline data" are defined as two baseline measurements (B4 and B5). The "Test data" are defined as one baseline measurement (B5) and the test measurement (Figure 2.15). The mean coefficient of variation in Table 2.7 is expressed as mean of the five tests for each the test condition in each participant.

The Table 2.7 shows that the IPFM, MPFM, LC, DC test conditions significantly influence the change in the variation of the baseline data. VAL test condition has not shown to have an influence on the variation of the baseline measurement.

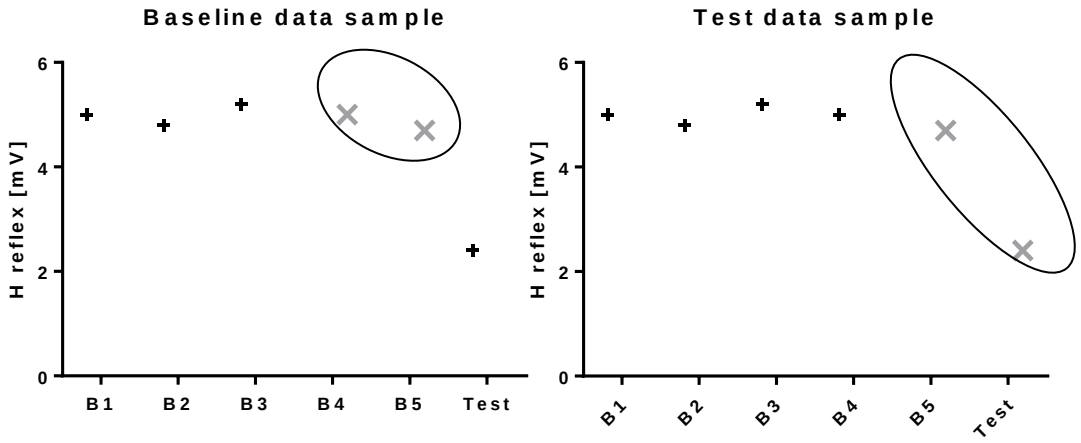


Figure 2.15 Illustration of the data used for calculation of the coefficient of variation

Table 2.7 Coefficients of variation

Pt	IPFM		MPFM		LC		DC		VAL	
	Base	Test	Base	Test	Base	Test	Base	Test	Base	Test
1	0.11	0.12	0.08	0.57	0.06	0.58	0.11	0.58	0.12	0.27
2	0.07	0.06	0.12	0.05	0.11	0.16	0.09	0.21	0.12	0.11
3	0.20	0.43	0.18	0.62	0.19	0.16	0.38	0.90	0.29	0.25
4	0.10	0.13	0.10	0.14	0.06	0.19	0.06	0.22	0.07	0.12
5	0.14	0.17	0.15	0.15	0.12	0.14	0.17	0.24	0.10	0.17
6	0.18	0.22	0.24	0.43	0.23	0.51	0.16	0.49	0.26	0.38
7	0.05	0.12	0.05	0.31	0.05	0.07	0.04	0.21	0.04	0.04
9	0.26	0.29	0.08	0.29	0.27	0.29	0.18	0.54	0.29	0.31
10	0.07	0.06	0.05	0.14	0.04	0.06	0.05	0.09	0.05	0.07
11	0.11	0.24	0.21	0.70	0.09	0.27	0.21	0.98	0.13	0.07
12	0.20	0.25	0.20	0.19	0.39	0.23	0.25	0.50	0.24	0.14
13	0.15	0.18	0.21	0.43	0.09	0.11	0.21	0.22	0.16	0.14
Mean	0.137	0.185	0.150	0.334	0.146	0.233	0.166	0.427	0.157	0.172
SEM	0.016	0.028	0.021	0.056	0.028	0.043	0.027	0.076	0.024	0.028
P value	0.0044		0.0049		0.0378		0.0002		0.4648	

2.7. **Conclusions**

Previously reported studies of H reflex changes during bladder filling have suggested a linkage between bladder afferent nerve activity and H reflex magnitude (Conte et al., 2011, Carbone et al., 2002). However, the pilot experiments have challenged these findings and raised a question as to whether the H reflex magnitude changes are likely to be caused by a concomitant activation of PFM during bladder filling rather than the bladder nerve activity alone. The further volunteer study has shown that the H reflex magnitude is significantly decreased during maximum pelvic floor muscle contractions and during deep cough. In comparison to the bladder filling studies this effect has not been observed in all of the participants. Isolated pelvic floor muscle contraction and Valsalva manoeuvre seem to either decrease or increase the H reflex magnitude inconsistently, which first was one has also been observed elsewhere in the literature (Mai and Pedersen, 1976). Finally, it has been shown that all of the PFM activities except those related to Valsalva manoeuvre have an impact on the variation of H reflex magnitude when compared to the variation of baseline measurements, thus destabilising it. Despite the best effort to explain the IPFM and VAL exercise to the participants the inconsistency in these observations might also be linked to the inability of the participants to perform the tests consistently.

The main limitation of the volunteer study presented here was the inability to objectively measure the performance of each of the test conditions which may have varied in each of the test condition and across the participants.

The results of the studies presented in this chapter do not lead to a robust conclusion that H reflex would be a useful surrogate measure for overactive bladder symptoms. Previous claims about its usefulness for observing modulation of bladder nerve activity need to be clarified in relation to the findings in this chapter.

Further work to find a suitable surrogate measure was not carried out during this thesis because the literature did not support any alternative avenues of investigation. Instead, the focus of the next chapter is directed towards producing more physiologically effective electrical stimuli.

Chapter 3 **Sensory Barrage Stimulation – a novel concept of multichannel electrical stimulation**

The work in this chapter has been published in:

M. Slovak, J. Chindo, M. Reeves, B. Heller, A. T. Barker, S. Nair. Sensory Barrage Stimulation in the treatment of elbow spasticity: a cross over double blind randomized pilot trial. Neuromodulation. 2016; 19:220-226. DOI: 10.1111/ner.12383

T. Mufti, M. Slovak, A. T. Barker, T. F. D. Farrow. 24-channel transcutaneous electrical sensory stimulation of the forearm: Effects on cognitive performance and autonomic arousal compared with single electrode stimulation. Cogent Medicine, 2016; 3: 1149992. DOI: 10.1080/2331205X.2016.1149992

3.1. **Introduction**

As described in Chapter 2, a surrogate measure leading to a tool to determine optimal stimulation parameters for OAB therapy could not be identified using the resources available and within the timescale of this project. Therefore the project moved onto the development of a potentially more effective general purpose stimulation technique.

Electrical stimulation for therapeutic purposes remains an active research area. Variants of electrical stimulation waveforms combining various features with an aim to enhance the effect of currently available techniques are regularly introduced (Neurocare, 1993, Shen et al., 2011). However these developments are rarely supported by any robust rationale and do not involve a direct comparison with currently available techniques.

TENS is a well-established form of electrical stimulation therapy (Khadilkar et al., 2008) usually uses a single pair of electrodes placed on a specific site and delivers a continuous stream of repeated stimuli at a low intensity level, below that which causes muscle contraction. The development presented in this chapter hypothesised that the effects of TENS may be enhanced with a form of stimulus delivery encompassing the following two features.

The first feature addresses the hypothesis that it would be beneficial to stimulate a larger area of skin and hence target more sensory fibres. This could be potentially important in sacral site stimulation for the treatment of OAB symptoms, where the area to be targeted is relatively large, the optimal site of stimulation is unclear and where existing methods are not likely to be stimulating the deep sacral nerve roots themselves. It would be possible to target a larger area of tissue/nerve structures by using larger electrodes. However the stimulus current density would not be distributed evenly over the electrode and, in particular, would be expected to be greater at its edges (Reilly, 1992). An alternative approach is to use a number of discrete electrodes distributed over the area of tissue to be stimulated, each driven by a constant current generator. To achieve this a 64-channel programmable electrical stimulator previously developed for use in foot drop therapy (Heller et al., 2012) has been modified to allow delivery of stimuli using an array of 64 small individually controlled electrodes.

The second feature addresses the hypothesis that constant frequency (monotone) TENS might cause participants to habituate to the stimuli and for it therefore to become less

effective. The concept for addressing this habituation process has its origin in our understanding of neuroplasticity. This has been studied partly in the context of post-injury plasticity. Whilst the mechanisms involved are not completely understood, it is postulated that neural networks are undergoing a 'rewiring' process (Nudo, 2006). Electrical stimulation is widely used as an aid to return functioning post-stroke. Areas of the cortex can take on new functionality in response to injury or as a natural process following learning. It has been shown that attention plays an important role in learning and thus may influence plasticity (Stefan et al., 2004). Hence stimulation capable of producing time-varying 'interesting' (or 'salient') sensations via multiple electrodes (as opposed to a single electrode), may improve neuroplasticity effects via the maintenance of attention to the salient stimulus. In addition, a patterned sensory stimulation has been shown to be effective in inducing plasticity in reciprocal Ia sensory inhibition in comparison to monotone stimulation (Perez et al., 2003). The technique proposed here aims to target superficial sensory cutaneous nerve fibres originating from receptors in the skin rather than in deeper nerve bundles (trunks) which require stronger electrical stimuli to activate because of their greater depth. The two features described above, namely time varying signals and multi-channel stimulation has led to the novel electrical stimulation concept which has been named Sensory Barrage Stimulation (SBS).

The remainder of this chapter looks into the practicality and effects of the SBS approach. However similarly to techniques described in Chapter 1 the challenges are how to determine the optimal parameters of this form of stimulation and how to evaluate its effectiveness.

Although the specific focus of this thesis is on the treatment of overactive bladder, the evaluation of this novel stimulation technique was explored in two different experimental models of peripheral stimulation, chosen because of their relatively easily measurable endpoints. In both models the response to SBS has been compared with a standard form of TENS. The two models chosen were the habituation of normal volunteers to sensory stimuli and the effect of SBS versus TENS on subjects with upper limb spasticity.

3.2. **Development of multichannel electrical stimulation technique**

To deliver the stimuli with the features specified in the introduction section, the ShefStim apparatus (Heller et al., 2012) was modified. As described below, modifications were

made to support an external programming interface for the stimulator to allow the stimulator to be controlled during the experiments, and firmware modifications were made to enable a repeating complex pattern of stimuli to be delivered. These allow the ShefStim apparatus to activate individual or subset of electrodes, at specified current amplitudes and time durations and thus creates a virtually infinite number of patterns

The pattern in which the stimuli are delivered is uploaded to the ShefStim's FLASH memory in a form of a table. The pattern is represented by a set of records in, which is repeated throughout the stimulation. A purpose made Windows application was developed to create a dataset for the table and to visualise the pattern (Section 3.2.3).

The electrodes used during the spasticity study were in the form of an electrode array as used in the foot drop application (Heller et al., 2012) or, for the habituation study, with discrete electrodes interfaced to the stimulator using a purposed made breakout accessory.

The ShefStim hardware was controlled either by a PC or a laptop, which were electrically isolated from the subject environment using a homemade PC isolation interference of 4kV boundary. The ShefStim remote control can provide control and adjustment of stimulation level, but in this study was only used for status checking (error messages, etc.). The block scheme of the ShefStim system is shown in Figure 3.1.

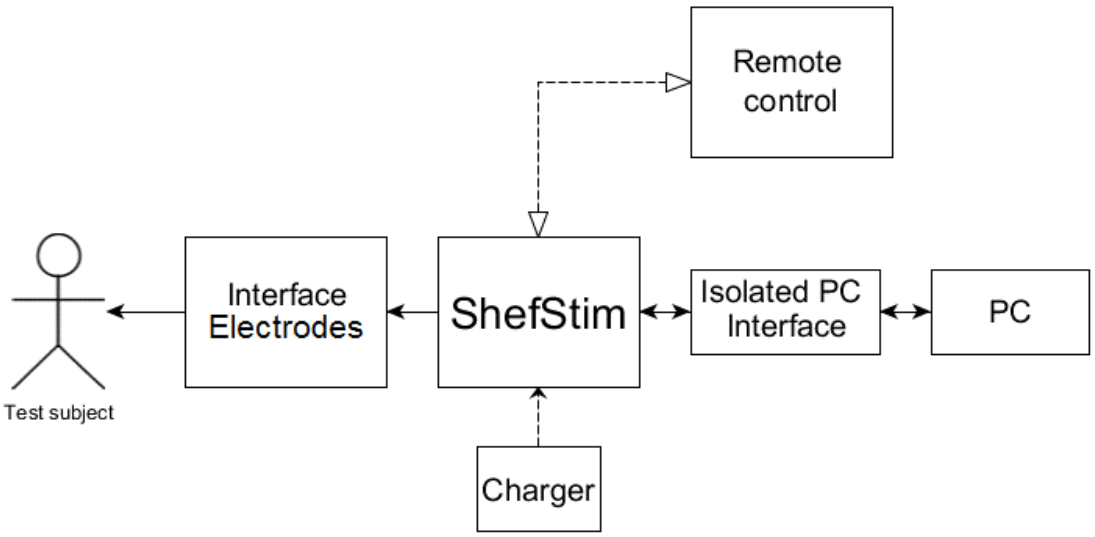


Figure 3.1 The block scheme of the ShefStim system

3.2.1. **The 64 electrode array**

The array consists of 64 individual 8x8 mm square electrodes with a 3 mm gap between each on a flexible printed circuit board (Figure 3.2). An adhesive hydrogel sheet ST GEL-high impedance grade SCBZAB-05M (Sekisui Plastics, Japan) with a resistivity of 1.3 kΩ*m and a thickness of 0.5 mm was laid over the surface of the electrode array to act as the interface between the electrodes and the skin. This relatively high resistivity, low thickness hydrogel layer avoids 'blurring' of the stimuli that could occur due to current flow along the layer as opposed to through it (Cooper et al., 2011). The overall dimension of the electrode array is 91x91 mm.

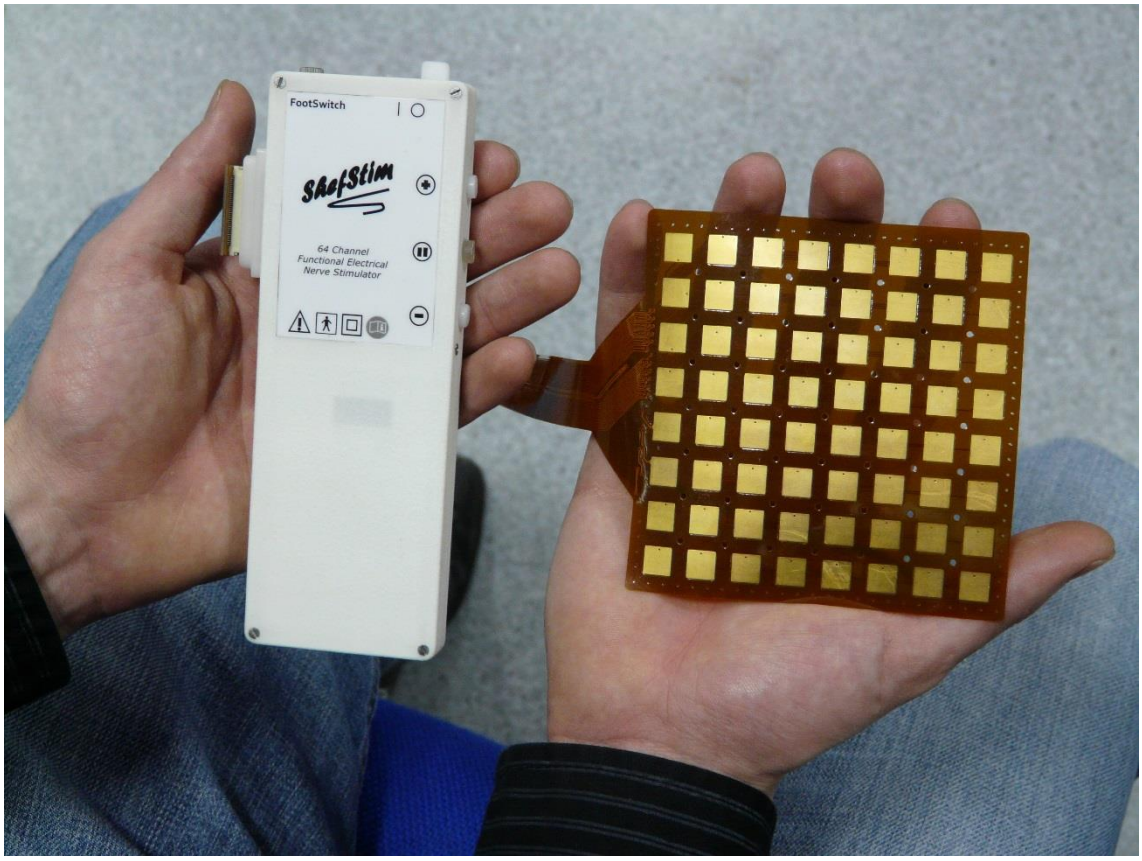


Figure 3.2 ShefStim apparatus with a 64 cathode electrode array

3.2.2. **The breakout accessory**

The breakout accessory consisted of two separate boxes connected to the ShefStim apparatus (Figure 3.3). The smaller box connected to the ShefStim apparatus provides the anode connection and the bigger box provides individual cathode connections. Standard safety sockets (2 mm pin) are used for electrode connections. This allows the use of a

wide range of commercially available electrodes. Although the ShefStim provides 64 channels of maximum output 10 mA/channel, the accessory is designed to provide 32 channel with double output for a channel. This is provided by connecting two ShefStim output channels to one channel of the breakout accessory socket. This combining of channels works because each ShefStim channel is a constant current source. It could not be used for a constant voltage stimulator.

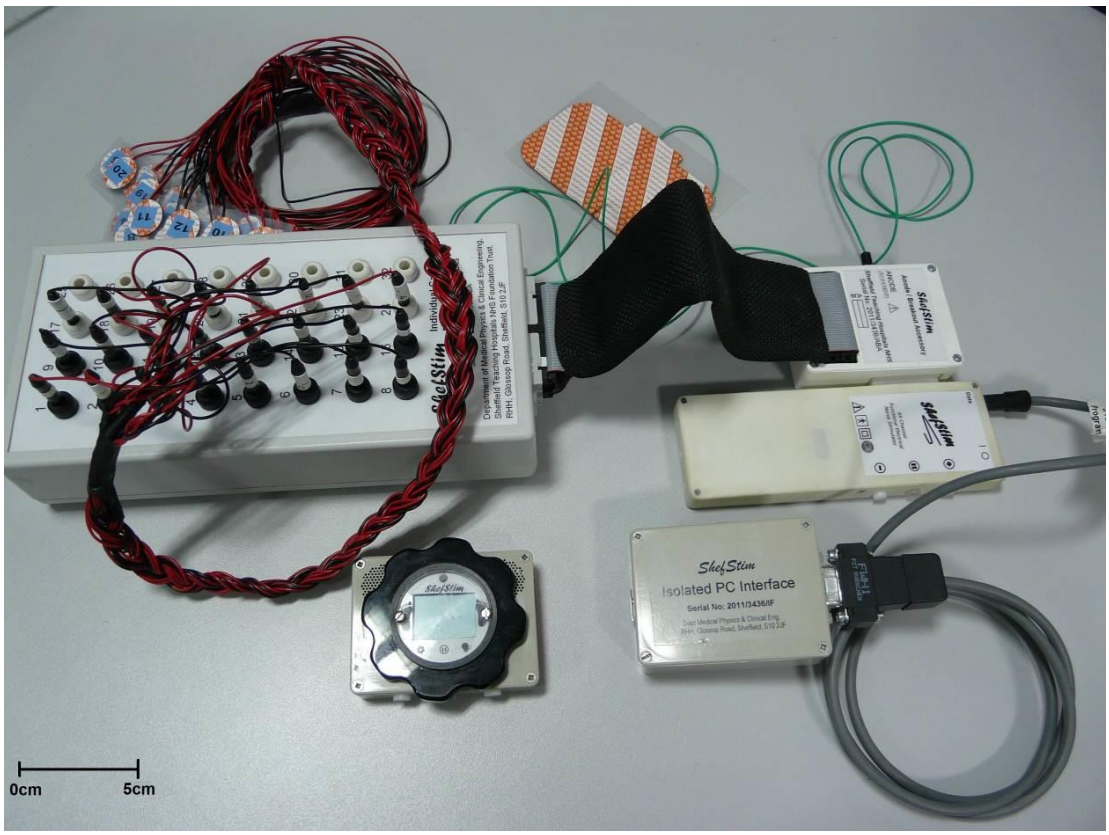


Figure 3.3 The ShefStim system with a breakout accessory box. The overall system consists of the modified stimulator, a remote control, an isolated PC interference and the breakout accessory.

3.2.3. **Stimulation pattern design**

A bespoke software tool to allow an easy and visual design of the stimulus pattern was made. Each pattern is created as a sequence which allows the activation of between 1 to 64 channels at the same time. The stimulation current to be delivered from each channel can be set between 0 to 10 mA and pulse width 100 µs to 600 µs. The maximum instantaneous output of the stimulator is limited to 90 mA. Each sequence can deliver between 1 to 500 pulses at a frequency of 10 to 125 Hz, with amplitudes which gradually increase or decrease in their intensity in predefined ramp window of up to 3 s. Frequency

below 10 Hz can be provided using a pattern with no stimuli periods between the active sequences which would serve as a pulse repetition rate.

3.3. **Study 1: Salience and habituation features of SBS**

The specific features of Sensory Barrage Stimulation to deliver 'interesting' or 'salient' stimuli and thus enhance the effects of neuroplasticity as indicated in Section 3.1 is indirectly evaluated further in this Study 1. There is a virtually infinite number of stimuli which can be delivered using the modified ShefStim apparatus. Consequently the evaluation of all stimulation patterns which might be created remains a challenge. It has been hypothesised that SBS stimulation patterns might induce more plasticity when compare to conventional stimulation due to their 'salience' and directing the attention to the stimuli.

Thus this project has compared several SBS patterns to a conventional TENS stimulation using a pair of electrodes with reference to:

1. Performance of cognitive tasks and two-point discrimination
2. Differences in skin conductance responses as measures of autonomic arousal
3. Subjective description of the cutaneous sensation produced by patterns

It is hypothesized that more 'interesting' or 'salient' patterns produce more distraction to the subject hence interfere with the task performance and increase the autonomic arousal. Thus the study aims to determine if SBS patterns are more likely to produce this distraction and ideally determine the best SBS pattern to achieve this.

3.3.1. **Materials and Methods**

Ethical approval for this study was obtained from the Ethic committee at University of Sheffield (Appendix D). Study design and data collection were carried out by BMed. student Miss Tabitha Izmirova (Department of Neuroscience, University of Sheffield, 2011), Mr Martin Slovak carried out development of stimulation technique and the data analyses. The supervision of the study was carried out by Dr Tom FD Farrow from the Academic Clinical Psychiatry, University of Sheffield and Prof Anthony T. Barker from

the Department of Medical Physics & Clinical Engineering, Royal Hallamshire Hospital, Sheffield.

3.3.1.1. **Participants**

In total, 67 healthy, right handed volunteers (34 male and 33 female, mean age 28 years ± 11.5 years; range 18-60 years) gave informed consent and participated in the study. Participants had no reported history of any serious psychological or neurological condition, no reported reading difficulties (of relevance because of the nature of the neuropsychological tasks), no contraindications to electrical stimulation (e.g. fitted pacemaker or other electronic device) and no skin disease or broken skin on their left forearm. The experimental session was carried out at the Academic Clinical Psychiatry, Northern General Hospital, Sheffield.

3.3.1.2. **Study design**

During the experimental session each participant received five 8 min. periods of stimulation, consisting of four different SBS patterns and one conventional TENS signal in a pseudo-randomised order. During each of these stimulation periods the participant completed a cognitive sensory tasks whilst their autonomic arousal was recorded using the skin conductance response. The stimuli were delivered to the subject's forearm on grounds of convenience. The level of stimulation was set to produce significant sensation, but below the point where stimulation causes pain or motor response. The study flow diagram is shown in Figure 3.6 in Section 3.3.1.9.

3.3.1.3. **Electrodes placement**

Both type of stimulation were delivered using the ShefStim and breakout accessory as described in Section 3.2.2. The electrodes consisted of a set of 24 individual cathode hydrogel electrodes (CareFusion Disposable Disk Electrodes REF 019-415000) and a larger anode electrode (CareFusion Disposable 2''x4'' Ground REF 019-4222). The 24 cathode electrodes were separated into four vertical (distal to proximal) columns of six equidistant electrodes as shown in Figure 3.10. The larger sized anode was placed on the skin between the body of the left biceps and triceps. Body landmarks and rubber bands were used as an aid to consistent placement of electrodes across the participants scaled approximately pro-rata to arm size. The TENS stimulation used electrode no. 1 (cathode)

and no. 2 (anode) as shown in Figure 3.4. A cohesive bandage was wound over the electrode to maintain a firm mechanical pressure (and hence good electrical connection) between the skin and electrodes.

As the stimulation was carried on a sensation level the cathodes were placed not less than 35 mm apart, thus the produced sensation will be distinctive to the targeted area. This distance was based on the relatively poor two point discrimination of the forearm, which is between 35-40 mm in healthy volunteers (Nolan, 1982).

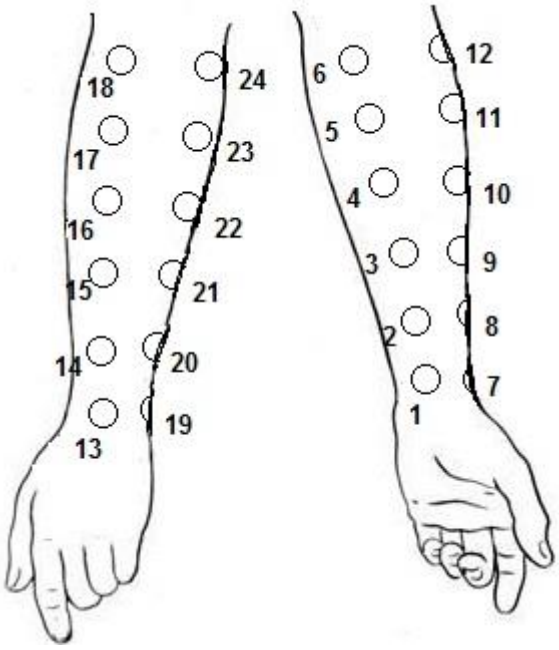


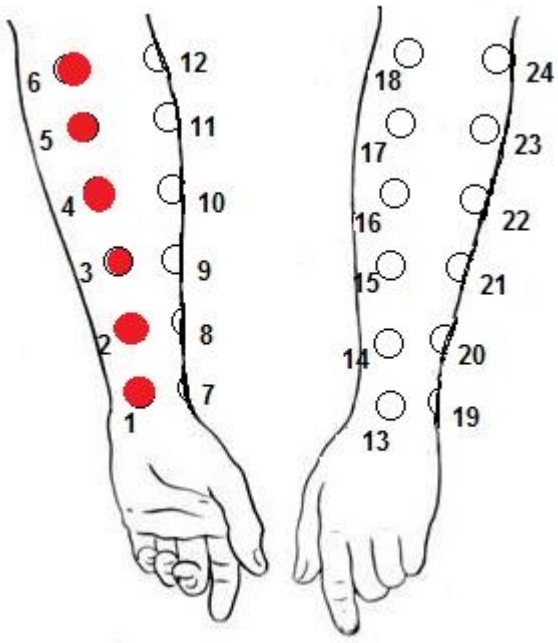
Figure 3.4 The placement of electrodes (cathodes) used in the habituation study

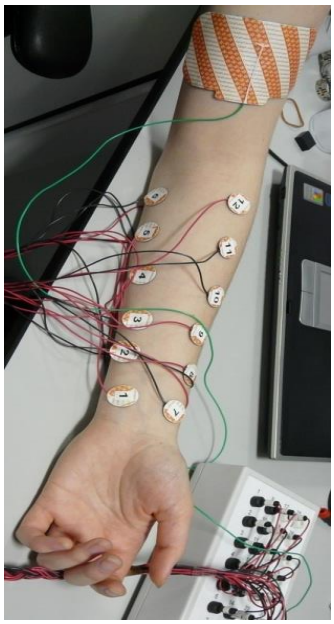
3.3.1.4. **Patterns**

There is virtually an unlimited number of patterns which could be created using the SBS system. The four patterns used in the study were chosen, in pilot experiments, to feel perceptually different, whilst using the same stimulation features as described below.

1) Only one electrode activated at a time.
2) Number of pulses per electrode activation was set to n = 3 to achieve a strong perception of sensation in a brief period
3) Constant frequency of pulses delivered f = 50 Hz
4) Constant pulse width of pulses delivered t = 150 μs

It was noted during pilot experiments that applying the same level of stimulus current to electrodes in different positions produces different level of sensation. It is possible that this might be related to the distribution of cutaneous sensory nerves. Sensation threshold was expressed for each electrode site, relative to the mean value for the arm, in pilot measurements on 10 heathy volunteers (Figure 3.5). A clear anatomical pattern has been identified showing sensitivity increases from distal to proximal sites. In the study, the stimulus intensity used was mapped according to this variation and then adjusted as a global percentage. This global percentage adjusted each of the electrodes so that the adjustment is relative to the mapped variation identified.





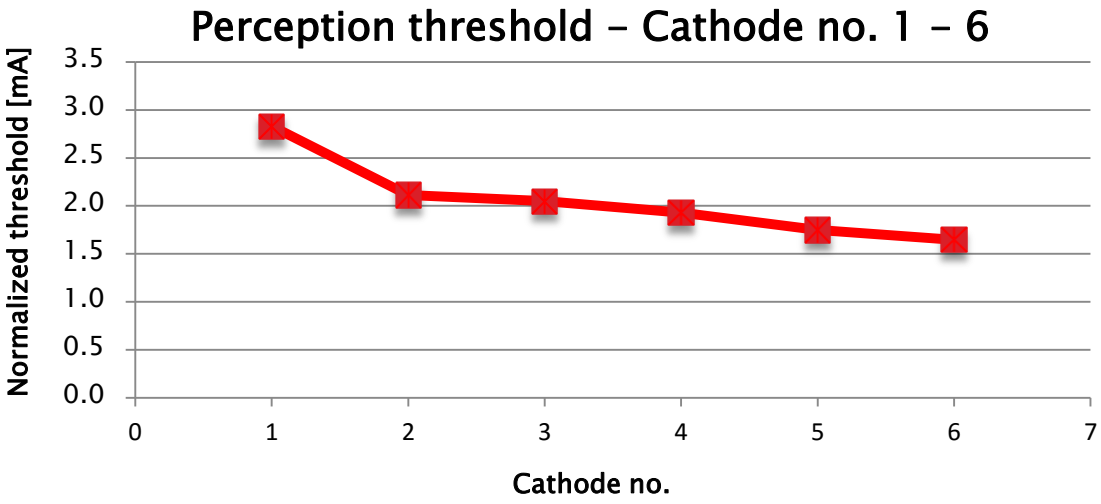


Figure 3.5 Top left and right – position of the electrodes on the forearm, Bottom – perception threshold current normalised to the overall mean threshold, shown for electrodes 1-6 as an example

Two of the patterns were designed as predictable (the participant can identify the repetitive pathway of the stimuli) and two as unpredictable (the participant cannot distinguish if the pattern is being repeated). The patterns were named after their perceived sensation.

The unpredictable pattern ("fly") was designed to emulate the sensation of an insect moving on the forearm in a random direction, but it could be sensed also as a "snaking" sensation. The second unpredictable pattern ("random") caused an intermittent sensation by a consecutive activation of all 24 electrodes in a random order. The first predictable pattern ("lines") had some similarities to the fly pattern, but this was a repetitive pathway from one side to the other side and the participant could easily identify the movement of stimuli. The second predictable pattern "ring" simulated the movement of the ring sensation, which was going up and down on the forearm in a way such that it produced a sensation of a ring or bracelet moving on the forearm.

TENS stimulation was performed by delivering stimuli between electrode no. 1 and electrode no. 2 at a frequency of 10 Hz, as commonly used in transcutaneous PTNS (de Seze et al., 2011) or in sacral stimulation (Walsh et al., 1999) for the treatment of OAB.

3.3.1.5. **Psychiatric tasks**

All the participants underwent five different tasks in the same order. During each task, they were stimulated by one of the patterns for 8 min, with the order of these patterns being randomised between subjects. The tasks are briefly described below.

Colour task – The Stroop test

The participant was presented with a list of written colours, some of them in the same colour as the word and some in a different colour e.g. (BLUE, BLACK, GREEN, RED). The participant's task was to read the colour of text, rather than reading the word (Stroop, 1935). It was hypothesised that the pattern of the electrical stimuli would distract the participants, and by making them focused on stimuli rather than the task would cause them to erroneously read the word rather than the text colour.

Puzzle task - Tangoes Shape Builder

The participant was presented with a set of cards – tangoes (Rex Games Inc.: Smart tangoes, 2012) on each of which was a shape (e.g. a boat). The participant's task was to build the presented shape as fast as possible using several plastic pieces of different sizes and shapes. The time taken to complete each puzzle was recorded as the outcome of this task.

Text task – Count the letter

This task consisted of 15 short paragraphs from fictional literature. Above each paragraph was a specified letter which appeared in the text (Barlett, 2004). The participant's task was to count the number of times this letter appears in the paragraph. The participant was instructed to be as quick, but as accurate, as possible and also that it was not necessary to read the text. This task requires participant to select only important ('salient') information (the letter) and ignore the non-salient information (the text). It was hypothesised that under a combination of time pressure and the challenge to attention created by a SBS pattern would lead to an increase in participant's errors.

Visual task – Spot the differences

The participant was presented with pairs of pictures every two minutes. The participant task was to find and mark the difference between the pair of pictures (Smart-Kit, 2012). The outcome of the task was a number of spotted differences. It was hypothesised that the challenge to attention created by a SBS pattern would lead to an increase in participant's errors.

Sensory task – two point discrimination on the finger

The participants were asked to wear an eye mask so they could not observe the test. At a random time interval the participant was touched using a thin piece of pencil lead on a fingertip. The participant's task was to identify which finger was touched and whether the touch was performed by one or two pieces of pencil which were 4 mm apart. The outcome of the task was a number of correct responses, defined as correct answers to both finger identification and number of touches. It was hypothesised that, again, the challenge to attention created by a SBS pattern would lead to an increase in participant's errors.

3.3.1.6. **Debrief questions**

After each of the tasks the participant was asked to fill in feedback related to the task difficulty (not further analysed in this thesis) and stimulation sensation perceived. The participant was also presented with a list of 40 descriptive words and marked those which corresponded to the sensation perceived in a particular pattern. Each descriptive word was assigned to one of the following groups (Table 3.1). These groups were blinded to the participant and words were randomly spread across the page. The words were obtained from the McGill Pain Questionnaire (Melzack, 1975), and the Leeds Assessment of Neuropathic Symptoms and Signs (Bennett, 2001).

Table 3.1 Word description of the pattern and assigned groups

Pain	Sharp, Sore, Shooting, Stabbing, Hurting, Unbearable, Burning, Stinging, Piercing
Neutral	Pulsing, Jumping, Tingling, Spreading, Pressing, Radiating, Vibrating, Pins&needles
Positive	Exciting, Relaxing, Pleasant, Interesting, Stimulating, Comfortable
Intense sensation	Throbbing, Vigorous, Intense, Penetrating, Prickling, Heavy
Slight pain	Pinching, Hot, Tender, Tight, Smarting, Aching
Negative experience	Dull, Annoying, Itching, Numb, Squeezing
Moderate sensation	Bursting, Beating, Tickling, Pounding

The data from the debrief questionnaires were analysed as a subjective description of the perception of the pattern. The relative number of words in each group for a particular pattern then determined a score for the group.

3.3.1.7. **Skin conductance responses as a measure of autonomic arousal**

During each task the dermal activity was continually recorded using an in-house build system. A pair of electrodes was attached on index and middle finger on left hand. The system measure the changes in impedance based on the voltage changes for a defined constant current ($Z = U/I$). Decompositions and optimization of these data were performed by Ledalab V3.4.1 (Benedek and Kaernbach, 2010) in Matlab R2011a. The Ledalab software produced minute-long epochs of skin conductance response showing the number of skin conductance responses (nSCR) and the integration area of skin conductance responses (ISCR).

3.3.1.8. **The experimental procedure**

Just before the experiment, or at home prior to the experiment, the participant filled in several standard questionnaires to assess his/her sensory profile and demographic information (not further analysed in this thesis).

The experiment started with an identification of the global stimulus intensity level at which patterns were to be delivered. As the goal was to achieve a strong but comfortable sensation, but with no muscle stimulation response. Following that the subject underwent all the tasks with one stimulation pattern randomly assigned to each task. After each of the tasks the participant completed the debrief questionnaire.

3.3.1.9. **Statistical analysis**

The One way ANOVA tests were used for task performance and skin conductance measures. When the significant difference between particular groups wanted to be identified the unpaired Student's T-test was used.

The debrief questionnaire groups were further coalesced to two opposite groups, namely 'intense' and 'neutral'. The intensity score was calculated as a sum of ranks from the "intense sensation" and "positive" groups. The neutrality was calculated as a sum of ranks from the "moderate sensation" and "neutral" groups. The ranks were obtained from the order of the total number of words used in each of the groups for all the patterns.

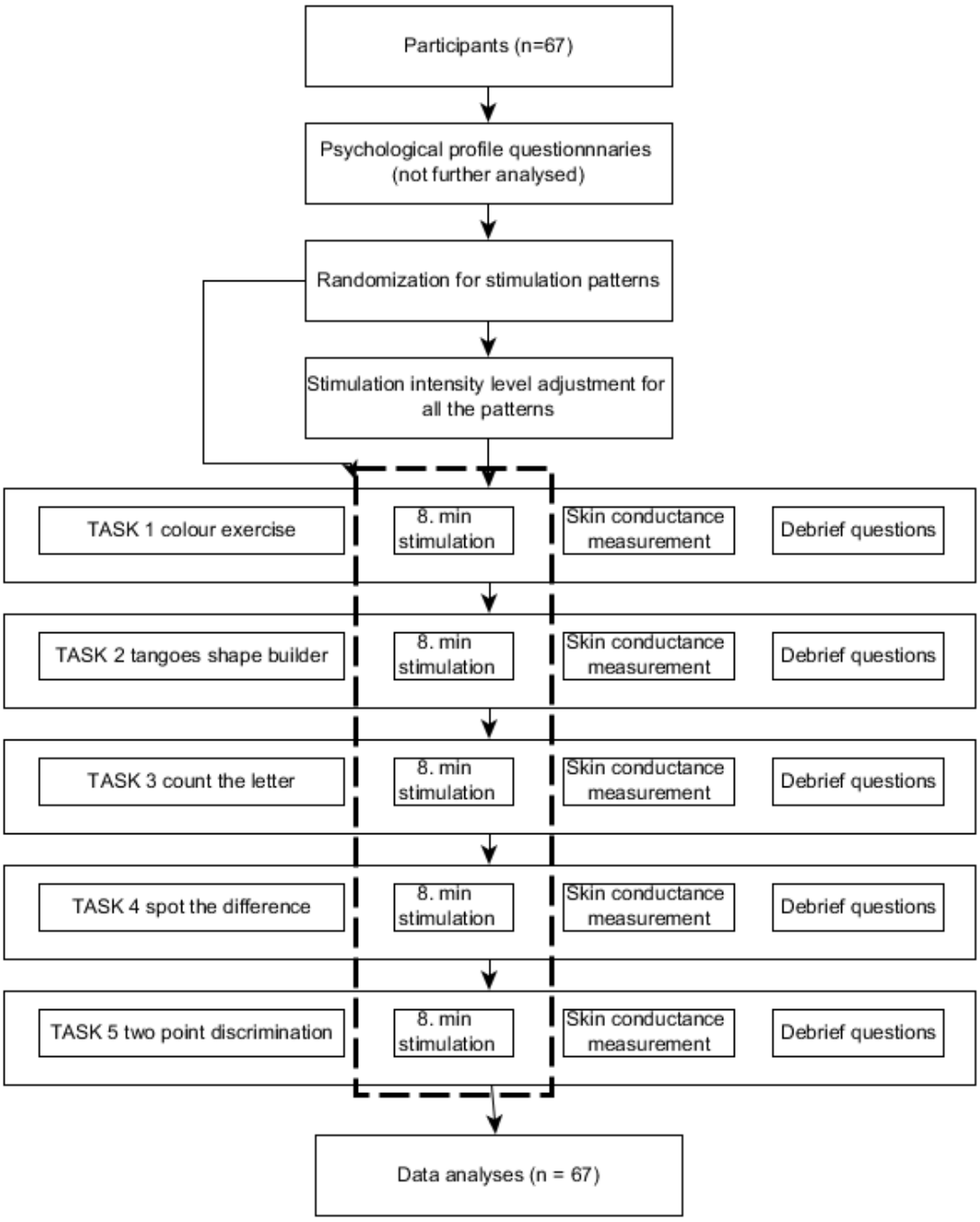


Figure 3.6 Study 1 flow diagram

3.3.2. **Results**

3.3.2.1. **Demographic**

Sixty seven participants (34 male and 33 female, mean age 28 years ± 11.5 years; range 18-60 years). Body mass index (n = 41, the rest of the participant did not want to provide their weight information) ranged from 16.7 to 30.5 (22.8 ± 3.0).

3.3.2.2. **Stimulation current used**

Gender was found to be a determining factor for the stimulation intensity used to achieve sensation described as "strong, but comfortable" (males = 3.8 mA, females = 3.3 mA; $p = 0.012$) for the pattern stimuli. These gender related differences were also significant for the TENS stimulation (males = 4.8 mA, females = 3.7 mA; $p < 0.001$).

3.3.2.3. **Effects measured using the task performance**

There were no significant pattern-specific effects on task performance ($p > 0.1$; multi-variate ANOVA) except for a significant difference between patterns as a whole and the TENS stimulation condition for the sensory two-point discrimination task ($p = 0.023$; post hoc Fisher LSD test; Figure 3.7). Specifically, two-point discrimination task performance in the TENS stimulation condition (9.0 ± 1.8 errors) was significantly worse than for the unpredictable "fly" pattern (4.2 ± 1.0; $p = 0.005$; Student's T-test), the predictable 'lines'

pattern (4.2 ± 1.9; p = 0.009) and the predictable 'ring' pattern (3.8 ± 0.8; p = 0.01), but not significantly different from the unpredictable 'random' pattern (6.9 ± 1.9; p = 0.06).

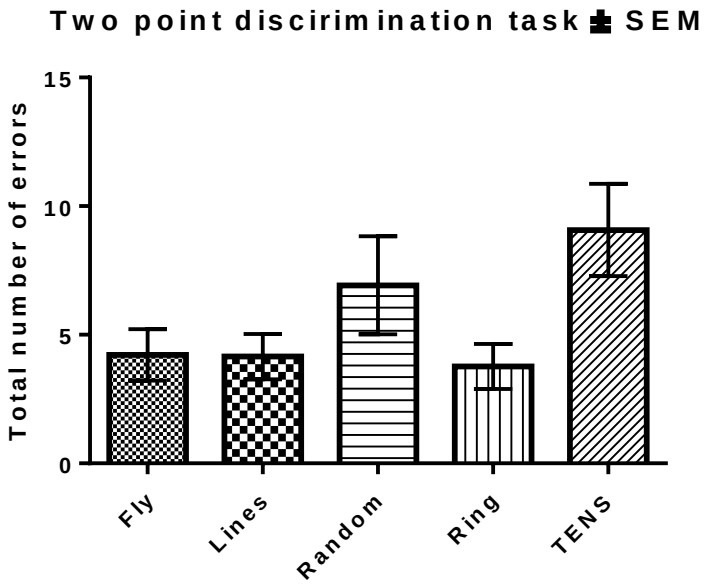


Figure 3.7 Results of two point discrimination

3.3.2.4. **Effects measured using skin conductance responses**

The mean number of nSCR was calculated as a mean of all tasks for a specific pattern (Figure 3.8 on right). TENS stimulation had the lowest nSCR in each minute of stimulation; however this was not statistically significant. Integration of skin conductance responses (ISCR) also showed no significant difference between patterns (Figure 3.8 on left). There is a significant difference of ISCR at the first minute when compare to the second and consequent minutes in each of the pattern (p > 0.033), but there is no difference between second and any other consequent minute of the experiment.

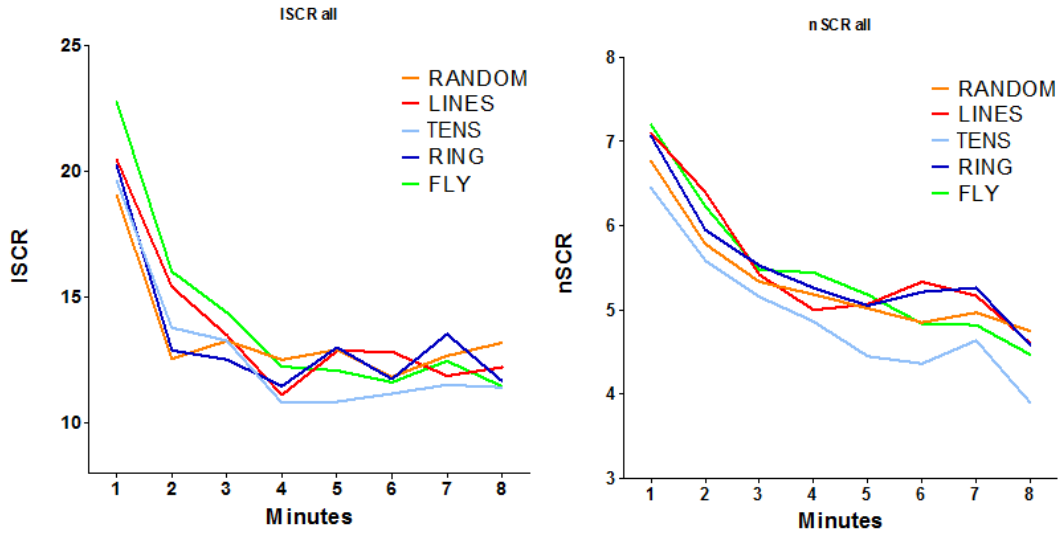


Figure 3.8 nSCR and ICSR means for all of the tasks using different stimulation patterns

3.3.2.5. **Subjective description of the cutaneous sensation produced by patterns**

In the subjective description of the pattern sensation, each word was associated with one of the groups in Table 3.1. The total number of words in each group was calculated (Table 3.2) and gave the score for each of the patterns (Table 3.3). The fly pattern had the highest pain and positive score. Single stimulation was described by the lowest number of words, but obtained the highest negative experience score.

The most interesting pattern was defined as to be intensive, but not be neutral, therefore the intensity and neutrality scores were calculated (Figure 3.9). The highest intensity scores with lower neutrality scores were obtained for the random and fly patterns. Ring and lines patterns obtained higher neutrality scores then the intensity scores. TENS stimulation obtained the lowest score in both of the scores.

Table 3.2 Number of words used in the description of patterns using descriptive groups

Pattern	**Pain**	**Intense sensation**	**Negative experience**	**Slight pain**	**Moderate sensation**	**Neutral**	**Positive**
FLY	22	46	24	7	37	169	119
LINES	18	47	23	13	40	171	102
RANDOM	19	53	27	15	35	157	108
RING	14	37	25	15	38	171	103
TENS	10	33	31	11	27	119	92

Table 3.3 Ranking of each group based on number of words used

Pattern	Pain	Intense sensation	Negative experience	Slight pain	Moderate sensation	Neutral	Positive
FLY	5	3	2	2	3	4	5
LINES	3	4	1	4	5	5	2
RANDOM	4	5	4	5	2	3	4
RING	2	2	3	5	4	5	3
TENS	1	1	5	3	1	2	1

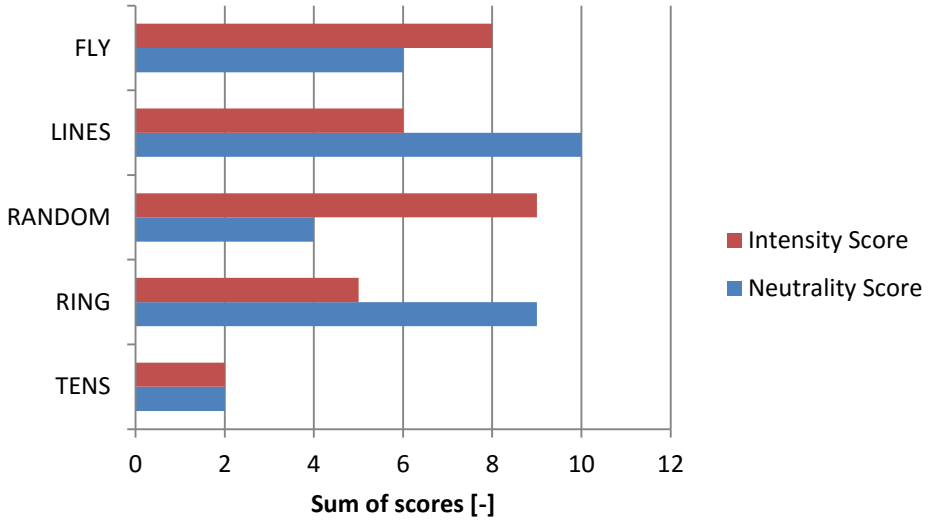


Figure 3.9 Intensity and neutrality score used for subjective description of patterns

3.3.3. **Discussion**

The aim of this study was to investigate the salience of the SBS patterns. The importance of salience was hypothesised to be based on the linkage between plasticity and attention. Therefore the SBS patterns were designed to be more ‘salient’ and thus more difficult to habituate/ignore than a conventional single channel TENS.

In this study it was hypothesised that the distraction of the SBS pattern might lead to a decrease in task performance and differences in the performance will lead to the most ‘salient’ pattern. However, the tasks performance analyses have shown no significant differences except for the two point discrimination task, where the TENS single channel stimulation showed the opposite of what was hypothesized (more errors in the task made). An explanation for this might be that in the discrimination task the multichannel pattern

helped the subject be alert during the task (because this task was the last one in the session, an eye mask was worn during it and some of the participants felt tired). Therefore the stimulation improved the performance, rather than distracted the attention. The overall explanation for no significant difference in task performance might be linked to stimulation levels administered (subjectively "strong but comfortable"). This might be distracting (i.e. salient) at rest, but insufficient to impact on the focused activity of task performance.

The ISCR and nSCR demonstrated habituation effects versus time (first minute significantly higher than the others), but no significant difference between the stimulation patterns delivered. Although it was noted that TENS had the lowest number of nSCR and thus suggesting lowest autonomic arousal.

The main limitation of this study was a lack of control group. A group without stimulation would be useful to determine how much the actual stimulation has affected the outcomes and how the performance of cognitive tasks and skin conductance differ during each of the stimulation period.

The findings of this study do not indicate that the SBS patterns directly influence the attention of the participants. However, random and fly patterns showed higher sensation ranking of intensity then neutrality, whereas lines and ring patterns showed the opposite. This correlates with the predictability (or lack of predictability) of these patterns, indicating that more "interesting" patterns are unpredictable. This findings also suggesting that the participants are able to distinguish between the sensations of these patterns and thus further patterns of stimuli can be developed according to sensation which might be e.g. relaxing as showed in the Study 2.

3.4. **Study 2: A pilot clinical trial comparing TENS and SBS in patients with spasticity at the elbow**

Spasticity is a disorder of sensorimotor control, resulting from an upper motor neurone lesion and presenting as intermittent or sustained involuntary activation of muscles (Pandyan et al., 2005). It can interfere with functional recovery and lead to contractures, which impact significantly on patients' everyday living activities. As indicated below, the treatment pathway for these patients is similarly challenging to that of OAB patients.

Pharmacological treatment is the first line treatment option but this is often not well tolerated due to side effects such as weakness, dizziness and drowsiness.

Non-pharmacological approaches such as muscle vibration, extracorporeal shock wave therapy, and various forms of magnetic or electrical stimulation have been tried in the treatment of spasticity (Kheder and Nair, 2012). However, there is insufficient evidence to justify using these modalities routinely (Amatya et al., 2013). TENS applied to the sural nerve was reported to reduce spasticity in patients with hemiplegia (Potisk et al., 1995). Similar effects were noted in patients with spinal cord injury immediately after 60 min of 100Hz stimulation using TENS (Ping Ho Chung and Kam Kwan Cheng, 2010). Several long term studies showed promising results (Cuypers et al., 2010, Armutlu et al., 2003), although a study with multiple sclerosis patients did not demonstrate a reduction in spasticity (Miller et al., 2007) but did help to reduced pain.

It has been proposed that TENS reduces spasticity via modulation of spinal inhibitory circuits or those of the central nervous system (Ping Ho Chung and Kam Kwan Cheng, 2010).

The aim of this pilot trial was to assess the feasibility of using SBS for the treatment of spasticity affecting the elbow flexor muscles and to compare this with conventional TENS stimulation applied using two electrodes.

3.4.1. **Methodology of the study**

The study was designed as a crossover double blind randomized trial comparing SBS and TENS. The stimulation was delivered during two single 60 minutes sessions delivered one week apart. The principal clinical investigator of this study was Dr Sivaraman Nair, the data were collected by MSc Clinical Neuroscience student Mr Joseph Chindo, and Prof Anthony Barker, Mr Mark Reeves and Dr Ben Heller provided technical advice in the development of the equipment used in the study. The design of the system software and hardware, the stimuli patterns and data analysis were carried out by Mr Martin Slovak.

3.4.1.1. **Participants**

The study was approved by the Yorkshire & The Humber regional ethics committee (Appendix E). Between March and June 2013, 17 potential participants, with spasticity of the flexor muscles of the elbow of grade 2 or more on the Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987), were identified from the Neurology clinics at the Royal Hallamshire Hospital, Sheffield.

3.4.1.2. **Study visits**

The potential participants were provided with an information sheet and contacted two weeks later. If they decided to participate in the study they were invited to attend two study visits spaced one week apart. At the first visit the participants were screened for inclusion and exclusion criteria (Table 3.4) and gave their informed consent. The eligible participants were randomized into one of two groups. Group 1 underwent SBS at their first study visit and TENS one week later. Group 2 underwent the same interventions in the opposite order, TENS first and SBS one week later.

Table 3.4 Inclusion and exclusion criteria for the pilot trial of SBS in the treatment of spasticity

Inclusion criteria	
1)	Male or Female aged 18 and above
2)	Experiencing spasticity at elbow of grade 2 or more on the modified Ashworth scale
3)	Neurologically stable for 6 months
Exclusion criteria	
1)	Cognitive impairment that would interfere with their ability to comply with the experimental protocol or provide informed consent
2)	Any dermatological, rheumatologic or orthopaedic complications that might interfere with stimulation of the affected arm
3)	Pre-existing severe cardiovascular disease; active cancer or renal disease; end stage pulmonary or cardiovascular disease; psychiatric illness including severe alcohol or drug abuse and depression
4)	Inability to perform the baseline assessments
5)	Severe tactile hypersensitivity as assessed by a non-stimulation approach
6)	Participation in other, spasticity related, studies

3.4.1.3. **Interventions**

The design of the moving SBS pattern is shown in Figure 3.10 and was chosen to mimic a stroking sensation. For SBS the electrode array was divided into eight strips (each eight electrodes long). Each individual strip was activated for approximately 0.3 s with a burst

of fifteen 250 μs current pulses at 50 Hz applied simultaneously to all electrodes in the strip. The next strip was then activated while the previous one deactivated and this cycle was repeated until the last strip had completed its sequence of stimulation pulses. This was followed by a pause of approximately 2.5 s, when no current was delivered. In combination this provided a pattern mimicking the sensation of vertically stroking the arm proximally to distally. This sensory pattern was chosen because there is some evidence in the literature that mechanical stroking may have beneficial effects in spasticity to mimic this sensation, it was hypothesised that such sensation might help to relax the participant (Brouwer and Andrade, 1994). The pulse repetition rate of 50 Hz and the on/off periods were chosen because, in pilot studies, they gave the most convincing subjective sensation of stroking. All electrodes delivered the same current and this was adjusted by the operator according to just below each individual participant's motor threshold.

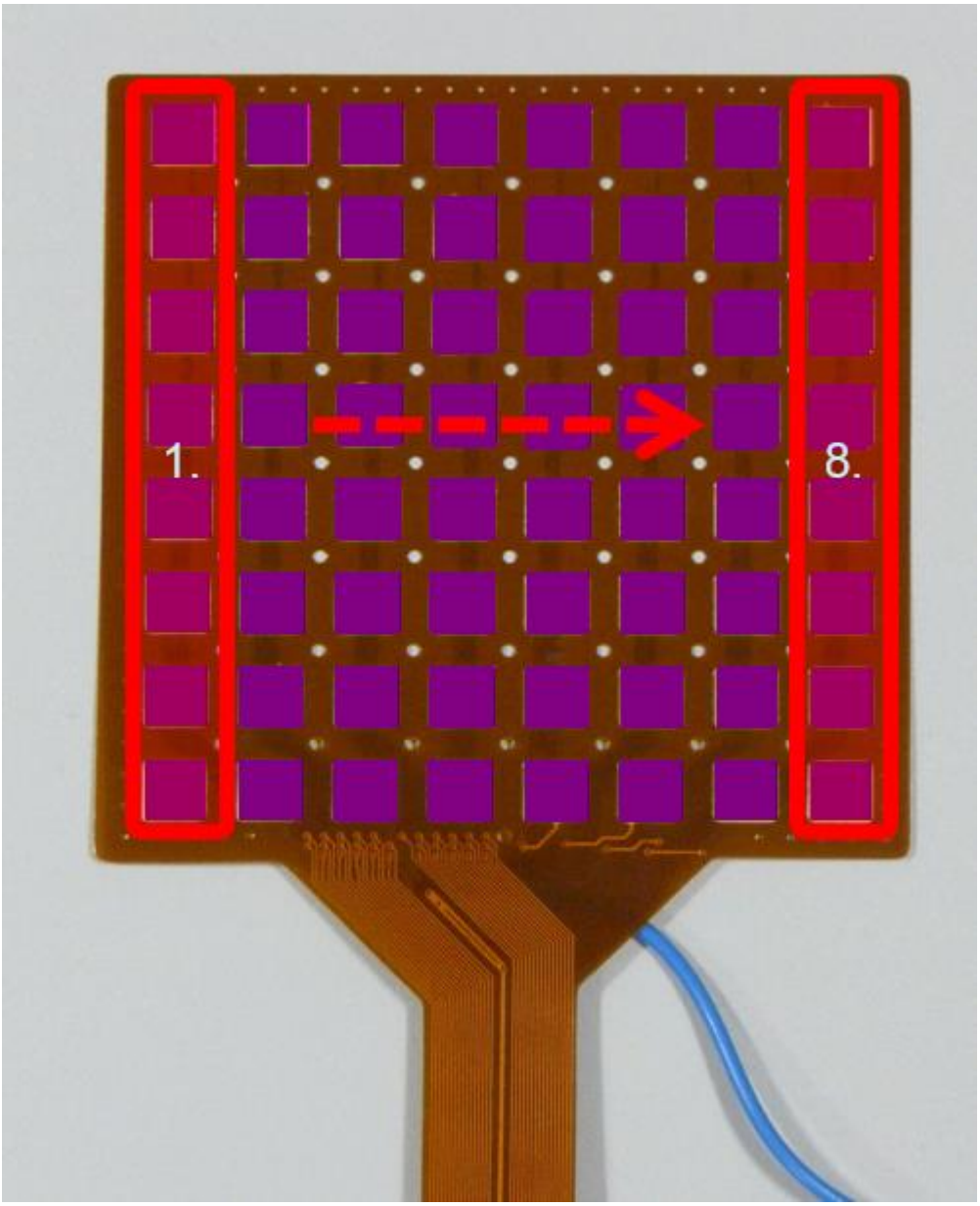


Figure 3.10 Moving Sensory Barrage Stimulation pattern

TENS was delivered using a commercial stimulator (Multi-TENS, NeuroTrac, VerityMedical Ltd., UK). The parameters of the stimulation were set as pulse repetition of 100 Hz as used in previous studies (Miller et al., 2007, Perez et al., 2003, Ping Ho Chung and Kam Kwan Cheng, 2010), 250 µs pulse width with an "on phase" of 6 seconds including a 1 second rising edge ramp, a 1 second falling edge ramp and a 4 seconds "off phase" in which no current was delivered. To mimic the physical setup of SBS and to blind participants to which system was being applied, the cathode electrode (50x50 mm, VS50, VerityMedical Ltd., UK) was placed centrally underneath the array used for SBS

stimulation. This electrode was connected to the TENS stimulator. The participants were not informed as to which type of stimulation they received.

The arrays (both for SBS and TENS) were placed on the middle of the triceps brachii on the dorsal aspect of the affected arm and strapped with a cohesive bandage to ensure consistent contact between the electrode and the skin (Figure 3.11). An anode electrode (100x50 mm, VS10050, VerityMedical Ltd., UK) was placed proximally on the deltoid muscle of the shoulder on the same arm for both types of stimulation.

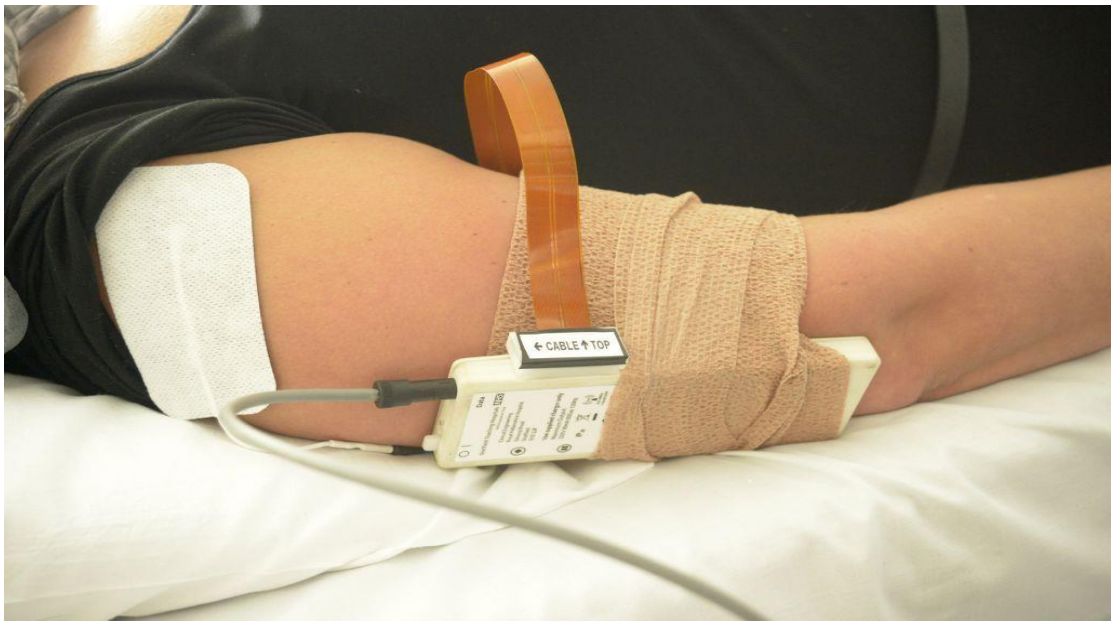


Figure 3.11 Position of the sensory barrage stimulator on the left elbow.

Both interventions were applied for 60 minutes at a level just below the threshold for motor contraction. The intensity was gradually increased until a visible motor contraction was observed and then decreased to a level where it just ceased. If this level could not be achieved due to discomfort, then the strongest comfortable intensity was used.

3.4.1.4. **Outcomes**

The assessment protocol was the same for both the SBS and TENS study visits. Participants were assessed before the stimulation was applied, immediately after stimulation and one hour after the stimulation was finished.

The primary outcome metric was the Modified Ashworth Scale (MAS) for the elbow (Pandyan et al., 1999). Secondary outcome measures used were the power of elbow extension (PEE) and flexion (PEF) based on the Medical Research Council grades

(Council., 1981) and a Visual Analogue Scale (VAS) of the perceived effect on spasticity rated by the participant on a 13 cm line with the left end being the worst imaginable spasticity and right end being no spasticity. VAS was subsequently normalized to a percentage where 0% represented the participant experiencing no spasticity and 100% representing the worst spasticity they could envisage. The participants who had a reduction in spasticity of at least one grade on the MAS when combined with a 30% decrease of spasticity relative to the baseline value on the VAS was considered to have had a clinically significant improvement. The clinical assessments were performed by the same clinician throughout the study. The clinician was blinded as to the intervention applied to the participant.

3.4.1.5. **Pendulum test**

It was thought desirable to perform an objective assessment of spasticity independent of the participant or clinician performing the clinical assessment of the Modified Ashworth Scale. A promising method, using a pendulum test, had been previously reported to show a significant correlation with spasticity (Lin et al., 2003). Therefore a similar apparatus was built.

The system comprised of the pendulum apparatus and the data acquisition system. The pendulum apparatus consisted of a pendulum arm pivoted about a rotary potentiometer attached firmly to a Table. The 100 cm long shaft of the pendulum arm had a 1.5 kg weight at one end and a sliding height adjustable wrist support at the other end. The pendulum arm was attached to a low friction rotary potentiometer (Penny&Gilles Ltd, UK) at approximately 60 cm (measured from the bottom) and create a pivot of the pendulum. The potentiometer was connected to the data acquisition unit (National Instruments NI-6009, Austin, Texas, USA). The pendulum arm was attached to a Table using clamps (Figure 3.12 left). The participant's wrist was attached to the pendulum wrist support and strapped with Velcro tape (Figure 3.12 right).

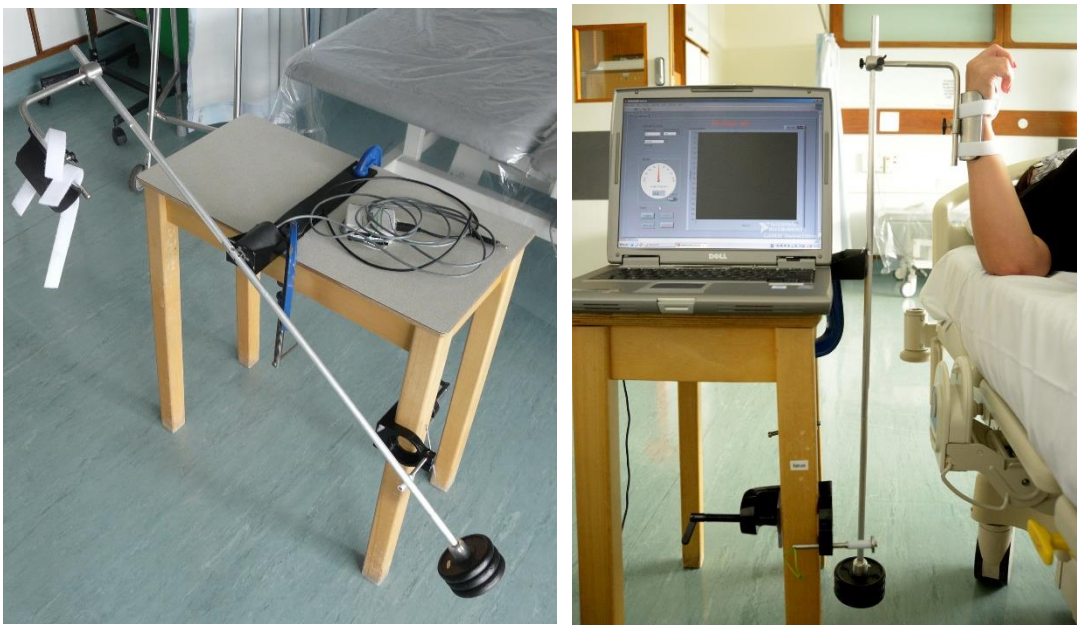


Figure 3.12 Pendulum apparatus

The pendulum data acquisition system consisted of the data acquisition unit (National Instruments NI-6009, Austin, Texas, USA) and in-house written software using LabView (Figure 3.13). In accordance with IEC 60601-2-10 for medical electrical devices, a battery operated laptop was used to isolate the participants from any potential pathway to mains power or earth. The clinician present at the patients' visits operated the software. The captured data were seen on the screen of the laptop during the pendulum motion. The post-capture analysis was carried out using Matlab R2011a (MathWorks, USA).

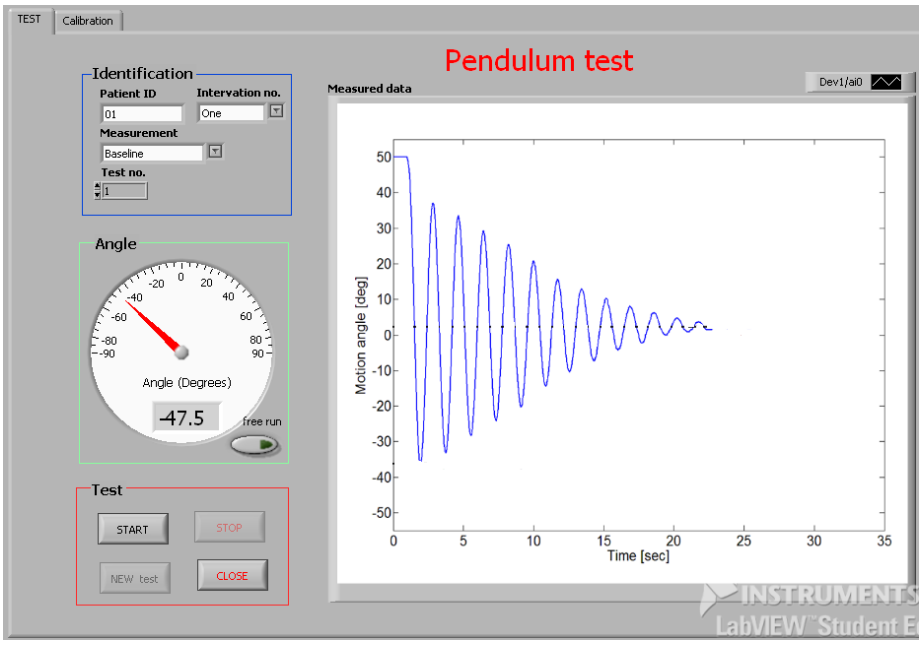


Figure 3.13 Labview software for capturing raw pendulum data

3.4.1.6. **Experimental procedure**

The participant lay on a height-adjustable hospital bed in the supine position. The Table with the pendulum apparatus was placed next to the bed on the side of the affected arm. The height of the bed was adjusted such that the centre of rotation at the elbow and pendulum arm were in line. This setup was different to the one in the referenced study (Lin et al., 2003) where the apparatus was fixed to a bed and the centre of pendulum and elbow rotation were not in line. The wrist support was adjusted to a comfortable height and the wrist was fasten using Velcro tape.

The lower part of the pendulum arm was slowly moved, such that the elbow joint angle between the forearm and upper arm was 50º. The pendulum arm was secured using a pin release mechanism on the leg of table. As muscle tone can depend on previous movements (Lin et al., 2003), the 50º elbow joint position was maintained for 2 minutes. The data collection was started and the pin released without notifying the participant. The subject was instructed to relax as much as possible and not to interfere with the pendulum's movement. During the swing movement the investigator was able to observe correct data collection in a form of a graph on the screen of the laptop. Once the pendulum arm has stopped swinging the data collection was terminated and the test was repeated. Altogether there were five repeats of the test for each of baseline, immediately after the stimulation and one hour later, for each of the participants.

3.4.1.7. **Offline pendulum analysis**

Representative pendulum data are shown in Figure 3.14. In this example, pendulum motion started at 50° and stopped after 14 swings. Due to gravity, the weight of the pendulum arm should have stopped at the 0° position, however for some of the participants the motion stopped in a slightly different position e.g. -10°. Therefore the baseline angle was considered to be the one when the pendulum stopped, in order to minimise errors in the further analysis.

More prominent spasticity would be expected to cause a decrease in the number of swings, the magnitude of swings and the total time of pendulum motion.

The magnitude of the pendulum motion without the load of the participant forearm would decrease over time, however the damping effects were considered negligible in the data analysis, with undamped oscillations continuing for over several minutes.

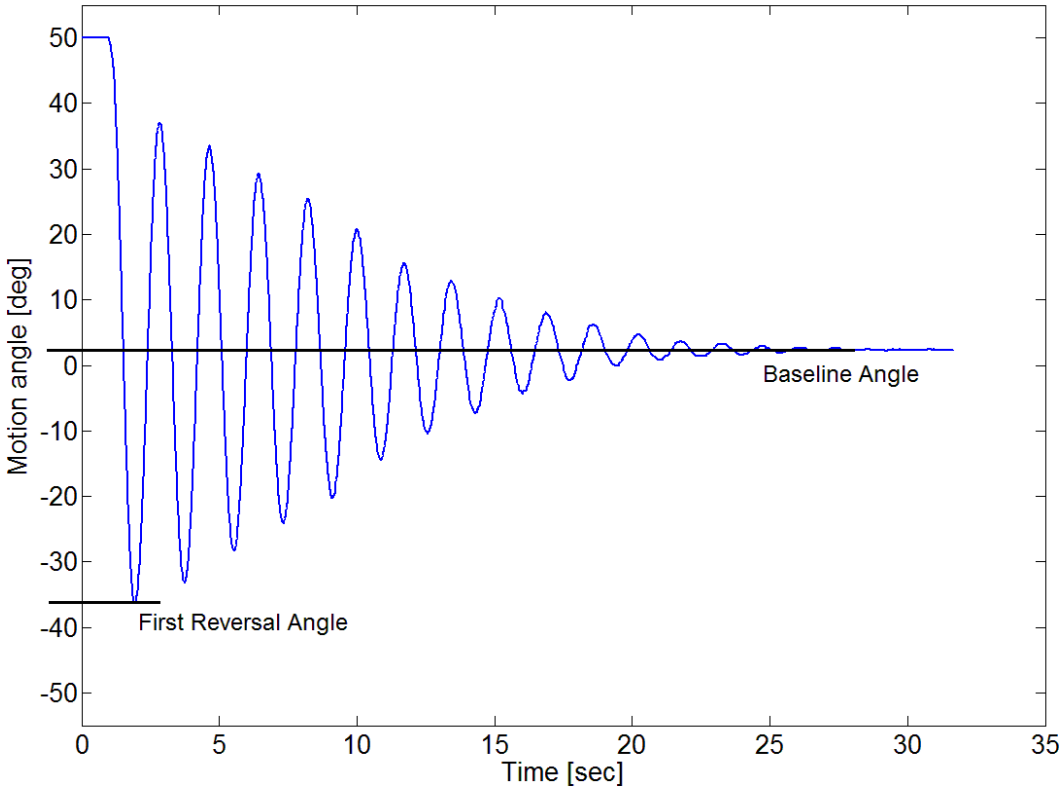


Figure 3.14 An example of the pendulum data from one participant

A previous study (Lin et al., 2003) used a complex analysis of a biomechanical model of the elbow joint and accessory, and derived a formula to quantify the damping coefficient. The main aim in this study was to quantitatively compare the motion before and after the intervention, therefore only simple measures derived from the system were obtained.

3.4.1.8. **Outcomes of the pendulum test**

Three parameters were derived from the curve:

The **First Reversal Angle** (FRA) is the first forearm peak angle in flexion. It is expected that the forearm will swing towards -50° (Figure 3.14).

The **Area Under the Curve** (AUC) is the total area of the modulus of the angle-time curve.

The **Maximum Velocity to First Reversal** (MVFR) is the maximum gradient of the angle-time curve between the start of pendulum movement to the peak of first reversal.

3.4.1.9. **Analysis of the data**

Baseline data were compared with those immediately and one hour after the interventions, using the Wilcoxon signed rank test because of the non-parametric nature of the outcome measures. TENS and SBS were compared using the Mann-Whitney's test at each assessments period. The Friedman non-parametric test was used to compare the pendulum data. GraphPad Prism version 6.00 for Windows (GraphPad Software, San Diego California, USA) was used for the analyses. All analyses was performed using intention to treat.

3.4.2. **Results**

In total, 17 patients were approached to participate in the study and ten consented. Four did not wish to participate, two were not able to participate due to problems with transport, and one had an implanted device - an exclusion criteria for the study. The study flow diagram is shown on Figure 3.15.

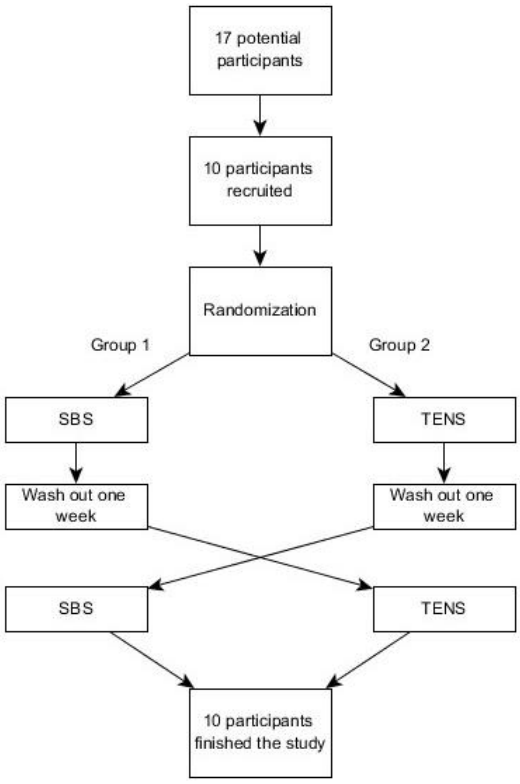


Figure 3.15 Study flow diagram

3.4.2.1. **Demographic**

Among the 10 recruited participants there were five men and five women. Their ages ranged from 18 to 65 years (40±17 years). The aetiology of spasticity was: cerebral palsy (4), stroke (3), traumatic brain injury (2) and multiple sclerosis (1). The duration of spasticity symptoms varied from six to 38 years. All tolerated the interventions well and completed the study.

Adverse events reported after SBS were one case of muscle spasm and one of an ache localised over the triceps muscle. One participant reported experiencing a sensation of pins and needles over his little finger after TENS.

3.4.2.2. **Stimulation current**

Across all participants the average current during a pulse was in the range of 8 to 16 mA with a mean of 10.9±2.2 mA (mean ± SD) for TENS (excluding the ramp period). The average total current from the eight simultaneously activated SBS electrodes was in the range of 7.2 to 15.2 mA with a mean of 12.9±2.5 mA.

3.4.2.3. **Primary outcome**

Immediately after the stimulation the MAS (Table 3.5) showed significant reduction for both TENS ($p = 0.016$) and SBS ($p = 0.0039$). The VAS (Table 3.6) also reduced significantly for both TENS ($p = 0.027$) and SBS ($p = 0.0059$). At one hour after the stimulation with TENS, there was no significant change in MAS compared to baseline whilst the patient's perception (as recorded with VAS) continued to show a significant change. One hour after SBS a significant reduction in spasticity both on the MAS and VAS was noted. There was no statistically significant difference in the MAS score between TENS and SBS immediately after ($p = 0.63$) and one hour after ($p = 0.063$) stimulation. However a trend was noted for a better response with SBS at one hour after stimulation compared to TENS.

Table 3.3.5 Modified Ashford Scale results

MAS	TENS (n = 10)	SBS (n = 10)
Baseline - Mean (SEM)	2.8 (0.2)	2.8 (0.2)
Immediate - Mean (SEM)	1.9 (0.3)	1.7 (0.3)
One hour - Mean (SEM)	2.1 (0.4)	1.6 (0.4)
Baseline - immediate		
Mean difference (SEM)	-0.9 (0.2)	-1.1 (0.2)
95% two side CI	-1.4 to -0.4	-1.5 to -0.7
P value	0.016	0.0039
Baseline – one hour		
Mean difference (SEM)	-0.7 (0.3)	-1.2 (0.2)
95% two side CI	-1.3 to –0.1	-1.7 to -0.7
P value	0.063	0.0039

Table 3.6 Visual Analogue Scale results (percentage of maximum imaginable spasticity)

VAS	TENS (n = 10)	SBS (n = 10)
Baseline - Mean (SEM)	61.7 (7.2)	70.1 (8.6)
Immediate - Mean (SEM)	47.1 (8.9)	38.6 (8.5)
One hour - Mean (SEM)	41.4 (6.7)	38.1 (9.5)
Baseline - immediate		
Mean difference (SEM)	-14.6 (5.3)	-31.5 (8.2)
95% two side CI	-26.6 to -2.6	-50.0 to -12.9
P value	0.027	0.0059
Baseline – one hour		
Mean difference (SEM)	-20.3 (7.6)	-32.0 (9.5)
95% two side CI	-37.6 to -3.0	-53.4 to -10.6
P value	0.025	0.0098

3.4.2.4. **Secondary outcome**

There were no significant changes in the MRC grades of elbow flexion and extension with TENS and SBS although confidence intervals indicate a slight improvement (less than one grade) in TENS and SBS (Table 3.7 and Table 3.8).

Table 3.7 MRC elbow extension power summary of the results

MRC power elbow extension	TENS (n = 10)	SBS (n = 10)
Baseline - Mean (SEM)	4.3 (0.4)	4.3 (0.5)
Immediate - Mean (SEM)	4.4 (0.5)	4.6 (0.3)
One hour - Mean (SEM)	4.6 (0.4)	4.7 (0.3)
Baseline - immediate		
Mean difference (SEM)	0.1 (0.2)	0.3 (0.3)
95% two side CI	-0.3 to 0.5	-0.3 to 0.3
P value	>0.99	0.5
Baseline – one hour		
Mean difference (SEM)	0.3 (0.2)	0.4
95% two side CI	-0.2 to 0.8	-0.1 to 0.9
P value	0.5	0.25

Table 3.8 MRC elbow power flexion summary of the results

MRC power elbow flexion	TENS (n = 10)	SBS (n = 10)
Baseline - Mean (SEM)	4.0 (0.4)	3.9 (0.5)
Immediate - Mean (SEM)	4.2 (0.5)	4.5 (0.3)
One hour - Mean (SEM)	4.5 (0.4)	4.4 (0.3)
Baseline - immediate		
Mean difference (SEM)	0.2 (0.2)	0.6 (0.3)
95% two side CI	-0.4 to 0.8	- 0.003 to 1.2
P value	0.69	0.13
Baseline – one hour		
Mean difference (SEM)	0.5 (0.2)	0.5 (0.3)
95% two side CI	-0.001 to 1.0	-0.1 to 1.1
P value	0.13	0.25

3.4.2.5. **Clinically significant improvement**

A reduction in spasticity of at least one grade on the MAS when combined with a 30% decrease of spasticity relative to the baseline value as assessed by the participant using the VAS was considered to be a clinically significant improvement. Immediately after TENS there were 2/10 responders and after SBS in 6/10 participants (Table 3.9). One hour after the interventions, these effects persisted in both TENS responders and in four of SBS responders, however two additional TENS and one additional SBS participants fulfilled the defined criteria at this point and were considered as responders as well resulting in 4 TENS responders and 5 SBS responders.

Table 3.9 Participants showing clinically significant improvement versus treatment and time (✓ = responder, - = non-responder).

Pt no.	TENS		SBS	
	Immediate	1 hour	Immediate	1 hour
1	-	-	-	-
2	-	✓	✓	✓
3	-	✓	✓	✓
4	-	-	-	-
5	-	-	-	✓
6	-	-	✓	-
7	-	-	✓	-
8	-	-	✓	✓
9	✓	✓	-	-
10	✓	✓	✓	✓

3.4.2.6. **Pendulum data**

Altogether 292 tests out of an estimated 300 were analysed. Eight waveforms were not collected due to a technical fault. Further technical problems did not capture peak measurements in 37 tests and these had to be corrected to their approximate values. These corrections to the AUC were in a range of 4 to 17 degree seconds, which was considered negligible as the mean AUC values were at least an order of magnitude higher. Due to the same technical issue, three FRA test measurements were also corrected. An abnormal trajectory was observed in 12 tests such that the swing motion became larger with time. These tests were excluded from the analysis.

The means of the test data for each pendulum outcome, in each of the participants are summarised in the Appendix F. An example of the data collected are shown in Appendix G. The mean values of all pendulum outcomes are in Table 3.10 and 3.11. The Friedman non-parametric test showed no difference in any of the pendulum outcomes for both interventions.

Table 3.10 Mean ± SEM of pendulum outcome at each assessment for TENS intervention. FRA – First Reversal Angle, MVFR – Maximum velocity to First Reversal angle, AUC – Area Under the Curve

TENS	FRA [deg]	MVFR [deg/s]	AUC [deg*s]
Baseline	32.8 ± 2.4	134.4 ± 2.6	253.0 ± 55.3
After intervention	31.0 ± 2.8	130.5 ± 2.2	238.1 ± 51.4
P value (Base-After)	0.322	0.160	0.492
One hour after	30.2 ± 2.8	129.2 ± 4.4	270.0 ± 53.2
P value (After-One)	0.625	>0.999	0.322

Table 3.11 Mean ± SEM of pendulum outcome at each assessment for SBS intervention. FRA – First Reversal Angle, MVFR – Maximum velocity to First Reversal angle, AUC – Area Under the Curve

SBS	FRA [deg]	MVFR [deg/s]	AUC [deg*s]
Baseline	32.0 ± 3.4	130.6 ± 4.8	211.7 ± 42.9
After intervention	32.3 ± 3.3	127.5 ± 4.8	201.4 ± 38.1
P value (Base-After)	>0.999	0.496	0.625
One hour after	34.8 ± 3.3	135.3 ± 3.5	269.7 ± 66.1
P value (After-One)	0.910	0.164	0.491

Table 3.12 and Table 3.13 express the change in each pendulum outcome in each individual from baseline to immediately after and one hour after the intervention (indicated by red colour font). Increases of more than 24% for FRA, 16% for MVFR and 44% for AUC were considered a significant improvement. This was based on the mean variation of the pendulum tests calculated as a percentile ratio of two standard deviations and means in each test.

Table 3.12 Percentage change of the pendulum outcomes in TENS intervention

Pt	FRA		MVFR		AUC	
	After	One hour	After	One hour	After	One hour
1	6%	-2%	-1%	1%	-7%	35%
2	3%	-3%	7%	-2%	-29%	23%
3	-2%	-4%	-6%	1%	20%	37%
4	-17%	-26%	5%	-13%	7%	-37%
5	12%	-7%	1%	-14%	80%	67%
6	-29%	-16%	-7%	-10%	-23%	-12%
7	-5%	1%	-6%	5%	-16%	-31%
8	-6%	-7%	-3%	0%	6%	-8%
9	-25%	-6%	-6%	-1%	-50%	20%
10	5%	-19%	-10%	-7%	-9%	-3%

Table 3.13 Percentage change of the pendulum outcomes in SBS intervention

Pt	FRA		MVFR		AUC	
	After	One hour	After	One hour	After	One hour
1	-5%	-15%	-2%	3%	-14%	-17%
2	53%	61%	7%	12%	140%	326%
3	-1%	19%	-6%	12%	48%	234%
4	-3%	-	-9%	-	-40%	-
5	20%	25%	9%	11%	47%	98%
6	1%	-46%	-8%	-20%	-15%	-63%
7	4%	-1%	1%	1%	-23%	-62%
8	-9%	-4%	-10%	1%	-5%	-7%
9	-27%	-10%	-4%	-2%	-63%	-49%
10	-2%	-7%	0%	-1%	-29%	-24%

The pendulum outcome data did not appear to show a significant treatment improvement. Comparing the responders in the pendulum data (red values Table 3.12 and 3.13) with the responders in Table 3.9. only the Participant #2 in the SBS intervention was consistent. The Participant #5 in the SBS intervention show a possible trend towards this correlation, as all three outcomes positively changed, however he was not considered as a responder only one hour after the intervention (Table 3.9). Participant #5 in the TENS intervention (non-responder, Table 3.9) and Participant #3 in the SBS stimulation (responder, Table 3.9) might showed improvements in AUC, but not in the other two pendulum parameters.

3.4.3. **Discussion**

Of the 17 potentially eligible subjects, 10 could participate in this study and all completed the trial protocol. All participants tolerated the interventions well and there were no significant adverse events. This study demonstrated the feasibility and practicality of using SBS; a new type of electrical stimulation for the treatment of spasticity.

TENS stimulation, below motor threshold, has been reported to have positive effects on spasticity in spinal cord injury (Ping Ho Chung and Kam Kwan Cheng, 2010), in chronic hemiplegia after stroke (Potisk et al., 1995, Sullivan and Hedman, 2007) and in multiple sclerosis (Armutlu et al., 2003) patients. Although optimal TENS stimulation parameters have not yet been determined, 100Hz seems to be effective (Armutlu et al., 2003, Potisk et al., 1995). In our study, TENS reduced spasticity as measured on MAS immediately after 60 minutes of stimulation, however the effect did not persist at one hour. In comparison, the novel concept of sensory barrage stimulation, which allows delivery of stimuli at multiple sites and with spatio-temporal patterns, continued to show a significant response both immediately and one hour after stimulation. A combination of improvement in both MAS and in the participants' VAS outcome measures was assumed to be a clinically robust way of evaluating the effects of stimulation, and altogether this identified seven SBS responders compared to four in the TENS group in the immediately after and one hour after datasets are combined. Although the Wilcoxon signed rank test showed significant differences in MAS and VAS immediately after TENS, SBS showed greater differences in mean values compared to baseline with higher statistical significance and persisted for at least one hour after stimulation. These results give a promising indication that SBS is better than TENS in reducing spasticity.

The extension and flexion power did not show significant improvement, although this could possibly be explained by already high grades, indicating a low severity muscle weakness in 6 out of 10 participants, who displayed normal extension power (MRC grade of 5) throughout the full test procedure with both TENS and SBS.

The pendulum outcome data did not appear to be sensitive and consistent enough to show improvements as reported by VAS or MAS. A further development allowing determination of optimal parameters (weight, length) of the pendulum and its influence on sensitivity is required.

SBS might also be beneficial in rehabilitation techniques where peripheral electrical nerve stimulation has been proposed to enhance motor deficits or tactile sensation (Sullivan and Hedman, 2007, Cuypers et al., 2010) as well as in combination with standard rehabilitation programmes (Lin et al., 2003, Kaelin-Lang, 2008). This study only investigated the short-term effects of stimulation. Although patients tolerated SBS well, further investigations are required to assess the tolerability and acceptability of several sessions of stimulation. If patients are more likely to benefit from several sessions it would be preferable that they were managed at home, as this would be both more cost-effective and convenient for the patient. We think that this should be practical both for SBS and TENS. Future studies on TENS and SBS need to use more patient reported outcome measures and functional goals.

3.4.3.1. **Study limitations**

The limitation of this pilot study was the absence of a placebo group. Future studies should be placebo-controlled, although there are challenges in using a placebo group in studies using electrical stimulation, because the active stimuli can be felt. Participants should also be stratified based on different pathologies and severity of symptoms, which was not practical with the limited size of this study.

3.5. **Conclusions**

Sensory Barrage Stimulation, as introduced in this chapter, is a novel concept of stimulation which aims to enhance the effects of conventional TENS, using stimulation below the motor threshold level. The spasticity study showed promising support for this approach and the salience and habituation study utilised SBS with time varying stimuli. However it remains to be demonstrated that this will enhance the process of plasticity by focusing attention. The approach of evaluating this feature using measurements of performance during cognitive tasks has not produced a significant evidence for this claim.

Chapter 4 **The assessment of an electrical stimulation waveform developed to treat overactive bladder symptoms**

The work in this chapter has been published in:

M Slovak et al., The assessment of a novel electrical stimulation waveform recently introduced for the treatment of overactive bladder. Physiol Meas 2013; 34 479

4.1. **Introduction**

Sacral neuromodulation is a well-established form of neuromodulation for the treatment of overactive bladder symptoms (Bartley et al., 2013). Stimulation of the pudendal nerve originating from the S2,S3 and S4 sacral nerve roots has emerged as a superior alternative (Peters et al., 2005). Both of these stimulation sites are relatively deep in the body, covered by overlying tissue, and hence are difficult to stimulate using surface electrodes. They are therefore usually accessed using implanted wire electrodes as it is in the sacral neuromodulation.

To non-invasively target these deep branches, which are involved in bladder control, has remained a challenge. Recently however, a novel stimulation technique using a 'transdermal amplitude modulated signal' (TAMS) has been introduced (Figure 4.1 right). This TAMS waveform has been described (Shen et al., 2011) as 'a high frequency sinusoidal carrier waveform (210 kHz) amplitude-modulated by low frequency, monophasic rectangular pulses (1 ms pulse width)'. Preclinical studies have evaluated the effect of TAMS stimuli of the pudendal nerve on the bladder in cat models (Shen et al., 2011, Tai et al., 2011, Tai et al., 2012). This latter paper reported that 'TAMS uses a 210 kHz sinusoidal carrier waveform that has a minimal skin impedance and is optimal for stimulating nerves under skin and muscle' (Tai et al., 2012). However, there is no literature to support this statement, based on comparative human studies. Low skin impedance would be an important advantage in all transcutaneous electrical stimulation techniques, not just those used for overactive bladder therapy, because it will result in less electrical energy being required to deliver the charge required for stimulation. In addition, and more importantly, if a particular electrical stimulation waveform is more effective in stimulating deep nerve structures such as the pudendal nerve this would have major implications for the whole field of non-invasive electrical stimulation.

The TAMS waveform has been used in a commercial neuromodulation system, which has been introduced into clinical practice as the VERV^{TM} Patient-Managed Neuromodulation System (PMNS, Ethicon Endosurgery Inc.). This system transmits the TAMS waveform through two hydrogel electrodes applied to the skin in the sacral region (Monga et al., 2011a). The results of an initial open study (Monga et al., 2011a) have shown beneficial effects, although placebo control studies are still required to

demonstrate a direct effect of the electrical stimulation. Further outcomes of the VERV system are discussed at the end of this chapter.

As mentioned previously the claims made for this waveform could also be beneficial in other applications where deeper nerve structures are to be electrically stimulated. However because there is no literature describing the specific physiological effects of stimulation using the TAMS waveform in human a more basic investigation is required. An initial evaluation using a simplified equivalent multilayer model for skin impedance in a SPICE model did not identify specific benefits of the TAMS waveform. However, this did not consider any non-linear tissue properties, for example at the nerve membrane. Further assumptions would be needed to investigate this problem theoretically and may not lead to a robust conclusion. Therefore, the main aim of the work in this chapter was to experimentally compare the TAMS waveform with a conventional electrical stimulation waveform both in terms of electrical parameters and acute physiological effects on healthy volunteers. This will provide a direct assessment of some of the claims for TAMS.

4.2. **Materials and Methods**

This study has been designed to compare the TAMS waveform with a conventional electrical stimulation waveform, both at sensation and motor stimulation intensity levels. The study was reviewed by the Clinical Research Office of Sheffield Teaching Hospitals NHS Foundation Trust and an ethic waiver was obtained. Ten (five male + five female, age range 23–62) healthy volunteers participated in the study. The study flow diagram is shown in Figure 4.7 further in the text.

4.2.1. **Equipment**

Figure 4.1 shows schematically the two waveforms delivered in the experiment. A block diagram of the experimental setup is shown on Figure 4.2.

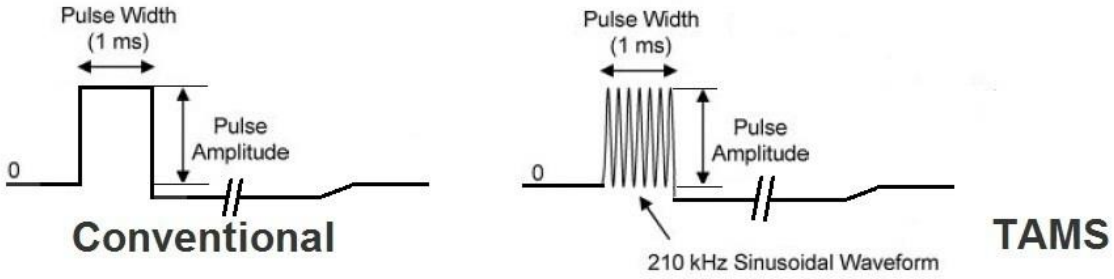


Figure 4.1 A Sketch of the conventional and the TAMS waveforms redrawn from (Shen et al., 2011)

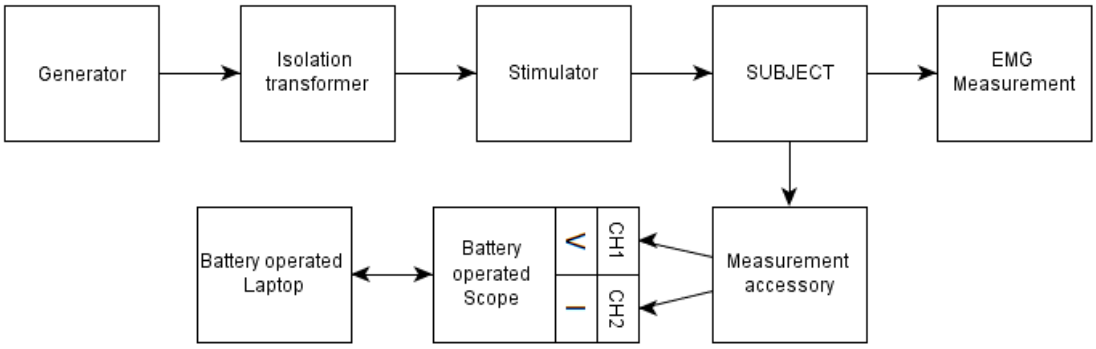


Figure 4.2 Block diagram of the experimental system

A purpose designed constant current stimulator (Appendix H), able to deliver both the TAMS and conventional stimuli was developed in accordance with IEC 60601-2-10 for medical electrical devices (nerve and muscle stimulators). The stimulator consisted of a 9 V battery and a voltage step-up circuit, which created a 160 V voltage source. Further circuitry provided a constant current stimulator. An assessment characteristic is shown on Figure 4.3. and shows a good stability of the output current with a variable load. The decrease at around 62 kΩ, caused by the voltage source limit, is above the expected load in this experiment.

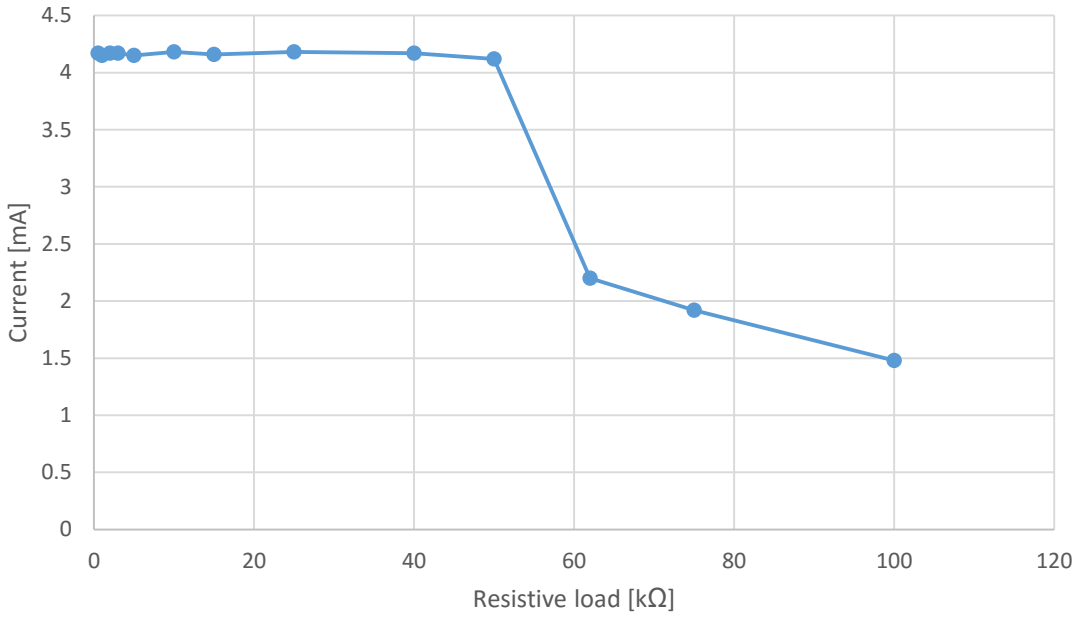


Figure 4.3 a stimulator constant current source characteristic

A function generator (Textronix AFG 3102) was used to generate the two waveforms under the test in this experiment and to drive the stimulator. The system was designed to deliver charge-balanced pulses by including a series capacitor in the electrode lead of value 1 µF to avoid electrochemical reactions. A battery operated oscilloscope and laptop were used both to ensure electrical isolation of the subject and to avoid measurement errors due to capacitive coupling and earth loops. The oscilloscope was connected to a purpose made accessory box (Measurement accessory, Figure 4.2) consisting of a serial combination of a 1 µF capacitor a 100 Ω resistor in order to measure the charge (voltage on the capacitor), current (voltage on the resistor) and the voltage across between the electrodes.

4.2.2. **Experiment**

Participants underwent stimulation at four intensity levels (sensation threshold, strong sensation, motor threshold and the intensity that produced 50% of maximal motor response), as described below in Section 4.2.4. Stimulation electrodes (Carefusion Disposable Disk electrodes, type 019-415000) electrodes were placed in different positions for the sensory and motor tests. For the sensation tests, the electrodes were placed near the wrist, 3 cm apart (Figure 4.4).

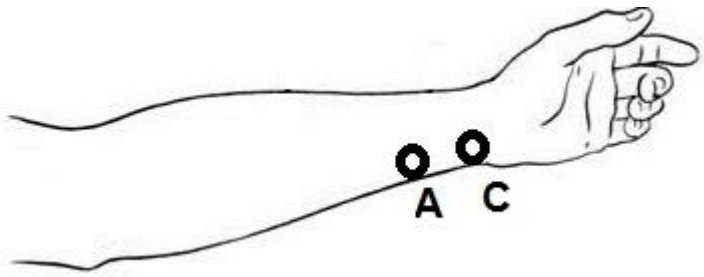


Figure 4.4 Placement of stimulation electrodes for the sensation measurements. A – anode, C – cathode

For the motor tests, electrodes were placed just above the elbow sulcus 3 cm apart (Figure 4.5). 10 Hz stimulation was used for the sensation tests, and 1 Hz was used for the motor tests (the latter to avoid tetanic contraction). Stimulation electrodes were placed on the subject for at least 10 min. before the measurements to allow the electrode–tissue interface to stabilize. EMG signals were recorded using an XLTEK Neuromax 1004. A Medelec recording electrode (SE20 intra-electrode distance 20 mm) was placed over the abductor digiti minimi muscle (ADM). A ground electrode (CareFusion 5×10 cm ground electrode, type 019-422200) was placed between the stimulation site and the recording electrodes. Participants were instructed to relax, with their arm resting on a soft foam support.

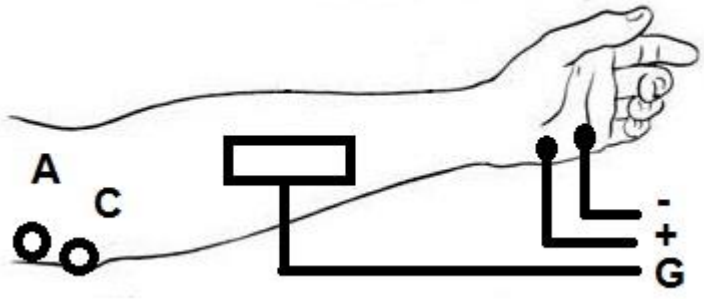


Figure 4.5 Placement of stimulation and recording electrodes for the motor measurements. A – anode, C – cathode, G – ground pad, + active electrode, - reference electrode

4.2.3. **Experimental protocol**

The following stimulation levels were used by adjusting the stimulator output intensity, the sensation levels being subjective to each subject whilst the motor levels were objective being based on EMG measurements (see below):

- Sensation threshold

- Strong but comfortable sensation
- Motor threshold
- 50% of supra maximal motor response

To determine the sensation threshold level, the stimulation current was gradually increased by the experimenter until the subject first reported sensation. The strong but comfortable sensation level was chosen by subjects for the TAMS waveform, and the intensity of the conventional stimuli were adjusted until subjects reported the same subjective sensation when the stimuli were switched between conventional and TAMS. Control buttons of the generator were used to switch between the waveforms applied. Motor threshold levels were defined as an EMG response of 200 μV pk–pk, if noise levels were high then 300 μV was used instead for both of the waveforms. The maximal motor response was generated using the inbuilt conventional stimulator of the XLTEK and its amplitude measured using the on-screen cursors. Data was then collected at 50% of this amplitude for both waveforms.

4.2.4. **Data collection**

After the stimulation intensity was set to the appropriate level for the measurement being made, the voltage across the stimulation electrodes (*V*), current through the electrodes (*I*), delivered power (*P*) and delivered charge (*Q*) waveforms were recorded using a battery operated oscilloscope (Tektronix THS 720) connected to the relevant points in the measurement accessory. The voltage was measured between the stimulation electrodes on the oscilloscope channel CH1 and current was calculated as

$$I[A] = \frac{U_r\ [V]}{R\ [\Omega]} \tag{4.1}$$

The U_r voltage was measured across resistor R = 100 Ω on the oscilloscope channel CH2. The recorded waveforms were then processed offline to give mean values for each pulse. The waveforms were uploaded using serial connection commands and HyperTerminal application.

The measurement of power was performed as a multiple of the channels CH1 and CH2. Electrode-skin impedance was calculated retrospectively as instantaneous voltage across the electrodes divided by current through the electrodes (bulk body impedance is assumed

to be negligible for this purpose). The delivered charge was derived from the voltage (V_C) on a 1 μF capacitor (C) connected in series with the subject, calculated as

$$Q\ [\mu C] = C[\mu F] * Vc\ [V] \tag{4.2}$$

In addition, the impedance presented by the body and electrode-tissue interface was calculated as,

$$Z\ [\Omega] = \frac{V\ [V]}{I\ [A]} \tag{4.3}$$

at five time points (0.1, 0.3, 0.5, 0.7 and 0.9 ms, in each case averaged over five cycles of the 210 kHz waveform) during a representative pulse for each subject to investigate any intra-pulse waveform differences.

Sensation obtained during the motor threshold and 50% of maximal motor response tests were recorded by the subjects on a visual analogue scale (VAS). The VAS was 100 mm long, with the left end of the VAS representing no sensation and the right end representing very uncomfortable or painful sensation (Figure 4.6). The sensation score was defined as the distance in mm of the position marked by the participant from the left end. Participants were blinded as to which waveform was being applied and the order of stimulus waveform was randomized.

Figure 4.6 Visual analogue scale 100 mm long

4.2.5. **Data analyses**

The paired Student's *t*-test was used in the resultant statistical analysis, and no correction was made for multiple testing in order to maximize the likelihood of the study to detect differences between the two waveforms.

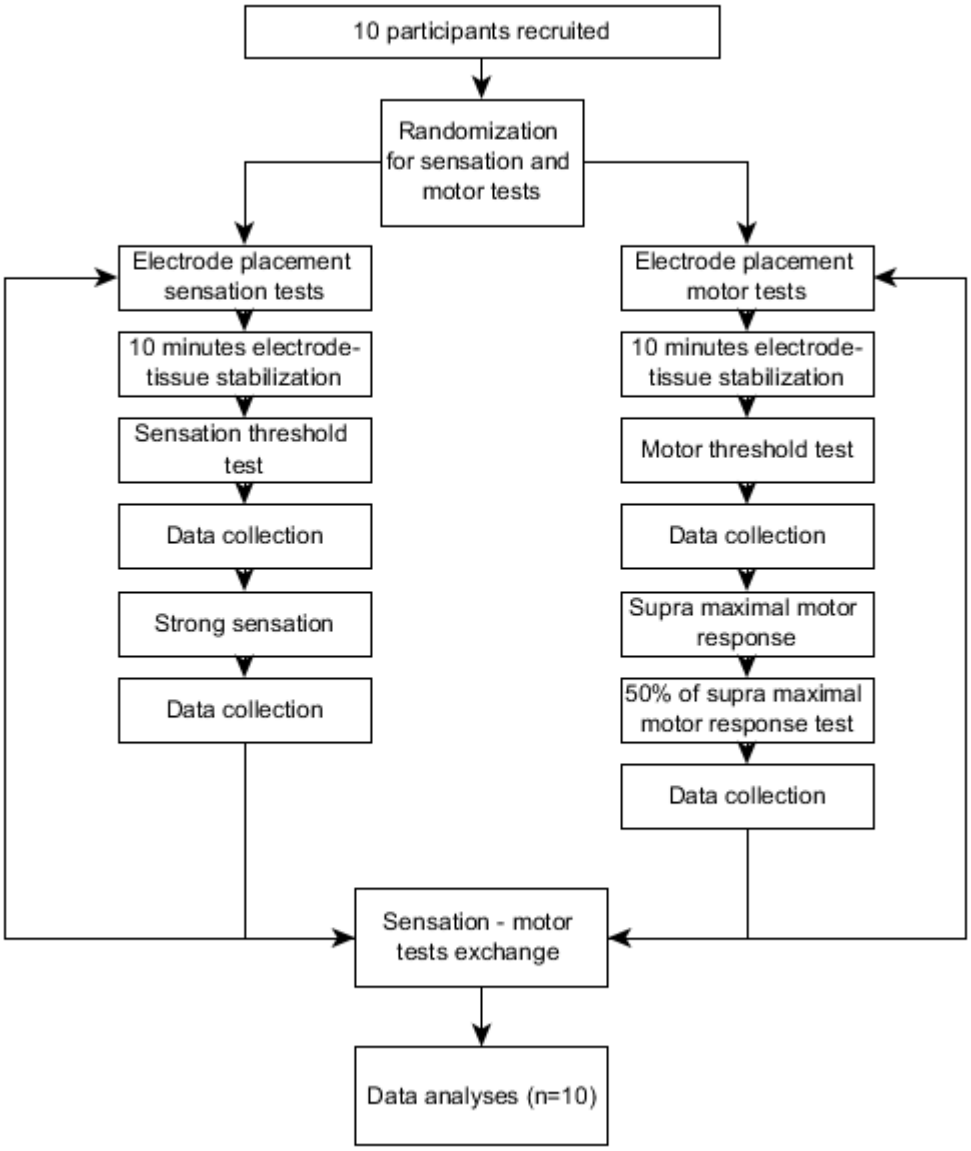


Figure 4.7 Study flow diagram

4.3. **Results**

10 participants completed the test. Voltages across the electrodes, current through the electrodes and delivered charge waveforms were recorded for all subjects at four different levels of stimulation. Four of the eighty power waveforms were not recorded due to unexpected technical problems in the data collection. Where these waveforms were not obtained the equivalent paired recording from the other stimulation type was excluded from the analysis.

Skin impedance was compared by the shape analysis and by the comparison of means (as described in Section 4.3.1). Current through the electrodes, voltage across the electrodes and delivered power were compared by the average of the whole pulse waveform. Delivered charge was compared as the maximum delivered amount.

Representative measurements of current, voltage and power are showed in Figure 4.8 for both types of the stimuli. The mean values ± SEM of all recorded parameters are presented in Table 4.1 altogether with p values. None of the electrical parameters showed a significant difference (all p values ≥0.250) by paired Student's T-test.

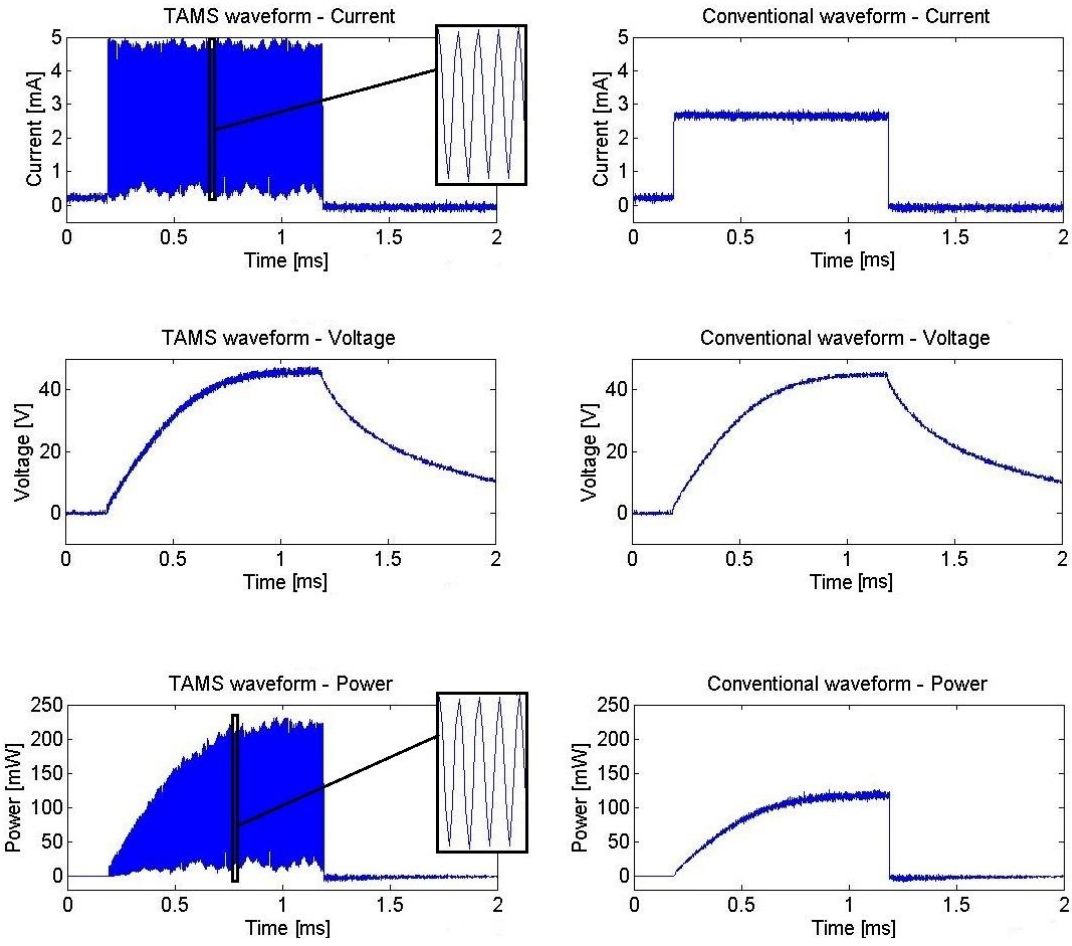


Figure 4.8 Representative measurements of current through the stimulating electrodes, voltage across the electrodes and delivered power for TAMS (on left) and conventional stimuli (on right)

Table 4.1 Mean values ± SEM of recorded electrical parameters at four intensity levels (n=10 subjects) and P values of paired Student t-test

		Sensation threshold	Strong sensation	Motor threshold	50% of Max.
Mean current [mA]	TAMS	1.11±0.12	1.92±0.28	3.81±0.77	6.32±0.98
	Conv.	1.10±0.12	1.93±0.28	3.84±0.68	6.26±0.92
	P value	0.769	0.539	0.793	0.710
Mean voltage [V]	TAMS	25.92±3.66	36.68±5.19	42.51±4.80	58.12±4.53
	Conv.	26.12±4.02	36.92±5.07	42.45±4.57	58.19±4.74
	P value	0.721	0.275	0.942	0.936
Mean charge [µC]	TAMS	1.14±0.13	1.98±0.28	3.83±0.84	6.62±1.04
	Conv.	1.13±0.13	1.98±0.28	3.84±0.77	6.45±0.93
	P value	0.732	0.725	0.883	0.430
Mean impedance [kΩ]	TAMS	22.98±1.19	19.66±1.23	12.54±1.19	10.91±1.61
	Conv.	23.02±1.27	19.76±1.24	12.33±1.30	10.80±1.51
	P value	0.896	0.368	0.503	0.642
Mean power [mW]	TAMS	33.69±9.75	76.28±23.82	198.8±69.07	405.9±91.84
	Conv.	33.30±9.80	76.08±22.51	187.6±60.51	386.6±87.48
	P value	0.770	0.907	0.250	0.277

4.3.1. **Intra-pulse skin impedance waveform differences**

Mean skin impedance showed no significant differences between TAMS and convention stimulation (Figure 4.9, paired t-test, all p values ≥ 0.368). To analyse changes in the shape of waveform intra-pulse analyses of the ratio of average current and voltage conventional waveforms were performed in five different time points of the pulse.

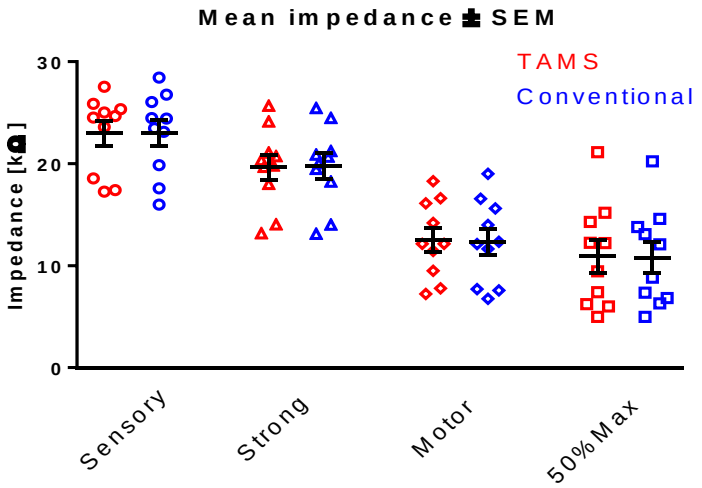


Figure 4.9 Mean skin impedances measured at four intensity

The results of Student's T-test p values are shown in Table 4.2. After Bonferroni correction (($p \geq 0.03$) there were no significant differences in the shape analysis.

Table 4.2 P values of paired t-test in the shape analysis (not corrected for multiple testing)

	Sensation thres.	Strong sens.	Motor thres.	50% of Max.
0.1ms	0.998	0.034	0.533	0.068
0.3ms	0.848	0.312	0.312	0.802
0.5ms	0.816	0.183	0.183	0.573
0.7ms	0.397	0.163	0.163	0.569
0.9ms	0.330	0.186	0.186	0.715

4.3.2. **Sensation**

The mean sensation recorded at the motor threshold level in all of the participants was 34.9 ± 6.6 mm for the TAMS stimuli and 39.2 ± 7.1 mm for the conventional stimuli (paired t-test p = 0.242). At 50% of supra-maximal response the results were 49.2 ± 5.0 mm for the TAMS and 50.3 ± 5.2 mm for conventional stimulation (paired t-test p = 0.687). The graphical presentation is showed on Figure 4.10.

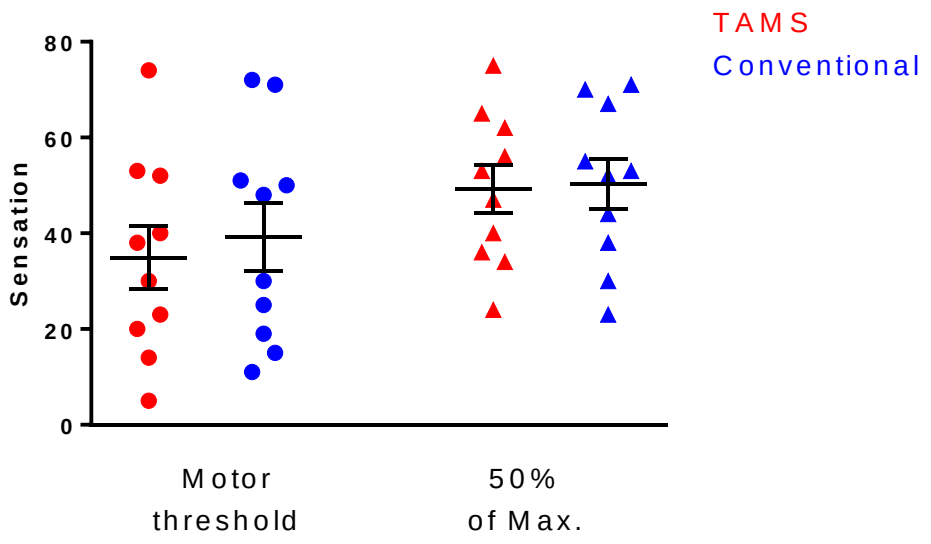


Figure 4.10 Sensation level for both types of the stimuli in ten subjects

4.4. **Discussion**

TAMS has been recently introduced as a novel stimulation waveform for the treatment of OAB, however there is no background literature on the physiological effect of this

specific stimulation waveform in man. Shen et al (Shen et al., 2011) suggests that the well-known decrease in skin impedance with frequency (Rosell et al., 1988), observed with sinusoidal excitation, can also be obtained using the TAMS waveform. However, this study has shown no difference in impedance when stimulating with TAMS as compared to conventional waveforms. High frequency sinusoidal signals, having no net DC component penetrate skin more easily due to tissue capacitance, mainly but not exclusively within the stratum corneum. The TAMS waveform, in contrast to sinusoidal signals, is offset relative to zero and hence has a net unidirectional component (Figure 4.1 left). As a result, charge build up in tissue capacitance occurs in the same way as with conventional unidirectional stimuli and the frequency dependent impedance changes associated with non-offset sinusoidal signals are not seen. This can be observed in Figure 4.6 which show the same rise in stimulator output voltage during the pulse for both stimulation waveforms as the electrode and skin interfacial capacitances charge up. Nerve membranes have an electrical time constant, typically of the order 150 μs (Barker et al., 1991, Reilly, 2011), caused by their capacitance and the relatively high internal resistance of the cell body and this acts as a low pass filter to incoming stimuli. Because the TAMS waveform high frequency component is well above this filter frequency it is integrated at the nerve membrane in the same way as is the conventional stimulus waveform. This results in the mean current required to achieve stimulation being the same for both signals. It should however be noted that the peak current delivered by the TAMS waveform needs to be twice that of the conventional waveform in order to deliver the same mean current. The decrease in impedance at higher levels of stimulation, shown in Figure 4.9, is consistent with established tissue non-linearity as a function of current (Dorgan and Reilly, 1999).

The TAMS waveform has been further studied in a multilayer volume conductor model with a nerve represented by a cable model (Medina and Grill, 2014). This study partly utilised the data presented in this chapter and their model also showed no difference between conventional and TAMS waveform stimulation. Their further analyses failed to show any differences in a strength-distance curve that would allow stimulation of deep nerve structures at a lower threshold then those more superficial. This corresponded to the experimental work presented here where no significant differences in sensation levels between the two stimuli tested was obtained. This suggests that the same nerve structures were being targeted by both of the waveforms.

In conclusion, this study has shown no significant differences in either electrical, or physiological, metrics between TAMS and conventional stimuli waveforms. Hence it is unclear what advantages TAMS may have over conventional stimuli.

Postscript

The commercially available system VERV^{TM} Patient-Managed Neuromodulation System (PMNS, Ethicon Endosurgery Inc.), which used TAMS waveform up to date have not been fully available on the market.

After the work described in this chapter was completed, results of a randomised double blind sham stimulation trial of VERV^{TM} system were published (Ethicon Endo Surgery, 2014). This showed that there was no significant difference between the active and sham version of VERV^{TM} system (the same device but no stimulation) in any of the parameters measured (urinary frequency, urgency incontinence, mean voided volume and various OAB questionnaire). Also the number of responders (greater than 50% decrease in the mean number of urgency incontinence episodes) in active version of VERV^{TM} system (31/80) vs. (38/83) in the sham version did not proof benefits of this system (Monga et al., 2011a, Monga et al., 2011b, Monga and Linsenmeyer, 2011).

The results in this Chapter showed that there is no difference between TAMS waveform (used in the VERV^{TM} system) and conventional stimuli. Thus in order to target the deep nerve structures (e.g. pudendal nerve, S3 spinal cord root) which would potentially be able to produce an effect on overactive bladder symptoms high intensity of stimuli would be needed. However due to the discomfort cause this would be very difficult to achieve and thus presumably VERV^{TM} system produced only low amplitude stimuli. This might then explain the no difference between the active and sham version of VERV^{TM} system.

The results of the VERV^{TM} clinical trial shows also that a placebo response in overactive bladder patients can be high.

Chapter 5 **Numerical modelling of posterior tibial nerve stimulation**

5.1. **Introduction**

As introduced in Chapter 1 there are two techniques available for the stimulation of posterior tibial nerve as a treatment of overactive bladder symptoms. The percutaneous form of Posterior Tibial Nerve Stimulation (PTNS) is more established and several studies have shown its benefit in the treatment of various lower urinary tract symptoms (Finazzi-Agro et al., 2010, Peters et al., 2010). However this technique has the disadvantage of being invasive and requires patient visits to clinics, which is expensive. In contrast to this, the transcutaneous form of PTNS is less well established, but has the advantages of being completely non-invasive, can be administered by the patients at home and is low cost. The work in this chapter numerically models these two techniques in order to compare their potential physiological effects.

The percutaneous form of PTNS is relatively well established in clinical practice and a commercial device (Urgent-PC, Uroplasty Inc, USA) is available on the market. The most recent systematic review has concluded that there is strong evidence of efficacy for frequency and urgency urinary incontinence (Moossdorff-Steinhauser and Berghmans, 2013). However, further high quality studies are needed to improve the level of evidence for the outcomes of urgency and nocturia.

Nonetheless, despite the significant body of evidence for the percutaneous form of stimulation, the National Institute for Health and Care Excellence (NICE) has changed its original statement on its use (which originally recommended the use of PTNS for the treatment of OAB symptoms). The current recommendation says percutaneous tibial nerve stimulation for the treatment of OAB symptoms should not be offered unless there has been a multidisciplinary discussion, failure of conservative management including OAB drugs, and the patient does not want botulinum toxin or percutaneous sacral nerve stimulation (National Institute for Clinical Excellence, 2013). This places PTNS therapy towards the end of the patient's treatment pathway. It is not clear whether this view has been reached, at least in part, because of the cost effectiveness of percutaneous PTNS. The NICE guidelines further state that the transcutaneous form of PTNS should not be offered, because there is insufficient evidence for it to be recommended.

Despite these NICE recommendations, the evidence for percutaneous PTNS can be seen as persuasive (Moossdorff-Steinhauser and Berghmans, 2013), but the associated

treatment costs is high, around £3200 per patient annually (Walleser Autiero et al., 2014). Due to these costs percutaneous PTNS might not be suitable for large-scale clinical implementation even if evidence of efficacy becomes stronger. However, transcutaneous stimulation might be a suitable alternative if of comparable efficacy, due to its lower cost.

Both techniques, presumably, are designed to act in the same way, namely physiological effects produced by the stimulation of posterior tibial nerve. A relevant question to ask is whether these effects can be achieved by both techniques and are comparable. This might ultimately allow transcutaneous PTNS to be supported by using evidence from its percutaneous form. The description of the commercially available technique of PTNS is that it is designed to stimulate the posterior tibial nerve approximately 5 cm posterior from the medial malleolus (Uroplasty Ltd, 2013) at an intensity level just below a muscle/toe contraction. The aim of the modelling work presented in this chapter is to determine what stimulation current is needed in order to produce the same physiological effect obtained with percutaneous stimulation when the transcutaneous form of PTNS is used. In addition, the optimal position of the electrodes for the transcutaneous form of PTNS is explored.

5.1.1. **How to determine the same physiological effect?**

Potentially, the monitoring of nerve action potentials produced by the stimulation of the posterior tibial nerve would give insight into these effects, but this presents a number of technical challenges, primarily due to electrode positioning, small signal size and signal to noise. Therefore, a theoretical method of modelling the stimulation was chosen instead.

The physiological effects might be quantified by studying differences in the excitation of axons between the transcutaneous and percutaneous forms for a particular current intensity. This can be performed by quantifying the excitation caused by a known current applied percutaneously and then calculating the current needed to cause the same size of excitation in the transcutaneous form.

To quantify the excitation of a nerve axon, the so called activating function is used (Rattay, 1986, Rattay, 1988). This is the spatial derivate of the electrical field along the nerve fibre. A gradient of sufficient size is able to exceed the threshold level change in

transmembrane potential resulting in membrane depolarisation and subsequent propagation of a nerve action potential via the normal mechanisms.

5.2. **Numerical modelling**

To obtain an activation function and to study the distribution of electrical current in the tissue, electromagnetic field computer models are used. These models aim to find an approximate solution to Maxwell's equations such that they satisfy a defined set of conditions (Morris, 2012).

There are several mathematical simulation techniques available. Finite Element Method (FEM) and Finite Difference Time Domain (FDTD) method are the most common methods used and these are available in a number of commercial software packages. These methods could analyse arbitrary shaped 3D structures. FEM algorithms solve Maxwell's equations implicitly through the solution of a matrix, such that the entire volume of the simulation domain is discretised. FDTD algorithms solve Maxwell's equations in a fully explicit way. FDTD analysis requires that the objects being simulated are placed within a box-like volume which truncates space and defines the simulation domain. FDTD uses a time stepping algorithm which updates the field values across the mesh cell time-step by time-step, thus explicitly following the electromagnetic waves as they spread through the structure (Morris, 2012).

SEMCAD X has been chosen for the modelling presented in this thesis. This is because the package includes realistic body phantoms, an essential requirement because of the effect of tissue conductivity on field distributions and because of the availability of the software licence within the department. The low frequency solver used for the modelling as described below in section 5.2.1 uses FEM method.

The modelling work described further below starts with an introduction to the software package and a description of the model used. Following that it goes on to describe homogeneous models of increasing geometric realism to evolve an understanding of the source of the fields involved. It then moves to the partially defined model in order to gradually understand the complexity of the full model. And finally the full anatomic models of both transcutaneous and percutaneous stimulation are considered along with the effect of different electrode positions and sizes. This leads to the aim of this chapter,

to explore what stimulation current is needed in order to produce the same physiological effect obtained using both forms of PTNS.

5.2.1. **SEMCAD X**

SEMCAD X (IT'IS Foundation, Switzerland) is a commercially available full wave 3D electromagnetic and thermal simulation software package. The great advantage of this software is the availability of whole-body human anatomical CAD models created by the IT'IS Foundation currently known as Virtual Population (Christ et al., 2010). Hence the creation of the physical representation of the anatomy around the posterior tibial nerve (ankle) was greatly simplified.

SEMCAD X places the geometrical model into an automatically generated XYZ grid and the user is able to specify its resolution (Figure 5.1). The computational approach is based on FEM that defines the anatomical structures as solids and the user defines impedance in terms of Electrical Conductivity, Magnetic Conductivity, Permittivity and Permeability. However, only the electrical conductivity was used in this exercise as explained further. To determine the application of the electrical field and its distribution in the tissue only Electrical Conductivity is defined and the 'Electro Quasi Static Ohmic Current Dominated' solver was used. This solver finds a solution to simplified Maxwell's equations based on Gauss's law (5.1). Other aspect of Maxwell's equations are neglected.

$$\omega\varepsilon \ll \sigma_E \qquad \nabla \cdot \sigma_E \nabla \varphi = 0 \tag{5.1}$$

ω – Angular frequency

ε - Absolute permittivity

∇ - Three dimensional gradient operator

σ_E - Electrical conductivity

φ – Scalar potential function

This solver was chosen because of the following:

- Electro Quasi-Static solver neglects the temporal change of the magnetic flux B. Eddy current are negligible and would not affect the solution of the model significantly.

- Electrical stimulation uses short pulses of particular frequency. However the model consider only one pulse which is equal to direct current (DC). Therefore the condition in 5.1 is satisfied.

The equation only consider the electrical conductivity therefore other properties such as permittivity and permeability were ignored.

The geometrical model is represented by two solid structure types, namely materials with resistive and dielectric properties (dielectrics) and metal (considered to be a Perfect Electrical Conductor or PEC) i.e. electrodes and wires.

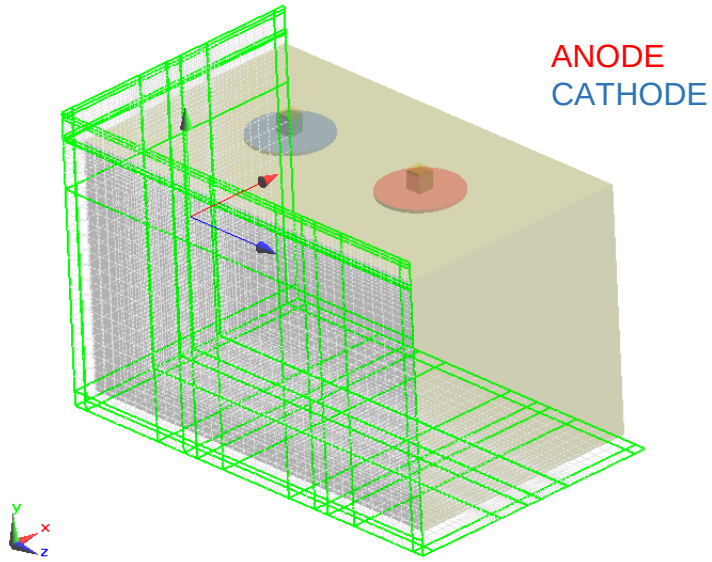


Figure 5.1 An example of a simple model of a conductive material block with two electrodes on top

This approach results in a calculated electrical potential and current density distribution throughout the grid. The resolution of the grid can be predefined by the user and refined in regions where higher levels of detail are required.

The equation (5.1) is solved using iterative technique until defined conditions are satisfied. These conditions were set for the modeling in this chapter to 'medium' convergence criteria. These criteria monitor the size of the changes between each the iterative solutions. This explicitly defines the convergence criteria as relative value of $1*10^{-8}$, absolute value of $1*10^{-50}$ and divergence value of $1*10^{50}$. Divergence can be interpreted as a slope of the curve of iteration change.

SEMCAD X modelling objects are assigned a voxelling priority, which is important for handling areas where two objects might overlap. In these overlap areas, voxels are assigned the material parameters with the highest priority. The part of the object with the lowest priority will thus became invisible for the solver. This process was specifically used for the design and integration of the electrodes within the model (Section 5.2.5)

5.2.2. **Creation of the physical model**

As mentioned previously, one of the main advantages of SEMCAD X is its capability to use Virtual Population models. To model the posterior tibial nerve stimulation a right ankle section was dissected from 'Duke' (Figure 5.2), a 34-year-old male adult from the Virtual Population project (Christ et al., 2010). The ankle section was placed into a grid and oriented such that the posterior section is approximately parallel with the z-coordinate and the sole of foot lies approximately on the x-axis.

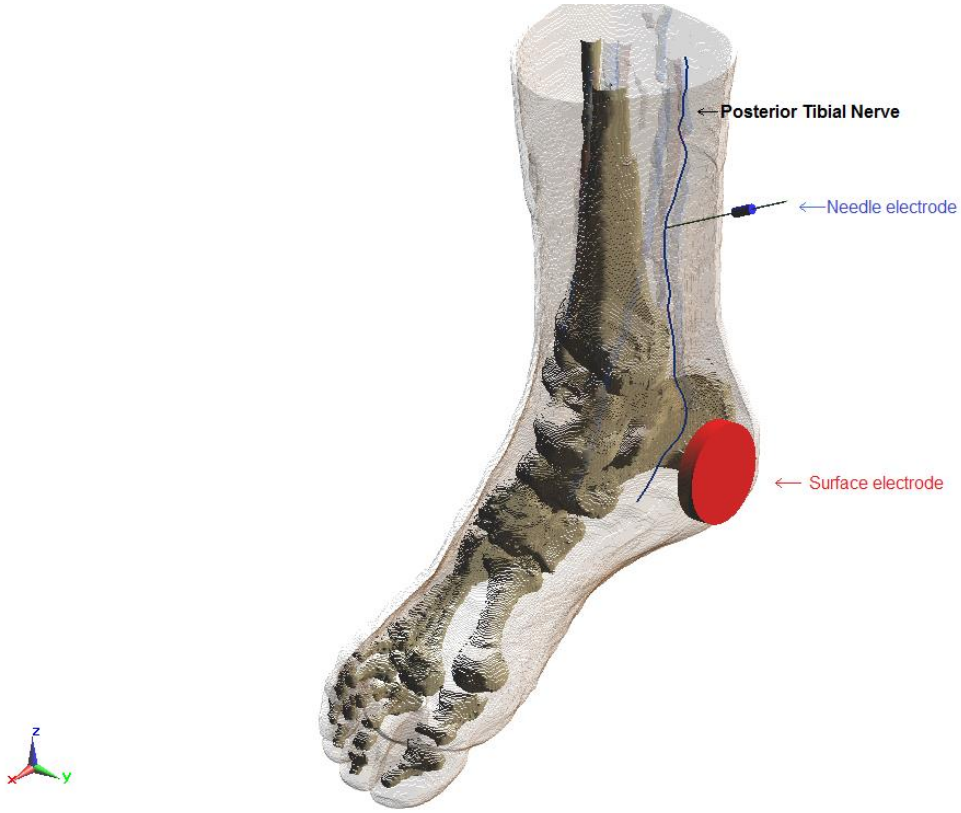


Figure 5.2 The ankle section used, highlighting the bone structures, the approximate position of the posterior tibial nerve, and surface and needle electrodes placed close to the nerve. Other structures are not shown for simplicity.

The resolution of the model enabled construction of all large anatomical structures such as bones, muscle, fat, SAT, tendon ligaments and skin. However, voxels of smaller structures such as veins and arteries are not contiguous in some places or end prematurely due to the resolution of the MRI scan on which the Virtual Family models are based (for peripheries 1.0 x 1.5 x 1.0 mm^{-3}(Christ et al., 2010), Figure 5.3). These discrepancies will cause electrical discontinuities and thus affect the results. Hence a specific design for the nerve to minimise these abnormalities was created, as described below.

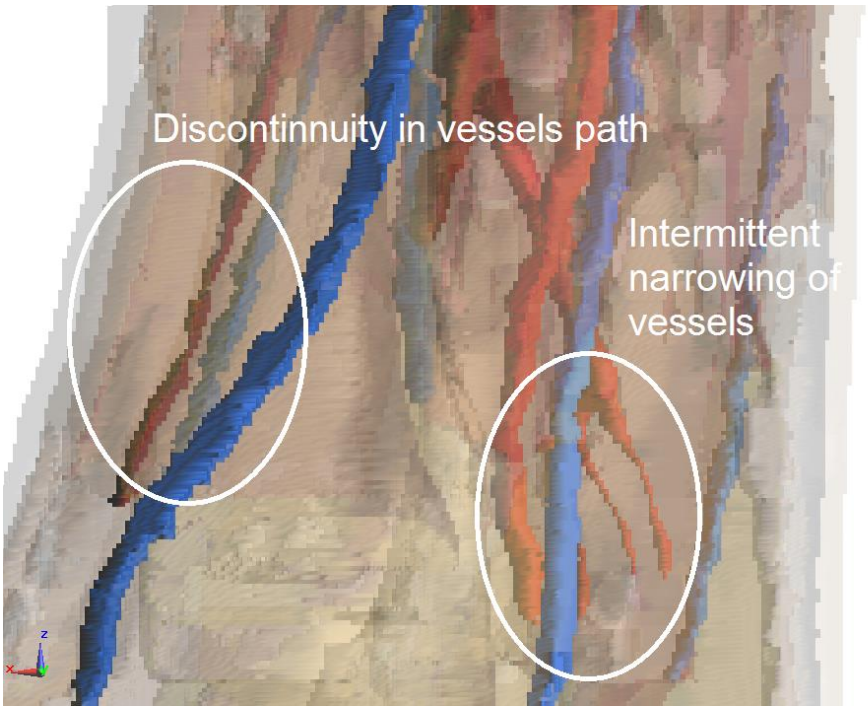


Figure 5.3 Discrepancies of the arteries (red) and veins (blue) in the model

The "Duke" model does not contain the tibial nerve or any other nerve structures except spinal cord and optic nerve (this was a recognised limitation of the model (Christ et al., 2010)) and hence it was necessary to create a nerve according to anatomical knowledge. An alternative would be to use a model of higher resolution which includes smaller structures, which has very recently became available (Gosselin et al., 2014), but was not available during the work described here. However, from initial exploration it was noted even this more detailed model only shows peripheral nerves with limited accuracy.

5.2.3. **Model of the nerve**

This section describes the process by which the tibial nerve was created. A peripheral nerve consists of numerous structures. Nerve fibres (also called axons) are collected into

bundles wrapped in connective tissue called perineurium (Figure 5.4). The posterior tibial nerve at the site of the stimulation is relatively large (approximately 4 mm in diameter) and contains several of these bundles which are surrounded in turn by a connective tissue sheath called the epineurium (Figure 729. (Davies and Coupland, 1967)). The majority of the nerve fibres are myelinated. In addition, a nerve contains fat cells and blood vessels.

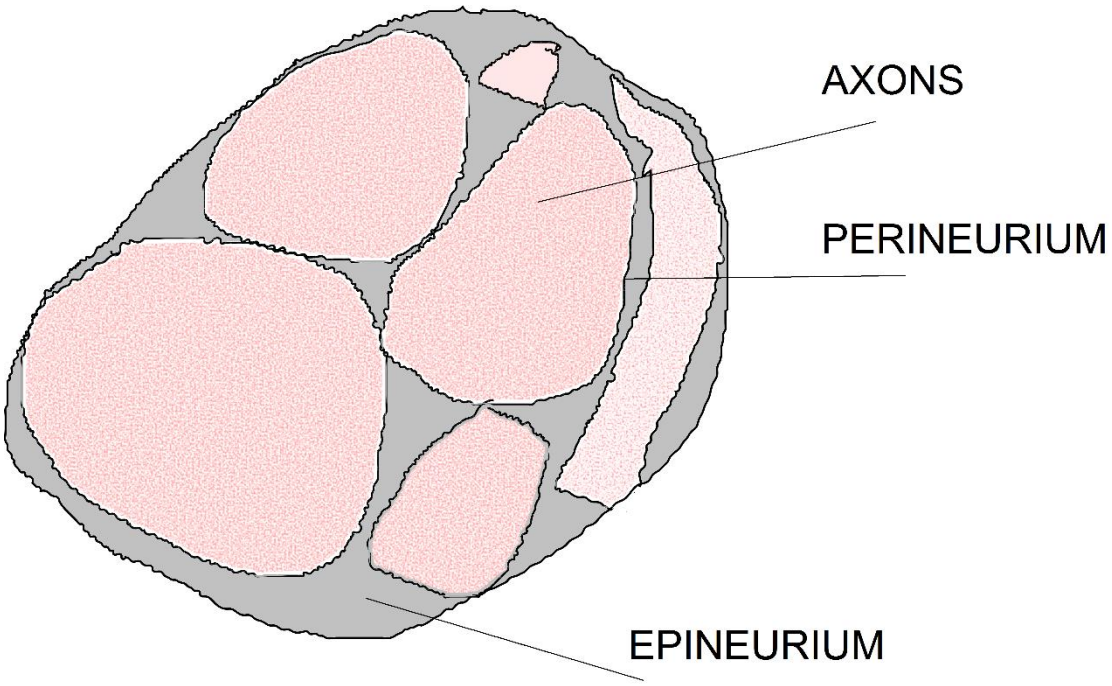


Figure 5.4 A transverse cross section of a peripheral nerve, redrawn from Gray's Anatomy (Davies and Coupland, 1967) p. 1133

It is assumed that PTNS targets the myelinated fibres rather than the unmyelinated and small diameter c-fibres, which have a much higher stimulation threshold. A myelinated fibre is covered with a layer of insulation called myelin sheath with regular exposed sections known as nodes of Ranvier.

The modelled nerve has to include a description of its electrical and geometric characteristics as well as its geometry. It would be intrinsically difficult to define the voxels to model a nerve as shown in the Figure 5.4 because of its small diameter and convoluted path. Such detailed resolution also would not be consistent with the dissected section of the "Duke" model, where only larger structures can be seen.

Instead, the modelled nerve in this work has been defined as a generalised bundle of axons and epineurium. This is based on previous mathematical analysis (Altman and Plonsey,

1988) who described the anisotropic resistivity of the whole nerve in both the radial (transverse) and longitudinal (axial) direction for axons and epineurium. Axons are relatively conductive along their length and hence have relatively low resistance to current flow in the longitudinal direction. The epineurium conductivity is assumed to be similar to that of myelin and therefore is less conductive.

Further simplification of the modelled nerve and its electrical characteristics need to be made and, along with the geometrical characteristic of the nerve, are described in the following two sections.

5.2.3.1. **Geometrical characteristic**

The diameter of the nerve model has been based on a diagram of the transverse section through the right leg 6 cm above the tip of the medial malleolus in Grey's Anatomy Figure 725. (Davies and Coupland, 1967). The posterior tibial nerve descends alongside the posterior tibial artery to a position between the heel and medial malleolus, where it divides into the medial and plantar nerves. The model described here did not consider these two branches because their bifurcation occurs below the stimulating electrodes and the model did not extend into this region. The nerve diameter was chosen as 4 mm.

The exact XYZ coordinates of the nerve were chosen to maintain its appropriate position relative to the artery and veins visible in the model. Altogether, 13 points spaced 10-20 mm apart along the z-coordinate were taken to create two solid spline tubes using the SolidWorks 3D CAD package. The nerve was then exported into the SEMCAD ankle section and placed at the correct anatomical position. The nerve structure is shown on Figure 5.5 (green structure) alongside the arteries (red) and veins (blue).

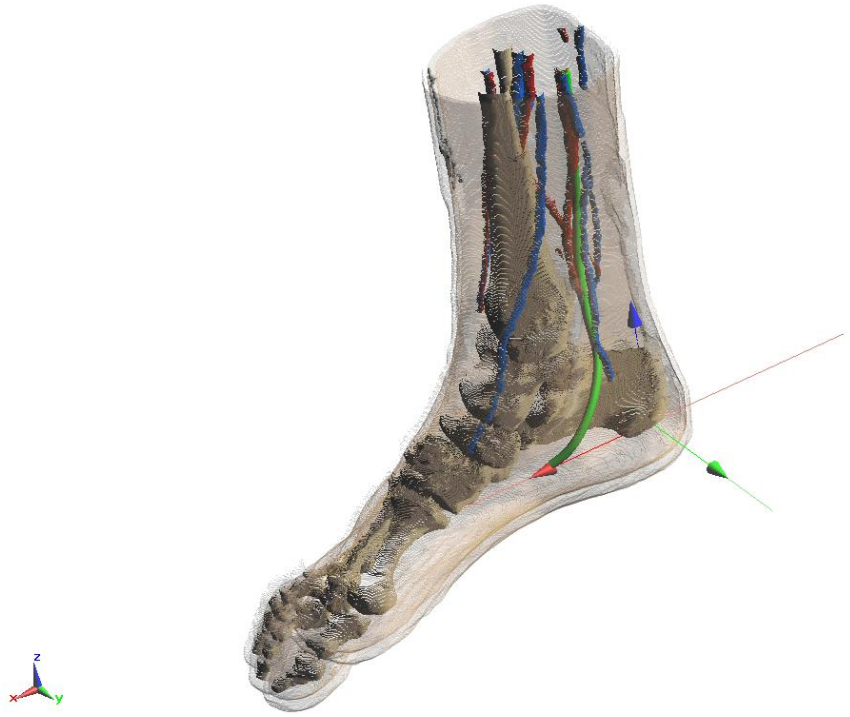


Figure 5.5 The phantom of the ankle used and the modelled posterior tibial nerve

5.2.3.2. **Electrical characteristic**

The electrical characteristics of the generalised nerve bundle of axons and epineurium were calculated as follows. The values for longitudinal and transverse resistivity below were taken from a mathematical model (Altman and Plonsey, 1988). The transverse resistivity was ρ = 110.5 Ωm, (equivalent conductivity σ_T = 0.00904 S/m). The longitudinal resistivity was derived from resistance per unit length as ρ = 1014.8 Ω*cm, (equivalent conductivity σ_L = 0.0985 S/m – ten times higher than the transverse conductivity.

According to the mathematical model by (Altman and Plonsey, 1988) the cross-section of a typical peripheral nerve (Figure 5.6 A) can be generalised into two concentric bundles (Figure 5.6 B), called, in this work, inner and outer nerve tubes. In the model the inner nerve tube contains all the nerve fibres and the outside nerve tube represents epineurium as 30% of the total bundle cross-section area. The value of 30% is based on an experimental work by (Tasaki, 1964). As the overall nerve is being modelled with a diameter of 4 mm the inner tube diameter is thus 3.35 mm with the remainder of this diameter (0.65 mm) forming the outer tube.

However these figures result in a small annular diameter (~0.325 mm) for the epineurium (Figure 5.6 B). This is challenging to model as the size of voxels is limited by the computational capacity (smaller voxel = more voxels in the model = more computational capacity required) of the modelling computer. Additionally a low number of voxels representing structures of different conductivities are likely to cause discrepancies (the voxel size and gridding setup is further discussed in section 5.2.3).

Hence an approach has been taken to change the ratio of the outer and inner diameters such that the cross sections will be of the same size whilst maintaining the overall diameter of the nerve at 4 mm. The inner tube diameter used was thus 2 mm and outer tube was 4 mm in outer diameter (Figure 5.6 C). This will allow more voxels to be placed in the outer tube without changing its size and thus total number of voxels.

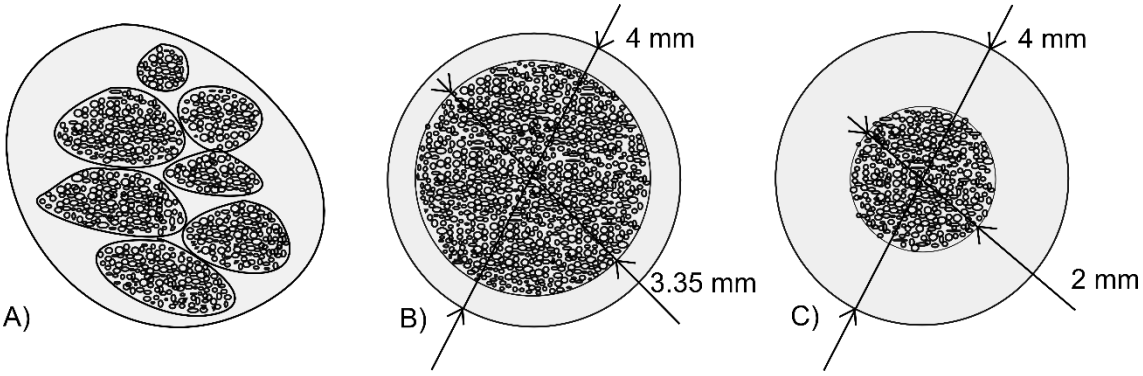


Figure 5.6 Cross section of the nerve – A) typical cross section of a nerve, B) simplified section of a nerve, C) resized sections of the nerve

To derive electrical conductivity values of the inner and outer nerve section based on longitudinal conductivity σ_L and transverse conductivity σ_T (Altman and Plonsey, 1988) would be challenging to solve mathematically. Whilst longitudinal conductivity for the inner and outer nerve tube can be easily derived from the equation 5.2, the transverse conductivity cannot readily be represented easily by a mathematical formula because of the cylindrical shape of the nerve. Thus a SEMCAD X modelling approach was used to determine the values of the inner and outer nerve tubes.

$$R_{LONG} = \frac{R_{IN} * R_{OUT}}{R_{IN} + R_{OUT}} = \frac{\rho_{IN} * \rho_{OUT} * l}{\rho_{IN} * A_{OUT} + \rho_{OUT} * A_{IN}} \qquad (5.2)$$

This approach was based on the assumption that the transverse magnitude of the current vector in the vicinity of the nerve would not be affected if the transverse conductivity of

the external medium is the same as the conductivity of the nerve. In another words the nerve will be electrically invisible to the current flow.

A nerve section consisting of the inner and outer nerve tubes were placed into the middle of a brick shaped volume conductor, with a positive electrode and a negative electrode on each side (Figure 5.7). The conductivity of the brick was set as that of transverse conductivity (σ_{brick} = 0.00904 S/m) required for the nerve. The inner tube conductivity was set as the longitudinal σ_{IN} (0.0985 S/m), as this inner tube should represent conductive axons. The outer tube conductivity, representing epineurium was set initially to an arbitrary value, but such that it would be much lower than that of the inner tube (σ_{OUT} = 0.006 S/m).

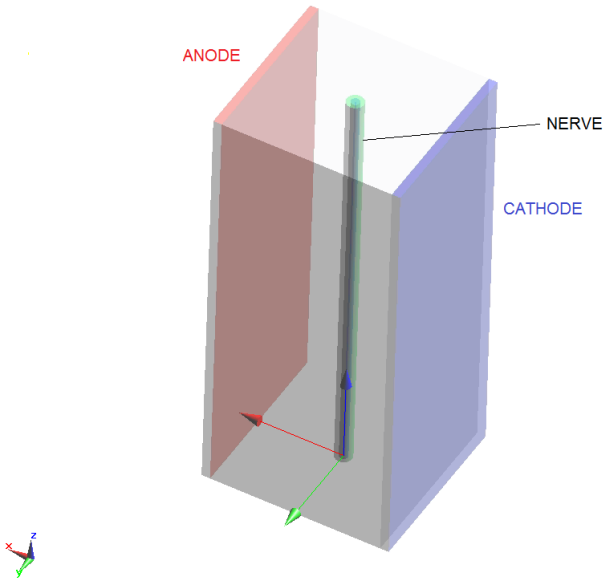


Figure 5.7 Model of a nerve between an anode and cathode

The graph in Figure 5.8 shows a cross-sectional current density through the nerve along the x-axis. This represents the current flow in the x-direction, and to satisfy the transverse conductivity the value of the current density should not change when it enters the nerve (the nerve will be electrically invisible). The blue line shows that the current density increases (i.e. the nerve is too conductive) and at 0.005 S/m this changed to the opposite direction. Using an iterative process an optimal value was determined to satisfy the transverse conductivity of 0.00542 S/m. To satisfy the required longitudinal conductivity value of 0.0985 S/m, the inner conductivity was derived from the formula 5.1 as 0.378 S/m. This characterised the modelled nerve as shown on Figure 5.9.

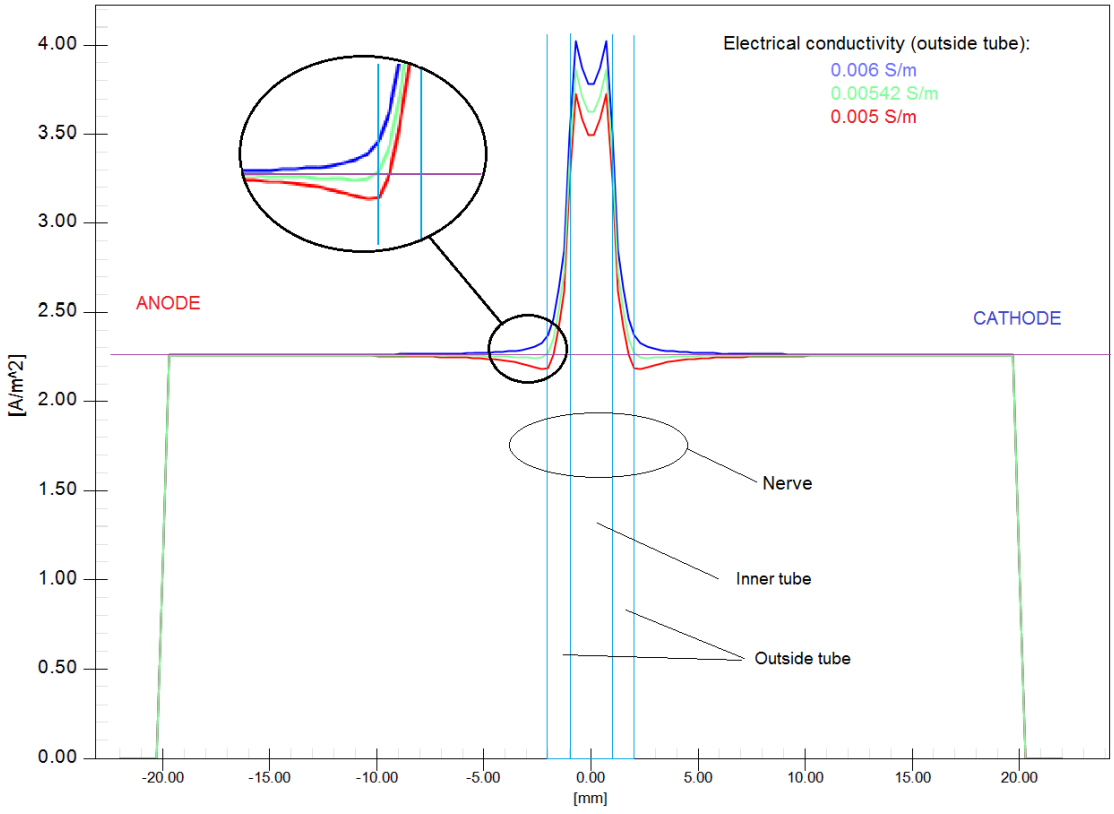


Figure 5.8 Distribution of the current density in the model along a x-axis in the middle section of the nerve

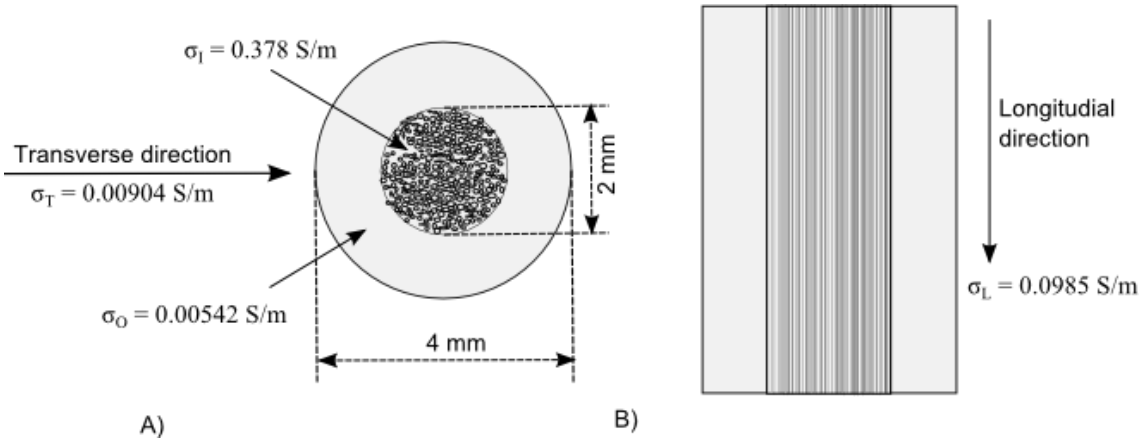


Figure 5.9 Scheme of the modelled nerve with the calculated conductivities A) a cross section of the nerve in transverse direction B) a cross section in longitudinal direction (lines representing the axons). The axons drawings are only for a diagrammatic purposes, individual axons are not included in the model.

In the middle of the inner nerve tube (representing the axons) is placed a field extraction line which represents a single axon and allows to produce the distribution of electrical field along this axon using a Line Extractor Tool in SEMCAD X. Further post processing in Matlab as described in Section 5.2.4 produced the activating function of this axon.

5.2.4. **Electrical conductivities of tissue types**

The anatomical structures in the model need to have their electrical conductivities specified. These values have been sourced from a database of dielectric properties (Gabriel et al., 1996).

Table 5.1 Material properties

Structure	Type	Conductivity [S/m]
Artery	Dielectric	0.307087
Blood vessel	Dielectric	0.307087
Bone	Dielectric	0.020157
Connective Tissue	Dielectric	0.382706
Fat	Dielectric	0.041671
Marrow Red	Dielectric	0.118807
Muscle	Dielectric	0.321157
SAT*	Dielectric	0.041671
Skin	Dielectric	0.000200
Tendon ligament	Dielectric	0.382706
Vein	Dielectric	0.307087
Nerve inner	Dielectric	0.378000
Nerve outer	Dielectric	0.005420

*SAT – Subcutaneous Adipose Tissue

The anatomy of the virtual leg is voxeled such that each voxel belongs to one type of structure, however any other structure (such as the externally generated and inserted nerve) placed into the model will overlap these voxels. To ensure SEMCAD voxelates these structures correctly the inner and outer nerve tubes were set to higher priorities within the SEMCAD gridding options such that they over-ride the underlying tissue.

5.2.5. **Modelling of electrodes**

A typical surface stimulation electrode consists of a conducting, flexible, self-adhesive hydrogel layer laid on the skin with a metallic connection to the external surface. This creates a contact which conforms to the uneven surface of the body.

To create such an electrode in the model, an object that conformed to this surface would need to be created. As this surface geometry varies with anatomic site such an approach would require a different electrode surface for each anatomical position of the electrode. An alternative approach to overcome this was adopted. The electrode was created as a hydrogel cylinder (σ = 2 S/m) which overlapped the body structures (light blue, Figure 5.10) over its entire cross-section. The model electrical conductivity priority was set to a lower level than that of the surrounding structure thus making the hydrogel layer electrically invisible where overlapped with the body structures. On the top of the hydrogel cylinder a Perfect Electrical Conductor (PEC) layer (equivalent to a metal sheet) was placed to provide a uniform distribution of the current from the source (dark blue, Figure 5.10)

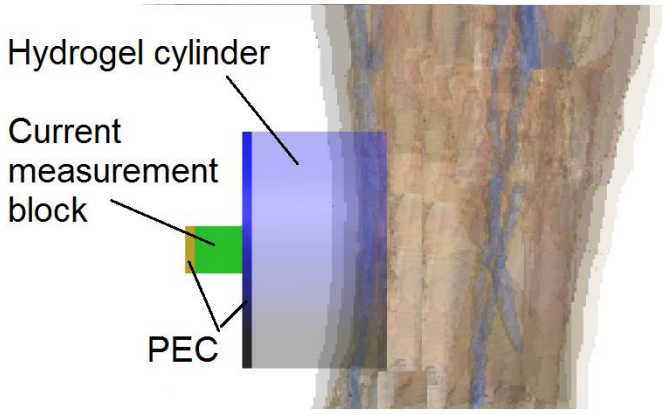


Figure 5.10 Electrode montage

Additionally the electrode in the model must provide the source of the stimulation and to allow the measurement of the voltage/current applied. SEMCAD cannot deliver a constant current, which is the normal output of an electrical stimulator, as it solves the relevant equations in terms of potential. Hence it is necessary to measure the current in the electrode for an applied potential. To determine the electrode current a block of conductive material (arbitrarily chosen with σ = 1 S/m and 1 cm^2 cross section is placed between two layers of PEC (hydrogel cylinder plate and source rectangular plate) as shown in green on Figure 5.10. The source rectangular layer (PEC, brown) is pre-set to

an arbitrary potential amplitude (cathode electrode 0 V, anode electrode +10 V). This montage allows a uniform distribution of the current in the measurement block as well as on the external surface of the hydrogel layer in contact with the tissue. The current is measured using the SEMCAD X line extractor tool of current density J in a random place of a known size of 1 cm^2 cross-section of the measurement block. The current I is thus calculated from

$$I = J * A \tag{5.2}$$

In the percutanous model of PTNS a combination of a 34 gauge needle electrode (0.19 mm diameter) is used as the cathode and a surface electrode (35 mm diameter) for the anode. The needle electrode was modelled as a cylinder and a cone to form a bevelled tip using a PEC (metal) material.

5.2.6. **Gridding**

The modelling requires the modelled object to be gridded. The grid needs to be sufficiently fine to resolve the smallest geometrical structures in the model. In this model the smallest structure is the nerve and, in the percutaneous model, the needle. Therefore the grid of these structures requires the finest gridding. The resolution of the grid and thus the total number of voxels is limited by the computational capacities available, thus there needs to be a balance between finer resolution and computational capacity. The gridding method used for the modelling consisted of a specific non-uniformed mesh, with the finest gridding around the nerve and the electrodes.

The capacity of the PC used (Intel Xeon CPU E5420 @ 2.5GHz, 20GB RAM) enabled grid sizes up to 145 MCells to be solved within RAM. A typical solve time for the full anatomical model described in section 5.3.5 is 10-12 hours.

The boundary conditions specify the values that a solution needs to take along the boundary and could be set either to Dirichlet or Neumann. Dirichlet conditions specify the value of the solution and Neumann conditions specify the value of the derivative. Dirichlet conditions were used for the modelling in this chapter. This incorporates continuity at a tissue/tissue boundary of the domain and infinite impedance in the volume external of the anatomy to accommodate the tissue/air interface.

5.2.7. **Processing of the data**

Once the grid is generated, the SEMCAD Low Frequency Solver is used to solve the defined model until the residual convergence tolerance is reached, at which point the solution is regarded as changing negligibly with successive iterations. After the simulation is complete, the calculated results are available for extraction. The tools used further in this chapter are the slice view of the electrical field E or current density J and extrapolation of the electrical field tangential to the field extraction line (axon/nerve). This field extrapolation is performed every 0.01 mm and produce a distribution of electrical field along this line. Once the electrical field tangential to the nerve is extrapolated, the data are processed in Matlab 7.10 (R2011a) in order to obtain derivatives of the electrical field along the nerve and thus the activating function. The Matlab processes involved extrapolation of the data to equally spaced coordinates of 0.01 mm. This is because SEMCAD X did extrapolate this data equally in one of the XYZ coordinate system but the field extraction line is variable in all XYZ coordinates. The noise generated by the differentiation process was minimised numerically (Chartrand, 2011).

The results section includes the activating functions defined as a spatial derivative of electrical field E along the nerve l, therefore the symbol for activating function used throughout is dE/dl.

5.3. **Results**

The presented results begin with a simplified version of the transcutaneous electrical stimulation model. Subsequently, the model gradually adds more features towards the full PTNS model for both the transcutaneous and percutaneous form. In addition, a variety of montages for the transcutaneous form of PTNS are presented later in this chapter.

5.3.1. **A simple block of conductive material**

The simplest model to help understand the current and voltage distributions in electrical stimulation is in a homogeneous volume conductor. Thus a brick model was created in order to understand the distribution of the electrical field versus depth. Two round surface electrodes (5 cm in diameter) as described in Section 5.2.5 were placed on the top of a

brick formed of a conductive material (σ = 0.5 S/m) and dimensions of 7.5x7.5x30 cm. The anode voltage source was set to +10 V and the cathode to 0 V.

A cross-sectional view of the modulus of the electrical field through the centre of the electrodes is shown in Figure 5.11. Because the volume conductor is uniform, J is proportional to E and hence the current density distribution would have the same shape. As the contours of the electrical field are the modulus of the electrical field, only absolute values can be seen. The outside edges of the electrodes represent a negative electrical field (with respect to the horizontal axis) and on the inside edges of the electrodes there is a positive electrical field. Deeper into the brick model in the vertical direction the electrical field gradually declines.

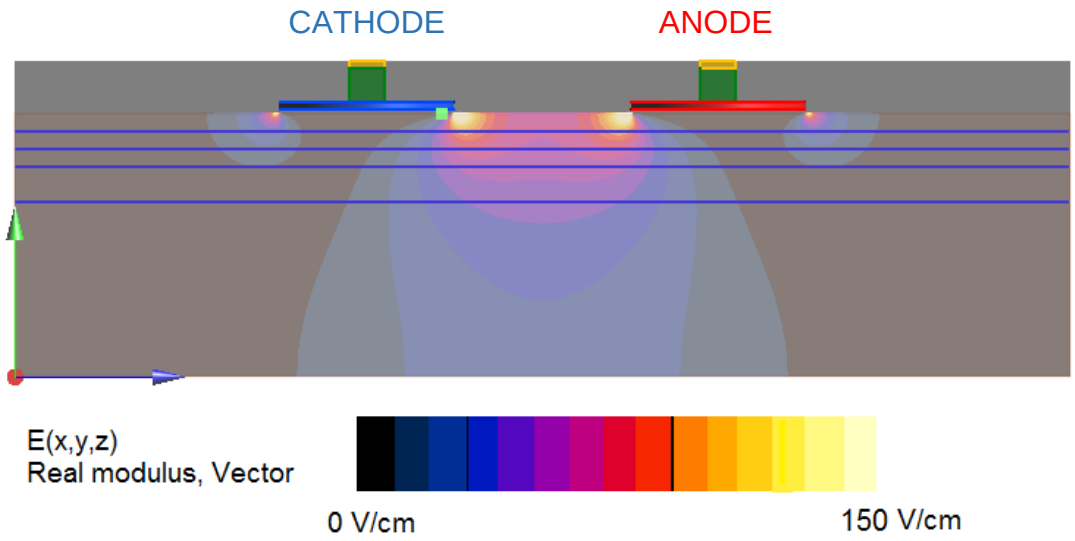


Figure 5.11 A cross-sectional distribution of the electrical field in the horizontal direction

Thus the electrical field can be seen to decline with depth below the electrodes and the higher peaks of the electrical field seen close to the electrodes became more diffuse (Figure 5.12).

This simple model corresponds to the analytical solution for a negative (blue) and a positive (red) charge in Figure 5.12. The highest density of the electrical field contours is directly between the two points, similarly to two electrodes in Figure 5.11. Less dense contours and decline of the electrical field could be seen further from the points respective electrodes.

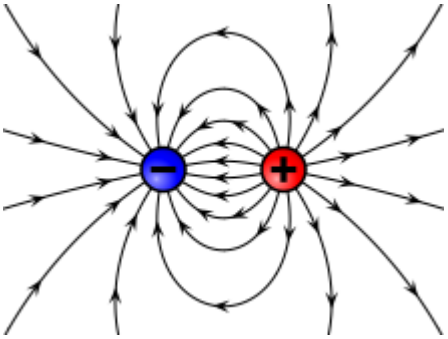


Figure 5.12 Electrical field surrounding two points of opposite charge

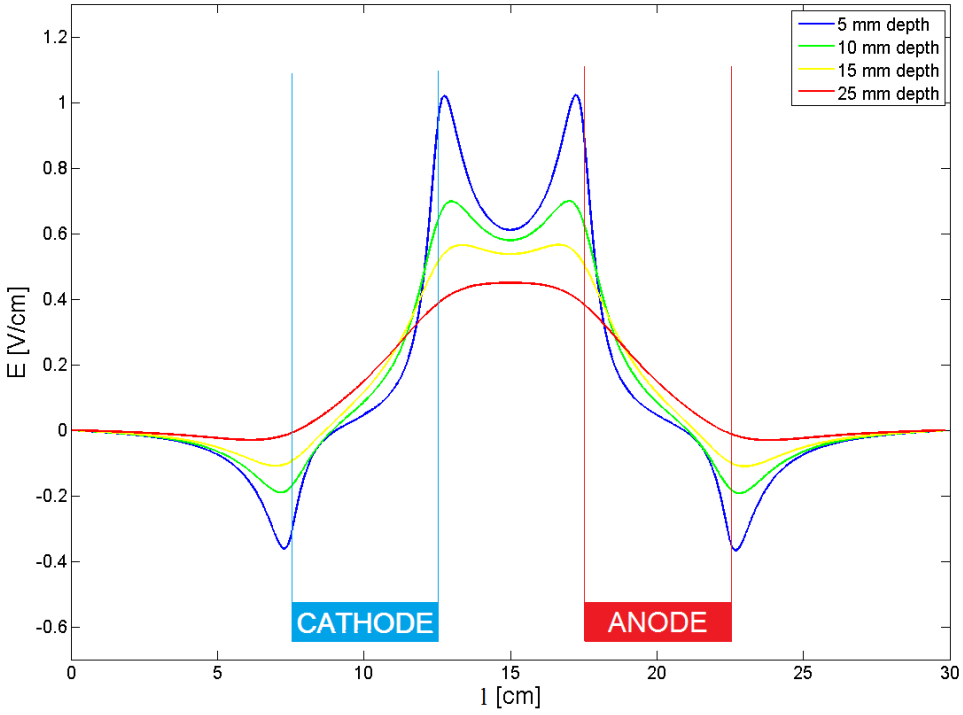


Figure 5.13 Distribution of the electrical field along the lines at different depths

This decrease in amplitude, and flattening of the electrical field profiles, changes the gradients of electrical field and thus the activation function (Figure 5.14) of nerves at different depth because, in this model, the activating functions are represented by derivatives of the electrical field tangential to a line in various depths of the brick model.

To produce the same maximal gradient of an electrical field at a depth of 25 mm as it is produced at a 5 mm depth, the source of the stimulation (i.e. stimulus current or voltage) would need to be at least 10 times bigger (Table 5.2) in this uniform model. The approximate site of the stimulation also changes with depth from the edges of the electrodes towards the centre of the individual electrodes (Table 5.2).

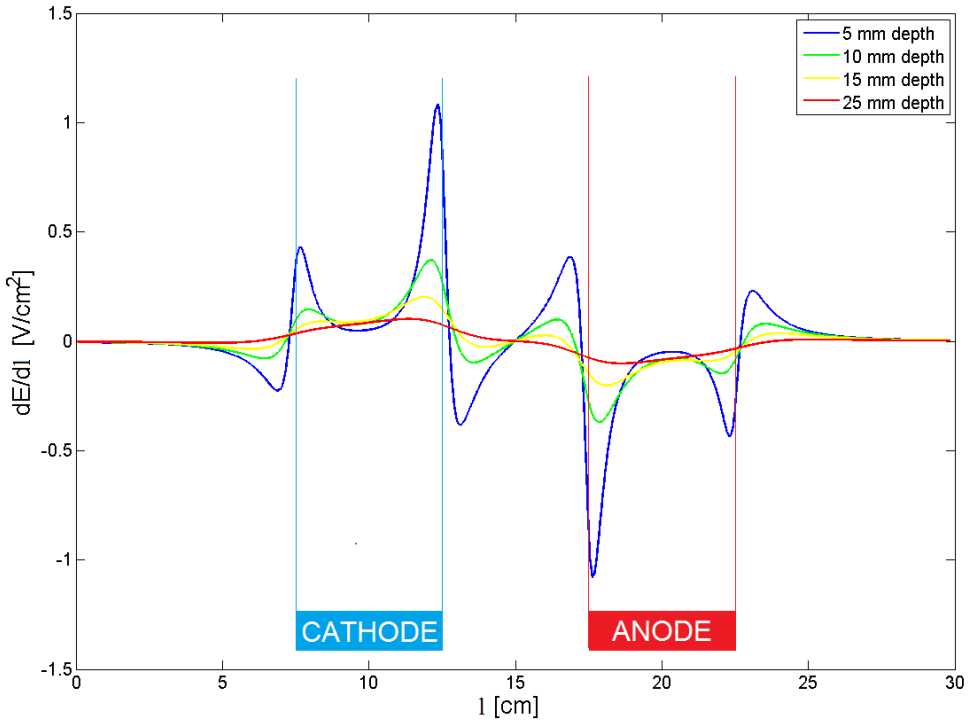


Figure 5.14 Activating functions of simplified nerve fibres in different depths

Table 5.2 Relationship of the gradient produced in different depths of penetration

Depth of penetration	dE/dl [V/m^2]	Position of peak value of dE/dl from the centre of the cathode electrode [cm]
5 mm	1.084	2.35
10 mm	0.370	2.11
15 mm	0.202	1.87
25 mm	0.101	1.41

These findings generate the information needed to understand more complex models. Thus to summarise:

- The electrical field and current density is larger on the edges of the electrodes.
- The activating function of a nerve function is dependent on their depth below the electrodes.
- Although distribution of electrical field in other planes was not shown for brevity, the electrical field would also gradually decline if the electrodes are positioned distally from the axon in other planes.

5.3.2. **Transcutaneous electrodes – cylindrical model – straight nerve**

The model in this section uses the straight nerve equivalents of the posterior tibial nerve as defined in Section 5.2.3. In order to understand effects of nerve geometry in a simple model in this section and next section, the models are solved with uniform conductivity $\sigma = 0.1$ S/m. The shape of the cylinder is similar to the anatomy of the ankle and was defined as 22 cm in height and 15 cm in diameter. The model used the same transcutaneous electrodes as in the previous brick model, placed 10 cm apart (Figure 5.15). Three straight nerves (5 mm depth, 20 mm depth and a sloped nerve) were placed into a cylindrical model of uniform conductivity. However the model was solved three times, for each of the nerves separately, thus have no influence in each of the solution.

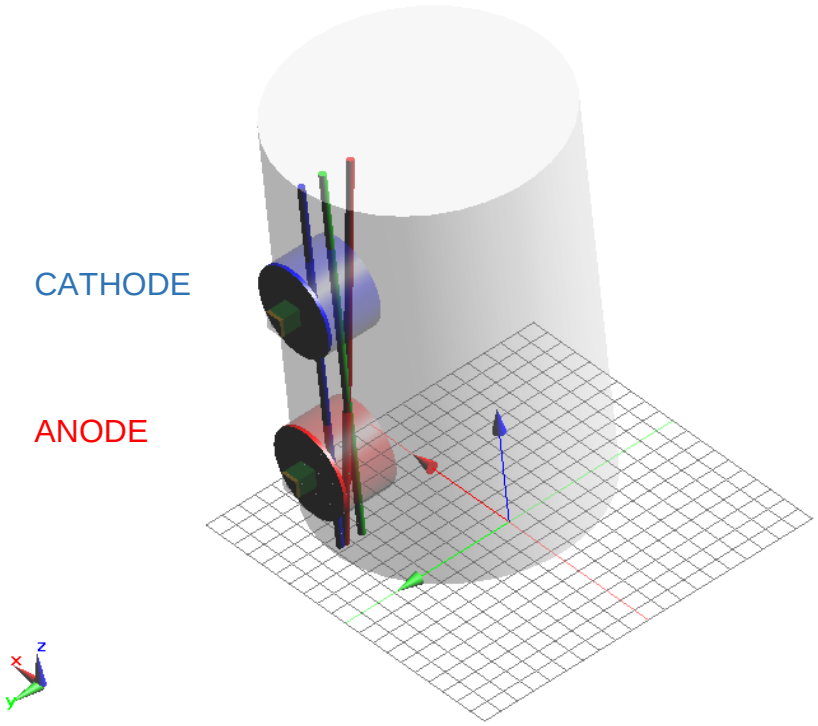


Figure 5.15 Uniform conductivity model with three different nerves

The findings from the previous model showed that the electrical field becomes weaker in depth, thus flattening the activation function (5 mm nerve vs 20 mm nerve depth). This is seen in this cylindrical model as well (blue and green, Figure 5.16, Figure 5.17). The sloped nerve slightly altered the electrical field and thus flattened the activation function (red, Figure 5.18) where the nerve was deeper below the cathode electrode.

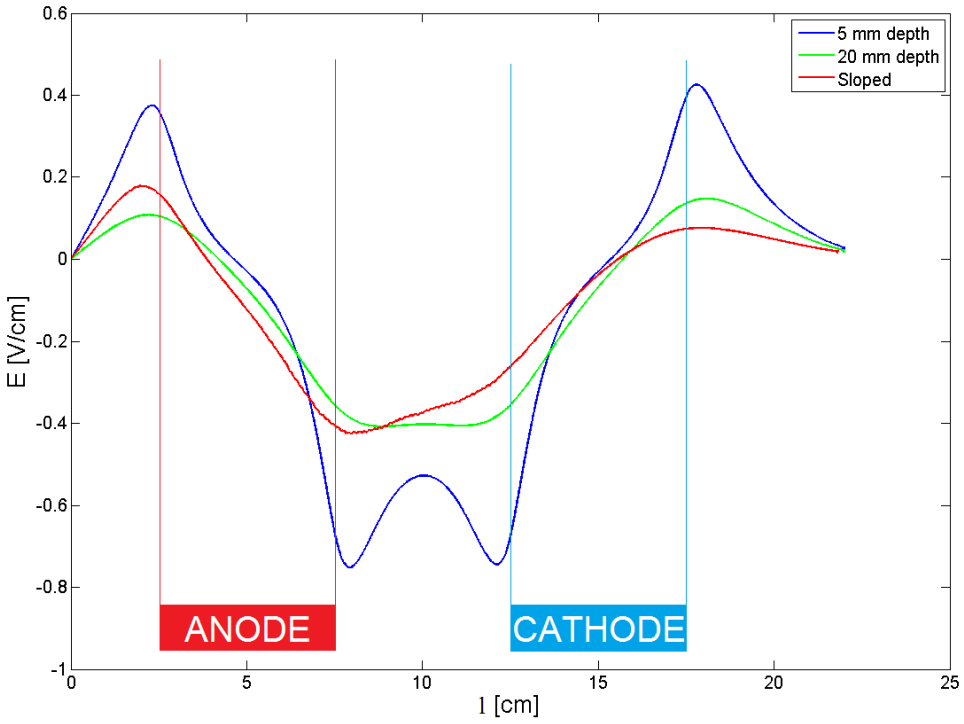


Figure 5.16 Distribution of the electrical field tangential to the nerve

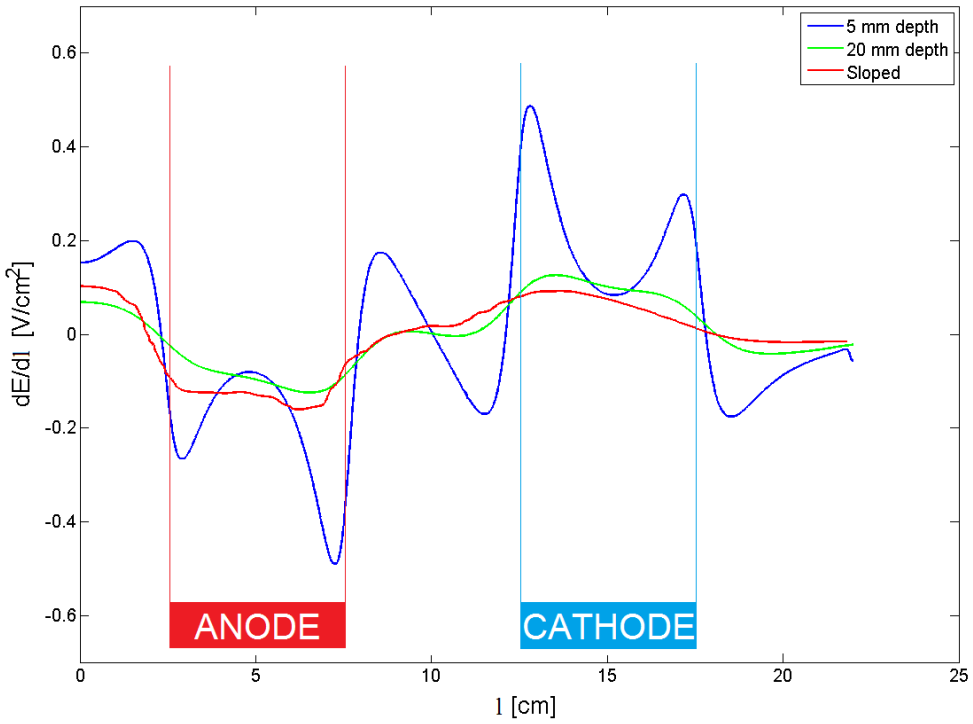


Figure 5.17 Activiating function of three nerves in a cylindrical model

5.3.3. **Transcutaneous electrodes – cylindrical model - posterior tibial nerve**

Human nerve axons are however not straight as shown in the previous section. The peripheral nerves usually follow arteries and veins and thus create curved structures. The next cylindrical model as described previously, contains a section of the posterior tibial nerve (Figure 5.18) as defined in method Section 5.2.3. This enables the methodology of the inserted curved nerve to be tested. The section of the posterior tibial nerve is placed at approximately the same position, relative to the electrodes, as in the further models of this project. This allows to study the changes in electrical field distribution in a uniform conductivity cylinder due to a realistic nerve geometry without other anatomical structures being involved. The choice of anode and cathode position, relative to the nerve, has been determined by that used in the clinical trial of Posterior Tibial Nerve Stimulation as presented in Chapter 6 and on which the subsequent clinical trial in this work has been based.

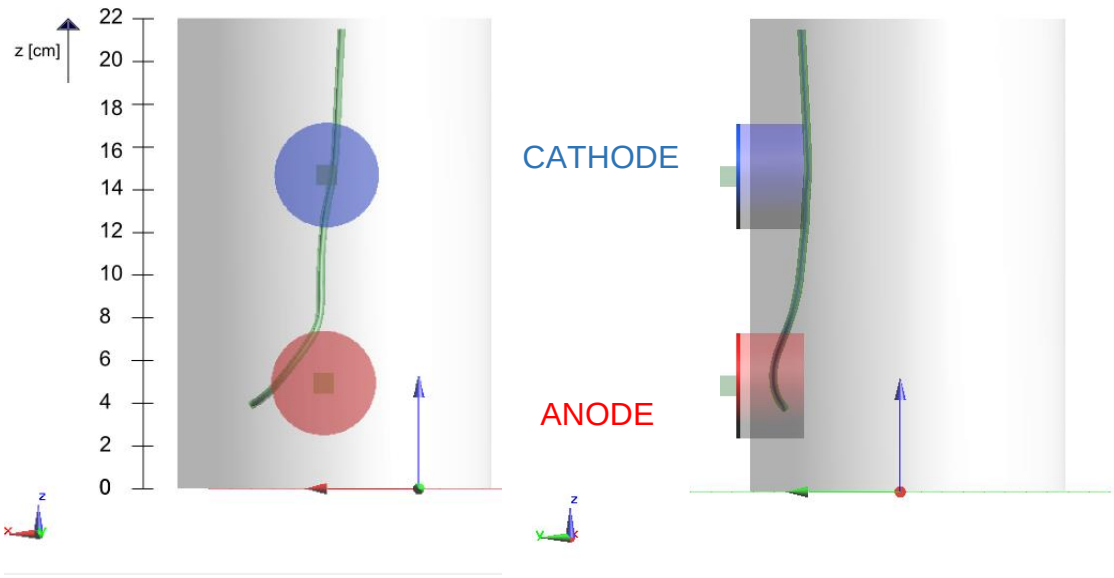


Figure 5.18 A cylinder with a section of the posterior tibial nerve (red electrode – anode, blue electrode – cathode)

It should be noted that the nerve does not run parallel to the cylinder z axis. To aid the reader's understanding of the activating function and electrical field along the nerve at a particular point in the cylinder, the activating function relative to the z-axis [cm] instead of along the direction of the nerve is shown in Figure 5.19. Also as described in the section 5.2.5 priority of the hydrogel layer was set to a lower level than that of the surrounding

structure thus making the hydrogel layer electrically invisible where overlapped with the cylinder.

As defined previously, stimulation is produced when the membrane potential is exceeded; this process is called depolarisation. This happens when a rapid increase from a negative to positive potential is presented. The activating function shows this by a peak as shown in a uniform conductivity model, although there can be several gradients. The maximal peak is considered to be the site of the stimulation. At this point this model does not consider what value of the maximal gradient is needed to exceed the membrane potential and thus cause the stimulation (this is because it would be difficult to define it and it has not yet been relevant). The activating function in Figure 5.19 shows that the site of stimulation would be below the cathode at z = 14 cm. However, it should be noted that there is a significant negative gradient below the anode, which is approximately six times higher than that below the cathode. This is caused by the nerve being closer to the anode than the cathode. Therefore, if the polarity of the electrodes is reversed, then to achieve the same size of gradient the stimulation source needed can be six times lower. The site of stimulation then would be at z = 5 cm. Another observation (which is important to be noted for further models) is that at around z = 8 cm another gradient, which is visible but not dominant can be seen. This is at the position where the nerve bends slightly inside the cylinder in the y plane (Figure 5.18, right) and in combination with the high electric field produce a higher gradient.

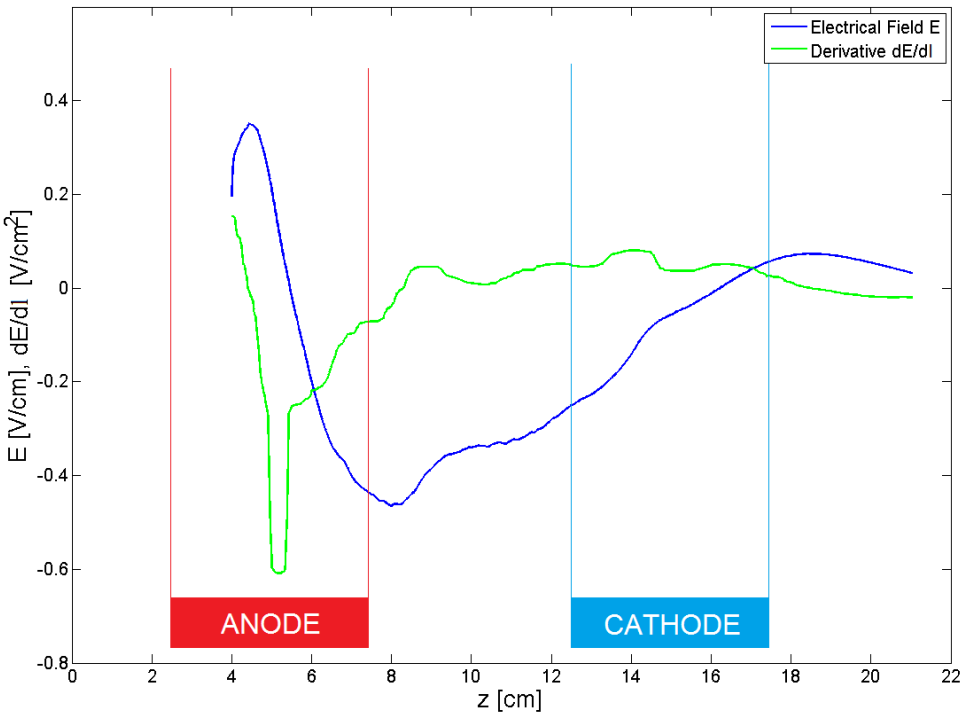


Figure 5.19 Activating function of the posterior tibial nerve in a transcutaneous cylindrical model

5.3.4. Transcutaneous electrode montage – leg model and PTNS uniform conductivity

When the nerve is placed into a phantom of the leg, both the external shape of the leg and anatomical structures within it (e.g. muscle, bones) will affect the distribution of the electrical potentials. This next model uses the same electrical conductivity ($\sigma = 0.1$ S/m) for all the anatomical structures, except the nerve and hence they have no impact on the distribution of electrical potentials. The changes of the electrical potentials as compared to the cylindrical model are therefore only related to the anatomical shape of the leg.

Indeed, the distribution of the electrical field is similar to that in the cylindrical model previously (Figure 5.20, blue). Four notches are highlighted as rapid changes in the electrical field in Figure 5.20 (as #1-4) and these are discussed further in order to understand their origins where position of z coordinates is found in Figure 5.21. Notch #1 (Figure 5.20) shows a maximum negative electrical field as the nerve passing through the high electrical field region at the edge of the anode. Notch 2# shows a decrease on electrical field because the nerve section is between the edges of the electrodes and the electrical field is thus disperse into the tissue. The similar effect was previously observed in the cylindrical model for the straight nerve close to the surface (5 mm, Figure 5.16).

Notch #3 is again related to the increasing E field near the edge of the electrode and a small notch #4 is caused by the dispersion of the field below the electrode. This dispersion relates to the electrical field vector (electrical field lines), which for the middle of the electrode curves perpendicularly to the surface of the electrode and also perpendicularly to the nerve. Thus the vector of electrical field along the nerve at the centre of the electrode decreases. This notch would be more significant if the nerve will be placed closer to the electrode as observed in the simple block model where the electrical field decreases to 0 V/cm at the centre (5 mm depth, Figure 5.13).

The maximal gradient dE/dl is seen in a similar place to the cylindrical model at z = 13.5 cm. If the polarity of the electrodes was swapped then an approximately three times higher gradient would be obtained at the edge of the electrode (z = 8 cm). There are another two gradients between z = 8.5 and z = 11 cm, which by their magnitudes are lower than the two gradients mentioned, but their position is similar as the gradient in the previous cylindrical model of a uniform conductivity. This gradient relates to the notch #1 and #2 and slight bend in the nerve towards the surface.

The glitch on the cathode electrode edge at ~ z = 12 cm is a model artefact related to a high electrical field on the edge of the electrode. These artefacts are discussed and corrected further in Section 5.3.5.1.

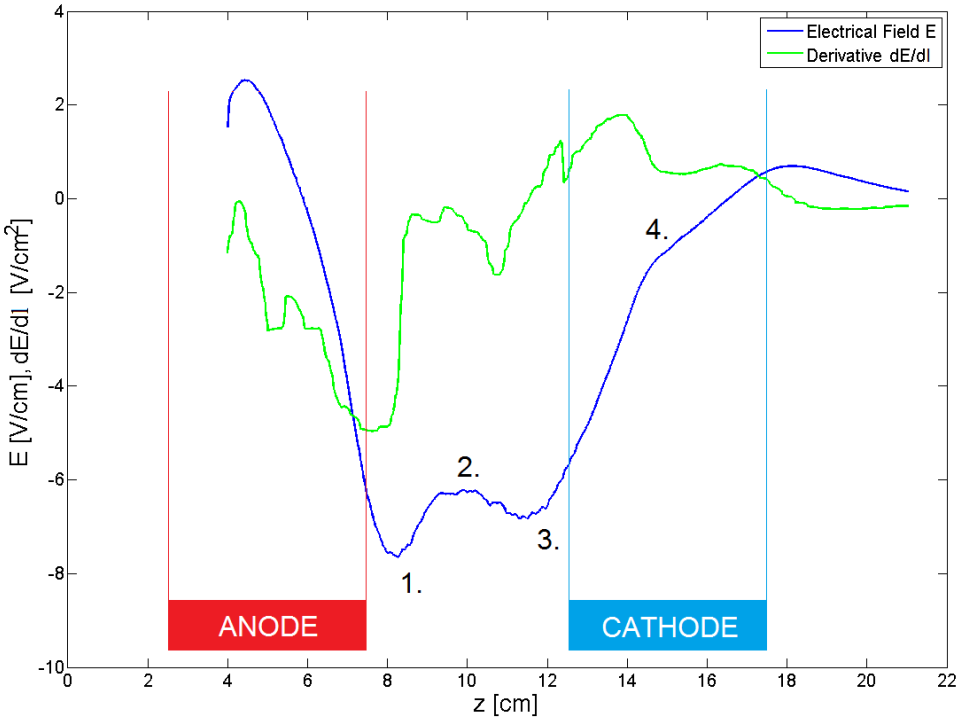


Figure 5.20 Activating function of the posterior tibial nerve in the uniform conductivity leg model

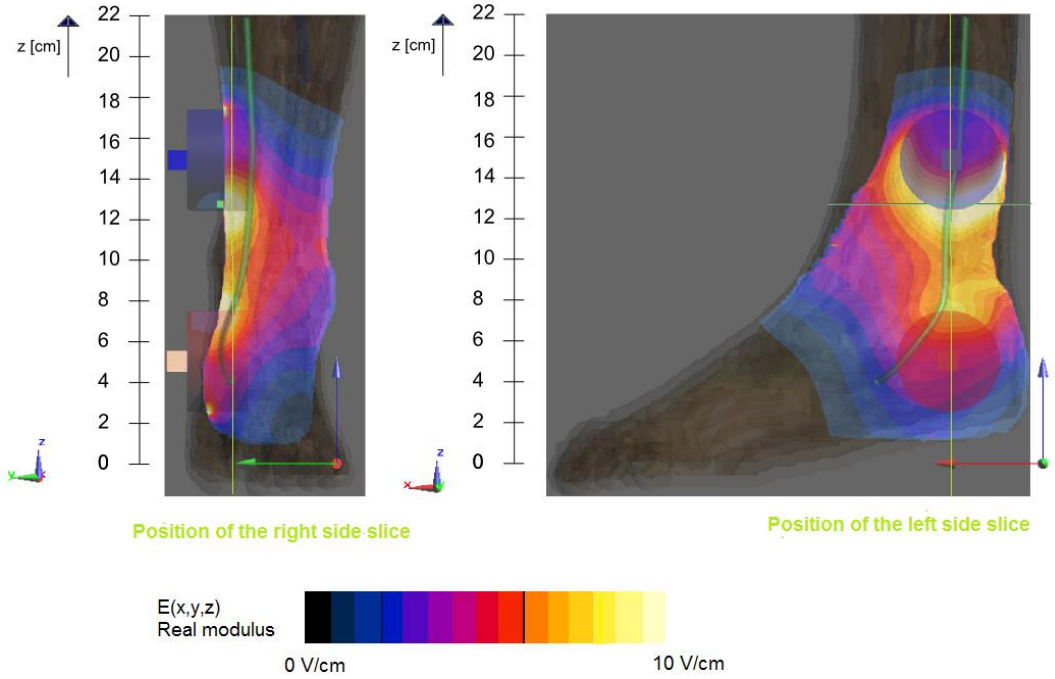


Figure 5.21 Cross-section of the uniform conductivity leg model (red electrode – anode, blue electrode – cathode)

This model indicates that anatomical shape of the leg has only a slight impact on the electrical field distribution when compared to the cylindrical model. The maximal

gradients and thus the site of stimulation would be near the edges of the electrodes. In particular the gradient below the anode is at the edge of the electrode and dominates because the nerve is superficial.

5.3.5. **Transcutaneous PTNS electrode montage – PESTOB**

The model above already contains all the anatomical structures and the electrodes are placed in the same positions that will be used in the clinical trial methodology (Chapter 6). This section thus moves into the full anatomical model of transcutaneous PTNS, which allows exploration of the activating function of the montage used in the trial and comparison of this to the percutaneous model, which then follows.

The solved model shows that the electrical field below the cathode is relatively weak in comparison to the rest of electrical field along the nerve (Figure 5.22, blue line). The highest electrical fields anywhere in the model are seen immediately underneath both electrodes, and penetrating approximately 5 mm into the tissue (shown as the yellow area, Figure 5.23). The activating function is dominated by a positive peak around z = 8.8 cm (Figure 5.22, red line). This gradient peak was previously shown to be presented in both the cylinder and in the uniform conductivity leg but is larger in this full model.

Figure 5.23 and 5.24 shows that there is a high electrical field along the anode electrode. This path of high electrical field corresponds to the layer of SAT and causing the current to flow closer to the surface. This helped to create a significant gradient around z = 9 cm which is the site of the stimulation.

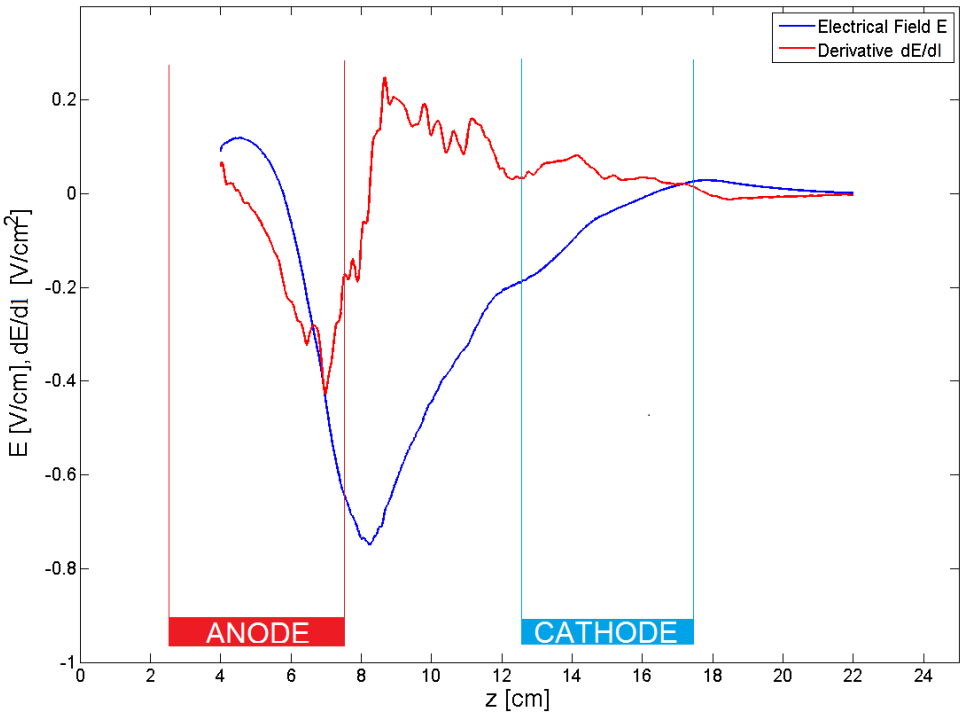


Figure 5.22 Activating function of the transcutaneous PESTOB model

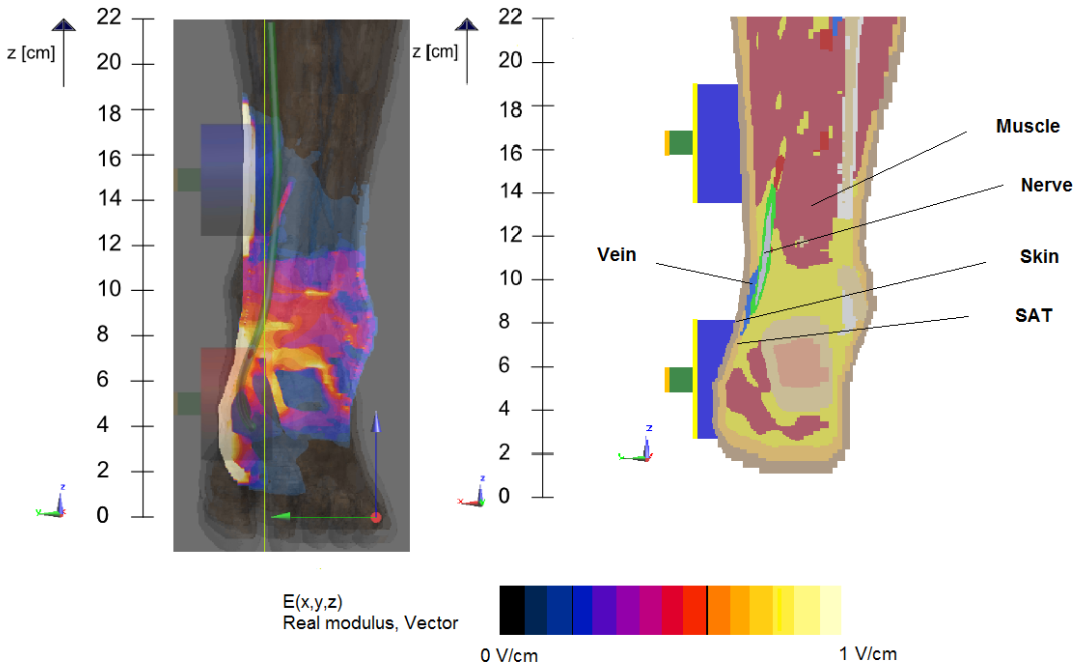


Figure 5.23 Cross-section of the transcutaneous PESTOB model in two planes (red electrode – anode, blue electrode – cathode)

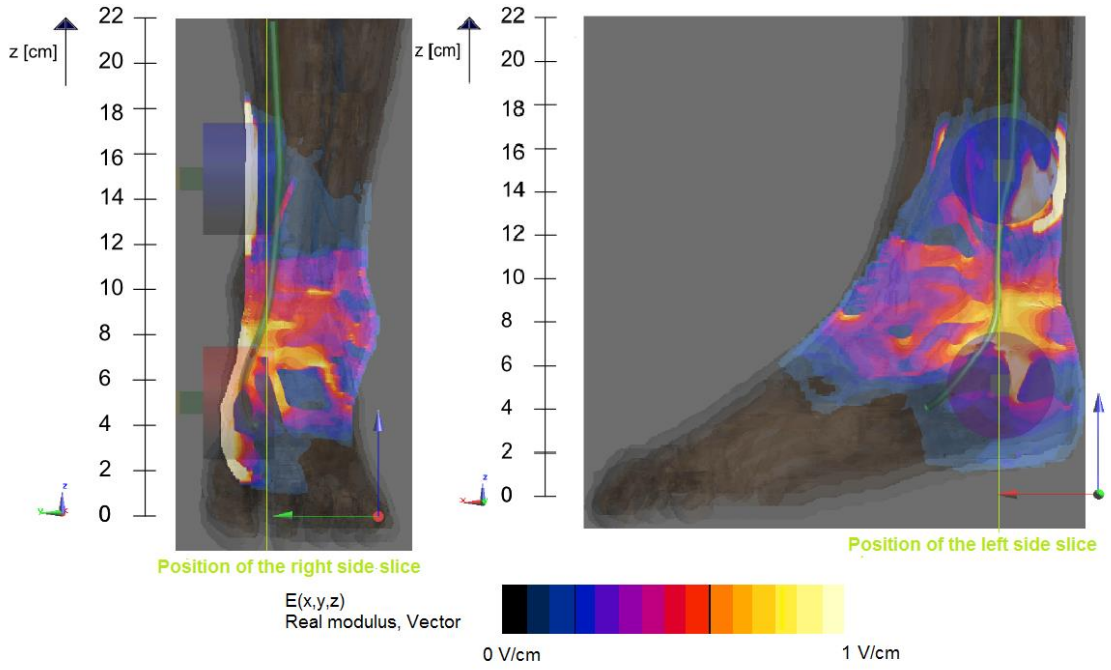


Figure 5.24 Cross-section of the transcutaneous PESTOB model in two planes (red electrode – anode, blue electrode – cathode)

Similarly to the uniform conductivity leg model, the activating function shows the gradient dE/dl below the edge of the anode electrode (approximately twice as large as elsewhere along the nerve) would be expected to cause stimulation if the polarity of the electrodes is exploited.

Although the above findings and more precise measurements will determine the maximum gradient, it was noted that the activation function presents noticeable multiple points of inflexion (particularly between z = 8 cm and z = 11 cm), which may affect the solution of the model. It is assumed that these points of inflexion are caused by a combination of discontinuities of conductivity at tissue boundaries and modelling artefacts. In the former case significant artefacts are presented as hot spots and are dependent on the position of the grid relative to the structures and thus affect the activating function. Furthermore, these were dependent on the exact position of the grid and might affect the results. The model was gridded to the maximum possible scale of 145 million cells determined by the PC computational capacity, therefore a finer grid could not be used, although would help to address these artefacts.

To illustrate this problem in more detail, three activating functions from the same model, but using three different grids are shown in Figure 5.25. Whilst the differences in the

absolute numbers of voxels is relatively small, such changes will alter the position of the grid lines relative to the discontinuities of conductivities at tissue boundaries. The calculated maximum value of dE/dl of these activating functions in the model of 133 MCells, 141 MCells and 146 MCells are 0.248 V/cm^2, 0.222 V/cm^2 and 0.235 V/cm^2 respectively. This indicates that the solution obtained varies by at least 10% as a function of the actual grid position and the grid size along the nerve.

For this reason a method of multiple solutions from a range of spatially displaced grids were combined in order to average these discrepancies in the model and thus provide a unified solution.

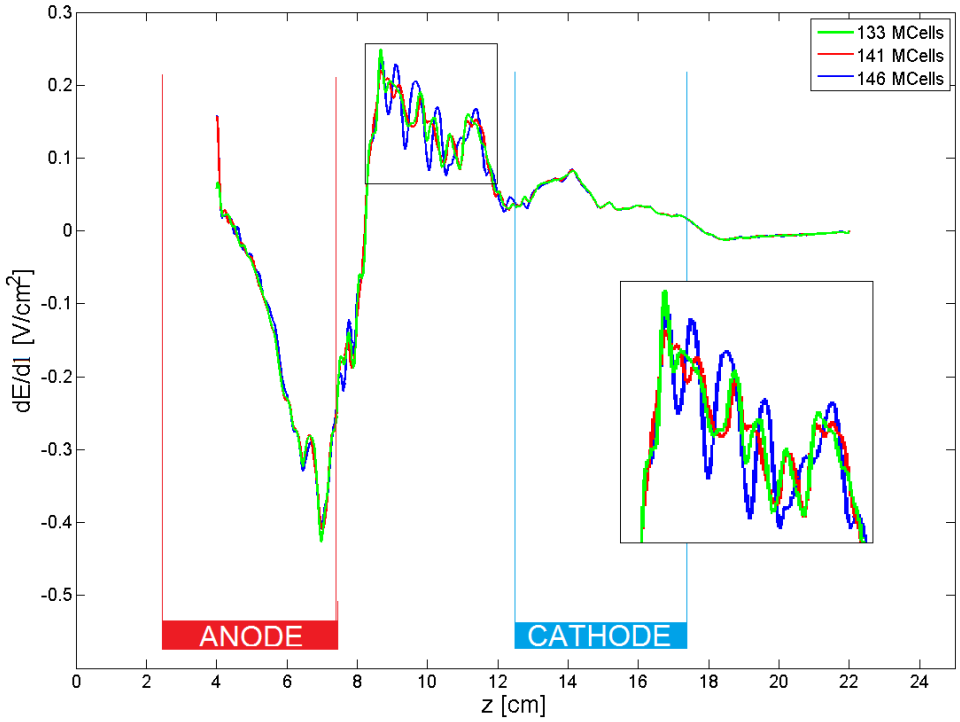


Figure 5.25 Activating functions of three different grid settings

5.3.5.1. **Minimizing discrepancies - grid displacement method**

To minimize the discrepancies as observed in the previous solution N – the number of activating functions from a range of N grids was combined. This allowed shifting of the grid slightly between the structures. Thus several solutions could create a combination of activating functions calculated from grids that intersect slightly differently with the anatomical structures.

The combination process was implemented as an average value at each point for N activating functions. In order to determine the N, the relationship between the number of combined solutions (N activating functions) and the numerical difference between N and N-1 activating functions was obtained (Figure 5.26). This numerical difference between the two nearby combinations was calculated as a mean average of differences between the activation functions at the each point.

Figure 5.26 shows that the mean difference between the activating function of combined solutions decreased with the increase in the number of activation functions (solutions) used. Figure 5.27 shows an effect of increasing the number of combined activation functions on the solution (maximum derivative of the activation function), which does not change significantly for N > 20. Both graphs helped to determined that 20 activating functions for a range of grid between 108-146 MCells is an appropriate compromise between computational time/data processing and effect on results.

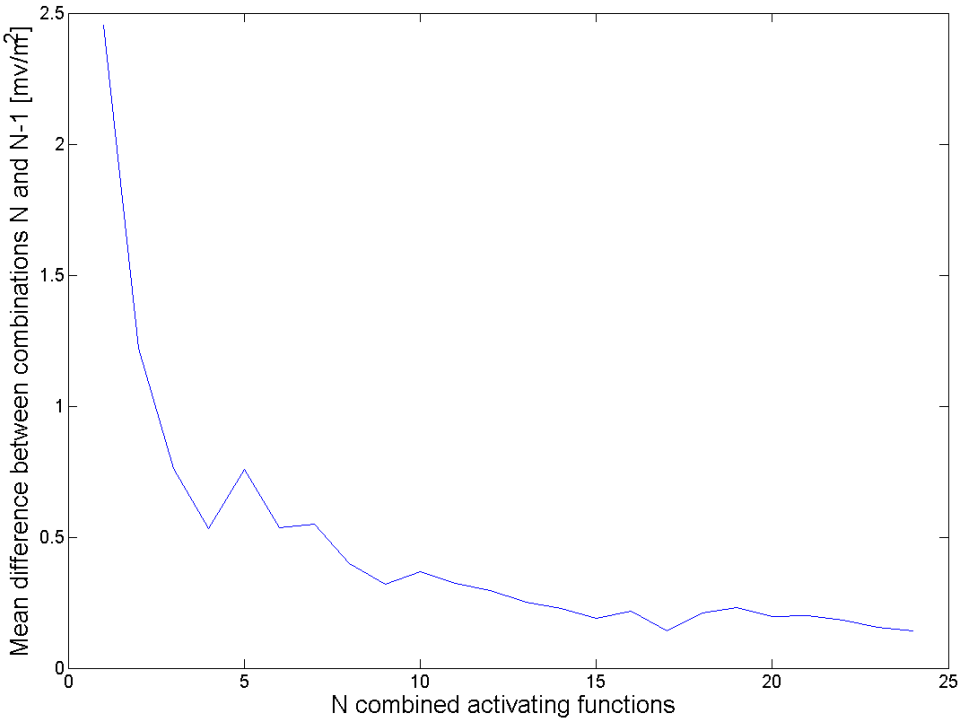


Figure 5.26 Mean difference in activating functions

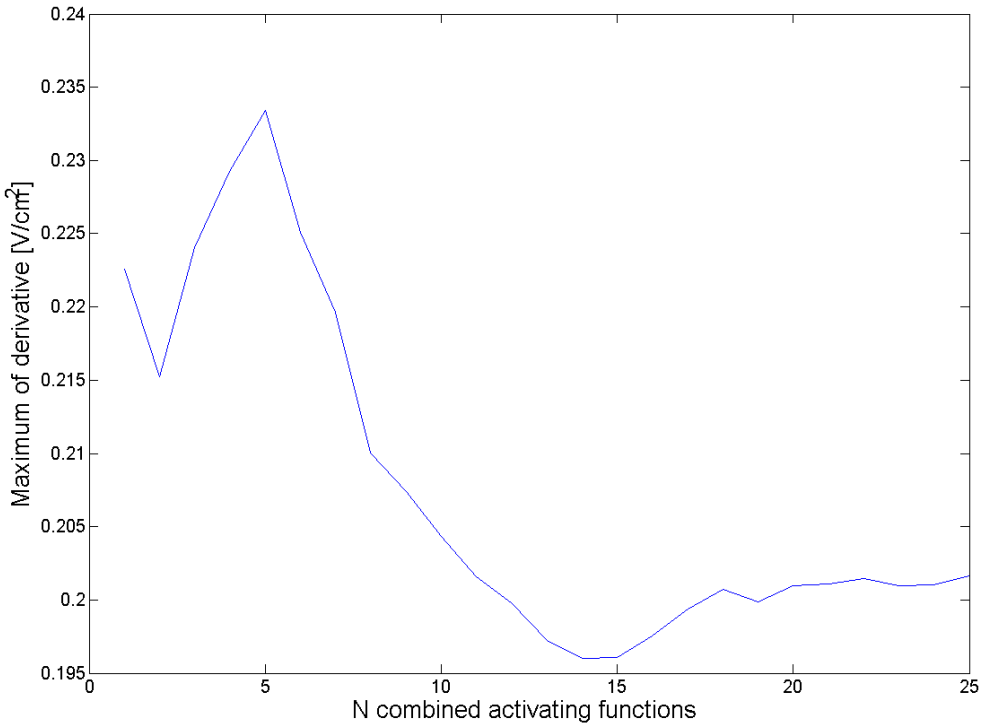


Figure 5.27 Mean difference in solutions

A combination of N=20 activating functions is thus used as a solution for further models.

5.3.6. **Transcutaneous electrodes PTNS montage – grid displacement method results**

The combined activating function is shown in Figure 5.28. The maximum peak of this activating function was presented at z = 8.77 cm and had a value of 0.2011 V/cm^2. The stimulation current in the model which produced this gradient was 8.8 mA. If each of the N = 20 activation functions was taken as a separate solution then the mean peak would be at z = 8.79 ± 0.001 cm (mean ± SD) and had a value of peak 0.231 ± 0.013 V/cm^2. In comparison to the original solution (without combined solutions in Figure 5.22) this gradient became slightly flattened. If the reverse polarity of the electrodes was used then the maximum gradient of 0.409 V/cm^2 would be presented at z = 7 cm.

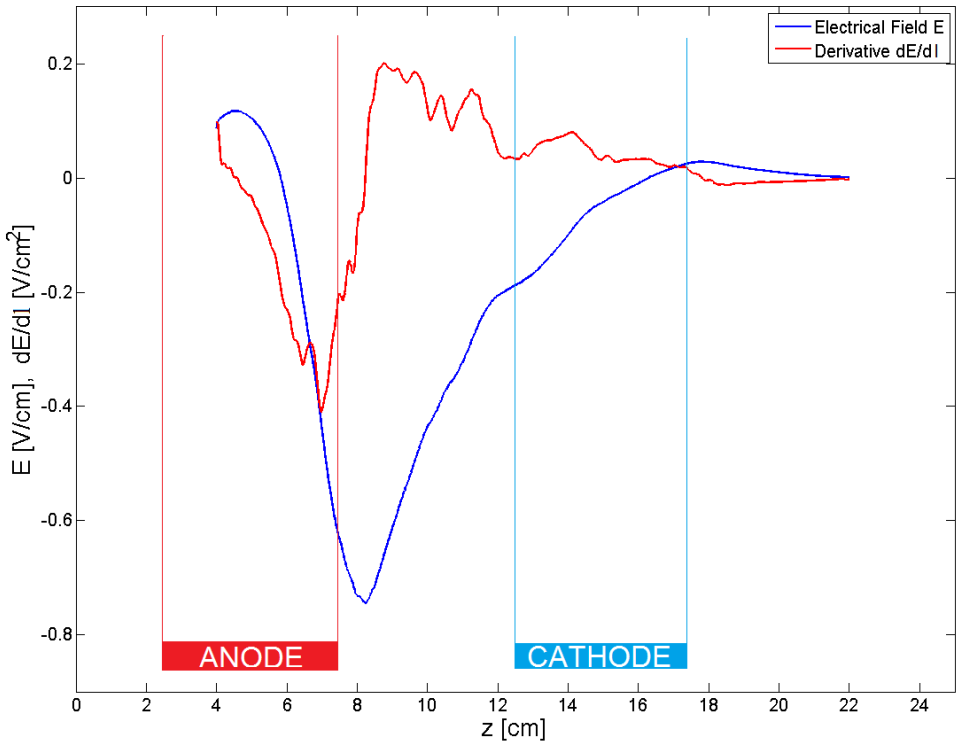


Figure 5.28 Activating function of transcutaneous PESTOB model (grid displacement method)

Although the activating function oscillations/points of inflexions on Figure 5.27 are not much smaller than on Figure 5.22, the grid displacement method is a more reproducible solution.

5.3.7. **Percutaneous – needle electrode model**

In this model a combination of a 34 gauge needle electrode (0.19 mm diameter) and a surface electrode (35 mm diameter) is used. The electrodes were placed according to the description for the commercially available percutaneous stimulation system (Urgent PC, Uroplasty Ltd.). The needle electrode was placed 5 cm proximal from the medial malleolus and 2 cm posterior to the tibia. The surface electrode was placed on the medial aspect of the calcaneus (Figure 5.29).

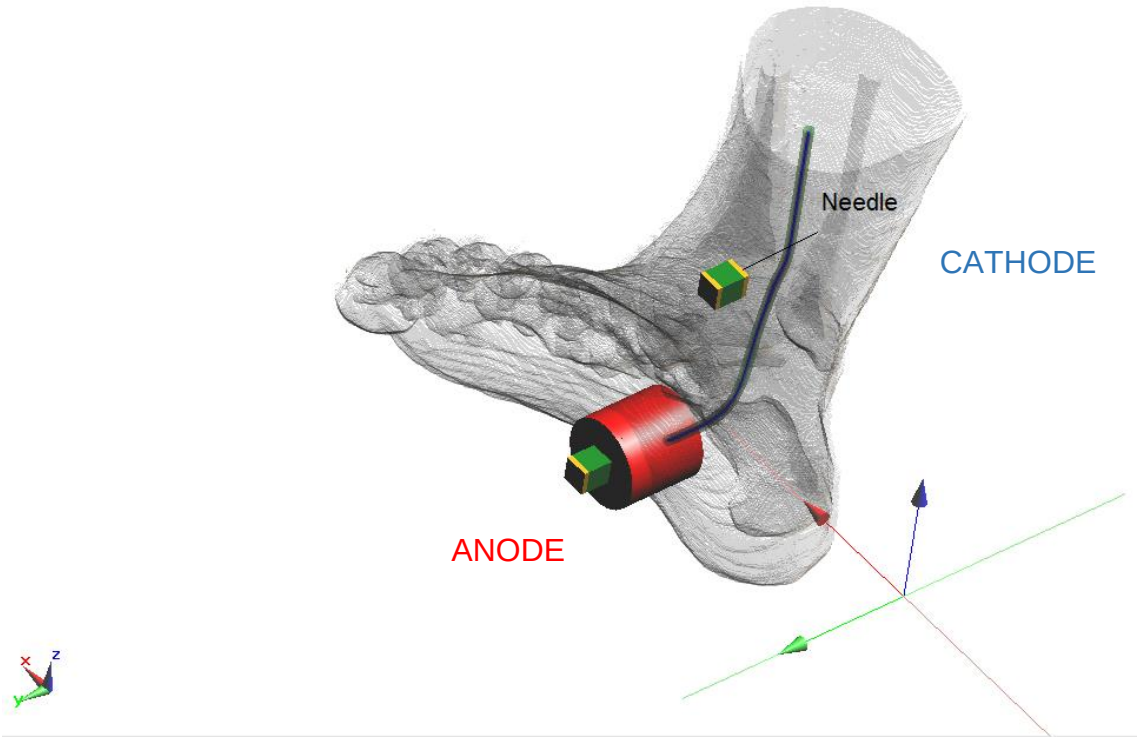


Figure 5.29 Position of the electrode for percutaneous PTNS (red electrode – anode, needle electrode – cathode)

The solution of this model showed that the distribution of the electrical field around the anode surface electrode and proximal to the needle is similar to the transcutaneous form (Figure 5.30). The electrical field gradient in this are decreasing towards its bottom peak around z = 8 cm. Further however there is a rapid increase of the positive electrical field caused by the close proximity of the cathode needle electrode to the nerve causing a localised increase in the stimulating function (Figure 5.31). Hence the activating function shows a dominate peak gradient at z = 14.95 cm and had a value of 0.346 V/cm^2. The simulation current in this model was 3.3 ± 0.04 mA (mean ± SD). This current was based on them mean current used in the study of percutaneous PTNS for the treatment of overactive bladder symptoms (van der Pal et al., 2006b).

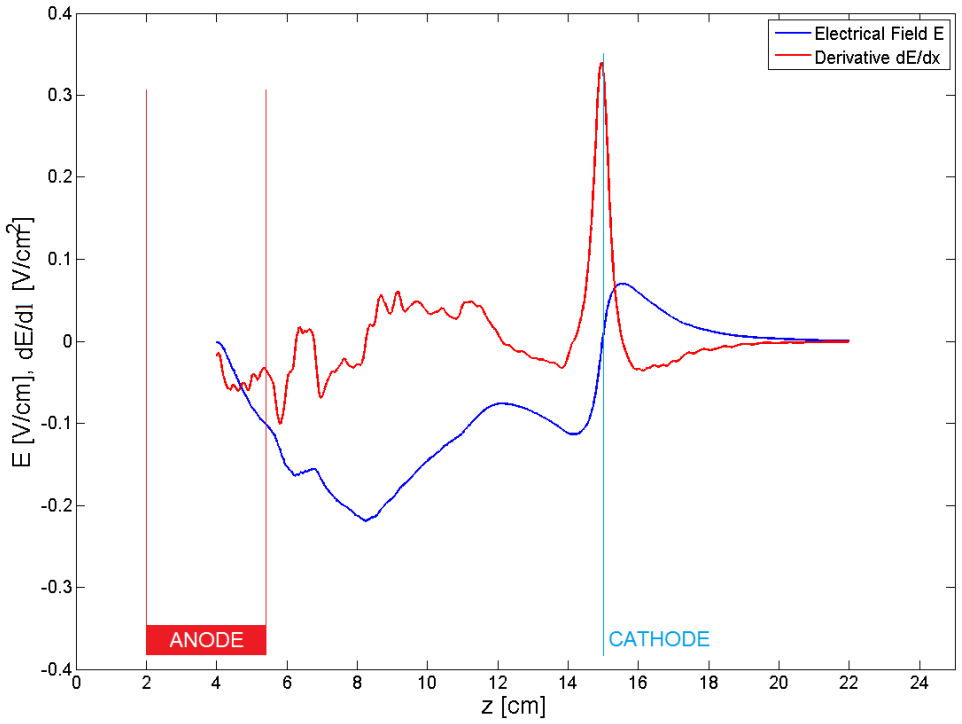


Figure 5.30 Activating function of the percutanous model

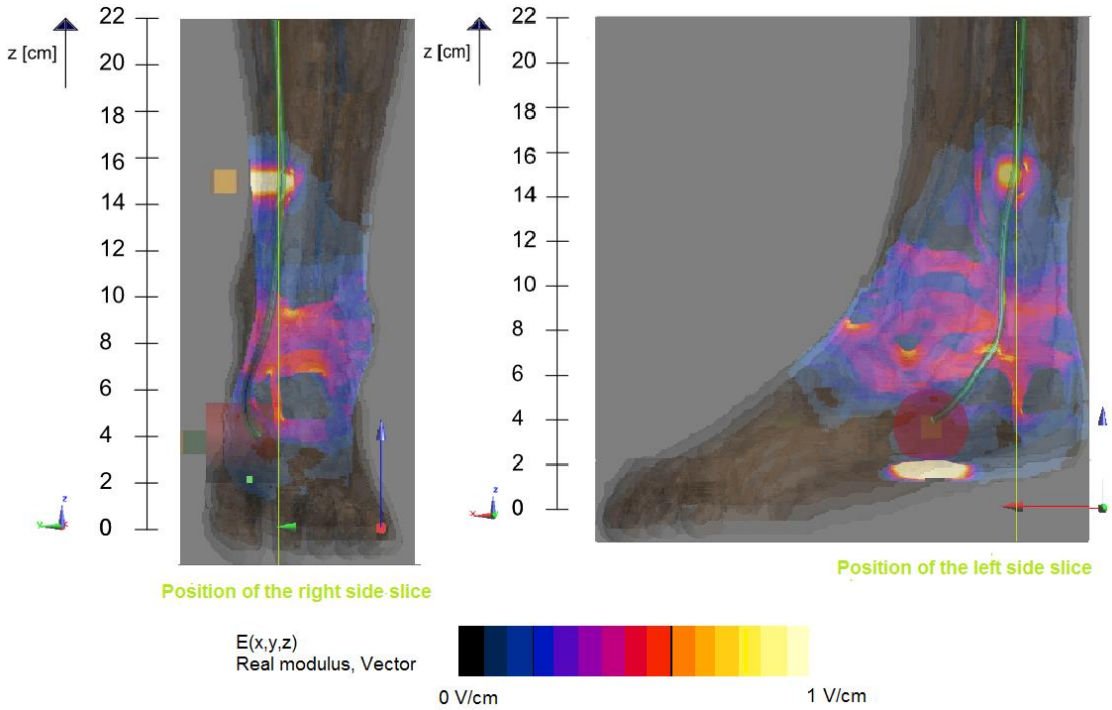


Figure 5.31 Cross-sectional distribution of the electrical field in the percutaneous model (red electrode – anode, blue electrode – cathode)

5.3.8. **What current is needed to produce the same physiological response?**

A study investigating the percutaneous stimulation approach (van der Pal et al., 2006b) used a mean pulse current intensity of 3.3 mA as used in this model. Such current produced a peak gradient of 0.346 V/cm^2 in the SEMCAD model.

The primary aim of this modelling work was to determine the current needed to produce the same peak value of activating function between the percutaneous and transcutaneous forms of PTNS. Thus, the following is calculated:

Maximum gradient of percutaneous M_{PERC} = 0.346 V/cm^2

Maximum gradient of transcutaneous M_{TRAN} = 0.201 V/cm^2

Simulation current measured on transcutaneous electrodes I_{SIM} = 8.8 mA

$$I_{Transc.} = \frac{M_{PERC}}{M_{TRAN}} * I_{SIM} = \frac{0.3469}{0.2011} * 8.8 = 15.2\ mA$$

From the equation above, the current needed to produce the same physiological response is 15.2 mA (approximately five times higher than for the percutaneous form).

This chapter will further explore whether a variation in the electrode position and size of the electrode significantly reduces the stimulation current needed in order to produce the same activating function gradient.

5.3.9. **Further transcutaneous montage 1 – smaller electrodes**

Current density, and thus electrical field, is proportional to the cross-sectional area of the electrodes. Electrodes with a smaller diameter would be expected to increase local electrical field for a given stimulation current density and might move the localisation of the stimulus to below the electrodes rather than between the electrodes as seen in the previous transcutaneous model. Thus a model with 50% smaller area of electrodes was created (Figure 5.32) and solved.

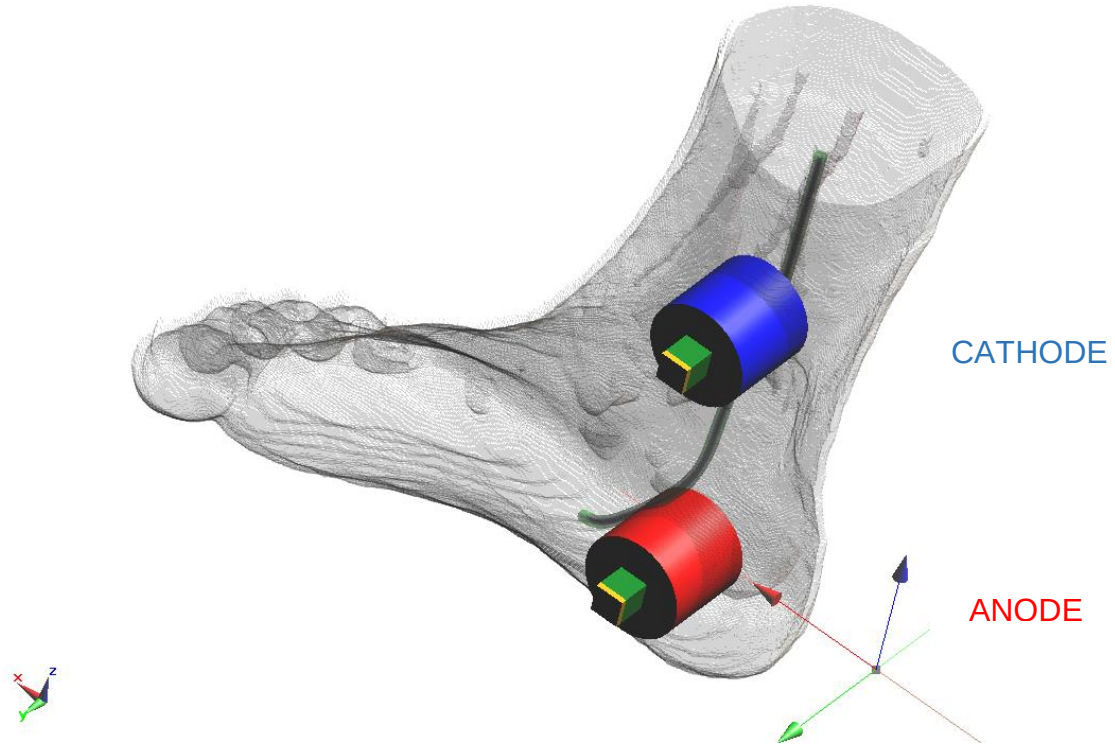


Figure 5.32 Position of the smaller 35 mm electrodes montage in the transcutaneous model (red electrode – anode, blue electrode – cathode)

Figure 5.33 shows the activating functions of the previous transcutaneous montage with electrodes of 50 mm size and the solution for the smaller 35 mm electrodes. The activating functions are normalised to the same intensity of the current (15.2 mA) in order to make a comparison between the two montages. The activating function of the 35 mm electrodes shows a dominating peak of gradient (0.330 V/cm^2) at z = 8.7 cm. This peak is similar to the previous gradient in the 50 mm electrodes model (~5% smaller). Further, there is another gradient peak which became more apparent below the cathode electrode at z = 14.2 cm, with a peak value of 0.228 V/cm^2 (~20% bigger). If the polarity of the electrodes is swapped then the peak will around 0.776 at z = 6.4 cm.

These results show that the cathode gradient may become more dominant with smaller electrodes. However, 50% smaller electrodes setup reduced the gradient peak to 87% of the bigger electrode gradient peak and the reversal polarity gradient peak increased to 110%. As another peak around z = 14.2 cm became more apparent there is no simple ratio which will suffice to predict relative change of the gradient with smaller size of electrodes. Presumably a further reduction in the electrode diameter would be needed in order to localise the stimulus below the cathode electrode for the specific anatomy being

modelled. The smaller electrodes might have a practical disadvantage as position laterally from the centre of the nerve will become more critical.

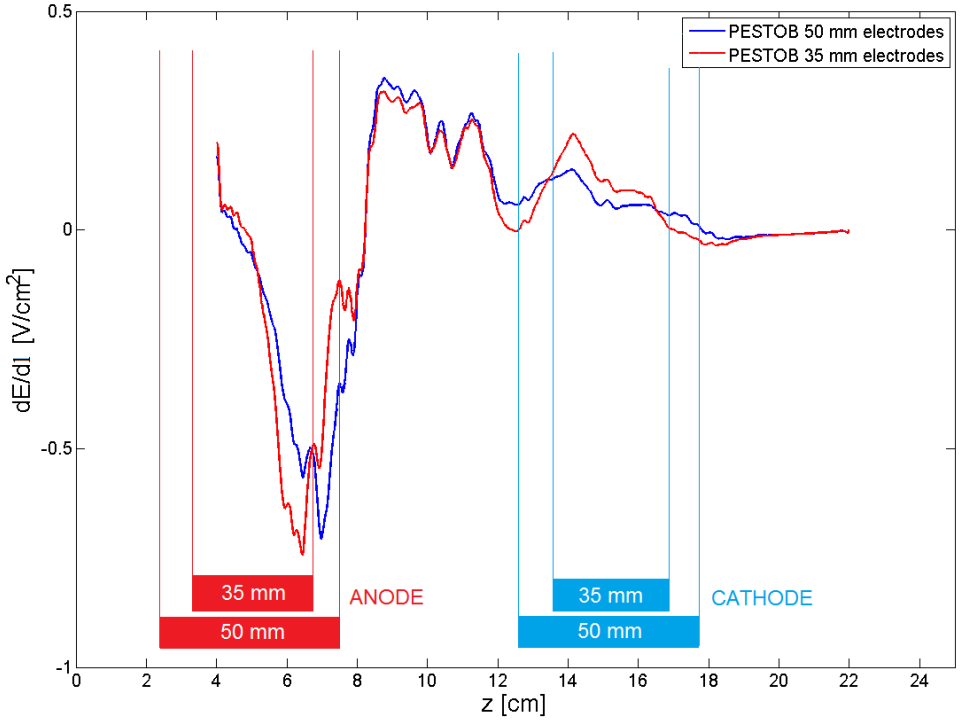


Figure 5.33 Activating functions of the PESTOB montage 50 mm electrodes and 35 mm smaller electrodes

5.3.10. **Further transcutaneous montage 2 – posterior to foot**

Another montage which was previously used in the studies of transcutaneous PTNS (Ammi et al., 2014) placed the electrodes posterior to foot on the ankle, on the Achilles Tendon (Figure 5.34). The model in the study placed the anode electrode above the cathode, however for the consistency of this work the anode is placed below the cathode. Further comparisons can be made by swapping the polarity as suggested below. The same size of the electrodes as in the first transcutaneous PTNS model are used (50 mm diameter). The anode electrode geometry was changed such that the contact area will be that of the circle shaped electrode. This was due to a narrow part of Achilles tendon at the position of anode.

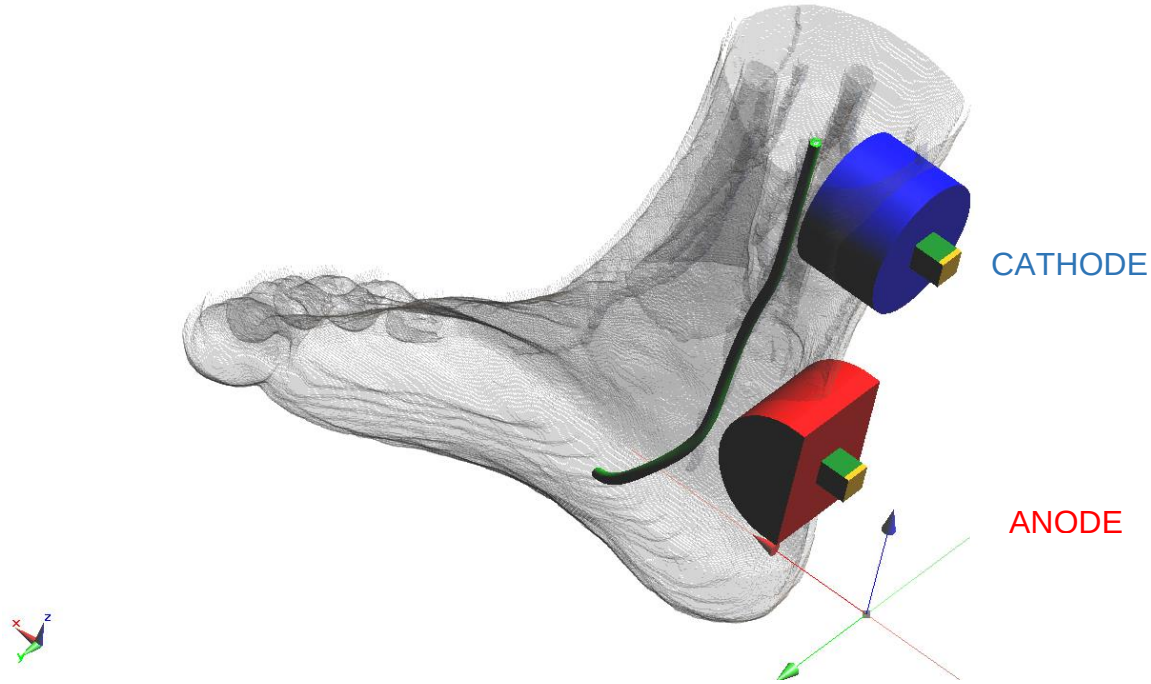


Figure 5.34 Position of the electrodes for the posterior montage (red electrode – anode, blue electrode – cathode)

Both activation functions in Figure 5.35 represent the distribution of electrical potentials again for the 15.2 mA stimulation current calculated in Section 5.3.8. This posterior electrode montage produced the highest gradient of 0.161 at z = 11.4 cm. In comparison to the PESTOB 50 mm electrodes montage the stimulation would be less effective. If the electrode polarity is swapped then the peak gradient will be 0.253 at z = 8.2 cm.

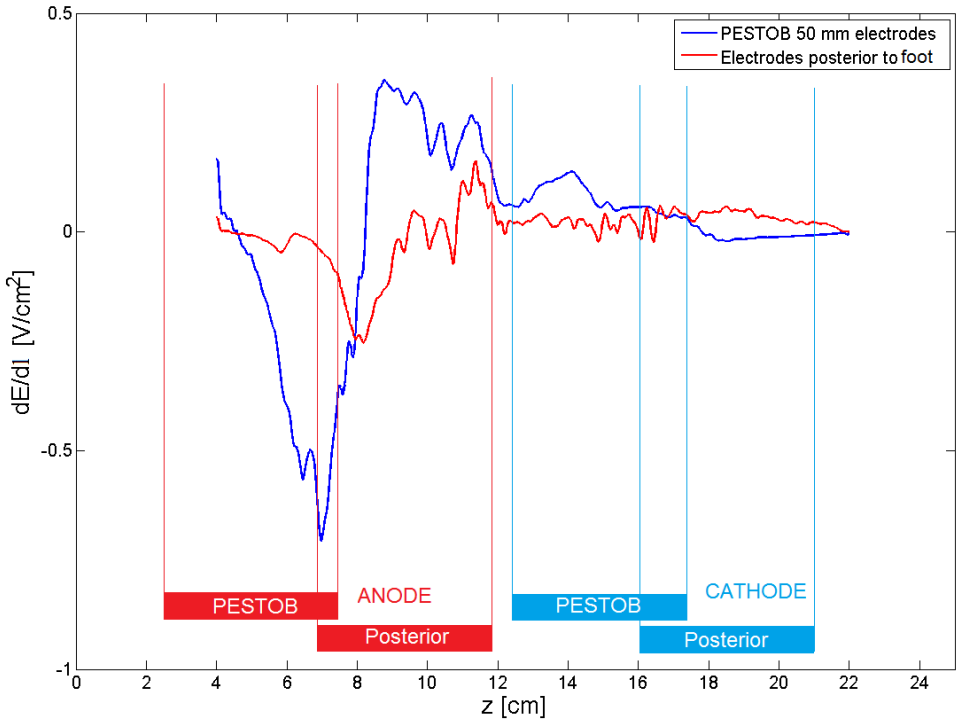


Figure 5.35 Activating functions of PESTOB montage 50 mm electrodes and electrodes placed posterior to the ankle

5.3.11. **Summary**

The modelling of the percutaneous form of posterior tibial nerve stimulation showed the maximum gradient 0.346 V/cm^2 at z = 14.95 cm for a typical stimulation current of 3.3 mA. The stimulation current needed to achieve the same physiological response (represented by the value of this maximum gradient) as in percutaneous PTNS is summarised in Table 5.3.

Table 5.3 Current needed to produce the same activating function gradient as in the percutaneous form

Montage	**Current needed [mA]**	**Multiples of percutaneous form current needed [-]**
Percutaneous form	3.3	
Transcutanous 50 mm	15.2	4.6
Transcutanous 50 mm - reverse	7.5	2.3
Transcutanous 35 mm	15.9	4.8
Transcutanous 35 mm – reverse	6.8	2.1
Posterior to ankle	32.6	9.9
Posterior to ankle – reverse	20.8	6.3

The most effective approach seems to be to reverse the polarity of the electrodes from the originally modelled transcutaneous 50 mm position, i.e. the cathode on the medial side of the heel and anode above. This reversal of electrodes, and the resultant significant decrease in the stimulation current used (by a factor of approximately 2) has the dual advantage of decreasing the electrical energy that needs to be applied and of the expected resultant decrease in cutaneous sensation due to the stimulation.

The placement of the electrodes behind the medial malleolus (posterior to the ankle) as suggested previously in the literature does not have an advantage in terms of requiring a lower stimulation current.

Model verification and validation are important processes in numerical modelling. An experimental validation would be beneficial and seems to be the most practical pathway for this Chapter. However, due to the time constraints and resources available for this thesis this was not achieved and is left for further work. Nonetheless this model has usefully informed understanding about the model from homogeneous volume conductor towards the full PTNS model.

The modelling in this chapter provides evidence that similar field gradients at the nerve due to percutaneous posterior tibial nerve stimulation can be achieved using the transcutaneous form. It has enabled an estimate to be made of the relative currents that are needed in the two methods. However it should be noted that the position of stimulation along the nerve is somewhat different for the electrode montages considered and the electrical current needed to produce the same effect is larger.

Chapter 6 **A pilot clinical trial of Transcutaneous Posterior Tibial Nerve Stimulation for the treatment of overactive bladder**

6.1. **Introduction**

Chapter 1 has identified the potential for using Posterior Tibial Nerve Stimulation for the treatment of overactive bladder syndrome symptoms. Specifically the transcutaneous approach using surface electrode seems to be attractive, because it is completely non-invasive, low cost and can be self-administered by patients at home.

There is only inadequate evidence available to support this approach as seen in Chapter 1 - reviews have identified only limited evidence of its efficacy, and the lack of placebo control studies in this area is of particular concern. The technology that can be used for this approach (a TENS stimulator) is widely available on the market and does not require any further development. Thus it seems ideal to evaluate this approach in a placebo controlled study. The further aims and objectives of this pilot clinical trial are described in the following sections.

6.1.1. **Extend the De Sèze study to a different patient group**

The most promising transcutaneous PTNS study to date in the literature was conducted by (de Seze et al., 2011). It reported clinical improvement of its primary outcome measure (a combination of warning time, an urgency subscale and frequency from a 3 days voiding chart) in 82.6% of MS patients after one month of treatment.

The study evaluated effects after 30 and 90 days. The largest improvement was seen at day 30. After this time clinical efficacy parameters remained stable or declined slightly. The study mentioned that the efficacy of transcutaneous PTNS appeared in the first week, but they did not make a formal clinical assessment at this time. To confirm this observation the study design in this thesis should include an assessment after one week and apply the treatment for a total of 4 weeks with the same stimulation parameters as de Seze. Their study focused only on MS patients. However, idiopathic OAB symptoms affected patients present a larger clinical problem and hence this patient group has been chosen for this study.

6.1.2. **Inclusion of a placebo control group**

The investigation of placebo effects is arguably essential in the evaluation of new therapies and this is particularly the case with electrical stimulation techniques. However, because of the sensations caused by the stimulation, the production of sham electrical stimulation can be difficult. An interesting methodology was reported in a study of children with OAB, where in one arm of the study, the same type of stimulation was applied over the scapula, where no effects on lower urinary tract control would be expected to occur (Lordelo et al., 2010). Similarly Hasan et al. applied TENS over the T12 dermatome which acted as placebo (Hasan et al., 1996).

Electrical stimulation below motor threshold levels causes a tingling sensation due to the stimulation of cutaneous sensory nerve structures. Thus an alternative option may be to gradually decrease the stimulation intensity to zero after a few seconds of usage and tell the subject that stimuli sensation might fade with time. This is an approach widely used in techniques such as Transcranial Direct Current Stimulation (Russo et al., 2013). In reality, the subject may habituate to the stimuli such that they are genuinely not able to recognise whether the stimulation still persists or not. This habituation is likely to depend on the frequency used, the strength of the applied stimuli and on personal subjective responses.

Another approach to the investigation of placebo effects may be to apply stimulation over the same area of the skin but with zero stimulation current (Hagstroem et al., 2009). However, for this to be an effective placebo the patient must be naive to electrical stimulation and unaware that it causes sensation.

Leroi et al. performed a randomised sham-controlled trial in which patients were not told that they might receive sham stimulation (Leroi et al., 2012). Patients were then randomized into active and sham stimuli groups. This methodology was approved by their local ethics committee, although the editors of the journal in which they subsequently published strongly discourage further investigators to use this methodology as it might represent a breach of the Declaration of Helsinki. However this could be an appropriate method to overcome the technical problems of sham stimuli if approved by the appropriate ethics committee.

There is just one study, that evaluates a placebo effect using transcutaneous PTNS (Bellette et al., 2009). This study used treatment sessions in the clinic rather than at home, and chose as its placebo electrodes applied to the skin without any stimulus being delivered. Patients were told that they may or may not feel the stimulation. They found improvement in 30% patients in the placebo group.

In summary, the complete absence of stimulation cannot be relied on as an adequate placebo because patients may well not be naive to the fact that electrical stimulation causes sensation and hence will be able to deduce that they are in the placebo group. Instead, the method chosen for this study is to use the approach of (Lordelo et al., 2010), i.e. a comparable intensity of electrical stimulation in the placebo group but applied to a site that is regarded as being irrelevant to bladder control.

6.1.3. **Is bilateral stimulation more effective?**

The majority of studies used unilateral stimulation, applied to just one ankle, and do not specify which ankle (left or right) should be stimulated. Therefore one arm of the study will investigate whether bilateral stimulation can be beneficial, when compared to both control and unilateral leg stimulation in a three arm study.

6.1.4. **How long do the effects of stimulation last?**

There is no clear evidence about the duration of the effect after transcutaneous PTNS in OAB treatment. A study (van der Pal et al., 2006a) used percutaneous (6 patients) and transcutaneous (5 patients) PTNS and the authors suggested that subsequent maintenance treatment is necessary. All patients had subjective deterioration and 9 of 11 patients had objective deterioration of their symptoms over a period of 6 weeks. The study in this thesis assesses patients for four weeks after treatment has ceased to assess the carryover of any therapeutic benefit.

6.1.5. **Investigation of sympathetic pathways in the automatic nerve system**

There are several studies which have investigated automatic nervous system dysfunction in overactive bladder patients (Ben-Dror et al., 2012, Mehnert et al., 2009, Hubeaux et al., 2007, Hubeaux et al., 2011) . Various measures, including heart rate variability, have

been used. (Hubeaux et al., 2011) showed that idiopathic OAB patients have sympathetic dysfunction using a hand grip exercise and cold pressure test during which changes in blood pressure were recorded. For this reason an investigation as to whether this study of idiopathic OAB patients having sympathetic dysfunction was included, based on a hand grip exercise and measurement of resultant blood pressure changes, and whether any resultant subgroup of patients is correlated with the results of the treatment.

The main aim of this clinical trial and the hypothesis being tested is to determine whether transcutaneous posterior tibial nerve stimulation should be considered for further, larger, studies and subsequent deployment into clinical practice.

6.2. **Material and methods**

This study was designed as a placebo randomized single-blind placebo controlled trial.

The participants were randomly assigned to receive either unilateral PTNS, bilateral PTNS or shoulder stimulation using 40 minutes self-administered stimulation every day for a duration of four weeks. As described earlier (Section 6.1.2) stimulation on the shoulder was regarded as sham stimulation because there is no obvious neural connection to the bladder control mechanism and therefore such a site should not affect the symptoms of OAB. The outcome measures were recorded prior to the therapy, after the first week of the treatment, after the treatment was completed and four weeks after the treatment finished. The participants attended three visits as indicated in the study flow diagram (Figure 6.1).

The study was presented to the participants as a comparison of three different stimulation sites in order to blind the participant to the focus on PTNS. Hence the title for the study was chosen as “Peripheral Electrical Stimulation for the Treatment of Overactive Bladder”, abbreviated to “PESTOB”.

The study, using the placebo methodology described above, was approved by the Yorkshire and Humber regional committee (Appendix I) and registered in the public domain (http://clinicaltrials.gov/show/NCT01783392).

Martin Slovak conducted the clinical trial and was involved in all parts of the trial including study design, planning, securing ethic approval, study coordinating,

recruitment, intervention training, data collection, data analyses and dissemination. In all aspects supervised by Professor Anthony Barker and Professor Christophe Chapple. Dr Nadir Osman and Dr Christopher Hillary were the study doctors and Mrs Suzanne Hulton, Mrs Alison Hyde, Mrs Anne Frost supported the trial as research nurses. The costs of the stimulators (6 x £50) were covered the EU Marie Curie training network TRUST.

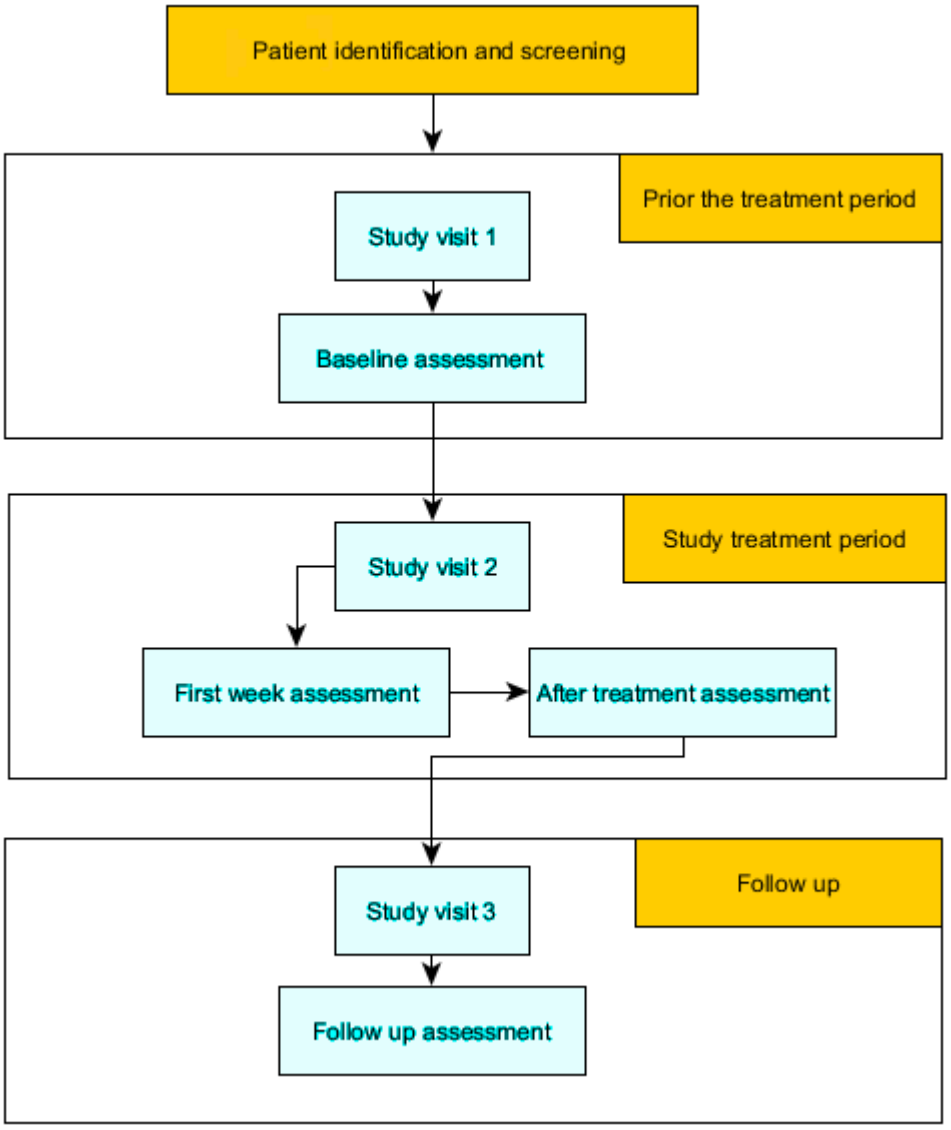


Figure 6.1 Study flow diagram

6.2.1. **Participants**

Adult (>18 years of age) patients diagnosed with the idiopathic symptoms of overactive bladder, with or without urodynamically proven detrusor overactivity and who had failed

primary therapy were enrolled into the study. The most frequent exclusion criteria were predominant stress urinary incontinence in females and clinically significant bladder outlet obstruction in males. The full list of inclusion and exclusion criteria list is included in the Appendix J. The participants were allowed to stay on any existing medication throughout the study as long as they did not change its type or dose. They were also asked not to alter their fluid drinking habits whilst they were involved in the study, which was monitored by bladder diary assessments.

6.2.2. **Participants' identification and screening**

The participants were recruited from the urology, urogynaecology and community continence services of Sheffield Teaching Hospitals NHS Foundation Trust from April 2013 to October 2014. From February 2014 the study was also advertised in order to increase the recruitment rate. This was done using a printed advertisement at relevant local clinics and online at two overactive bladder patient's supportive organizations, the Cystitis & Overactive Bladder Foundation (http://www.cobfoundation.org/) and the Bladder & Bowel Foundation (http://www.bladderandbowelfoundation.org/). In addition, potential participants were also identified from the Bladder and Bowel Foundation client database.

The participants were required to attend three study visits. Before their first visit they were provided with the study information sheet and were initially screened against the inclusion and exclusion criteria by a study research nurse. Following that the participant had at least 24 hours to decide if he/she would like to take part in the study before the date for the first study visit was arranged. The participant was then attended their first study visit at the Urology Outpatient Department at the Royal Hallamshire Hospital in Sheffield.

6.2.3. **Prior the treatment period – study visit 1**

At the first visit, one of two study doctors took a detailed record of the participants' symptoms, demographic data and drug history. At the same time the study doctor also performed a physical examination in order to determine whether the participant fulfilled the study inclusion and exclusion criteria.

The participant then signed a study consent form.

At the same visit an autonomic nervous system test (described later in this methodlogy section) was performed. Following that the participant was taught how to complete a 3-day bladder diary and the relevant questionnaires (see Section 6.2.7 for details) during the week to prior their second visit.

6.2.4. **Randomisation of the participants – study visit 2**

Randomisation of the participants took place at the second visit. The participants were stratified by the number of voids per day into one of three groups to ensure that the baseline number of micturitions could be closely matched between the three arms.

Group 1 – less than 15 voids and more than 8 voids

Group 2 – more than 15 voids

Group 3 – less than 8 voids (urgency patients)

A clinical scientist not involved in data collection provided a randomisation sequence for the study arms which was concealed in three sets of consecutively numbered opaque envelopes, one for each group. The appropriate envelope was opened to determine the study arm for that participants once they had consented and their number of baseline voids on their second visit was known.

Group 3 was added later and consequently should formed a small sub-study focused on participants only with urgency. This was decided as a challenging consequence of otherwise excluded and highly motivated participants (the original criteria excluded the participants with less than 8 voids) at the second study visit. So, all the participants who fulfilled the study inclusion and exclusion criteria were randomized. The participants in Group 3 were only randomized into two out of the three study arms (the unilateral posterior tibial nerve stimulation and placebo arm). However, altogether there were only two participants randomized into this sub-study, but one did not comply with the study protocol and other decided to withdraw from the study due to significant deterioration of symptoms. Therefore this sub-study group is not further discussed.

Following randomization on study visit 2, the investigator provided training for the participant according to their allocated group. This training was provided in two parts and the participants obtained a leaflet with instructions to take home (Appendix J). In the first

part the investigator showed the participant how to place the electrodes and control the stimulator unit, and provided a short demo session (~5 minutes) of stimulation. In the second part the participant was tasked to show that he/she was able to independently use the stimulator according to the protocol and performed the first full (40 minutes) stimulation session whilst in the clinic.

6.2.5. **Methodology of study arms**

All study arms used the same length of treatment sessions (40 minutes); the same two output channel device (MultiTens Neurotrac, Verity Medical Ltd., UK) and the same stimulation setting (10 Hz, 200μs pulse width). This stimulation setting was chosen to be the same as the study by (de Seze et al., 2011). The participant placed self-adhesive hydrogel electrodes (50 mm round, Verity Medical Ltd., UK) on the site of body according to their allocated group, as described below. The stimulation was self-administered daily by the participant for a duration of four weeks.

It was important to record participant's compliance with the study protocol, therefore the stimulator used in the study was chosen in part because it had an inbuilt logging facility. Further features of the stimulator allowed modification of all of the stimulation parameters and locking of these settings into the device. The maximum output of the stimulator was 60 mA per channel

The low cost of the stimulator and electrodes were also important requirements in terms of the health economics of this type of therapy. The stimulation unit cost ~£50 and the cost of the electrodes was ~£5 per pack of four.

6.2.5.1. **Unilateral stimulation group**

The participant was presented with a set of instructions (Appendix K). These instructions were consistent for each of the stimulation groups, the only difference being in how the electrodes were positioned. In particular, the same distance between the electrodes and the same level of intensity (as described further in Section 6.2.5.4) was used at all sites. The participants in the unilateral stimulation arm were instructed to stick the electrodes on the right ankle as shown in Figure 6.2. As mentioned in the introduction Section 1.3.2, it is uncertain as to which leg the electrodes need to be placed and whether this matters. Stimulation on the right ankle was chosen from the methodology by (de Seze et al., 2011)

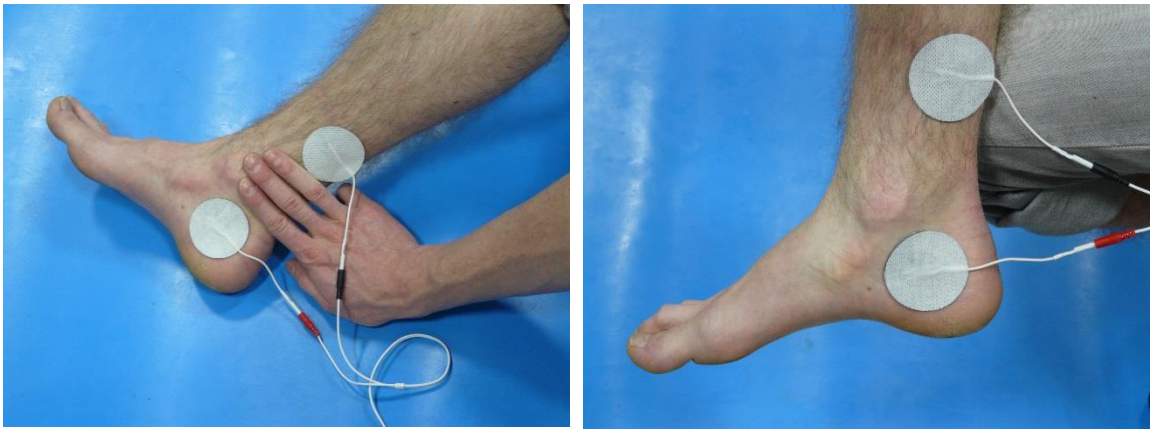


Figure 6.2 Position of the electrodes for unilateral stimulation Left – cathode electrode 3 finger widths between above the medial malleolus. Right – electrodes placed on right ankle

Specifically, the participants were firstly instructed to place the electrode with the black connector (cathode) 3 finger widths (approx. 5 cm, 2 inches) above the right ankle bone on the edge of the leg and then place the electrode with the red connector (anode) between the ankle bone and the heel of foot.

The participant was then instructed to connect the electrode wire into the stimulation unit, switch on the unit and set the intensity.

6.2.5.2. **Bilateral stimulation**

Similarly to the unilateral stimulation group, the participants placed the cathode electrode above, and the anode electrode below, the medial malleolus, over the posterior tibial nerve on both legs and set the stimulation intensity (Figure 6.3).

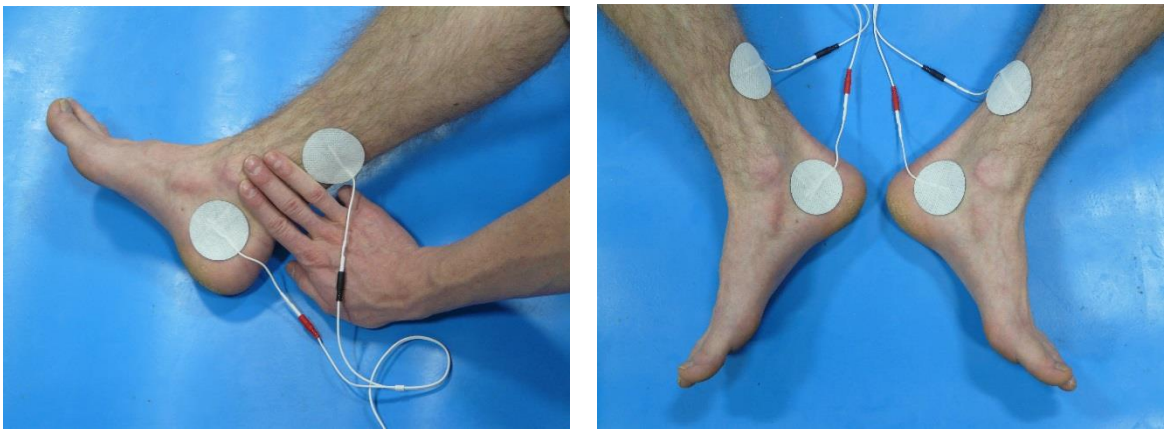


Figure 6.3 Position of the electrodes for the bilateral stimulation group. Left – cathode electrode 3 finger widths between above the medial malleolus. Right – electrodes placed on both ankles

6.2.5.3. **Sham stimulation**

The participants were instructed to place the cathode and the anode electrodes on the lateral side of the left shoulder. Firstly, the participant was instructed to place the electrode with the black connector (cathode) at the middle front side of the shoulder then place the electrode with the red connector (anode) 3 finger widths (approx. 5 cm, 2 inches) below as shown in Figure 6.4.

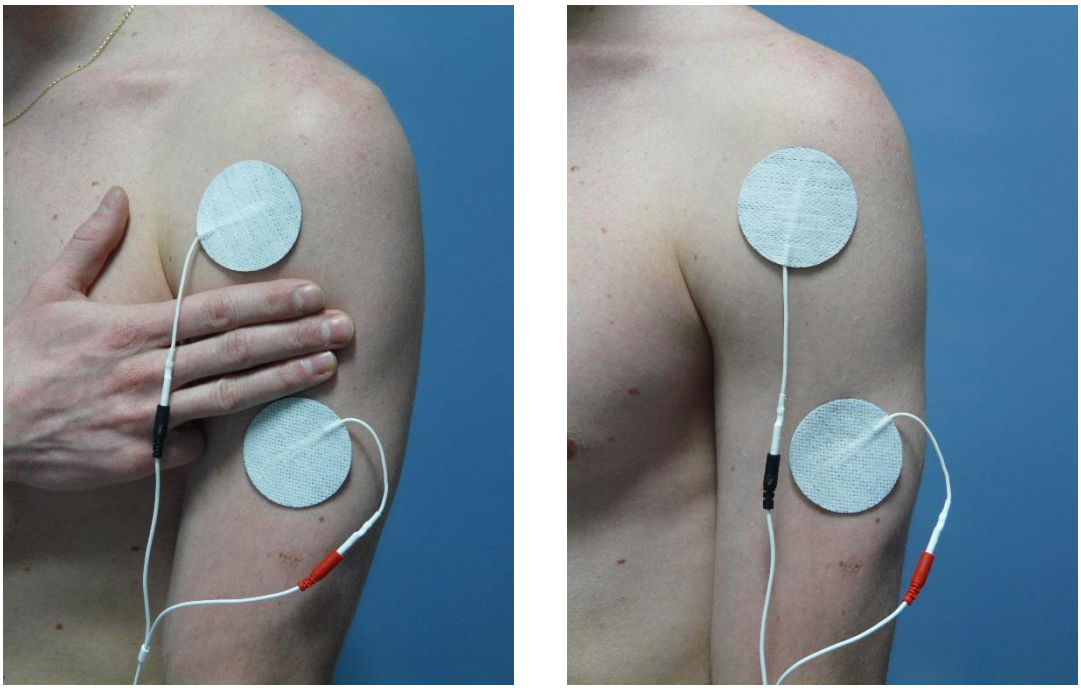


Figure 6.4 Position of the electrodes for the bilateral stimulation group. Left – 3 finger widths between above the stimulation electrodes. Right – electrodes placed on left shoulder

6.2.5.4. **Stimulator amplitude settings**

PESTOB sought to confirm the effect of the treatment reported by (de Seze et al., 2011) and hence their parameter settings were used in all arms of the study, namely pulse width 200 µsec and pulse frequency 10 Hz. In regards to the stimulation intensity level the de Seze paper states that:

"*The intensity level was just above the perception threshold but before that which caused pain"*

To try and standardise the intensity used, the participants were specifically asked to use 'the maximum comfortable intensity which does not cause pain or muscular contraction, ideally just below that which causes muscular contraction. If the sensation is tolerable it is recommended that the stimulus is increased until muscular contraction is perceived and then

decreased slowly until contractions just cease". This wording was also used in the written instructions they were given and was chosen because it could also be used for the control group and was easy for patients to understand. The average current was recorded for each session by the stimulator, thus also allowing patient compliance to be checked.
The participants were allowed to change the stimulation intensity throughout the stimulation session if the sensation of the stimulation became unpleasant or too weak as long as they complied with the study protocol.

6.2.6. **Study visit 3**

At the third study visit the participants returned both, the stimulator, and completed assessments from the week 1 and after the treatment (as described in the Section 6.2.7). The second autonomic nerve system response test was also performed (Section 6.2.8).

During this visit the participants also underwent a brief interview about the change in his/her bladder condition and their stimulation tolerance. Typical questions were focused on whether he/she had perceived a benefit from the stimulation irrespective of the study assessments used and their willingness to continue with the therapy on their own.

The participant were also given a further follow up assessment pack to be completed four weeks after their last stimulation session. Usually a further clinic appointment was arranged for the patient in order to continue their treatment pathway outside of the study.

6.2.7. **Study assessments and outcomes**

The study assessment tools to collect data and outcome measures were based on standardised questionnaires and a bladder diary as follow:

Bladder Diary

Accurate assessment of overactive bladder symptoms requires their objective interpretation using a urinary diary (Chapple, 2014). The International Consultation on Incontinence Questionnaire (ICIQ) established the first validated 3 day bladder diary for the assessment of LUTS (Bright et al., 2014). There were changes made to the layout and the study bladder diary did not record fluid input, as suggested by (Bright et al., 2014). This is because this information was not regarded as important for the study aims because

any alternation of the fluid intake would be captured by the total volume voided and analysed individually. The bladder diary used can be found in (Appendix L).

The following outcome measures were calculated manually by the investigator from each of the bladder diary:

- Mean number of micturition per 24h
- Mean number of urgency episodes per 24h
- Mean number of nocturia episodes per 24h
- Mean number of urinary incontinence episodes per 24h
- Maximum voided volume in 72h bladder diary period
- Voided volume per 24h
- Mean nocturia polyuria calculated as a ratio of the total night time voided volume and the total day time voided volume

The change in the mean number of micturition per 24h and in the mean number of urgency episodes were the primary outcomes of the study.

Patient Perception of Bladder Condition (PPBC)

This is a validated and well established single item global tool for the measurement of bladder condition (Coyne et al., 2006a). The score ranges from 0 to 5 with higher score indicating greater severity of the symptoms.

Patient Perception of Change in Bladder Condition (PPCBC)

The above questionnaire was also modified such that instead of the score range, the participants indicated whether they perceived that their bladder condition had changed from the last assessment. This assessment was named Patient Perception of Change in Bladder Condition (PPCBC). The participants were able to choose from improved a lot, improved slightly, stay the same, got worse or got a lot worse. PPCBC was later used in the definition of the responder 6.2.11.

OAB-q Short Form

The Short Form of the OAB questionnaire (OAB-q) has been demonstrated to be an economical and efficient alternative to the full-length form (Coyne et al., 2014). The

questionnaire captures the full spectrum of OAB Symptoms Bother (SB) and Heath-Related Quality of Life impact (HRQL).

Both scores are transformed on a 0 to 100 point scale using the equations below. A higher Symptom Bother score indicates greater severity of symptoms and a lower HRQL score indicates a greater impact of the symptoms on the patient's quality of life.

A minimally important difference in the OAB-q has been recommended as a change of 10-points for both SB and HRQL, although this is based on the OAB-q long form (Coyne et al., 2006b).

To allow the score to be between 0-100 following calculation took place. Lower SB score indicates less bothersome symptoms and lower HRQL score indicates lower quality of life.

$$SB\ score = \frac{(Actual\ score - 6)}{30} \times 100 \quad (6.1)$$

* 6 indicates the lowest possible score, 30 indicates the possible raw score range

$$HRQL\ score = \frac{(78 - Actual\ score)}{65} \times 100 \quad (6.2)$$

* 78 indicates the highest possible score, 65 indicates the possible raw score range

ICIQ OAB

The ICIQ has established a questionnaire assessing the presence or absence of symptoms of overactive bladder using a 5-point scale for each condition (frequency, urgency, nocturia, incontinence). A score of 0 indicates no presence of a symptom and score of 4 great symptom severity. Each symptom questions is followed by a scale to assess bother associated with the symptom (Abrams et al., 2006) on a scale between 0 to 10, where 0 indicates not bothered at all and 10 indicates "a great deal". Two scores are created from this questionnaire:

- ICIQ-OAB Score – range 0-16
- ICIQ-OAB Bother score – range 0-40

RAND36

The RAND36 is a widely used health-related quality of life questionnaire. There are eight outcome group scales derived from the questionnaire: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions (Hays and Morales, 2001).

Table 6.1 Summary of the questionnaires used with assessment period. X – Questionnaire was used

Questionnaire	Assessment			
	Baseline	First week	After treatment	Follow up
3 days bladder diary	X	X	X	X
PPBC	X	-	X	X
PPCBC	X	X	X	X
OAB-q	X	-	X	X
ICIQ-OAB	X	-	X	X
RAND36	X	-	X	X

6.2.8. **Autonomic nervous system**

A test of autonomic nervous system function was performed prior to the study at the participants' first visit and just after the study at the patient's third visit. The test consisted of a hand grip exercise test during which blood pressure was measured. The hand grip exercise test is a cardiovascular test, measuring the response of the sympathetic nerve system to static exercise generated by the hand grip (Hubeaux et al., 2011).

The participant was asked to maintain a hand grip at 30% of maximum over 3 min using a hand grip dynamometer. Blood pressure was measured at the baseline and then after each minute of the exercise using an Omron 705CP monitor on the opposite arm.

A dysfunction of the sympathetic pathway in the autonomic nerve system causes a lack of the rapid increase in diastolic blood pressure that is observed in normal subjects. If the difference in diastolic blood pressure before starting the test and just before release was <10 mmHg the test was considered abnormal.

Participants with a resting blood pressure greater than 160/100 mmHg were excluded from this test but were still able to participate in the study.

6.2.9. **Sample size calculation**

PESTOB was designed as a three arm, single centre pilot study. It has been reported that, in general a sample size of 12 patients per group is suitable for such a pilot study (Julious, 2004). Alternatively the following power calculation can be made.

Assuming:

- Average number of voids per day = 12
- Standard deviation of voids/day = 2 (ie. 97.5% of patients have 8 or more voids per day assuming a normally distributed population)
- Significant clinical improvement = decrease of 4 voids per 24 hours

Then, from S.J. Pocock (Pocock, 1983) (P128) :

$$n = 2\sigma^2 \frac{f(\alpha, \beta)}{(\mu 2 - \mu 1)^2} \quad (6.3)$$

Where,

n = number of patients on each treatment

σ = standard deviation of population 1,

μ2-μ1 = difference in means to be detected = δ

f(α,β) = 13.0 (for type I and type II errors both equal to 0.05))

The formula calculated that the number of participants required in each arm is seven. However, to allow for dropout and participants non-compliance the plan was to recruit 12 participants into each arm.

6.2.10. **Data Analyses**

Friedman test (a non-parametric version of a one way ANOVA) was used to compare the changes in frequency, urgency, incontinence and nocturia between the assessments. The resultant findings will be indicated by confidence intervals (Lee et al., 2014).

Any other statistical testes used are defined in the result section.

Participants who satisfactorily completed fewer than 80% (22 out of 28 or fewer) of the sessions (as determined by the stimulator log) were excluded from the analyses.

6.2.11. **Responders**

The responder was defined as a participant who decreased their number of micturitions and/or urgency episodes by at least 30% and responded to the PPCBC question as improved slightly or improved a lot. This definition combined the objective assessment of the symptoms as measured by the bladder diary and the participant's subjective perception of change in their symptoms. Such combination should give a better overview of the changes, because sometimes the participants might have only perceived a non-demonstrable change in their symptoms or the change in the bladder diary was not clinically important for the participant.

6.3. **Results**

Altogether 22 participants commenced the treatment protocol. One participant (randomised to bilateral stimulation) withdrew from the study after 4 sessions of stimulation. The reason was related to nightmares, feeling dizzy and hangover in the mornings since he commenced the stimulation technique. It was thought that these were not directly related to the stimulation as they were not experienced by other participants and have not been reported in other TENS studies. Another two participants (one unilateral and one sham stimulation) did not follow the study protocol (both did not complete more than 50% of stimulation sessions, as recorded by the stimulator log, and one also significantly altered their fluid intake) and therefore were excluded from the further analyses. A total of 19 participants (9 men and 10 women) were included in the study analyses. Study flow diagram is shown in Figure 6.5.

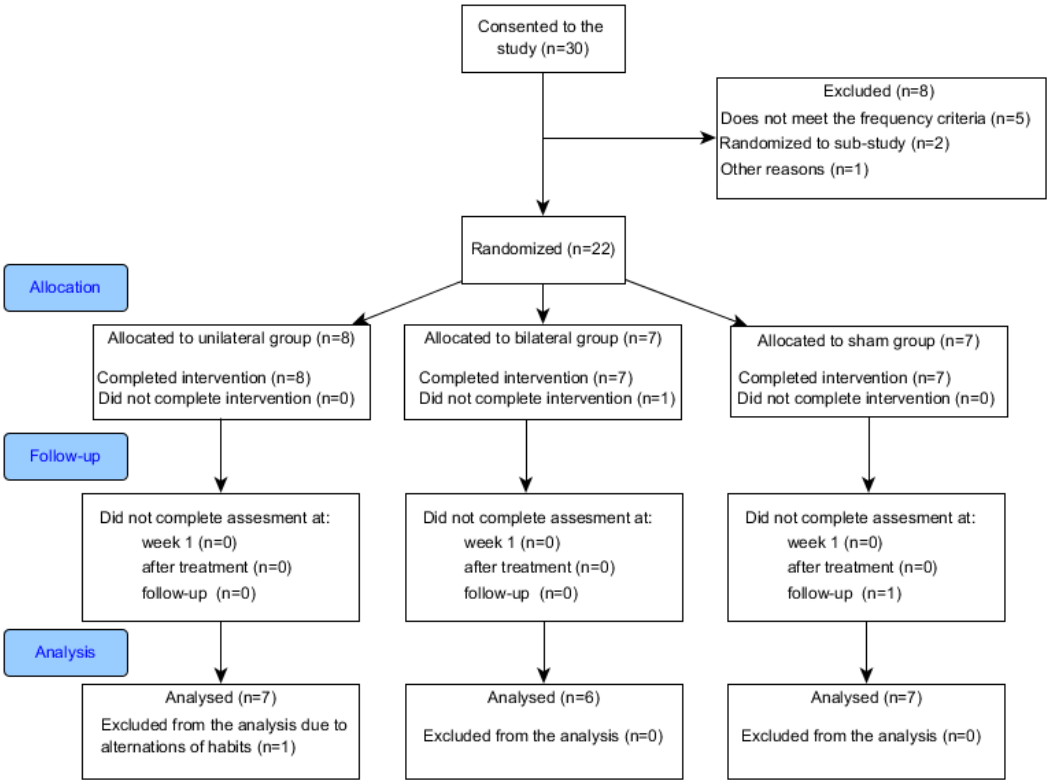


Figure 6.5 Study flow diagram

6.3.1. **Patient demographic**

The study randomization did not consider gender thus there is an unequal distribution of men and women in the unilateral and the sham stimulation groups (Table 6.2). The Kruskal-Wallis test showed no difference in age ($p = 0.973$) or the Body Mass Index (BMI) between the stimulation groups ($p = 0.532$).

Table 6.2 Demographic information about the study participants that completed the study

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Sex, n(%)			
Male	2	3	4
Female	5	3	2
Age			
Mean (SD)	58.9 (4.4)	57.5 (4.9)	59.5 (2.9)
Range	54 to 66	39 to 69	51 to 69
Race, n			
White	6	6	4
Asian	0	0	1
Black	1	0	1
Body Mass Index, kg/m^2			
Mean (SD)	30.8 (2.9)	27.2 (1.5)	26.2 (3.2)
Range	21.5 to 42.2	21.4 to 30.3	16.5 to 40.1

A summary of the participants' symptoms as they were recorded in the baseline bladder diary is shown in Table 6.3. All participants presented with a frequency of at least 8 voids per 24 hours. Two participants in each of the stimulation groups had more than 15 voids per 24 hours. Urgency (at least two episodes per 24h) was present in all participants, except one in the bilateral stimulation group who was affected by frequent micturition (~12voids per 24h). Urgency incontinence was presented in 42% (8/19) participants, and 79% (15/19) had nocturia (more than one night time void). 73% (14/19) of participants presented with more than 33% of their urine volume produced during the night time (nocturia polyuria). This was unequally distributed between the groups and was less prevalent in the sham stimulation group (Table 6.3).

All participants had failed at least one antimuscarinic drug before entering the study. The majority of the participants had tried a variety of the antimuscarinic drugs available but, due to lack of efficacy or intolerance to side effects, decided to discontinue them. 63% (12/19) participants were on a stable dose of either an antimuscarinic (8/19) or ß3 antagonist (Mirabegron, Astellas) (3/19) drug throughout their study involvement.

Some participants who had previously tried a ß3 antagonist drug were offered Mirabegron after the trial or counselled for consideration of Botulinum Toxin A bladder injection therapy.

Table 6.3 No of. participants presenting with various symptoms of overactive bladder symptoms, nocturia polyuria and type of medications taken throughout the study

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Symptoms of OAB baseline			
Frequency <15 voids / 24h	5	4	4
Frequency >15 voids / 24h	2	2	2
Urgency	7	5	6
Urgency incontinence	4	2	2
Nocturia	5	5	5
Nocturia polyuria	6	6	2
Study OAB medications			
Antimuscarinics	4	3	1
β3 antagonist	1	1	1

6.3.2. **Compliance with the treatment protocol and stimulation current used**

Two participants, who were not included in the analyses, claimed daily usage of the stimulation technique, but underwent only 13/28 (sham stimulation group) and 14/28 (unilateral stimulation group) sessions respectively. Both stimulators' internal logs were checked upon return for correct operation of recording. The non-compliant, sham stimulation participant did not adhere to the protocol as the frequency of usage stimulation dropped down significantly towards the end of the treatment period, this was probably due to lack of efficacy. The participant using unilateral stimulation reported a problem with forgetting things, which presumably contributed to their low compliance.

The rest of the participants adhered well to the protocol (Table 6.4). Some of the participants underwent more than the prescribed maximum of 28 sessions. This was due to their last study visit (return of the stimulator) being arranged later than 28 days and them not following the guidance to stop the stimulation after four weeks.

The stimulation current used was similar in both active stimulation groups, but approximately 50% lower in the sham stimulation group, probably because of the greater superficial musculature at the shoulder.

The participants in the active stimulation groups were instructed to increase the intensity until a visible motor contraction of the toes was observed and then to decrease the stimulation intensity to just below that. However only 5/13 participants were able to demonstrate this at the first treatment session. This was due to the discomfort they

perceived by the stimulation below the motor contraction. The rest of the participants 8/13 instead described a significant referred sensation in toes and/or sole of the foot, which suggested that the tibial nerve is being targeted.

The correlation between the treatment efficacy and the visible motor contractions observed is further assessed in Section 6.4.5.

Table 6.4 No. of stimulation sessions performed by participants and stimulation current used

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Sessions			
Mean (SD)	27.9 (2.5)	27.5 (4.0)	26.5 (2.1)
Range	25 to 33	23 to 34	24 to 29
Stimulation current used [mA]			
Mean (SD)	35.4 (14.0)	30.3 (12.7)	17.7 (8.2)
Range	16 to 60	16 to 50	10 to 33
Motor contraction			
Was able to obtain	3	2	6
Was not able to obtain	3	4	0
No information	1	-	-

6.3.3. **Efficacy - Primary outcomes**

Mean number of micturition per 24h

The primary outcome, the mean number of micturitions per 24h, in each of the assessments is summarised in the Table 6.5. The only statistically significant difference was identified between the baseline and first week of assessment in the bilateral group. Figure 6.6 summarises graphically the change in the mean number of micturitions ± SEM and individual changes for each of the participants. The individual participant's values are in Appendix M.

Table 6.5 Mean number micrutions per 24h in each of the stimulation groups at each assessment

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Baseline			
Mean (SEM)	12.8 (2.3)	13.1 (1.9)	13.2 (1.0)
Range	8.3 to 26.0	8.3 to 21.7	9.0 to 16.0
First week			
Mean (SEM)	11.5 (1.5)	9.1 (0.8)*	11.7 (0.9)
Range	8.3 to 19.7	6.3 to 11.7	8.7 to 14.3
After the treatment			
Mean (SEM)	11.1 (1.3)	10.3 (0.7)	12.5 (1.5)
Range	7.7 to 17.0	7.0 to 12.3	8.3 to 18.7
Follow up			
Mean (SEM)	10.5 (1.1)	12.0 (2.1)	11.5 (0.9)
Range	7.3 to 15.3	7.3 to 22.0	8.7 to 15.0
P value Friedman Test	0.291	0.016*	0.414

SEM = standard error of mean, * Dunn's multiple comparisons test showed significance

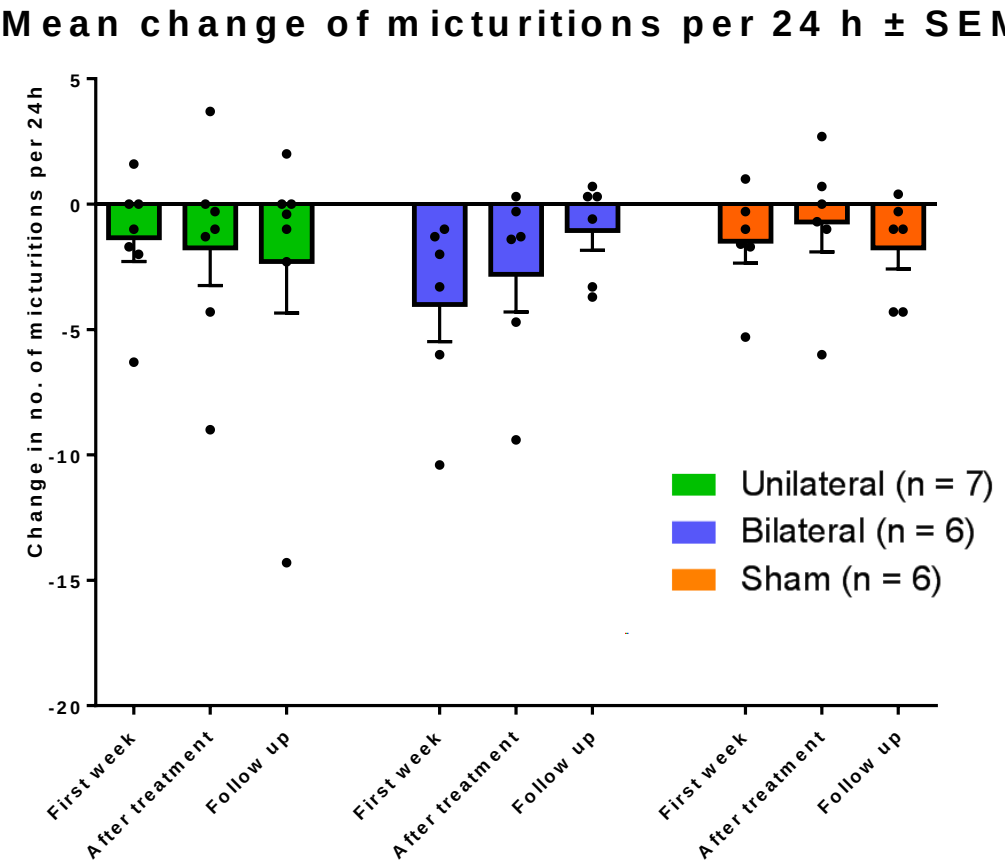


Figure 6.6 Mean change in number of micturitions including each participant measurements

After the first week of treatment the size of the decrease in unilateral and sham stimulation seems to be comparable (Table 6.5). Bilateral stimulation showed the largest, statistically significant, effects after the first week (95% CI relative to baseline, -7.8 to -0.1), but the effect lessened (95% CI relative to baseline, -6.6 to 1.0) after the treatment (not significant). Similarly the initial effect after the first week (95% CI relative to baseline, -3.7 to 0.7) in the sham stimulation group slightly lessened (95% CI relative to baseline, -3.7 to 2.3) after the treatment. The unilateral stimulation group showed similar effect in the first week (95% CI relative to baseline, -3.6 to 0.9) and after the treatment (95% CI relative to baseline, -5.4 to 1.9).

The differences after the treatment indicates larger effects in the active stimulation groups compared to sham stimulation. Unilateral stimulation decreased the mean number of micturitions by 1.0 more micturitions than sham stimulation (95% CI, -3.2 to 5.3). Bilateral stimulation showed a larger effect with a decrease of 2.1 micturitions compared to sham stimulation (95% CI, -2.1 to 6.3).

Although only slightly, the number of micturitions after follow up seemed to decrease even further in the unilateral and sham stimulation groups compared to after treatment values. However the bilateral stimulation group increased the number of micturitions in the follow up period by a mean of 1.7 (95% CI, -2.7 to 6.2).

6.3.3.1. **How much did the overall voided volume change?**

It is important to determine whether the change in the number of micturitions per 24 h can be attributed to the change in the voided volume per 24 h. The changes in the mean volume might not recognise changes in the fluid intake throughout the study assessments. Therefore these changes were studied on an individual basis and the participants who altered their fluid intake significantly were excluded from the analyses. These were the two participant who also did not follow the study treatment protocol as mentioned previously.

Participant #13 in the sham stimulation group was not included in the calculation of voided volume because information about the recorded volume was missing in over 50% of their bladder diary.

Overall the mean voided volume did not change significantly between each of the assessments (Table 6.6). The only trend in mean voided volume was showed in the sham stimulation group (decrease of 463 ml between the baseline and after treatment).

Table 6.6 Mean voided volumes per 24h in each of the groups

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Baseline			
Mean (SEM) [ml]	1571 (263)	1600 (142)	2323 (282)
Range [ml]	775 to 2647	1183 to 2020	1620 to 3317
First week			
Mean (SEM) [ml]	1780 (266)	1695 (270)	1971 (264)
Range [ml]	1130 to 2431	760 to 2740	1530 to 3000
After the treatment			
Mean (SEM) [ml]	1905 (202)	1788 (227)	1860 (305)
Range [ml]	1193 to 2917	1193 to 2502	1158 to 2767
Follow up			
Mean (SEM) [ml]	1848 (211)	1763 (182)	1807 (218)
Range [ml]	1193 to 2917	1193 to 2458	1378 to 2567
P value Friedman Test	0.324	0.459	0.066

Mean number of urgency episodes per 24h

The mean numbers of urgency episodes per 24h in each of the assessments are summarised in Table 6.7. Figure 6.7 summarises graphically the change in the mean number of urgency episodes ± SEM and individual changes for each of the participants. The individual participant's values are in Appendix M. The greatest effects, close to the significance level ($p = 0.068$), were observed in the bilateral stimulation group (Table 6.7).

Similarly, the mean number of micturitions per 24h and the number of urgency episodes seems to be more progressive in the active arms compared to sham stimulation. In particular, bilateral stimulation group showed a decrease of 2.5 more urgency episodes per 24hour in compare to sham stimulation (95% CI, -3.2 to 5.8).

Table 6.7 Mean number of urgency episodes per 24h in each of the stimulation

	Unilateral Stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham Stimulation (n = 6)
Baseline			
Mean (SEM)	8.9 (2.1)	7.5 (2.9)	8.6 (1.6)
Range	2.7 to 19.7	0 to 21.3	4.0 to 15.3
First week			
Mean (SEM)	7.2 (1.4)	3.8 (1.6)	6.8 (1.5)
Range	1.7 to 13.3	0 to 11.3	1.0 to 10.7
After the treatment			
Mean (SEM)	7.5 (1.8)	4.2 (1.1)	7.9 (2.0)
Range	0.7 to 15.0	0 to 8.7	1.3 to 15.7
Follow up			
Mean (SEM)	7.4 (1.9)	5.9 (3.1)	6.2 (1.5)
Range	1.0 to 15.3	0 to 20.7	0.7 to 11.7
P value Friedman Test	0.662	0.068	0.592

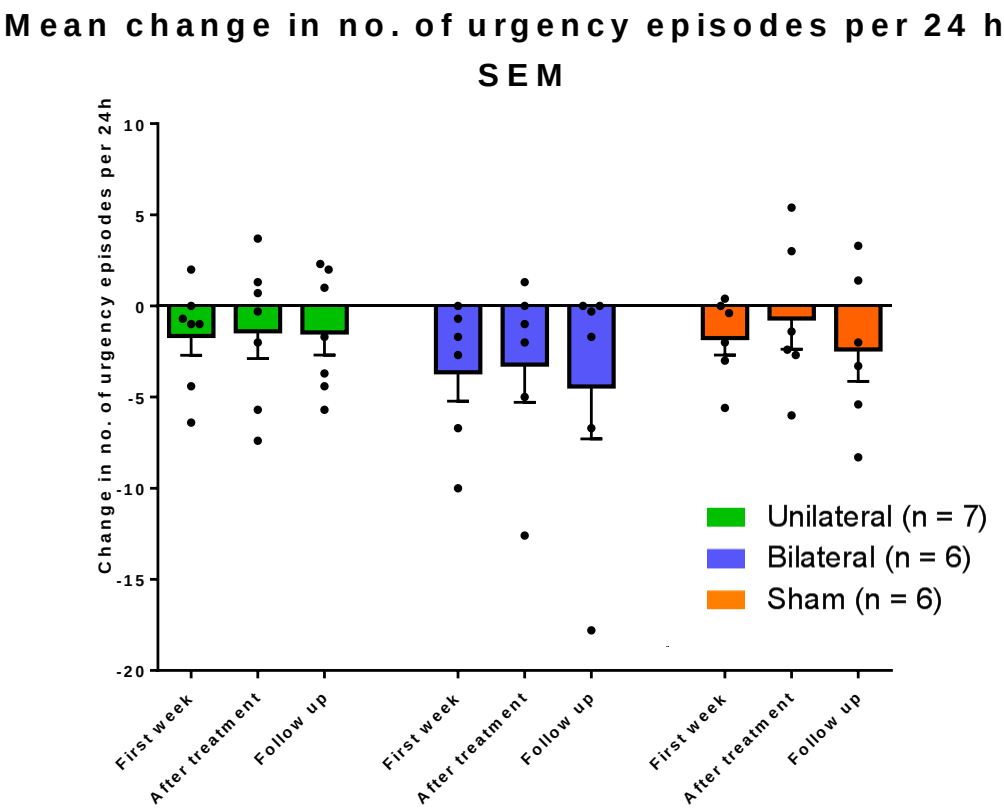


Figure 6.7 Mean change in number of urgency episodes including each participant's measurements

6.3.4. **Secondary outcomes**

Mean number of incontinence episodes per 24h

Incontinence, any unintentional leakage of urine, was presented in 52% (10/19) participants in the baseline. There were six incontinent patients in the unilateral stimulation group, two in the bilateral stimulation group and two in the sham stimulation group. The mean number of incontinence episodes is summarised in Table 6.8.

Table 6.8 Mean number of incontinence episodes per 24h in each of the stimulation groups

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham Stimulation (n = 6)
Baseline			
Mean (SEM)	2.7 (1.3)	2.5 (2.1)	0.7 (0.4)
Range	0 to 10.0	0 to 13.0	0 to 2.7
First week			
Mean (SEM)	1.5 (0.7)	0.8 (0.7)	0.2 (0.1)
Range	0 to 4.7	0 to 4.0	0 to 0.7
After the treatment			
Mean (SEM)	2.4 (1.5)	0.5 (0.3)	0.5 (0.3)
Range	0 to 11.3	0 to 1.7	0 to 1.7
Follow up			
Mean (SEM)	2.6 (1.6)	1.7 (1.5)	0.4 (0.2)
Range	0 to 12.0	0 to 9.7	0 to 1.0
P value Friedman Test	0.590	0.333	0.437

There was a slight decrease or no decrease in the participants of unilateral stimulation and sham stimulation groups. A dramatic decrease of incontinence episodes was observed only in one of the bilateral stimulation participants. This participant returned to baseline values at follow up (Figure 6.8, Appendix I). The individual participant's values are in Appendix I.

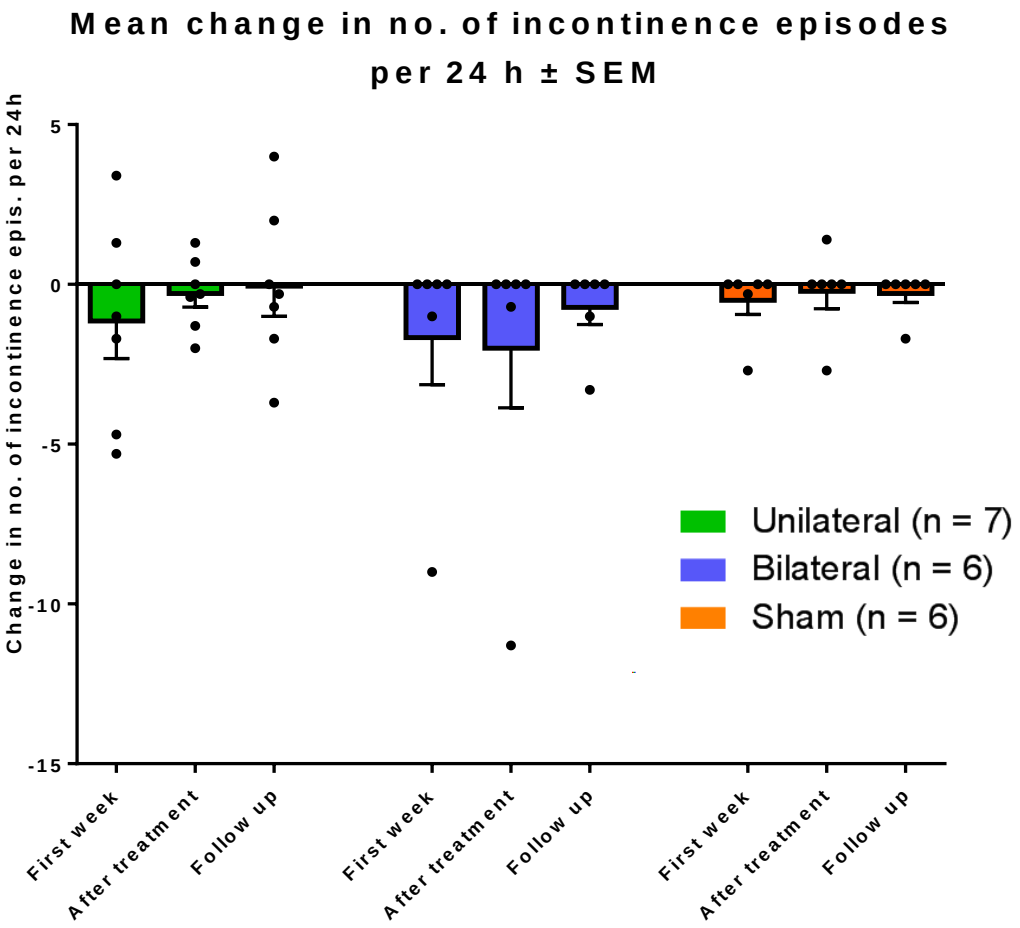


Figure 6.8 Mean change in number of incontinence episodes including each participant's measurements

Mean number of nocturia episodes

Nocturia episodes (a need to wake to pass urine at night) were presented in 89% (17/19) participants. This correlates with 73% (14/19) of participants who presented with more than 33% of urine volume produced during the night time (nocturia polyuria) in the baseline.

There was no statistical differences in the number of nocturia episodes nor in nocturnal polyuria (data not shown for brevity) between the assessment periods (Table 6.9). However all the groups (3/6 in bilateral, 3/6 in unilateral and 2/6 in sham stimulation group) showed individual changes (Table 6.12).

Table 6.9 Mean number of nocturia episodes per 24h in each of the stimulation groups

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Baseline			
Mean (SEM)	2.2 (0.6)	2.5 (0.5)	1.7 (0.4)
Range	0 to 4.7	1.0 to 4.3	0 to 2.7
First week			
Mean (SEM)	1.9 (0.7)	1.4 (0.4)	1.3 (0.3)
Range	0 to 4.7	0 to 2.7	0 to 2.0
After the treatment			
Mean (SEM)	2.3 (0.9)	1.8 (0.7)	1.3 (0.3)
Range	0 to 7.0	0 to 4.3	0 to 2.0
Follow up			
Mean (SEM)	2.3 (0.8)	2.2 (0.5)	1.3 (0.3)
Range	0.3 to 5.7	1.0 to 4.0	0 to 2.3
P value Friedman Test	0.540	0.554	0.310

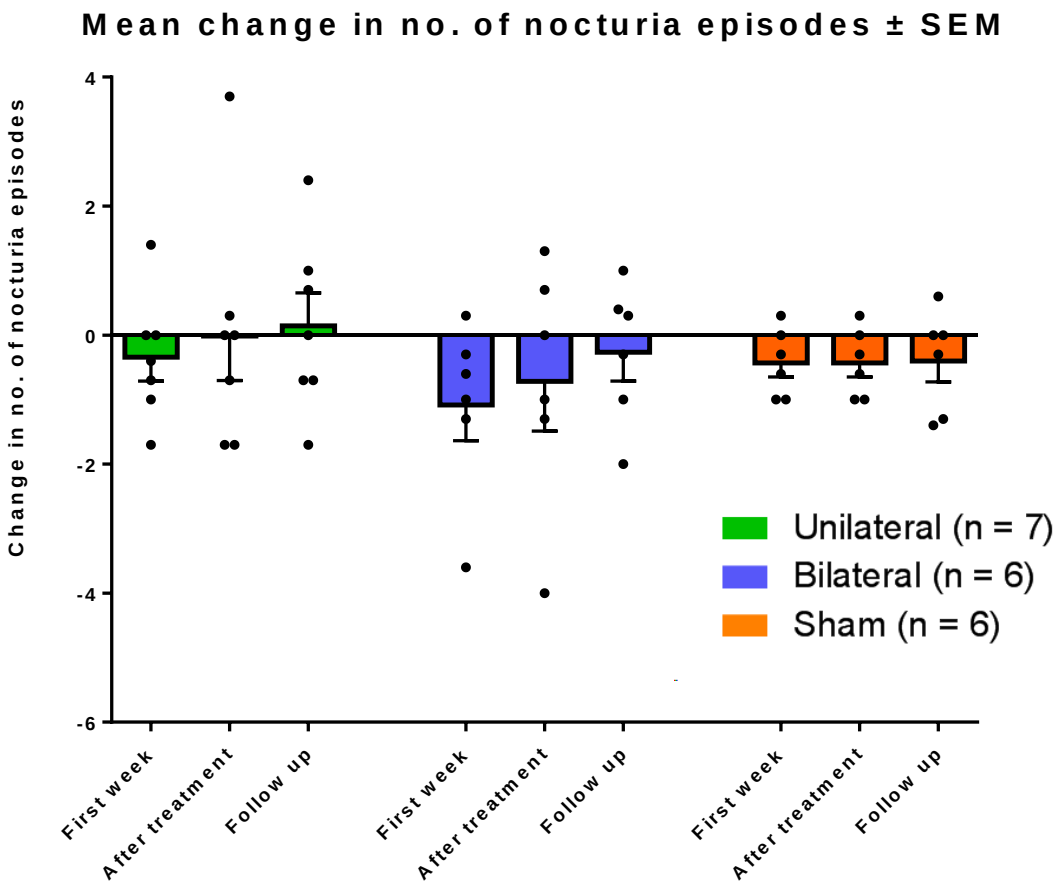


Figure 6.9 Mean change in number of nocturia episodes including each participant measurements

Questionnaires assessments

There was no missing data in the questionnaires from the 19 subjects analysed. The mean values for baseline scores suggests the unilateral stimulation group participants are the most affected by the OAB symptoms as shown in four of the five questionnaires (Table 6.10). The greatest changes were seen in the OAB-q Symptom bother and HRQL scores in the bilateral stimulation group. These changes reverted to baseline at the follow up assessment.

Table 6.10 Mean values of questionnaires

Mean (SEM)	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
PPBC			
Baseline	3.9 (0.3)	3.6 (0.5)	3.2 (0.2)
First week	3.6 (0.3)	3.2 (0.3)	3.2 (0.2)
After treatment	3.3 (0.3)	3.3 (0.2)	3.0 (0.0)
Follow up	3.6 (0.3)	3.3 (0.4)	3.1 (0.2)
OAB-q Symptom bother			
Baseline	58.6 (8.1)	51.1 (12.3)	47.2 (7.0)
After treatment	57.1 (8.2)	38.9 (3.7)	42.8 (3.2)
Follow up	54.3 (9.4)	52.2 (13.5)	41.1 (6.1)
OAB-q HRQL			
Baseline	53.3 (8.4)	40.0 (11.0)	59.2 (6.1)
After treatment	59.0 (7.1)	50.8 (8.3)	57.2 (3.5)
Follow up	56.3 (9.9)	40.0 (12.5)	62.6 (3.6)
ICIQ-OAB Score			
Baseline	11.4 (0.9)	9.2 (2.0)	8.8 (0.7)
After treatment	10.4 (1.0)	6.5 (1.3)	8.3 (0.8)
Follow up	10.6 (1.0)	8.2 (2.1)	8.3 (1.3)
ICIQ-OAB Bother score			
Baseline	28.0 (5.1)	20.8 (6.4)	25.0 (2.7)
After treatment	25.0 (4.7)	17.7 (6.2)	27.7 (2.3)
Follow up	22.7 (4.6)	18.3 (6.4)	25.0 (3.7)

Patient perception of change in their bladder condition (PPCBC)

Results of the PPCBC questionnaires are summarised in Table 6.11. The following text briefly summarises these findings and combined with face to face conversations between the investigators and the participants about treatment benefits.

Two participants in the unilateral stimulation linked their improvement to a decrease in number of voids and all three to the decrease in the intensity of urgency.

Altogether five participants in the bilateral stimulation group showed improvement on the PPCBC questionnaire at the after treatment assessment, although one of these participants did not report improvement at their third visit when interviewed about the study. Another participant of this group has reported improvement in voided volume (although this was not confirmed by the bladder diary assessment) and an intensity of urgency/level respectively.

One participant in the sham stimulation group responded as "improved slightly" which he described as greater control of his bladder.

Table 6.11 Responses of the participants to the Patient Perception of Change in Bladder Condition questionnaire. 'Got worse' is in comparison to their previous assessment

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
First week			
Got worse	0	0	0
Stayed the same	4	2	4
Improved slightly	3	4	2
Improved a lot	0	0	0
After treatment			
Got worse	0	0	0
Stayed the same	4	1	5
Improved slightly	3	4	1
Improved a lot	0	1	0
Follow up			
Got worse	1	2	1
Stayed the same	5	3	4
Improved slightly	1	1	1
Improved a lot	0	0	0

6.3.5. **Responders to the treatment**

The above reported findings indicate larger improvement effects in the active arms of the treatment compared to sham stimulation. Ideally, the effect of a treatment is shown by the number of responders. Therefore the overall outcome changes are summarised in Table 6.12. As previously described (Section 6.2.11), a responder is a participant who has decreased his/her number of micturitions and/or urgency episodes by at least 30% and responded to the PPCBC questions as improved slightly or improved a lot.

Altogether three participants were identified in the unilateral stimulation group, two in the bilateral stimulation group and one in the sham stimulation group. The following text describes these individual responders in more details in order to understand their symptom history, stimulation tolarencae and follow up:

Unilateral stimulation:

Participant #1, a 55-year-old woman, who could not tolerate an antimuscarinic drug due to side effects (dry mouth) and who partly responded to Mirabegron 50 mg (reduced amount of urgency) presented at baseline with 26 voids a day, accompanied one third of the time by urgency. A visible motor contraction of her toes was obtained at the first stimulation session, around 20 mA. This participant demonstrated a decrease in number of micturitions, urgency and incontinence episodes, which lasted for at least one month as demonstrated by the follow up assessment after the 4 weeks. The participant described the improvement better than that she had achieved from various drug therapies over several years of trialling. At follow up, the participant unexpectedly demonstrated even further improvement in symptoms. However, several months after the study, the participant was consulted at a regular clinical visit and had experienced symptoms again. She therefore decided to recommence the study treatment on her own, which in further clinic assessments led to significant improvement in her symptoms.

Participant #14 was a 66-year-old woman, who did respond to antimuscarinic drug and still continued to take a 10 mg dose of Solifenacin during the study. Her main symptoms presented at baseline were sudden urgency (which happened even if she had recently been to the toilet) often accompanied by a small leak. During the stimulation treatment period the participant was unable to obtain motor contraction of her toes due to sensation becoming a limiting factor even when alterations to the electrode position were made, however a significant referred sensation in her toes was noted. After the treatment period the participant's symptoms slightly improved, however an occasional leakage accompanied by urgency was still present. The participant reported a positive effect, but did not wish to consider continuation of the therapy beyond the duration of the study.

Participant #26, a 54-year-old man who could not tolerate any antimuscarinic drugs due to dry mouth presented at baseline with increased frequency (>15 voids a day) and nocturia (~5 voids a night) always accompanied by urgency. A visible motor contraction

of his toes was obtained at the first stimulation session accompanied by a referred sensation in his toes. After the stimulation the participant reported improvement in both urgency and frequency. He felt that he was able to control his bladder better. However the participant also speculated that the symptom improvement might be a combination of a recent weather change (it got warmer) and the stimulation. The participant asked for the details of the stimulation technique and wished to continue the therapy on his own after the study. His symptoms had returned to baseline at the one month follow up assessment.

Bilateral stimulation:

Participant #3, a 47-year-old woman who was on antimuscarinic therapy throughout the study, presented at baseline with severe frequency (>20 voids a day), accompanied always by urgency and half of the time with incontinence. The participant was not able to obtain motor contraction of her toes due to sensation being a limiting factor, however felt significant sensation around the electrodes and sole of the foot. The participant greatly improved in all OAB symptoms as demonstrated by the bladder diary and questionnaire assessments (Table 6.12). However this improvement returned to baseline after one month without stimulation. The participant wished to continue with the therapy on her own.

Participant #23, a 59-year-old man, was severely bothered by frequency, urgency and nocturia but no incontinence at baseline, and entered the study after failure of antimuscarinic drugs (not effective and with side effects). The participant was able to obtain motor contraction at the first session on one leg, but found it difficult to hunt for the motor threshold throughout the study. The participant pointed out that stimulation was uncomfortable. Nonetheless he perceived and demonstrated a reduction of day time voids and an increase in voided volume, suggesting an increase in bladder capacity. The participant was keen to continue with the therapy. The improvement seemed to continue at the follow up assessment as reported by the bladder diary, however the participant reported that his symptoms got worse.

Sham stimulation:

Participant #17, a 55-year-old male, was severely bothered by all OAB symptoms with urgency incontinence and urodynamically demonstrated detrusor overactivity, and

entered the study after no improvement with antimuscarinic drugs. The participant felt a slight improvement in bladder control, which translated into a great reduction of day time voids as demonstrated by bladder diary. This improvement did not last in the follow up assessment. The participant wished to continue with the therapy on his own, although there was no information whether he has at the time of writing this thesis.

Table 6.12 Overall outcome changes from the baseline to after treatment

Pt no.	Gender, age, BMI	Change at least by 30% from baseline in red				Change in the volume voided per 24h	Change in Max. voided volume	PPBC change by a grade	PPCBC	Improvement by at least 10% in red			
		Micturitions per 24h	Urgency per 24h	Incontinence 24h	Nocturia episodes					ICIQ OAB symptom score	ICIQ OAB Bother score	OABq symptom score	OABq HRQL score
Unilateral stimulation													
1	F55, 38.9	-9.0	0.7	-2.0	-1.7	-6%	+17%	↓	*	-6%	-10%	0%	-10%
5	F59, 42.2	-1.0	1.3	0.7	-0.7	22%	-20%	↓	-	-18%	-20%	0%	8%
14	F66, 30.0	-1.3	-2.0	-1.3	0.3	6%	+20%	↓	*	6%	10%	10%	2%
19	F63, 21.5	-0.3	-5.7	-0.4	-	10%	0%	-	-	0%	-15%	-16%	-3%
21	F59, 32.0	3.7	3.7	1.3	3.7	10%	0%	-		6%	0%	-3%	-20%
26	M54, 22.3	-4.3	-7.4	-0.3	-1.7	84%	+100%	↓	*	-12%	-5%	3%	-3%
27	M56, 28.5	0.0	-0.3	-	0.0	1%	0%	↓	-	-18%	-20%	-3%	-2%
Bilateral stimulation													
3	F47, 29.8	-9.4	-12.6	-11.3	-4.0	69%	+100%	↓↓	**	-29%	0%	-63%	-30%
11	F39, 28.1	-1.3	-2.0	-0.7	-1.3	-36%	-4%	-	*	-18%	-18%	-30%	-32%
12	M63, 21.4	0.3	-1.0	-	0.0	-2%	+15%	-	*	-6%	0%	7%	4%
23	M59, 30.3	-4.7	-5.0	-	0.7	-7%	+47%	-	*	-29%	-45%	-6%	-8%
25	F69,23.6	-1.4	0.0	-	1.3	10%	0%	-	-	0%	3%	3%	3%
29	M68, 29.7	-0.3	1.3	-	-1.0	-5%	11%	↓↓	*	-12%	-18%	16%	-2%
Sham stimulation													
13	M69, 24.0	2.7	5.4	-	-1.0	3%	0%	-	-	0%	3%	7%	3%
15	F68, 16.5	0.0	-2.7	-	-1.0	-10%	+20%	-	-	-6%	8%	-3%	8%
16	F68, 45.6	-1.0	3.0	-2.7	0.3	1%	-14%	-	-	-12%	10%	0%	0%
17	M55, 40.1	-6.0	-6.0	0.0	-0.6	-37%	-13%	↓	*	-6%	5%	-26%	-20%
22	M51, 29.0	-0.7	-2.4	-	-	-10%	-20%	-	-	0%	10%	7%	22%
28	M56, 25.0	0.7	-1.4	-	-0.3	-16%	+38%	-	-	6%	5%	-10%	0%

↓ improvement by one grade, ↓↓ improvement by two grades, *improve slightly, **improved a lot

6.3.6. **Responders changes in the first week and follow up assessments**

The following analyses only include those participants who have been classed as responders at the end of the treatment period (Table 6.13). Almost all responders perceived an improvement of the symptoms after the first week of the therapy, except participant #23 who demonstrated an improvement only as measured by bladder diary.

The majority of the participants got worse after the one month without treatment thus demonstrating no obvious carry over effect. Interestingly Participant #1 has further improved the symptoms.

Table 6.13 responders changes in the first week and follow up assessments

Pt	First week - baseline			Follow up – after treatment		
	Micturitions per 24h	Urgency per 24h	PPCBC	Micturitions per 24h	Urgency per 24h	PPCBC
Pt1	-6.3	-0.7	improved	-5.3	-4.4	improved
Pt14	-1.0	-1.0	improved	+1.3	+0.3	stayed
Pt26	-2.0	-6.4	improved	+4.3	+3.0	got worse
Pt3	-10.4	-10.0	improved	+8.3	+12.0	got worse
Pt23	-6.0	-6.7	stayed	+1.4	-1.7	got worse
Pt17	-5.3	-5.6	improved	+1.7	-2.3	got worse

6.3.7. **Autonomic nervous system response test**

The autonomic nerve system response test (described in Section 6.1.5 and 6.2.8) was conducted in 15/19 participants at baseline and in 14/19 participants after the treatment (Table 6.14). No readings were obtained in three and four participants respectively, which led to their exclusion from the analyses. This was due to a technical problem with the equipment. One participant was excluded from the test due to their blood pressure being high (the test exclusion criteria, >160/100mmHg) before exercise.

6/15 participants who conducted the test were taking hypertension medication during the study.

Means of mean arterial pressure (MAP, defined as systolic pressure plus one third of diastolic pressure) increase significantly between baseline and after three minutes

(Friedman test, Dunn's Multiple Comparison) in all groups at baseline (Table 6.15) and after the treatment except in the bilateral group after the treatment (Table 6.16, $p < 0.056$).

Similarly, means of diastolic blood pressure increase significantly between baseline and after three minutes except the bilateral stimulation at baseline and after treatment tests, and in the unilateral stimulation group after the treatment test.

Table 6.14 Number of participants who took the part in the autonomic nerve system response test at baseline and after treatment

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)
Baseline test			
Conducted	5	4	6
Not-conducted	2	2	0
After treatment test			
Conducted	4	4	6
Not conducted	3	2	0
Hypertension medication in participants for whom the test was conducted	3	1	2

Table 6.15 Means (SEM) of mean arterial and diastolic blood pressure as measured at baseline

	Baseline	After 1 minute	After 2 minutes	After 3 minutes	Post
Unilateral					
Mean BP	98 (4)	104 (4)	105 (4)	111 (7)	97 (4)
Diastolic BP	82 (3)	88 (3)	87 (2)	95 (7)	81 (4)
Bilateral					
Mean BP	93 (7)	97 (6)	96 (7)	104 (5)	88 (0.9)
Diastolic BP	74 (7)	79 (6)	78 (8)	82 (2)	72 (3)
Sham					
Mean BP	96 (3)	107 (5)	110 (4)	116 (6)	96 (3)
Diastolic BP	77 (3)	85 (6)	89 (6)	91 (7)	77 (3)
Total					
Mean BP	95 (2)	102 (3)	105 (3)	111 (4)	100 (5)
Diastolic BP	78 (2)	83 (3)	86 (3)	91 (4)	85 (7)

Table 6.16 Means (SEM) of mean arterial and diastolic blood pressure as measured after the treatment

	Baseline	After 1 minute	After 2 minutes	After 3 minutes	Post
Unilateral					
Mean BP	90 (6)	96 (4)	99 (6)	101 (7)	94 (7)
Diastolic BP	75 (5)	79 (4)	82 (4)	83 (5)	77 (4)
Bilateral					
Mean BP	90 (5)	95 (8)	98 (6)	103 (10)	90 (6)
Diastolic BP	71 (5)	77 (7)	78 (5)	82 (8)	71 (4)
Sham					
Mean BP	94 (5)	109 (8)	114 (6)	123 (8)	100 (6)
Diastolic BP	77 (4)	94 (10)	95 (9)	105 (11)	85 (9)
Total					
Mean BP	91 (3)	101 (4)	105 (4)	111 (5)	95 (3)
Diastolic BP	75 (3)	84 (5)	87 (5)	92 (6)	78 (4)

The number of participants who were considered as positive (no autonomic nerve system dysfunction, diastolic blood pressure increased by more than 10 mmHg) is shown in Table 6.17. Unfortunately, 3 out of 5 participants who were considered as responders for the treatment in the active arms did not complete the test and thus correlation with the treatment response in relation to the test results was not possible. In the other two participants one completed the test as positive (Participant #14) and one as negative (Participant #26, blood pressure did not increase by more than 10 mmHg).

It has been noted that the hypertension drug might supress the rise in the blood pressure and therefore the test would be negative (2/5 who were scored a negative test results were taking hypertension medication throughout the study). In comparison to the positive test results where 3/10 were taking hypertension medication. The Fisher's exact test did not show that hypertension drug was the cause of negative test results ($p = 1.0$, relative risk = 1.167), however in such a small sample size the significance level ($p>0.05$) will be achieved only if 5/5 who scored a negative test results would be taking hypertension medication. Further, a negative score on the test might be linked to some participants relaxing briefly during the supposedly continuous squeeze as those have not been excluded from the analyses.

The number of participants who obtained positive or negative test results in comparison between baseline and after the treatment tests differed (Participant #14 did not performed the test after the treatment, Participant #25 in bilateral stimulation changed to a negative

results, Participant #13 and Participant #16 in sham stimulation group change to positive results, Table 6.17).

Table 6.17 Number of participants considered as positive or negative responders

	Unilateral stimulation (n = 7)	Bilateral stimulation (n = 6)	Sham stimulation (n = 6)	All groups
Baseline test				
Positive	3	3	4	10
Negative	2	1	2	5
Diastolic BP change [mmHg]	+13 (5)	+8 (6)	+14 (5)	+12 (3)
After treatment test				
Positive	2	2	6	10
Negative	2	2	0	4
Diastolic BP change [mmHg]	+8 (2)	+11 (4)	+28 (11)	+17 (5)

6.3.8. **Cost implications**

Any new treatment option considered for adoption into clinical practice needs to be analysed for cost effectiveness and compared to therapies currently available. Recently a cost-effectiveness study of sacral nerve stimulation (SNS) for the refractory overactive bladder (wet) patients indicated a long term cost-effectiveness of the technique (Walleser Autiero et al., 2014). Based on this report, a greatly simplified analysis for the refractory overactive patients can be made for a duration of five years of ongoing treatment (Table 6.18). The success rate of self-administered transcutaneous PTNS has been assumed to be that of percutaneous PTNS. This rate is an estimate because there is a lack of long-term data for both PTNS therapies. However the relative costs are so much in favour of transcutaneous PTNS that even if this estimate was significantly overoptimistic it would not alter the conclusions of this analysis.

Table 6.18 Treatment success rates and cost taken from (Walleser Autiero et al., 2014) and estimates for transcutaneous PTNS

	Costs	Success rate
Self-administer transcutaneous PTNS	£305*	19%
Percutaneous PTNS	£16205	19%
Repeated BoNT-A	£12450	59%
SNS	£28850	75%

* *calculated as 1hour Nursing time £70,1x Stimulator £50, 25x Electrodes sets /batteries £175*

Although the success in a 5 year projection might be relatively low, the self –administered transcutaneous PTNS thus appears to be a fraction of the cost of all other alternative therapies.

The responders in this study perceived and demonstrated the initial benefit in the first week of the treatment. Therefore, if the technique will be considered for adoption into clinical practice, the initial cost of trialling the therapy in an individual subject is estimated to be one hour of nursing time (£70) for training and a set of electrodes (£5), which is similar to the cost of medication for two months (BNF, 2015b, BNF, 2015a).

6.4. **Discussion**

This pilot study demonstrates that there are individual patients who may benefit from this non-invasive approach of posterior tibial nerve stimulation technique. Although the effects do not seem to be large, they are comparable to the success rates observed in the latest OAB drug trials (Khullar et al., 2013) where typically mean number of micturitions episodes decrease by 1.9 (CI 95%, 2.2 to 1.7) voids per 24h. Furthermore, the non-invasive stimulation has no significant side effects, is low cost and easy to administer, and hence may potentially offer an additional treatment option for patients with OAB symptoms. The following sections discuss the findings and challenges of this trial in order to help future work in this field.

6.4.1. **Study participants**

The study was focused on idiopathic overactive bladder symptoms patients.

As this pilot trial implemented various recruitment pathways (urology outpatient, continence community centres, advertisement) there was variety in the history details of the patient's symptoms, which led to challenges concerning their eligibility for the study.

For example: the inclusion criteria “Failure on primary OAB treatment, such as behaviour modification or fluid/diet management”. One of the patients who was excluded from the analyses, had presented with the idiopathic OAB symptoms and mean of 5.4 l of voided volume per 24h in the baseline. This high volume is indicative of excess fluid intake but the patient has regarded this to be normal and has never been informed that this might be a potential cause of the symptoms, although they had tried several medications. Other challenges often related to a definition of clinically significant bladder outlet obstruction and post void residual volume. The post residual volume was defined to be excessive over 100 ml. However it has been perceived that the voided volume should be considered in order to normalise this to the total volume voided and the participant should have their bladder full before the voiding.

Clearly a more specified and standardised way of assessing the patient would be desirable for future studies. However, the diversity of the patients’ symptoms might then lead to a significant limitation of recruitment rate.

6.4.2. **Methodology of the study**

In studies where participants self-administer a clinical trial treatment it is important to monitor their compliance. The choice of the stimulator allowed us to monitor this and the data demonstrated generally good compliance by the participants (Table 6.4). Those patients who did not comply with the study protocol were excluded from the analyses, although the reduced number of sessions of stimulation they did use might have had a beneficial effect.

One of the uncertainties of transcutaneous PTNS is the intensity of stimulation needed in order to achieve an effect. The percutaneous form of PTNS aims to stimulate the tibial nerve by inserting a stimulation needle close to the nerve. The method is then to adjust the intensity such that a visible motor contraction of the toes is seen. Transcutaneous stimulation targets more cutaneous nerve structures which, because of the resultant sensation, may limit the intensity to a level below that needed to penetrate to deeper structures. Some participants were not able to achieve the motor contraction of toes due to this sensation and thus the stimulation intensity may have been inadequate if the posterior tibial nerve is the putative target. Nonetheless, all of the participants perceived a strong sensation in their toes and/or sole of their feet, which suggests that the nerve was

being at least partially stimulated. This is consistent with the experience of percutaneous PTNS at Gastrointestinal Investigation Unit of Sheffield Teaching Hospitals (conversation with Lynne Smith – Clinical Manager) who use percutaneous form of PTNS for the treatment of faecal and urinary incontinence. It was observed that a visible motor contraction is not able to be achieved in all of the patients even if the needle is repositioned. However a strong sensation in patient's toes and/or sole of their feet is always present and desirable. In the context of effectiveness in this trial, only two of the participants (out of five who were considered as responders) were able to obtain the motor contraction of toes which suggests that motor contraction may not be essential as long as a significant referred sensation is produced. If the stimulation current and local sensation below the electrodes would be a limiting factor than a reverse position of the electrode (cathode below and anode above medial malleolus) might be used, as shown in numerical model in Chapter 5.

Further to the methodology of this trial, in many sham-controlled studies the effectiveness of the blinding of the participants is evaluated by asking participants which arm they think they were allocated to. However, this was not possible in the context of this study, due to the fact that the participants were not informed that one of the study arms would be viewed as sham stimulation.

6.4.3. **Stimulation current in numerical modelling**

The mean stimulation current in the PESTOB clinical trial was 35.4 ± 14.0 mA (mean ± SD) for unilateral stimulation group and slightly lower current of 30.3 ± 12.7 mA (mean ± SD) for the bilateral stimulation group. The numerical modelling showed that approximately half of this stimulation current is needed in order to achieve the same physiological effect. Although these values compare the theoretical calculations and experimental values, the difference might be explained by presumably larger layer of subcutaneous fat in this study population in compare to the virtual model used in Chapter 5. The Virtual Population model "Duke" used in this work was a 34-year-old male adult with BMI of 23.1 kg/m^2 in compare to clinical trial population which was the mean BMI of 30.8 kg/m^2 in the unilateral stimulation group and 27.2 kg/m^2 in the bilateral stimulation group.

6.4.4. **Autonomic nervous system response test**

As proposed previously, a negative result in the hand grip exercise test may show an autonomic nervous system dysfunction and thus explain idiopathic overactive bladder symptoms in this group of patients (Hubeaux et al., 2011). The findings of study presented here looks similar to findings in (Hubeaux et al., 2011). However, when both tests (baseline and after treatment) are combined, there was 9/29 negative tests, which may in four cases be explained by a concomitant hypertension medication, thus suppressing the blood pressure increase; in two cases participants did not squeeze the dynamometer continuously (they briefly relaxed their grip during the 3 minute squeeze period) and one to impaired heart rate variability (as communicated by the participant during the study). It is not clear if the second was considered as an exclusion criterion by (Hubeaux et al., 2011).

This study did not include a control group as in the previous study, where all control participants scored the test as positive (Hubeaux et al., 2011). Although, their study has excluded cardiovascular or hypertensive diseases in both groups it was assumed that the same methodology of this study allow to use the Hubeaux et al study results in the context of his study.

Unfortunately the autonomic nervous system response data have not been collected in 3/5 responders in the active arms (due to a technical problem with the equipment) and thus it was not possible to investigate the correlation between the result of the test and symptom change. In the context of the previous explanation of negative results of tests (e.g. hypertension drug, non continues squeeze of dynamometer), overall in this study, there was just one participant who might have an autonomic nervous system dysfunction, as indicated by a hand grip test. This participant was considered as a responder to the treatment.

Further investigation with a control group and a larger study is required to draw any conclusion as to whether overactive bladder symptoms might be related to autonomic nervous system dysfunction.

6.4.5. **Stimulation effects**

The primary outcomes of the study (mean change of micturitions and urgency episodes per 24 hours) show larger effects in the active stimulation groups compared to the sham stimulation group. In particular, the bilateral stimulation showed larger effects in the number of micturitions and urgency episodes. These findings were also confirmed by a number of responders (5/13 in active arms vs. 1/6 in the sham stimulation). Interestingly the larger effects in number of micturitions and urgency episodes in the bilateral than in unilateral stimulation group were not presented in the number of responders (two in bilateral and three in unilateral stimulation groups). This can be explained by the fact that the mean change of micturitions or confidence intervals in such a small group sample size is sensitive to small changes, which may not reflect a true change of the symptom. For example, the bilateral stimulation group non-responder participants #11 and #25 demonstrated a reduction of ~1.3 micturitions per 24h but did not perceive any overall benefit, whereas unilateral stimulation group participant #21 increased by ~3.7 micturitions per 24h (Table 5.14) and thus changed the overall group outcome values. This reflects the importance of determining clinically important changes, which this pilot trial has effectively covered by its definition of responders.

It is perhaps noteworthy that five of the six participants who presented with a larger mean number of micturitions per 24h (>15voids) are responders (2/2 in the unilateral, 2/2 in the bilateral, 1/2 in the sham stimulation group). The only other responder in the bilateral stimulation group perceived improvement only in urgency, however this participant only presented with a mean of 9.3 micturitions per 24 h in the baseline and frequency was not his most bothersome symptom. The majority of the responders (2/3 in the unilateral, 2/2 in the bilateral) were on a stable dose of OAB medications throughout the study and the sham stimulation responder did not take any OAB medication. These effects are not linked into the changes in the overall voided volume, although the responder in the sham stimulation group reduced the mean voided volume per 24 h by approximately one third compared to baseline.

It can be argued that the primary outcome of the study (a change in the mean number of micturitions or urgency episodes per 24 h) might not be sensitive enough to capture a small change in the participants who presented with a low number of micturitions/episodes in the baseline. Other changes (not considered in the definition of

responders) where related to the intensity of urgency perceived, however it will be challenging to quantify these.

Nocturia episode changes corresponded to the changes observed in 24 h micturitions. Similarly the incontinence episodes only improved in responders. Changes in the ICIQ-OAB and OABq questionnaires were not statistically significant and although improvement of at least 10% was noted in some responders, this was not consistent across the group.

In conclusion, this pilot trial demonstrates that there are patients who may benefit from this non-invasive type of therapy, which shows similar results to those obtained in percutaneous PTNS using a needle electrode (Peters et al., 2010). However, the technique presented here is completely non-invasive, can be self-administered by the patient at home and is thus low cost. Although the effects do not seem to be large they, if confirmed by a larger study, could be comparable to the success rates observed in the latest OAB drug trials (Khullar et al., 2013).

Furthermore, this non-invasive stimulation has no significant side effects and hence may potentially offer a useful additional treatment option for these patients. Participants in this trial had severe OAB symptoms despite numerous drug therapies and would usually be offered more invasive treatments such as Botolinium Toxin injections or sacral neuromodulation in order to manage their symptoms. Therefore TPNTS may be seen as an attractive alternative, particularly for those who are either unwilling to perform intermittent self catheterisation or unfit to undergo operative management. Further potential ways forward are discussed in the next chapter.

Chapter 7 **Summary**

7.1. **Summary**

This thesis investigates techniques of transcutaneous electrical nerve stimulation with a specific focus on the treatment of overactive bladder. The thesis starts with an overview of the current usage of transcutaneous techniques to treat overactive bladder. The current consensus is that the most promising target for stimulation is the S3 area of the spinal cord, accessed either via stimulation over the sacral region or over the posterior tibial nerve. However, it is not clear which approach to stimulus delivery is the most effective. Little is known about the underlying mechanisms of action and which exact structures need to be stimulated. Furthermore, there are also several gaps in the literature. These mainly include: what is the placebo effect of transcutaneous techniques; what is the carry-over effect of these techniques; what is the optimum length, frequency and duration of the treatment session; what are the optimum parameters for the stimuli settings (pulse width, frequency, intensity); is bilateral PTNS more beneficial than unilateral; and what is the optimal electrode position in sacral dermatome stimulation?

The standardization and evaluation of various parameters of stimuli would be beneficial in order to optimize the techniques used and to achieve maximal effectiveness. However, a clinical evaluation of all these parameters would be both costly and time consuming. Therefore considerable effort was made in this thesis to find a suitable surrogate measure that would enable the various stimulation parameters to be evaluated quickly. Based on the previous research in this area, the Hoffman reflex (H reflex) was identified as a suitable candidate. Specifically, H reflex magnitude measurements were assessed as a potential measure of bladder nerve activity and thus of the subjective symptoms of urgency in overactive bladder patients, and hence as a surrogate measure. Unfortunately, the results of the study presented in this thesis showed that other actions related to bladder control mechanisms also influence the H reflex magnitude, as shown during the pelvic floor muscle study exercises in healthy volunteers. These results are new findings and do not support the previous conclusions that the H reflex would be a useful surrogate measure. Previous claims about its usefulness for observing modulation of bladder nerve activity need to be clarified in relation to these findings. Further work to find a suitable surrogate measure was not carried out during this thesis because the literature did not support any obvious and practical alternative avenues of investigation. Although animal models have their limitations, recently new approaches have been explored which might be suitable, but currently these were beyond the scope of this project (Brink et al., 2015).

The evidence for TENS effects in the treatment of overactive bladder remains limited. Despite the lack of clarity with regard to the stimulus parameters, it has been hypothesized that the lack of major effects may be due to a decrease in response following repeated exposure to the same stimulus. Therefore a stimulus methodology which produces more variable stimulation, both temporally and spatially, was developed and investigated. The stimulus methodology incorporated two features; large (in terms of targeted area) sensory stimulation combined with a spatial-temporal pattern of stimuli designed to enhance attention to the stimuli. This concept was named Sensory Barrage Stimulation. The technique was developed and delivered using a 64 channel stimulator, ShefStim, previously used for foot drop therapy. Firstly the salience and habituation study aimed to evaluate the stimulation pattern feature using measurements of performance during cognitive tasks, but no significant evidence for this claim was produced. Nonetheless the spatial-temporal patterns used in this study demonstrated that the sensation was distinguishable and unique for each pattern. Thus it was possible to develop a suitable pattern of sensation to evaluate this technique in an alternative therapy model, namely patients with elbow spasticity. The pattern was designed such that it mimics stroking. Stroking was previously reported to be beneficial in muscle relaxation. The resultant pilot clinical trial demonstrated the feasibility and practicality of using SBS on patients at the clinical setting and showed a higher efficacy response compared to conventional TENS stimuli assessed by the numbers of responders on these elbow spasticity patients. Home based application of this type of therapy would be a desirable approach and further development should continue with that direction.

The pundendal nerve has been considered as another target for the treatment of overactive bladder symptoms (Bartley et al., 2013). This nerve originates from the S2, S3 and S4 sacral nerve roots. It is thought to be a superior alternative to sacral neuromodulation (Peters et al., 2005). As the pudendal nerve is relatively deep in the body, covered by overlying tissue, implanted wire electrodes (as in sacral neuromodulation) were used. It is difficult to target these deep branches non-invasively. Recently however, a novel stimulation technique using a ‘transdermal amplitude modulated signal’ (TAMS) was introduced for this purpose. This TAMS waveform has been described (Shen et al., 2011) as ‘a high frequency sinusoidal carrier waveform (210 kHz) amplitude-modulated by low frequency, monophasic rectangular pulses (1ms pulse width)’. Preclinical studies have evaluated the effect of TAMS stimuli of the pudendal nerve on the bladder in cat models

(Shen et al., 2011, Tai et al., 2011, Tai et al., 2012). This latter paper reported that 'TAMS uses a 210 kHz sinusoidal carrier waveform that has a minimal skin impedance and is optimal for stimulating nerves under skin and muscle' (Tai et al., 2012). However, there was no literature to support this statement, based on comparative human studies. If a particular electrical stimulation waveform is more effective in stimulating deep nerve structures such as the pudendal nerve, this would have major implications for the whole field of non-invasive electrical stimulation. This claim was evaluated in this thesis and no significance difference between a conventional stimulation waveform and TAMS waveform were shown when comparing skin impedance and a variety of other relevant electrical parameters.

The last two chapters of this thesis cover the stimulation of the posterior tibial nerve using a transcutaneous form of stimulation. In comparison to the more established and commercially available percutaneous technique, this has the advantages of being completely non-invasive, low cost and performable by the patients at home. The numerical model used here showed that the same physiological effect (assessed by the activating function) can be achieved for both transcutaneous and percutaneous techniques. The model has enabled an estimate to be made of the relative currents that are needed in the two methods. However, it should be noted that the position of stimulation along the nerve is somewhat different for the electrode montages considered and that the electrical current needed to produce the same effect is larger in transcutaneous from. The findings in this chapter showed that the optimal stimulation electrode position (with the lowest current required) is such that the cathode is placed below the medial malleolus and the anode above. However, the position of the electrodes for the clinical trial was chosen to be the same as that used in previous studies of PTNS, where the cathode is above the medial malleolus, in order to produce more directly comparable data with the previous studies and also because chronologically the clinical trial started before the outcomes of numerical modelling were known. According to the numerical model this combination required approximately double the current of the optimal electrode position. Although the optimal position of electrodes should be considered in further clinical evaluation, a referred sensation in the toes or motor contraction of the toes was observed in all participants, thus indicating that the target nerve was stimulated. This second PTNS chapter describes a randomised clinical trial of the home-based application of the non-invasive form of PTNS in patients with symptoms of overactive bladder. The participants

of this trial complied well with a daily 40-minute application of PTNS using a TENS machine. Although the sample size is small in this study, some benefit was demonstrated, particularly in participants with more severe symptoms.

7.2. **Further work**

As mentioned previously the standardization and evaluation of various parameters of stimuli would be beneficial in order to optimize the techniques used and to achieve maximal effectiveness. However challenge still remains how to do this effectively and ideally prior a clinical evaluation. Therefore, researchers have tended to use the previous parameters without any further investigation on a small scale due to limited resources available.

A larger clinical trial with sufficient power to investigate the effects of transcutanoues PTNS or any other technique for the treatment of overactive bladder symptoms in detail would be both costly and labour-intensive. Recruitment rates are often limited by attempts to obtain homogeneity in the investigated group and overactive bladder symptoms are often accompanied by various pathological conditions which preclude many of these patients from participating. Therefore, in view of the very low cost technique (£300 course of treatment for 5 years) and absence of side effects, NHS Trusts and patient care organisations may wish to now consider deploying this technique. If a standard evaluation protocol was used this would enable its benefits to be evaluated locally and, retrospectively, on a wider scale using meta-analyses. However, this is clearly a less scientific approach and ideally future work should be focused on a randomized multicentre trial based on the experience gained from the design of this pilot clinical trial. A promising target group for PTNS might also be in the population of elderly adults in residential care. Posterior tibial nerve stimulation in both percutaneous and transcutaneous form has been reported to show benefits in faecal incontinence, which affects this group of patients as well (Thomas et al., 2013, George et al., 2013). There is a real need for alternative methods of continence management in this population as current management using absorbance pads is not considered to be dignified and is expensive.

7.2.1. **Trial methodology**

As discussed in section 6.4.2 and in view of the trial undertaken in this thesis a more specified and standardised way of assessing the patient would be desirable for future studies. However, the diversity of the patients' symptoms might then lead to a significant limitation of recruitment rate. Thus only way forward seems to be to conduct a multicentre trial, which will increase the recruitment rate and make the trial results more robust.

The sham methodology presented in the trial in this thesis (comparable intensity of electrical stimulation in the placebo group but applied to a site that is regarded as being irrelevant to bladder control) seemed to be scientifically effective. The participants in the trial were not told that they could be randomized into the sham arm. This sometimes was not well supported by the team conducting the trial, who was not originally involved in the trial design. In that view, it was not perceived a as being fair to the participants (although the local ethical committee did not consider this as a problem). Therefore the further trials should consider cross over design or allowing the participants an access to the active arm after the trial. Alternatively this could be discussed with patients before the trial using a Patient and public involvement (PPI) activity. PPI in the treatment and research development is currently essential for any further work and to securing any form of funding.

Another area where PPI could be beneficial, is in the definition of stimulation protocol. As mentioned previously there is lack of investigation about the optimal parameters of the stimuli and strategy of the treatment. PPI activity groups could help to determine for example how many sessions of stimulation and how long (session time) they would prefer to do. However this needs to be balanced with previous scientific knowledge and not be entirely based on the patient's convenience.

7.2.2. **What sample size would be needed for a larger clinical trial?**

To answer this questions the study aims and outcome measures would need to be decided. The following is a calculation based on the data presented in this study and the primary outcome is considered as the difference between the number of responders. The calculation only considers two group (active and sham stimulation groups).

Therefore, the aim of this calculation is to determine what sample size would be required in order to detect the difference between the number of responders in active stimulation group (5/13, 38%) and sham stimulation group (1/6, 16%) with 90% power using a cut off for statistical significant of 0.05.

$$n = \frac{[p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2} = \frac{[0.38(1-0.38) + 0.16(1-0.16)]}{(0.38 - 0.16)^2} = 80$$

The formula used (Whitley and Ball, 2002) identified that 80 participants in each group would be needed.

7.2.3. **Sensory Barrage Stimulation**

The concept of Sensory Barrage Stimulation introduced in this thesis is a novel approach to electrical stimulation which can be potentially beneficial in stroke/spasticity rehabilitation and, perhaps, for OAB. However further studies in this area need to be undertaken. In the context of overactive bladder symptoms using this technique for foot/posterior tibial nerve or sacral dermatomes stimulation as identified in the literature review could perhaps be explored. Ideally one would evaluate a variety of stimuli using a non-clinical surrogate measure as was suggested originally in this thesis, but finding a suitable approach still remains a challenge. Nonetheless, this could be less challenging in another treatment population groups such as in stroke and spasticity.

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Appendix A – Ethics approval for study in Chapter 2

Downloaded: 24/04/2015
Approved: 11/08/2014

Martin Slovak Oncology

Dear Martin

PROJECT TITLE: Investigation of a potential surrogate measure of bladder nerve activity

APPLICATION: Reference Number 001645

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 11/08/2014 the above-named project was approved on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

University research ethics application form 001645 (dated 01/08/2014).
Participant information sheet 002333 (01/08/2014)
Participant consent form 002334 (01/08/2014)

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Jean Lazenby Ethics Administrator Medical School

Appendix B – Inclusion and exclusion criteria for study in Chapter 2

Department of Oncology
Martin Slovak
Tel: +44 (0) 114 271 1610
E-mail: m.slovak@sheffield.ac.uk

Investigation of a potential surrogate measure of bladder nerve activity

VOLUNTEER QUESTIONNAIRE

This is confidential information. The information provided will be only link to the participant ID.

Participant ID:	

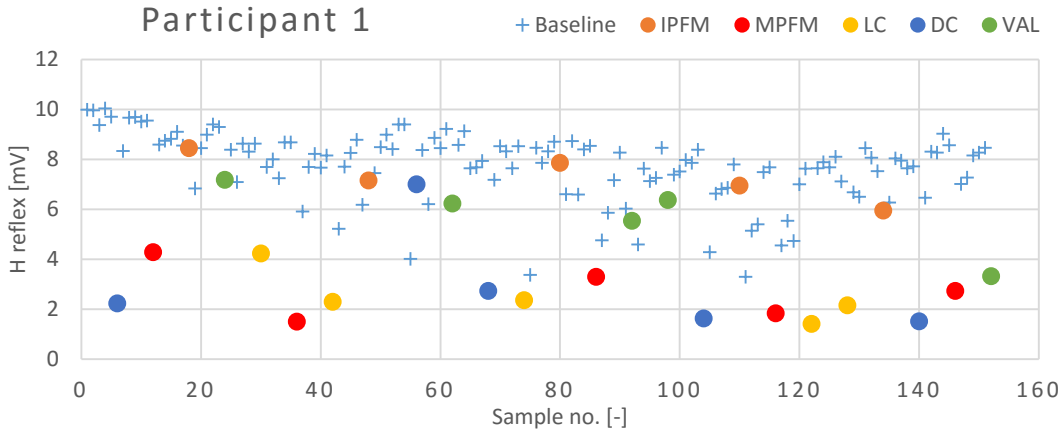
Personal information:

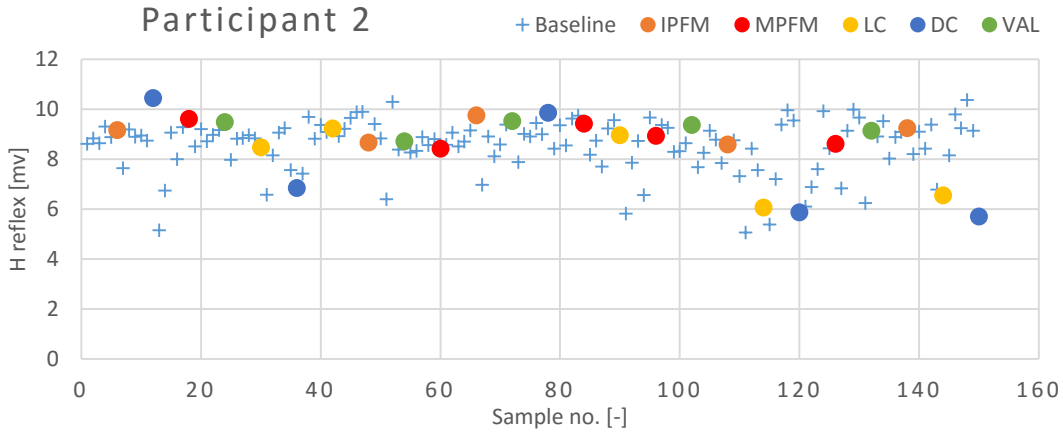
Age:	
Weight:	
Height:	

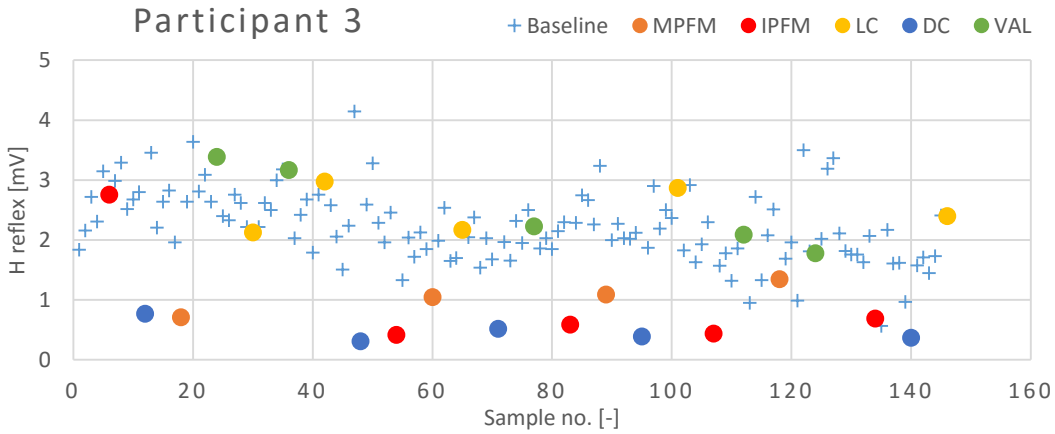
EXCLUSION CRITERIA *(please tick all that apply)*	YES	NO
History of heart condition	☐	☐
Unresponsive arterial hypertension	☐	☐
Diabetes	☐	☐
Chronic back pain	☐	☐
Sciatica	☐	☐
Peripheral neuropathy	☐	☐
Rheumatoid arthritis	☐	☐
Active joint deformity of arthritic origin	☐	☐
Alcohol or drug abuse	☐	☐
Epilepsy	☐	☐
Any drugs acting primarily on the central nervous system	☐	☐
Any drugs acting on disorders of the blood coagulation system	☐	☐
Any lower urinary tract disease		
Pregnant women	☐	☐

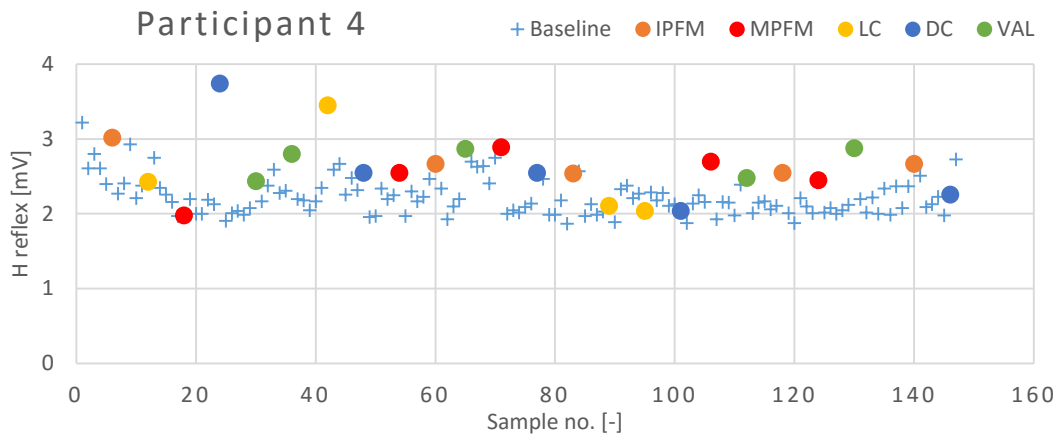
Any other significant medical condition, please specify.....

Appendix C – Individual measurements in the H reflex study





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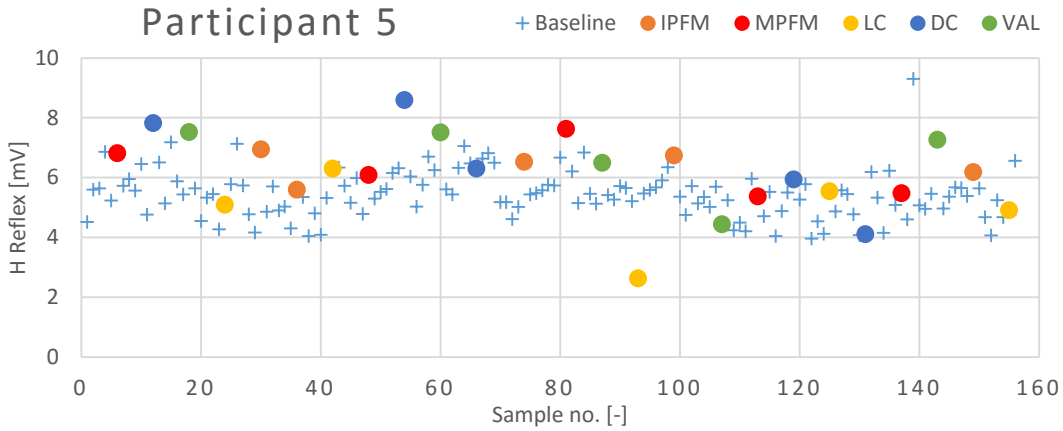
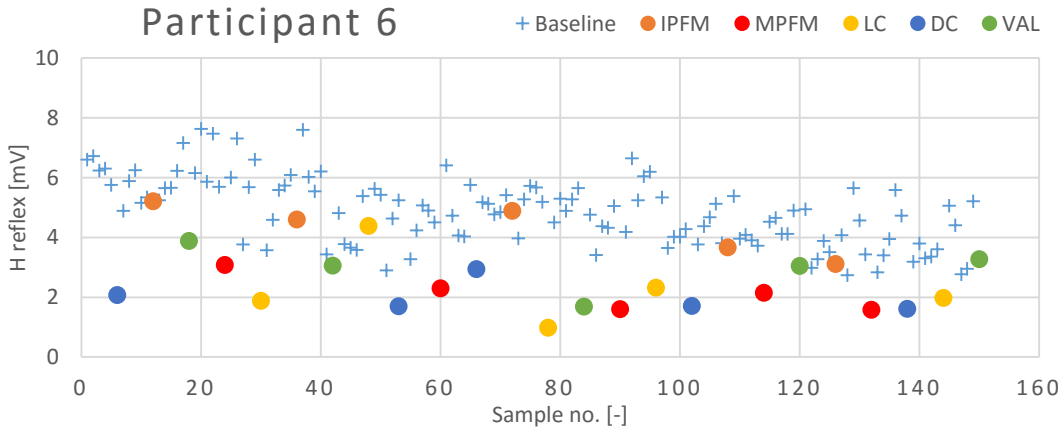
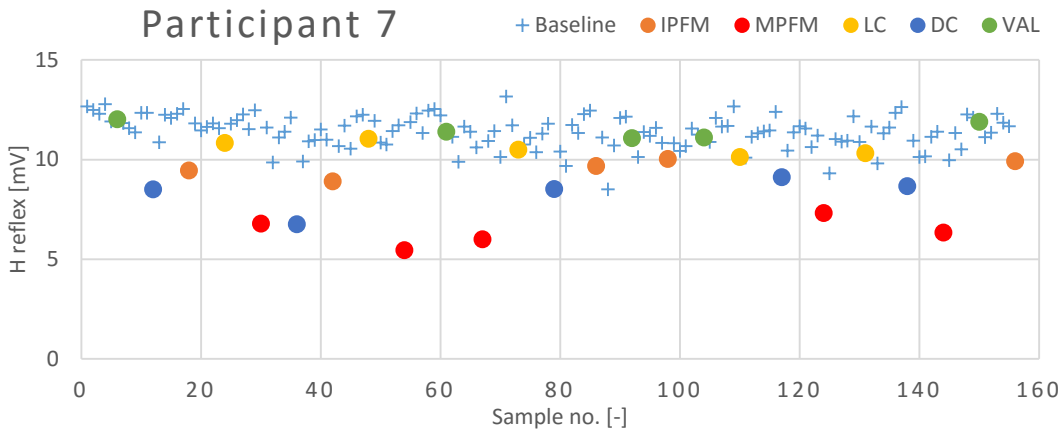
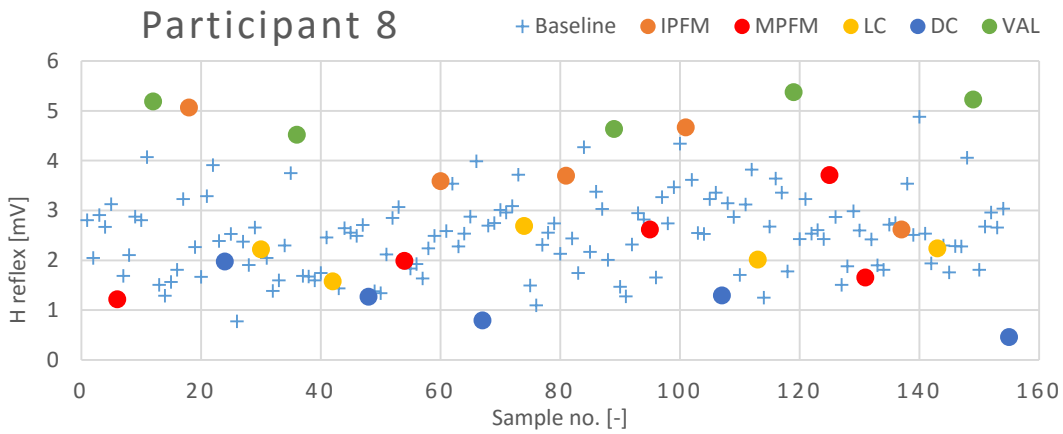
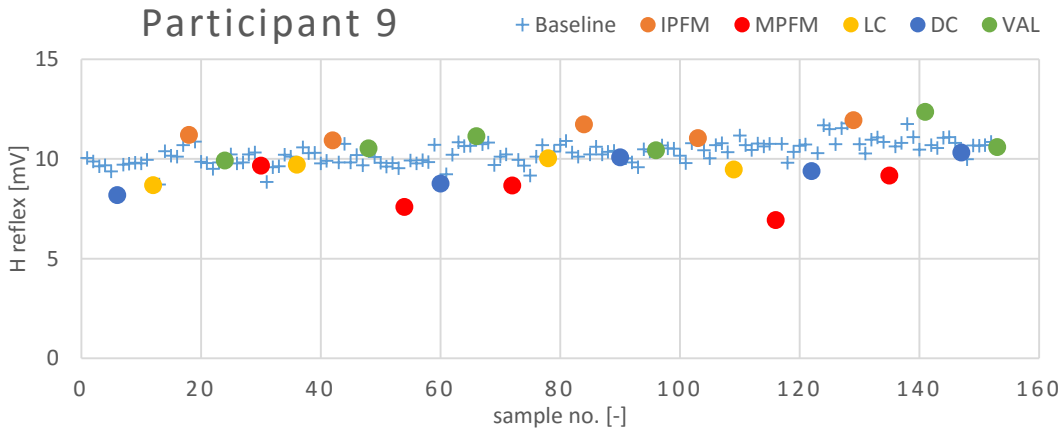
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
Sample no. [-]

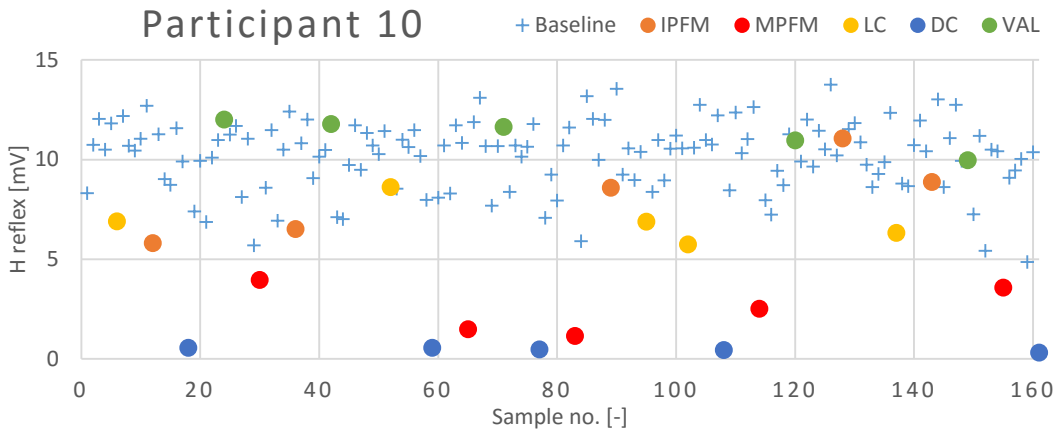

Participant 5
Baseline
IPFM
MPFM
LC
DC
VAL
H Reflex [mV]
Sample no. [-]


Participant 6
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
Sample no. [-]


Participant 7
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
0
5
10
15
0
20
40
60
80
100
120
140
160
Sample no. [-]


Participant 8
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
0
1
2
3
4
5
6
0
20
40
60
80
100
120
140
160
Sample no. [-]


Participant 9
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
0
5
10
15
0
20
40
60
80
100
120
140
160
sample no. [-]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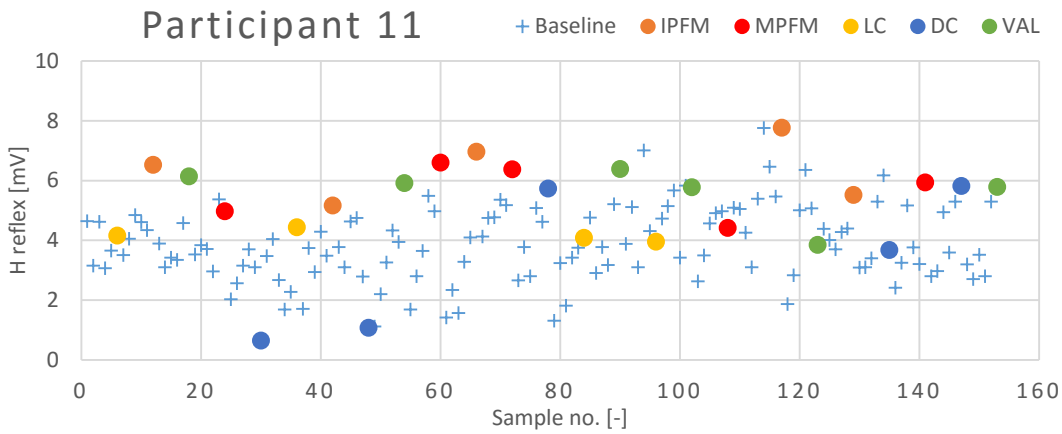
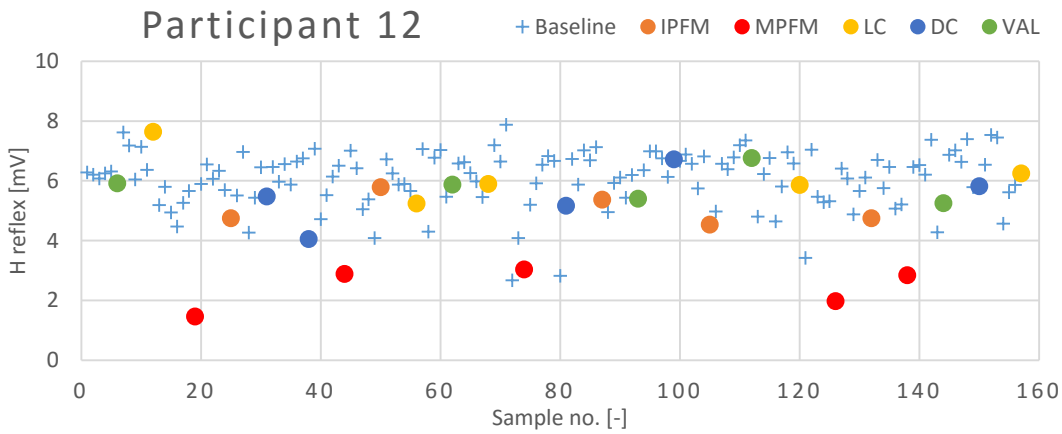
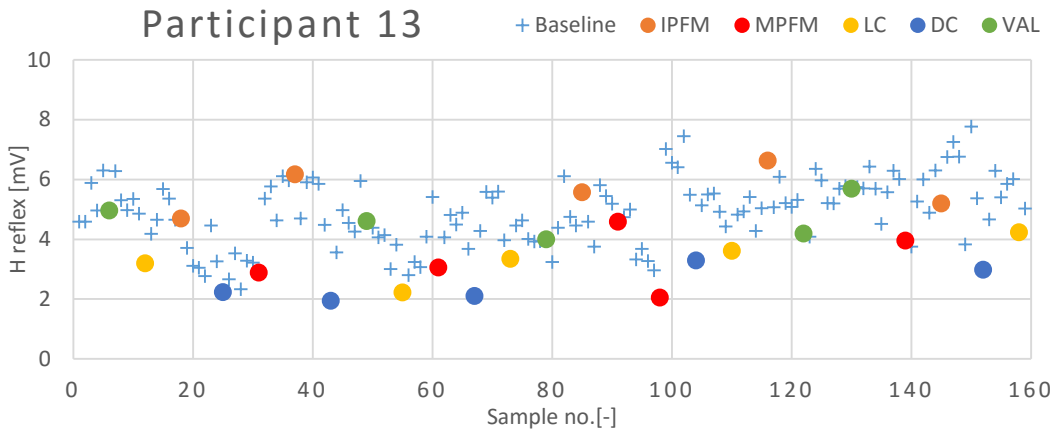
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
Sample no. [-]


Participant 11
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
Sample no. [-]


Participant 12
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
Sample no. [-]


Participant 13
Baseline
IPFM
MPFM
LC
DC
VAL
H reflex [mV]
10
8
6
4
2
0
0
20
40
60
80
100
120
140
160
Sample no.[-]

Appendix D – Ethics approval for the habituation study in Chapter 3

The University Of Sheffield.

The Medical School.

Tom Farrow
Academic Clinical Psychiatry
The Longley Centre
Northern General Hospital
Herries Road, Sheffield

Medical School Office
Sara Watkinson
Research Ethics Administrator
Beech Hill Road
Sheffield S10 2RX

Telephone: +44 (0) 114 226 1456
Fax: +44 (0) 114 271 3960
Email: s.watkinson@sheffield.ac.uk

24 June 2011

REF: SMBRER191

Dear Tom

Salience and habituation in cutaneous sensory stimulation

I am pleased to inform you that on *24 June 2011* the School's Ethics Reviewers **approved** the above-named project on ethics grounds, on the basis that you will adhere to and use the documents that you submitted for ethics review. The reviewers made a few comments which I have included with this letter.

Please find attached the final versions of the documents you should use.

If during the course of the project you need to deviate from the above-approved documents, please inform me. The written approval of the School's Ethics Review Panel will be required for significant deviations from or significant changes to the above-approved documents. If you decide to terminate the project prematurely, please inform me.

Yours sincerely

Sara Watkinson
School Research Ethics Administrator

Enc

Appendix E - Ethics approval for the spasticity study in Chapter 3

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds East
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

13 February 2013

Mr Joseph Chindo
Flat 41 Atlantic one
1 St George's Walk
Sheffield
S3 7AP

Dear Mr Chindo

Study title:	**Effect of Sensory Barrage Stimulation and Transcutanous Electrical nerve Stimulation on spasticity at elbow : A pilot randomised single blind controlled cross over trial**
REC reference:	**13/YH/0031**
Protocol number:	**Version-3**
IRAS project ID:	**119997**

The Research Ethics Committee reviewed the above application at the meeting held on 05 February 2013. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Anne Ward, nrescommittee.yorkandhumber-leedseast@nhs.net.

Ethical opinion

The Chair, Dr Carol Chu, welcomed Dr Sivaraman Nair (Chief Investigator) to the meeting and thanked him for attending.

Members questioned who would be identifying patients who were suitable for taking part in the study

Dr Nair confirmed that he will be responsible for approaching potential participants. He added that he runs a neurology and neurorehabilitation clinic and that patients will be recruited from here

This was confirmed to be acceptable, as the researcher is also part of the clinical care team

It was questioned whether any previous evidence was available to show that one device may be more painful and/or uncomfortable than the other.

Dr Nair replied that the two methods were more or less matched in terms of levels of pain and discomfort, and that a similar design had been used to conduct motor stimulation using higher currents, and that this had been well-tolerated, so he was not anticipating patients to have any

adverse experiences

It was also questioned whether the patient would be able to stop the session at any time

Dr Nair replied that they would be able to stop at any time, and that they would be excluding patients from the study if they were obviously more sensitive to stimulation and or pain. He added that they would be gradually increasing the current, up to the patients' maximum tolerable level

The researcher left the room.

The Committee discussed the responses.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Further Conditions Specified by the Committee:

1. Changes to the Participant Information Sheet(s):

    a) The information describing visit one rewritten to be less confusing

    b) Amended to make it clear that patients may not benefit from taking part in the study, and to emphasise that there is no guarantee that this machine can be used after the end of the study

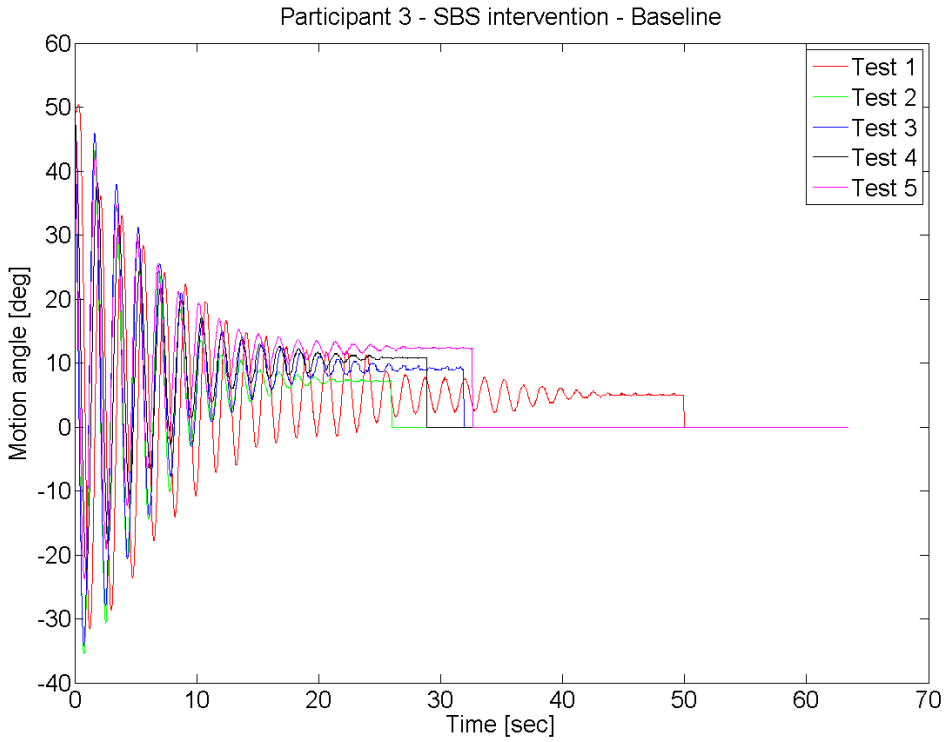
    c) Addition of information regarding reimbursement for travelling on public

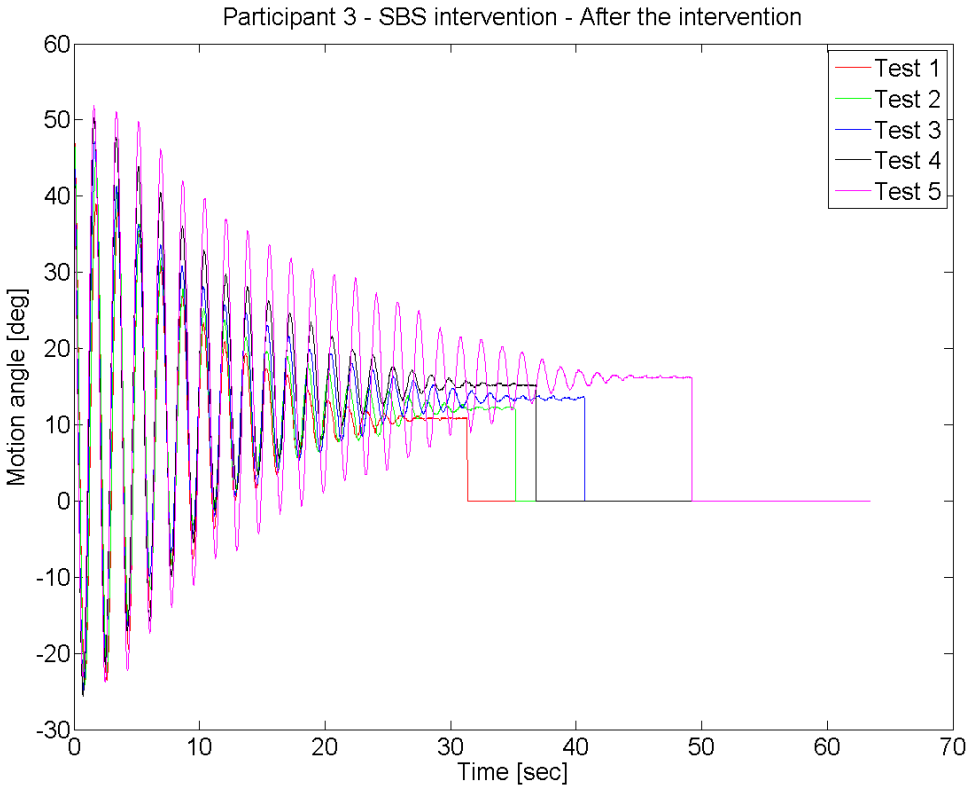
Appendix F – Individual measurement of pendulum outcomes

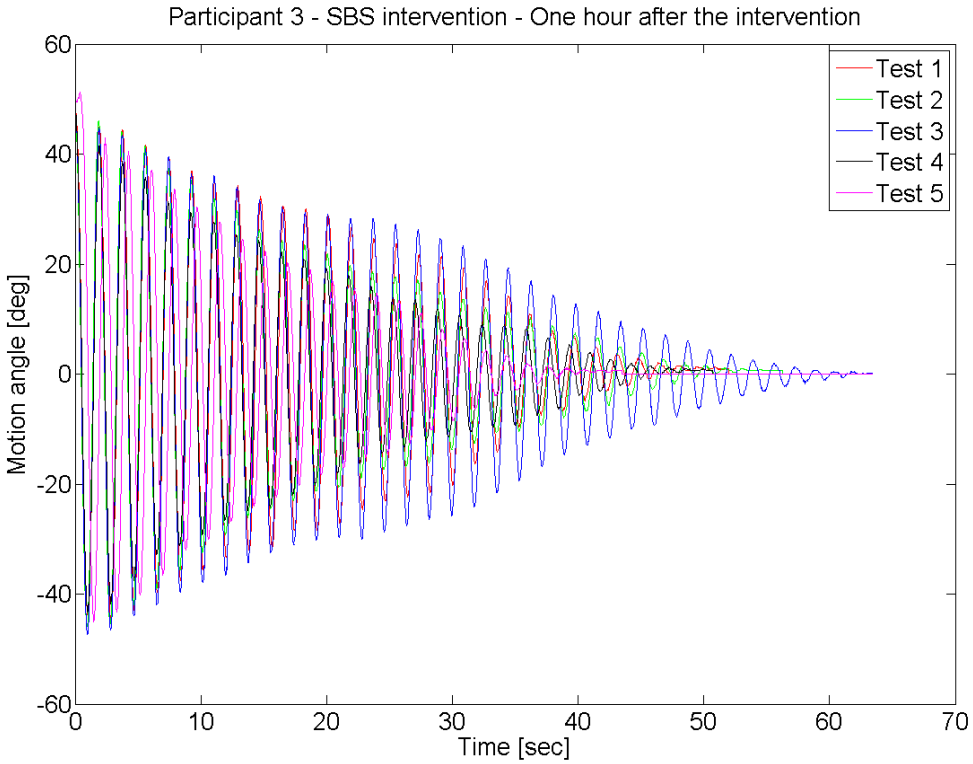
	TENS								
	First reversal angle [°]			Maximum velocity to first reversal [°/sec]			Area under the curve [°*sec]		
No.	Base	After	One hour	Base	After	One hour	Base	After	One hour
1	23.6	25.1	23.0	127.1	125.4	129.0	65.5	60.8	88.7
2	38.1	39.2	36.9	136.3	145.4	133.0	356.5	253.7	438.7
3	39.0	38.1	37.3	139.0	130.6	140.1	262.1	314.3	359.8
4	18.0	14.9	13.3	120.1	125.5	104.4	58.5	62.4	36.8
5	34.4	38.5	31.9	131.4	132.3	112.6	201.0	361.8	336.2
6	28.4	20.2	23.7	130.6	121.0	117.5	84.5	64.7	74.8
7	39.9	37.9	40.3	144.4	135.8	151.6	518.5	433.8	355.7
8	39.1	36.6	36.5	130.8	126.7	131.1	187.3	198.3	171.8
9	37.2	28.1	34.9	136.6	128.7	135.3	251.6	126.2	301.6
10	30.4	31.9	24.6	147.9	133.3	137.7	554.6	505.4	535.3

	SBS								
	First reversal angle [°]			Maximum velocity to first reversal [°/sec]			Area under the curve [°*sec]		
No.	Base	After	One hour	Base	After	One hour	Base	After	One hour
1	20.8	19.8	17.8	119.1	117.3	123.1	43.3	37.3	36.0
2	25.1	38.4	40.3	126.7	135.6	141.4	90.1	216.1	384.1
3	38.4	37.9	45.7	130.6	122.2	146.0	196.5	291.7	655.8
4	9.6	9.3	-	104.4	95.4	-	32.6	19.6	-
5	29.6	35.3	37.0	112.1	122.5	124.9	215.2	315.4	425.7
6	32.6	32.9	17.8	150.6	138.3	121.1	163.0	139.3	60.6
7	40.6	42.4	40.3	150.0	151.0	152.0	450.1	348.7	171.2
8	37.9	34.3	36.3	135.3	121.5	136.8	329.9	312.6	308.1
9	41.1	29.9	37.1	139.9	134.3	137.1	267.8	99.0	136.6
10	43.8	43.1	40.6	137.0	137.4	135.2	328.5	234.3	248.8

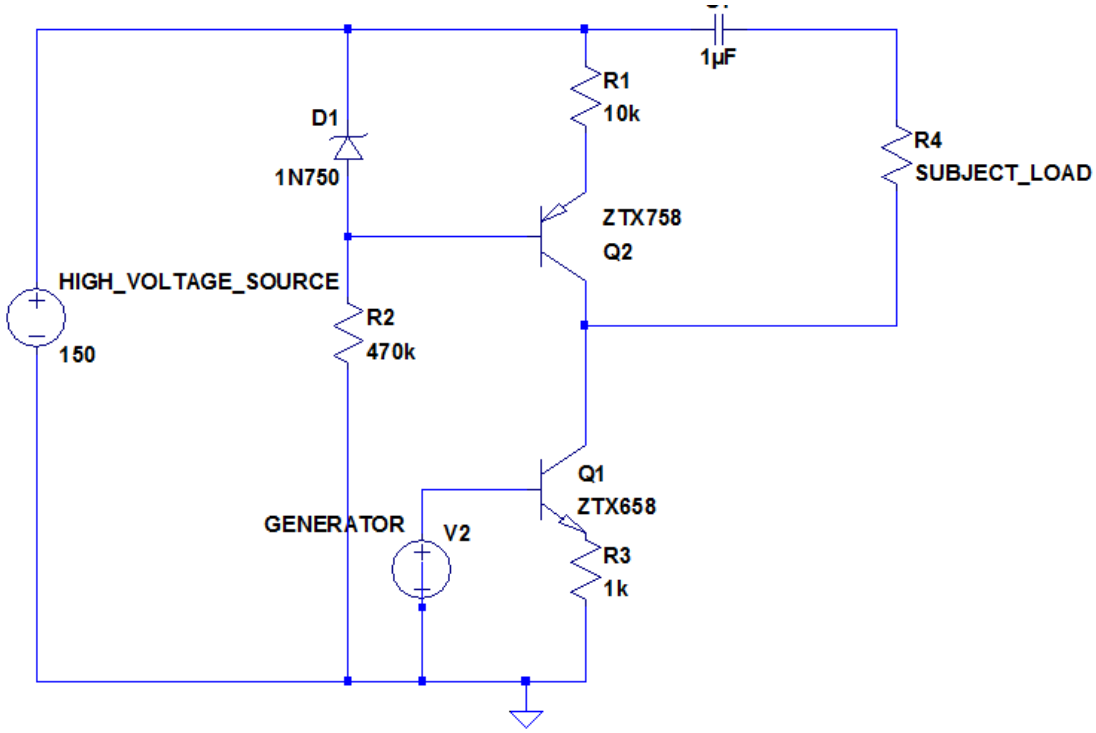
Appendix G – Typical pendulum outcome data






Participant 3 - SBS intervention - One hour after the intervention
Test 1
Test 2
Test 3
Test 4
Test 5
Motion angle [deg]
Time [sec]
60
40
20
0
-20
-40
-60
0
10
20
30
40
50
60
70

Appendix H - Stimulator schema



Appendix I - PESTOB study - Ethics approval

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - South Yorkshire
North East REC Centre
Unit 002, TEDCO Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 428 3387
Facsimile: 0191 428 3432

04 March 2013
(Reissue 09 April 2013)

Professor Christopher Chapple
Consultant Urological Surgeon
Sheffield Teaching Hospitals NHS Foundation Trust
Department of Urology
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Professor Chapple

Study title:	**Peripheral Electrical Stimulation for the Treatment of Overactive Bladder**
REC reference:	**13/YH/0076**
IRAS project ID:	**121775**

The Research Ethics Committee reviewed the above application at the meeting held on 28 February 2013.

Ethical opinion

The Chair, Ms Susan Hampshaw, welcomed the Student, Mr Martin Slovak, Academic Supervisor Professor Tony Barker and Co-investigator Dr Nadir Osman and thanked them for attending.

The Committee noted that the researchers had indicated that although 7 participants would be sufficient to reach the study aims they intended to recruit 12 participants and questioned why this was the case.

Professor Barker responded that due to timescales and patient availability some participants may choose to withdraw from the study and 7 participants would be sufficient for the statistical methods employed in the analysis of data. Twelve was an arbitrary number chosen in case of withdrawals.

Members commented that a paper had been released recommending that there were 12 participants in pilot studies.

Professor Barker replied that this had caused a debate among statisticians, with some saying that it was not necessary to recruit 12 participants.

The REC noted that in the response to question A62 of the IRAS form the researchers had indicated that they would analyse the results using ANCOVA, but could not find any evidence

of what would happen after analysis was complete.

Professor Barker replied that the results would be published, but what happened after that would depend on the nature of the results. Dr Osman continued to state that if the results were shown to be positive they would recruit a larger cohort with the aim of introducing this into standard clinical care.

The Committee questioned why the shoulder had been chosen as the area to place the electrodes.

Professor Barker responded that the electrodes needed to be placed on the body where there would be no link to it having an effect on bladder control. Control groups needed to be treated differently in this situation because participants will be able to feel an electrical stimulation. Any placebo or blinding would be undone if controls knew they were placed in this group because they could not feel the stimulation. Therefore the stimulus should be delivered to an area where participants won't think they should feel something there.

It was noted that participants would undergo training as to the use of the device but the REC queried the mechanisms behind the delivery of the training.

Mr Slovak confirmed that he would train all participants in the Urology Department at Hallamshire Hospital. The instructions he gave to participants would be based upon the available literature. He will teach participants how to place the electrodes and run the stimulation, and would only let them take it home once he was satisfied that they could do this correctly.

Members questioned what participants would do if they encountered any problems with the device at home.

Mr Slovak responded that they would have his office telephone number and he would be able to talk them through any issues they may have. Dr Osman went on to say that there were three research nurses at the urology department who would also be able to help.

The Committee questioned how the researchers would diagnose the problem with the machine.

Dr Osman clarified that the researchers would prefer it if problems were diagnosed and resolved by telephone. If the problem could not be resolved on the phone, the participants would be required to bring the device to the clinic, or if they could not attend a researcher would be able to visit them at home.

Members informed the research team that they would need to follow their organisation's lone working policy if they would be attending participants' homes.

The Committee commented that parking was quite expensive at the Hallamshire Hospital.

Professor Barker confirmed that parking costs would be reimbursed as part of participants' expenses.

Professor Barker showed the device to the Committee and demonstrated the ease with which the electrodes could be placed.

The researchers left the room.

The Committee discussed the responses.

Members felt that the researchers may struggle to recruit participants. Furthermore, they felt that the researchers would struggle to randomise participants into groups due to the low numbers required.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		12 February 2013
GP/Consultant Information Sheets	1	11 December 2012
Investigator CV		22 January 2013
Other: Summary CV for supervisor (student research)		22 January 2013
Other: Summary CV for student		22 January 2013
Participant Consent Form	1	22 January 2013
Participant Information Sheet	2	06 February 2013
Protocol	5	09 February 2013
Questionnaire: OAB-q short form	1	12 February 2013
Questionnaire: ICIQ-OAB	1	12 February 2013
Questionnaire: PPBC	1	12 February 2013
Questionnaire: RAND 36	1	12 February 2013
REC application		12 February 2013

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/YH/0076	Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

S. Hampshaw

pp
Ms Susan Hampshaw
Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" SL-AR2

Copy to: *Mrs Angela Pinder, Sheffield Teaching Hospitals NHS Foundation Trust*

NRES Committee Yorkshire & The Humber - South Yorkshire

Attendance at Committee meeting on 28 February 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Jo Abbott	Consultant in Public Health	No	
Dr A H Abdelhafiz	Consultant Physician, Elderly Medicine	Yes	
Reverend Joan Ashton	Co-ordinator of Chaplaincy Services	Yes	
Ms Helen Barlow	Knowledge Service Manager	Yes	
Professor Nigel Beail	Consultant Clinical Psychologist & Professor of Psychology	Yes	
Mr Ian Cawthorne	Chief Pharmacist	Yes	
Ms Susan Hampshaw	Head of Research, Evaluation and Innovation	Yes	
Mr Neil Marsden	Police Staff	Yes	
Dr Anton Mayer	Consultant in Paediatric Intensive Care	Yes	
Mrs Andrea Porritt	Community Specialist Practitioner	Yes	
Mr Jaydip Ray	Consultant ENT Surgeon	No	
Ms Stephanie Rhodes	Neonatal Sister	Yes	
Dr Paul Spencer	Consultant Radiologist	Yes	
Mrs Carole Taylor	Deputy Chief Pharmacist	No	

Also in attendance:

Name	*Position (or reason for attending)*
Richard Baetke	Observer
Miss Sarah Grimshaw	Committee Coordinator
Louise Jackson	Observer

Appendix J - PESTOB study - Inclusion and exclusion criteria

Inclusion criteria:

PESTOB potential subjects must have satisfied the following criteria in order to be enrolled in the study:

- Males and Females, at least 18 years of age
- Demonstration of ability to fill in voiding diary at DAY-0
- Documented symptoms of idiopathic overactive bladder for at least 3 months
- Failure on primary OAB treatment, such as behaviour modification or fluid/diet management
- Patients can remain on stable medication
- Willing and capable of understanding and complying with all requirements of the protocol
- Signed Informed Consent to participate in the study after full discussion of the research nature of the treatment and its risks and benefits.

Exclusion criteria:

Potential subjects who meet any of the following criteria were excluded from participating in the study:

- Urinary retention or post voiding residual greater than 100 ml
- Clinically significant bladder outlet obstruction
- Stress predominant mixed urinary incontinence
- Neurological disease affecting urinary bladder function, including but not limited to Parkinson's disease, multiple sclerosis, stroke, spinal cord injury.
- Pelvic surgery (such as sub-urethral sling, pelvic floor repair) within the past 6 months
- Denovo OAB following pelvic surgery sub-urethral sling

- Intravesical or urethral sphincter Botulinum Toxin Type A injections within the past 6 months
- Percutaneous Tibial Nerve Stimulation (PTNS) therapy for overactive bladder within the past 6 months
- Any form of electric stimulation to the pelvis of lower limbs within 4 weeks
- Vaginal prolapse greater than Stage II in the anterior compartment of the vagina using International Continence Society (ICS) Pelvic Organ Prolapse Quantification (POPQ) criteria.
- Prior peri-urethral or transurethral bulking agent injections for bladder problems within the past 12 months.
- History of pelvic radiation therapy
- Any skin conditions affecting treatment sites
- Lacking dexterity to properly utilize the components of the device system.
- Presence of an implanted electro-medical device (e.g. pacemaker, defibrillator, InterStim®, etc.),
- Pregnant, nursing, suspected to be pregnant (by urine pregnancy method), or plans to become pregnant during the course of the study.
- Transurethral instrumentation within the preceding month.
- Recurrent Urinary Tract Infections (>3 UTI's in the past year)
- History of, or current, lower tract genitourinary malignancies
- Any clinically significant systemic disease or condition that in the opinion of the Investigator would make the patient unsuitable for the study
- Any other clinical trial within 6 months
- Patients whose resting blood pressure is greater than 160/100mm Hg will be excluded from the handgrip test.

Appendix K –PESTOB study - Instructions for use

Instruction for use - STIMULATION

You have been allocated to the group which will stimulate right ankle. Please use the equipment as described in your training at the clinic. The following instructions should help to remind you how to use the equipment correctly. If you need further help, please do not hesitate to contact the technical support or research nurses.

Please be aware that the stimulator must be used only for the purpose of this trial and only by yourself. As part of the study, the stimulator records all usage for later analysis.

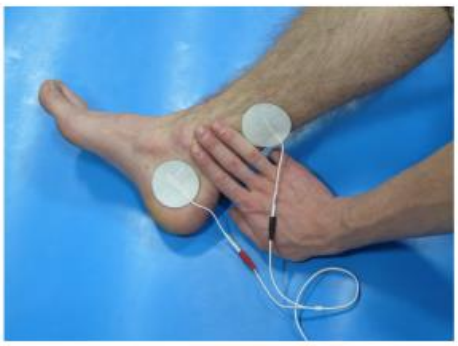
Please use the stimulator once each day at a time which is convenient for you. Each session lasts for 40 minutes and will finish automatically. Please remember to stick the electrodes to your bare skin (tights or socks must not be worn).

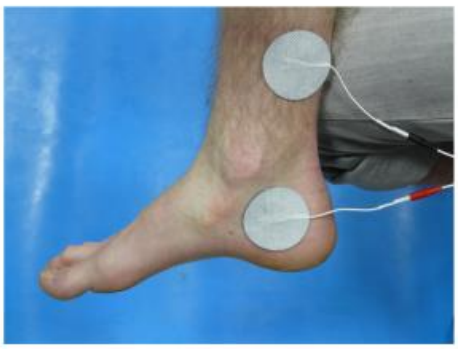
Stimulator

- The equipment consists of the stimulator itself, two cables and 2 electrodes.

Stimulation session – repeated every day

- Insert the plug of cable into the socket labelled A of the stimulator (left socket on the top).
- Remove the electrodes from the bag provided.
- Whilst the electrodes are still stuck to the plastic sheet, connect one electrode to each of the pin connectors at the end of each lead wire.
- Stick the electrodes on right ankle according to the figures. Firstly, place the electrode with the black connector 3 finger widths (approx. 5cm, 2 inches) above the right ankle bone on the edge of the leg then place the electrode with the red connector between the ankle bone and the heel of foot. See the diagram below for guidance on the electrode position.





- Sit comfortably with electrodes placed on the skin and connected to the stimulator.
- Switch on the device by pressing the Power Button ⏻.
- The intensity is controlled by + or – (increase or decrease) buttons on the left side of the device.
- To start the stimulation press +, and increase the stimulation intensity until the maximum comfortable level which does not cause pain or muscular contraction is felt.
    - If the sensation is tolerable it is recommended that the stimulus is increased until muscular contraction is seen and then decreased slowly until contractions just cease.
- You should feel a strong tingling sensation during the whole of the 40 minutes stimulation session. If required you can adjust the intensity during the session using the + or – buttons for each channel.
- From the start of the stimulation the clock on the stimulator display starts counting down the 40 minutes. You can see the remaining time on the LCD screen. The device will make a bleep sound once the session has finished and the stimulator will turn itself off.
- Switch off the stimulator by pressing the Power Button ⏻.
- Disconnect electrodes from the wire.

- Remove each electrode and moisture them by sprinkling few drops of tap water on a sticky side and leave them to soak in for a few seconds after each usage. This will provide good stickiness of electrodes during the whole study,
- Place the electrodes onto their plastic sheet and seal them in the provided bag to stop them drying out.

Battery replacement

If the low battery indicator is flashing on LCD display, please replace the battery.

- To change the battery open the battery door on the rear of the device by pressing down the rib-patterned area just below the belt clip and sliding the cover open.
- Remove the old battery and place the new battery provided according to their polarity.

Troubleshooting

If zero mA is flashing on LCD display, please check on the following:

- Check that electrodes are connected to the device and placed on the skin.
- Check that the electrodes are plugged into the cable.
- Check if both electrodes are making a sticky contact on your skin. If not, turn off the unit and moisture electrodes by sprinkling few drops of tap water on the sticky side.
- Check if the cable appears damaged or broken.

Warnings

- Use the stimulation only according to the instruction provided for the study. As part of the study, the stimulator records the usage for later analysis.
- Do not use stimulator on anybody else.
- Do not insert lead wires into a mains power supply.
- Do not immerse unit in water or any other substance.
- Do not use the unit in the presence of a flammable anaesthetic gas mixture or with Oxygen or Nitrous Oxide.
- Use only the battery provided. Never connect the unit to a battery charger or to any other equipment. Do not attempt to recharge the batteries that are provided.
- Keep out of reach of children.
- Operation in close proximity (e.g. 1m) to shortwave or microwave therapy equipment may produce instability in the stimulator output and should be avoided.

In a case of accidental damage to the stimulator, wires or electrodes; or in any other problems/questions please contact immediately the technical support on the following numbers:

Training and technical support:	Mr Martin Slovak, Non Clinical Research Fellow
Telephone:	(0114) 2711610 (office hours)
Mobile:	0758 135 1985 (out of office hours)

Version 1, 9.7.2013

Appendix L – PESTOB study – Bladder diary

Peripheral **E**lectrical **S**timulation for the **T**reatment of
Overactive **B**ladder (PESTOB)

Assessment no.: ☐ Pt ID No.: ☐☐☐

Pt Initials: ☐☐☐

	Date	Time
Diary started	___/___/____	
Diary ended	___/___/____	

	1. day		2. day		3. day		4. day	
	Date:___/___/____		Date:___/___/____		Date:___/___/____		Date:___/___/____	
	Wake up time:		Wake up time:		Wake up time:		Wake up time:	
Time	Volume [ml]	Urgency level	Volume [ml]	Urgency level	Volume [ml]	Urgency level	Volume [ml]	Urgency level
6-7 am								
7-8 am								
8-9 am								
9-10 am								
10-11am								
11-12 noon								
12-1 pm								
1-2 pm								
2-3 pm								
3-4 pm								
4-5 pm								
5-6 pm								
6-7 pm								
7-8 pm								
8-9 pm								
9-10 pm								
10-11pm								
11-12 midnight								
12-1 am								
1-2 am								
2-3 am								
3-4 am								
4-5 am								
5-6 am								
	Sleep time:		Sleep time:		Sleep time:		Sleep time:	

S – did not need to go, went just in case
0 - normal desire to pass urine

1 – had urgency, but passed away
2 – had urgency, but got to the toilet before leaking
3 – had urgency and leaked
W –urinary incontinence /leaked (without urgency)

1

How to use this bladder diary

- Please complete over a continuous 3 day period (72 hours)
  - For example 19/4/2013 Fri 8am to 22/4/2013 Mon 8am
  - Record the date and time the bladder diary was started and finished in the box.
  - If you have started the diary at the first pass urine of the day it is important that you finished at the first pass urine of the day after 3 days.
  - Please do not alter your bladder routine or normal activities

- Each day record the time
  - When you wake up with an intention to be awake (wake up time).
  - When you go to bed with an intention to sleep (sleep time).

- Volume of urine passed
  - Measure the volume with the jug each time you pass urine (day and night) and record this measurement in the white column indicating the time of passing urine.
  - If you cannot measure your urine volume for any reason then please just make a tick in the white column, etc. while opening your bowel at the same time. It is more important to record all of the events, when you pass urine than worry too much about the accuracy of the volume measured.
  - Write records towards the left side of the column to leave the space for further events.

- Level of urgency
  - Each time you pass urine record the level of urgency you experienced prior to passing urine in the shaded column using the following scale

SCORE	LEVEL OF URGENCY
S	No sensation of needing to pass urine, but passed urine for "social or other reasons", for example just before going out, or unsure where next toilet is.
0	Normal desire to pass urine, no urgency.
1	Urgency, but urgency passed away you did not need to pass urine at this occasion.
2	Urgency, but managed to get to toilet, still with urgency but did not accidently leak urine.
3	Urgency and could not get to toilet in time so leaked urine accidently.

- Urinary incontinence/leakage
  - If you are wet due to urinary incontinence/leakage without urgency e.g. during the night, then record this on the diary with a "W" at the time that you first noticed the incontinence/leakage.

Appendix M – PESTOB study – Individual bladder diaries values

		Micrutions per 24 h				Urgency episodes per 24 h				Incontinence episodes per 24 h				Nocturia episodes per 24 h			
		Baseline	After 1 week	After treatment	Follow up	Baseline	After 1 week	After treatment	Follow up	Baseline	After 1 week	After treatment	Follow up	Baseline	After 1 week	After treatment	Follow up
Unilateral stimulation group																	
1	F55	26.0	19.7	17.0	11.7	8.0	7.3	8.7	4.3	5.0	0.3	3.0	1.3	2.0	0.3	0.3	0.3
5	F59	8.7	10.3	7.7	8.3	3.7	5.7	5.0	6.0	0.0	1.3	0.7	4.0	1.7	1.3	1.0	1.0
14	F66	9.3	8.3	8.0	9.3	2.7	1.7	0.7	1.0	2.0	1.0	0.7	1.3	1.0	1.0	1.3	1.7
19	F63	8.3	8.3	8.0	7.3	9.7	5.3	4.0	4.0	1.7	0.0	1.3	0.0	0.0	0.0	0.0	1.0
21	F59	11.3	11.3	15.0	13.3	11.3	11.3	15.0	13.3	10.0	4.7	11.3	12.0	3.3	4.7	7.0	5.7
26	M54	15.3	13.3	11.0	15.3	19.7	13.3	12.3	15.3	0.3	3.7	0.0	0.0	4.7	3.7	3.0	4.7
27	M56	11.0	9.3	11.0	8.7	7.3	6.3	7.0	8.3	0.0	0.0	0.0	0.0	3.0	2.3	3.0	2.3
Bilateral stimulation group																	
3	F47	21.7	11.3	12.3	22.0	21.3	11.3	8.7	20.7	13.0	4.0	1.7	9.7	4.3	0.7	0.3	3.3
11	F39	8.3	6.3	7.0	7.7	7.0	5.3	5.0	6.7	2.0	1.0	1.3	1.0	1.3	0.0	0.0	1.0
12	M63	10.0	8.7	10.3	10.7	6.0	3.3	5.0	6.0	0.0	0.0	0.0	0.0	1.0	1.3	1.0	1.3
23	M59	15.0	9.0	10.3	11.7	7.7	1.0	2.7	1.0	0.0	0.0	0.0	0.0	2.3	1.7	3.0	2.7
25	F69	12.7	11.7	11.3	13.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	2.7	4.3	4.0
29	M68	11.0	7.7	10.7	7.3	3.0	2.3	4.3	1.3	0.0	0.0	0.0	0.0	3.0	2.0	2.0	1.0
Sham stimulation group																	
13	M69	16.0	14.3	18.7	15.0	10.3	10.7	15.7	11.7	0.0	0.0	0.0	0.0	1.7	0.7	0.7	2.3
15	F68	13.3	14.3	13.3	13.7	4.0	1.0	1.3	0.7	0.0	0.0	0.0	0.0	2.7	1.7	1.7	1.3
16	F68	11.7	10.7	10.7	10.7	5.7	5.7	8.7	9.0	2.7	0.0	0.0	1.0	1.7	2.0	2.0	1.7
17	M55	15.3	10.0	9.3	11.0	15.3	9.7	9.3	7.0	1.0	0.7	1.0	1.0	2.3	1.7	1.7	1.0
22	M51	9.0	8.7	8.3	8.7	6.7	4.7	4.3	4.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
28	M56	14.3	12.7	15.0	10.0	9.7	9.3	8.3	4.3	0.0	0.0	0.0	0.0	2.0	1.7	1.7	1.7