Investigation of Transcutaneous Neuromodulation Techniques and Development of a Wearable Device for Control of the Bladder following Spinal Cord Injury

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy of University College London.

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I, Sean Patrick Doherty, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.
Abstract

Spinal Cord Injury (SCI) causes unwanted and uncontrolled bladder contractions (NDO). Urological management goals are to protect the upper urinary tract and eliminate incontinence. Neuromodulation is a potential treatment that may accomplish this using transcutaneous electrical stimulation.

Surface stimulation of the Dorsal Genital Nerve (DGNS), Tibial Nerve (TNS), Sacral Nerves (SNS) and Spinal Cord (SS) was studied in two experiments. Five participants with no SCI received stimulation at each site and anal sphincter EMG was recorded. In 4/5 DGNS evoked a reflex response, in 2/5 SNS evoked a short latency response and in 2/5 a reflex response to TNS was recorded at 1.5 x and 1.8 x the latency of participants DGNS responses. Seven participants with SCI and NDO trialled stimulation of the four sites during cystometry. Only DGNS significantly (p=0.016) increased bladder capacity by 153±146 ml and suppressed 2 ±2 detrusor contractions. Maximum Detrusor Pressure was significantly increased by TNS only, by 10±13 cmH₂O. DGNS, TNS and SNS all significantly increased to volume from first detrusor contraction to the maximum capacity.

To assess existing bladder sensation, 313 urodynamic records were analysed. 77% were found to have preserved sensation, including 45% of those with complete injuries. Of those with supra-sacral SCI, 75% reported sensation, of whom approximately 86% could replicate this during urodynamic investigation.

Five participants trialled DGNS during Ambulatory Urodynamic Monitoring (AUM) and over a week at home. During AUM, self-triggered simulation was used in 4/5 and both intermittent and continuous stimulation was trialled in 1/5. DGNS significantly increased bladder capacity (p=0.008), decreased MDP (p=0.016) and decreased average peak detrusor pressure (p=0.016) from baseline. Void volumes recorded in a bladder diary did not change significantly (p=0.250), nor did ICIQ scores. All participants continued existing antimuscarinic regimes, therefore improvements were in addition to existing medication.
Impact Statement

This project was conducted to meet our overarching goal of delivering a novel, non-invasive technique to restore control over storage of urine in the bladder following Spinal Cord Injury (SCI) in the form of a wearable device. To deliver a device to clinicians and patients we must establish an efficacious technique in the laboratory, determine the technique's safety and effectiveness in the real world, design a device that is acceptable to patients and meets the core clinical requirements, pass all regulatory hurdles and successfully commercialise a device in a sustainable manner. The completion of this could have substantial impact upon the lives of people with SCI and potentially many other similar conditions worldwide. We have described our work that goes some way to reaching this goal and in doing so, itself, delivers considerable impact. Specifically, we have presented new data from three experimental studies and one retrospective study that aim to answer questions required for translation of a new therapy and we have completed device development activities in line with what is required for translation of a new device.

Successful triggering of a stimulation system is imperative for the success of a conditional neuromodulation system and as yet there is no artificial means of assessing bladder activity in daily life. We have presented the largest data sample of reported bladder sensation in people with chronic SCI, showing the large proportion of retained bladder sensation following SCI and the range in its quality and use. This has importance both for the design of our subsequent work presented in this thesis and highlights an area for future research.

There has never previously been a direct comparison of neuromodulation sites within humans with SCI and an optimal site for chronic delivery of neuromodulation remains unknown. We show that stimulation of the genital nerve is the most robust method of abolishing detrusor overactivity alongside highlighting avenues of research to further investigate other techniques that hold promise.

Delivery of a new therapy into clinical practice requires clinical trial data. To begin the
process towards appropriate design of a clinical trial, we have conducted a short pilot study involving five people with SCI. The data from this trial has delivered impact in three ways: through participant feedback on the technique and the device used, through the new data that has been published in this thesis and presented at conference and through the lessons learned during this short study of difficulties in appropriate evaluation of outcomes.

A surface stimulation system would be a medical device, requiring CE marking in Europe and appropriate documentation in its own technical file. Through our collaboration with OML and a six month secondment of the author to the company we have generated a significant amount of documentation that will be required for commercialisation of a device in the future.

We have presented elements of the work in this thesis at 5 conferences, ensuring dissemination of our results and ideas into the relevant scientific and clinical communities.
Acknowledgements

As with all projects such as this, it is a team that is required. Therefore I would like to acknowledge and thank:

The brave souls who participated in the experiments presented within this thesis. For no personal gain, as individuals both with and without spinal cord injuries, you volunteered to partake in our work and without you it is guaranteed our research would go nowhere.

The INSPIRE Foundation, whose staff, fundraisers, trustees and scientists make this work possible. You put forward genuine research requirements of those living with spinal cord injury and have been a pleasure to work with.

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<tr>
<td>AD</td>
<td>Autonomic Dysreflexia</td>
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<td>AM</td>
<td>Antimuscarinic Medication</td>
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<td>APDP</td>
<td>Average Peak Detrusor Pressure</td>
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<td>ASIA</td>
<td>American Spinal Injuries Association</td>
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<tr>
<td>AUM</td>
<td>Ambulatory Urodynamic Monitoring</td>
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<tr>
<td>BTX</td>
<td>Botulinum Toxin Type A</td>
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<td>CMG</td>
<td>Cystometrogram</td>
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<td>DGNS</td>
<td>Dorsal Genital Nerve Stimulation</td>
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<tr>
<td>DSD</td>
<td>Detrusor Sphincter Dyssynergia</td>
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<td>EAS</td>
<td>External Anal Sphincter</td>
</tr>
<tr>
<td>EUS</td>
<td>External Urethral Sphincter</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>EFV</td>
<td>End Fill Volume</td>
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<td>FPDP</td>
<td>First Peak Detrusor Pressure</td>
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<td>ICIQ</td>
<td>International Consultation on Incontinence Questionnaire</td>
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<tr>
<td>IDUC</td>
<td>Indwelling Urethral Catheter</td>
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<td>ISC</td>
<td>Intermittent Self Catheterisation</td>
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<td>LUT</td>
<td>Lower Urinary Tract</td>
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<td>LSCIC</td>
<td>London Spinal Cord Injuries Centre</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>MCC</td>
<td>Maximum Cystometric Capacity</td>
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<td>MDP</td>
<td>Maximum Detrusor Pressure</td>
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<td>NDO</td>
<td>Neurogenic Detrusor Overactivity</td>
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<td>OAB</td>
<td>Overactive Bladder</td>
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<tr>
<td>OML</td>
<td>Odstock Medical Limited</td>
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<tr>
<td>PAG</td>
<td>Periaqueductal Gray</td>
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<tr>
<td>PMC</td>
<td>Pontine Micturition Centre</td>
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<tr>
<td>RNOH</td>
<td>Royal National Orthopaedic Hospital</td>
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<tr>
<td>RV</td>
<td>Reflex Volume</td>
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<td>SARS</td>
<td>Sacral Anterior Root Stimulation</td>
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<td>SCI</td>
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<td>SNS</td>
<td>Sacral Nerve Stimulation</td>
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<td>SPC</td>
<td>Suprapubic Catheter</td>
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<td>TNS</td>
<td>Tibial Nerve Stimulation</td>
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<td>VtL</td>
<td>Volume to Leakage</td>
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Chapter 1

Introduction

1.1 Research Rationale

Spinal Cord Injury (SCI) is a significant cause of disability and has profound, life-long consequences for millions of people worldwide [Lee et al., 2014]. The impact of SCI is far reaching and alongside paralysis and lost sensation it impacts all aspects of bladder function.

Two conditions arise in the chronic phase of suprasacral SCI, Neurogenic Detrusor Overactivity (NDO) and Detrusor Sphincter Dyssynergia (DSD), affecting both storage and voiding of urine. NDO causes large, involuntary, contractions of the detrusor and DSD causes co-contraction of the sphincter. For voiding, where a contracting detrusor and relaxed sphincters are required, DSD impedes low pressure emptying leading to high residual volumes and high detrusor pressures. During storage, the combination of NDO and DSD leads to low bladder capacities, high detrusor pressures and regular incontinence episodes. These conditions are prevalent in both complete and incomplete SCI populations. Restoration of control over the bladder, both for voiding and storage, is a high research priority for people with SCI [Anderson, 2004, Ditunno et al., 2008, Braaf et al., 2017].

Neurostimulation of sacral anterior roots has been used with success to enable micturition following SCI. However, to overcome DSD and NDO posterior rhizotomy is required, electively abolishing any residual sensation and reflex sexual function. This method, developed by Brindley et al., is now a commercially available implanted device used by over 3000 patients worldwide, in some for over 30 years [Brindley, 1994, Van Kerrebroeck et al., 1993]. Despite being a highly effective solution, the price of rhizotomy is high and voiding itself makes up under one percent of the micturition cycle. The combination of increasing numbers of incomplete injuries, availability of other options for voiding and hope for new restorative treatments has contributed to declining use of SARS
in its current form. A focus on enabling efficient storage and on suppression of DSD during voiding, through less destructive means, is required.

The effects of SCI on the ability to store urine effectively in the bladder are a major cause of concern regarding quality of life, up to 74% of people with SCI experience ongoing urinary incontinence, linked with decreased quality of life [Lee et al., 2016, Liu et al., 2010]. The current treatment methods, pharmacological or surgical, are somewhat successful [Reitz et al., 2004, O’Leary et al., 2003], yet have downsides including often intolerable side-effects. Therefore, this research focuses on the storage phase and on investigating methods of providing control over NDO.

Neuromodulation, delivered using electrical stimulation, has the capacity to suppress bladder overactivity and prolong continence [Craggs and McFarlane, 1999]. It has the potential to elicit a coordinated storage response on demand, a relaxed detrusor and closed sphincter, and could foreseeably be a means of providing artificial control over the bladder. However, there is no therapy available to patients and no clear data showing how stimulation may be best applied for people with SCI.

The focus of this research was to gain a better understanding of how neuromodulation may be used in a non-invasive way to inhibit NDO following SCI and on how to apply it in the home environment. Enabling the translation of useful results and technology is important. Therefore, work was undertaken to understand the practical issues of using neuromodulation at home and to build a device to enable a subsequent trial leading on from the sets of pilot data presented in this thesis.

1.2 Thesis Overview

The outline of this thesis is set out here and the core research aims are described at the end of Chapter 2. Following this, original experimental work is presented with a view to answering the questions posed.

1.2.1 Chapter 2: Review of Literature

Chapter 2 presents an overview of current knowledge regarding the Lower Urinary Tract’s structure, function, innervation and control in health. We describe the effects SCI has on the body, with particular focus on the LUT. This includes the development of bladder overactivity and the loss of coordination within the LUT, before outlining current methods available to enable both voiding and storage.
The next part of this chapter presents new data, obtained from an audit of the London Spinal Cord Injury Centre patient population’s urodynamics reports, that gives information on bladder sensation following SCI and the appropriateness of using self-triggered stimulation in an ongoing neuromodulation paradigm.

We go on to describe the current state of the art regarding neuromodulation for bladder control following SCI. We assess the literature available on three specific topics, with a view of generating research questions pertinent to the translation of a neuromodulation technique into a clinically usable device. First, we outline the literature with respect to stimulation sites that may be viable for long term treatment. Secondly, we describe the previous approaches taken that attempt to close the loop in a conditional neuromodulation system, providing feedback in realtime on bladder activity of filling. Thirdly, literature where neuromodulation has been trialled in the patients home environment is presented.

Finally, the research questions to be asked of this thesis are outlined.

1.2.2 Chapter 3: The Effects of Stimulation Site on External Anal Sphincter Activity

Chapter 3 presents the first of two experiments into stimulation site. We compare the effects of four stimulation sites on EMG activity in the anal sphincter. The results present outcomes from 5 participants with no neurological injury.

1.2.3 Chapter 4: Urodynamic Comparison of Stimulation Site

Chapter 4 presents our second study of four stimulation sites, assessing the effect of each on bladder overactivity in participants with SCI. It describes a urodynamic study, completed by 7 participants, where bladder capacities and detrusor pressures were measure at baseline and with each of Dorsal Genital Nerve Stimulation (DGNS), Tibial Nerve Stimulation (TNS), Sacral Nerve Stimulation (SNS) and Spinal Stimulation (SS) applied in independent sessions.

1.2.4 Chapter 5: Developing a System to Apply and Assess Neuromodulation in Practice

Chapter 5 describes the design of a stimulation system to be used to trial neuromodulation protocols in a home based study of DGNS. The system aims to provide wireless control, deliver appropriate stimulation parameter, be usable by the target population. This development allowed the implementation of stimulation protocols based on timers.
Further to this, bladder diary parameters may be entered at the press of a touchscreen button and all uses of stimulation is logged, enabling us to semi-automate collection of outcome measures during home based studies and determine the values that correspond with stimulation use.

1.2.5 Chapter 6: Pilot Study of Neuromodulation in the Home

Chapter 6 describes a pilot study of DGNS, delivered using the system outlined in Chapter 6. DGNS outcomes are compared to baseline outcomes using ambulatory urodynamic monitoring over two physiological filling cycles and bladder diary outcomes. Data is presented from 5 participants, each with SCI and NDO.

1.2.6 Chapter 7: Future Directions and Conclusions

Chapter 7 proposes specific areas that require further work prior to the delivery of a clinically useful intervention and, finally, we summarise our principal conclusions from each aspect of this thesis.
Chapter 2

Review of Literature

Spinal Cord Injury (SCI) causes severe disruption to neural control of the body, including the Lower Urinary Tract (LUT). This chapter outlines: the structure and function of the LUT; the effects of SCI on the body and specifically on LUT function; and the current treatment options used in cases of chronic SCI for ongoing management of the LUT.

2.1 The Lower Urinary Tract

2.1.1 Structure of the LUT

The LUT is comprised of the urinary bladder and its outlet, the urethra and sphincters. The bladder may be divided into an upper and lower part. The upper part is a compliant, extensible dome, whereas the lower part is fixed and includes the trigone, a triangular area between the three orifices (two ureteral and one urethral orifice). The bladder consists of the detrusor muscle, lined by a mucosal layer called the urothelium [Birder and de Groat, 2007]. The detrusor is a smooth muscle whose fibres are randomly orientated in indistinguishable layers in the upper dome, whilst forming three structured layers at the base. The fibres align to form a funnel orientation down into the urethral orifice.

The outlet to the bladder consists of the smooth and striated urethral sphincters. The internal smooth sphincter is a direct continuation of the smooth detrusor muscle, under similar autonomic control. The external striated sphincter is under voluntary control.

There are differences between the male and female urethra and sphincters. The male urethra is 18-20 cm long with the first 3-4 cm surrounded by the smooth internal sphincter, providing passive continence through sympathetic supply. The following distal 2 cm are surrounded by the striated external sphincter. The female urethra is around 4 cm long, with the proximal two thirds surrounded by the striated external sphincter.
2.1. The Lower Urinary Tract


2.1.2 Function of the LUT

The LUT’s function is to cyclically store and void urine in an efficient, safe and socially acceptable manner known as the micturition cycle. Storage and voiding involve coordination of the detrusor and sphincters which in turn are controlled by complex interactions between central and peripheral components of the sympathetic, parasympathetic and somatic nervous systems.

Storage of urine in the urinary bladder occurs for 99.7% of the time, where smooth detrusor fibres stretch to accommodate an increasing volume, with increasing afferent signals registered in the brain [Mundy, 2010]. Continence is maintained by a relaxed detrusor muscle alongside constricted smooth and striated urethral sphincters stopping flow into the urethra and facilitating low pressure storage.

Voiding occurs for 0.3% of the day (approx 5-8 times a day), it is voluntarily initiated in a switch like manner at a convenient time [Mundy, 2010]. Flow of urine is enabled by coordinated contraction of the detrusor and relaxation of smooth and striated urethral sphincters.

2.1.3 Innervation of the LUT

Innervation of the LUT is complex, involving interaction of the autonomic and somatic neural circuits in the brain, spinal cord and peripheral ganglia. Continence is enabled by sympathetic and somatic input, and voiding enabled through parasympathetic input. Afferent information is conveyed back to central structures through the same nerves.
2.1.3.1 Peripheral innervation

Three peripheral nerves innervate the LUT: the hypogastric (sympathetic), pelvic (parasympathetic) and pudendal (somatic) nerves.

Sympathetic outflow from the intermediolateral thoracolumbar cord [Morgan et al., 1981], T11-L2, is mostly projected through the post-ganglionic hypogastric nerve [de Groat et al., 1981, Blok, 2002]. The sympathetic component of LUT control has the global effects of detrusor inhibition, and of excitation of the bladder neck and urethra via inhibition of parasympathetic activity and direct release of noradrenaline at the bladder wall and neck [Fowler et al., 2008].

Parasympathetic outflow, mediated through the pelvic nerve, provides the main excitatory mechanism for micturition. The pelvic nerve originates from the second to fourth sacral segments of the spinal cord, merging in the pelvic plexus from where fibres reach the bladder dome, causing detrusor excitation, and base, initiating the relaxation of the internal urethral sphincter and enabling micturition [Fowler et al., 2008].

The somatic component of LUT control is mediated through the pudendal nerve. This originates from a pool of motor neurons called Onuf’s nucleus, in the base of the anterior horn of S2-4. This pathway is under reflex and volitional control.

Afferent activity in the bladder is transmitted via sympathetic, parasympathetic and somatic pathways. Predominantly afferent activity from the bladder is carried through the pelvic nerve and dorsal root ganglia to the parasympathetic nucleus. The hypogastric nerve carries some afferent fibres from both the bladder wall and neck. Somatic afferents from the urethra, alongside the rest of the pelvic floor and the striated anal sphincter, travel to the sacral cord through the pudendal nerve [Jänig and Morrison, 1986].

Afferents in the bladder are mostly of Aδ or C type. In the healthy LUT Aδ fibres convey the majority of information about bladder distention and fullness. Humans detect filling through these pathways at a pressure of 5-15 mmH₂O [Jänig and Morrison, 1986]. Aδ fibres are myelinated, low threshold mechanoreceptors. C fibres are unmyelinated fibres which are mostly 'silent', with a high mechanical threshold and sensitivity to pain or cold [Häbler et al., 1990, Fall et al., 1990].

Further afferent activity in the LUT is conducted within the bladder mucosa, the urothelium may control activity in the bladder’s afferent innervation through production of mediators such as ATP, thus participating in the control of micturition reflexes.
2.1.3.2 Control of storage and voiding

During the storage phase, the bladder slowly fills and mechano-sensitive receptors activate an increasing amount of afferent activity that is transmitted through the pelvic and hypogastric nerves [de Groat and Saum, 1972]. This initiates a series of storage reflexes at a spinal level. Afferent activity has been shown to increase sympathetic output to the detrusor (inhibitory) and bladder neck (excitatory), where the afferent branch may involve both pelvic and hypogastric afferents [de Groat and Lalley, 1972, de Groat and Theobald, 1976, Schondorf et al., 1983]. The striated sphincter remains tonically active during storage, maintaining a seal to the bladder and enabling continence. This activity increases with filling, a Guarding reflex demonstrated by sphincter EMG recordings obtained during filling of the bladder [Loewy et al., 1979, Beckel and Holstege, 2011].

Figure 2.2: Storage reflexes controlling the LUT. Beckel and Holstege, 2011. Image reproduced with permission of the rights holder, Springer Nature.

Control of the micturition cycle is believed to act like a switching circuit [de Groat, 1997], under volitional supervision [Yoshimura, 2004]. The Pontine Micturition Centre (PMC) is responsible for this switching that involves coordination of reflexes to enable normal micturition [Barrington, 1925, Loewy et al., 1979]. Stim-
ulation of this region produces a response mimicking micturition: a decrease in urethral pressure, relaxation of the pelvic floor and increase in detrusor pressure [Mallory et al., 1991, Tanagho and Miller, 1970]. Pudendal efferent activity is simultaneously inhibited by interneurons in the sacral cord, rather than directly by the PMC, causing external sphincter relaxation in parallel with the contracting detrusor [Blok, 2002, Blok et al., 1997]. Facilitatory reflexes exist, from urethral afferents to pelvic efferents to assist voiding when urine is flowing through the urethra [Yoo et al., 2007].

2.2 Spinal Cord Injury

The spinal cord, housed within the vertebral canal and meninges, transmits impulses to and from the brain. It extends from the brain stem at the medullary-spinal junction down the spinal canal to approximately the first lumbar vertebrae, below this the lumbar and sacral nerves continue to run down the vertebral canal, forming a bundle of nerve roots called the cauda equina. Peripheral nerves arise from the spinal cord in 31 segmental pairs serving to innervate most of the body. Afferent axons carry sensory information to the spinal cord via the dorsal roots, while efferent axons carry motor commands away via the ventral roots. Both leave the vertebral column through the intervertebral foramina. Generally, ventral and dorsal roots join and sensory and motor axons travel together in spinal nerves to the body [Scanlon and Sanders, 2018].

Injury to the spinal cord (SCI) is a major cause of disability; globally in 2007 there was an estimated incidence of 23 traumatic SCI cases per million (179,312 cases per annum) [Lee et al., 2014], incidence in Europe has been reported as 10 to 58 per million [Noe et al., 2015, Martins et al., 1998]. Non-traumatic SCI is similarly prevalent to traumatic SCI, with 11 to 26 per million [New and Sundararajan, 2008, van den Berg et al., 2012]. There are approximately 40,000 people living with chronic SCI in the UK [Spinal Injuries Association, UK].

Acute SCI is a two step process involving primary and secondary mechanisms. Primary injury is the immediate reaction due to mechanical force being exerted on the spinal cord, secondary injury describes the pathological events initiated by the mechanical insult, encompassing a cascade of biochemical and cellular processes and causing ongoing cellular damage and death. SCI can result from a variety of primary injury mechanisms, the most common occurrence is a combination of impact and persisting compression [Tator, 1995].

Immediately following SCI the body is said to go into neurogenic shock, where there
is a brief increase in heart rate and blood pressure before prolonged bradycardia and hypotension. This neurogenic shock is due to a combination of decreased sympathetic tone and unopposed cardiac vagotonia [Tator, 1995].

Spinal shock, separate to neurogenic shock, is a state entered in the hours following SCI, involving a complete loss of spinal reflexes [Atkinson and Atkinson, 1996]. Muscle spindle reflexes begin to return days to weeks following injury, generally in a caudal to cephalad direction. Further to this, during the period where reflexes are absent, a collateral reorganisation of posterior root input is thought to occur, partially underlying the development of overactive reflex arcs and spasticity that presents as a significant morbidity into the chronic stages of SCI.

The severity of SCI can be assessed both in relation to the level of the lesion (with a high lesion seen as more severe), and also to the ’completeness’ of the injury. This term refers to the extent to which neural pathways remain intact, which may allow some preservation of function below the lesion. This is evaluated clinically using the ASIA scale, where A describes a state where there is no detectable motor or sensory function preserved below the lesion level and E, at the other end of the scale, describes a neurologically intact person [Kirshblum et al., 2011].

In the first 1-2 years of injury the majority of physiological adaptation will occur and the spontaneous recovery of function generally ceases. The chronic stages of SCI are accompanied by ongoing co-morbidities including loss of bone mineral density, lower urinary tract dysfunction, muscle atrophy, decreased cardiac and respiratory output, spasticity and Autonomic Dysreflexia (AD).

AD is a condition that develops following SCI, usually above T6 spinal level and often increasing in severity with high level injuries, where a gross sympathetic outflow is generated as an exaggerated response to stimuli applied below the lesion level [Johnson et al., 1998]. This exaggerated outflow from the splanchnic into the sympathetic system is uninhibited and causes dangerous increases in blood pressure, bradycardia, sweating and headache [Guttmann, 1973]. AD is a common response to painful stimuli associated with the bladder, among other stimuli such as faecal impaction or physical injury below the injury level.
2.2.1 Lower urinary tract function following SCI

The complexity of the healthy LUT, as described in section 2.1, lends itself to a wide variety of neurological problems. SCI, involving disruption to neural pathways, has profound consequences for LUT function.

Supra-sacral injury to the spinal cord leads to disruption in the spinobulbospinal pathways between the pons and the lumbar and sacral control centres [Craggs et al., 2006]. This disruption severely affects the reception of afferent signals, the coordination of storage and micturition reflexes, the voluntary initiation of voiding and control of the striated sphincter. Injury to the lumbosacral cord segments directly interferes with the spinal processing centres involved in LUT control, this type of injury can destroy somatic control and reflex activity and typically leads to chronically flaccid bladder and sphincters in a near opposite response to supra-sacral SCI. This thesis has focussed on chronic supra-sacral SCI, where segmental reflex arcs are left intact.

In the 'spinal shock' period the bladder cannot empty and is routinely catheterised [de Groat, 1995]. Reflexes below the level of transection are then seen to return, in both the limbs and viscera [de Groat, 1998]. As reflex activity returns with the absence of supraspinal input, an aberration in reflex activity develops. This includes Neurogenic Detrusor Overactivity (NDO), where sudden, high pressure contractions of the detrusor muscle occur, leading to urinary incontinence or vesico-ureteric reflux [de Groat et al., 1990]. A combination of reduced supraspinal control and a change in the activity of previously 'silent' C-fibres is believed to cause NDO [Craggs and McFarlane, 1999], responding to low volume filling with reflex micturition. Studies on cats have shown the development of a new spinal micturition reflex, dependent on C-fibre firing [de Groat et al., 1990]. Here, capsaicin was injected into the detrusor of cats to block C-fibre activity, subsequent suppression of NDO was found. Despite being highly effective in cats, this method of capsaicin injection fails to adequately abolish NDO in humans.

A loss of coordination between the detrusor and the sphincters, leading to co-contraction of the EUS and the detrusor, is a further consequence of SCI on LUT function. This co-contraction is termed Detrusor-Sphincter-Dyssynergia (DSD) and both prevents natural voiding and leads to high intravesical pressure [de Groat, 1995, de Groat, 1998].

SCI leads to a loss of sensation in areas of the body innervated caudal to the lesion level. The LUT is similarly impacted meaning afferent information from the sphincters,
detrusor and the wider pelvic region is lost. The loss of sensation may be complete, as it is
in many cases, but is most often partial [Ersoz and Akyuz, 2004].

Loss of LUT function can be a distressing consequence of SCI that precipitates several
health and social issues in the chronic phase of injury. Loss of voluntary control paired with
reduced sensation and unpredictable, uncontrolled detrusor activity may lead to regular in-
continence episodes. The prevalence of incontinence has been reported as 34% in a Korean
study [Lee et al., 2016], 49% in a Danish study of women with SCI [Elmelund et al., 2018],
73% in a Turkish study [Cetinel et al., 2014] and in a UK study 56% [Liu et al., 2010]. Reg-
ularity of urinary incontinence has been reported as daily in 12 to 35%, weekly in 13 to 23%
and monthly in 9 to 21% [Elmelund et al., 2018, Liu et al., 2010].

2.3 A Retrospective Analysis of Bladder Sensation Following SCI

2.3.1 Introduction

To understand whether neuromodulation paradigms such as subject-controlled stimulation
may be widely applicable in our target SCI population, it is important to understand the
prevalence and quality of preserved bladder sensation. To do this, relevant literature was
reviewed and an audit was conducted using the past urodynamic records of the SCI pa-
tient group that attends the urodynamics clinic at the Royal National Orthopaedic Centre’s
(RNOH) London Spinal Cord Injury Centre (LSCIC).

Following SCI, it is often assumed that when the majority of sensation is lost, so is
awareness of bladder filling and/or bladder events. Our experience and the limited literature
suggests that some degree of bladder sensation is prevalent in a majority of SCI patients,
including some of those classified neurologically as ASIA A, or complete. Sensation of
bladder and bowel is important in the chronic management of the bladder, to prevent incon-
tinence and promote emptying at lower pressures.

Ersoz et al. (2004) performed a prospective urodynamics study on 73 persons with SCI
(21 incomplete, 18 complete above T11, 34 complete below T10) [Ersoz and Akyuz, 2004].
Sensation to some degree was observed in 100%, 39 % and 82% of the incomplete, com-
plete above T11 and complete below T10 cohorts respectively. Earlier work reported that
’of the 42 patients, with a lesion diagnosed clinically as complete, 15 (36%) perceived blad-
der filling, electrical stimulation or both stimuli’ [Wyndaele, 1991]. This is reiterated in a
subsequent article from the same author [Wyndaele, 1997].

2.3.2 Methods
Following RNOH internal approval, a review of 345 patients to attend the LSCIC’s urodynamics clinic for standard cystometry (CMG) between 2013 and 2017 was conducted. In the clinic, questions are asked about residual bladder sensation and patient reported sensations of bladder filling are recorded during filling of the bladder [Craggs, 2005]. By manually extracting this data from patient records, we are able to build a picture of the proportion of the SCI population here that have residual bladder sensation, how they report this sensation, and how accurate the sensation is during standard fill urodynamics.

2.3.2.1 Data collection and analysis
The data that was collected from each urodynamics report was: date of investigation, patient age, sex, level of injury, ASIA grade, year of injury, method used for voiding, any treatment to facilitate storage, self-reported urgency, self-reported incontinence (urgency or stress), presence of bladder sensation, whether sensation is used to time voiding, self-reported urgency score reached during CMG (see article by Craggs, 2005), whether reported sensation was confirmed during CMG, whether leakage was seen in CMG, the type of sensation reported.

Data was anonymised and then analysed using Excel (Version 15.14 for Mac, Microsoft, USA).

2.3.2.2 Results
Data was collected from 345 urodynamics reports. Of these 345, 17 had Cauda Equina Injuries and 15 had incomplete records, both were excluded. An SCI population of 313 was analysed, of this population 109 (35%) had complete SCI and 204 (65%) had incomplete injuries.

The mean ($\pm$ std) age was 50 ±17 years and 74 % of the population were male. There was a larger proportion of females in the incomplete subgroup 28% versus 22% in the complete group. Mean age was 50 years in both male and female subgroups, though the average age of the complete subgroup was 45 ±15 years whilst 52 ±17 years in the incomplete group. At the date of investigation, patients were 8 ±11 years from injury, complete patients were 11 ±12 years where incomplete patients were 7 ±10 years from injury.

Some form of treatment for reducing NDO in the storage phase was used by 72% of the group. Antimuscarinic (AM) medication was the most common, 49% used this alone.
2.3. A Retrospective Analysis of Bladder Sensation Following SCI

Eleven percent had received Botulinum-A toxin (BTX) injections alone and a further 12% had combined BTX with ongoing AM. One percent had undergone a posterior roots rhizotomy, performed alongside implantation of a SARS device. Patients were on treatment during the assessment, which is likely to influence the presence and type of sensation reported. Posterior rhizotomy, most extremely, should abolish all sacral sensation, though could in theory still leave visceral fullness type sensation.

Fifty-six percent of the group reported experiencing incontinence at home, 45% reported urge incontinence, 6% stress incontinence and 4% mixed incontinence.

Table 2.1: Population characteristics. IDUC - Indwelling urethral catheter, IDUC clamped - indwelling urethral catheter used with clamping regime, ISC - intermittent self catheterisation, ISC and sheath - intermittent self catheterisation used with sheath, SPC - suprapubic catheter, SPC clamped - suprapubic catheter used with clamping regime, AM - antimuscarinic medication, BTX - botulinum toxin type-A injected into detrusor, BTX and AM - AM used in conjunction with BTX, Rhizotomy - sacral posterior roots rhizotomy performed with sacral anterior root stimulator implantation

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (std)</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>232</td>
<td>74</td>
</tr>
<tr>
<td>Female</td>
<td>81</td>
<td>26</td>
</tr>
<tr>
<td>ASIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>109</td>
<td>35</td>
</tr>
<tr>
<td>B-D</td>
<td>204</td>
<td>65</td>
</tr>
<tr>
<td>Years from injury mean (std)</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Method of voiding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDUC</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>IDUC Clamped</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>ISC</td>
<td>117</td>
<td>38</td>
</tr>
<tr>
<td>ISC and sheath</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Mitrofanoff</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sheath</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SPC</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>SPC Clamped</td>
<td>43</td>
<td>14</td>
</tr>
<tr>
<td>Natural voiding</td>
<td>66</td>
<td>21</td>
</tr>
<tr>
<td>Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>88</td>
<td>28</td>
</tr>
<tr>
<td>AM</td>
<td>152</td>
<td>49</td>
</tr>
<tr>
<td>BTX</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>BTX and AM</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>Rhizotomy</td>
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<td>1</td>
</tr>
<tr>
<td>Incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>137</td>
<td>44</td>
</tr>
<tr>
<td>Urge</td>
<td>139</td>
<td>45</td>
</tr>
<tr>
<td>Stress</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Mixed</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>238</td>
<td>77</td>
</tr>
<tr>
<td>Present</td>
<td>73</td>
<td>23</td>
</tr>
</tbody>
</table>

Bladder sensation was present in 77% of the whole group, 93% of those with incom-
2.3. A Retrospective Analysis of Bladder Sensation Following SCI

Complete injuries and 45% of those with complete injuries. When split into groups of injuries above T11 and injuries below T10, prevalence of sensation was 92% and 98% in incomplete injuries and 47% and 50% in those with complete injuries.

Figure 2.3: Prevalence of bladder sensation amongst people with complete and incomplete SCI, within the LSCIC population.
Table 2.2: Prevalence of bladder sensation reported during urodynamics in those with complete and incomplete SCI above T11 and below T10

<table>
<thead>
<tr>
<th></th>
<th>Above T11</th>
<th></th>
<th>Below T10</th>
<th></th>
<th>All levels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
<td>Incomplete</td>
<td>Total</td>
<td>Complete</td>
<td>Incomplete</td>
<td>Total</td>
</tr>
<tr>
<td>n</td>
<td>89</td>
<td>153</td>
<td>242</td>
<td>18</td>
<td>46</td>
<td>64</td>
</tr>
<tr>
<td>No sensation</td>
<td>52.81%</td>
<td>7.84%</td>
<td>24.69%</td>
<td>50.00%</td>
<td>2.17%</td>
<td>15.62%</td>
</tr>
<tr>
<td>Sensation</td>
<td>47.19%</td>
<td>92.16%</td>
<td>75.31%</td>
<td>50.00%</td>
<td>97.83%</td>
<td>84.38%</td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>203</td>
<td>311</td>
<td>54.63%</td>
<td>6.90%</td>
<td>23.47%</td>
</tr>
<tr>
<td></td>
<td>45.37%</td>
<td>93.10%</td>
<td>76.53%</td>
<td>45.37%</td>
<td>93.10%</td>
<td>76.53%</td>
</tr>
</tbody>
</table>
Table 2.3 shows the type of sensation patients reported as linked to bladder filling. Examples of 'non-specific bladder awareness' include: "sensation of discomfort in lumbar region", "leg and abdominal spasms", "AD symptoms with increased spasm". These sensations were prevalent in 21% of the whole group, or in 32% of complete injuries and 14% of those with incomplete injuries.

There were 221 records of those with self-reported sensation, of all injury levels, that had recorded sensations during bladder filling. Eighty-seven percent of these reports matched recorded sensations with urodynamic findings. Of those classified as having non-specific bladder awareness (n=51), 67% matched urodynamic findings. Whereas 84% of those with reduced sensation (n=57), 97% with normal sensation (n=108) and 100% with pain sensations (n=5) matched urodynamic findings.

Methods used for voiding are shown in table 2.6 for patients with sensation, showing the proportion of each group who report using sensation within their bladder management.
Table 2.3: Proportion of patients with sensation and injuries above T11 whose reported sensations match urodynamic findings

<table>
<thead>
<tr>
<th>Type of sensation</th>
<th>n</th>
<th>Not matched</th>
<th>Matched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced sensation</td>
<td>42</td>
<td>11.90%</td>
<td>88.10%</td>
</tr>
<tr>
<td>Normal sensation</td>
<td>74</td>
<td>1.35%</td>
<td>98.65%</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
<td>0.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Non-specific bladder awareness</td>
<td>45</td>
<td>37.78%</td>
<td>62.22%</td>
</tr>
<tr>
<td>Grand Total</td>
<td>165</td>
<td>13.94%</td>
<td>86.06%</td>
</tr>
</tbody>
</table>

as a signal to empty. Figure 2.5 shows the voiding techniques used across the whole population.

Table 2.4: Voiding method and whether sensation is used by individuals in their chronic bladder management. This only accounts for those who reported having sensation. IDUC - Indwelling urethral catheter, IDUC clamped - indwelling urethral catheter used with clamping regime, ISC - intermittent self catheterisation, ISC and sheath - intermittent self catheterisation used with sheath, SPC - suprapubic catheter, SPC clamped - suprapubic catheter used with clamping regime.

<table>
<thead>
<tr>
<th>Voiding method</th>
<th>n</th>
<th>Does Not Use Sensation</th>
<th>Uses Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDUC</td>
<td>8</td>
<td>75.00%</td>
<td>25.00%</td>
</tr>
<tr>
<td>IDUC clamped</td>
<td>4</td>
<td>25.00%</td>
<td>75.00%</td>
</tr>
<tr>
<td>ISC</td>
<td>80</td>
<td>7.50%</td>
<td>92.50%</td>
</tr>
<tr>
<td>ISC and sheath</td>
<td>3</td>
<td>100.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Mitrofanoff</td>
<td>1</td>
<td>0.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Sheath</td>
<td>7</td>
<td>0.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>SPC</td>
<td>28</td>
<td>60.71%</td>
<td>39.29%</td>
</tr>
<tr>
<td>SPC clamped</td>
<td>42</td>
<td>19.05%</td>
<td>80.95%</td>
</tr>
<tr>
<td>Natural voiding</td>
<td>65</td>
<td>0.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Grand Total</td>
<td>238</td>
<td>17.23%</td>
<td>82.77%</td>
</tr>
</tbody>
</table>

2.3.2.3 Discussion

The results from this retrospective study present the largest published sample of people with SCI assessed with respect to bladder sensation. We provide interesting results which indicate that some form of sensation is present in almost all those with incomplete SCI and in close to half those with complete SCI. This corroborates previous work that found sensation was present in 100% of incomplete injuries (n=21) and in 82.4% of the patients with complete lesions below T10 (n=34), and 38.9% of the patients with complete lesions above T11 (n=18) [Ersoz and Akyuz, 2004]. Our finding of sensation, reproduced during CMG, in 86% of those with supra-sacral SCI (above T11) and reported sensation suggests that in the region of 65% of those with supra-sacral SCI have reproducible and reliable bladder sensation.
2.3. A Retrospective Analysis of Bladder Sensation Following SCI

Fifty-six percent of the population reported symptoms of incontinence, predominantly urge incontinence (45%). This is comparable to previous reports that range from 34% [Lee et al., 2016] to 73% [Cetinel et al., 2014], with a study within our centre also finding that 56% of the population had some history of incontinence [Liu et al., 2010]. Within the subgroup of those who had sensation, and reported using it to time voiding, 58% experienced incontinence. Other aspects of our population are comparable to a previous study within our centre [Liu et al., 2010], where age was 45 ±15 years and 74% was male.

The high prevalence of both incontinence and of sensation, both used in bladder management chronically and confirmed during urodynamic investigation, suggests that self-triggered neuromodulation is a feasible strategy to use prior to the availability of a closed-loop system.

These results are an important precursor to the work presented in chapters 5 and 6, where we aimed to develop a system to trial self-triggered neuromodulation and to assess its use in a range of people with SCI and varying bladder sensation. The wide range of sensations reported by patients and their relevance to functional use in self-triggered stimulation paradigm should be assessed during natural filling of the bladder, this is addressed in Chapter 6.

Our conclusions are limited by the study’s retrospective nature, and, given that it reports on attendees of a urodynamics clinic, may be skewed in favour of those with ongoing urological issues. Whilst our results are valuable, future prospective studies should be con-
ducted to better define the SCI population with regards to bladder sensation.

2.4 Current LUT Management

The loss of ability to void and the overactivity of reflex pathways leads to distinct problems for safe management of micturition and storage. Clinical management goals are to maintain low pressure storage, maintaining continence until an appropriate time to void, and to allow efficient voiding at a socially convenient time leaving low residual volume [Drake et al., 2016a].

2.4.1 Voiding

To enable efficient voiding at low pressures following supra-sacral SCI there are several options employed to overcome DSD and the lost voluntary drive of the detrusor.

2.4.1.1 Catheterisation

Urine may be voided from the bladder by the introduction of a catheter into the bladder, this may be left in place for longer periods of time, indwelling catheterisation, or performed intermittently to void the bladder before removing the catheter, intermittent catheterisation.

Intermittent self catheterisation (ISC) involves the insertion of a disposable catheter through the urethra into the bladder to allow emptying of urine, performed approximately 4-6 times a day on urge or scheduling. This is currently seen as the gold standard intervention [Drake et al., 2016a, Weld and Dmochowski, 2000], however there are issues limiting applicability to 41% of persons with SCI [Krebs et al., 2015]. Limitations include gender, level of physical impairment, mental impairment and social situation. It has previously been reported that tetraplegia, gender, age and duration of injury all significantly increase the odds of indwelling catheter usage following SCI [Krebs et al., 2015]. ISC has been linked to greater incidence of urinary incontinence than indwelling catheter use [Elmelund et al., 2018], this may be one barrier to greater uptake. Whilst ISC has been shown to be safer than other techniques [Weld and Dmochowski, 2000], users of ISC who require an attendant to perform ISC have been found to have the worst emotional condition [Liu et al., 2010] and increased risk of depression [Oh et al., 2005]. The mitrofanoff procedure, creating an artificial outlet to perform catheterisation through, is a surgical option that may enable catheterisation to be performed by an increased population of patients [Abrams et al., 2008].

Indwelling catheter usage is recommended in cases where intermittent catheterisation
is not possible. This may be indwelling urethral catheters (IDUC) or supra-pubic catheters (SPC). Long-term satisfaction of SPC has been reported as good, although there may be additional risk of urinary tract damage potentially when free drainage is used continuously [Sheriff et al., 1998].

2.4.1.2 Reflex voiding and sheath drainage

Triggered reflex voiding and external expression techniques are no longer recommended techniques for voiding due to the high intra-detrusor pressures generated and, in the case of external expression, the high rate of renal complications seen [Drake et al., 2016a]. This change in recommendation is highlighted in a 20 year follow up of 80 of the same SCI patients in the UK between 1990 and 2010 that showed the percentage using expression/straining reduced from 15.2% to 7.1% [Savic et al., 2018]. This older population (time from injury) also had a lower percentage of ISC users at 18.8% in 2010, yet up from 3.8% in 1990, relative to the 41% reported more recently [Krebs et al., 2015].

Condom, or penile sheath, drainage is a method of managing incontinence by externally attaching a drainage bag to a sticky penile sheath allowing social continence for people with continuous leakage. It is an extremely popular method of bladder management historically, often combined with intermittent catheterisation to void residuals. The size of the population using sheath drainage does appear to be dropping, those using condom drainage from 49.4% to 29.4% in the same UK study [Savic et al., 2018], perhaps in line with the increased range of techniques available for managing incontinence.

2.4.1.3 Pharmacological or surgical intervention

Where DSD is present, alpha blockers such as Tamsulosin can be used to reduce outlet resistance. In a similar vein, less conservative approaches to reducing outlet resistance include surgery such as sphincterotomy, where the striated sphincter is injured to reduce its efficacy [Abrams et al., 2008].

2.4.1.4 Sacral anterior root stimulation

Sacral Anterior Root Stimulation (SARS) is a method for bladder emptying developed by Brindley and delivered using the Brindley-Finetech stimulator [Brindley, 1977]. SARS targets efferent fibres as they exit the sacral cord using implanted electrodes. By using on demand stimulation from an external stimulator patients are able to void efficiently. Alongside on demand, efficient, voiding of the bladder, a reduction in residual volumes and urinary tract infections is seen, and stimulation may be used to elicit a bowel move-
ment or an erection in men. Since the first implants over 30 years ago there has been over 2500 implanted worldwide and several reviews have outlined the device’s efficacy [Van Kerrebroeck et al., 1993, Brindley, 1994].

However, there are significant downsides to this device. Due to the pre-existing NDO and DSD associated with SCI, rhizotomy of the sacral posterior roots is required to eliminate incontinence. Posterior rhizotomy is irreversible and leads to loss of reflex erectile and bowel function as well as a loss of all sensation from dermatomes linked to the cut roots. Therefore, it is currently only indicated for people with complete SCI who are willing to have this destructive procedure.

2.4.2 Storage

NDO must be managed to enable low pressure, predictable storage of urine and to reduce incontinence. Current management options include behavioural, pharmacological and surgical techniques [Drake et al., 2016a].

2.4.2.1 Pharmacological

Cholinergic transmission is a major excitatory mechanism in the bladder, the first line treatment for NDO is a range of anticholinergic, or antimuscarinic, medications that target acetylcholine transmission in the smooth (detrusor) muscle [Drake et al., 2016a]. These include Oxybutinin [Yarker et al., 1995], Solifenacin [Krebs and Pannek, 2013], Tolteridine [Nilvebrant et al., 1997] and Tropsium chloride [Stöhrer et al., 1991]. Unfortunately, antimuscarinics are often discontinued due to lack of efficacy or side effects such as dry mouth or constipation [Kessler et al., 2011]. Further to this there are concerns about the long-term effects of antimuscarinic medication on cognitive function and decline [Gray et al., 2015].

Beta-3 adrenoreceptor agonists are a more recently developed medication to manage bladder overactivity and, where antimuscarinics target parasympathetic pathways, stimulate sympathetic pathways causing bladder relaxation. This aims to reduce detrusor activity and may be used in a complimentary manner to antimuscarinics to good effect [Drake et al., 2016b, Wöllner and Pannek, 2016].

2.4.2.2 Botulinum-A Toxin

Surgical techniques for storage of urine include the injection of Botulinum-A Toxin (BTX) into the detrusor muscle, injecting 20 to 30 sites and sparing the trigone [Schurch et al., 2000]. BTX has generated excellent results in clinics [Reitz et al., 2004, Patki et al., 2006]. However, it requires repeat injections and the long term outcomes are
unknown.

2.5 Neuromodulation: an alternative solution for NDO?

As discussed, there are methods deployed by clinicians that aim to address the problems in storage of urine posed by SCI, commonly including antimuscarinic (AM) medication and Botulinum-A Toxin (BTX) injections. The high prevalence of incontinence still reported in the SCI population illustrates the remaining need for new methods to manage the storage of urine [Elmelund et al., 2018, Liu et al., 2010]. Existing therapies are able to reduce peak detrusor pressure, increase bladder capacity and reduce incontinence episodes. However, each has its downsides and none are able to restore control over bladder activity.

Electrical stimulation of afferent pathways linked to control of the bladder has been shown to improve symptoms of bladder overactivity in a variety of pathologies, including acute suppression of NDO following SCI [Gaunt and Prochazka, 2006, Craggs and McFarlane, 1999, McGee et al., 2015]. Whilst acute studies have shown excellent results for restoring some level of control over the LUT, no devices are commercially available for clinical treatment of people with SCI. The next sections review the techniques that have been used in the past both in acute and chronic settings.

2.5.1 Putative mechanisms of neuromodulation of the LUT

Neuromodulation, electrical stimulation and neurostimulation are variously described in literature as all encompassing terms for stimulation of the nervous system. For the purpose of clarity, in this thesis I use the term electrical stimulation to describe the act of applying electrical stimuli to the body, neurostimulation to describe the stimulation of nervous tissue and neuromodulation, following the definition of Craggs and McFarlane (1999), to describe the act of modulating pre existing neural activity through synaptic interaction by applying external stimuli, in this case electrical stimulation.

The mechanism of neuromodulation of the lower urinary tract may be described at several levels, from activity at the synapse, to more global accounts of excitation or inhibition at specific points in the nervous system. From the large number of studies that have been conducted, it is clear that different neuromodulation strategies exploit different mechanisms and may be more or less suitable for different pathologies and individuals. Indeed, the precise mechanism (or combination of mechanisms) of action for a continuous sacral nerve stimulation system used in an idiopathic OAB group may be different to that of posterior
tibial nerve stimulation used in a neurogenic MS group, or dorsal genital nerve stimulation
used in a group with complete SCI. However, there are similarities that appear to be true for
all.

That neuromodulation works via activation of afferent pathways is commonly
agreed now, where it had been thought that inhibition was achieved through activa-
tion of the pelvic floor which in turn relaxed the bladder via intramural ganglion cells
[Tanagho and Schmidt, 1988], it has now been shown that stimulation of purely affer-
ent nerves such as the dorsal genital nerve has similar effects to stimulation of mixed
nerves such as the pudendal or sacral nerves, and that stimulation of mixed nerves be-
low the motor threshold also has an ongoing neuromodulatory effect. There are sev-
eral stimulation sites that appear to elicit the same effect on the LUT and it is thought
that stimulated fibres must enter the central nervous system at the same region as af-
ferent fibres travelling from the LUT, in the lumbosacral cord. Commonly, stimulation
at distinct sites including the genital nerve, tibial nerve and sacral nerves are all able
to act on the sacral cord and all appear to reflexively stimulate the striated sphincters
[Varma et al., 1986, Sheriff et al., 1996, Previnaire et al., 1996, Pedersen et al., 1978].

With afferent activity having entered the lumbosacral cord, neuromodulation of the
LUT has been seen to work in several distinct ways. It can be applied conditionally, to
acutely modulate overactivity of the micturition reflex and suppress neurogenic detrusor
overactivity [Kirkham et al., 2001] or urgency [van Breda et al., 2016]. This modulation
appears to remain intact following complete transaction of the spinal cord, showing that
neuromodulation can occur at a spinal segmental level. It can be applied continuously,
where either NDO can be held at bay for a period (again following complete SCI) or OAB
symptoms may be reduced. For those with OAB symptoms, including both with and with-
out urinary incontinence, it is thought that stimulation of sacral nerve fibres modulate fore
brain structures involved in awareness and alertness, which in turn are able to modulate
the PMC, leading to the micturition switch, from storage to voiding, not being activated
[Blok, 2018]. Neuromodulation may also occur when stimulation is applied intermittently,
where a regime of stimulation either applied daily or weekly over several weeks appears
to lead to to significant reduction in LUT symptoms in OAB and some neurogenic groups
[Peters et al., 2013, Zecca et al., 2016]. This carryover effect does not always appear to be
present, and may rely upon access to supraspinal structures (not present following com-
plete SCI) to allow plastic changes within the brain. Functional imaging studies of various stimulation paradigms have shown changes in brain activity over prolonged use of neuromodulation [Zempleni et al., 2010] and during stimulation [Gill et al., 2017].

For stimulation to effectively inhibit reflex activity at a spinal level it may be that small diameter A$_{\delta}$ and C-type nerve fibres must be activated, requiring greater amplitudes of stimulation to be applied and higher likelihoods of failure. This has been seen in animal studies [Sato et al., 1983] and in human studies of genital nerve stimulation where stimulation amplitude is linked to inhibition [Bourbeau et al., 2018a]. This does not appear to be the case in those with idiopathic symptoms, where lower level stimulation still appears to have significant neuromodulatory effects [Peters et al., 2013, Blok, 2018].

The inhibitory effect on the detrusor at a spinal level, at least during genital nerve stimulation, is down to activation of inhibitory reflexes mediated by both sympathetic and parasympathetic systems. This may act at low volumes through the hypogastric nerve, a sympathetic mechanism and at high volumes through a parasympathetic mechanism involving the pelvic nerve [Lindström et al., 1983]. A further effect promoting continence appears to be due to activated sympathetic pathways controlling the bladder neck [Reitz et al., 2003] and contraction of the EUS.

For developing an appropriate and effective intervention it is important to be able to define the best protocol for each pathology where neuromodulation is to be applied and to understand the mechanisms of observed effects.

### 2.6 Stimulation Sites for Reducing Bladder Overactivity

The array of neural pathways responsible for LUT control presents many potential targets for therapeutic intervention, as outlined by Gaunt and Proschaka (2006), see figure 2.6. Here, we review techniques that have been previously tested in humans with SCI, with potential for clinical translation using surface stimulation.

#### 2.6.1 Dorsal genital nerve stimulation

The pudendal nerve originates from the S2-4 segments of the sacral spinal cord and stimulation of pudendal afferents has been shown in clinical studies to both inhibit and excite bladder voiding reflexes when applied at different frequencies [Kirkham et al., 2001, Yoo et al., 2007].

The Dorsal Genital Nerve (DGN) is a purely afferent branch of the pudendal nerve
that provides sensory innervation to the penis and clitoris. It is a superficial nerve accessible via surface stimulation of the penis or clitoris. DGN stimulation (DGNS) is able to evoke reflex contractions in the anal and urethral striated sphincters, the pudendo-anal or -urethral reflexes [Podnar and Vodusek, 2001], and a longer latency response in the internal sphincter [Reitz et al., 2003]. It has been shown in several acute urodynamic studies to robustly suppress NDO, reduce incontinence and increase bladder capacity in SCI and other neurogenic patient populations [Vodusek et al., 1986, Nakamura and Sakurai, 1984, Kirkham et al., 2001, Goldman et al., 2008, Fjorback et al., 2006, Horvath et al., 2010, Opisso et al., 2008, Godec and Cass, 1978, Brose et al., 2018, Bourbeau et al., 2018a, Lee et al., 2011, Dalmose et al., 2003, Previnaire et al., 1996, Lee et al., 2003].

DGNS is thought to activate a reflex striated sphincter and bladder neck response, alongside inhibition of the overactive detrusor muscle, thus providing a coordinated storage response [Reitz et al., 2003, Lindström et al., 1983]. Importantly for translation in SCI, DGNS elicits a reflex bladder inhibitory response that remains present following complete
2.6. Stimulation Sites for Reducing Bladder Overactivity

spinal cord transection [Tai et al., 2011, McGee et al., 2015].

A recent meta-analysis of eight studies, involving 97 participants, showed that DGNS increased bladder capacity from baseline by 131 ± 101 ml, providing an increase of 50 ml or greater in 79/97 of individuals. Alongside increasing capacity, peak detrusor pressure was reduced and the time before incontinence occurred was increased [Bourbeau et al., 2018a].

There have been several successful studies of DGNS in the laboratory environment, though only a handful of studies have trialled the technique out of the lab. These are discussed in section 2.8.2.

The use of DGNS on an ongoing basis presents problems in application and acceptability. This could be avoided should stimulation of less intimate sites elicit a comparable suppressive effect on NDO. Should stimulation of alternative sites be insufficient, further work is required on improving device’s acceptability and on appropriate stimulation electrodes.

2.6.2 Tibial nerve stimulation

The tibial nerve is a mixed nerve, a branch of the sciatic nerve, containing fibres projecting from L4 to S3 spinal segments. The tibial nerve is not involved explicitly in LUT control, however it originates from the same spinal segments in the cord as the pelvic and pudendal nerves that control the lower urinary tract. Tibial Nerve Stimulation (TNS) was first shown to inhibit detrusor overactivity by McGuire et al. in 1983, since then testing of TNS has taken many forms.

TNS is used clinically for the treatment of Overactive Bladder (OAB) syndrome and similar idiopathic lower urinary tract symptoms. It is generally delivered percutaneously, intermittently in weekly 30 minute sessions, with stimulation set at a comfortable amplitude between 0.5 and 9 mA, using 200 µs pulses at 20 Hz. This has been investigated in large randomised controlled trials versus sham, AM medication and in long follow-ups of three years [Peters et al., 2010, Peters et al., 2009, Peters et al., 2013]. These studies have shown significant improvement in OAB symptoms of urinary frequency, urgency, nocturia and urge incontinence. However, diary results report relatively small improvements that were not significant against sham results [Peters et al., 2010]. In addition to percutaneous delivery, both transcutaneous stimulation [de Sèze et al., 2011] and implanted device studies [Heesakkers et al., 2017] have shown similar improvements to the percutaneous approaches in both neurogenic and OAB populations, though each has been studied in smaller popu-
2.6. Stimulation Sites for Reducing Bladder Overactivity

lations and without sham control. Whilst results are encouraging for several populations, much is unknown regarding how best to deliver TNS, how to predict success and regarding the mechanism of its therapeutic effect.

The acute effect of TNS has been studied using urodynamic testing with mixed results. One study, involving a mixed neurogenic population, applied transcutaneous TNS continuously during bladder filling, at an amplitude below that required to elicit a motor contraction of the toes. In this study, 22/44 participants had a positive response to TNS, defined as either greater than 50% or 100 ml increase in the volume at first detrusor contraction or at Maximum Cystometric Capacity (MCC). This study included 15 participants with SCI [Amarenco et al., 2003]. Kabay et al. (2008 and 2009) have found continuous, percutaneous TNS to have an acute effect on bladder filling in trials with both Multiple Sclerosis (MS) and Parkinsons Disease (PD) populations. In the MS trial the volume at first detrusor contraction increased from 138 ± 6 ml (60 to 225 ml) to 230 ± 9 ml (145 to 375 ml) during stimulation, in the PD trial similar (significant) changes were seen when TNS was applied [Kabay et al., 2008, Kabay et al., 2009]. Both of these studies trialled stimulation following a baseline fill, with no post stimulation control fill or randomisation of order. This study design may be susceptible to an effect of repeated bladder filling on bladder capacity [Ockrim et al., 2005].

Successful application of TNS in SCI has previously been reported in a case report [Andrews and Reynard, 2003] where bilateral, transcutaneous, TNS was delivered at 20 Hz during standard cystometry. The stimulation was started midway through bladder filling and applied continuously until the end of each fill. Both volume at first detrusor contraction and MCC were increased, with some carry-over effect noted.

Whilst TNS appears to have the capacity to improve bladder outcomes, one study with participants with NDO and MS trialled conditional stimulation, applied at the onset of a detrusor contraction, and found TNS to have no effect. This was following finding acute suppression of NDO using DGNS in the same participants [Fjorback et al., 2007b]. A study conducted in cats showed that bladder inhibition elicited in cats with no SCI was abolished following spinal cord transection, suggesting a supra-spinal role in TNS induced bladder inhibition [Xiao et al., 2014]. Should some connection with supra-spinal centres be a necessity, it may be that TNS only works in those with partial lesions.

The tibial nerve is an appealing target for chronic stimulation treatments due to its ease
of access and the potential for using either transcutaneous or implantable stimulators with existing technology. However there is a paucity of knowledge on the acute effect of TNS on the LUT, its applicability to SCI and its mechanism that needs addressing.

### 2.6.3 Sacral nerve stimulation

Sacral Nerve Stimulation (SNS) targeting the S3 spinal nerve, is a widely used approach for treatment of OAB syndrome and various other non-neurogenic LUT symptoms. It has been used in a limited number of neurogenic cases with mixed results in incomplete SCI [Chartier-Kastler et al., 2000, Wöllner et al., 2016]. A study of its acute effect during urodynamics with people with incomplete SCI reported significant changes in maximum bladder capacity, detrusor pressure or bladder volume at first detrusor contraction [Chartier Kastler et al., 2001].

There have been several reports of improvement in LUT dysfunction using transcutaneous stimulation in OAB populations [Quintiliano et al., 2015, Barroso et al., 2013, Walsh et al., 1999] in addition to implantable devices, although also a study reporting no effect on NDO in a small MS cohort [Fjorback et al., 2007a].

An acute inhibitory effect of SNS on NDO has been shown in several animal studies [Ren et al., 2016, Su et al., 2012, Snellings and Grill, 2012]. Using magnetic stimulation, NDO has been acutely suppressed in humans with complete SCI [Sheriff et al., 1996] and interestingly, early application of SNS in the acute stages of complete SCI has prevented the development of NDO in the chronic phase of injury [Sievert et al., 2010].

### 2.6.4 Spinal stimulation

Spinal Stimulation (SS), using transcutaneous or epidural stimulation of the dorsal surface or dorsal roots of the spinal cord at the level of the T12 vertebra, has had promising reports of improved lower limb and bladder control from both pre-clinical and clinical studies [Gad et al., 2016, Ren et al., 2016, Harkema et al., 2011, Gerasimenko et al., 2015, Hofstoetter et al., 2014, Herrity et al., 2018, Gad et al., 2018]. A study of epidural stimulation conducted with MS participants has reported acute improvements in LUT function, including in the suppression of NDO with some carry-over effect noted [Meglio et al., 1980]. Animal work has reported acute suppression of detrusor contraction using both dorsal root and sacral nerve stimulation in rats, whilst stimulation of ventral roots was unable to suppress detrusor activity [Ren et al., 2016]. More recently, application of epidural, magnetic and transcutaneous SS has yielded promising results for both storage and voiding, each
in pilot studies involving humans with chronic SCI [Herrity et al., 2018, Gad et al., 2018, Niu et al., 2018].

2.7 Triggers and Regimes for Neuromodulation

2.7.1 Modes of application

Neuromodulation may be applied in several distinct ways. Continuous neuromodulation involves continuous provision of stimulation pulses applied to the target area. This method is used successfully in ongoing treatment of several bladder related conditions using implantable sacral nerve stimulators such as the Medtronic Interstim (Medtronic, USA) [van Kerrebroeck et al., 2007]. Continuous DGNS has been shown to reduce NDO during acute urodynamic studies [Nakamura and Sakurai, 1984, Vodusek et al., 1983, Previnaire et al., 1996, Kirkham et al., 2001] and also in limited long-term studies [Bourbeau et al., 2018b, Wheeler et al., 1994]. There is concern that chronic use of continuous neuromodulation may lead to habituation of the reflex pathways believed to be required for the technique to work, as well as issues with skin irritation, and would require large battery capacity to deliver over longer periods. However, a recent one month long intervention of continuous neuromodulation in two people with SCI found there to be no habituation of reflexes and no adverse effects [Bourbeau et al., 2018b].

Intermittent neuromodulation is the application of stimulation in time-based patterns, for example for one hour on, four hours off; or for five seconds on, five seconds off. Intermittent DGNS has been previously trialled in a small SCI study, reporting results equivalent to continuous stimulation when using a five seconds on five seconds off paradigm [Stöhrer et al., 1999]. Several periods of intermittent stimulation trialled using the Medtronic Interstim for SNS were as successful as continuous stimulation [Nguyen et al., 2017].

Conditional neuromodulation involves starting the stimulation at the onset of an episode of bladder overactivity, requiring a reliable trigger. Studies where this trigger was based on detrusor pressure demonstrated that conditional neuromodulation can be as effective as continuous neuromodulation in increasing bladder capacity and reducing incontinence [Kirkham et al., 2001, Hansen et al., 2005]. A person with residual sensations may use the system in open loop mode, selecting when to initiate the neuromodulation based on sense of urgency. However, for users without residual sensations, or for closed-loop control, the physiological process from which the trigger is derived (detrusor activity or other), must
be monitored and fed back appropriately.

2.7.2 Triggers for conditional neuromodulation

There have been many approaches to finding an appropriate trigger for conditional neuromodulation previously tested, though currently there is no system that has established efficacy for chronic use, either as an approved product or prototype [Melgaard and Rijkhoff, 2014]. I have outlined below some of the approaches that may be appropriate for the SCI population.

2.7.2.1 Electromyography (EMG) and electroneurography (ENG)

Detrusor electromyography (EMG) would seem like an ideal starting place for developing a feedback system reporting on muscle activity. However, the ability to detect such a signal remains elusive [Ballaro et al., 2003]. The core problem lies in that smooth muscle action potential is calcium dependent. Therefore, rather than a large extracellular electrical signal, as seen with striated muscle activity, which reflects the net change in potential produced by transmembrane sodium currents, the extracellular signals generated during smooth muscle activity are so small they remain undetectable [Ballaro et al., 2003].

Striated sphincter EMG, of both the external anal sphincter (EAS) and the external urethral sphincter (EUS), have been evaluated with success as indicators of NDO. Being striated muscles they are not subject to the same issues as the detrusor and it is possible to record a good signal using surface electrodes. Due to the occurrence of dyssynergic sphincter activity with NDO following SCI, as discussed in Chapter 2, it is possible to detect the occurrence of a detrusor contraction by measurement of the external sphincter with good accuracy, both in animals and in humans [Knight et al., 2018, Hansen et al., 2007, Wenzel et al., 2006]. Indeed, a study of six SCI individuals trialling an EMG and stimulation device placed in Alcock’s canal found a positive predictive value of $0.8 \pm 0.2$. Issues remain prior to implementation of this technique in terms of electrode placement, particularly in terms of safety and acceptability of chronic electrode placement inside of the anal canal or urethra of persons with limited sensation. No testing has yet established the value of EMG obtained outside of a controlled laboratory setting.

Electroneurography (ENG), measuring the electrical activity of afferent sacral nerve roots or pudendal nerves is correlated with bladder pressure, and can be used to detect bladder contractions in animals and humans. It is a further avenue of research that holds promise yet is restricted due to the small signals, the conflicting signals in the
nerves such as from sacral dermatomes and the lack of appropriate and approved devices [Chew et al., 2013, Mendez et al., 2014].

While conditional stimulation should consume less energy than continuous stimulation, the power consumption of any system monitoring signals in order to trigger stimulation must be evaluated and negate the energy saved.

2.7.2.2 Pressure measurement

Measurement of pressures within the bladder and abdomen is known to provide a suitable feedback signal for conditional neuromodulation, having been proved to be efficacious in several laboratory studies in the SCI population [Kirkham et al., 2001, Fjorback et al., 2003, Opisso et al., 2008]. However, a catheter is required to be inserted into the bladder and rectum to obtain such a signal and it is recognised that this is not suitable for chronic use. A one channel pressure measurement system, able to detect detrusor activity without the abdominal pressure line providing a reference, may be an attractive option should a pressure measurement device be implanted in the bladder wall [Majerus et al., 2017] or for chronic indwelling catheter users who may use a pressure measurement device attached externally. Recent work on use of software functions to filter one channel of pressure data to be able to detect bladder events is promising [Karam et al., 2015, Karam et al., 2016] and this may be a technique possible to integrate with some of the SCI population in the foreseeable future. For the implementation of implantable devices, lessons must be learnt from the past, where although initial results from implanted sensors on the bladder wall were efficacious, in 4/4 patients trialling a system devised by Brindley and Donaldson the sensors were detached from the bladder wall within one year [Brindley and Donaldson, 1986]. Ongoing research into implantable pressure measurement devices is promising, the miniaturisation of instrumentation and processing hardware alongside extremely low-power consumption may make this avenue increasingly feasible [Clausen et al., 2018].

2.7.2.3 Bladder volume measurement

Methods for estimation of bladder volume may provide feedback for a closed loop neuromodulation system or directly to people with SCI to inform their bladder management. To achieve this, several techniques may be used. Ultrasound devices are used clinically for this purpose, with portable devices commercially available, including the Bardscan device, however these devices are very bulky and not suited to chronic, real-time measurement.
2.7. **Triggers and Regimes for Neuromodulation**

Functional Near-Infrared Spectroscopy (fNIRS) is another non-invasive imaging technique that may be used for estimation of bladder volume. Recent work on this technique has been able to distinguish between the full and empty bladder in phantoms and a healthy volunteer, though the accuracy and clinical usefulness of such a device is yet to be tested [Fong et al., 2018]. The core problems for translation of these techniques into a chronically usable device are: the size of the device required, the unknown accuracy during day-to-day life, and the method of application for use outside of a clinical setting.

### 2.7.2.4 On-demand stimulation

Subject controlled, conditional neuromodulation may be the most feasible approach to developing a working system. In such a system the person with SCI must retain some sensation of bladder fullness or overactivity to reliably trigger neuromodulation early enough following the onset of NDO to be able to suppress it. This method has been tested during standard CMG, where subject controlled stimulation was as effective as conditional stimulation triggered at a rise in detrusor pressure [Opisso et al., 2008]. In this study, 17 participants retained enough sensation to trial subject controlled stimulation, of 33 participants who had originally trialled DGNS regardless of sensation. A concern using this technique is the ability of patients to quickly recognise, and trigger, stimulation reliably, at the beginning of NDO. Another study found that on average five seconds was taken by participants to trigger a stimulator [Fjorback et al., 2006]. Opisso et al. found that people took considerable time to press the button and/or to detect that the detrusor contraction was occurring. A study assessing suitability of residual sensation for triggering a conditional neuromodulation system reported that 73% of participants has residual sensation in daily life. During conventional CMG 73% of those with NDO could detect NDO, within this group 72% of NDO episodes were detected a mean of 16 seconds following onset. Only 41% were able to detect NDO during natural fill urodynamics, detection rate was 23% at a mean time of 57 seconds following onset [Martens et al., 2010].

The bulk of home trials of DGNS suggest that residual sensation, when present following SCI, is a suitable and feasible trigger for conditional neuromodulation [Lee and Creasey, 2002, Lee et al., 2011, Lee et al., 2012, Opisso et al., 2008, Opisso et al., 2013, Fjorback et al., 2006, Bourbeau et al., 2018b]. However, it is necessary to establish the proportion of the SCI population who may benefit from this technique and to thoroughly assess the suitability of an individual’s residual sensation for triggering of neuromodulation and to
implement a controller that will reduce the time required to access stimulation triggers. It is also necessary, as demonstrated by Martens et al. (2010), to assess the ability of individuals with sensation to trigger DGNS appropriately during urodynamic monitoring. Given the discrepancy of accuracy in NDO detection between natural-filling and retrograde-filling urodynamics, it is important to assess this trigger in the closest to real life way, ambulatory urodynamic monitoring.

In a further development of on-demand neuromodulation, semi-conditional neuromodulation was trialled in SCI participants [Lee et al., 2011, Lee et al., 2012]. This involved using subject initiated stimulation, which was then performed automatically in an intermittent fashion. The intermittent regime was determined by previous urodynamics, taking the off time as the minimum time found between consecutive detrusor contractions, minus 5 seconds.

2.8 Home Use of Neuromodulation in SCI

Use of neuromodulation to manage the LUT following SCI has mostly been confined to laboratory based experiments. Some studies have trialled neuromodulation techniques in user’s home environments with mixed results. Some have reported success with the intervention, though noting that devices were unsuitable for long term use, and others have reported that techniques were ineffective.

2.8.1 Sacral nerve stimulation

The Finetech-Brindley Sacral Anterior Root Stimulator (SARS) is a system with impressive results over the long-term for the provision of efficient voiding following complete SCI [Van Kerrebroeck et al., 1993]. A significant downside to the device, is that it requires posterior root rhizotomy to enable efficient emptying and abolish NDO. As discussed, another method of abolishing NDO is the stimulation of sacral afferents. In a case study involving five participants with complete SCI, this was achieved using a SARS device. The device was implanted encapsulating mixed nerves or both anterior and posterior roots, without performing a rhizotomy, and therefore able to stimulate the posterior roots of S2-4 (SPARS) [Kirkham et al., 2002].

Three of five participants still had NDO during urodynamic testing post-operatively. All three responded positively to neuromodulation applied during CMG in the laboratory. One participant went on to use the system at home, using colostomy products to attach
the external pulse generator for delivery of continuous and intermittent (on/off) stimulation regimes. Neuromodulation was trialled intermittently over 4 months. The median volume at self-catheterisation (excluding volume leaked) was 100 ml in the control period, and 250 ml in each of the continuous, on/off and oxybutynin periods subsequently trialled [Kirkham et al., 2002].

Implantable SNS devices, targeting the S3 nerves as the exit the foramen, are widely used to treat LUT symptoms [van Kerrebroeck et al., 2007] and have been trialled in a small number of people with SCI. In one instance, Medtronic Interstim (Medtronic, USA) implants were tested in 2 people with SCI and NDO. Both experienced significant improvement in frequency, voided volumes and incontinence events recorded in bladder diaries. Only one showed improvements in MCC during urodynamic evaluation. After 6 months, baseline urodynamic parameters were unchanged [Chartier-Kastler et al., 2000].

A later retrospective analysis, including 35 people with SCI and NDO, found 67% of people with NDO responded, defined as a 50% or greater improvement in symptoms and patient satisfaction, to SNS during a percutaneous evaluation period. Following implantation, 80% of patients reported being continent and there were significant decreases in pad use. Eight complications were observed from 35 implants, 2 were explanted and 6 were technical failures [Wöllner et al., 2016].

SNS has had promising results in both complete and incomplete SCI for reduction of symptoms and improvement in urodynamic parameters over long periods. However, failure rates are not insubstantial and procedures are invasive.

2.8.2 Home based DGNS studies

There have been just 5 studies published trialling DGNS to suppress NDO following SCI in participants’ homes [Bourbeau et al., 2018b, Opisso et al., 2013, Lee and Creasey, 2002, Lee et al., 2012, Wheeler et al., 1994], including a total of 25 SCI participants, 19 of whom completed the respective studies.

Four of the 19 participants used a continuous stimulation paradigm [Wheeler et al., 1994, Bourbeau et al., 2018b], the remaining 15 triggered stimulation on urge [Bourbeau et al., 2018b, Opisso et al., 2013, Lee et al., 2012, Lee and Creasey, 2002]. Six of the 15 trialled semi-conditional stimulation, where an automatic on-off regime of stimulation persisted after the user had triggered on urge [Lee et al., 2012], and 9/15 used stimulation controlled manually (on urge) [Bourbeau et al., 2018b, Lee and Creasey, 2002, Opisso et al., 2013].
2.8. Home Use of Neuromodulation in SCI

Outcome measures were recorded using standard cystometry (CMG), bladder diaries and video CMG and varied across studies. Table 2.5 and 2.6 outline the results.
Table 2.5: Outline of previous home based studies of DGNS with SCI participants

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of participants</th>
<th>Test for DGNS effect</th>
<th>Control period</th>
<th>DGNS period</th>
<th>Outcome measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeler, JS et al. Management of incontinent SCI patients with penile stimulation: preliminary results. J Am Paraplegia Soc. 1994 Apr;17(2):559.</td>
<td>9 (8 SCI, 2 completed the study)</td>
<td>Baseline CMG then repeated CMGs with DGNS</td>
<td>2 weeks</td>
<td>6 weeks</td>
<td>Pre and post CMG, incontinence diary</td>
<td>P01 used for 8 weeks increased MCC from 110 to 150 mL, CMG, MDP decreased from 100 to 60 cmH2O. Diary volumes increased from 180 to 300 mL. P02 became continent but used intermittently for 3 weeks reporting increase in time between CISC 1 to 2.5 hours.</td>
</tr>
<tr>
<td>Lee, Y-H and Creasey GH. Self-controlled dorsal penile nerve stimulation to inhibit bladder hyperreflexia in incomplete spinal cord injury: A case report. Archives of Physical Medicine and Rehabilitation. 2002 Feb;83(2):2737.</td>
<td>1</td>
<td>Baseline CMG, then rapid infusion 'provoked' to test suppression with DGNS</td>
<td>None</td>
<td>3 weeks, used 12 times</td>
<td>Bladder diary</td>
<td>DGNS was used 12 times over 3 weeks, mean voided volume increased from 205 ±55 mL to 353 ±37 mL, a drop in incontinence was noted when DGNS was applied. An increase in time between catheterisations was also recorded from 242 ±59 minutes to 284 ±108 minutes with DGNS.</td>
</tr>
<tr>
<td>Lee, YH et al. The effect of semi-conditional dorsal penile nerve electrical stimulation on capacity and compliance of the bladder with deformity in spinal cord injury patients: a pilot study. Spinal Cord. Nature Publishing Group; 2012 Apr 1;50(4):28993.</td>
<td>6</td>
<td>Baseline CMG, then CMG with stim. Then programmed stimulation on-off regime.</td>
<td>None</td>
<td>13 times daily for 1428 days</td>
<td>Voiding diary and Standard CMG with semi-conditional ES was performed before and after the 24 weeks of treatment.</td>
<td>CMG data only was collected. After 2-4 weeks of DGNS volume at first contraction increased from 45 ±24 mL to 165 ±156 mL. MCC increased from 204 ±78 mL to 360 ±70 mL. In addition vesicoureteral reflux was present in four cases before the treatment disappeared, and the severity of bladder wall deformity improved in five cases after the treatment.</td>
</tr>
</tbody>
</table>
### Table 2.6: Outline of previous home based studies of DGNS with SCI participants

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of participants</th>
<th>Test for DGNS effect</th>
<th>Control period</th>
<th>DGNS period</th>
<th>Outcome measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opisso, E et al. Subject controlled stimulation of dorsal genital nerve to treat neurogenic detrusor overactivity at home. Neurourol Urodynam. Wiley Subscription Services, Inc., A.Wiley Company; 2013 Sep 1;32(7):10049.</td>
<td>11 (5 SCI)</td>
<td>Baseline CMG then CMG with DGNS.</td>
<td>Day 1, Day 2, 3 and 4</td>
<td>Day 5, Day 4</td>
<td>Bladder diary and Standard CMG without/with DGNS on day 1 and 5</td>
<td>MCC increased in baseline CMG from 150 ±48 mL on day 1 to 202 ±83 mL on day 5. Bladder diaries showed increased mean voided volumes in all days following day 1.</td>
</tr>
<tr>
<td>Bourbeau, DJ et al. At-home genital nerve stimulation for individuals with SCI and neurogenic detrusor overactivity: A pilot feasibility study. The Journal of Spinal Cord Medicine. Taylor and Francis; 2018 Jan 15.</td>
<td>5</td>
<td>Baseline CMG, test DGNS amplitude/PAR, up to 6 CMGs randomised DGNS or control</td>
<td>4 weeks pre DGNS and 4 weeks post</td>
<td>4 weeks</td>
<td>Bladder diary</td>
<td>Leaks were reduced from 1 ±0.5 to 0.1 ±0.4 in 4 participants in the stimulation month. Bladder capacity measured both with CMG and in diaries did not change significantly. All participants felt they met their ‘bladder management goals’.</td>
</tr>
</tbody>
</table>
2.8. Home Use of Neuromodulation in SCI

2.8.3 Reported issues in previous studies of DGNS

Previous studies of DGNS have reported promising results, generally showing the ability to decrease incontinence episodes and increase cystometric capacity. The majority of studies have utilised commercially available electrical stimulation units, remarking on several factors of existing device design that were problematic in daily usage.

Bourbeau et al. conducted a four-week trial of DGNS in five SCI participants [Bourbeau et al., 2018b]. An Empi portable stimulator, measuring 12 cm x 7 cm x 2.5 cm, was used with 2 cm round surface electrodes. 3/5 subjects with residual sensation were instructed to trigger the stimulation based on urge, the 2/5 subjects that had no residual sensation utilised continuous stimulation over the intervention period. The two using continuous stimulation did so “during the daytime” and the three using on-demand stimulation did so 3.6 ± 2.8 times a day. DGNS significantly reduced incontinence episodes and enabled patients to meet their bladder-related management goals. However, participants were dissatisfied with the device, finding it too bulky; too cumbersome with long electrode wires easily caught on clothes or assistive devices; and finding that sometimes surface electrodes came off and had to be reattached when they were applied for long periods. Participants would have found it easier with wireless control of the stimulation trigger and stimulation amplitude. Indeed, four subjects did not participate in the trial citing system bulkiness and the electrode set-up as the reason. Whilst all five subjects who completed the trial professed they would like to continue with DGNS, when invited onto a year-long trial, two participants cited the systems bulkiness or usability as a reason not to partake.

The Bourbeau trial is the most thorough trial of chronic DGNS use in SCI participants yet reported. During the trial they used paper-based self-reported bladder diaries as primary outcome measures. Some subjects struggled to keep a bladder diary over a long period and the authors suggest that some method of automation might have been helpful.

Empi stimulators have previously been used in two other trials of DGNS. In a 2002 case study by Lee and Creasey [Lee and Creasey, 2002], one SCI participant with residual sensations of urgency trialled DGNS for three weeks. In this period he found it successful for prolonging continence long enough to get to the toilet, though he only used the stimulator 12 times over the three weeks. Minor technical problems were reported in this study to do with arranging cables and keeping electrodes in place over long periods. The participant did purchase a stimulator to continue to use following the trial. A second study by Lee et al.
in 2012, trialled DGNS in six participants with SCI over a period of 2 to 4 weeks. Again, 
stimulation was triggered on urge, however following the initial trigger ‘semi-conditional’ 
neuromodulation was used to alternate stimulation between off and on until the participant 
was able to find a toilet. Patients who had an SCI above C7 were unable to place the elec-
trode by themselves and urine and sweat made surface electrodes detach easily. Despite 
these issues, encouraging results of improved capacity at first contraction and improved 
bladder compliance from CMG’s performed before and after the stimulation period were 
reported.

The first report of DGNS as a home-based therapy was by Wheeler et al. in 1994 
[Wheeler et al., 1994]. A 6 week trial of DGNS was conducted using continuous stimula-
tion, using an NL-2, Lifetech portable stimulator with Unipatch electrodes placed on the 
dorsum of the penis. It was found to be beneficial, enabling complete continence, in 2 out 
of the 9 SCI subjects tested. 3 subjects dropped out due to finding ’bothersome’ sensations 
even at sub-threshold level and complaining the technique was too cumbersome. 3 subjects 
in this study had arreflexive bladders during urodynamics and did not trial DGNS at home,
in later trials of DGNS these subjects would have been excluded prior to participation as it 
is known that intact sacral reflexes are required for DGNS to have any effect.

One further trial of home based DGNS, where subjects with SCI have participated, has 
been reported. In 2013, Opisso et al. conducted a study with 11 participants trialling surface 
DGNS at home for three days [Opisso et al., 2013]. This study used an Odstock two chan-
nel stimulator with an attached switch and 2.5 cm diameter PALS electrodes. Stimulation 
was commenced by the participant based upon feelings of urgency and was automatically 
stopped by the device after 30 seconds. The stimulator usability was found to be ‘good, 
although not excellent’ as subjects sometimes had difficulty with operating the amplitude 
knob. The usability of the technique as a whole was criticised by participants, where the ex-
ternal simulator, cables and predominantly the electrodes were reported as the main issues. 
However, positive results were reported during the trial and 3 of the 11 subject decided to 
purchase a stimulator for their personal use at home following participation.

A study of percutaneous DGNS, conducted in non-neurogenic patients with urinary 
urge incontinence by van Breda et al., accessed the DGN using a Medtronic percutaneous 
stimulation kit [van Breda et al., 2016]. Issues in quick activation of stimulation when ex-
treme urgency was felt were noted by participants. Further to this the author’s recommen-
2.9 Research Aims

The overarching aim of this project is to develop a non-invasive, wearable device that is able to suppress episodes of NDO, restoring some control over the storage phase of micturition for people with SCI. Following careful review of the literature, the following research aims were posed for this project:

- To assess the effect of surface stimulation sites on sacral reflex pathways, through analysis of External Anal Sphincter electromyography.
- To assess the comparative effect of surface stimulation sites for neuromodulation of Neurogenic Detrusor Overactivity following SCI.
- To develop a stimulation system to deliver and assess neuromodulation protocols outside of the laboratory, in participants homes.
- To determine the effect of on-demand, continuous or intermittent DGNS on bladder capacity and detrusor pressure during natural filling.
- To determine the effect of on-demand, continuous or intermittent DGNS on bladder storage symptoms in the day to day environment.

The subsequent chapters cover in detail the methods used to try to meet these aims, the results obtained and discussion critiquing how the results published here fit with the literature and with our end goal.
Chapter 3

External Anal Sphincter Activity in Response to Stimulation Site

3.1 Introduction

Neuromodulation, described as ‘activity in one neural pathway modulating the pre-existing activity in another through synaptic interaction’ [Craggs and McFarlane, 1999], may be used for control of the bladder following Spinal Cord Injury (SCI) in various modes of application [McGee et al., 2015]. The array of neural interactions involved in control of the bladder presents several potential targets for external manipulation, many of which may be targeted using transcutaneous stimulation techniques [Gaunt and Prochazka, 2006, McGee et al., 2015]. Studies have been conducted in people with SCI using a variety of stimulation targets, reportedly to good effect [Bourbeau et al., 2018a, Amarenco et al., 2003, Gad et al., 2018]. It is possible that the optimal approach (and stimulation site) may vary across individuals in tune with precise diagnoses and associated co-morbidities.

Four stimulation sites, each with some evidence of efficacy for the reduction of NDO following SCI, were selected for review. These were the Dorsal Genital Nerve (DGNS), Tibial Nerve (TNS), Sacral Nerves (SNS) and the dorsal roots of the Spinal Cord over the T12 vertebrae, popularly known as Spinal Stimulation (SS).

This chapter and the following chapter describe two studies undertaken to compare the effect of stimulating four distinct sites, in this chapter on electromyographic (EMG) activity in the External Anal Sphincter (EAS) in people with no neurological damage and in Chapter 5 on urodynamic outcomes in people with SCI.
3.1.1 Anal sphincter reflex responses

The Pudendo-Anal Reflex (PAR) is a polysynaptic reflex pathway that incorporates the afferent dorsal genital nerve, the S2-4 spinal cord segments and the efferent pudendal nerve branch to the EAS. It is well defined, where surface stimulation of the penis or clitoris elicits a response in the External Anal Sphincter (EAS) at a latency of approximately 38.5 ms [Varma et al., 1986] and it is often used to study the integrity of sacral reflex pathways. Following supra-sacral SCI this reflex remains intact and has been used to set stimulation amplitude using DGNS for inhibition of NDO [Kirkham et al., 2001, Previnaire et al., 1996]. Stimulation of the tibial nerve, using transcutaneous electrical stimulation, and the sacral nerves, using magnetic stimulation, have both been shown to elicit an EAS response at long, 93-213 ms, and short, 4-8 ms latencies respectively [Pedersen et al., 1978, Mai and Pedersen, 1976, Eardley et al., 1990, Sheriff et al., 1996]. SS has been shown to elicit a response in the External Urethral Sphincter (EUS) in participants with SCI and to modulate DSD during voiding [Gad et al., 2018, Niu et al., 2018].

3.1.2 Study objectives

In this study we set out to compare EMG responses in the EAS to stimulation pulses delivered at each of the four sites, see figure 3.1. We aimed to evaluate: whether EMG activity was present in the EAS, the average amplitude of responses, the latency of responses and the amplitude of stimulation applied to elicit a response. This study was undertaken as a short pilot involving five neurologically intact participants, to gain initial data and to support a urodynamic study with SCI participants.

In a short extension to the study, where EAS activity was found in response to multiple sites and time allowed, we trialled combined stimulation to assess whether any cumulative effect on EAS amplitude was found.

3.2 Methods

Prior to commencing the study ethical approval was obtained from UCL ethics committee. All participants gave written informed consent prior to their participation in the study.
3.2. Methods

3.2.1 Participant recruitment

3.2.1.1 Inclusion and exclusion criteria

Table 3.1: Inclusion, exclusion and withdrawal criteria for recruiting into the pilot EAS EMG study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No known neurological injury or disease</td>
<td>- Cardiac pacemaker</td>
</tr>
<tr>
<td>- Male or Female</td>
<td>- Past surgery on anal sphincter</td>
</tr>
<tr>
<td>- Over the age of 18, at or under the age of 75</td>
<td>- Poorly controlled epilepsy. Acceptable where epilepsy is controlled by drugs or</td>
</tr>
<tr>
<td></td>
<td>- there have been no fits experienced for a reasonable period.</td>
</tr>
<tr>
<td></td>
<td>- A cancerous tumour in the area of the electrical stimulation</td>
</tr>
<tr>
<td></td>
<td>- Active sepsis</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy</td>
</tr>
<tr>
<td></td>
<td>- Exposed orthopaedic metal work in the area of electrical stimulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Withdrawal criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Request of participant</td>
<td></td>
</tr>
<tr>
<td>- Intolerance to stimulation</td>
<td></td>
</tr>
</tbody>
</table>

3.2.1.2 Risk

The only small risk identified for participation in the study was embarrassment or discomfort from stimulation or recording electrodes. This was minimised as far as possible by allowing participants to apply genital nerve electrodes and the anal plug recording electrode in private, following instructions.

3.2.2 Experimental protocol

Experimental sessions were conducted within the research laboratory at the Spinal Cord Injury Centre in the Royal National Orthopaedic Hospital. Participants were invited to attend one session lasting approximately two hours.

The basic study involved recording EAS EMG when applying paired pulses of stimulation at each site, study set up is shown in figure 3.2. Stimulation pulses were delivered in pairs, 2 ms apart, in cycles of 10. Each cycle was repeated three times.

An additional part of the study was added where time allowed, following a break, to look at interactions between TNS and DGNS responses. In this section, pulses were delivered to both the tibial nerve and dorsal genital nerve at set intervals. Paired pulses of DGNS were given a time point 0 ms, with single pulses of TNS applied at -80 ms, -40 ms, -20 ms, -10 ms, -5 ms, 0 ms and 5 ms. A cycle of 10 was repeated at each time interval.
3.2.2.1 Stimulation

To stimulate the dorsal genital nerve, electrodes were either placed on the dorsum of the penis shaft, 1 cm paddle electrodes (Ambu Neuroline 710) were placed approximately 2 cm apart, the cathode was placed proximally, or placed over the clitoris (cathode) and labia majora (anode). Tibial nerve electrodes were 2.5 cm round surface electrodes (PALS, Axelgaard Ltd, USA) placed unilaterally 1 cm posterior and approximately 3 cm superior to the medial malleolus (cathode) and approximately 5 cm superior (anode). Sacral electrodes were 5x5 cm (PALS) electrodes placed over either side of the sacrum, at the level determined to be over the S3 foramina through manual palpation of the sacrum. Spinal stimulation used 5 cm circular and 7.5x10 cm electrodes (PALS) over T11-12 and the abdominal areas respectively [Hofstoetter et al., 2014].

Figure 3.1: Simulation sites electrode positioning. a) Dorsal Genital Nerve (DGNS) b) Sacral Nerves (SNS) c) Tibial Nerve (TNS) d) Spinal Cord (SS)

Stimulation pulses were cathodic, monophasic and of 200 $\mu$S duration, delivered using a Digitimer DS7 (Digitimer Ltd, UK) isolated constant current stimulator. Stimulation to all sites was delivered in paired pulses, 2 ms apart [Rodi and Vodusek, 1995]. Stimulation was slowly increased in 2 mA steps until either a response was seen in the EAS, strong
motor contraction was elicited in adjacent muscles, or maximum tolerable stimulation was reached. This stimulation amplitude was used for cycles of EMG to be recorded.

3.2.2.2 Recordings

EMG activity was recorded from the EAS using an anal probe electrode (Anuform, Patterson Medical, UK) and a self adhesive electrode placed on the iliac crest as a reference electrode. EMG signals were amplified with a gain of 3,000 and filtered (10 Hz - 2 kHz) using a CED 1902 isolated preamplifier (Cambridge Electronic Design Ltd, UK). Signals were digitally sampled at 4 kHz by a CED 1401plus and analysed using Signal Software (Cambridge Electronic Design, UK).

![Figure 3.2: Equipment set up for study of external anal sphincter response to stimulation sites.](image)

3.2.3 Analysis

All analysis of EMG was carried out using Signal 6.05 software (Cambridge Electronic Design Ltd, UK). EMG signals were averaged from 10 cycles, repeated 3 times at each site. The latency of responses was measured from the onset of the first stimulus to the onset of a clearly defined response at the EAS. Peak-to-peak amplitude was measured from the responses and the amplitude of stimulation was recorded.

3.3 Results

3.3.1 Participant characteristics

Five participants were recruited into the study. Five went through the standard protocol and P05 went through the standard protocol plus the additional part of the study, involving looking at interactions between DGNS and TNS evoked responses.
3.3. Results

Table 3.2: Age and sex of participants

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>61</td>
<td>F</td>
</tr>
<tr>
<td>P02</td>
<td>48</td>
<td>F</td>
</tr>
<tr>
<td>P03</td>
<td>38</td>
<td>F</td>
</tr>
<tr>
<td>P04</td>
<td>75</td>
<td>M</td>
</tr>
<tr>
<td>P05</td>
<td>65</td>
<td>M</td>
</tr>
</tbody>
</table>

### 3.3.2 Stimulation amplitude

Table 3.3: Stimulation amplitudes applied at each site (mA), in each participant to evoke a sensory (S), EAS and maximum tolerable response (Max). The amplitude required to evoke a toe twitch in response to TNS was also recorded.

<table>
<thead>
<tr>
<th>ID</th>
<th>DGNS S Max EAS</th>
<th>TNS S Toe Max EAS</th>
<th>SNS S Max EAS</th>
<th>SS S Max EAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>3 40 40</td>
<td>2 30 65 N</td>
<td>3.5 90 N</td>
<td>6 90 N</td>
</tr>
<tr>
<td>P02</td>
<td>1.5 32 N</td>
<td>2.5 N 53 N</td>
<td>5.5 47 24</td>
<td>6 33 N</td>
</tr>
<tr>
<td>P03</td>
<td>1 15 9</td>
<td>5 35 74 74</td>
<td>6 45 45</td>
<td>6 50 N</td>
</tr>
<tr>
<td>P04</td>
<td>7 30 20</td>
<td>6 40 90 N</td>
<td>12.5 90 N</td>
<td>13 68 N</td>
</tr>
<tr>
<td>P05</td>
<td>6 65 15</td>
<td>11 30 75 60</td>
<td>9 80 N</td>
<td>15 60 N</td>
</tr>
</tbody>
</table>

### 3.3.3 EAS Response latency and amplitude

There was a response to DGNS in 4/5 subjects. In two subjects, a response to TNS was seen and in two subjects we saw a short latency (4-7 ms) response to SNS. No EAS response to SS was seen in any participant.

DGNS evoked a stable response in the EAS at 25 ± 10 mA. The two female subjects in whom a PAR was seen had longer latency responses of 59 and 73 ms, outside the typical range 38.5 ± 5.8 ms found by Varma et al. (1986). These two responses were evoked at amplitudes 13 and 9 times the sensory thresholds respectively. The 2 male subjects had consistent responses of 29 and 30 ms latency, evoked at 2.9 and 2.5 times the sensory thresholds.

SNS evoked very short latency responses in 2/5 participants. The other three participants saw some saturation of the signal across this period. Therefore further responses may have been elicited in other participants that we were unable to detect. In P02 an extremely large peak-to-peak response of 722 µV at a 4 ms latency was elicited when stimulation was applied at 47 mA. During setting of stimulation a smaller response of 74 µV at a longer latency of 8 ms was found when stimulation was applied at 24 mA, an example of this is shown in figure 3.3. In P03 a much smaller response of 46 µV, inline with that recorded...
from DGNS and TNS in the same participant, was recorded in response to 45 mA stimulation pulses at a latency of 6.5 ms. These responses appeared to be due to stimulation of pudendal efferent fibres, of the same latency (4-8 ms) as previous authors have reported using magnetic stimulation over the sacrum [Sheriff et al., 1996, Eardley et al., 1990].

No response to SS was seen in any participant. Where a sphincter response has been reported previously [Gad et al., 2018], stimulation parameters have been different: with much higher amplitudes (over 100 mA) and longer pulse widths trialled (1 ms), along with a high frequency carrier signal (10 kHz) being used within pulses. In addition to this, it is possible that electrode positioning was an issue, though given surface stimulation over T12 has previously elicited EUS responses, it is plausible that an EAS response could be elicited using similar electrode positioning.

![Example EAS responses from P02 to SNS at 47 mA (a) and 24 mA (b)](image)

**Figure 3.3:** Example EAS responses from P02 to SNS at 47 mA (a) and 24 mA (b)

An EAS response to TNS was seen in two participants, this appeared at approximately two times the motor threshold found for toe flexion, at a higher amplitude than that required for DGNS to evoke a response. TNS evoked an EAS response of peak-to-peak magnitudes lower than DGNS in P03 (75%) and much larger than DGNS in P05 (193 %). The latency of TNS responses was at 134 ms (1.8 times DGNS latency) for P03 and 46 ms (1.5 times DGNS latency) for P05.

### 3.3.4 DGNS and TNS interaction case study

In one participant (P05) we performed additional tests in which we looked at EAS response of both TNS and DGNS where TNS was applied at varying time intervals before and after paired DGNS pulses. Results from this and averaged (10 cycles) EMG traces are shown in table 3.5 and figure 3.4.

When TNS pulse was applied 80 ms before DGNS there was an EAS response at -33 ms, a 47 ms latency from the TNS pulse, as seen in TNS tests above. Similarly, when
3.3. Results

Table 3.4: EAS EMG responses to DGNS, TNS and SNS, all non-responses are left blank

<table>
<thead>
<tr>
<th>ID</th>
<th>DGNS Amp /mA</th>
<th>DGNS Latency /ms</th>
<th>DGNS Peak-Peak /µV</th>
<th>TNS Amp /mA</th>
<th>TNS Latency /ms</th>
<th>TNS Peak-Peak /µV</th>
<th>SNS Amp /mA</th>
<th>SNS Latency /ms</th>
<th>SNS Peak-Peak /µV</th>
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</thead>
<tbody>
<tr>
<td>P01</td>
<td>42</td>
<td>59</td>
<td>47</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47</td>
<td>4</td>
<td>722</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P03</td>
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<td>134</td>
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<td>45</td>
<td>6.5</td>
<td>46</td>
</tr>
<tr>
<td>P04</td>
<td>25</td>
<td>29</td>
<td>89</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>47.75</td>
<td>58.50</td>
<td>69.50</td>
<td>90.00</td>
<td>71.50</td>
<td>46</td>
<td>5.25</td>
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</tr>
<tr>
<td>SD</td>
<td>10.16</td>
<td>18.91</td>
<td>18.99</td>
<td>4.50</td>
<td>44.00</td>
<td>42.50</td>
<td>1.41</td>
<td>1.77</td>
<td>478</td>
</tr>
</tbody>
</table>

Figure 3.4: Example EAS responses from P05. a) DGNS b) TNS c) SNS d) SS

applied 40 ms prior to DGNS a response was seen at 6 ms, a 46 ms latency from the TNS pulse, and at 20 ms prior a response was seen at 27 ms, a 47 ms latency. When the TNS pulse was moved to 10, 5 and 0 ms prior to DGNS, the latency of the first response remained at 23 or 24 ms as TNS pulses were delivered after DGNS pulses suggesting the response was evoked by DGNS.

Where TNS pulses appeared to evoke a responses prior to an expected DGNS response, when applied 80 and 40 ms before DGNS, the shape and peak to peak amplitude was similar to that evoked by TNS alone and the expected response to DGNS around 25-35 ms was unclear and subdued. When TNS was applied at -10, -5, 0 and 5 ms time points, there appeared to be 2 clear peaks, where the second was of greater amplitude than the first. At
3.3. Results

-5, 0 and 5 ms time points this was 119, 125 and 120% of the baseline DGNS peak to peak amplitude and 150, 158 and 151% of baseline TNS amplitudes. Interestingly the DGNS only trace obtained following this set of testing (which was not in a randomised order), also appeared to have two peaks, though a similar amplitude to the baseline DGNS value.

Figure 3.5: Interaction tests with P05
### 3.4 Discussion

EAS EMG may be use as a surrogate for urethral sphincter EMG [Podnar and Vodusek, 2001], a finding attributed to the close proximity of motor neurones innervating both in Onuf’s nucleus. One way to elicit a reflex response in the EAS is by electrical stimulation of the genital nerve, using surface electrodes placed over the penis or clitoris and doublet stimulation pulses, 2-4 ms apart [Rodi and Vodusek, 1995]. This Pudendo-Anal Reflex (PAR) has been repeatedly used for setting the stimulation amplitude of DGNS when applied for suppression of bladder overactivity, where twice the stimulus amplitude required to elicit an anal reflex response is required to optimally suppress NDO [Previnaire et al., 1996]. Kirkham et al. (2001) found the PAR and Pudendo-Urethral Reflex (PUR) to be elicited at a similar amplitude and correlated to DGNS’ success at suppressing NDO [Kirkham et al., 2001]. Stimulation of the tibial nerve, sacral nerves and lumbosacral cord each can affect bladder overactivity. Improved understanding of their effect on EAS activity may inform the application of each. The comparative effect on sacral reflex activity has not been previously assessed, this study aimed to do so by evaluating the EAS responses to stimulation delivered over the four distinct sites.

#### 3.4.1 Response to DGNS

DGNS was able to evoke an EAS reflex response in 4/5 people tested in this study. For two male subjects a typical EAS response was recorded, in line with expected latencies and stimulation amplitudes [Varma et al., 1986]. In two of the three female participants there were longer latency responses to DGNS (59 and 73 ms) and in one we detected no response.

There are several possible reasons for this divide between male and female participants,
though it is difficult to draw any firm conclusions given the small sample size. A prolonged PAR latency has been described as common for multiple neuropathies, for example Varma et al (1986) found latencies of $56 \pm 12$ ms in patients with faecal incontinence. No neuropathy was reported by participants on entry into the study and this was not within the scope of the study to investigate or screen. Further to this, obstetric history was not included in selection criteria and parity between subjects was not ensured in this small sample, both could contribute to the results and should be considered in future study design. Another possible explanation may be that as participants were applying their own electrodes, this could have been more difficult for the female participants and lead to poor placement or adhesion, thereby altering stimulation efficacy. In one participant (P03) a response to TNS was detected at a long latency (134 ms) as well as to DGNS (73 ms) and a response to SNS was found at a short latency (6.5 ms), suggesting that it may the central part of the reflex pathway that is affecting the latency, as TNS and DGNS have separate afferent limbs.

### 3.4.2 Response to SNS

Sheriff et al. (1996) used magnetic stimulation of the sacral roots to acutely suppress detrusor overactivity. When mapping stimulation location they recorded EAS responses with a latency of 4-6 ms. Eardley et al. (1990), also using magnetic stimulation to evoke an EAS response, recorded a mean latency of 8 ms and determined that pudendal efferent fibres were being stimulated. In 2/5 participants we found a similar, short latency, EAS response to transcutaneous SNS. The proximity of recording and stimulation electrodes during SNS lead to saturation in 3/5 participants’ recordings, covering this period of 0-10 ms. The use of paired pulses appears to have been misguided in this instance, there are two clear peaks in P03’s response to SNS at 45 mA. The short latency suggests we are stimulating pudendal efferents within the sacral nerves to evoke an EAS response, as suggested by Eardley et al. (1990). In P02 we saw a small response to SNS at 24 mA (8 ms latency, 74$\mu$V peak-peak), then a consistent much larger response at a reduced latency when 47 mA stimulation was used (4 ms latency, 722$\mu$V peak-peak), this is shown in figure 3.3. In P02 we were unable to evoke a response to DGNS, but were able to elicit this large, short latency response to SNS.

### 3.4.3 Response to TNS

An anal sphincter reflex response to TNS has been reported just twice in the literature, by Mai and Pedersen in 1976 and Pedersen in 1978. Here, 5 x 1 ms pulses of stimulation, 1
Figure 3.6: EAS response to SNS at 45mA in P02. Two clear peak are seen

ms apart, delivered transcutaneously over the tibial nerve, elicited a reflex EAS response in all participants. A mean ± standard deviation stimulus amplitude of 4.1 ± 1.57 mA was required and latency at threshold was 213 ± 52 ms and the minimum latency was 93 ± 21.1 ms, obtained during maximal stimulation. Pedersen also showed urethral sphincter reflex responses to TNS in 10 people with Multiple Sclerosis.

In this study we observed a reflex response to TNS in 2/5 participants, the stimulation was also transcutaneous but was delivered at much higher amplitudes than previously reported. In P03 and P05, toe twitch was seen at 35 and 30 mA respectively and a stable EAS response was seen at 74 and 60 mA. The latency of response was longer than DGNS in both participants, at 134 and 46 ms. The latency of an EEG signal recorded at the L1 vertebral level in response to TNS, taken as the peripheral conduction time, has been measured as 22.5 ms, and at the scalp as 39.7 ms [Jones and Small, 1978]. Haldeman (1982) found the peripheral conduction time of TNS to be 24 ms and DGNS to be 12 ms [Haldeman et al., 1982]. The latency of P05’s response was 46 ms, relative to a DGNS latency of 29 ms, suggesting this is a spinal reflex.

This response suggests recruitment of nerve fibres originating in Onuf’s nucleus. Urethral sphincter motor neurons also originate in Onuf’s nucleus and may be simultaneously stimulated [Podnar and Vodusek, 2001]. A convergence of DGNS and TNS in the sacral cord is supported by a recent study in a cat model, where neuronal activity, arising as pelvic nerve afferent activity due to bladder filling, in segments of the S2 cord was seen to be similarly attenuated by both pudendal and tibial nerve stimulation [Yecies et al., 2018].

Combined, the preliminary findings from this study and recent animal work suggests
that TNS acts on the sacral cord, via an inter-segmental pathway, in an at-least partially similar manner to DGNS. Yecies et al., (2018) speculated that this action on S2 neuronal activity may be due to either inter-segmental pathway or to activation of a supraspinal centre that in turn generates a descending inhibitory input to S2. Our finding of a relatively short latency EAS response to TNS of 45 ms, in one person, in comparison to 30 ms PAR latency and a tibial nerve peripheral conduction time of 22.5 ms [Jones and Small, 1978], suggests that there is indeed a spinal reflex pathway. There is no evidence in humans for the precise mechanism of TNS for neuromodulation of the LUT or of the entry patterns to the spinal cord of tibial nerve afferent activity. This data provides information on the effect of neurostimulation on EAS activity, which may be pertinent to any neuromodulatory effects on NDO, as with DGNS. We evaluate the capacity of TNS to neuromodulate NDO in the next chapter.

3.4.4 Interaction between tibial and genital nerve stimulation

Reflex responses were recorded from both TNS and DGNS in P05. In this one participant we were able to subsequently trial stimulation of both sites in combination, with pulses applied at varying intervals from each other. This aimed to investigate the effect of combined stimulation on EAS reflex responses. Baseline DGNS stimulation and response amplitudes in this part of the study were increased from the initial control values, as following a short break electrodes were reapplied and a higher amplitude was found to be more tolerable and to elicit a clear response.

PAR amplitude can be facilitated by prior delivery of a Motor Evoked Potential (MEP) of the EAS, in people with and without incomplete SCI, in a time dependant fashion [Vasquez et al., 2015]. Using the same type of measurement probe and stimulator, we found that EAS response increased in amplitude by up to 25% when DGNS and a TNS pulses were delivered within 5 ms of each other. We did not trial TNS at an interval of -15 ms, where the input into the cord would converge with that of DGNS in P05, based on our individual site findings, and may have been amplified. This way of defining timing should be used in further study of this combined stimulation.

Our results from this part of the study are tentative, obtained from one person with limited repeat measures taken. However the possibility of combined stimulation sites producing an additive effect on sacral reflexes is an exciting one that could open up new avenues for treatment and should be investigated further. To do so was not within the remit of this
3.5. Conclusions

3.4.5 Study limitations

This study was a pilot study and results must be interpreted within this context. The EAS was selected as a site to monitor EMG activity that would be used as a surrogate for EUS activity as it removes the need for either catheters or needle electrodes. However this removal from direct measurement of EUS activity must be treated with caution. The use of surface electrodes is convenient and less invasive, though variation in design and position is known to affect the amplitude of responses [Binnie et al., 1991]. Further to this, whilst the EAS is a good surrogate and has been shown to act in synergy with the EUS in people with SCI [Kirkham et al., 2001], this may not always be the case. Future studies would ideally measure EUS activity directly where possible.

The heterogeneous group of participants was a further limitation in this pilot study. A more rigorous inclusion criteria, to ensure parity of participants, particularly in small groups, and to screen for potential neuropathies and obstetric history, should be included in future study design.

3.5 Conclusions

This short pilot study provided interesting information regarding the relative effects of DGNS, TNS, SNS and SS on sacral reflex pathways. From the data we gathered, it appears that: DGNS has the most consistent effect on sacral reflexes; that TNS is able to elicit a strong reflex contraction in the EAS, though not consistently and at both a higher amplitude and a longer latency than DGNS and SNS; that transcutaneous SNS may directly stimulate pudendal efferent fibres innervating the EAS in a similar way to magnetic SNS; and that SS is unable to elicit a recordable response in the EAS, when delivered at a maximum tolerable amplitude using 200 µs wide pulses.

If we proceed with the assumption that eliciting a reflex contraction in the striated sphincters of the pelvic floor plays a role in predicting whether stimulation will inhibit NDO, our results would indicate that: DGNS may inhibit NDO most consistently, in the most people and at the lowest amplitudes; that in some people TNS may be able to suppress NDO and may possibly be more effective than DGNS; that a short latency response to SNS may indicate that SNS is able to achieve reflex inhibition when applied using surface stimulation, as the sphincter response is similar to previous work where NDO was acutely
3.5. **Conclusions**

inhibited by magnetic SNS [Sheriff et al., 1996]; and that SS will not directly affect detrusor overactivity.

Future work that would be of particular interest following these results would be a more thorough study of TNS’ effect on pelvic reflex pathways, in people with and without SCI. This may be important in determining what the optimum setup is for TNS and in determining where this technique may be effective. It is also important to assess the link between reflex sphincter activation and detrusor inhibition.
Chapter 4

Urodynamic Comparison of Stimulation Sites

4.1 Introduction

Surface stimulation may be used to alter activity in the bladder when applied over several distinct sites on the body [Gaunt and Prochazka, 2006]. Four types of non-invasive neuromodulation that have previously been shown some acute suppressive effect on bladder overactivity in individuals with SCI are Dorsal Genital Nerve Stimulation (DGNS), Tibial Nerve Stimulation (TNS), Sacral Nerve Simulation (SNS) and Spinal Stimulation (SS) [Bourbeau et al., 2018a, Andrews and Reynard, 2003, Sheriff et al., 1996, Gad et al., 2018].

In Chapter 3 we presented results from a pilot study that aimed to measure External Anal Sphincter responses to stimulation at each of these sites. This was conducted in people with no neurological injury. We found that DGNS produced the most consistent response, that SNS elicited a short latency response in some participants and that TNS evoked a reflex response in some participants when amplitude was approximately twice that required to evoke a motor response in the toes. SS had no observable effect on EAS EMG in any participant.

No neuromodulation technique is currently available to patients with SCI for restoration of bladder control. Whilst each of the above sites has promising early data, the comparative efficacy of each is unknown. Direct comparison of neuromodulation sites has been evaluated in rats (SNS, DGNS, TNS), cats (DGNS, pudendal trunk and SNS) [Snellings and Grill, 2012] and in human subjects with Multiple Sclerosis (DGNS, SNS and TNS) [Fjorback et al., 2007b, Fjorback et al., 2007a]. It has not been reported previously in...
humans with SCI.

The purpose of this study was to compare the acute urodynamic effect of transcutaneous stimulation of four anatomical sites, to assess their capacity to lower detrusor pressure, reduce incontinence and increase bladder capacity. This was done in participants with chronic SCI and NDO, enabling within-individual comparison of results.

4.2 Methods

4.2.1 Ethical approval

Ethical approval was granted by the Queens Square Regional Ethics Committee and the Health Research Authority in England prior to beginning the study. The study was subsequently conducted in accordance with The Declaration of Helsinki and Good Clinical Practice guidelines. The study was retrospectively listed on a clinical trials database (ISRCTN99373118).

4.2.2 Participants

4.2.2.1 Inclusion and Exclusion criteria

Table 4.1: Inclusion, exclusion and withdrawal criteria for recruiting into the stimulation site urodynamic study

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Suprasacral Spinal Cord Injury</td>
<td>- Cardiac pacemaker</td>
</tr>
<tr>
<td>- Male or Female, over the age of 18, no upper age limit</td>
<td>- Previous surgical intervention on bladder/sphincters</td>
</tr>
<tr>
<td>- Injury sustained more than 6 months ago</td>
<td>- Showing positive leucocytes and nitrites on urinalysis on the day of investigation</td>
</tr>
<tr>
<td>- Urodynamically proven Neurogenic Detrusor Overactivity</td>
<td>- Poorly controlled epilepsy. Acceptable where epilepsy is controlled by drugs or there have been no fits experienced for a reasonable period.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Withdrawal criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- No NDO in baseline CMG</td>
<td>- Patients with a cancerous tumour in the area of the electrical stimulation</td>
</tr>
<tr>
<td>- Intolerance to stimulation</td>
<td>- Active sepsis</td>
</tr>
<tr>
<td>- Autonomic Dysreflexia as a result of stimulation</td>
<td>- Pregnancy</td>
</tr>
<tr>
<td>- Request of participant</td>
<td>- History of significant Autonomic Dysreflexia</td>
</tr>
<tr>
<td></td>
<td>- Recipient of intradetrusor Botulinum toxin injections within the last 6 months</td>
</tr>
<tr>
<td></td>
<td>- Patients with exposed orthopaedic metal work in the area of electrical stimulation</td>
</tr>
</tbody>
</table>
4.2.2 Recruitment

Recruitment took place within the Royal National Orthopaedic Hospital’s (RNOH) patient population, first contact was made by a member of the clinical care team. Participants were approached if they were suitable candidates either in person, telephone or invitation letter. We also used flyers, explaining the project, displayed in the hospital and online with contact details for further information.

The study was explained to suitable patients and a participant information sheet provided to those who were interested. Following a 24 hour period, any questions about the study and its associated risks were answered. If the patient wished to proceed, an appointment was made for the first experiment session in which informed consent was obtained prior to participation.

4.2.3 Standard cystometry

Standard cystometry (CMG) [Rosier et al., 2017] was performed to record bladder pressures and capacity at baseline and when stimulation was applied. During all tests the participant was supine. A 10.5 Ch catheter was placed urethrally and used to fill the bladder with room temperature 0.9% saline at 60 ml/min. Pressure was measured using Medex (Smiths Medical Ltd, UK) pressure transducers placed at the level of the symphysis pubis, through 4.5Ch water filled catheters, placed urethrally to measure vesical pressure ($P_{ves}$) and rectally to measure abdominal pressure ($P_{abd}$). Detrusor pressure was calculated as $P_{det} = P_{ves} - P_{abd}$. Infused volume was measured using a weight transducer. Signals were amplified using a CED 1902 isolated amplifier, digitised through a CED 1401 and recorded on Spike 2 software (Version 4, Cambridge Electronic Devices, UK) used to display data and trigger stimulation.

![Figure 4.1: Equipment set-up for standard CMG applied with and without stimulation](image-url)
4.2.4 Stimulation sites

To stimulate the dorsal genital nerve, electrodes were placed on the dorsum of the penile shaft. 1 cm paddle electrodes (Ambu Neurolines 710) were placed approximately 2 cm apart, the cathode was placed proximally. Tibial nerve electrodes were 2.5 cm round surface electrodes (PALS, Axelgaard Ltd, USA) placed unilaterally 1 cm posterior and approximately 3 cm superior to the medial malleolus (cathode) and approximately 5 cm superior (anode). Sacral electrodes were 5x5 cm (PALS) electrodes placed over either side of the sacrum, at the level determined to be over the S3 foramina through manual palpation of the sacrum. Spinal stimulation used 5 cm circular (cathode) and 7.5 x 10 cm (anode) electrodes (PALS) over the T11-12 vertebrae and the abdominal areas respectively [Hofstoetter et al., 2014]. See figure 3.1 in Chapter 3 for electrode positioning.

All stimulation pulses were monophasic, cathodic, 200 μS pulses delivered at 15 Hz from an electrically isolated constant current stimulator (DS7, Digitimer Ltd., UK).

To set the stimulation amplitude, 15 Hz bursts of one second were given, increasing the amplitude until either: twice the threshold for contraction of the External Anal Sphincter (EAS_{thresh}), detected visually, was reached; a strong motor contraction was elicited in adjacent muscles; or stimulation was intolerable. EAS contraction was monitored visually by a research nurse with the participant lying left laterally as stimulation amplitude was increased.

4.2.5 Experimental protocol

Each stimulation site was tested in a separate session, on a separate day. Participants were asked to stop taking antimuscarinic medication for 5 days prior to each session. During each session, a control CMG was conducted initially, followed by between one and three experimental CMGs where stimulation was applied conditionally at a rise in detrusor pressure of 10 cmH₂O, a further control CMG with no stimulation was then conducted. A gap of at least five minutes was left between each fill. The number of experimental CMGs was determined in agreement with participants on the day depending on time available. A further CMG using continuous stimulation, applied throughout the fill, was conducted when possible following the second control CMG in TNS, SNS and SS sessions.

4.2.6 Outcome measures and analysis

The outcome measures used in this study were obtained through CMG. They were: Reflex Volume (RV); bladder capacity, measured as the volume infused at end of fill (EFV), where
end of fill is defined as when leakage occurred, participant was unable to tolerate sensation or when a detrusor contraction was sustained at > 45 cmH₂O; Volume to Leakage (ViL), calculated as $ViL = EFV - FDCV$; First Peak Detrusor Pressure (FPDP) and Maximum Detrusor Pressure (MDP). Each set of results had its own control recorded from the individual on the same day, change from baseline was used for comparison of stimulation sites. Figure 4.2 illustrates how these were obtained. The occurrence of leakage and stimulation amplitudes were recorded.

Figure 4.2: Outcome measures shown on a typical CMG detrusor pressure trace. Volume infused is taken as the volume infused over the time indicated on the pressure trace for RV and EFV.

This protocol was designed to allow us to compare the effect of stimulation site within individuals versus baseline taken on the same day, control fills were conducted before and after stimulation fills to try and offset the potential effect of repeat fills on cystometric capacity [Ockrim et al., 2005]. Conditional stimulation triggered at a rise in detrusor pressure was used to determine the acute effects of stimulation on a detrusor contraction, whilst also allowing comparison of volume at first detrusor contraction during the same conditions in all fills (i.e. no stimulation).

The aim of this study was to quantify the effects of stimulation of four distinct sites on the ability of individuals with SCI and NDO to store urine at low pressure, at normal capacity and without incontinence. The assess this during CMG we quantified the change in bladder capacity, through the measures EFV and ViL, in bladder pressures, looking at FPDP, MDP and the number of suppressed NDO episodes. We considered an episode of NDO to be suppressed where a detrusor contraction was not terminal (leakage, severe urgency or sustained) and peaked at a pressure below MDP. Average peak detrusor pressure was used
4.3 Results

4.3.1 Participant characteristics

Ten male subjects with complete or incomplete SCI and history of NDO were recruited into this study. Two were withdrawn during baseline screening as no NDO was found on the day of study and a further one participant withdrew due to unavailability. Other exclusion criteria included BTX in the preceding 6 months or surgery to the LUT. Seven participants completed the study, two of whom were excluded from SS due to metal implants under the stimulation site. Participants stopped taking AM for the 5 days preceding each experimental session. The mean age of the group that completed the study was 53 ±8 years, 100% were male, 43% had complete injuries, the mean time from injury was 10 ±8 years and 100% experienced some ongoing incontinence.
Table 4.2: Participant characteristics with respect to injury level, ASIA grade, cause of injury and age. Bladder management for storage (AM = Antimuscarinic medication) and voiding (ISC is Intermittent Self Catheterisation) is shown as is presence of self-reported bladder sensation and self-reported incontinence.

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Sex</th>
<th>Injury</th>
<th>ASIA</th>
<th>Years from SCI</th>
<th>Cause of SCI</th>
<th>Voiding</th>
<th>Storage</th>
<th>Previous botox</th>
<th>Sensation</th>
<th>Incontinence</th>
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<td>P01</td>
<td>44</td>
<td>M</td>
<td>T4</td>
<td>A</td>
<td>5</td>
<td>Trauma</td>
<td>ISC + Sheath</td>
<td>AM</td>
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<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>P03</td>
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<td>D</td>
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<td>ISC</td>
<td>AM</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P04</td>
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<td>L1</td>
<td>A</td>
<td>1</td>
<td>Trauma</td>
<td>ISC</td>
<td>AM</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
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<td>ISC</td>
<td>AM</td>
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<td>Y</td>
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<td>2</td>
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<td>Voids</td>
<td>AM</td>
<td>N</td>
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</table>

Mean | 53  | std | 8     | Median | 50 | 10 |
### Table 4.3: Stimulation amplitudes

<table>
<thead>
<tr>
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<td>Max</td>
<td>Sensory</td>
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<tr>
<td>std</td>
<td>4</td>
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<td>10</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>28</td>
<td>40</td>
<td>15</td>
</tr>
</tbody>
</table>
4.3.2 Baseline bladder capacity in repeated CMGs

To check for carryover effect of stimulation or effect of repeated filling within a session we analysed the changes in EFV between pre and post stimulation control fills. We also looked at RV changes across all fills in a session to check for changes that may bias our with-stimulation results.

Mean ± std baseline EFV during all control CMGs was 205 ±109 ml. The pre-stimulation control EFV was 198 ±96 ml and post stimulation control was 211 ±122 ml. The change between pre and post stimulation fills in a session was 17 ± 81 ml, p=0.414. For individual sites it was 23 ± 97 ml in DGNS tests, 36 ± 91 ml in TNS, 36 ± 55 ml in SNS and -48 ± 49 ml in SS.

VtL in control fills was 42 ± 29 ml and change from pre- to post-stimulation control VtL was 6 ± 28 ml.

RV across all fills (including with stimulation fills, before stimulation was applied) was 167 ± 96 ml, the mean change from the first fill in each session was -1 ± 68 ml. Figure 4.3 shows change, in percentage of first fill volume being 100%, of subsequent fills in a session.

![Figure 4.3](image-url)

**Figure 4.3:** Median (and interquartile range) of the percentage change in Reflex Volume (RV) from fill one (100%) during successive fills within a session. Data is from all seven subjects, each with three or four sessions of multiple fills considered separately. Error bars denote range.
4.3. Results

4.3.3 Stimulation amplitude

EAS contraction was observed during thresholding in 6/7 subjects during DGNS, 2/7 subjects during TNS, 5/7 during SNS and 0/7 during SS. Stimulation amplitudes are shown in table 4.3. 3/7 participants could tolerate DGNS at a level of twice EAS_{thresh}.

4.3.4 Effect of neuromodulation on urodynamic outcomes

The effect of neuromodulation at each site on bladder capacity was analysed. Individual results are displayed in table 4.4, 4.5 and 4.6.

DGNS increased EFV by 153±146 ml (range 16 to 460 ml, p=0.016), or 117±201% (range 11 to 571%). VtL was also increased, by 161±175 ml (range 6 to 530 ml, p=0.016). DGNS was able to suppress NDO in 5/7 participants, in whom the mean number of suppressed contractions was 2±2 (range 1 to 6). At least one contraction was suppressed at a peak pressure of less than 40 cmH₂O in all 5/7. Incontinence was prevented using DGNS in 3/6 participants who had leaked in control fills. FPDP was reduced by a mean of 34±35 cmH₂O (p=0.078), or 42±38%, to below 30 cmH₂O in 3/7 participants. Average peak detrusor pressure was reduced by 22±28 cmH₂O (range -63 to +7, p=0.156), or by 26±31%. MDP was not changed by DGNS, 0±12 cmH₂O (p = 1.00).

TNS did not suppress NDO in any participant, consequently FPDP was the same as MDP as all first NDO episodes were terminal, which was increased by 10±13 cmH₂O (range 0 to 38 cmH₂O, p=0.031), or 11±16%. Some changes in bladder capacity were seen, however. Increases in EFV were inconsistent (p=0.680) but VtL was increased by 46±62 ml (range -2 to 177 ml, p=0.031).

SNS similarly did not suppress any detrusor contractions and changes in EFV and MDP were not significant (p=0.680 and p=0.625). VtL was increased by 34±33 ml (range 4 to 98 ml, p=0.016).

SS did not significantly change outcomes, though trends were observed in the smaller (n=5) cohort. EFV decreased in all (n=5) participants by -33±26 ml (range -11 to -73 ml, p=0.063) and VtL by -7±7 ml (range -12 to 1 ml, p=0.125). As with TNS and SNS, no episodes of NDO were suppressed and FPDP was equal to MDP, which was not changed significantly, by 3±10 cmH₂O (p = 1.00).

A Friedman’s test was used to compare results across the four sites. Firstly including all 7 participants, just looking at changes in EFV in DGNS, TNS and SNS sessions. Here p=0.0038 and post-hoc analysis found the DGNS session’s change in EFV to significantly
differ from both SNS and TNS. Secondly, the test was conducted across all 4 sites, with just results from n=5 included (as this test requires each participant has results for all groups and only 5/7 were able to trial SS). P=0.0036, and post-hoc analysis showed only DGNS and SS results to differ significantly from each other.

4.3.5 DGNS results from responders

Results presented in table 4.6 detail pressure and volume responses to DGNS in those participants where at least one success criteria was met. All 5 responders had at least one NDO successfully inhibited at a peak pressure of below 40 cmH\textsubscript{2}O, two of the 5 had average peak detrusor pressure drop below this threshold. All 5 also increased bladder capacity, either EFV or VtL, by at least 100 ml or 50%. Therefore successful reduction of at least one episode of NDO and meaningful increases in bladder capacity were considered to be made concurrently when DGNS was applied in 5/7 participants. In this group, mean bladder capacity was increased from 213 ml to 402 ml.
Table 4.4: Detrusor pressure results from baseline and conditional stimulation fills. All results are the mean of any repeat fills conducted in the same session. Results are presented for DGNS - dorsal genital nerve stimulation, TNS - tibial nerve stimulation, SNS - sacral nerve stimulation, SS - spinal stimulation. FPDP - first peak detrusor pressure, APDP - average (mean) peak detrusor pressure across all NDO episodes in a fill (only applied where there was multiple episodes of NDO), MDP - maximum detrusor pressure in cmH₂O, NDO supp - the number of NDO episodes suppressed by stimulation. Columns with C present results obtained during control filling (no stimulation) and those with S present results from fills with conditional stimulation applied. Results are highlighted in green where they are considered to have reached a meaningful improvement defined in section 4.2.6

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Table 4.5: Bladder capacity results from baseline and conditional stimulation fills. All results are the mean of any repeat fills conducted in the same session. Results are presented for DGNS - dorsal genital nerve stimulation, TNS - tibial nerve stimulation, SNS - sacral nerve stimulation, SS - spinal stimulation. EFV - end fill volume or bladder capacity in ml, VtL - volume to leakage in ml. Columns with C present results obtained during control filling (no stimulation) and those with S present results from fills with conditional stimulation applied. Results are highlighted in green where they are considered to have reached a meaningful improvement defined in section 4.2.6.

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4.3. Results
4.3. Results

Figure 4.4: a) Boxplot of End Fill Volume and b) Maximum Detrusor Pressure change from baseline for each site. Boxes show median, interquartile ranges and error bars denote the range. c) Amplitude of stimulation vs change in VtL for each site. DGNS appears to deliver increased gains when applied at greater amplitudes \( R^2 = 0.75 \). d) Changes from baseline in end fill volumes (EFV) in continuous (green) and conditional (white) stimulation fills. Boxes represent the median and interquartile range of within session changes in EFV, whiskers show the range. e) Individual changes in VtL as mean values obtained during control and conditional stimulation fills from each session.
### Table 4.6: CMG results for DGNS session from participants who responded to DGNS only. The number of suppressed NDO episodes that peaked below 40 cmH2O are listed, differing from suppressed episodes of NDO shown in table 4.4 and 4.5. Results are highlighted in green where they are considered to have reached a meaningful improvement defined in section 4.2.6

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### 4.3.6 Comparison of continuous and conditional stimulation

Continuous mode was applied using TNS in n=5, SNS in n=5 and the SS in n=3. No significant change from baseline in either RV or EFV was noted. TNS produced a change of 59 ± 161 ml (p=0.625) in EFV and 6 ± 83 ml (p=1) in RV. SNS 87 ± 125 ml (p=0.156) in EFV and 44 ± 58 ml (p=0.156) in RV. SS, -92 ± 34 ml (p=0.25) in EFV and -85 ± 42 ml (p=0.25) in RV.

### 4.4 Discussion

This investigation was a pilot study to compare the acute urodynamic effect of transcutaneous stimulation of four anatomical sites on detrusor pressure, incontinence and bladder capacity. In the participants tested, DGNS was the most effective at increasing bladder capacity and reducing leakage. Only DGNS had a meaningful effect on bladder capacity and detrusor pressure illustrated by increasing volumes by at least 100 ml or 50% and decreasing peak detrusor pressure in 5/7 participants. Though DGNS, TNS and SNS all lead to significant increases in volume from RV to EFV, VtL. Only TNS lead to any significant change in MDP, increasing it by 10±13 cmH2O (p=0.0313), which may be a worrying effect of neuromodulation attempts requiring further investigation. The relevance and value of the presented study’s results are discussed in further detail throughout this section.
4.4. Discussion

4.4.1 Stimulation amplitude

Maximum tolerable amplitude was used in all sites, apart from in participants with no sensation where either twice the $EAS_{thresh}$ or an amplitude that did not evoke strong contraction in adjacent muscles was used. During set up, twice the $EAS_{thresh}$ was used as a target based upon previous research of DGNS [Previnaire et al., 1996]. In animal models of TNS and SNS, 3-4 times the motor threshold for toe twitching is required to suppress detrusor activity [Kovacevic and Yoo, 2015, Su et al., 2012]. This was used as an amplitude target for TNS and SNS. In practice we were not always able to reach these targets, average DGNS amplitude was $41 \text{ mA}, 1.7 \times EAS_{thresh}$, and TNS was $55 \text{ mA}, 2.6 \times Toel_{thresh}$. SNS had no observable effect on the toes, though both TNS and SNS elicited a visible contraction in the EAS in 2/7 and 5/7 participants. SNS, applied using magnetic stimulation but not transcutaneous stimulation, has been shown to stimulate pudendal efferent fibres, generating EAS responses at short latencies [Eardley et al., 1990, Sheriff et al., 1996]. Two studies provide evidence of a Tibial-Anal reflex pathway in the literature, showing long latency responses of over 90 ms [Mai and Pedersen, 1976, Pedersen et al., 1978]. Neurophysiological study of the link between neuromodulation site and EAS or urethral sphincter activity may provide useful information regarding both the mechanism of neuromodulation techniques and inform optimal electrode placement. For future investigation of neuromodulation sites, we recommend thorough assessment of this during stimulation set up. A meta-analysis of previous DGNS studies has shown a link between DGNS amplitude and bladder capacity gains, a trend also found in our results, figure 4.4 [Bourbeau et al., 2018a].

4.4.2 Change in post reflex volume capacity

The volume infused following an initial detrusor contraction (VtL) gives an indication of the direct effect of stimulation, removing the variation in RV that may cause EFV to vary. This measure may also give us an indication of the acute changes that stimulation produces.

As we filled the bladder continuously at 60 ml/minute this also represents the time (s) from RV to leakage or intolerable urgency in these non-physiological conditions. At baseline this was $42 \pm 29 \text{ ml}$. DGNS increased VtL to $206 \pm 157 \text{ ml}$, TNS to $90 \pm 69 \text{ ml}$, SS to $71 \pm 40 \text{ ml}$ and SS decreased VtL to $36 \pm 22 \text{ ml}$. This demonstrated the superior capacity of DGNS for use in a conditional neuromodulation system for people with SCI, however also suggests that TNS and SNS are suitable for further evaluation.
4.4.3 TNS results

TNS has been reported to increase bladder capacity in SCI when applied transcutaneously at 10 Hz [Amarenco et al., 2003] and 25 Hz [Andrews and Reynard, 2003]. In both of these studies continuous stimulation was used, it was reported to delay onset of NDO and increase capacity by between 75 and 170 ml. In the seven participants studied, we found TNS had no significant acute effect on maximum bladder capacity but did significantly increase MDP and VtL. One participant appeared to respond in a similar fashion to previous positive reports.

4.4.3.1 One participants response to TNS

Participant 5 (P05) in this study showed a large increase in capacity in response to TNS, however NDO was not clearly suppressed. Interestingly, similar to the case report by Andrews and Reynard [Andrews and Reynard, 2003], capacity was increased from 91 ml in pre-stimulation control, to 406 and 303 ml with conditional stimulation. Following conditional TNS, EFV was 273 ml in the control fill and then with continuous stimulation applied EFV was 372ml. In each of the other sessions, trialling different sites, post-stimulation control was similar to baseline control.

The volume at first detrusor contraction, reflex volume (RV), for the baseline control and conditional stimulation fill 1 (i.e. until stimulation was first applied) was 73 and 70 ml. Following the first stimulation fill, RV was 164, 173 and 200 ml in conditional stimulation, control and continuous stimulation fills respectively. P05s individual fill results are shown in figure 4.5. P05s response to DGNS and SNS was the most positive in this participant group, mean EFV was improved by 459 ml during DGNS and 165 ml during SNS.

The existence of a tibio-anal reflex pathway may suggest that increased sphincter activity prevents incontinence, yet is unable to directly suppress detrusor activity. In our EMG study we found TNS elicited a reflex EAS response at a higher amplitude to DGNS, at approximately twice the amplitude required to stimulate a motor response in the toes. In animal studies TNS has inhibited bladder overactivity when applied at 3 to 4 times this motor threshold [Bansal et al., 2017]. For P05 in our EAS EMG (different participant, with no SCI) study this would equate to 90 to 120 mA. Given that the ability of DGNS to suppress NDO correlates with amplitude, relative to PAR threshold [Previnaire et al., 1996], it may be possible that a greater stimulation amplitude is required using TNS to elicit the same inhibitory response in the detrusor as DGNS.
4.4. Discussion

Figure 4.5: Participant 5: TNS session results. RV and EFV are shown for each fill in the session (fills sequential on x-axis). Following the first conditional TNS fill, a noticeable change in RV (volume prior to the first detrusor contraction) was seen in each subsequent fill both with and without stimulation.

Although a study in cats has shown that inhibition of the bladder due to TNS is abolished by resecting the L7 nerve roots, whereas inhibition as a result of pudendal nerve stimulation is abolished when the S1 and S2 nerve roots were transected, showing (in cats) a reliance on different entry points to the spinal cord to achieve inhibition of the bladder [Bansal et al., 2017]. A convergence of DGNS and TNS in the sacral cord is supported by a recent study, again in a cat model, where neuronal activity, arising as pelvic nerve afferent activity due to bladder filling, in segments of the S2 cord was seen to be similarly attenuated by both pudendal and tibial nerve stimulation [Yecies et al., 2018].

The TNS response of P05 here is similarly positive, in increasing bladder capacity, to those reported in the literature, but is alone in the 7 participants tested here [Andrews and Reynard, 2003, Amarenco et al., 2003, Kabay et al., 2008], emphasising the need to develop a better understanding as to whether this is repeatable, how to best elicit a response or predict a responder; and the need for a larger trial.
4.4. Discussion

Figure 4.6: Detrusor pressure trace from initial control (baseline) fill (top) and first conditional stimulation fill (bottom) of P05 trialling TNS. Leakage cause termination of the initial control fill and in all other control fills during other sessions P05 leaked as in the first trace. Using TNS P05 remained continent though NDO was not clearly suppressed, appearing as compound NDO with no leakage.

4.4.4 SNS results

SNS has previously been seen to have a direct suppressive effect on provoked detrusor contractions when magnetic stimulation is applied at an amplitude above that required to evoke a big toe contraction and an anal sphincter contraction [Sheriff et al., 1996] and when posterior nerve roots of S2-4 were stimulated using an implanted Finetech-Brindley stimulator [Kirkham et al., 2002]. By applying surface electrodes over the sacrum and applying maximum tolerable stimulation at 15 Hz, we found SNS had no observable effect on NDO in all of the 7 patients tested. While anal sphincter activity was seen in 5/7 participants, with stimulation amplitude then set above this threshold in each experimental fill, the acute suppressing effect on NDO that was observed using magnetic stimulation was not observed here [Sheriff et al., 1996]. A similar urodynamic study using similar surface electrode positioning, with MS participants, also found there to be no effect on NDO [Fjorback et al., 2007a]. It seems most likely that it requires more selective, deeper penetrating, stimulation to elicit the effect reported in previous work and that transcutaneous stimulation in this position is unable to provide this. The reported effect of continuous sub-motor threshold stimulation was not tested here and may be worth pursuing in a chronic setting following reports from
4.4. Discussion

Other groups [Quintiliano et al., 2015, Barroso et al., 2013, Walsh et al., 2001].

4.4.5 SS results

SS, applied at 15 Hz using the electrode arrangement described in fig 3.1, reduced bladder capacity by a small, not significant, margin in all five participants tested, by \(-33 \pm 26\) ml when applied conditionally and by \(-85 \pm 42\) ml in the three participants who trialled continuous stimulation. The array of stimulation parameters reported in the literature is wide. Here we tested SS with the parameters set to the same as the other sites, based on previous work in our centre finding 15 Hz stimulation to be optimal for storage [?]. The decrease in bladder capacity seen here may be due to increased excitability of spinal reflex activity, the result of increased abdominal pressure caused by contraction of abdominal muscles or given the sample size, within the natural range of change seen in repeat CMGs. Changes in EFV were not found to be significant (p=0.06) in the group of 5.

The small decreases in bladder capacity during SS, in the context of several short studies published this year, would be of interest to explore further. Gad et al. (2018) found that the use of stimulation, delivered in high frequency bursts of 1 ms duration over T12 vertebrae, at 1 Hz resulted in improved voiding efficiency, increased flow rate, decreased residual volume and improved coordination between the detrusor and sphincter. At 30 Hz significantly decreased NDO was observed, alongside increased MCC and improved coordination of detrusor and sphincters for voiding. Several differences exist between the methods employed in this study and in ours, that may explain the discrepancy in results. This study firstly issued stimulation in high frequency bursts, a technique with unclear differences to conventional monophasic stimulation. Secondly stimulation was delivered at exceptionally high amplitudes (110-195 mA). When applied continuously, at 15 Hz and 59 \(\pm 12\) mA, we found SS to decrease RV (from baseline) by \(85 \pm 42\) ml, while Gad et al. found an increase in RV of \(80 \pm 50\) ml in 7 participants, during continuous 30 Hz stimulation.

Herrity et al. (2018), presented urodynamic data from five SCI participants who received epidural spinal-cord stimulation implants and had undergone intensive rehabilitation regime. Increased voiding efficiency was enabled, in a frequency dependent manner, where 30 Hz optimally increased efficiency. This was also reported by Gad et al. where transcutaneous stimulation delivered at 30 Hz increased storage capacity, while stimulation at 1 Hz improved voiding efficiency.

Finally, Niu et al. (2018) trialled magnetic stimulation over the T12 vertebra in five
individuals with chronic SCI. Participants underwent a 16 week program where 1 Hz stimulation was applied once a week in three four-minute bursts (a total of 12 minutes of stimulation a week). Participants were instructed to attempt voiding naturally for up to 10 minutes prior to catheterisation in their daily lives. Remarkably, the authors describe that all five participants regained the ability to urinate voluntarily 5.6 ± 1.5 weeks following the start of stimulation. This ability was maintained for 3.2 ± 0.8 weeks following the cessation of stimulation, within a six week period of sham stimulation. This sustained and dramatic recovery of voluntary function contrasts with other studies of SS on bladder function, where no persisting effects of stimulation have been reported [Gad et al., 2018, Herrity et al., 2018]. However, there is ongoing research in this area alongside the effects on locomotor function.

The overall picture from the limited number of separate experiments available suggests that SS does have significant capacity to affect the LUT, appearing to increase the excitability of a spinal micturition reflex with the potential, as has been published recently with regard to locomotion [Wagner et al., 2018, Angeli et al., 2018], to restore voluntary control. These improvements were reported to be frequency and location dependant, in the presented work we have trialled only one electrode configuration and frequency (15 Hz) and have not assessed voiding efficiency. Further acute study of SS at varying frequencies during storage and micturition would be valuable.

### 4.4.6 DGNS results

DGNS has been repeatedly shown to acutely inhibit NDO in suprasacral SCI. A recent meta-analysis of eight acute studies, with a total of 97 SCI subjects, showed a mean ± SD change in bladder capacity from baseline of 131 ± 101 ml [Bourbeau et al., 2018a]. The increase in bladder capacity (EFV) of 153 ± 146 ml reported here is comparable to past studies of DGNS, as is the number of successive suppressed contractions (range 1-6).

Schurch et al. (2000) published initial results of BTX used to treat NDO in 19 SCI patients. At 6 weeks post intervention Maximum Cystometric Capacity (MCC) had significantly increased from 296.3 ± 145.2 ml to 480.5 ± 134.1 ml and 17 of 19 patients were continent (p < 0.016). This was followed up by a multi centre study of 200 patients which saw a smaller, still significant, increase from 272 ml to 420 ml at 12 weeks and 272 ml to 352 ml at 36 weeks. A decrease in MDP was found from 61 to 30 cmH\textsubscript{2}O at 12 weeks and from 61 cmH\textsubscript{2}O to 44 cmH\textsubscript{2}O at 36 weeks [Reitz et al., 2004]. A later study of 37 patients reported increases in mean MCC from 259 (range 40-600) to 522 (range 40-1000)
4.4. Discussion

ml [Patki et al., 2006]. These increases are larger than those recorded in trials of AM medication, where one trial of 10 people with SCI using self titrated oxybutynin (10-30 mg) saw an increase in MCC from baseline 274 ml to 380 ml (p=0.008) [O’Leary et al., 2003]. Our study showed that DGNS has the capacity to increase bladder capacity to a similar extent to existing therapies, though MDP may not be reduced to the same extent. However, the different mechanism of action could allow DGNS to feasibly be used either as an adjunctive to existing therapies or an alternative. An additional advantage of potential on-demand neuromodulation techniques in the potential to give the user control, improving storage at the press of a button. Further investigation of on-demand DGNS and DGNS combined with existing therapies is required to understand it’s place.

In this study we found 5/7 participants responded to conditional DGNS with increased bladder volumes (EFV or VtL) of at least 100ml of 50% and with at least one episode of NDO being suppressed at a peak pressure of below 40 cmH₂O. Two participants (P03 and P05) responded with large increases in bladder capacity to over 500 ml and decreases in average peak detrusor to under 40 cmH₂O, eliminating incontinence. These two participants both had ASIA A SCI with no bladder or genital sensation, allowing use of 2 x EAS\textsubscript{thresh}. The other 3 responders (P03, P06 and P07) all showed increased bladder volumes and at least one suppressed episode of NDO peaking at below 40 cmH₂O, however, average and maximum peak detrusor pressures rose above this threshold. These three participants all had some retained bladder and genital sensation. DGNS may provide a way of decreasing peak pressures during initial episodes of NDO whilst appropriate toileting arrangements are made, thus preserving continence and low pressure storage without terminal MDP ever being reached. Whilst those (such as P01 and P05) without sensation, for whom some form of feedback on bladder activity would be required to initiate preparation for voiding, may use DGNS to prolong continence, increase bladder capacity and decrease storage pressures when applied at a higher amplitude.

The optimal amplitude of DGNS to acutely suppress NDO is close to 2 x EAS\textsubscript{thresh} [Kirkham et al., 2001, Previnaire et al., 1996, Brose et al., 2018], here 3/7 participants were able to tolerate this amplitude, 2 of whom had complete lesions with no pelvic sensation. In other participants, the maximum tolerable amplitude was at 1, 1.04 and 1.33 x EAS\textsubscript{thresh} and one participant we found no EAS response at the 18 mA they tolerated. A study of 23 incomplete SCI subjects found DGNS to be tolerable and ef-
fective [Brose et al., 2018], showing DGNS may be applicable across a broad range of SCI patients. DGNS has been applied with some success as a home based intervention in short pilot studies, reducing incontinence episodes and increasing voided volumes [Lee and Creasey, 2002, Lee et al., 2012, Martens et al., 2010]. This success is tempered by problems found with chronic use of available surface electrodes, particularly with female users, and the lack of effective trigger to close the loop in a conditional neuromodulation system suitable for those with no pelvic sensation [Lee et al., 2012, Martens et al., 2010]. The location of electrodes on the penis or clitoris may be unacceptable to some patients, which makes evaluating alternatives important, however, it offers significant capacity to manage NDO and attempts should be made to deliver an acceptable device.

4.4.7 Control results

The mean change in control fill EFV within a session was $17 \pm 81$ ml and in RV was $-1 \pm 68$ ml across all fills in a session. There was no consistent carry over effect from either stimulation or repeat fills, this is consistent with previous findings in an SCI group [Ockrim et al., 2005].

4.4.8 Limitations

There were several limitations in this study that are important to highlight. Baseline data was collected during a complete bladder fill conducted at the beginning and at the end of each session. Between baseline fills, one to three experimental fills were carried out, during which conditional stimulation of one of the four sites was performed in each session. Overall four sessions took place on separate days, there is a possibility that baseline bladder behaviour would have changed between the days as the result of this cumulative effect of stopping AM medication. We attempted to offset any effect from this by requesting participants stop for five days prior to each session, therefore the AM effect should have washed out prior to every session.

Studies of new interventions with spinal cord injured participants are difficult to conduct in large numbers and the small sample size of seven in this study is a limitation. To offset this as far as possible we designed the study to allow within individual comparison, taking baseline recordings within each session.

Despite these limitations, we believe our results present useful evidence to be used in the further development of neuromodulation for bladder control. In particular, the use of individual participants as their own control adds strength to our conclusions.
4.5 Conclusions

Our results provide useful insight into the practical application of DGNS, TNS, SNS and SS. However, they must be interpreted within the context of a small sample size, fixed stimulation parameters and limited repeats for each subject.

Within this study, we present the beneficial effects of DGNS for suppressing NDO and increasing bladder capacity. DGNS, TNS and SNS all appeared to increased the volume held following initial detrusor contraction. TNS also lead to a significant increase in MDP. SS was trialled in 5 people, in whom small, not significant, decreases in bladder capacity were observed.

The small changes observed in TNS, SNS and SS require further exploration and their potential should not be discounted. Examining their interactions with the neural control of LUT in an acute setting, alongside study of stimulation parameters, could inform future protocols. DGNS has a clear and robust effect on NDO and practical challenges in its real world applicability should be addressed.

In conclusion, NDO following SCI continues to present an important clinical problem with limited solutions available for chronic management. Transcutaneous stimulation is an interesting, and non-invasive, potential treatment option requiring further research to understand its effect and range of application. This study is the first direct comparison of the effect of transcutaneous stimulation sites on NDO in SCI participants in which we have found that DGNS was the most effective site for the group tested.
Chapter 5

Developing a System to Apply and Assess Neuromodulation in Practice

5.1 Introduction

The main aim of this thesis is to critically assess the possibility of using transcutaneous electrical stimulation, delivered using a wearable device, as a chronic treatment for bladder overactivity following Spinal Cord Injury (SCI). In the first step to achieving this aim, Chapters 3 and 4 presented two clinical studies undertaken to assess four potential transcutaneous stimulation sites identified from previous studies. In the first study, the link between four stimulation sites and reflex responses in the external anal sphincter was assessed using paired pulses and surface EMG. In the second study, each stimulation site was trialled in a separate session of urodynamics in participants with SCI and associated Neurogenic Detrusor Overactivity (NDO). Only stimulation of the Dorsal Genital Nerve (DGNS) provided a robust suppressive effect and was able to elicit an anal reflex contraction in the majority of subjects tested. Therefore to enable a trial of DGNS to occur in participants’ home environments, a system was designed to deliver and assess specific neuromodulation protocols. This chapter outlines the background to, design, development and testing of a stimulation system for a clinical study of DGNS in the home-environment for people with SCI.

5.2 System Specification

Based upon the results reported in Chapters 2, 3 and 4; and on a review of reported issues with stimulators in the past, a specification for a neuromodulation system to stimulate the DGN and to record outcome measures in the form of a bladder diary was developed.
5.2.1 Clinical requirements

- To provide stimulation of the Dorsal Genital Nerve at a frequency of 15 Hz, an amplitude of 10-80 mA and a pulse width of 200 µs using charge balanced pulses
- To provide patients control over intensity, either through varying pulse width or amplitude
- To provide the user with on-off control of stimulation
- To provide time-based stimulation triggers
- To enable automatic time out of stimulation
- To allow individually set on/off regimes, the time set within the system User Interface (UI)
- To use electrodes suitable for surface stimulation of the DGN
- To meet safety requirements expected of a medical device and identified during risk analysis

5.2.2 Research requirements

- To record data on all user interactions with device
- To record timestamps bladder diary data
- To allow the researcher to adjust bladder diary parameters
- To record all interactions between user interface and stimulator
- To allow a set of stimulation modes to be programmed for each individual participant

5.2.3 User requirements

- To provide an accessible user interface, appropriate for users with reduced dexterity, equivalent to someone with a C5 SCI and below
- To be able to trigger stimulation immediately (max 1 second delay)
- To feed back on stimulator state (on/off)
- To be easily portable for wheelchair users or ambulatory but disabled users
- To provide one full day of use between charges

5.2.4 Engineering specification

5.2.4.1 Latency specification

Low latency is required in a wireless stimulation system, both to ensure smooth user interaction and no delay in stimulation starting. For smooth user experience it is recommended that user interaction with user interface is immediately acknowledged and that
action taken should happen within 0.1-1 seconds to be viewed as a smooth system to be trusted [Nielsen, 1993]. For DGNS application, stimulation should be applied in the first five seconds following onset of NDO [Kirkham et al., 2001, Opisso et al., 2008]. The specifications for the system are that acknowledgement of interaction with the user interface should be less than 0.1 seconds and the limit for stimulation triggering from pressing the appropriate button on the UI should be one second.

5.2.4.2 Reliability specification

Wireless reliability must match that of a wired system. This must be considered as approaching 100%, as wired system should in theory be 100% reliable. The percentage of communication attempts that are successfully completed will be regarded as the overall reliability of the wireless connection in optimum conditions. This should be over 99%.

5.2.4.3 Power consumption

As each wireless component in the network requires a separate power supply and the device is being designed to be portable when used in everyday life, designing for low power consumption is important. To allow use of the device throughout the day without interruption, the device should last for a minimum of 24 hours on a single charge. To do this whilst remaining compact and portable, low power consumption is required.

5.2.4.4 Safety

The risk of the system not triggering is low in this case, if disappointing. There lies greater risk in a system continuing stimulation out of the user’s control, for example if the wireless connection is lost. Therefore the system shall automatically switch off stimulation in the event of a lost connection. Furthermore, the system shall have a physical off switch to stop stimulation via hardware.

5.3 System Design

Problems reported by users of previous systems have included system bulkiness, difficult to use stimulation controls, too many wires being in the way and getting caught, and difficulty in timely triggering of stimulation. A wireless controller with an easy to use interface to both trigger stimulation and adjust its intensity would address several of these issues. Further to this, some automation in the collecting of bladder diary data would be beneficial for the assessment of DGNS in the home environment.

Wireless systems have the capacity to provide an easily accessible controller to a larger
component of the system that can be fixed elsewhere. In application to a DGNS system, wireless control would provide the benefit of allowing wires and stimulator to be attached close to the stimulation site and remove the need to move the stimulator to trigger stimulation.

Implementing the user interface on a touch-screen device enables all of our target population, including those with reduced dexterity, to use the same system. The bladder diary was also implemented on the same touch screen device, to provide some automation as the user just presses touchscreen buttons and time stamped events are saved in a digital diary for the researcher to analyse.

Figure 5.1 outlines the high level architecture of the proposed system.

![Figure 5.1: Overview of the proposed system interaction with regards to user interface, stimulation controller, stimulator, patient and researcher](image)

5.3.1 Safety, standards and CE marking

To be placed on the market in Europe, medical devices require CE marking and to demonstrate compliance with medical device regulation [Commission, 2017]. As the system being developed for this project was an in-house tool, it did not need to be CE marked. However, equipment used in research must be safe to protect both participants and researchers from harm. In-house devices must also meet requirements for basic safety, as outlined in the MDR and relevant safety standards. Therefore, the system was developed to meet essential requirements for electrical safety outlined in the medical electrical safety standard BS EN
With regard to electrical safety, electrical stimulation systems are also in the position where there are conductive connections between the user and the device. Special attention in the design of these devices must be paid to adequately mitigate risk. Stimulation output must not be provided at a level and in a manner where cardiac problems are caused; electrolysis leading to skin damage must be prevented by protecting against direct current delivery; and given that electrical stimulations equipment may be connected to external equipment that is potentially connected to mains (e.g. a computer), it must protect against electric shock.

Several other components of stimulator design must be taken into account to design a safe device. Electrical isolation from mains current must be provided to reduce the risk of electric shock mentioned above. For chronic use of electrical stimulation, charge balancing of stimulation pulses is recommended. As the electrode-tissue interface has a capacitive element as well as resistive element, monophasic pulses applied over a period leads to a buildup of charge under the stimulating electrode which may lead to electrolysis, in turn leading to skin irritation and harmful skin damage. Biphasic electrical stimulation pulses are required to discharge the interface capacitor when using polarisable electrodes.

We considered the feasibility of using a commercial stimulator, CE marked and already designed to mitigate against the above risks. In designing a control system for an existing stimulation device there are still residual risks to consider, as indeed there are in trialling a new applications of electrical stimulation.

### 5.3.2 Stimulator selection

The stimulation parameters required, as identified in previous research [Previnaire et al., 1996] and confirmed during the investigations presented in Chapters 3 and 4, were stimulation pulses frequency of 15 Hz, amplitude of 10-80 mA and pulse width of 200 $\mu$s. Given the chronic setting in which stimulation was to be applied, charge-balanced biphasic stimulation pulses were considered necessary to prevent breakdown of skin. To enable a custom control system, the stimulator must have the option of applying or of being operated with an external trigger.

An Odstock Medical Ltd (OML) Pace one channel stimulator (ODFS Pace) was selected as the most suitable. From a safety perspective, aside from appropriate CE marking, the ODFS Pace is a voltage source providing pulses at a set voltage (current calculated based on assumed 1kOhm//500nF) which reduces the chances of increased voltage pulses
being delivered. This is considered preferable in a chronic environment, particularly where electrodes may slip. The ODFS Pace was modified by OML to allow 15 Hz stimulation.

The ODFS Pace is also a small device, designed to be carried around throughout daily life by disabled users with drop foot [www.odstockmedical.com].

5.3.2.1 Wireless protocols

High reliability, low latency and low power consumption are important to provide patients with a device they can trust to trigger stimulation when it is required, in a manner that is not frustrating to use and is able to be housed in a compact device that is easily portable.

Further conditions to consider in the design of the system are potential interference from other systems in the same frequency spectrum and the suitability of a wireless protocol for a wearable device where parts of the system are worn on the body.

Two protocols were considered, Bluetooth Low Energy (BLE) and Zigbee. Both have been used in commercial medical devices in the past and are designed as Body Area Networks. BLE is a version of the Bluetooth specification (4.0 and higher) [www.bluetooth.com] that has become extremely well supported in recent years due to its low energy consumption and low cost. Zigbee is an older standard similarly supporting low energy, low latency data transmission at a low cost. Peak power consumption is higher than BLE, though like Zigbee based products can last on coin cell batteries for long periods of time.

<table>
<thead>
<tr>
<th></th>
<th>Bluetooth low energy</th>
<th>Zigbee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak current consumption</td>
<td>&lt;15mA</td>
<td>&lt;150mA</td>
</tr>
<tr>
<td>Security suitable for medical device</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Throughput</td>
<td>125kbit/s-12Mbit/s</td>
<td>250kbits/s</td>
</tr>
<tr>
<td>Range</td>
<td>&gt;100m</td>
<td>10-100m</td>
</tr>
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</table>

BLE was chosen due to the slightly lower reported power consumption [Dementyev et al., 2013] and the compatibility it has with the vast majority of smart devices, where Zigbee would involve the design of a custom remote hardware. Given that we wanted to implement a touchscreen user interface, we decided to use a smartphone and custom app as a basis for a controller with a BLE module to switch the stimulator.

In addition to low latency, low power consumption and high reliability, consideration was given to the future of this prototype system as a medical device. Therefore compatibility, security features and the possibility of introducing further components (eg. feedback
mechanism) into the same network topology were all considered in the selection of suitable technologies.

### 5.3.3 App design

Android was selected as the most suitable development platform, due to the lower cost of development tools and of Android hardware. A Samsung J3 smartphone (2017) was selected, due to availability and the provision of Bluetooth low energy 4.0 specification and Android operating system greater than 5.1.

![Diagram](image)

**Figure 5.2:** A block diagram outlining the call functions and structure of the developed Android app

The application class’s life-cycle is from the very beginning to the very end of our process, continuing if the app is exited and not destroyed. Within this class the Bluetooth low energy service is bound, started and destroyed. The Bluetooth low energy service similarly runs throughout the use of the app and the app life-cycle. This provides all Bluetooth low energy related functionality to communicate with the android Bluetooth low energy stack, including functions to connect to devices, maintain connections with devices, read and write to/from Bluetooth Characteristics, to disconnect devices and to communicate with external activities (i.e. the user interface). Only two activities are used in the final version of the app, each representing a different stage of interaction with the user interface: "Test set up" or "Patient". Each one representing a separate user interface. The main activity was to be
used by participants and included all functionality for recording time stamped diary data, selection of stimulation modes, running of timers set during the app use, feedback from the smart switch onto the user interface and communication with the smart switch over BLE.

5.3.3.1 User interface

The user interface should be suitable for users with no hand function, in the case of SCI suitable for a C5 tetraplegic, as well as users with full hand function. It must also be usable by individuals with the equivalent of a high school education and users with reduced sight (requiring reading glasses).

![Figure 5.3: A picture of the Android App UI used in the study described in Chapter 6. 1) Clinician set up page, test ID entered and diary variables selected 2) Checkbox to include stimulator control functionality, add mode button to add new stimulation switching mode 3) Stimulation mode set-up 4) Confirm to create new test or back to return to previous test 5) Test and connection information bar, connection state is automatically updated 6) Refresh connection button to refresh the BLE connection 7) App diary function. A recording is made if the button is held down for 500 ms, a toast is displayed recorded. If held down for less than 500 ms a toast is displayed Please hold down to record 8) Stimulation control panel. Modes are displayed and may be selected by pressing radio buttons 9) Direct on/off control button to stimulator. Changes automatically to reflect stimulator stat if automatic switch mode is selected 10) Menu to go into settings or refresh BLE connection 11) Password entry to enter Clinician set-up mode](image)

5.3.4 A smart switch

To enable the wireless control of the ODFS Pace required to develop a Bluetooth low energy connecting switch, attached to an existing port and replicating a standard force sensitive resistor that would switch stimulation on the device. This method would allow wireless control of stimulation triggering without any modification to the CE marked stimulation itself.
5.3.4.1 BLE microcontroller

An Adafruit Feather BLE 32u4 Microcontroller was chosen, to be programmed using the Arduino programming language. This module was selected due to the small size (51 mm x 23 mm x 8 mm), built in battery charging capacity and integrated BLE module.

5.3.4.2 Stimulation switching

A small circuit was designed to replicate the function of a Force Sensitive Resistor (FSR), which, in its intended operation, is used for the external trigger of the ODFS Pace. The function required was to adjust the resistance from roughly 10 kOhm (FSR compressed) to $\infty$ Ohm (FSR open), switching between these two states was to be controlled by a digital I/O pin from the microcontroller.

To accomplish this, an N-channel MOSFET switch circuit was designed, as shown in figure 5.4. A MOSFET was used rather than a BJT as they are voltage, rather than current, driven. A Fairchild 2N7000 N-Channel enhancement mode field effect transistor was used as it is highly suited to low voltage, low current applications and provides fast switching.

![Figure 5.4: Circuit diagram of the N channel MOSFET switch circuit used to replicate the function of a force sensitive resistor foot switch, only to be triggered by the digital I/O pin 3.7 V from the Adafruit feather (MCU IO)](image)

5.3.4.3 Power supply

An external power supply was required to power the microcontroller circuit at 3.7 V. The Adafruit Feather BLE reportedly consumes close to 10mA when using the Bluetooth functionality. When tested it was found to be 12mA. Therefore to meet the design specifications of lasting for at least 24 hours and to reduce size and weight as far as possible a 350 mAh Li-Po battery was used. This was a small ‘flight’ battery with rigid casing and inbuilt charge protection circuitry.
5.3.4.4 Enclosure design

An enclosure for the smart switch was designed, to house the microcontroller and MOSFET switch together, with the battery stored in a separated internal compartment with rigid casing and a small amount of leftover space. The Adafruit Feather is held secure by four posts, in a position where the USB port could be accessed from outside of the enclosure. A 1.5 mm jack plug extends via a cable from the enclosure to be attached to the external trigger port of the ODFS Pace. The enclosure was designed using on shape CAD software manufactured using filament deposition modelling 3D printing techniques on a Ultimaker 2 plus 3D printer.

![Enclosure design](image)

**Figure 5.5:** CAD models of the enclosure a) showing the battery compartment with sliding lid, b) showing the microcontroller compartment with clip-on lid and c) a picture of the final smart switch, housed in the 3D printed enclosure

5.3.4.5 Code

The programmes tasks were: maintain the BLE connection, this was done utilising the provided BLE libraries written by Adafruit; monitor for low battery level, this was not done precisely but by monitoring battery voltage it is possible to communicate when the battery is running low and requires charging; receive stimulation modes, designing a stimulation trigger command and regime; and react to stimulator triggers received from the App.

Trigger timers, eg. turn stimulation on in 30 minutes, were set in the App. However, short timers for intermittent stimulation were set and triggered on the smart switch.

5.3.5 Electrode selection

Three commercial surface electrodes were tested for their suitability for chronic application to the penis or clitoris. These were Schwa-Medico 15x75 mm electrodes, PALS platinum 2.5 cm diameter electrodes and Ambu neuroline 710 paddle electrodes, all shown in figure...
5.3. System Design

5.3.6 Stimulation set-up

The different parts of the system presented thus far were combined as set out in figure 6.1. A guide was developed to go with the ODFS Pace instructions for use document, this outlined how to use the system for both stimulating and for recording a bladder diary and was given to participants in the study outlined in the Chapter 6.
5.4 Testing

5.4.1 Test 1: System bench test

A bench test evaluated the following two specifications: (i) minimum 24 hours of operation between charges, and (ii) at least 99% reliability.

The test lasted 24 hours, during which intensive operation was simulated by the Android app automatically sending on and off commands to the smart switch at 0.2 Hz. The smart switch acknowledged each command received with an echoed response. A time-stamped event for each sent or received message was recorded on the phone. A total of 17280 messages were expected to be sent and received over the 24 hours of the test.

The reliability was defined as the percentage of send and receive operations completed.

These were optimum conditions (though intensive operation), in practice wireless interference may negatively affect in system reliability. However, this was not specifically considered here as the Bluetooth module being used has passed the relevant regulatory hurdles and the prototype being developed would be for the sole use of pilot studies.

To pass the test, to meet specification requirements, the system had to maintain battery power for the 24 hours and reliability must be greater than 99%.

The system was still running at the end of the 24-hour test, thus passing test (i) and meeting the specification.

A successful transmission is regarded as the completion of the intended input to output across the BLE connection. Reliability is defined as the percentage of button presses that receive acknowledgement of receipt from the smart switch. 17280/17280 messages were sent and received confirmation, meaning that in these ideal circumstances reliability was 100%, passing test (ii).

5.4.2 Test 2: User test

To test the system in a real-world scenario. Two ‘system users’, volunteers with no prior experience of the system, were asked to test the system over 6 hours. Over this period they were asked to record a paper diary of random diary inputs, noting the time and also pressing the relevant diary input button on the smartphone app. They were provided with a stimulator, connected to the smartphone app, with no stimulating electrodes. They noted on a paper diary each time they pressed the stimulation button, this was recorded in the smartphone diary, and they were asked to note whether the stimulator LED lit up and the stimulator made a small clicking noise.
Both users found the system easy to use. All 47 diary inputs matched those written on the paper diary as did 9/10 stimulation attempts. On 1/10 stimulation attempts they were unable to start the stimulator as it had become disconnected. This was as they had left the smart phone and walked off with the stimulator in their pocket at one point, moving out of the connection range and not refreshing the connection before trying to start stimulation. The problem was rectified by pressing the ‘refresh connection’ button at the top of the user interface. As required by the safety specification, the stimulator would have stopped stimulation in this instance.

5.5 Work Towards a Commercial Device

Following the design of the system and subsequent pilot study presented in Chapter 6, a collaborative project with Odstock Medical Ltd. (OML) was undertaken to integrate the functionality of the system into the ODFS Pace XL stimulator. Work was completed on the documentation required for certification of a wearable DGNS device, including risk analyses, specifications, usability and test plans, and on redesigning an existing expansion board for the Pace, to increase its functionality and add BLE communication. This work would improve our prototype system by decreasing the device size, reducing overall power consumption, improving reliability and security and shifting from two to one power sources.

We built upon work completed in a previous PhD thesis [Mecheraoui, 2011] and subsequently commercialised by OML, allowing wireless (Zigbee) communication between a foot switch and stimulator for treatment of drop foot. The new designs were in part based upon those previously done by Mr R. Batty, Dr C. Mecheraoui and Dr E. Merson (Clinical Engineers, OML).

5.5.1 Expansion board development

The shape of the Printed Circuit Board (PCB) was pre-defined as it was required to fit safely within an existing certified device, footprints for this were provided by OML. We designed a circuit to include capability to: communicate via SPI with the stimulation board, allow both ZigBee and BLE communication using a wireless module (Mighty Gecko, Silicon Labs) and allow on-board storage of data on a removable microSD card. This was achieved using a central microcontroller (PIC18F47J13, Microchip) to communicate with peripheral components and the stimulator, as shown in figure 5.8. The manufactured and assembled board (minus SD holder) is shown in figure 5.9. Software development and testing for this
board is ongoing in collaboration with OML.

**Figure 5.8:** Block diagram of core components in expansion board circuit. UART communication was enabled between the PIC MCU and BLE module. SPI communication was enabled between the expansion board and the Pace, and a shared SPI line was enabled between the PIC MCU and peripheral storage and clock.

**Figure 5.9:** Assembly of manufactured PCB to integrate BLE and ZigBee functionality into the ODFS Pace stimulator. a) Bottom view of the new expansion board PCB b) Top view of expansion board PCB c) ODFS Pace without expansion board d) Assembled Pace with new expansion board

### 5.6 Conclusions

Existing neuromodulation devices are not suitable to implement DGNS as a clinically useful treatment. The most often cited issues are: device usability, device size, excess wires, electrode adhesion and appropriate stimulation triggers for conditional neuromodulation.
A further issue is how to enable reliable assessment of neuromodulation’s effect during long-term studies.

Specifications for a new research device were drawn following a review of the systems used in the literature, and an audit of the bladder sensations retained amongst the LSCIC patients. Primary requirements are that it must guarantee user safety and implement three stimulation paradigms on a wireless user interface to be used for both control of stimulation and recording of bladder diary input.

To meet the electrical safety requirements, the stimulation system was designed using an Odstock Medical Ltd one channel Pace stimulator. The system uses a smart phone with Bluetooth Low Energy capability, with a custom built Android app providing a touchscreen user interface enabling both control of the Pace stimulator and the recording of the user’s bladder diary. The Pace stimulator is connected to the app via BLE implemented in a custom-designed smart switch, replacing the traditional FSR foot switch. The system was found to be both reliable and user-friendly in short controlled experiments.

This system was used to trial DGNS in SCI patients, both during ambulatory urodynamics and a week-long home trial. These experiments are described in the next chapter.
Chapter 6

Pilot Study of Neuromodulation in the Home

6.1 Introduction

Spinal Cord Injury (SCI) leads to severe aberration in the neural pathways responsible for control of the Lower Urinary Tract (LUT) [Craggs et al., 2006]. Neurogenic Detrusor Overactivity (NDO) and Detrusor Sphincter Dyssynergia (DSD) are two common conditions developed following supra-sacral SCI causing high intra-detrusor pressures that increase risk of ureteral reflux and incontinence. Incontinence is prevalent in the SCI population and may be detrimental to quality of life [Liu et al., 2010]. Stimulation of pudendal afferents inhibits NDO and may be achieved superficially by targeting the Dorsal Genital Nerve (DGNS), placing electrodes on the penis or clitoris [Bourbeau et al., 2018a].

This thesis has thus far outlined steps taken to determine the most effective transcutaneous stimulation site, see Chapter’s 3 and 4, and to develop a system to assess DGNS in a home based setting, see Chapter 5. This chapter outlines a study conducted with SCI participants to trial DGNS during natural filling of the bladder both in clinic and in their home environments.

6.1.1 Triggers and regimes for DGNS

In acute studies in the laboratory, conditional neuromodulation is conventionally triggered at the onset of an unwanted detrusor contraction, identified as a rise in detrusor pressure which requires a indwelling catheter. This method produces similar results to continuous [Kirkham et al., 2001] or intermittent DGNS [Stöhrer et al., 1999]. However, conditional DGNS is considered optimal due to the reduction in stimulation time required. This may be important as battery life of portable devices may be greatly reduced using continuous stimulation and there are (currently not evidenced) concerns that the reflex inhibition produced by DGNS may habituate with overexposure to stimulation. No physiological triggers, able
to detect the onset of NDO, currently exist in a format that may be applied chronically in peoples daily lives [Melgaard and Rijkhoff, 2014]. As such, three alternative options were considered for trialling DGNS with SCI participants: self-triggered stimulation; continuous stimulation; and intermittent stimulation.

Self-triggered stimulation, used for the immediate suppression of NDO, relies on preserved sensation of bladder activity. Following SCI approximately 77% of people have at least partially preserved bladder sensation, and many use this sensation in their current bladder management strategy [Ersoz and Akyuz, 2004]. It is therefore not surprising that positive results have been reported in the small number of pilot studies trialling on-demand DGNS [Bourbeau et al., 2018b, Opisso et al., 2013, Lee and Creasey, 2002, Lee et al., 2012]. However, issues remain with the assessment of the suitability of residual sensation and also in the accessibility of stimulation triggers to allow fast application of DGNS [Martens et al., 2010, van Breda et al., 2016]. The safety of using partially preserved sensation must also be investigated, as missed detrusor contraction may lead to ongoing high intra-detrusor pressures and risk ureteric reflux.

For those without residual sensation, self-triggered conditional DGNS based upon sensation is not an option. For this group, in the absence of a physiological trigger, the options are continuous or intermittent stimulation. Continuous stimulation has been shown to be effective during standard cystometry [Nakamura and Sakurai, 1984, Vodusek et al., 1986, Kirkham et al., 2001] and in a limited number of patients (4) trialling continuous stimulation over longer periods between 4 and 8 weeks [Bourbeau et al., 2018b, Wheeler et al., 1994].

Intermittent DGNS has been shown to be effective in one lab based standard cystometry study of 5 SCI participants [Stöhrer et al., 1999]. A 5 seconds on, 5 seconds off regime was trialled during slow (10 ml/min) fill cystometry, this increased maximum capacity by 120 ml which was comparable to a 135 ml increase seen during continuous DGNS (p=0.4441). Intermittent DGNS has not been trialled in either Ambulatory Urodynamic Monitoring (AUM) or in a home-based study.

The aim of non-continuous approaches is to reduce stimulation time to preserve battery life and reduce the chance of habituation. Intermittent stimulation provides one method of doing this. Another method is to use behavioural management, as is already applied as first line treatment for managing incontinence [Drake et al., 2016a]. This would involve trigger-
ing stimulation based on behavioural patterns, for example a set time after the previous void or before embarking on tasks known to trigger bladder overactivity. The functionality to set timers for triggering stimulation was designed into the NEUROMOD system but not used in this study.

6.1.2 NEUROMOD stimulation system

As described in Chapter 5, a system was developed to enable the wireless control of a commercial stimulator to deliver the stimulation paradigms mentioned in 6.1.1. This system includes: an Android smartphone with a custom app for recording of diary data, set-up of stimulation modes and control of an ODFS Pace stimulator; a one channel, ODFS Pace stimulator; a bluetooth connected trigger (smart switch) for the stimulator; and 2.5 cm diameter PALS surface electrodes. The complete stimulation kit is shown in figure 6.1.

Figure 6.1: The stimulation kit given to participants to take home. A) surface electrodes B) spare batteries C) a study guide outlining how to use the app and stimulator controller D) user instruction manual for the ODFS Pace E) cable to attach stimulation electrodes to the simulator F) smartphone with custom Android app, set so that only this one could be used as Bluetooth would be on the whole time to maintain a connection G) ODFS Pace one channel stimulator H) custom smart switch, enabling Bluetooth control of the stimulator

6.2 Aims and Objectives

6.2.1 Study objectives

The objectives of the presented study were:

- To assess the effect of patient specific (self-triggered, continuous or intermittent) DGNS on: number of incontinence episodes, bladder capacity, detrusor pressure and incontinence related quality of life.
6.3. Methods

To assess the feasibility of using a wirelessly controlled stimulation system in participants’ home environments.

6.2.2 Outcome measures

Baseline and experimental results were recorded for all individuals to enable within-individual comparison. The outcome measures used were:

- Ambulatory urodynamic monitoring (AUM) to assess intra-detrusor pressures and bladder capacity at baseline and whilst using DGNS, during natural filling of the bladder.
- A self-reported digital bladder diary, reporting on urgency, voided volumes and incontinence episodes.
- Recording of stimulator usage.
- International Consultation on Incontinence Questionnaire Urinary Incontinence - Short Form (ICIQ-UI-SF), a short validated questionnaire giving a score of 0-21, where 21 represents maximum impact on quality of life.

6.3 Methods

6.3.1 Ethical approval

All relevant permissions were obtained from the Stanmore Regional Ethics Committee and Health Research Authority. The study was conducted in accordance with the Declaration of Helsinki and in line with Good Clinical Practice guidelines.

The study was prospectively registered on the ISRCTN [ISRCTN17182264].

6.3.2 Participants

6.3.2.1 Recruitment

Recruitment took place within the Royal National Orthopaedic Hospital’s (RNOH) patient population, first contact was made by a member of the clinical care team. Participants were approached if they were suitable candidates either in person, telephone or invitation letter. We also used flyers, explaining the project, displayed in the hospital and online with contact details for further information. Participants from the previous study, presented in Chapter 4, were invited to participate in this study.

The study was explained to suitable patients and a participant information sheet provided to those who were interested. Following a 24 hour period, any questions about the
Table 6.1: Inclusion, exclusion and withdrawal criteria for recruiting into the home trial of DGNS

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Surasacral Spinal Cord Injury</td>
<td>- Cardiac pacemaker</td>
</tr>
<tr>
<td>- Male or Female, over the age of 18, no upper age limit</td>
<td>- Previous surgical intervention on bladder/sphincters</td>
</tr>
<tr>
<td>- Injury sustained more than 6 months ago</td>
<td>- Showing positive leucocytes and nitrites on urinalysis on the day of investigation</td>
</tr>
<tr>
<td>- Urodynamically proven Neurogenic Detrusor Overactivity</td>
<td>- Poorly controlled epilepsy. Acceptable where epilepsy is controlled by drugs or there have been no fits experienced for a reasonable period.</td>
</tr>
</tbody>
</table>

| Withdrawal criteria | |
|--------------------|-
| - No NDO in baseline CMG | - Patients with a cancerous tumour in the area of the electrical stimulation |
| - Intolerance to stimulation | - Active sepsis |
| - Autonomic Dysreflexia as a result of stimulation | - Pregnancy |
| - Request of participant | - History of significant Autonomic Dysreflexia |
| | - Recipient of intradetrusor botulinum toxin injections within the last 6 months |
| | - Patients with exposed orthopaedic metal work in the area of electrical stimulation |

...study and its associated risks were answered. If the patient wished to proceed, an appointment was made for the first experiment session in which informed consent was obtained prior to participation.

6.3.3 Participant characteristics

Participant characteristics are set out in Table 6.2. Four out of the 5 participants had retained sensation, defined as sensation used in their daily lives for timing of bladder voiding. The mean age was 52±11 years old and time from injury was 12±5 years. All participants were on some form of antimuscarinic (AM) medication, continued over the study period, and 4/5 had previously undergone Botulinum-A toxin (BTX) injections (all more than 6 months prior to participation). Four out of 5 participants voided by using Intermittent Self Catheterisation (ISC) and one reflex voided into a sheath drainage system. All participants experienced incontinence of varying regularity.

Four of the 5 participants had participated in our previous neuromodulation study, Chapter 4. They were matched as follows, with their previous study ID followed by this study ID, P01 - P01, P03 - P03, P06 - P05, P07 - P04.
Table 6.2: Information on participants with regard to SCI and bladder management

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Sex</th>
<th>Injury</th>
<th>ASIA</th>
<th>Years from SCI</th>
<th>Cause of SCI</th>
<th>Bladder voiding</th>
<th>Bladder storage</th>
<th>Past botox</th>
<th>Sensation</th>
<th>Incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>45</td>
<td>M</td>
<td>T4</td>
<td>A</td>
<td>6</td>
<td>T</td>
<td>ISC + Sheath</td>
<td>AM</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>P02</td>
<td>38</td>
<td>F</td>
<td>T10</td>
<td>A</td>
<td>8</td>
<td>T</td>
<td>ISC</td>
<td>AM</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P03</td>
<td>69</td>
<td>M</td>
<td>C5</td>
<td>D</td>
<td>12</td>
<td>Not - T</td>
<td>ISC + Pad</td>
<td>AM</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P04</td>
<td>48</td>
<td>M</td>
<td>C5</td>
<td>C</td>
<td>18</td>
<td>T</td>
<td>Sheath</td>
<td>AM</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>P05</td>
<td>61</td>
<td>M</td>
<td>C6</td>
<td>D</td>
<td>16</td>
<td>T</td>
<td>ISC</td>
<td>AM</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
6.3.4 Study protocol

The experiment was carried out in 5 phases: a screening assessment where the participant underwent cystometry (CMG) to test for NDO and test the suppressive effect of DGNS; a control week completing a bladder diary whilst continuing usual care; an in clinic assessment of bladder pressures at baseline and with DGNS; an experimental week completing a bladder diary whilst using DGNS on top of usual care; and a second in clinic assessment of bladder pressures following a week of DGNS use.
Table 6.3: Outline of the study regarding what happened to participants, time and location

<table>
<thead>
<tr>
<th>Session</th>
<th>Duration</th>
<th>Day</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Diary instruction and screening</td>
<td>30 mins</td>
<td>1</td>
<td>RNOH</td>
</tr>
<tr>
<td>After providing informed consent, this involved answering some questions on the impact of their injury on their bladder, the level of sensation with regard to bladder function and being shown how to complete the bladder diary. A smart device with a dedicated app to record a standard bladder diary was provided for the participant. Screening assessment involved standard filling CMG being performed at baseline to determine if NDO was present. If so, DGN electrodes were attached as described in Chapter 3 and set at $2 \times EAS_{\text{thresh}}$ or the maximum tolerable level. A further CMG was performed with DGNS applied at a rise in detrusor pressure. Participants were invited to continue in the study when DGNS was tolerable and found to visibly suppress NDO.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - Recording bladder diary at home</td>
<td>7 days</td>
<td>1 to 8</td>
<td>Home</td>
</tr>
<tr>
<td>The participant was provided with the device in order to continue recording a bladder diary for the following 7 days. This involved pressing the appropriate buttons regarding leakage events, voided volumes and urgency through the week.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Questionnaire, AUM and stimulator set-up</td>
<td>6 hours</td>
<td>8</td>
<td>RNOH</td>
</tr>
<tr>
<td>To assess each participant's baseline bladder function during normal activities they first completed the short International Consultation on Incontinence Questionnaire (ICIQ-UI-SF). The participant then underwent AUM, this involved a catheter being placed into the bladder and rectum to measure pressures over the course of two natural bladder filling cycles. The participant was shown how to set up and use the stimulation equipment. This was checked by urodynamic measurement in a second cycle.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Home use of stimulator with diary</td>
<td>7 days</td>
<td>8 to 15</td>
<td>Home</td>
</tr>
<tr>
<td>Following a successful setup session, the participant was provided with the portable stimulator to take-home. They were asked to use this to control unwanted bladder overactivity over the next 7 days and to continue recording a bladder diary in the same app. Sticker electrodes were worn when the system is in use.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 AUM and questionnaire</td>
<td>6 hours</td>
<td>15</td>
<td>RNOH</td>
</tr>
<tr>
<td>Finally, following 7 days of home use, participant were asked to attend the clinic. This involved completion of the same questionnaire (ICIQ), followed by undergoing AUM without DGNS then whilst using the stimulator to restrict bladder overactivity.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.3. Methods

Figure 6.2: Flow chart outlining the route of a participant through the study. Participants who had trialled DGNS in the study in Chapter 4 were able to proceed without further screening urodynamics. During screening, where DGNS was able to suppress at least one episode of NDO, as defined in Chapter 4, participants were invited to proceed into the main study.
6.3.5 Stimulation set-up

A history of each participant’s bladder management was taken and participants were assessed as having residual bladder sensation adequate to empty the bladder or not. For those with residual bladder sensation, direct (on/off) control of stimulation from the app was set-up and they triggered stimulation on urge and turned stimulation off when any sensation of urge or NDO subsided. It was made clear to keep the same sensation of strong urge as the study end point in each filling cycle. For participants with no residual bladder sensation, two stimulation modes were set-up. i) direct control for continuous stimulation, and ii) an automatic stimulation sequence (alternating five seconds on and five seconds off) to be initiated by participants as an alternative to continuous stimulation. The value of five seconds on five seconds off for intermittent stimulation was determined in a previous project as the optimum sequence [Stöhrer et al., 1999].

The stimulation amplitude was set during the participants’ first visit to the clinic. This was done by visual detection of External Anal Sphincter response (EAS\textsubscript{thresh}) to increasing stimulation amplitudes. The amplitudes used in the study were then set as close to twice EAS\textsubscript{thresh} as possible. In the event that no EAS activity was seen, or twice EAS\textsubscript{thresh} was not tolerable the maximum tolerable amplitude was set to 40 mA. A two second ramp at the initiation of stimulation was set on the stimulator as this was found empirically to be most comfortable for participants.

Participants were shown during the first session how to set up electrodes. Male participants placed electrodes on the dorsum of the penis, approximately 2 cm apart with the cathode (black lead) placed proximal to the anode, and female participants were instructed to place the cathode over the clitoris and the anode to either side on the labia majora or inner thigh.

6.3.6 Ambulatory urodynamic monitoring

Ambulatory Urodynamic Monitoring (AUM) involves continuous measurement of vesical (P\textsubscript{ves}) and abdominal (P\textsubscript{abd}) pressures during physiological filling cycle. In contrast to the filling CMG performed in the acute study of stimulation site, AUM is able to record bladder activity in a close to real life scenario, where the patient is able to move around freely [van Waalwijk van Doorn et al., 2000].

Pressures were recorded using a commercial data logging system (Gaeltech Nanologger), commercial pressure transducers zeroed at atmospheric pressure (Medex, Smiths Med-
ical), and catheters placed into the bladder ($P_{ves}$) and rectum ($P_{abd}$). Detrusor pressure was obtained by $P_{det} = P_{ves} - P_{abd}$.

As a majority of SCI participants in this study performed catheterisation to empty the bladder, a standard ch12 Foley urethral catheter was used with a three-way tap to record pressure and to empty the bladder when the participant felt they would catheterise. This decision was made to minimise the number of catheterisations required within each session. The end of each fill was defined as when leakage occurred or when the participant felt strong urge to void, at this point the trace was marked with an event and urine was withdrawn from the bladder through the catheter.

In addition to pressure, urinary leakage, maximum cystometric capacity (MCC), urge and stimulation timing was recorded.

The end of each fill was defined as when leakage occurred or when the participant felt strong urge to void, at this point the trace was marked with an event and urine was withdrawn from the bladder through the catheter.

![Figure 6.3: Outline of set up for male participants in the AUM testing. Shown is an example pressure trace from P01 viewed following one filling cycle](image)

### 6.3.7 Analysis

Urodynamic data was analysed in Gaeltec Nanollogger software. Further analysis was conducted using Matlab to filter signals for presentation. Average Peak Detrusor Pressure (APDP), Maximum Detrusor Pressure (MDP) and Maximum Cystometric Capacity (MCC) were recorded and changes from baseline were analysed within individuals.

Diary data was exported from a smartphone as a .csv file. This was subsequently analysed in Excel. Outcomes were volume voided, incontinence episodes, recorded urgency, number of voids (frequency).
6.4 Results

We recruited 5 participants with chronic suprasacral SCI and urodynamically proven NDO. Each trialled DGNS during physiological filling both in the hospital environment and in their home environment.

6.4.1 Stimulation set-up

Following instruction all participants were able to set up the stimulation system or able to instruct another to do so as part of any existing care support. P04 used a sheath (Convene optima) for voiding, he was able to place the electrodes under the sheath when using stimulation at home.

Stimulation amplitude was set on the device at the start of the week. The mean stimulation amplitude was 55 ± 10 mA, range 44 to 70 mA. Pulse width was set to 200 μS and was able to be changed by participants over the week as a means of adjusting intensity (as per ODFS Pace instructions for use).

Four out of the 5 participants had pelvic sensation and were instructed to trigger the stimulation from the smartphone app on urge.

P01 had no pelvic sensation and was set up with intermittent (5 seconds on, 5 seconds off regime) and continuous stimulation modes to be selectable on the smartphone app, both modes were trialled during AUM and were successful and therefore, continued as options for the participant to use at home, though continuous stimulation only was used.

6.4.2 Baseline data

Baseline AUM was conducted both before and after the week of home DGNS use. A bladder diary was filled out for one week during normal care (no change to routine medication or lifestyle) and a quality of life questionnaire (ICIQ-UI-SF) was completed based upon the same week as the baseline diary.

All data is presented in Tables 6.4, 6.5 and 6.6. During AUM, MCC was 244±59 ml
for all 5 participants, varying slightly from an MCC of 204±109 ml in the earlier study using standard CMG, though participants had remained on AM medication in this study. There was 1.5±1.4 rises in Pdet prior to leakage or urgency requiring emptying, APDP was 56±16 cmH₂O and MDP was 58±18 cmH₂O.

Baseline ICIQ scores were 12±8.

Diary data showed a mean recorded void volume of 240±37 ml, where 32±5 voids were recorded per participant over the week. 11±9 incontinence events and 34±10 urgency events were also recorded in the week.

### 6.4.3 Ambulatory urodynamic monitoring

#### 6.4.3.1 Overall AUM results

All 5 participants attended at least one AUM session. P02 was unable to attend the second session due to personal circumstances and travel arrangements, P03 attended both sessions however in the second session was withdrawn due to issues with catheterisation. Additionally, P03’s AUM pressure data in week 1 was not recorded as a wire was knocked out of place during ambulation. All AUM outcomes are shown in Table 6.4.

DGNS was able to suppress NDO in all participants, the number of rises in detrusor pressure, before leakage or urgency requiring emptying, increased from 1.5 ± 1.4 during control to 4.3 ± 1.7 when using DGNS, p=0.0234. MCC was increased from 244 ± 59 to 346 ± 61 ml using DGNS, p = 0.0078. MDP was 58 ± 18 cmH₂O in control and 47±18 cmH₂O with DGNS, p=0.0156. APDP was reduced from a baseline value of 56 ± 16 cmH₂O to 31 ± 18 cmH₂O with DGNS, p=0.0156.

No changes in continence were seen. P01 and P03 were the only participants who experienced leakage during the test, P01 was the only participant with absent sensation and was only aware of needing the toilet when he was wet, the test was terminated after leakage had occurred both at baseline and with DGNS. P03 leaked during baseline, but leakage recording failed during the DGNS trial. All other participants terminated the test when they felt a strong desire to void, prior to leakage occurring.

#### 6.4.3.2 Participant specific results

P01 was able to increase MCC, attenuate initial detrusor contractions and reduce MDP using DGNS. Due to limited time, baseline measurement used filling of the bladder at 50 ml/min up until the start of a detrusor contraction, hence the short time period in figure 6.4. Both intermittent and continuous stimulation increased MCC by 125 and 123 ml respectively.
Baseline MCC in the second week increased from 200 ml in week 1 to 375 ml in week 2. This change may be an effect of using DGNS over long periods, though may be due to inter-session variability (see range in control bladder diary volumes).

No NDO was recorded during baseline filling for P02, despite urgency being felt. Subsequently during the with DGNS cycle NDO was seen and suppressed.

AUM was largely unsuccessful with P03, for several reasons. One cycle was captured showing baseline overactivity. Volumes voided during DGNS in the first AUM session were recorded, though pressure data was lost.

P04 had excellent sensation of bladder filling, confirmed during urodynamics where detrusor pressure rose shortly following reports of mild urgency. DGNS was applied successfully on urge, in week one only DGNS was applied 4 times on urge, correlating with 3 rises in $P_{\text{det}}$. P04 had poor dexterity but was able to trigger the device independently.

P05 also had excellent sensation, he demonstrated repeated suppression of NDO using DGNS triggered on urge in both sessions. Small increases of 60 and 20 ml in MCC were seen using DGNS in week 1 and 2, both APDP and MDP were reduced in both sessions.

Individual AUM traces are shown in figures 6.4 to 6.8.
Figure 6.4: P01 detrusor pressure vs time traces from five natural filling cycles both without (blue) DGNS and with (red) DGNS. The top three traces are from the session prior to a week of home use and the bottom two following a week of home use. One episode of leakage occurred in each test, marked by the end of test arrow. Presence of leakage was monitored and heralded the end of a test.
6.4. Results

Figure 6.5: P02 detrusor pressure vs time traces from two natural filling cycles without (blue) DGNS and with (red) DGNS, both recorded prior to trialling DGNS at home. No NDO was seen in the baseline fill, though urgency was reported and the test was terminated. There was no leakage in either cycle.

Figure 6.6: P03 baseline ambulatory urodynamic $P_{\text{det}}$ trace. Leakage occurred at the end of the test.
Figure 6.7: P04 detrusor pressure vs time traces from four natural filling cycles without (blue) DGNS and with (red) DGNS. The top two traces are from the session prior to a week of home use and the bottom two following a week of home use.
Figure 6.8: P05 detrusor pressure vs time traces from four natural filling cycles without (blue) DGNS and with (red) DGNS. The top two traces are from the session prior to a week of home use and the bottom two following a week of home use.
### Table 6.4: AUM data from all participants

<table>
<thead>
<tr>
<th>Participant</th>
<th>Week</th>
<th>Amplitude mA</th>
<th>Regime</th>
<th>Number of Pdet rises</th>
<th>Leakage</th>
<th>Vol withdrawn mL</th>
<th>APDP cmH₂O</th>
<th>MDP cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control DGNS Change</td>
<td>Control DGNS Change</td>
<td>Control DGNS Change</td>
<td>Control DGNS Change</td>
<td>Control DGNS Change</td>
</tr>
<tr>
<td>P01</td>
<td>1</td>
<td>70</td>
<td>Intermittent</td>
<td>1 4 3 Y Y</td>
<td></td>
<td>200 326 126</td>
<td>78 24 -54</td>
<td>78 62 -16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>70</td>
<td>Continuous</td>
<td>1 7 6 Y Y</td>
<td></td>
<td>375 445 70</td>
<td>58 28 -30</td>
<td>58 56 -2</td>
</tr>
<tr>
<td>P02</td>
<td>1</td>
<td>64</td>
<td>Urge</td>
<td>0 2 2 N N</td>
<td></td>
<td>200 375 175</td>
<td>NA 37 NA</td>
<td>NA 40 NA</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td></td>
<td>NA NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>P03</td>
<td>1</td>
<td>50</td>
<td>Urge</td>
<td>2 NA NA</td>
<td>NA</td>
<td>375 140</td>
<td>50 NA</td>
<td>62 NA</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA NA NA NA</td>
<td></td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>P04</td>
<td>1</td>
<td>44</td>
<td>Urge</td>
<td>1 3 2 N N</td>
<td></td>
<td>200 330 130</td>
<td>48 16</td>
<td>48 31 -17</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>44</td>
<td>Urge</td>
<td>1 6 5 N N</td>
<td></td>
<td>200 260 60</td>
<td>47 22</td>
<td>47 40 -7</td>
</tr>
<tr>
<td>P05</td>
<td>1</td>
<td>48</td>
<td>Urge</td>
<td>1 5 4 N N</td>
<td></td>
<td>200 260 20</td>
<td>79 71</td>
<td>86 83 -3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>48</td>
<td>Urge</td>
<td>5 4 -1 N N</td>
<td></td>
<td>200 260 20</td>
<td>79 71</td>
<td>86 83 -3</td>
</tr>
<tr>
<td>Mean</td>
<td>1.5</td>
<td>4.1</td>
<td>2.8</td>
<td>244 344 165</td>
<td>56 30</td>
<td>-31  58</td>
<td>48  -12</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>1.4</td>
<td>1.7</td>
<td>2.1</td>
<td>59 58 45</td>
<td>16 17 16</td>
<td>18 17</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
6.4.4 Bladder diary

Table 6.5: Bladder diary data from each participants. Baseline data for P04 is unavailable.

<table>
<thead>
<tr>
<th>ID</th>
<th>Mean void volume</th>
<th>Recorded Voids</th>
<th>Incontinence</th>
<th>Urgency</th>
<th>Stim used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>DGNS</td>
<td>Baseline</td>
<td>DGNS</td>
<td>Baseline</td>
</tr>
<tr>
<td>P01</td>
<td>239</td>
<td>260</td>
<td>31</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>P02</td>
<td>224</td>
<td>340</td>
<td>39</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>P03</td>
<td>298</td>
<td>371</td>
<td>30</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>P04</td>
<td>NA</td>
<td>301</td>
<td>NA</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>P05</td>
<td>198</td>
<td>179</td>
<td>26</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean | 240      | 290  | 32       | 11     | 11       | 4    | 29       | 21   | 29  |
Std  | 37       | 67   | 5        | 6      | 9        | 6    | 10       | 20   | 19  |

Participants were asked to record bladder diaries over one week without and one week with stimulation. There was no significant changes in void volumes between baseline and stimulation weeks. Table 6.5 and figure 6.9 show baseline and DGNS week diary results.

There was a large drop in recorded voids over the DGNS week from 32 ±5 in the baseline week to 11 ±6, suggesting reduced compliance with completion of the bladder diary and/or less frequent voids Therefore the drop in incontinence episodes reported and urgency episodes reported may not be reliable. By matching automatically recorded stimulation times with recorded void time we were able to extract the recorded void volumes that were associated with stimulation use and use these for our analysis of volume change.

6.4.4.1 Stimulator usage

Stimulator usage was recorded by logging each time a stimulation trigger initiated on the smartphone app received confirmation from the smart switch and was followed by a confirmed stimulation off event (ie. one complete stimulation cycle). This method makes the assumption that the stimulator was turned on and connected to the patient. A stimulation event was only recorded if it lasted longer than three seconds to exclude erroneous switching.

Stimulation was used by participants 29 ±19 times over the week, range 8 to 54 times. It was used on urge in four participants and in continuous mode by one.

Stimulation was used just 8 times by P01, though in continuous mode for a period of 84 ±58 minutes.

6.4.5 ICIQ quality-of-life questionnaire

No decrease from baseline was found in any participant. In fact, P05 increased his score by two points. Table 6.6 shows the scores from each participant. P02 did not attend the
Figure 6.9: Boxplot of individual void volumes recorded in baseline and DGNS weeks. Box denotes interquartile range, error bars standard deviation and red line median value.

post-DGNS week appointment and did not complete the second ICIQ based on the DGNS week.

Table 6.6: International Consultation on Incontinence Urinary Incontinence Short Form (ICIQ UI-SF) results for each participant

<table>
<thead>
<tr>
<th>Participant</th>
<th>Baseline score</th>
<th>DGNS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>P02</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>P03</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>P04</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>P05</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

6.4.6 Feedback

An unstructured feedback form was given to participants. Several interesting comments were made regarding both the system used and the effect of DGNS on the participant. The device was found to be a little bulky and having to charge both the phone and the smart switch was an annoyance.

DGNS was tolerated well by all participants, who found any discomfort from stimulation quickly dissipated. The two participants with best sensation (P04 and P05) both
commented that it robustly suppressed urgency.

The wireless control via smartphone app received positive feedback, users with C5 injury were able to trigger stimulation with ease.

Some individual comments of significance were:

- P05 commented that electrodes would detach over longer periods, particularly due to sweat or urine.
- P04 felt that DGNS capacity to suppress overactivity was much greater when urine was less concentrated.
- P01 noted that he may have had an increase in neuropathic pain on one day using DGNS. This participant was using continuous stimulation and did note that he had

Figure 6.10: Mean daily void volumes recorded in baseline and DGNS weeks
ongoing neuropathic pain which may or may not have been triggered by the neuro-modulation. This should be monitored in future studies of chronic DGNS.

6.5 Discussion

This was the first trial of DGNS in people with SCI both using a wirelessly controlled stimulation system and assessed during natural filling micturition cycles. When DGNS was trialled during AUM, bladder capacity was increased and peak detrusor pressures were reduced. However, we saw no significant changes in voided volumes recorded by participants in the diary either day to day or from baseline week to DGNS week. No change was found in ICIQ-UI-SF score from baseline to stimulation weeks. Participants 4 and 5 who had the best sensation of bladder activity, did report that DGNS was able to suppress multiple detrusor contractions when they used the system at home, however, diary data did not show corresponding increases in void volume. Whilst supported by urodynamic evidence, poor compliance in diary completion during the stimulation week has lead to inconclusive proof of short-term, at home, effectiveness.

6.5.1 The effect of DGNS on bladder capacity

When trialled in clinic, during AUM, DGNS increased bladder capacity by 102 ±47 ml (p=0.0078), from a mean baseline of 244 to a mean with DGNS capacity of 344 ml. This is less than the previously reported average of 131 ±102 ml seen in acute studies [Bourbeau et al., 2018b] and the 153 ±146 ml seen in our earlier study (Chapter 4). However, significantly, this increase was found whilst patients continued their AM regime and therefore is shown as an additional increase in bladder capacity to that by AM. Volumes recorded in bladder diary increased by 48 ±51 ml, in the five patients who underwent the trial, although this change was found to be insignificant when matched pairs were tested (p=0.25). Individual baseline and DGNS week results are shown in figure 6.10.

Previous studies of DGNS using AUM have been conducted with people with Multiple Sclerosis using event driven stimulation [Fjorback et al., 2006]. DGNS was able to suppress at least one contraction in 7/8 participants who had observable NDO and a mean of 12 (range 3 to 22) detrusor contractions were suppressed.

In our study an average of 4.1 unwanted contractions were suppressed. The differing diagnosis and, more likely, the lower amplitude of stimulation used in our study may affect this. Amplitude is known to be linked to suppressive capacity of DGNS.
Further to this, the use of a conditional system using pressure feedback to trigger stimulation at a rise of 10 cmH\textsubscript{2}O in P\textsubscript{det} will have an effect of the outcome. The system trialled by Fjorback et al. unfortunately is not suitable for chronic use as it uses indwelling urethral and rectal catheters [Fjorback et al., 2006, Fjorback et al., 2003].

Both intermittent and continuous DGNS were found to increase MCC in P01, in week one by 125 and 123 ml, or 62%, and in week two continuous stimulation increased baseline capacity by 75 ml. Further to this, both DGNS regimes decreased maximum detrusor pressures and attenuate initial detrusor contractions when trialled in one participant with complete SCI. A suitable timed trigger in combination with intermittent stimulation may be trialled in the future to reduced stimulation time whilst increasing capacities. Neither stimulation regimes were able to prevent incontinence, as the problem of lost sensation is still severely limiting.

6.5.2 Effects on detrusor pressure

Effects were also found on peak detrusor pressures. Using DGNS, at least one rise in detrusor pressure was attenuated in each natural filling cycle and a mean of 4.1 ±1.7 rises in detrusor pressure were suppressed. The suppression of NDO brought down the average peak detrusor pressure from 56 ±16 to 30 ±17 cmH\textsubscript{2}O, as in those triggering stimulation on urge, DGNS was timed at the onset of NDO and able to suppress both the sensation of urge and NDO peaked at lower detrusor pressures. The bladder was able to fill to greater volumes. This finding is an advocate of DGNS’ capacity to meet the urological management goal of reducing detrusor pressures for protection of the upper urinary tract [Drake et al., 2016a]. This significant drop in peak detrusor pressures is consistent with previous findings using AUM [Fjorback et al., 2006] and standard filling CMG [Kirkham et al., 2001, Bourbeau et al., 2018a].

Whilst DGNS appeared to reduce both average peak and maximum detrusor pressures in each trial here, there is a risk with all new interventions that the opposite may occur. Therefore, given the at risk nature of those with suprasacral SCI to damage of upper urinary tract, the thorough assessment of risk for individual candidates by an appropriate clinician should be key to selection. However, as seen in both this study and in the study of stimulation site, inter session changes in maximum detrusor pressure are high within individuals and should be treated as a snapshot, adding to the need for appropriate clinician assessment of risk.
The increase in episodes of NDO is attributed to each one being attenuated or suppressed by DGNS until a point where any inhibitory effect is overcome and either leakage or a strong desire to void occurs, at which point a test was terminated. Episodes of NDO were of smaller magnitude when DGNS was applied shown in the reduced APDP values in DGNS filling cycles.

P05 had a noticeable change in baseline outcomes in week two, following a week of DGNS use. Both peak detrusor pressures and the number of (leakage free) episodes of NDO were increased from 47 to 86 cmH$_2$O (MDP) and from 1 to 5 respectively. P04 also saw an increase in MDP between week one and two baseline fills, from 30 to 48 cmH$_2$O. This change was not reflected in all participants, in P01 we saw a drop in detrusor pressures between week one and two, from 78 to 58 cmH$_2$O. Should DGNS increase baseline MDP values over time with use, this would be a worrying effect contrary to that seen thus far in other studies. It is likely, given the inter session variability seen within individuals in this and our previous study (Chapter 4) that these changes in baseline MDP occur naturally. However, it is of importance that future, longer assessments of DGNS measure this parameter thoroughly over the course of DGNS use by conducting regular urodynamic study before, during and after the intervention as adverse consequences for the upper urinary tract could not be tolerated.

6.5.3 Diary data

Figure 6.11 shows the change in number of recorded voids from each participant over the whole week (both baseline and DGNS weeks). This generally ties in with participants’ comments that they struggled to record diary data over the week while using the DGNS.

The reliability of self recorded bladder, or urinary, diaries is subject to appropriate completion by the user. In this study we opted to use a seven day bladder diary both at baseline and over the week trial of DGNS. Three-day bladder diaries have previously been shown to be sufficient and preferred in minimising patient burden. This longer (7-day) period was selected in our study design as it was thought that the outcomes may change over the whole seven days, as previously found [Opisso et al., 2013] over a three-day DGNS intervention. However, significantly fewer recordings were made during the DGNS week of the study. Indeed P01 and P02, who had both verbally reported issues in compliance with using DGNS each day due to unrelated illnesses or diary clashes and with recording the bladder diary, decreased recorded volumes from 31 to 6 and 39 to 5 respectively. It has
6.5. Discussion

Figure 6.11: Number of voids volumes recorded by each participant in baseline and DGNS weeks of the study. No baseline diary is available for P04

previously been noted that compliance can be an issue in research, more than in clinical setting [Bright et al., 2014].

Other studies of home use of DGNS have used self recorded bladder diaries [Opisso et al., 2013, Bourbeau et al., 2018b, Wheeler et al., 1994, Lee and Creasey, 2002]. Lee et al, (2012) were unable to include diary data, instead analysing before and after DGNS CMG results. Bourbeau et al, (2018) also expressed dissatisfaction with the reliability of diaries, suggesting some form of automation as necessary for improved compliance. By automatic time stamping events and using a ‘digital diary’ we attempted to ease the burden on participants, however still had issues with compliance.

Based upon what we report here, future studies should consider shorter diary periods, for example utilising the ICIQ validated three day bladder diary at predetermined points in the treatment cycle [Bright et al., 2014]. Further to this, it is conceivable that by using an updated digital bladder diary, with reminders prompting users to complete entries, compliance may increase.

6.5.4 ICIQ-UI-SF Score

The ICIQ-UI-SF is a validated questionnaire [Avery et al., 2004] designed to assess the frequency, severity and impact on quality of life of urinary incontinence. It is relatively quick and simple to be filled in. It was completed by participants at the end of both baseline and with-DGNS weeks in the study. The range of scores given was 2-20, mean 12 ±8 and remained unchanged in all but one participants, P05’s score increased by 2.
Interestingly, the two participants who reported DGNS as working well (P04 and P05) did not feel they particularly suffered from incontinence at baseline, as reflected in scores of 2/21 and 6/21 in their baseline ICIQ-UI-SF assessments. P04 was a sheath user which may explain this and P05 had more issues with high pressures and urgency than incontinence. P03 saw improvements in recorded diary data, however still suffered episodes of incontinence, continuing to use a pad to absorb leakage.

The two participants with the highest ICIQ scores (P01 and P02) used the system the least, reportedly due to unrelated illnesses and clashing busy work weeks. A more discrete system would have been preferred based upon feedback given.

The use of the ICIQ-UI-SF was a limitation in this study. In its validated form it is for use over 4 weeks, where we asked participants to consider just one week prior each time, either the week recording the baseline diary or the week using DGNS. Further to this, results will be altered in users of sheath drainage, where incontinence and its impact may not be properly assessed, as with P04. In future, we’d recommend other measures, such as the I-QoL questionnaire which have been better validated in a neurogenic population.

### 6.5.5 Sensation as a trigger

Four out of 5 participants used their sensation of urge to trigger DGNS. We have complete urodynamic data for two of the four participants, who were both able to suppress multiple contractions using DGNS. All four participants were able to tolerate stimulation at a level that was able to suppress detrusor contractions. This data corroborates a previous study of DGNS tolerability in people with incomplete SCI, describing DGNS as tolerable and effective in this population [Brose et al., 2018].

### 6.5.6 Neuropathic pain

P01 reported increased neuropathic pain on one day of using the stimulation, he stopped the stimulation and reported that the pain subsided over the next day. He was the only participant to use continuous or intermittent stimulation, set at 70 mA. P01 was clear that this was not necessarily linked to the DGNS, as it is something he has chronically and an increase may have been coincidental.

There have been no previous reports of this occurring from the experience of DGNS in the literature. However, there is some history of electrical stimulations effect on neuropathic pain, [Sipski et al., 1989] a survey of FES ergometer users found that 6/9 users with existing neuropathic pain perceived an increase in this pain with FES training. There is the poten-
tial for alteration of sensory pathways and for changes in cortical activity as a result, even following complete SCI. An interesting fMRI study found increased activity in the areas responsible for bladder control following two weeks of genital nerve stimulation in incomplete SCI subjects [Zempleni et al., 2010]. This study was in subacute incomplete patients, already with preserved, though diminished, bladder sensation, who underwent a two-week training programme of 2x15 minute daily sessions of DGNS delivered at a non-painful intensity. Pilot studies suggest sensory cortico-spinal pathways often exist in some form following complete SCI and are subject to change [Krhot et al., 2017, Wietek et al., 2008]. This is something to monitor in future trials of DGNS.

6.5.7 Limitations

As a pilot study of 5 people with SCI and associated NDO, it is limited by several factors. The number of participants is too low to draw any definitive conclusions from our findings and the poor compliance with diary recording has limited the value of diary data in this study. Each participant acted as their own control and the study was not blinded so their awareness of the treatment may have adjusted their behaviour from baseline to intervention weeks. A controlled trial will be necessary in future development of the technique.

Further to this, the assessment of bladder sensations during natural filling of the bladder and their suitability for triggering NDO could have been better assessed by the inclusion of bladder sensation recordings alongside the pressure recordings. Whilst users triggered stimulation based on their sensation (self-triggered DGNS), this should be added to future protocols to better capture the escalation of sensations and their relationship to both detrusor pressure and DGNS use.

6.6 Conclusions

This chapter presents a prospective, interventional pilot study of DGNS, delivered using a custom, wirelessly controlled stimulation system in people with SCI and associated bladder overactivity. This builds on work outlined in the preceding chapters on assessing transcutaneous stimulation sites and developing a system suitable for delivery and assessment of DGNS in a home environment.

Five people were recruited into the study, recording baseline diary data over a week before trialling DGNS during natural filling urodynamics in clinic at the RNOH. DGNS was then used by participants at home over one week, in a schedule determined by the
participant, to inhibit episodes of NDO. Baseline and DGNS AUM data was again collected following this week of home use.

Urodynamic data showed significant increases in bladder capacity and decreases in average peak and maximum detrusor pressures. This occurred when DGNS was applied on urge (n=4), continuously (n=1) or intermittently (n=1) indicating that DGNS may be applied in an ambulatory setting to good effect.

Compliance in the collection of diary data was variable and poor overall. Useful data collected on void volume showed increases of 48 ±51 (p=0.25).

In future study of DGNS we would recommend redesign of diary data collection methods, increased timeframes and assessment of carryover effects. Further assessment of device usability and acceptability of DGNS as a therapy would be recommended.
Chapter 7

Future Directions and General Conclusions

7.1 Future Directions

This thesis provides several sets of pilot data that open interesting possibilities for future work towards a new treatment of bladder overactivity following SCI. This section describes work that could be carried out to further our understanding of neuromodulation for lower urinary tract control following SCI, both in theory and in its application in the real world.

7.1.1 Long term assessment of on-demand DGNS

We have presented results from a study involving a one-week DGNS intervention showing that urodynamic parameters can be significantly improved during natural filling by on-demand DGNS used in addition to existing AM therapy. Previous studies have all shown significant changes in bladder outcomes (in reduced incontinence events or in increased bladder capacity, or both) yet the maximum period DGNS has been used for is 8 weeks, in just one participant [Wheeler et al., 1994, Lee and Creasey, 2002, Lee et al., 2012, Opisso et al., 2013, Bourbeau et al., 2018b]. Each of these studies have reported that stimulation was tolerable, yet that device acceptability was low.

In combination with device development, longer studies of DGNS in the home environment should be conducted. The study should pay particular attention to facilitating compliance with data collection in the form of bladder diaries and other subjective measures to assess the acceptability of DGNS as a long-term treatment. Poor compliance with filling out bladder diaries has been noted in several studies including our own [Wheeler et al., 1994, Bourbeau et al., 2018b].
7.1. Future Directions

7.1.1.1 Carry over effect of DGNS

Urodynamic [Wheeler et al., 1994, Opisso et al., 2013] and bladder diary [Bourbeau et al., 2018b] outcomes without stimulation present have been shown to improve following periods of DGNS use, when compared to pre stimulation values, in pilot studies ranging from 3 days to 8 weeks. Our study evaluated baseline activity using AUM before and after a week of DGNS use, results before and after were collected in three participants, no pattern of improvement was seen and no statistical tests were conducted due to low numbers. A larger, longer, study is required to determine whether a carry over effect is present following prolonged use of DGNS.

7.1.1.2 Effects on pelvic sensation

Alongside potential urodynamic improvements, previous work has shown that daily DGNS applied at a low amplitude over a period of weeks may increase sensory activation in the brain, displayed on fMRI scans during bladder filling [Zempleni et al., 2010]. Recent fMRI findings have elicited some interesting information regarding cortical activity during stimulation of both the pelvic region and other somato-sensory pathways caudal to complete lesions [Komisaruk et al., 2004, Wietek et al., 2008, Awad et al., 2015, Krhut et al., 2017]. It has been suggested that extra-spinal sensory pathways develop after the injury, with the vagal nerve potentially playing a role in pelvic sensation [Komisaruk et al., 2004, Krhut et al., 2017]. Future work may assess the impact on existing sensation as DGNS is applied over long periods. It may be that there is potential to re-learn ‘new’ bladder sensation following SCI, something that could be supported or strengthened by outside intervention.

In long-term study of DGNS as an intervention, particular attention should be paid to whether any negative effects of the therapy appear. The possibility of increased neuropathic pain should be taken into account, as we reported in Chapter 7, one participant felt that stimulation may have triggered an episode of neuropathic pain.

7.1.2 Sphincter responses to TNS in SCI and non-SCI individuals

TNS is a widely used therapy that is poorly understood. The presence of a reflex pathway between TN and anal sphincter has been little studied yet may provide useful information regarding the mechanism of TNS therapy and in the optimisation of TNS delivery. In this study the EAS response to TNS should be characterised in a larger number of participants and in a group with SCI. Comparison with PAR responses may provide useful information
to help optimise a stimulation protocol and to further our understanding of relative mechanisms. Should reproducible effects be found in both groups, it would be interesting to undertake a further urodynamic study of the effects of TNS on NDO following SCI.

In addition, further investigation of combined DGNS and TNS in a larger group would be useful. If there is any beneficial effects of combined stimulation on EAS response, it would be worth evaluating the effect of combined stimulation on urodynamic outcomes. In designing this study, care should be taken to randomise the sequence in which stimulation tests take place and to increase the number of cycles. As well as above (EAS) threshold stimulation, it will be interesting to look at the response of the EAS when stimulation is combined at a sub-threshold amplitude.

### 7.1.3 Spinal Stimulation

In our studies of SS, we found that when applied at maximum tolerable amplitude SS had no observable effect on EAS activity in healthy participants and no significant effect on urodynamic outcomes in people with SCI. However, three recent pilot studies have reported promising results using similar interventions [Gad et al., 2018, Herrity et al., 2018, Niu et al., 2018]. Most interestingly, the use of magnetic stimulation, applied for just 12 minutes per week, to restore voluntary voiding in the chronic stages of SCI certainly needs follow-up [Niu et al., 2018]. Alongside replication of this work, this can be expanded upon by comparing effects of transcutaneous and magnetic stimulation and by studying appropriate dosage. Further studies into the acute effect of SS will be required to further elucidate the mechanism of action of any effect and to further develop an efficient clinical treatment.

### 7.1.4 Acute intervention

Sievert et al. (2010) published a pilot study looking at using SNS implants, implanted in the acute phase of injury, to prevent the development of NDO. Results showed detrusor acontractility and bladder capacities of 582 (range 480-650) ml in the 16 participants, where the 6 in the control group developed typical NDO and began AM medication, on which bladder capacity was 208 (range 57-314) ml. Further to this, a recent report of a further pilot study using TNS for just 30 minutes daily over two weeks in the acute phase of injury again showed a decrease in the progression of NDO [Stampas et al., 2018]. The results presented in Chapter 4, showing DGNS to have significant inhibitory effects on the overactive bladder, may be worth considering in applying DGNS in the acute phase of injury rather than stimulation of other sites.
The prospect of preventing development of NDO at all is an exciting one. Given it is stimulation of sacral afferents that is likely to be causing this positive effect, DGNS may present an easy non-invasive method of applying stimulation to this end. Should a non-invasive method be efficacious it may prove preferable, given the three new implants and 6 lead revisions required in this group of 16 [Sievert et al., 2010]. This course of action may be of particular importance given the current worries around use of AM medication, particularly when employed before the development of NDO (i.e. when not required) [Krebs et al., 2017]. An interesting study would compare the effects of no intervention, AM medication and of DGNS on the development of NDO and DSD following the acute stage of SCI.

### 7.1.5 Device development

Some of the remaining barriers to DGNS becoming a clinically useful therapy are in the appropriate engineering of a usable device and in the commercialisation of technology that has been proved as effective and acceptable. Whilst commercial stimulators provide adequate stimulus for DGNS, and the modifications discussed and used in this thesis provided encouraging results, there are specific developments we recommend.

#### 7.1.5.1 Surface electrode design

Several studies of DGNS have noted that existing electrode designs are unsatisfactory for users of the technique, in particular for female users [Lee et al., 2012, Opisso et al., 2013, Bourbeau et al., 2018b]. One of the five participants in our study commented on occasional slippage of electrodes, they felt this was due to either sweat or urine. Others commented when asked that electrodes were not problematic, though overall device bulkiness could be reduced. For chronic application to the genitalia, specialist electrodes should be designed taking into account the likelihood of wetness and the sensitive nature of the skin, along with the requirement to adhere reliably over the course of a day.

#### 7.1.5.2 On-demand control

In our study of DGNS in the home environment we used a custom stimulator control system, able to trigger stimulation wirelessly from a touchscreen Android device. Participants found this to be easy to use. However, the speed of triggering stimulation could be improved, as when not immediately to hand it took a few seconds to trigger stimulation. This trigger could be a wearable device, that is easily accessible at all times to avoid the few seconds wasted unlocking a smartphone. Further developments should take into account the speed...
of triggering, whilst guarding against accidental triggering, and assess any prototypes with regard to this.

7.1.5.3 Physiological feedback of bladder activity

As seen by Bourbeau et al. (2018) and within our study of DGNS, Chapter 6, use of continuous DGNS is inferior to on-demand DGNS due to the pre-existing problem of lost sensation, i.e. continuous DGNS may increase bladder capacity but won’t add control without obtaining feedback on bladder activity. Either the estimation of bladder volume or the detection of bladder overactivity must be enabled to allow closed-loop control of a neuromodulation system. Several avenues, discussed in Chapter 2, have been trialled with mixed success but each requires development and testing. This is a critical area for development to improve management techniques for those without sensation [Wheeler et al., 2018].

7.2 Conclusions

The aim of this thesis were to define a suitable neuromodulation protocol for suppression of the bladder following SCI and to trial this using a suitable device in the home environment. The specific research aims with their corresponding conclusions are set-out below.

1. To assess the effect of surface stimulation sites on sacral reflex pathways, through analysis of External Anal Sphincter (EAS) electromyography (EMG)

   - Transcutaneous stimulation of the genital nerve (DGNS), tibial nerve (TNS) and sacral nerves (SNS) can all produce a response in the EAS. However, these responses varied in the amplitude they were evoked at and in the latency of the response. DGNS and TNS appeared to evoke a spinal reflex response, where SNS appeared to stimulate pudendal efferents directly.

   - Spinal Stimulation (SS) applied over the T12 vertebra was unable to produce any response measured using EMG.

   - In one participant TNS and DGNS were trialled in combination. We found that TNS pulses delivered within 5 ms of paired DGNS pulses, appeared to amplify peak EAS EMG response by 25%.

2. To assess the comparative effect of surface stimulation sites for neuromodulation of Neurogenic Detrusor Overactivity (NDO) following SCI.
Bladder capacity was increased by conditional DGNS, in 5/7 participants bladder capacity increased by over 50% or 100 ml. We also compared DGNS to TNS, SNS and SS and found difference in bladder capacity changes between the four interventions.

First peak detrusor pressures were decreased by DGNS in 5/7 participants, all other sites were unable to prolong continence or suppress a single episode of NDO.

The volume stored between first detrusor contraction and maximum bladder capacity was increased by DGNS, TNS and SNS.

TNS increased maximum detrusor pressure while DGNS, SNS and SS had no effect on MDP.

Continuous TNS, SNS and SS were no different in effect to conditional stimulation and did not alter reflex volume from baseline.

We found that SS had a small effect (p=0.06) on urodynamic outcomes, observing consistent, small, decreases in bladder capacity that could be investigated further, in more people and with varying stimulation parameters.

From visual observation DGNS, TNS and SNS all activated the external anal sphincter in some people, this was in agreement with the finding of our EMG study presented in Chapter 3.

To develop a stimulation system to deliver and assess neuromodulation protocols outside of the laboratory, in participants homes.

A smart phone app controlled stimulation switch, to be used with Odstock Medical Limited (OML) stimulators, was developed and found to be both usable and reliable in controlled tests. A digital diary was implemented on the smartphone app, to timestamp data input and stimulation usage. There was poor compliance with inputting diary data over a 14 day period, from which we would recommend using 3 day bursts of diary for future studies. However, the function of recording stimulation use allowed accurate analysis of stimulation usage and voiding data.

The system was used during a pilot study where participants with SCI, both paraplegic and tetraplegic, used the device over 15 days including up to seven
days of stimulation use. Each participant could use the device with ease.

- Feedback on the device from the study participants was taken on board and a collaborative project with stimulator manufacturer (OML) was begun. This initiated device improvements and worked on regulatory documentation for a new technical file to aid future translation into patient use.

4. To determine the effect of on-demand, continuous or intermittent DGNS on bladder capacity and detrusor pressure during natural filling.

- DGNS increased maximum bladder capacity, reduced average peak detrusor pressure and reduced maximum detrusor pressure during natural bladder filling from baseline, where participants remained on pre-existing antimuscarinic medication throughout. We recommend that DGNS is developed further as a non-invasive intervention to control NDO.

- On-demand DGNS was effective in 4/4 people with SCI and retained bladder sensation, from ASIA A-D, clearly suppressing rises in detrusor pressure. The small group in our study did not have the inaccuracy of bladder sensation reported previously during ambulatory urodynamics by Martens et al. (2010) and were able to suppress an average of 2.4 consecutive detrusor contractions.

- Continuous and intermittent (5 seconds on/off cycle) stimulation were trialled in one participant. Both stimulation protocols increased bladder capacity and reduced average peak and maximum detrusor pressures. Incontinence was delayed, but not prevented as no feedback was available to replace lost sensation.

5. To determine the effect of on-demand, continuous or intermittent DGNS on bladder storage symptoms in the day to day environment

- No change in voided volumes was found across the group and other diary data was effected by poor compliance. There was no change in ICIQ score. DGNS was tolerated by all participants when used over a week at home. In future studies a change to shorter diary periods is recommended.

The results outlined in this thesis are a step towards realising an appropriate and effective neuromodulation treatment for chronic bladder storage issues following spinal cord injury. Our results point the way towards defining a successful therapy and throw light on
further areas of work required to deliver this. It is clear further work is required to establish the effectiveness of DGNS as an at-home, chronic, intervention. This will be need to be facilitated by improvements in device and study design.
References


References


nerve may increase cystometric capacity in patients with spinal cord injury. *Neurourology and Urodynamics*, 22(2):130–137.


References


References


References


References


References


Appendix A

Study Information and Consent Forms

- Sphincter response to stimulation site study participant information sheet
- Sphincter response to stimulation site study participant consent form
- Urodynamic stimulation site comparison study participant information sheet
- Urodynamic stimulation site comparison study participant consent form
- Neuromodulation at home study participant information sheet
- Neuromodulation at home study participant consent form
Title of Project: **Investigation of the reflex activity of the External Anal Sphincter in response to surface electrical stimulation of different branches of the sacral nerves**

This study has been approved by the UCL Research Ethics Committee (Project ID Number):

**Name**
Dr Sarah Knight

**Work Address**
London Spinal Cord Injury Centre, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, HA7 4LP

**Contact Details**
Tel 020 8909 5605 or email s.l.knight@ucl.ac.uk

We would like to invite non-neurologically impaired male and female participants to participate in this research project.

**Details of Study:**

The purpose of the study is to investigate the reflex activity of the external anal sphincter in response to small pulses of surface electrical stimulation at various branches of the sacral nerves. These will include the sacral roots, the tibial nerve, the genital nerve and the thoracic spinal cord. This study aims to improve our knowledge of surface electrical stimulation of the sacral roots, this will improve our practice in developing the technique for bladder control following Spinal Cord Injury.

During the study surface electrodes will be placed at each stimulation site, this will be on the skin of: the genitals (clitoris or penis), the ankle, the spine and the sacrum. These may be easily placed by yourself or by the research team’s registered clinical staff. The muscle activity of the external anal sphincter will be recorded via an anal plug EMG electrode. This will be an Anuform electrode, shown below, which can be inserted using KY jelly by yourself or by the research team’s registered clinical staff in a private room.

![Figure 1. Anuform anal plug electrode](image)

Small pulses of electrical stimulation will be delivered via an isolated current stimulator. This is often reported to feel like light plucking of hair. The current intensity will be increased until the sensory threshold is reached at each site. The stimulation intensity will only be increased with your agreement and you can request that the investigation be stopped at any time. We will record the parameters used and the responses seen.

The entire study should be completed in 1-2 hours, requiring only one visit. All data will be anonymised from collection.

The potential risks include:

- **Discomfort from the stimulation or Anuform, this risk is minimised by the design of the electrodes. All equipment is used in the clinic and community, designed for people to use in training to strengthen the pelvic floor. If you experience discomfort it may be stopped immediately and you can withdraw from the study at any point.**
• Loss of dignity, to minimise risk of this you will be able to place all electrodes in a private space, and remain clothed throughout the testing. Detailed instructions will be provided to enable you to easily do this or assistance may be provided by the research team’s registered clinical staff.

You will be kept informed of the study outcomes should you wish to be.

Please discuss the information above with others if you wish or ask us if there is anything that is not clear or if you would like more information.

It is up to you to decide whether to take part or not; choosing not to take part will not disadvantage you in any way. If you do decide to take part you are still free to withdraw at any time and without giving a reason. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of which you can keep.

What if I have further questions, or if something goes wrong?

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study you can contact the Principal Investigator using the details above for further advice and information:

All data will be collected and stored in accordance with the Data Protection Act 1998.

Thank you for reading this information sheet and for considering take part in this research.
Informed Consent Form for Participation in Research Studies

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

Title of Project: **Determining the presence of external anal sphincter activity during peripheral nerve neuromodulation in participants with no neurological disorders**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): **9067/001**

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

**Participant's Statement**

I

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- *Agree that my data, after it has been fully anonymised, can be shared with other researchers* [to satisfy Research Council funded projects as Research Councils have changed their guidance regarding data sharing]

Signed: ___________________________  Date: __________
PARTICIPANT INFORMATION SHEET

Study Title: Neuromodulation for reducing Neurogenic Detrusor Overactivity in SCI: Stimulation Site Comparison Pilot Study []

Helping you decide whether or not to join our study

You have been invited to participate in this clinical investigation because you have a spinal cord injury (SCI), which has led to some bladder dysfunction. The aim of this study is to investigate and compare the effect of neuromodulation using electrical stimulation at three different sites. Neuromodulation can be used to reduce unwanted bladder contractions that may lead to incontinence or damage to the urinary tract. We will describe the study and go through this information sheet, which we will then give to you for further consideration and questions if you feel it is necessary. We will then ask you to sign a consent form to show you have agreed to take part. Of course you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What is the purpose of this study?

Neuromodulation is the alteration of nerve activity through the delivery of electrical stimulation. The purpose of these investigations is to determine to what extent neuromodulation can reduce unwanted bladder contractions and leaking when delivered using skin surface electrodes over different nerves in the body.

The bladder is controlled by complex interactions between control centres both within the spinal cord and the brain. After SCI, signals to and from the brain are disrupted meaning the voluntary signals telling the bladder when and when isn’t a convenient time to empty and subsequently control emptying stop functioning properly. As a further result of SCI overactivity of the bladder muscle can become a problem, leading to frequent contractions at low volumes. This may result in leaking urine and/or damage to the bladder and kidneys.

Neuromodulation (using electrical stimulation) of nerves in the lower leg, penis (or clitoris), sacrum or spinal cord has been shown to reduce this bladder overactivity and improve continence. However, they have not all been researched thoroughly in people with SCI and have never been directly compared to assess the most effective solution. This information is important as we intend to use it to help design a device people with spinal injuries can use to reduce bladder overactivity and improve continence.
The aim of this pilot study is to compare the effect of neuromodulation at different sites on bladder function using standard urodynamics. We will compare the bladder capacity and pressures before and after stimulation. Because there may be some carry over of effect of stimulation each site will need to be tested on a separate occasion meaning that you could be asked to attend for up to 5 sessions. Prior to each session we will ask you to stop taking any anti-muscarinic medication (eg oxybutynin or solifenacin) for up to 5 days as this will affect your bladder function.

**What will happen to me if I take part?**

Each session will involve the monitoring of the bladder activity and pressures using standard cystometry (urodynamics) performed both with and without stimulation. First you will be required to provide informed consent and asked some questions about your condition. Then a filling Cystometrogram will be performed to measure your bladder capacity and activity before any stimulation takes place. It will involve lying the upon the bed whilst the bladder is filled through a urethral catheter. Catheters will be inserted into the bladder and rectum for measuring pressure whilst the filling occurs. You will be asked to record your sensation of urgency on a scale of 0 to 4 throughout filling using a custom-made device. Voice recording will be used throughout each test to aid later analysis.

Surface electrodes will then be placed on the skin over one of the sites described below (a different one each session) and the stimulation intensity will be set.

Next a second Cystometrogram will be performed, during which stimulation will be started each time the pressure in your bladder rises as a result of unwanted contractions. Again we will measure bladder activity and capacity. This will be repeated up to two times further before a second baseline fill is performed.

Neuromodulation will be delivered by electrically stimulating the sites outlined below:

- Genital sensory nerves (known as DPNS - Dorsal Penile Nerve Stimulation or DCNS – Dorsal Clitoral Nerve Stimulation), this will involve delivering stimulation through electrodes placed on the penis or clitoris.
- Posterior tibial nerves (known as PTNS – Posterior Tibial Nerve Stimulation), will involve stimulation through electrodes placed on the inside of your lower leg/foot.
- The Sacral Nerves (SNS) will involve stimulation through electrodes placed near the top of the buttocks.
- The Spinal Cord (known as SCS – Spinal Cord Stimulation), which involves stimulation via electrodes placed over the spine and abdomen.

To do this study we will ask you to stop taking your medication for bladder over-activity 5 days prior to the date of your tests. Once the tests are completed you can resume your normal medication.

If you agree to take part in the study you will be asked to come to the hospital for up to 5 visits. Each visit will take approximately 2 hours and we will reimburse you for travel expenses for each of your visits.

**What are the risks involved in the procedures in the study?**

There are some possible risks to the participant during this study, these are outlined below:

1. A small risk of Urinary Tract Infection (UTI).
2. Risk of increased incontinence over trial period as an effect of stopping antimuscarinic medication. This is routine in this kind of study as it treats the same problem as the intervention we are studying and would skew any results.

3. If your injury is above the T6 level then Autonomic Dysreflexia is a risk. This is a condition where a stimulus below the level of your injury causes a dangerous rise in blood pressure, it has not been reported to happen due to stimulation in previous studies however remains a risk. Nifedipine is a drug used to relieve this condition and will be given if you are suffering symptoms. Bladder filling and stimulation will be stopped as well.

4. Skin irritation from electrodes is a small risk, in this case stimulation will be stopped and the electrodes will be removed.

**Will there be any benefit to me?**

If you agree to take part, this study would help patients with spinal cord injury in the following ways:

- Improve our understanding of electrical stimulations’ capacity to treat bladder overactivity and how best to apply it. This will contribute to improving current bladder management and treatment options.
- A positive outcome for this study could lead to the development of a novel treatment for the improvement of continence and spasticity in the SCI population.

Of course we cannot promise that this study will necessarily help you but the information we get from this study may eventually help to improve the treatment of people with spinal cord injury.

**Will all the information be kept confidential?**

Everyone in the project will respect your confidentiality. All information which is collected about you during the course of the research will be kept strictly confidential. Data collected will be anonymised so that you will not be identified. The anonymised study results may be published in scientific journals.

**What if something goes wrong?**

If you have any concern about any aspect of the study you should speak to the researchers who will do their best to answer your questions. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Royal National Orthopaedic Hospital NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

**What should I do if I have a complaint?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this contacting the Patient Advice and Liaison Service via pals@rnoh.nhs.uk or 020 8909 5439/5717.

**Who has reviewed and funded the study?**
The INSPIRE National Scientific Committee has approved this project for funding and the appropriate Ethics Committee has given approval for this study to take place. The study is funded by INSPIRE Foundation charity.

If you have any further questions regarding this investigation please contact:

Dr Sarah Knight or Sean Doherty
at the Royal National Orthopaedic Hospital
020 8909 5343 or 020 8954 2300 ext 5605
**CONSENT FORM**

Study Title: Neuromodulation for Reducing Neurogenic Detrusor Overactivity in SCI: Site Comparison Pilot Study    Chief investigator for this study: Dr SL Knight

1. I confirm that I have read and understood the information sheet dated ___27/01/2016____ for the above study and have had the opportunity to ask questions.

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that parts of my medical notes may be looked at by researchers and by regulatory authorities where they are relevant to my taking part in this study. I give permission for these individuals to have access to my records.

5. I am happy for voice recording to be used during the study (for data analysis purposes only)

6. I understand that study documents may be looked at by authorised representatives from the UCL-RNOH Research and Development Unit (R&D), on behalf of the Sponsor (RNOH) to ensure that the study is being conducted to the required standard. I give permission for these individuals to have access such information.

7. I understand that information collected as part of this study will be kept confidentially and securely at the RNOH and that they may be re-assessed as part of future ethics approved studies.

7. I am happy for my GP to be informed about my participation in this study.

8. I agree to take part in the above study.

Version 2 27/01/2016
Patient’s signature or independent witness ________________________________

Name in BLOCK LETTERS _________________________________ Date ___________

Doctor’s signature

Name in BLOCK LETTERS _________________________________ Date ___________

[When completed, 1 copy for the participant; 1 for the research files; 1 (original) to be filed in clinical notes]
PARTICIPANT INFORMATION SHEET

NEUROMOD: Researching the effect of electrical stimulation on bladder overactivity following Spinal Cord Injury in a home pilot study

You have been invited to participate in this research because you have a spinal cord injury (SCI) which has led to some bladder dysfunction and you may respond well to neuromodulation for managing this. The aim of this research is to investigate the effectiveness of neuromodulation at improving continence in day to day life at home. This pilot study is part of a current PhD project developing wearable neuromodulation devices for use in controlling the bladder following SCI.

We will describe the study and go through this information sheet, we will then give you time for further consideration and answer any questions you have. Before starting the study we will ask you to sign a consent form to show you understand what will happen and agree to take part. Of course you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive. We will ask your permission to inform your GP that you have taken part.

What is the purpose of this study?

The bladder is controlled by both the spinal cord and the brain, which coordinate storing and emptying urine. After SCI, signals to and from the brain are disrupted meaning the voluntary signals telling the bladder when and when isn’t a convenient time to empty are stopped. As a further result of SCI overactivity of the bladder muscle can become a problem, leading to frequent contractions at low volumes. This may result in leaking urine and/or damage to the bladder and kidneys.

We are investigating a new management technique called neuromodulation for its effect on bladder overactivity. Neuromodulation is the alteration of nerve activity, in this case through the delivery of small pulses of electrical stimulation using surface electrodes to the nerves controlling the bladder. We know this can suppress bladder overactivity in controlled conditions, but not whether it is practical for use in everyday life.

In this pilot study we will use small electrodes placed on the penis or clitoris, over the genital nerve, and a portable stimulator controlled by you, through a smartphone app, to find out how effective this technique may be for managing your bladder overactivity at home.
The device being used is a non-commercial modification of a commercial stimulator that is currently used for other purposes, this is a modification that has been made to allow us to use this device for the new purpose being tested in this pilot study. The device you will use will not be available commercially when you complete the study.

**What will happen to me if I take part?**

If you have not trialled neuromodulation in our research clinic previously you will first need to attend our urodynamics clinic (screening clinic) to test whether neuromodulation can suppress your bladder overactivity. If you have previously trialled neuromodulation we will assess the results and if eligible invite you to participate in the main study outlined below.

**Screening clinic:**

Baseline urodynamic, as used in regular clinic for SCI patients, will be done first. This involves filling the bladder through a catheter and measuring bladder pressures simultaneously through fine lines placed in the bladder and rectum. This will be followed by a repeat urodynamic fill, a short break after the first, where surface stimulation will be applied over the genital nerve as pressure rises, to assess the bladders response. Where stimulation is able to suppress overactivity we will invite you to begin our main study outlined below.

**Location:** LSCIC **Time:** 1-2 hours

**Main study:**

<table>
<thead>
<tr>
<th>Session</th>
<th>Duration</th>
<th>Day</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 - Diary instruction</strong></td>
<td>30 mins</td>
<td>1</td>
<td>LSCIC or home</td>
</tr>
</tbody>
</table>

After providing informed consent, this will involve answering some questions on the impact of your injury on your bladder, the level of sensation with regard to your bladder function and being shown how to complete the bladder diary. A smart device with a dedicated app to
record a standard bladder diary will be provided to record fluid intake, output and incontinence events.

**2 - Recording bladder diary at home**
You will use the device in order to carry on recording a bladder diary for the next 7 days. This will involve pressing the appropriate buttons regarding fluid intake, leakage events, voided volumes and urgency through the week.

**3 – Questionnaire, ambulatory urodynamics and stimulator set-up**
To assess your baseline bladder function during normal activities you will first be asked to complete the short International Consultation on Incontinence Questionnaire (ICIQ).

You will then undergo ambulatory urodynamics, this will involve a thin line being placed into the bladder and rectum to measure pressures over the course of the natural bladder cycle. We will show you how to set up and use the stimulation equipment. This will be checked by continuing urodynamic measurement for a further cycle. This session is required to check the effect of the stimulation set-up, your ability to place electrodes and use the stimulator correctly before you take it home. Blood pressure will be taken at baseline and then at 15 minute intervals when stimulation is started to monitor for signs of autonomic dysreflexia (AD).

**4 – Home use of stimulator with diary**
Following a successful setup session, you will be provided with the portable stimulator to take-home. You will be asked to use this to control unwanted bladder overactivity over the next 7 days and to continue recording a bladder diary in the same app. Sticker electrodes will be worn when the system is in use, you will be provided with enough replacements.

**5 – Ambulatory urodynamics and questionnaire**
Finally, following 7 days of home use, you will be asked to attend the LSCIC. This will involve completion of the same questionnaire, followed by undergoing ambulatory urodynamics whilst using the stimulator to restrict bladder overactivity. This will allow the research team to better assess whether stimulation device is being used effectively and safely. You will be required to return the
provided stimulator and smart device following the study.

We will reimburse you for travel expenses for each of your visits.

What are the risks involved in the procedures in the study?

There are some possible risks arising from this study, these are outlined below:

- A small risk of Urinary Tract Infection (UTI) from use of catheters during urodynamics

- If your injury is above the T6 level then Autonomic Dysreflexia is a risk. This is a condition where a stimulus below the level of your injury causes a dangerous rise in blood pressure, it has not been reported to happen due to stimulation in previous studies however remains a risk. Stimulation will be stopped if symptoms occur. We will monitor your blood pressure at regular intervals when trialling stimulation in the clinic.

- Skin irritation from electrodes is a small risk, in this case stimulation should be stopped and the electrodes removed.

Will there be any benefit to me?

Unfortunately, we are unable to provide you with a device for use after the study period as we are still researching the technique. If you agree to take part, this study would help patients with spinal cord injury in the following ways:

- Improve our understanding of electrical stimulations’ capacity to treat bladder overactivity and how best to apply it. This will contribute to improving current bladder management and treatment options.
- A positive outcome for this study could lead to the development of a new treatment for the improvement of continence in the SCI population.

What happens when the research study stops?

When the study ends, you will no longer be able to continue using the system. We’re still working, through trials such as this, to establish an effective method of delivering the technique before seeking to include it in clinical options.

What do I need to do to take part?

If you would like to participate, please get in touch with a member of the team on the details below, or return the expression of interest form enclosed. We will talk on the phone to answer any questions and confirm your eligibility, then we will book you an initial appointment.

Will all the information be kept confidential?
Everyone in the project will respect your confidentiality. All information which is collected about you during the course of the research will be kept strictly confidential. Data collected will be anonymised so that you will not be identified. The anonymised study results may be published in scientific journals.

**What if something goes wrong?**

If you have any concern about any aspect of the study you should speak to the researchers who will do their best to answer your questions.

Should issues arise outside of working hours you should contact the London Spinal Cord Injury Centre desk on **0208 909 5588** who will contact a member of our team.

In the event that something does go wrong and you are harmed during the research and this is due to negligence then you may have grounds for a legal action for compensation against Royal National Orthopaedic Hospital NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**What should I do if I have a complaint?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this contacting the Patient Advice and Liaison Service via pals@rnoh.nhs.uk or 020 8909 5439/5717.

**Who has reviewed and funded the study?**

The INSPIRE National Scientific Committee has approved this project for funding and London-Stanmore Research Ethics Committee has given approval for this study to take place. The study is funded by INSPIRE Foundation charity.

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*If you have any further questions regarding this investigation please contact:*

**Dr Sarah Knight or Sean Doherty**

at the **Royal National Orthopaedic Hospital**

020 8909 5605 or sean.doherty.15@ucl.ac.uk
CONSENT FORM

NEUROMOD: Researching the effect of electrical stimulation on bladder overactivity following Spinal Cord Injury in a home pilot study

Chief investigator for this study: Dr SL Knight

1. I confirm that I have read and understood the information sheet dated ____________ for the above study and have had the opportunity to ask questions. [ ]

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study. [ ]

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

4. I understand that parts of my medical notes may be looked at by researchers and by regulatory authorities where they are relevant to my taking part in this study. I give permission for these individuals to have access to my records. [ ]

5. I understand that study documents may be looked at by authorised representatives from the UCL-RNOH Research and Development Unit (R&D), on behalf of the Sponsor (RNOH) to ensure that the study is being conducted to the required standard. I give permission for these individuals to have access such information. [ ]

6. I understand that information collected as part of this study will be kept confidentially and securely at the RNOH and that they may be re-assessed as part of future ethics approved studies. [ ]

7. I am happy for my GP to be informed about my participation in this study. [ ]

8. I agree to take part in the above study. [ ]
Patient’s signature or independent witness _____________________________________________

Name in BLOCK LETTERS ______________________ Date ____________

Doctor’s signature _________________________________________________

Name in BLOCK LETTERS ______________________ Date ____________

[When completed, 1 copy for the participant; 1 for the research files; 1 (original) to be filed in clinical notes]
Appendix B

Conference Abstracts

- Doherty SP, Vanhoestenberghe A, Hamid R and Knight SL. Home use of a wirelessly controlled stimulator to deliver dorsal genital nerve stimulation for suppressing bladder overactivity following SCI. Conference abstract: IFESS 2018.


- Doherty SP, Knight SL, Lintermans A and Vanhoestenberghe A. A system to deliver and assess neuromodulation protocols for management of Neurogenic Detrusor Overactivity in SCI. Conference abstract: IFESS 2017.

- Doherty SP, Knight SL and Vanhoestenberghe A. Developing a wireless device for the research of practical neuromodulation techniques to treat the neurogenic bladder. Conference abstract: IFESS 2016
Home use of a wirelessly controlled stimulator to deliver dorsal genital nerve stimulation for suppressing bladder overactivity following SCI

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Abstract: Incontinence is prominent in neurological patient populations such as Spinal Cord Injury. Electrical stimulation of pudendal afferents can increase bladder capacity and suppress reflex contractions. Presented is a single case study of an SCI subject using surface genital nerve stimulation at home over one week, using a wirelessly controlled stimulator and Android app based diary logger. An increase in voided volumes and time between voids was recorded, though incontinence, characterised by leak event rate and ICIQ score, remained unchanged.

Keywords: Bladder, Spinal Cord Injury, Incontinence, Dorsal Genital Nerve Stimulation, Neuromodulation

Introduction

Following spinal cord injury (SCI), neural control of the Lower Urinary Tract (LUT) becomes aberrant. This leads to the development of Neurogenic Detrusor Activity (NDO) and Detrusor-Sphincter-Dyssynergia (DSD) affecting the LUT’s ability to store and void urine. During storage, high intra-detrusor pressures and urinary incontinence become common, therefore urological management goals for storage of urine are to enable low pressures and maintain continence [1].

Electrical stimulation of sacral afferents can acutely inhibit NDO, reducing pressures and maintaining continence. This may be achieved superficially by stimulating the Dorsal Genital Nerve (DGNS), a purely afferent and superficial branch of the pudendal nerve, by applying electrodes to the dorsum of the penis or over the clitoris. DGNS is thought to both stimulate the striated sphincter and project onto autonomic pathways at a spinal level to inhibit detrusor activity [2]. It has been shown in standard cystometry studies to increase bladder capacity by 131 ± 101 ml, from 212±131 ml without DGNS to 343±159 ml with DGNS [3].

DGNS may be applied continuously or conditionally, having been shown to be equivalent in acute urodynamic study [4]. Continuous stimulation raises potential issues with habituation and device battery life, therefore a robust conditional stimulation paradigm is viewed as the gold standard option. Conditional stimulation requires knowledge of bladder activity to be fed back to appropriately trigger stimulation. This feedback may be provided automatically in a closed loop system utilising a means of physiological monitoring, or through a user’s preserved sensation.

Numerous efforts have been made to enable physiological detection of NDO in a manner suitable for chronic implementation, recent options include implantable vesical pressure measurement combined with context aware thresholding of bladder events [5], use of external anal sphincter EMG [6] and implantable devices capable of measuring sacral afferent ENG [7]. However, none have yet been implemented as a viable option for chronic treatment and there are questions regarding chronic use of DGNS, such as the appropriateness of using sensation as a trigger or of electrode configurations and whether reflex inhibition is habituated with long term use, that may already be investigated using available techniques.

To date, the majority of chronic studies using DGNS have recruited sensate patients, able to trigger their own stimulation conditionally [8-10]. This has predominantly been shown to be a valid approach [8-10], however issues with easy access to stimulation trigger in some patients may be a limiting factor [11]. Further to this, whilst there is a large proportion of persons with SCI who possess some degree of pelvic sensation, there is a portion of these for whom the ability to detect unwanted bladder contractions may be too late to trigger conditional neuromodulation and further proportion who have no sensation at all [11, 12].

We hypothesised that by implementing stimulator control on an easily accessible User Interface (UI) we may increase acceptability of the technique and reduce problems associated with access to stimulation triggers. The design of this system has been outlined previously [13].

We present a case study of DGNS use in the home environment over one week using the described device, with a participant who had some preserved sensation.

Methods

Ethical approval was obtained from our local ethics board and the study was conducted in accordance with the Declaration of Helsinki.

System used

The stimulation system used consists of four components. Commercially available 2.5cm round electrodes (PALS®, Axelgaard Manufacturing Co., Ltd.) were used along with commercially available Odstock Medical PACE stimulator (Odstock Medical Ltd.) modified to deliver 15 Hz stimulation. The traditional foot switch has been replaced with
a Bluetooth low energy (BLE) connected switch, consisting of a MOSFET switch controlled by a BLE microcontroller with power source. This switch receives a stimulation profile and switching updates from a custom Android application. To stimulate the DGN electrodes were placed on the dorsum of the penile shaft. Electrodes were placed approximately 2cm apart, the cathode was placed proximally. Stimulation was set to 200µS pulse width and biphasic.

**Figure 1: Wireless version of Odstock Pace stimulator with custom Android app**

**Experimental protocol**

The experiment was carried out in 3 phases: a screening assessment where the participant underwent cystometry (CMG) to test for NDO and test the suppressive effect of DGNS, a control week completing a bladder diary whilst continuing usual care and an experimental week completing a bladder diary whilst using DGNS on top of usual care.

To assess the effectiveness of DGNS the participant first underwent CMG [14] to record baseline and “with stimulation” bladder pressures and capacity. During these tests the participant was supine. A 10.5 Ch catheter was placed urethrally and used to fill the bladder with room temperature saline at 60ml/min. Pressure was measured using Medex (Smiths Medical) pressure transducers placed at the level of the pubic synthesis, through 4.5Ch water filled catheters placed urethrally to measure vesical pressure ($P_{ves}$) and rectally to measure abdominal pressure ($P_{abd}$). Detrusor pressure was calculated as Eq. 1.

$$P_{det} = P_{ves} - P_{abd} \quad (1)$$

Infused volume was measured using a weight transducer. Signals were amplified using a CED 1902 isolated amplifier, digitised through a CED 1401 and recorded on Spike 2 software (Version 4, Cambridge Electronic Devices, UK) used to display data and trigger stimulation. To threshold stimulation amplitude, 15Hz bursts of one second were given in increasing amplitudes until 2x the threshold for contraction of the external anal sphincter ($EAS_{thresh}$), detected visually, was reached. Stimulation was monophasic and delivered by a constant current stimulator (DS7, Digitimer, UK).

CMG was performed without stimulation, with DGNS applied at a rise of 10 cmH2O and again without stimulation. First Detrusor Contraction Volume (FDCV), Maximum Cystometric Capacity (MCC) and Maximum Detrusor Pressure (MDP) were used for analysis.

A baseline bladder diary was then completed using the smartphone app. Leakage events, volume voided, urgency sensations and fluid intake was recorded over 6 days in the participant home. From this diary, the time between Clean Self Intermittent Catheterisation (CSIC) was calculated, excluding overnight periods.

Following the control week, the participant was set up with the Pace stimulator and wireless controller. The amplitude was set to as close to 2 x $EAS_{thresh}$ as was tolerable. Stimulation was biphasic, 15Hz and set to 200µS pulse width. The stimulation mode was then set to User Controlled only, based on the participant having sensation of bladder activity. The participant then used DGNS at their discretion, to suppress bladder overactivity, over the following week at home whilst recording the same diary.

The International Consultation on Incontinence Urinary Incontinence Short Form (ICIQ UI-SF) was used as an additional measure, completed at the end of the control week and the end of the DGNS week. The ICIQ-UI Short Form is a brief patient-completed questionnaire for evaluating the frequency, severity and impact on quality of life of urinary incontinence in men and women.

**Results**

**Participant characteristics**

One 69-year-old male with a C5, ASIA D, SCI was recruited. Current bladder management was CSIC on urge, with chronic incontinence managed using pads and 10mg Oxybutinin od. Previous intra-detrusor botulinum type-A injections had been administered, though none in the preceding 12 months.

**Baseline cystometry**

Stimulation amplitude was set to 45mA, the maximum tolerable level, at 1.5 x $EAS_{thresh}$. Baseline CMG without stimulation had a mean volume from onset of NDO to MCC of 18ml, this increased to 125ml when DGNS was applied at onset of NDO. Results are shown in Tab. 1 and raw CMG traces in Fig. 2 below. No decrease in MDP was found, although two detrusor contractions were suppressed with increasing $P_{det}$.
Table 1: Standard CMG results. Including volume infused at first detrusor contraction (FDCV), Maximum Cystometric Capacity (MCC) and Maximum Detrusor Pressure (MDP)

<table>
<thead>
<tr>
<th>Fill</th>
<th>FDCV/ml</th>
<th>MCC/ml</th>
<th>MDP/cmH2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>92</td>
<td>109</td>
<td>67</td>
</tr>
<tr>
<td>DGNS 45mA</td>
<td>71</td>
<td>196</td>
<td>60</td>
</tr>
<tr>
<td>Control 2</td>
<td>95</td>
<td>114</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 2: Diary results including: volume voided expressed as mean ± standard deviation; incontinence events recorded per day expressed as mean; time between CSIC expressed as mean ± standard deviation, calculated excluding overnight periods; ICIQ UI-SF score

<table>
<thead>
<tr>
<th>Vol (ml)</th>
<th>Leak/day</th>
<th>Time between CSIC</th>
<th>ICIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>298 ±128</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>DGNS</td>
<td>371±112</td>
<td>5hr33 ± 2hr20</td>
<td>14</td>
</tr>
</tbody>
</table>

**Discussion**

The increase in void volume reported here of 73ml, or 25%, is a modest improvement. Acute studies have seen a mean increase of 131 ± 101 ml (62%) [3], whilst previous studies of DGNS use at home have reported increased void volumes of 145ml (72%) [8], and of 12% [10]. There was a large increase in time between voids whilst using DGNS of 3 hours 29 minutes, compared with 42 minutes reported in another case study [8].

Despite the increased volume and time between CSICs the leak event rate and ICIQ score remained unchanged. We know stimulating the pudendal nerve has a limited capacity to suppress ongoing NDO, average number of detrusor contractions suppressed has been 3 [15] and 4 [6]. One contributing factor may be an insufficient amplitude of stimulation, which was set to 1.25 x EAS\textsubscript{thresh}, below what we consider to be optimal. It may be that the incontinence episodes were offset but not avoided or the case that the participant delayed time between voids for as long as possible, to test the DGNS. As reported by Martins et al. [11], better assessment of the reliability of individual’s sensation as a trigger would be valuable.

Stimulation was tolerated well by the participant and no side effects were reported. Autonomic Dysreflexia (AD) remains a risk for SCI patients, generally it has not been reported [8-10] and sharp rises in blood pressure found during NDO have been decreased previously using DGNS [16]. Symptoms of AD were not reported in the presented case.

The application of surface electrodes to the skin of the penis/clitoris has been problematic in previous reports, understandably. This was not reported as a problem by the participant.

Sensation of bladder activity may be present in a majority of SCI patients, one study reporting partial or totally preserved sensation in 77% of the population tested, including in 67% of the 52 complete SCI patients included [12]. To use non-continuous stimulation in SCI persons with no sensation, it may be possible to delay the onset of NDO, triggering DGNS following a set interval based on a preceding bladder diary so as to cover periods of time where incontinence events occur. This functionality is in the developed system [13].

The system was found to trigger stimulation reliably and to provide an accessible UI for a tetraplegic to trigger stimula-
tion. It is necessary to test the system further and as such further case studies of DGNS are planned. The reported results are, of course, limited as this is a single case study and all measures were self-reported. Patient controlled, transcutaneous DGNS remains an intriguing possibility for treatment.

Acknowledgement
Thanks to The INSPIRE Foundation, Salisbury, UK for funding this research project.

References

Spinal Cord Injury’s bladder problem

Spinal cord injury (SCI) seriously disrupts the function of the lower urinary tract, affecting storage and voiding of urine. SCI can result in overactivity of the bladder (NDO), which often leads to chronic issues with urinary incontinence [1].

Incontinence and Quality of life

A 2010 study of London Spinal Cord Injury Centre outpatients reported 56% had incontinence on a minimum of a monthly basis, found to negatively influence quality of life measures [2].

Urodynamic assessment of bladder overactivity

Measuring bladder pressures whilst filling the bladder enables us to quantify bladder activity. The figure below shows an uncontrolled detrusor contraction resulting in leakage.

Assessing acute effect and comparing stimulation sites

Stimulation of several anatomical sites is reported to reduce bladder overactivity in neurogenic cases [3]. However, validity in SCI and agreement on the acute effect of stimulating each site have not been achieved. We conducted a urodynamic investigation of n=8 people with SCI and bladder overactivity, comparing stimulation at each of the sites in figure 2, to assess the acute effects.

- Only DGNS produced a significant change in bladder capacity (+118ml±124).
- Stimulation of the genital nerve was seen to suppress detrusor contractions when applied at sufficient amplitude.
- For clinical implementation patient selection will be key to effective use, intact reflexes are necessary.
- No significant changes in capacity or visual suppression of NDO seen during stimulation of other sites.

A wearable neuromodulation device?

The ability to switch off or delay a detrusor contraction presents an opportunity to develop a wearable device that may be used to reduce incontinence events.

Problems

There have been several issues identified in previous short trials of surface DGNS for management of incontinence. Variable levels of sensation to trigger stimulation, abundance of wires, lack of easy access to stimulation triggers, unknown best regimes and surface electrode design all present issues. We have implemented a system to look at some of these, figure 4.

Pilot study

We have recently begun a pilot study using DGNS over a week with SCI participants. Outcome measures are a digital bladder diary, ICIQ and ambulatory urodynamics compared to baseline values generated in a preceding week.

Conclusions

- Bladder overactivity following SCI may be acutely suppressed by stimulating the genital nerve
- Transcutaneous stimulation of the other 3 sites outlined in figure 1 showed no change in bladder capacity (+118ml±124).

References

Non-invasive neuromodulation to suppress neurogenic detrusor overactivity in spinal cord injury: a site comparison study

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Neurogenic detrusor over-activity (NDO) is prevalent in the SCI population and often refractory to current treatment. Neuromodulation through non-invasive electrical stimulation could add to existing pharmaceutical and surgical management options. The genital nerve (DGNS), tibial nerve (TNS), sacral roots (SRS) and spinal cord (SCS) have been suggested as effective stimulation targets.

We have assessed the acute effect of conditional stimulation over the 4 sites using standard urodynamics. Each site was tested in a separate session where baseline and with-stimulation fills were used to allow within-individual comparison. Conditional stimulation was triggered at a detrusor pressure of 10 cmH2O using stimulation parameters of 15Hz, 200µs PW and maximum tolerable amplitude in all sites. Maximum cystometric capacity (MCC), maximum detrusor pressure and time to leakage (Tsec) were recorded.

Six male patients with chronic supra-sacral SCI (ASIA A-D), urodynamically proven NDO and reported incontinence were tested. In all six subjects, DGNS was found to increase MCC and Tsec by more than other sites, with a mean(±SD) improvement from baseline of 176(±133)ml, range 85-460ml, and 187(±161)secs, range 44-530secs, respectively. TNS and SRS showed small improvements, SCS was tested in 4/6 participants and gave small negative results.

This study is limited by sample size and the fixed stimulation parameters used, however it does go some way to showing that DGNS is the most effective site to acutely suppress NDO following SCI. This is relevant in furthering design of a clinically useful tool to help manage incontinence.

Acknowledgment: This work is funded by The INSPIRE Foundation, Salisbury, UK
A system to deliver and assess neuromodulation protocols for management of Neurogenic Detrusor Overactivity in Spinal Cord Injury

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3 Université libre de Bruxelles

Introduction
Neurogenic Detrusor Overactivity (NDO) often arises following supra-sacral spinal cord injury (SCI). It affects the storage phase of the micturition cycle and, unmanaged, leads to high intra-detrusor pressures and incontinence [1]. Current pharmacological and surgical treatments may be ineffective. Neuromodulation of selected nervous pathways can suppress detrusor contractions, yet a clinically viable technique is elusive [2]. Our view is that by effective monitoring and delivery, an individualised stimulation protocol may successfully manage NDO using a common tool. This work aimed to develop a tool for delivery and assessment of patient specific neuromodulation protocols, first in clinic and then the patient’s home.

Method
The system requirements were; to capture outcome measures of ambulatory urodynamics, bladder diary and stimulation use, to allow set-up of multiple stimulation protocols based on time and user input, and to be user friendly for persons with wide ranging SCI. To meet these requirements, we have designed a flexible, modular system involving a central user interface (GUI), a Bluetooth (BLE) connected stimulation controller [3], and a BLE connected 2 channel ambulatory urodynamics data acquisition module. These have been designed to interact safely with commercially available stimulators (Odstock Medical) and pressure transducers (Medex LogiCal). The modular approach allows the system to be used for set-up, data capture and delivery as components may be subtracted as necessary, simplifying tasks for the patient.

Results
GUI design has been implemented on an Android application, used for set-up, control, data-logging, and displaying data. This sends and receives data to a test database and BLE microcontrollers responsible for urodynamic data acquisition and stimulation control.

Discussion and conclusions
This work is to facilitate a wider project looking into translation of an effective neuromodulation protocol. We are currently testing the described system with SCI individuals, with a view to presenting a case study of its use at this conference.


Supported by The INSPIRE Foundation, Salisbury, UK
Developing a Wireless Device for the Research of Practical Neuromodulation Techniques to Treat the Neurogenic Bladder

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Abstract—Neuromodulation of peripheral nerves has long been viewed as a viable alternative treatment modality for suppressing Neurogenic Detrusor Overactivity (NDO). Research has continued over decades yet translation into patient use remains elusive. Questions have been asked as to the long term efficacy of continuous stimulation and a viable system using conditional stimulation has so far not been realised. Herein lies an opportunity for the research and development of a practical, non-invasive, neuromodulation system to treat NDO. To do so, further investigation of practical stimulation triggers and regimes is necessary. This paper presents the design of a wireless device for flexible delivery and assessment of stimulation techniques outside of the laboratory.

I. INTRODUCTION

Supra-sacral spinal cord injury (SCI) causes serious disruption to the function of the lower urinary tract, often resulting in Neurogenic Detrusor Overactivity (NDO) and Detrusor Sphincter Dyssynergia (DSD). These two conditions affect the storage and voiding phases of the micturition cycle and can lead to both high intra-detrusor pressures and incontinence [1]. The impact of SCI on the bladder is keenly felt in the SCI population and research into this area is consistently cited as a priority [2].

Urological management goals are to protect the upper urinary tract and maintain continence. This is achieved by reducing NDO. Current management techniques do this pharmacologically, surgically or with implanted electrical stimulation devices. All have associated risks and side effects that may render them ineffective or unfavourable. Neuromodulation is an alternative treatment for NDO that takes advantage of the still intact lumbosacral spinal pathways following SCI, using electrical stimulation of theSacral or Pudendal nerves to suppress bladder activity and promote continence [3]. Transcutaneous neuromodulation techniques have been investigated for decades yet no system has been offered to SCI community [4].

Continuous stimulation has been shown to be effective at suppressing NDO in a laboratory setting but its clinical implementation is limited by problems of power consumption and the potential habituation of reflexes. Conditional stimulation, applied as NDO occurs, has been shown to be as effective [5] and may offer the advantage of reducing the problems mentioned above. The problem with this approach lies in implementing a conditional stimulation system. The chronic measurement of bladder activity has been a subject of much frustration and of ongoing research [6].

Other avenues have been explored to avoid the need for this measurement. Acute and more chronic tests of user initiated stimulation (UIS) and semi-conditional stimulation have reported favourable results [7]-[9]. These results suggest an effective device could be implemented that is not wholly conditional and that further research into alternative stimulation triggers and regimes is warranted.

This paper outlines the development of a device to aid research into the efficacy of neuromodulation in the ambulatory environment, with the capability to wirelessly deliver and assess a range of stimulation regimes and triggers. We will use this tool to design and assess practical methods of delivering neuromodulation to treat NDO through everyday life.

II. DESIGN

To be capable of controlling and assessing stimulation regimes the design consists of two main components, a controller for a commercially available stimulator (Odstock Medical stimulator (OMS)) and a app-based user interface, for researchers and patients to input and read information (see figure 2). Stimulation parameters of pulse frequency, pulse width, shape and amplitude are set on the commercially available stimulator and will be based on previous acute evaluation of response to neuromodulation in each user.

The user interface, delivered through a smart device based app, functions in three modes (illustrated in figure 1). First for the researcher or clinician to input the stimulation regime and trigger type they wish to implement along with relevant test information. This is loaded from the user interface to the controller, to complete the stimulation algorithm. Secondly, it offers a patient interface to be used for stimulation on-off control and diary entry of relevant information. Thirdly to collate the diary and stimulation data captured for a post test review and export. This data will be time-stamped in sync with simultaneously recorded ambulatory urodynamic data to allow review of stimulation tests against objective data.

![Figure 1. Initial designs for User Interface. From left to right - 1. Parameter and information input 2. Patient diary and control interface 3. Review and export window](image-url)

The role of the controller is to turn the stimulation on and off at the correct times, to deliver the program set by the researcher. This controller will be constructed from a microcontroller, Bluetooth module, RTC, SD module and power supply directly connected to the OMS through a single cable. The core stimulation algorithm is stored and actioned

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here, informed by specific parameters relating to stimulation regimes and triggers sent to the controller wirelessly from the user interface. This wireless communication between the controller and app-based user interface will be achieved using Bluetooth technology. The controller will be located with the OMS, during tests it need not be accessed by the patient. The user interface, with its patient diary function, should be easily accessible. Fig. 2. outlines the components in the system and their interactions.

Figure 2. Block diagram of system outlining components and interactions relative to both patient and researcher

Ambulatory urodynamic data, when relevant to a study, will be captured concurrently using a commercially available device. This involves measuring detrusor pressure (Pdet) over the course of a study. Abdominal (Pab) and vesicle (Pves) pressures are recorded from pressure transducers attached to urethral and rectal catheters, Pdet is then calculated as Pves−Pab. Previous research [10] has concentrated on conditional stimulation, relying on ambulatory urodynamic measurements to deliver stimulation in response to an increase in pressure. However, indwelling pressure measurement is not a long-term solution. The design presented here takes a different approach, using detrusor pressure measurement as an objective outcome measure as opposed to an active component in our system. Patient diary inputs and stimulation times will also be recorded. This will enrich the ambulatory urodynamic data to lead to a better understanding of the effects of each tested stimulation mode.

Constraints placed on the design of the controller relate to size, power consumption and safety. In addition, the user interface must address usability constraints. We have currently based specifications on being able to support seven day studies in the home environment. Users will range in mobility from wheelchair users with limited hand dexterity to walking users with full hand function. The design must accommodate all, throughout activities of daily living.

III. DISCUSSION

The main considerations in the design of this device have been to allow the user to maintain a true to life environment and to allow input flexibility whilst ensuring relevant data is captured. By developing a modular system, we aim to enable a future add-on for collection of urodynamic data within the same system. The option is also left open for greater use of software in the process, integrating the available data into one place may allow a more holistic view of outcomes and provide a basis for designing a more intelligent system.

Use of a wireless system will allow the whole assessment to take place with the stimulator in place, minimising the burden on the user and the risk of the system dislodging during activities of daily living. Untethered control allows easier access to the on-off control for the user, particularly users with limited hand dexterity who may also benefit from the use of a touchscreen user interface.

There are multiple regimes and triggers that may be suitable for effectively delivering stimulation. A key point in designing this device is to enable this range to be accessed and adapted through one common platform. This is particularly challenging in a population with such wide ranging requirements, where it is probable that individual adaptation of stimulation parameters and delivery techniques would be necessary. In this version, the device will provide a framework to assess semi-conditional, user initiated and timing based stimulation. The flexibility to modify, combine and add new trigger or regime paradigms will be built in. This flexibility will be used to develop a truly translational neuromodulation device, where personalised stimulation modes may be developed for individuals.

The device is currently under development and a prototype will be presented at the conference. It is intended to be used in ambulatory neuromodulation trials at London Spinal Cord Injuries Centre (LSCIC). Should this study be successful in identifying a practical neuromodulation paradigm, we will expand our prototype's capabilities and evaluate its suitability for clinical use.

REFERENCES