Degree	Year	Name of Author
M.D.	2005	DASGUPTA, R.

AN INVESTIGATION OF THE MECHANISM OF SACRAL NERVE STIMULATION IN RESTORING VOIDING FUNCTION

Thesis submitted for MD (Doctor of Medicine) degree
at the University of London

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ABSTRACT

Sacral nerve stimulation, or neuromodulation, has been shown to restore voiding in women with a specific type of urinary retention that is attributed to urethral sphincter overactivity. The therapy has gained popularity in this and other voiding dysfunctions, but its mechanism of action remains unexplained.

This thesis explores the effects of neuromodulation on women with urinary retention. It incorporates a urodynamic study of the effect of neuromodulation on bladder and urethral (peripheral) function, a functional brain imaging PET (Positron Emission Tomography) study of cerebral (central) effects, and a review of the long-term efficacy of the technique.

The urodynamics (including urethral pressure profilometry, cystometry, and sphincter electromyography) showed evidence of persistent urethral overactivity despite successful restoration of micturition. Together with the cystometric findings, this suggests that neuromodulation may facilitate voiding in this group by increasing detrusor contractility rather than by urethral relaxation.

Review of the sacral nerve implants performed at this centre over several years reveals that approximately 75% continue to void at upto 5 years after surgery, while considering reasons for the loss of efficacy in other patients.

The cerebral perception of bladder fullness was examined using PET scanning in a group of healthy female controls as well as women with retention treated by neuromodulation. The findings show that the brainstem activity which is present in healthy controls is not seen in retention patients until the neuromodulation is activated. The discussion addresses the respective roles of brainstem and cortical brain regions in the control of voiding function, and whether neuromodulation may 'normalize' cerebral activity.

In conclusion, this thesis provides evidence, for the first time, of changes in brain activity following sacral neuromodulation in urinary retention, confirming that its effects may well be mediated by afferent innervation.

There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy

William Shakespeare, 1601

A man will turn over half a library to make a book

Samuel Johnson, 1775

ACKNOWLEDGEMENTS

As for any undertaking in the field of medicine, conducting a body of research work depends on the support and teamwork of a number of colleagues. I am indebted to them as well as the patients without whom this work would not have been possible.

Foremost, the credit for inspiration and for developing my interest in this field lies with my supervisor, Professor Clare Fowler. I am most grateful for her guidance, encouragement, questions, and for fostering a research environment that was a joy to be a part of. Her experience in this field is unique, and it was a privilege to undertake research in this department.

My thanks to Collette Haslam and Gwen Gonzales in the Department of Uro-Neurology for their assistance throughout all parts of the study. My gratitude also to Dr Hugo Critchley for his expert advice and constructive comments, and for introducing me to functional brain imaging. The radiographers and technical support team at the world-class Functional Imaging Laboratory deserve special thanks for their help in the acquisition of the functional imaging data and for cajoling the cyclotron through difficult days.

I would like to acknowledge both the Wellcome Trust for the financial assistance through their Project Grant, and also Medtronic Inc. for their financial support.

The final word of thanks belongs to my parents who have been ever supportive throughout my development, both academic and beyond. Their interest in this work and illuminating external perspectives were much appreciated. Thank you.

CONTENTS

CHAPTER ONE

NEURAL CONTROL OF LOWER URINARY TRACT

The control of the human lower urinary tract is responsible for both urinary storage and for voiding in socially appropriate circumstances. It is therefore under the influence of coordinated sensory and motor neural pathways, abnormalities of which can lead to voiding dysfunction. The control of urinary storage and voiding, and the respective roles of spinal pathways and brain centres are discussed.

The four main neuronal pathways supplying the lower urinary tract are: i) parasympathetic (S2-4) preganglionic fibres, which synapse and run to the bladder and urethra, ii) sympathetic (T10-12, L1-2) preganglionic fibres which synapse and supply the trigone and prostate smooth muscle (including pre-prostatic sphincter), iii) somatic fibres from Onuf's nucleus that supply the intrinsic rhabdosphincter, and iv) pudendal nerve (S2-4) which supplies motor and sensory innervation to the urethra (Mundy 1999).

The neuronal factors that enable normal voiding function are a combination of reflex pathways and supraspinal modulation of these reflexes. The reflexes may be considered as the 'hard-wiring' while the modulation is the 'fine-tuning' of the system.

Spinal pathways

Urinary storage

With normal filling, bladder pressure is kept under regulatory control, a quality known as compliance. A bladder with normal compliance will demonstrate little pressure change for a significant increase in volume. Compliance may be considered to be a result of the bladder's visco-elastic properties as well as its neuronal influences; these features are described in respective 'myogenic' and 'neurogenic' theories, not discussed further here.

The *guarding reflex* is a sacral-thoracolumbar reflex whereby during bladder filling low-level vesical afferent activity (through the pelvic nerve) acts on sympathetic efferents (hypogastric nerve), as a 'negative feedback' mechanism. Stimulation of β-adrenergic receptors in bladder smooth muscle inhibits detrusor contraction, while stimulation of α-adrenergic receptors allows contraction of the bladder neck and proximal urethra, thereby maintaining continence. The pelvic nerve afferents also activate pudendal motoneurones, thereby inducing contraction of the striated external urethral sphincter. During bladder filling there is increase in sphincter electromyographic activity, reflecting an increase in efferent firing in the pudendal nerve (Yoshimura and de Groat 1997).

Furthermore there is descending input from the pons, activating the pudendal motoneurones to increase urethral resistance (Holstege, Griffiths et al. 1986).

Urinary voiding

As the bladder volume reaches the micturition threshold, vesical afferents trigger micturition reflexes, leading to contraction of the detrusor and relaxation of the urethra. The *voiding reflex* is a spinobulbospinal reflex by which pelvic nerve activity is relayed to the periaqueductal gray before reaching the pontine micturition centre (PMC), sometimes called Barrington's nucleus. This on/off switching circuit then stimulates the parasympathetic supply to the bladder (contraction) and internal urethral sphincter (relaxation), as well as inhibiting the sympathetic and pudendal supply to the bladder outlet (urethral relaxation). The descending signal, through an interneuronal pathway, also suppresses sympathetic inhibition of detrusor contraction.

This is the basic mechanism by which contraction and relaxation of the voiding apparatus is coordinated, and provides a framework for understanding how pathology can lead to different types of dysfunction. For example, a spinal cord transection above the lumbosacral region interrupts the normal micturition reflex, and can lead to detrusor-sphincter dyssynergia (DSD).

Other reflexes

A number of additional reflexes have also been described, mainly through animal studies.

Mechanical stimulation of the urethra by a catheter or urine flow can cause bladder contractions. The *urethral-bladder reflex* involves urethral afferent activity producing bladder emptying. The two components of this reflex described by Barrington include i) activity from a urethral somatic afferent (pudendal nerve) activating the PMC by a

supraspinal pathway, and ii) visceral afferent activity (pelvic nerve) facilitating detrusor contraction through a spinal mechanism (de Groat, Fraser et al. 2001).

The striated urethral sphincter can also have a modulatory effect on detrusor contraction. Studies in cats and monkeys have shown that contraction of the striated sphincter can suppress bladder emptying, possibly by muscle proprioceptive afferents activating central inhibitory mechanisms (de Groat, Fraser et al. 2001). A manifestation of this '*procontinence mechanism*' may be observed when people reduce their urinary urgency by squeezing their pelvic musculature, thereby postponing the time to void. Others have reported these inhibitory influences variously as the 'puborectalis-rectovesical inhibitory reflex' (Shafik and El-Sibai 2001) or the 'perineodetrusor inhibitory/ perineobulbar detrusor inhibitory reflex' (Mahony, Laferte et al. 1977).

The following chapter expands on how upregulation of this reflex may be the underlying cause of some women developing chronic retention. The role of sacral neuromodulation in restoring voiding in this patient group is discussed after this, addressing whether there may be a peripheral site of action. This includes studying the effect that this electrical therapy has on urethral sphincter function among patients with retention.

Supraspinal centres

As intimated earlier, a number of supraspinal centres are integral in facilitating urinary storage and initiation of voiding. These include the nucleus locus coeruleus (pontine micturition centre, or PMC), frontal lobe, periaqueductal gray (PAG),

somatosensory cortex, and hypothalamus, medial pre-optic area and other parts of the limbic system.

The early work establishing the functions of these areas was based on anatomical and lesional studies. Classic reports by Andrew and Nathan described urinary incontinence among patients with frontal lobe pathology (Andrew and Nathan 1964). More recently, the advent of functional brain imaging has enabled elucidation of roles played by different areas in bladder control. The techniques of Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) have identified key centres in the micturition pathway, which will be described in Chapter 5.

Another concept that will be further developed is that of a neural 'matrix' or 'network'. Comparisons can be made with our understanding of the cerebral processing of pain. The perception of pain is considered to be a product of a 'matrix', with a number of key brain areas being interrelated. And apart from afferent ascending signals, other factors can affect nociceptive processing, for example the effect of altered attention, a variable which can itself change the activity in the brain centres involved. The cerebral processing of pain is thus more complex than certain afferent signals reaching a 'pain centre' in the brain, but instead depends on the interaction of several centres. Further work is required to establish the pattern of information flow between these areas.

Similarly there are several brain regions related to the processing of sensations of bladder filling and desire to void. The PAG acts as a relay centre for bladder afferent

signals, and has interconnections with higher centres to influence the timing of voiding. In recent years there have been a limited number of functional brain imaging studies of cerebral control of micturition, from which certain common patterns are emerging. This thesis develops these ideas using PET scanning to examine the processing of urinary storage in healthy female volunteers, and to compare them with women with a specific type of urinary retention. The mechanism of sacral neuromodulation, used to treat this patient group, is subsequently examined by recording the activity of brain centres in response to this peripheral electrical stimulation. There have been few brain imaging studies of the central effect of neuromodulation, and this is the first to focus on women with urinary retention.

CHAPTER TWO

IDIOPATHIC URINARY RETENTION IN YOUNG WOMEN

2.1 Female urinary retention

Urinary retention or dysfunctional voiding in women is a rare but distressing condition which can present a challenging diagnostic conundrum. Such women may first be referred to a neurologist on the assumption that the condition is neurological, for example a problem of the spinal cord such as multiple sclerosis. Although multiple sclerosis can produce voiding dysfunction, investigations such as magnetic resonance imaging of the brain and spinal cord can now help promptly to exclude this as a cause. When no neuropathology is found, the patient may be assessed by a urologist to exclude an anatomical explanation for the symptoms. Typical assessment would include cystoscopy and possibly urodynamics. At this stage, the patient is sometimes treated by hydrodistension and/or urethral dilatation. The role of these therapeutic strategies in treating bladder outflow obstruction is still controversial but what is clear is that generally they provide only temporary relief, for up to a few months. In the case of some women with urinary retention, this may be due to the pathology actually being due to an 'overactivity' of the urethral sphincter.

In 1986, an abnormal electrical activity was detected during urethral sphincter electromyography (EMG) in a series of young women with urinary retention (Fowler and Kirby 1986). A high proportion of these patients was found to also have polycystic ovaries (Fowler, Christmas et al. 1988), leading to a hypothesis that the retention was due to an overactive sphincter, susceptible to hormonal influence.

2.2 Pathogenesis and clinical picture

2.2.1 Pathogenesis

The abnormal EMG signal may contain both complex repetitive discharges and decelerating bursts. This latter type of activity produces an EMG signal which sounds somewhat like myotonia, a disorder characterised by a failure of muscle relaxation. However single fibre EMG analysis of complexes shows low jitter consistent with the impulse being transmitted ephaptically, directly from muscle fibre to muscle fibre. By using special hooked wire electrodes to record EMG activity from the external urethral sphincter during voiding in women with voiding dysfunction, it was confirmed that bursts of complex repetitive discharges coincided with poor urinary stream (Deindl, Vodusek et al. 1998); this supports the concept that sphincter EMG overactivity is associated with impaired relaxation. Furthermore, this overactivity may be associated with inhibitory feedback of the detrusor as discussed later.

The EMG is recorded from the striated muscle, but the female urethral sphincter consists of a longitudinal inner smooth muscle ring being surrounded by the outer striated muscle ring. Their respective contributions to the state of over-contractility is not known. Wiseman et al suggested that the sphincter complex was hypertrophied in patients with the EMG abnormality (Wiseman, Swinn et al. 2002); however, due to the limited resolution of ultrasound, accurate measurement of striated versus smooth muscle components was not possible. Other imaging modalities with higher resolution such as magnetic resonance imaging may prove helpful.

The development of the sphincter abnormality may be under the influence of oestrogens, as suggested by the high association with polycystic ovaries. It could be a hormone-sensitive channelopathy which manifests as overactivity in the localised muscle. Channelopathies are a group of diseases caused by mutations in the genes

coding for ion channel subunits, and which may manifest as neuromuscular disorders due to disturbances of the membrane conducting system. They can be broadly classified as voltage-gated (skeletal muscle disorders, e.g. myotonia congenita, or central nervous system disorders, e.g.episodic ataxia) or ligand-gated (neuromuscular disorders, e.g. congenital myasthenia, or central nervous system disorders, e.g. nocturnal frontal lobe epilepsy). The similarity between EMG signals in sphincter overactivity and myotonia led to speculation about channelopathy underlying the sphincter abnormality.

One may reasonably question whether the sphincter overactivity is not simply an exaggeration of the guarding reflex, during which bladder filling results in reflex sympathetic activation of the pudendal efferents, producing an increase in outlet resistance. However, as can be observed from the experiments detailed later, the underlying neural mechanism in this condition is likely to be more complex, since restoration of voiding (following neuromodulation) occurs despite ongoing urethral overactivity. Furthermore in the guarding reflex, the quality of the EMG signal is normal, albeit with increasing amount of activity.

2.2.2 Clinical picture

A typical profile is of a woman in her 20s or 30s who develops urinary retention without necessarily having normal sensation of bladder filling until the distended bladder causes suprapubic discomfort. She is then catheterised, often with a residual volume in excess of over 1litre. In their questionnaire survey with responses from 91 women with complete retention, Swinn et al (Swinn, Wiseman et al. 2002) found that the mean age of presentation was 27.7years, and that whereas 35% of cases developed

retention spontaneously, two-thirds of the remainder followed an operative procedure (often a gynaecological operation).

Intermittent self-catheterisation was performed by 86/91 surveyed patients, many of whom typically described a sensation of "something gripping" when withdrawing the catheter. Polycystic ovaries were found in 50% of the cases as well as in the original series (Fowler, Christmas et al. 1988), pointing to a possible hormonal basis to the pathophysiology described previously.

Only 38 of the 91 patients with complete retention spontaneously recovered bladder function; early recognition and intervention during retention is crucial, and therefore awareness should be promoted among health care workers in acute settings (Williams, Taylor et al. 2003).

2.3 Investigations

In addition to a typical history as described, the basis for diagnosis remains the abnormality of the sphincter EMG. Cystometry generally shows a prolonged filling phase, with reduced sensations of filling; there is typically only limited detrusor pressure rise during the voiding phase. Other ancillary investigations described by Wiseman et al are the urethral pressure profile (UPP) and transvaginal ultrasound estimation of sphincter volume (Wiseman, Swinn et al. 2002). The maximum urethral closure pressure (MUCP), measured during UPP, was shown to be higher in retention patients and the EMG abnormality than in those with a normal EMG. There are currently attempts to standardise the terminology and methodology for measurement of urethral pressure (Lose, Griffiths et al. 2002), and its role as a clinical tool remains uncertain. Nevertheless, in conjunction with other tests, and in the appropriate clinical context, the elevated MUCP is a helpful indicator of increased urethral resistance. The

ultrasound volume was found to be higher in patients with the EMG abnormality (Wiseman, Swinn et al. 2002), supporting the previous finding using transrectal ultrasonography (Noble, Dixon et al. 1995). This suggests that the overactivity produces sphincteric hypertrophy, possibly of the striated sphincter. However, a recent morphological study has shown no evidence of hypertrophy of urethral rhabdosphincter fibres (Andrich, Rickards et al. 2005). Alternative imaging modalities, such as magnetic resonance imaging, could allow a quantitative assessment of the distinct components involved, as mentioned later in this thesis, though it should be emphasised that this result should not be interpreted in isolation.

There has also been a report that if psychological testing is incorporated into the assessment, patients with retention who are likely to fare best can be identified (Spinelli, Bertapelle et al. 2001). Perhaps as one might expect, improvement in voiding function following neuromodulation was more common in those with a normal psychological profile.

2.4 Management

The key principle in the management of any patient with urinary retention is to maintain the bladder as a low-pressure reservoir by ensuring adequate drainage. This is equally true for the patient population studied here.

The main plausible therapeutic methods, in order of increasing invasiveness include biofeedback, oral agents, catheterisation, intra-urethral injection, sacral nerve stimulation, urethral stent and urinary diversion surgery. Self-catheterisation has been traditionally offered to the patient as an alternative to a permanent drainage procedure (whether an indwelling catheter or a surgical solution). Although there have been attempts to relax the sphincter, for example using oral agents and also local injection

of botulinum toxin, the only treatment that has been conclusively shown to restore voiding so far is sacral nerve stimulation.

2.4.1 Bladder retraining

Although behavioural treatments have been used for urinary incontinence since the 1940s, there have as yet been no randomised controlled studies of these techniques in the treatment of women in retention. A variety of approaches could be adopted, including biofeedback, bladder drill and pelvic floor muscle retraining.

2.4.2 Oral agents

The stepwise medical treatment of bladder outlet obstruction in *men* involves the use of α-blockers (sometimes in conjunction with 5 α-reductase inhibitors, in case of significant prostatic enlargement), which allows relaxation of the sphincter mechanism. There are no prospective double-blind trials examining use of α-blockers in females, though there are a few isolated reports showing limited benefit. Kawabe and Niijima reported improvement in peak flow and residual volume in 4/5 cases using an α-blocker (Kawabe and Niijima 1987), while Kumar report 50% success in their series of 24 patients with what was described as 'functional bladder neck obstruction' (Kumar, Mandhani et al. 1999).

While there is a theoretical basis for the use of a β agonist such as salbutamol to relax the sphincter, no definite improvement in symptoms has yet been demonstrated (personal observation in 3 patients), possibly as a result of a concomitant inhibitory effect on detrusor contraction.

The role of a neuromuscular relaxant such as diazepam is also unclear. Kaplan described its success in 6 patients with 'urethral syndrome' who had an intermittent voiding pattern and evidence of increased sphincter activity during voiding (using pelvic floor EMG) (Kaplan, Firlit et al. 1980).

Rather than try to reduce outlet resistance, an alternative strategy would be to improve detrusor contractility. Indeed Wheeler et al have claimed that it is detrusor failure, and not urethral obstruction, which leads to female urinary retention in most cases (Wheeler, Culkin et al. 1990). Their series classified 68 women with retention as having an underlying neurogenic or non-neurogenic cause, though they attributed a total of 15/29 subjects in the latter group as having 'psychosocial problems'. However, they acknowledged that "prematurely labelling these patients as having psychosocial dysfunction without careful evaluation can overlook subtle abnormalities", and referred to the role of needle electromyography. They attempted to use the cholinergic agonist bethanechol to differentiate neurogenic from non-neurogenic bladders without success. While other groups have also described varying success for detrusor acontractility (Riedl, Stephen et al. 2000), evidence for its efficacy in women with sphincteric overactivity is lacking.

2.4.3 Botulinum toxin

Botulinum toxin inhibits the release of acetylcholine at the presynaptic neuromuscular junction, and its injection thereby paralyses the motor unit innervated. Neurologists have used this phenomenon to treat patients with disorders of muscle overactivity such as strabismus, spasmodic torticollis, blepharospasm, and hemifacial spasm.

Other applications include the treatment of sphincter of Oddi dysfunction, and the more widely publicised cosmetic reduction of facial wrinkles.

Since Dyskstra's initial reports of injecting it into the external urethral sphincter to treat DSD (Dykstra, Sidi et al. 1988) (Dykstra and Sidi 1990), there have been subsequent studies reporting similar success for DSD (Schurch, Hauri et al. 1996) (Beleggia, Beccia et al. 1997), (Petit, Wiart et al. 1998), (Gallien, Robineau et al. 1998). After Schurch et al published their results of successfully treating detrusor overactivity in 21 spinal cord injured patients with intradetrusor injections, there have been several reports of its impressive effectiveness for this indication.

There has been some success reported in treatment of bladder outflow obstruction in women with botulinum toxin injection (Phelan, Franks et al. 2001). A recent study of 21 patients (including 13 women) with impaired bladder emptying showed improved ability to void after injection of 80-100 units of botulinum toxin into the external urethral sphincter. The cause of voiding dysfunction was reported as neurogenic detrusor-sphincter dyssynergia in 12 cases, pelvic floor spasticity in 8 cases, and detrusor acontractility due to multiple sclerosis in 1 case. A more recent smaller clinical study from Taiwan also found favourable results following intra-urethral botulinum injections in neurogenic patients (Chen and Kuo 2004).

However, an earlier study of intra-sphincteric botulinum injection of 6 women with an abnormal sphincter EMG did not show symptomatic benefit (even though transient stress incontinence was achieved in 3 patients, showing that enough botulinum had been given to induce sphincter weakness) (Fowler, Betts et al. 1992).

2.4.4 Instrumentation

Either clean intermittent self-catheterisation (CISC) or permanent indwelling catheterisation is obviously a feasible treatment option. Both are associated with the risk of UTIs, and patients often report specific problems with CISC such as difficulty withdrawing the catheter. The prospect of an indwelling catheter is fairly unacceptable to most of these patients, as they are generally young and otherwise fit. Even the prospect of a lifetime of carrying CISC catheters is depressing for most. Nevertheless, this is a minimally invasive option which is available in the treatment armentarium.

Urethral stents and artificial sphincters are other examples of instrumentation which might seem to offer simple treatment concepts, but this has not been translated into clinical results.

2.4.5 Sacral nerve stimulation

Although electrical therapy has been used to treat bladder disorders since the 1950s, it was the pioneering work of Tanagho and Schmidt (Tanagho and Schmidt 1988) that led to development of implantable sacral nerve stimulators. These implantable pulse generators (IPG) [Interstim, Medtronic Inc.) consist of a battery attached to a stimulating electrode placed through the sacral foramen S3, delivering electrical current to the sacral nerve roots. Since gaining its European licence in 1994 and FDA approval in the United States in 1997, over 8000 stimulators have been implanted worldwide for a range of conditions. The indications include urgency-frequency, urge incontinence, and retention, as well as constipation, faecal incontinence, and pelvic pain more recently.

Clinical results

Sacral neuromodulation has been shown to restore voiding function successfully in women with urinary retention. A multicentre trial of 177 patients with retention (74% female) undergoing test stimulation found that 68/177 patients qualified for IPG implantation, one group receiving an IPG and the others acting as a control group by having their implantation delayed (Jonas, Fowler et al. 2001). The 24 patients who received an implant continued to show symptomatic benefit for up to 18 months, with 14/24 no longer needing catheterisation. A subset of these patients with a sphincter abnormality seems to respond particularly well, as also shown in 38 patients undergoing PNE (Swinn, Kitchen et al. 2000).

Shaker and Hassouna described the efficacy of neuromodulation in treating 20 patients (19 female) with non-obstructive retention, with a mean follow-up of 15 months (Shaker and Hassouna 1998). They also reported significant improvement in voiding function and found that most patients were unable to void without having sensation of the stimulation. This supports the proposition that the stimulation has a modulatory effect on afferent nerve pathways, as discussed later.

More recently Abosief reported the results of 20 patients (including 17 women) with non-obstructive urinary retention, 18 of whom were able to void with implantation of an IPG (Abosief, Tamaddon et al. 2002). The cause of their retention was not identified. Follow-up was up to 2 years, during which period they found few associated complications and significant improvement in symptoms.

However as for most surgical techniques, the lack of true placebo controls in these studies makes overall assessment of efficacy difficult. Another factor in the overall

availability of the therapy is the expense of the equipment (current cost of implant and leads is approximately £6000). Nevertheless no other treatment modality has been as successful in restoring voiding function to date; as other electrical therapies are developed it will be interesting to compare respective outcomes.

The safety and tolerability of sacral neuromodulation are now accepted (as outlined by published NICE guidelines: http://www.nice.org.uk/cms/ip/ipcat.aspx?0=56779). The complications of neuromodulation that are recognised include lead migration (less common since development of improved fixation techniques), pain at the site of the IPG box or in the ipsilateral leg, infection, and lack of efficacy following IPG implantation despite a successful PNE. Developments in the surgical technique have addressed some of these problems. The question of safety in pregnancy has also been addressed in a recent review of 6 cases of women with neuromodulation during pregnancy (Wiseman, van den Hombergh et al. 2002); although no adverse effects were observed, the recommendation was to deactivate the stimulator when a patient is discovered to be pregnant.

2.4.6 Urinary diversion

If these more conservative measures do not succeed, and the patient's quality of life is significantly adversely affected, then urinary diversion may be offered as a solution for adequate bladder drainage. This may be a continent (catheterisable) or incontinent diversion (ileal conduit), and discussed with their urologist. The invasive and irreversible nature of such a procedure is inevitably hard for some younger patients particularly to accept. Furthermore, these procedures can have associated

complications such as stomal stenosis, requiring revision surgery (Blaivas, Weiss et al. 2005)

CHAPTER THREE

NEUROMODULATION

3.1 Electrical therapies in voiding dysfunction

Since the discovery of the connection between electricity and muscular contraction during the pioneering work of Galvani and Volta, there have been significant advances in using electrical therapy to treat patients. Cardiac pacing and pain treatment were two of the earliest applications for electrical stimulation (Bemelmans, Mundy et al. 1999). The former involves stimulating cardiac muscle by its innervation in order to effect contraction, whereas the treatment of pain is more subtle, and involves modulation of central and peripheral nervous pathways. The principles used for treating lower urinary tract dysfunction with electricity may share certain features with those for pain.

For effective micturition, an adequate detrusor contraction must be accompanied by appropriate relaxation of the urethral sphincter. Historically several sites have been considered for the application of electrical stimulation: the bladder wall, the pelvic nerves, the spinal cord and the sacral nerves.

Intravesical stimulation

The first case of electrical stimulation being used for bladder emptying may have been in 1878 when the Danish surgeon MH Saxtorph treated patients with urinary retention by intravesical stimulation (Madersbacher 1990). He inserted a special catheter with a mounted metal electrode intraurethrally and placed a neutral electrode suprapubically. There were no further major efforts to treat voiding dysfunction with

electricity until the 1950s and 1960s, when people began to address the question of optimal mode and site of stimulation.

Experiments by McGuire (McGuire 1955) and Boyce (Boyce, Lathem et al. 1964) in animal models determined the most effective positioning and size of electrodes in the bladder to achieve adequate emptying; however further development of these techniques for the human bladder did not produce satisfactory bladder evacuation.

In the 1960s Caldwell (1963) and Alexander (1968) described their use of electrical stimulation to treat urinary incontinence (Caldwell 1963). Caldwell placed his electrodes in the sphincter with the secondary coil near the iliac spine. Alexander also used pelvic floor stimulation to increase urethral resistance and to inhibit the detrusor.

Pelvic nerve stimulation

Bladder overactivity can be suppressed by stimulation of pudendal afferent pathways. Different techniques have included dorsal penile nerve (or dorsal nerve of the clitoris) stimulation, anal or vaginal plug electrodes, magnetic stimulation of the sacral roots, and even stimulation of the posterior tibial nerve (van Balken, Vergunst et al. 2004).

Spinal cord stimulation

Spinal cord stimulation to achieve micturition was successfully demonstrated by Nashold et al (Nashold, Friedman et al. 1971), who reported the optimal location of the stimulating electrodes to be S1-S3 roots. However with further development of this technique the problem of simultaneous contraction of detrusor and urethral sphincter emerged.

Sacral nerve stimulation

In the 1970s Brindley's group developed an implantable stimulator that used sacral anterior root stimulation (SARS) to empty the bladder in paralysed patients (Finetech-Brindley SARS, Finetech Medical Limited) (Brindley, Polkey et al. 1982) and has proved very successful in treatment following spinal cord injury. This implant was combined with deafferentation of the S2-4 sacral sensory nerve roots (posterior rhizotomy) to overcome sphincter dyssynergia and reflex incontinence. The side-effects of this rhizotomy include loss of reflex erections. Therefore there are ongoing attempts to suppress reflex incontinence by stimulating the posterior roots rather than by a rhizotomy using the so-called sacral posterior and anterior root stimulator implant (SPARSI) (Jezernik, Craggs et al. 2002).

Tanagho et al performed a series of experiments that led to the development of sacral nerve stimulator implants. This group from the University of California San Francisco demonstrated that stimulation of the ventral root produced effective detrusor contraction and that this could be achieved separately from sphincter contraction. Detailed anatomical studies led to the identification of S3 nerve roots as being the most suitable location for placement of the electrode, and there was no evidence of nerve damage following chronic stimulation. Since the first ITREL I device, there have been several modifications of the implant, to produce the latest version, Interstim (Medtronic, Inc.).

3.2 Peripheral stimulation for urgency and urge-incontinence

Interestingly, as well as treating retention, sacral nerve stimulation is efficacious in the treatment of patients with overactive bladder, which is in fact its hitherto more common application (Abrams, Blaivas et al. 2003). The term *neuromodulation* has indeed been defined as "a physiologic process...in which the influence of activity in one neural pathway modulates the preexisting activity in another through synaptic interaction" (Bemelmans, Mundy et al. 1999).

Patients with detrusor overactivity (or Overactive Bladder, OAB) may have urgency-frequency and urge incontinence symptoms, the prevalence of this condition being estimated to be as high as 17.5 million women in the United States. With greater awareness of the healthcare costs associated with this condition, there is now increasing interest in symptom control. The management of OAB is not discussed much further here except to outline that after conservative measures (behavioural feedback, dietary) the mainstay of treatment is the use of anticholinergic medications; traditionally, patients who were refractory to these treatments would be considered for bladder surgery (eg augmentation cystoplasty, urinary diversion). More recently, in addition to botulinum therapy, electromagnetic stimulation of pelvic and other peripheral sites has provided an alternative modality between medical and surgical treatments. These include electrical stimulation of sacral nerves, anogenital/pelvic innervation, posterior tibial nerves, intravesically, and magnetic stimulation of sacral roots.

Studying some of the mechanisms involved in these therapies may shed some light on the basic principles of sacral neuromodulation that could be extended to its

application in retention. Despite success rates ranging from 50%-90% for these various therapies (Takahashi and Kitamura 2003), one should note that it is difficult to compare these with true sham controls, resulting in a general paucity of placebo-controlled studies.

3.2.1 Anogenital electrical stimulation

One such technique relies on the insertion of electrode plugs either intra-anally or intravaginally, and varying degrees of success have been reported since the original description by Magnus Fall's group in the 1970s (Takahashi and Kitamura 2003). Reasonably favourable intermediate-term results have been described in urge incontinence by different groups (Eriksen, Bergmann et al. 1989) (Primus and Kramer 1996) (Gladh, Mattsson et al. 2001), though when Bratt et al re-evaluated patients after 10 years, 78% of the 27 evaluable subjects reported symptoms of urge incontinence (Bratt, Salvesen et al. 1998). It is recognised that patients may require further repeat treatment sessions to maintain efficacy. Relatively few side-effects have been described with this therapy, which has also been applied in children (Trisnar and Kralji 1996) (Gladh, Mattsson et al. 2001). The mechanism of action has been proposed as through afferents that activate sympathetic hypogastric inhibition of the detrusor and central inhibition of pelvic parasympathetic motor output to the bladder (Lindstrom, Fall et al. 1983). This principle of stimulating the pudendal nerve forms the basis of stimulation of the dorsal nerve of the penis or clitoris with some success in patients with urge incontinence (Vodusek, Light et al. 1986).

3.2.2 Posterior tibial nerve stimulation

Since the first description of cutaneous stimulation over the posterior tibial nerve (McGuire, Zhang et al. 1983), a commercially available method of stimulating this nerve by a percutaneously placed 34-gauge needle was developed (Stoller 2000), variously called SANS (Stoller Afferent Nerve Stimulator) and PTNS (Posterior Tibial Nerve Stimulator). Success rates of over 70% have been reported, with few side-effects (Klinger, Pycha et al. 2000) (Govier, Litwiller et al. 2001) (van Balken, Vandoninck et al. 2001). Rather than acting directly on the pudendal nerve, this method stimulates a common central pathway through a more peripheral afferent site. A urodynamic study of 44 patients treated in this way demonstrated improvement in first involuntary detrusor contraction and maximum bladder capacity (Amarenco, Sheikh Ismael et al. 2003). There has been a recent report of the role of PTNS in idiopathic nonobstructive urinary dysfunction (Vandoninck, van Balken et al. 2003), in which the authors mention that "patients reported a more accentuated awareness of a desire to void", something typically seen in Fowler's syndrome patients following SNS.

3.2.3 Transcutaneous electrical nerve stimulation

Electrodes are held over the dermatomes related to the neural control of micturition, the most common sites being over the sacral foramina (S2-3), sacral dermatomes (S2-3, peri-anal region), dorsal penile or clitoral nerve, suprapubic region, thigh muscles, common peroneal nerve and posterior tibial nerve. The results have been mixed, and although no major complications have been reported, the long-term efficacy is limited.

3.2.4 Intravesical electrical stimulation

It is widely considered that the first case of neuromodulation for bladder dysfunction may have been performed by the Danish surgeon MH Saxtorph, who used intravesical electrical stimulation to treat urinary retention in 1873 (Madersbacher 1990). This modality involves introducing a catheter, with an electrode mounted on its tip, into the bladder transurethrally. The catheter is connected to a pressure monitor so that the patient can correlate sensations of urgency, and thereby learn to recognise and inhibit them by squeezing the pelvic floor. The practical use of this technique remains controversial (Kaplan 2000) (Decter 2000).

3.2.5 Magnetic stimulation

Just as an electric current induces a magnetic field, so in turn a magnetic field can induce changes in an electric field. Furthermore, whereas body tissues have high electrical impedance, they do not significantly attenuate magnetic energy. Hence functional magnetic stimulation (FMS) at the level of nerves can be of relatively high intensity without affecting skin and body tissue. There is experimental evidence that FMS of the sacral nerve roots can suppress detrusor overactivity (Sheriff, Shah et al. 1996) (McFarlane, Foley et al. 1997) (Yamanishi, Yasuda et al. 2000). With the availability of a commercially available magnetic stimulation 'chair' ('NeoControl' system, Neotonus Inc, Marietta, GA) on which the subject sits fully clothed for 20 minutes for full activation, there is increased interest in comparison of magnetic and electrical stimulation of the sacral roots. For example, one randomised urodynamic study found that while both modalities improved the maximum cystometric capacity, the increase was significantly greater following FMS (Yamanishi, Sakakibara et al. 2000). Another effect of FMS may be to increase the maximum urethral closure

pressure as suggested by Fujishoro et al (Fujishoro, Takahashi et al. 2002), which may also allow its application in stress incontinence.

However, just as certain features of the mechanism of SNS remain unclear, so there would also appear to be incongruity in terms of the effect of FMS on detrusor contraction. We have already alluded to the suppression of unstable contractions, but there is also evidence that FMS can increase detrusor pressure (Rodic, Schlapfer et al. 2002) (Brodak, Bidair et al. 1993). Bycroft et al recently concluded that the detrusor pressure rise seen after FMS relates to a delayed 'rebound' phenomenon, whereby detrusor pressure (hitherto suppressed by the stimulation) rose sharply after cessation of FMS (Bycroft, Craggs et al. 2004). Their findings supported the earlier hypothesis by Rodic et al that this detrusor contraction (seen only in their suprasacral spinal-cord injured patients) was the result of a late spinal reflex pathway, with possible contribution of sympathetic pathways (Rodic, Schlapfer et al. 2002). The authors refute the proposal by others that FMS induces voiding by direct parasympathetic (bladder efferent) activation. One may speculate that some of the mechanisms thus elucidated for FMS may be applicable for SNS, which shares a similar target for stimulation.

3.2.6 Sacral nerve stimulation

The efficacy of SNS in both refractory urge incontinence and urgency-frequency has been assessed in multicentre trials initiated in 1992. Patients in these two groups were recruited for randomised 'controlled' studies, whereby control patients underwent neuromodulator implantation 6 months after those in the other arm of the trial (Schmidt, Jonas et al. 1999) (Hassouna, Siegel et al. 2000). Therapy evaluation was

based on voiding diaries and quality-of-life questionnaires. The 222 patients with urgency-frequency showed statistically significant improvements in the frequency and voided volumes, which were sustained at upto 24 months. In the urge incontinence group of 184 patients, 47% were completely dry at 6 months, while another 29% showed greater than 50% reduction in incontinent episodes at the 6 month stage.

In another study, Janknegt et al found that a group of 96 implanted patients with refractory urge incontinence showed significant improvements in the number of incontinent episodes at an average of 31 months (Janknegt, Hassouna et al. 2001).

Defining 'cure' as greater than 50% reduction in urge incontinent episodes, Bosch and Groen reported a cure rate 80% at 1 year. This decreased to 65% at 1.5 years, but remained relatively constant thereafter upto 5 years post-implantation (Bosch and Groen 2000).

Also, in a smaller study of patients implanted for neurogenic urge incontinence, symptomatic results obtained at 6 months were maintained for a mean follow-up of 44 months (Chartier-Kastler, Bosch et al. 2000).

Electrical stimulation at the S3 level acts on mixed motor/sensory nerves, but it seems likely that neuromodulation has its main effect on the afferent innervation. While its main effect on detrusor overactivity may be by modulating local spinal reflexes (eg in spinal-cord injured patients), there may be supraspinal mechanisms involved also, such that the perception of urgency is affected also.

Summary

Urinary urge incontinence and urgency/frequency are more prevalent than urinary retention in women, and consequently a wider range of electrical and magnetic stimulation modalities have been applied in their treatment. Broadly speaking, they are focussed on afferent pathways, and while sacral neuromodulation acts on mixed nerves, the afferent component is likely to be the most relevant for its effects on detrusor overactivity as well as in urinary retention.

3.2.7 Acupuncture pathways

While sacral neuromodulation is based on the stimulation of nerves emerging from sacral foramina, it is interesting that another therapeutic modality, acupuncture, is based on the positioning of stimulating needles in a similar region, albeit with 'energy lines' being the substrate for intervention. It is worth briefly examining this therapy to see whether any common mechanisms of action can be extrapolated.

Acupuncture has been practised for over 2000 years in traditional Chinese medicine, and can be dated from its description in the Nei Ching (the classic Treatise on Internal Medicine, 305-204BC). Its introduction to Western Europe can be traced back to the teachings of George Soulie de Morant in the 17th century. More recently, there has been greater acceptance of a scientific basis to this ancient art, with evidence of acupuncture increasing the cerebrospinal fluid levels of endogenous opiates (endorphin and enkephalin). The effects of acupuncture seem to be reversed by the administration of the opiate antagonist nalaxone.

Murray and Feneley reported the effect of opioid blockade in lower urinary tract function in normal subjects, using intravenous naloxone (Murray and Feneley 1982). Their urodynamic study showed that administration of nalaxone produced a rise in detrusor pressure during filling, lower bladder capacity and lower urethral closure pressure, thus implying the involvement of endorphins in voiding function.

There are a few reports of acupuncture in urology. The most frequently described role for acupuncture in micturition-related problems is for patients with detrusor overactivity. This is also one of the key indications for sacral neuromodulation, though it is paradoxical how this treatment for retention can also help for bladder overactivity.

Philp et al found a moderate improvement in symptoms of bladder instability when applying acupuncture along traditional bladder meridians, but did not demonstrate any consistent urodynamic changes (Philp, Shah et al. 1988). A more recent study described the use of electroacupuncture in patients with neuropathic bladder after spinal cord injury (Cheng, Wong et al. 1998). They stimulated at different bladder 'acupoints' including the 'Tzu Liao' (UB32), which corresponds to the S2 sacral foramen. An increase in detrusor voiding pressures was reported after neuromodulation, though there was no corresponding data for the control group. Nevertheless, they speculated on the mechanism of action in this patient group being through stimulation of afferent nerve fibres, hormonal changes through action on the hypothalamus, or possibly reflex autonomic efferent pathways. There was a further urodynamic study by Chang for women with frequency, urgency and dysuria, in which acupuncture was found to reduce detrusor contractility (assessed by

cystometry) and to increase external sphincter contractions (increase urethral pressure profile) (Chang 1988). A major weakeness in all of these studies is that there is no true comparison with placebo effect, a criticism that may also be levelled at sacral neuromodulation.

Tanaka et al recently studied the effects of acupuncture in the sacral region in anaesthetized Sprague-Dawley rats, with assessment of electroencephalogram changes (Tanaka, Koyama et al. 2002). They concluded that the therapy had direct effects on the sleep-arousal system centrally, though the applicability of these findings to humans is not known.

The efficacy of acupuncture in voiding dysfunction requires further assessment by way of formal clinical trials, and the basis of its possible mechanism should also be investigated. In particular, the concept of restoring balance may share features with the 'normalization' of neural activity by neuromodulation as we perceive it.

CHAPTER FOUR

SACRAL NERVE STIMULATION

4.1 Development of sacral nerve stimulation

Knowledge of several factors is required for the safe and effective use of sacral nerve stimulators: anatomical understanding of the nerves emerging from the sacral foramina, electrical properties of the stimulating equipment and the response of tissues to such stimuli, predictors of response, and optimisation of stimulation parameters.

The anatomical studies performed by Tanagho's group on human cadavers helped establish the exact distribution of the sacral plexus, making it feasible to implant stimulators in this region. Subsequent work has allowed clinicians to distinguish between 'classical' S3 motor and sensory responses compared to stimulation at S2 or S4. This knowledge allows the accurate location of the stimulating electrode during peripheral test stimulation.

The safe development of neuromodulation also relied on the recognition that implantation can lead to both mechanically- and electrically-induced nerve damage. After even a few hours of stimulating a nerve at a dangerous amplitude and frequency, there can be signs of early axonal damage with histological evidence of the changes (Agnew, McCreery et al. 2002). There is greater risk of long-term damage, as one might expect, with continuous stimulation compared to intermittent stimulation. When patients present with signs of reduced efficacy, changes in amplitude, frequency, and order of active/inactive electrode can all be manipulated. However there is still little evidence of a protocol for such alterations.

Despite a few studies attempting to determine which factors are predictive of response to neuromodulation, there are no established criteria for this. Nevertheless, ongoing work attempts to identify key parameters for review.

4.2 Indications for SNS

The urinary problems that have been successfully treated by sacral neuromodulation are urgency-frequency, urge-incontinence and urinary retention. More recently, there has been evidence for its efficacy in treating bowel disturbances (both chronic constipation and faecal incontinence), pelvic pain and possibly interstitial cystitis.

More than 8000 stimulators have been implanted worldwide for urinary problems, since gaining its European licence in 1994 and FDA approval in 1997. Multi-centre trials have provided evidence of its efficacy in urgency-frequency, urge-incontinence and urinary retention (Schmidt, Jonas et al. 1999) (Hassouna, Siegel et al. 2000) (Jonas, Fowler et al. 2001), with published long-term results available over 3 years.

The subgroup of women with retention seems to respond particularly well to this stimulation (Swinn, Kitchen et al. 2000). For these patients, there has been no other effective alternative to self-catheterisation, and therefore the therapy has a different role to that in bladder overactivity where there are numerous alternative pharmacological treatments. Despite a significant revision rate for surgery (DasGupta, Wiseman et al. 2004), long-term efficacy has been demonstrated for this therapy in this group.

4.3 Technique of SNS

The traditional method for SNS, and that used for our study, starts with a test stimulation (Peripheral Nerve Evaluation, PNE) as an outpatient procedure. With the patient in a prone position, using local anaesthesia or sedation, a temporary stimulating electrode is inserted through the S3 foramen. Fluoroscopy may be used to assist with optimal placement. A satisfactory position is confirmed when connection of the electrode to its battery produces contraction of levator ani ('bellows response', so-called as it mimics bellows closing together) and induces a typical sensation of 'tingling' intravaginally or perineally. The stimulating electrode is secured externally, attached to the battery. This is left in-situ for 4-7 days, and the patient asked to return with a completed voiding diary, which is then compared to the baseline diary parameters, notably the voided volumes and residual volumes. If the patient shows a satisfactory improvement in voiding function, they are then selected for implantation of a permanent stimulator (Implantable Pulse Generator, IPG), traditionally under general anaesthesia.

There have been several modifications and refinements of the technique, as follows:

a) Two-stage implant

One of the drawbacks of the traditional approach is the high drop-off rate following a successful PNE – upto 40% of patients who respond well to a PNE do not continue to have a successful outcome with the IPG (Bosch and Groen 2000). One explanation for this is that the placement of the permanent electrode is unlikely to be exactly the same as that of the temporary electrode. Therefore, some centres have advocated placing the permanent electrode in S3 as the first screening stage, and if this produces a

successful result then the electrode is attached to the IPG battery at a simple second operation (leaving the electrode in the same position) (Janknegt, Weil et al. 1997) (Scheepens, van Koeveringe et al. 2002). If the patient does not respond, then the electrode is removed, and the second stage not performed.

b) Bilateral versus unilateral implantation

Following work in animal models, the use of bilateral electrode placement was proposed (Hohenfellner, Schultz-Lampel et al. 1998). However Scheepens et al compared unilateral versus bilateral neuromodulation in a series of 33 patients (27 female, 6 male), including 15 with partial or complete retention (Scheepens, de Bie et al. 2002), and for most patients, there was no significant difference between the approaches except for 2 cases with complete retention who were able to void to completion only with bilateral stimulation.

c) Fixation techniques

Lead migration was a problem reported by several centres in the early days of sacral neuromodulation, leading to modifications of the electrode (Carey, Fynes et al. 2001). A new 'tined' lead is also now available, which has special spikes (or 'tines') that secure the lead to the surrounding tissue, thereby fixing the electrode position without needing formal suturing of the electrode (Spinelli, Giardiello et al. 2003).

d) Minimally invasive approach

A promising recent development is the percutaneous placement of the stimulating electrode without requiring open dissection through the lower back (Chai and Mamo

2001) (Spinelli, Giardiello et al. 2003). It has now been shown that the entire technique, including the insertion of the IPG, can be performed under local anaesthesia, as a day-case procedure. An important advantage of this is that the patient's sensory responses can be taken into account during the initial placement of the stimulating lead in the test stage.

e) Buttock placement

Although the original site for placing the IPG was in a subcutaneous abdominal pouch, more recent reports have advocated buttock placement (Scheepens, Weil et al. 2001). This has the advantage that the patient does not have to be turned over intra-operatively, and thereby allows a quicker operation time.

4.4 Mechanisms for SNS

Despite the increase in number of stimulators implanted, for a variety of indications, the mechanism of action of neuromodulation is still not known, particularly in the paradoxical problems of retention and urge incontinence.

Fowler et al found the latency of anal sphincter contraction during PNE was longer than that compatible with a direct motor response (Fowler, Swinn et al. 2000). Several other sources of evidence also suggest that neuromodulation acts on the afferent innervation. This includes the clinical observation that the sensation of bladder fullness in women with retention returns sooner than the ability to void (Swinn, Kitchen et al. 2000) and work by Wyndaele et al which concluded that neuromodulation acts on afferents originating in the bladder (Wyndaele, Michielsen et

al. 2000). Recent immunostaining studies in rats indicate that neuromodulation may affect the expression of neurotransmitters involved in the transmission of signals from the bladder (Wang and Hassouna 2000) (Zhou, Wang et al. 2002); this raises the possibility that the electrical stimulation restores voiding by the release of neurotransmitters which have a modulatory effect on the aberrant electrical pathways.

In women with retention due to sphincter overactivity, there is a question of whether neuromodulation has a direct relaxant effect on the sphincter or facilitates an adequate detrusor contraction. There is some evidence that these patients are able to void despite a persistently overactive sphincter. Later we illustrate this with the observations made by recording EMG and urodynamics before and after neuromodulation; in this study patients voided with an interrupted flow pattern, with no significant reduction in the elevated MUCP and no change in the abnormal EMG signal (DasGupta and Fowler 2004). However, cystometry showed that detrusor pressure at maximal flow was only slightly elevated. This may be explained by neuromodulation overcoming an inhibitory effect of the sphincter on the detrusor, and therefore facilitating enough of a detrusor pressure rise to enable voiding.

Recent studies have started to address the effect of neuromodulation on the brain. Braun et al recorded the effects of neuromodulation on electroencephalogram activity, and proposed that its effects on sensory cortex signified a supraspinal site of action (Braun, Baezner et al. 2002). Previous work by Blok et al has used functional brain imaging techniques to demonstrate the brain centres involved in bladder control (Blok, Sturms et al. 1997) (Blok, Sturms et al. 1998). Ongoing research using functional brain imaging technology may provide helpful insights into supraspinal

neural processes of bladder interoception, and their responses to neuromodulation, as presented in abstract form (De Ridder, Sunaert et al. 2003) (Blok, Groen et al. 2003). This could then lead to a better understanding of our perception of bladder sensation and how sacral nerve stimulation can modify this perception.

CHAPTER FIVE

FUNCTIONAL BRAIN IMAGING

5.1 Background

The concept of localisation of function within the brain dates back to the 19th Century, with the science of Phrenology, demonstrated by Gall and Spurzheim. They proposed that the brain contained discrete areas related to moral, sexual and intellectual traits that could be distinguished by palpation of the skull. This crude principle underwent development by neurologists such as Broca, Jackson and Sherrington, who were able to relate specific pathology and anatomical abnormalities to regions of the brain. For example, Broca's localisation of a linguistic brain centre, Penfield relating the role of the temporal lobe in memory, and Sherrington demonstrating the role of the motor cortex in primates. Much of the information on the human brain was derived from subjects who had sustained major head injuries or who suffered various mental disorders. The development of imaging technology was a major advance in that the study of brain function no longer relied on anatomical dissection to localise function.

More recently, there have been moves towards integration of functional systems rather than simply 'localizing' specific brain areas, and investigators are beginning to realise the limitations of a single approach (whether neurophysiological, brain imaging, molecular genetic or psychological). There is a role for brain imaging in establishing patterns of functional connectivity.

With the advent of computerised tomography (CT) and magnetic resonance imaging, it was possible to localise areas damaged in brain-injured patients non-invasively. A

major advance came with the discovery of functional brain imaging, which has led to the development of the techniques of single photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG).

5.2 Functional brain imaging techniques

PET

Using the principle that regional cerebral blood flow (rCBF) is closely related to neural activity, this technique indicates the cortical area responsible for a task being performed. The imaging modalities of SPECT and PET both involve the use of radioactive nuclides. The measurement of cerebral blood flow dates from 1948 with the experiments of Kety and Schmidt (Kety and Schmidt 1948) who used nitrous oxide to measure the differences between the arterial input and venous outflow, from which cellular uptake could be determined. This only showed global cerebral blood flow, and was therefore developed by Glass and Harper in 1963 (Glass and Harper 1963), who used the radioisotope Xe-133 to measure regional cerebral blood flow. With the development of CT in the 1970s, the technique of SPECT was then able to map the distribution of radioisotopes.

Whereas SPECT involves the emission of gamma rays, positrons are emitted in PET, using radionuclides such as O-15 or F-18. The advantages of PET are better spatial resolution and greater sensitivity. In PET studies a *cyclotron* 'labels' specific drugs or compounds with radioactivity. A stable chemical isotope is loaded into a 'target chamber', where the cyclotron uses a proton beam to convert the stable material into a

radioactive isotope; these radioactive isotopes are unstable and decay by emitting positrons. Different tracers include oxygen (radiolabelled carbon dioxide or water), carbon or fluorine. The radiotracer is then injected into the bloodstream which carries it to the brain, where oxygen and glucose metabolism reflect the amount of brain activity in different brain regions. Sensors in the *PET camera* detect the radioactivity as the compound accumulates in the brain, and an image is recreated. Analysis can be performed by producing a *statistical parametric map* based on voxel-specific statistical comparisons between images.

Sources of error may include the activity of the tracer/ligand, recording of the PET data (scatter, noise amplification, altered signal gain for higher levels of radioactivity), the biological kinetic model (analysis is based on healthy brain models, and may be affected by diseased brain tissue) and patient-related error (eg head movement).

fMRI

The technique of fMRI relies on the magnetic properties of blood to enable visualization of blood flow in the brain during different activities. It is based on the principle of MRI, which provides images of the distribution of protons in tissue water. The MR image density depends mainly on the density of water protons, and may be modulated by tissue properties such as biochemical composition and magnetic heterogeneity. In an fMRI scanner, a large cylindrical magnet creates a magnetic field around the subject's head, and radio waves are sent through the magnetic field. Again sensors are used to construct an image. It is possible to measure blood perfusion

during fMRI by a sensitive contrast mechanism known as blood oxygen level dependent (BOLD) contrast.

Advantages over PET include the ability to image the brain over a much faster timescale (seconds rather than over a minute), higher spatial resolution, repeatability and the non-invasive nature of the test.

The most common source of error is head motion; if uncorrected, a movement of as little as 0.5mm can cause a 40% change of signal near a contrast boundary. Other potential errors include thermal noise, and also mislocalisation of functional signals (generally minimised by smoothing during analysis and performing a preliminary structural scan).

MEG

Recently the technique of MEG has been developed from the technique of electroencephalography (EEG) which measures the electrical signals from the brain. In MEG the tiny magnetic signals from neuronal firing are recorded rather than the electrical currents, and this enables greater spatial localisation. MEG is completely non-invasive and passive (does not even use externally applied magnetic fields).

5.3 Functional imaging and voiding control

Much of the current understanding of neural control of micturition stems originally from animal studies, such as described by Barrington. In his experiments with decerebrate cats he identified a pontine centre which, if ablated, resulted in urinary retention. This is known nowadays as either Barrington's nucleus or the Pontine Micturition Centre (PMC). In the early work of Holstege's group, it was proposed that there was a distinction between medial and lateral regions of the PMC, which sent projections to the sacral spinal cord (parasympathetic motor supply) and to Onuf's nucleus (somatic innervation) respectively. These were the so-called M- and L-regions, with corresponding facilitatory and inhibitory functions. Further research has questioned the validity of this simplistic pontine distinction.

Animal studies have shown bladder contractility to be affected during electrical stimulation of various supraspinal centres, including the hypothalamus, cingulate gyrus and periaqueductal grey (Gjone 1966). The work of Blok and Holstege helped to further delineate the pertinent anatomical connections, including the projections of the hypothalamus (medial preoptic area) and PAG to the PMC, and in turn the PMC to the sacral spinal cord (Blok and Holstege 1994). This helped to establish the concept that the PAG might act as a relay centre between the spinal cord and the pontine control centres. The medial preoptic area is part of the limbic system, and could contribute an 'emotional' component to voiding control. But although it may well have an 'executive' role (Blok and Holstege 1996), functional imaging studies have highlighted the greater complexity of the neural networks involved.

Several studies have focussed on the central processes involved in micturition. An early SPECT study by Fukuyama et al identified areas of the brain involved in the voiding reflex, including pons, sensorimotor cortex, frontal cortex and supplementary motor cortex (Fukuyama, Matsuzaki et al. 1996).

Blok and Holstege's imaging studies

However it was a series of PET studies by Blok et al which truly developed this area of investigation.

i) In 1997, they reported on PET scanning of male volunteers during micturition (Blok, Willemsen et al. 1997). Here they confirmed the activation of PAG, pons and hypothalamus during micturition. Their scans related to 4 conditions: 1) withholding scan (15 mins before micturition, with a full bladder), 2) micturition scan (just after the command to void), 3) empty scan (15 mins post micturition) and 4) empty scan (30 mins post micturition).

The analyses were performed as two separate groups, the first group being the 10 subjects who voided successfully, and the second group consisting of the 7 subjects who were unable to micturate.

For the 10 subjects who were able to void, a comparison was made between activation during scans 1 (withholding) and 2 (micturition); during micturition there was increased activity in the PAG, hypothalamus and the PMC on the right. Compared to an empty bladder, micturition was also associated with activity in broadly similar areas (scan 2 compared to scans 3 and 4).

A *decrease* in activity was also noted, such as in the anterior cingulate cortex during withholding (scan 1) compared to successful voiding (scan 2) and scans 3 and 4. This was interpreted as the general suppression of the sensory input and motor output, so that the urge to void was overcome during a full bladder state. The authors explained the decrease in activity by arguing that whereas cingulate activity is normally needed to facilitate a required response, in the case of urine withholding the opposite of a response facilitation is needed, in that the urge to void has to be *inhibited.* However, it could be argued that this suppression of urgency is in itself a response, and therefore if the cingulate has an executive role, it should still be activated.

Of the 7 who were unable to void during the experiment their activation patterns revealed activity in the ventral pons rather than the dorsomedial pontine micturition centre. This so-called lateral L-region was associated with closure of the external urethral sphincter and suppression of detrusor contractility, and its activity was interpreted as being related to the patients not feeling it was 'safe' to void. It should be remembered that this experiment required the subjects to have been trained in the act of voiding in the scanner.

ii) A study published in 1998 examined the activation patterns in 18 healthy female volunteers, using similar conditions of 1) full bladder, 2) micturition, 3) and 4) empty bladder sessions (Blok, Sturms et al. 1998).

Of the 18 volunteers, 10 were able to micturate. Broadly similar activation patterns were observed as in the male study, including increased activity in the PMC (as well as inferior frontal gyrus activity), and again a decrease in anterior cingulate activity;

however, the increase in activity in PAG and hypothalamus was not as pronounced as in the male study. There was also comment on the increased activity in the right anterior insula during the filled bladder condition (compared to other conditions) for both the female volunteers and also the males in the previous study. This area is associated with increased sympathetic discharge, and therefore may function by relaxing the bladder wall, reducing the urge to void and increasing the functional bladder capacity.

The predominance of the right brain centres in these studies (which both included right-handed subjects only) supports previous findings that correlated urge incontinence with right-sided brain lesions (Kershen, Kalisvaart et al. 2003).

iii) Blok et al extended their PET studies to examine the effect of pelvic floor contraction on supraspinal response in 6 healthy female volunteers (Blok, Sturms et al. 1997). The 4 conditions used in their experimental paradigm were 1) rest, 2) repetitive pelvic floor straining, 3) sustained pelvic floor straining, and 4) sustained abdominal straining.

The part of the motor cortex relating to pelvic floor contractions was found to be the superomedial precentral gyrus. It was suggested that this area had not been clearly identified in the classical electrical stimulation studies by Penfold and others due to its rather medial location making it difficult to access during these studies. However, bilateral destruction of this area is found to be associated with urinary retention, and when combined with a spastic paralysis of the lower limbs it is known as the paracentral lobule syndrome (Nathan 1976). The authors also drew attention to the

fact that this region was important in the *conscious* voluntary storage of urine, rather than directly as part of a storage reflex.

The anterior cingulate gyrus was activated during pelvic floor but not abdominal straining, again highlighting its role in the control of micturition generally, and pelvic contraction also produced activation of the cerebellum.

Nour et al: micturition in men

In 2000, Nour et al published the results of their PET study involving 12 healthy right-handed male volunteers (Nour, Svarer et al. 2000). The protocol had 3 conditions: 1) empty bladder, 2) micturition, and 3) withholding of urine, and the subjects underwent simultaneous cystometry, which confirmed detrusor contraction during the micturition phase. They confirmed Blok's earlier findings that micturition was associated with increased activity in the pons, inferior frontal gyrus, hypothalamus, and PAG, while also demonstrating activity in several other cortical areas (postcentral gyrus, superior frontal gyrus, thalamus, insula, and globus pallidus). When comparing the urine withholding (full bladder) condition with rest (empty bladder), no areas showed significant activation, though there was a tendency to activation in the left insula. There was also activation of the cerebellar vermis during micturition, supporting claims that the cerebellum has a facilitatory role during micturition.

The authors acknowledged the possible confounding effect of the urethral cystometry catheter, and its possible stimulation of urethral afferents.

The conclusion from this study was that there is likely to be a complex network of cortical and subcortical brain centres involved in the control of micturition.

Athwal et al: urinary storage in men

While the earlier studies had focussed on the micturition phase, Athwal et al looked at the central effects during urinary storage (Athwal, Berkley et al. 2001). Although the preceding studies had included storage conditions in the protocol and susbsequent analyses, this study was the first to concentrate on this phase of the urinary cycle. The 11 healthy male volunteers recruited were catheterised for this study, and filled to 6 randomly chosen proportions of their capacity with warmed saline for a total of 12 scans. They were asked to report their perceived urgency to void using a 0-4 scoring system previously shown to them (0=no sensation, 1= first sensation, 2=first urge to void, 3= strong urge, 4=uncomfortable urge).

Increasing bladder volumes were correlated with increased activity in the PAG, midline pons, mid-cingulate cortex and bilateral frontal cortex. There did not appear to be any relationship between brain areas activated during this passive filling and areas associated with urge to void A *decrease* in brain activity was noted in association with increased urge to void in the cingulate cortex, premotor cortex and hypothalamus. This was explained as a possible cerebral suppression of the urge to void in (or by) these particular areas. These authors also acknowledged the possible confounding influence of the urinary catheter, and accepted that despite counterbalancing there could have been some sensitisation to the repeated filling of the bladder through the catheter.

Matsuura et al: urinary storage in men

This group published their findings from a similar study in 2002, also examining the central processing of bladder sensation in healthy male volunteers (Matsuura, Kakizaki et al. 2002). As well as bladder distension, their study looked at the effect of cold stimulation on brain activity, using PET scanning. The 17 subjects were divided into two groups (n=11, n=6) who underwent bladder distension or instillation of ice-cold water respectively, using an 8Fr urethral catheter. The two conditions for the distension group were 1) bladder empty and 2) urine withholding (full bladder).

The areas of activation for a full bladder were the PAG, rostral pons, cerebellum, anterior insula, putamen and thalamus, and anterior cingulate gyrus. Ice water stimulation produced significant activations of the anterior cingulate gyrus, frontal lobes, parietal cortex and amygdala. The two stimuli did not show overlap of activated brain regions, suggesting that distinct neural pathways were involved.

Zhang et al: effect of pelvic floor contraction

A recent fMRI study of 12 healthy male volunteers examined the voluntary control of the micturition reflex, by pelvic floor contraction in a block design study with bladder either full or empty (Zhang, Reitz et al. 2005). The control condition was an empty bladder without pelvic floor contraction (ie. rest). Activation was seen in premotor cortex, basal ganglia and cerebellum following pelvic contraction with a full bladder. The authors extended previous observation that voluntary pelvic floor contraction increased a strong desire to void for a short time (Reitz, Schmid et al. 2003), to interpret the role of these brain regions in the inhibition of micturition.

Abstracts presented of ongoing work

Blok et al (2002): (Blok, Groen et al. 2002): Twelve patients with sacral nerve stimulators for urge incontinence underwent PET scanning with concurrent cystometry. Areas with increased activity during sacral neuromodulation were left frontal, left temporal and right insula, while reduced activity was seen in reticular formation, thalamus and cingulate gyrus. Although one interpretation of this was that the reduced activity related to the reduced sensation of bladder fullness, this is based on the presumption that reduction in activity is represented by reduced brain activity on scanning.

De Ridder et al (2003) (De Ridder, Sunaert et al. 2003): This abstract was submitted to the AUA meeting in Chicago, 2003, though the poster was not ultimately presented. They described an fMRI study of 14 women undergoing PNE stimulation (7 with retention, 7 with urge incontinence), and an on-off stimulation paradigm. The brain centres activated by 'subchronic' sacral stimulation were the PMC, PAG, amygdala, insula, somatosensory and prefrontal cortex.

Blok et al (2003) (Blok, Groen et al. 2003): This study of 8 patients with urge incontinence focussed on PET imaging at time of first activation of neuromodulation. The areas activated included mid cingulate, primary motor areas and lateral cerebellum, but not the brainstem. It was proposed that the motor and cerebellar activation related to the areas involved in learning behaviour, while the cingulate gyrus activation was a reflection of bladder sensation. Although the study described random switching on/off of the stimulator, there was no indication of the timing and whether a carry-over effect might occur.

Griffiths et al (2003) (Griffiths, Derbyshire et al. 2003): This was the first study to combine fMRI with urodynamics in the investigation of voiding control. With far greater temporal resolution than PET scanning, this technique should help to elucidate the changes in bladder sensation relating to filling. The findings of previous reports were confirmed with the activation of anterior cingulate, insula, cerebellum and frontal cortex during bladder filling.

Electrophysiology: to address central processing during neuromodulation

Electrophysiological techniques have also been applied in the investigation of the mechanism of sacral neuromodulation. Braun et al analysed evoked potential activity in 10 patients with sacral nerve implants (Braun, Baezner et al. 2002). This study described the detection of long latency somatosensory evoked potentials (SEPs) over the postcentral gyrus (somatosensory cortex) following stimulation of the sacral nerve roots; this was proposed as evidence of supraspinally mediated site of modulation (suggested to be sensory cortex). However, whereas early SEPs have become a routine tool for neuro-urological assessment in various neurological disorders, the significance of long latency SEPs remains more controversial. Furthermore the patient group was somewhat heterogeneous as it included 4 patients with neurogenic bladder dysfunction and 6 with idiopathic bladder dysfunction (of which only 2 had a hypocontractile bladder).

An editorial following the above report also commented on the finding that the evoked potential findings were reproducible in both patients who could and those who could not feel the neuromodulator being switched on/off. It was postulated that the SEP pathways were therefore independent of a cognitively mediated sensory input. The work of Wyndaele et al evaluated the effect of sacral nerve stimulation on electrosensation thresholds in the bladder, concluding that S3 stimulation sharpened bladder electrosensation for urgency and therefore worked on bladder afferents specifically (Wyndaele, Michielsen et al. 2000). The effect of stimulation was not associated with the clinical success of neuromodulation, with the conclusion that factors other than afferent pathways may also be involved, supporting the neurophysiological findings mentioned.

5.4 Functional imaging and other visceral stimulation

Although functional brain imaging has only been reported in a limited number of studies of bladder control, its application extends to the study of other visceral stimuli, such as gastrointestinal stimulation or visceral pain.

Gastrointestinal (GI) stimulation

Hobday et al used fMRI to identify the brain centres involved in the processing of anal (somatic) and rectal (visceral) sensation in healthy adults (Hobday, Aziz et al. 2001). Rectal stimulation produced activation of somatosensory cortex, insula, anterior cingulate and prefrontal cortex; anal canal stimulation produced similar regions of activity, though there was no anterior cingulate activity, and the primary somatosensory activation was slightly more superior. The activation of cingulate

cortex with rectal stimulation may signify the function of the limbic system in the processing of visceral stimuli. The processing of rectal sensation is relevant in bladder function since unlike other gut organs it has an important sensory role; the rectum is a visceral organ which has both unmyelinated C fibres and thinly myelinated Aδ afferents. The C-fibres are predominantly found in the muscular wall of the rectum, while the Aδ-fibres are found within the rectal mucosa. In contrast the anal canal has a somatic innervation from the pudendal nerve, and this study has highlighted the differences in its cortical representation from that of the rectum.

Derbyshire has reviewed the various brain imaging studies of visceral stimulation, including the above report (Derbyshire 2003). He highlights the differences between stimuli, whether esophageal distension, esophageal pain, rectal distension or patients with irritable bowel syndrome. Esophageal stimulation activated the insula most consistently, with other commonly involved areas including somatosensory and motor cortices; there was considerable variation in whether the PAG was activated or not. Lower GI stimuli predominantly activated the prefrontal and orbitofrontal cortices as well as the insula, with variability in cingulate activation. Overall, esophageal stimulation involved a more central sensory and motor neural circuit whereas lower GI stimulation activated areas with projections to autonomic and affective control centres, such as the brainstem and amygdala. The most commonly activated area overall was the insula, which has a key visceral sensory role, as will be discussed later.

Pain

There have been a large number of functional imaging studies investigating the central processing of responses to noxious stimuli. These have illustrated the range of central regions involved in the perception of pain, and include the midbrain, thalamus, cerebellum, insula, anterior cingulate, prefrontal cortex and somatosensory cortex. Thereby the concept of a 'matrix' of relevant areas rather than a single 'pain centre' has been forwarded (Rainville 2002). Furthermore there is distinction between the cerebral responses to somatic versus visceral pain.

PET studies have shown changes in opioid receptor binding in chronic neuropathic and inflammatory pain, many of these changes occurring in the perigenual anterior cingulate cortex and medial thalamus (which contain the highest concentration of opioid receptors). It has been recently discovered that placebo analgesia is, at least partly, mediated by endogenous opioid peptides; opiate and placebo-mediated analgesia seem to share a common network in the anterior cingulate cortex (Jones, Kulkarni et al. 2003).

CHAPTER SIX

AIMS & OBJECTIVES

The condition of urethral sphincter overactivity producing retention in women is now recognised, as is its treatment by sacral nerve stimulation (SNS). However, several key areas remain unexplained, including the pathophysiology of the condition, the mechanism of the therapy (notably its effects on the lower urinary tract and possibly on the cortical processes involved in voiding function), and the long-term outcome of neuromodulation in this group.

The perspective of this thesis was from that of a urologist, and required the author's acquisition of specialist skills for performing neuromodulation, conducting urodynamic testing and undertaking functional brain imaging. The last of these involved the experimental design and running of Positron Emission Tomography scanning, along with the analysis of the acquired data by statistical parametric mapping.

The main areas under investigation were:

Mechanism of action of neuromodulation

- by the urodynamic assessment of peripheral effects
- functional brain imaging to study central effects

Examining the long-term safety and efficacy of the procedure.

Urodynamic Assessment of effects of SNS

The diagnostic work-up for patients with Fowler's Syndrome includes performing UPP, sphincter EMG and also transvaginal ultrasound measurement of sphincter volume. Patients have usually also had urodynamic studies prior to undergoing sacral neuromodulation.

Hypothesis

As described earlier, the diagnosis partly depends on finding an abnormal EMG and elevated MUCP, suggestive of an overactive sphincter. It is not known whether patients with retention are able to micturate following stimulation of the sacral nerve roots due to a direct relaxant effect on the sphincter or through a more complex neural pathway.

Urethral pressure profilometry, electromyography and cystometry may be combined as a representation of urethral/bladder function, and therefore we hypothesise that if neuromodulation produces relaxation of the sphincter, one would expect these parameters to fall within normal limits following nerve stimulation. Alternatively, neuromodulation may not affect these urodynamic parameters, which implies that its effect is not to directly relax the overactive sphincter

Along with tests of sphincter function, we also conducted bladder function tests using formal cystometry. This enabled assessment of detrusor contractility following neuromodulation. We have described how these patients characteristically find it difficult to generate an adequate detrusor contraction with their large capacity bladders. Cystometry provides a method for recording detrusor pressure. Our

hypothesis was that the restoration of voiding by neuromodulation could partly be a function of altered detrusor contractility.

Functional brain imaging and neuromodulation

Functional brain imaging techniques can assist our understanding of the cerebral processing involved in voiding function and dysfunction. Here we perform a series of PET scans in both healthy females and in women with retention whose condition has been successfully treated by neuromodulation. The principle of PET scanning has been described, and we use this to identify the brain centres pertinent to bladder function.

Previous studies have begun to address how the brain perceives sensation of bladder filling, but this process is not understood in women with retention, nor is it clear how electrical stimulation induces changes centrally. Here, for the first time, we attempt to establish the feasibility of using this brain imaging technology in patients with a sacral nerve stimulator. Then by using a block design, applicable across both the control subjects and patients, we can make a valid comparison of the differences in brain activity in these respective groups, as well as among the patients pre- and post-neuromodulation.

Established software tools allow analysis of the data, using statistical parametric mapping techniques. In the discussion we elaborate on the significance of these findings in the context of previous anatomical and functional reports and recent brain imaging work.

Hypothesis

In earlier imaging studies, certain brain areas in healthy women have shown greater activity when the bladder is full, including the periaqueductal grey of the midbrain. Women in urinary retention due to Fowler's syndrome characteristically have reduced sensation of bladder filling, with large capacity bladder volumes. We hypothesise that in healthy females the PAG is also activated with a full compared to empty bladder; in contrast PAG activity may be reduced in retention patients, but possibly restored (or 'normalized') in patients following neuromodulation. Higher cortical centres may also show differential activity between baseline and after neuromodulation in this patient group, reflecting the central effects of sacral nerve stimulation.

Efficacy of Neuromodulation

The role of SNS is now established in women with urinary retention. However the long-term safety and efficacy of the treatment has not been described. We analyse the outcome of a series of patients treated by SNS at our centre over a 5-year period. The relevance of these findings is discussed in the context of need for revision procedures more recent developments in the technique.

CHAPTER SEVEN

METHODS

Ethics and Informed Consent

All of the experiments performed in this thesis followed the approval of the study by the local ethics committee (Joint Ethics Committee of UCLH/ NHNN Trust and the Institute of Neurology). The permission of this committee is detailed in Appendix A.

Subjects were provided with information sheets (Appendix B) and invited to participate by signing the consent form (Appendix C). For subjects undergoing PET scanning, a further consent form was required (Appendix C). We performed our PET imaging experiments under an ARSAC licence (Administration of Radioactive Substances Advisory Committee).

Patients were recruited among those already known to the department, based on referral with urinary retention. Healthy volunteers were recruited through advertisements placed locally in the hospital. All subjects were reimbursed for their time and travel.

7.1 Urodynamic studies

We recruited 30 women (aged 19-52 years, mean 36years) with urinary retention attributed to sphincter overactivity, who were either undergoing test stimulation or had been implanted with a sacral nerve stimulator. After giving informed consent, they were enrolled into this arm of the study.

As part of the diagnostic work-up for such urinary retention, many of these patients had already undergone certain tests including cystometry, urethral pressure profilometry, urethral sphincter EMG and ultrasonic measurement of urethral sphincter volume.

The two patient groups were those undergoing a test stimulation (PNE) for a period of 3-7 days, and those undergoing implantation or already with a sacral nerve stimulator (IPG). After the baseline tests, they underwent neuromodulation, which was followed by the urodynamic tests as detailed below.

Sphincter EMG

A standard peri-urethral approach was employed, using 2mls 1% lignocaine and a concentric needle electrode, as described previously (Fowler and Kirby 1985). Recordings were made on a Dantec Counterpoint with gain set at 100μ/div. All EMG recordings were performed by a single operator (CJF), with the outcome being described as positive, negative or equivocal. This depended on the pattern of abnormalities as well as their quality/quantity.

Urethral Pressure Profile

The UPP was performed using an infusion technique with an 8Fr catheter being withdrawn at 2mm/s and saline being infused at 2ml/min. The patient was placed in an identical position for all studies (supine, with the knees bent), and the catheter was always orientated at 12 o'clock so that the fluid orifices were at 9 and 3 o'clock. Each patient had 3-5 measurements of the MUCP while being asked to relax their pelvic musculature, and this was repeated with the subject prompted to contract their pelvic muscles (as though performing a 'stop test'); the latter test was to simulate the activation of a sphincter-detrusor reflex which reduces the sensation of urgency when bladder is full.

Transvaginal ultrasound

This test was mainly carried out as part of the initial diagnostic work-up, to estimate the sphincter volume. With the patient in position for a vaginal examination, an ultrasound probe was used to measure the volume (BK-Cheetah 2003). The value was then used as part of the overall assessment of urethral sphincter function. Although this parameter was not compared with the post-neuromodulation value, its role in assessment of the sphincter was used in the MRI part of the study, as discussed below.

Cystometrogram

Cystometry was performed with the patient in the sitting position, using a 6Fr dual lumen bladder pressure line and a 4.5Fr rectal pressure line. The bladder was filled with room-temperature normal saline at 50ml/min, recording the subject's sensations of desire to void (first sensation of filling, normal and strong desire to void). Bladder

filling was discontinued when the patient described discomfort or fullness of the bladder.

The parameters noted in particular were the maximum cystometric capacity (MCC), maximum flow rate (Qmax) and detrusor pressure at maximal flow (PdetQmax). If the patient was unable to void, she was catheterised and this residual volume recorded.

Voiding diaries

A few patients undergoing implantation of the stimulator kept frequency-volume charts immediately after the initial activation of the stimulator. This provided information on how quickly voiding function was restored.

Statistical analysis

Paired t-test analysis was performed to compare MUCP before and after neuromodulation, using a significance level of 0.05.

7.2 Functional brain imaging

Data acquisition

The Joint Medical Ethics Committee of the National Hospital for Neurology & Neurosurgery and the Institute of Neurology approved the study, and the appropriate ARSAC licence was available. Eight healthy female volunteers (aged 40-62years) and eight female patients with an implanted sacral nerve stimulator (aged 39-52years) were recruited. All patients gave written informed consent.

The subjects were asked to fill their bladder by drinking water, and to report their subsequent sensations of fullness based on a validated sensation scale (Oliver, Fowler et al. 2003). The bladder volume was measured at different perceived levels of fullness by ultrasound scanning.

The subjects then underwent PET scanning, the two groups being healthy volunteers and patients with an implanted sacral nerve stimulator. All subjects had 12 PET scans with intervals of 8 minutes between successive scans. The bladder volume was measured by ultrasound just before each scan (Goode, Locher et al. 2000), and the subject asked to report their sensation of bladder fullness. PET scanning involved a standard oxygen-15 bolus technique (Siemens ECAT PET scanner). Images were pre-processed by registration, normalization and smoothing using a 12mm Gaussian kernel, and analysed using Statistical Parametric Mapping (SPM99b, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square).

Each healthy control underwent a 6-scan session with the bladder empty (having voided just before the session), and 6 scans with the bladder full (filled by drinking water rapidly, and reporting a sensation of urgency); the order of having either a full or empty bladder was counterbalanced. During the 12 scans, subjects were asked to contract their pelvic musculature for 6 scans (randomised across the 2 sessions), prompted just prior to start of the scan. Up to 3 contractions were performed, each lasting for 5-10 seconds, in the interval immediately following injection of bolus (ie just before maximal activity of the radiolabelled contrast).

Each patient with a stimulator had 6 scans with the IPG on and 6 with the IPG deactivated (switched off at least 3 days before this session to minimise carry-over effects of neuromodulation). For each of the 6 scans, 3 were with a full bladder and 3 with an empty bladder. The orders for stimulator activation/deactivation and bladder empty/full were counterbalanced. With the stimulator switched off, patients generally described a sensation of suprapubic discomfort or heaviness, rather than urgency, with an increase in bladder volume. As before, patients were prompted to contract their pelvic musculature for half of the scans, in a randomised order.

Data analysis

On a MATLAB framework, we used SPM-99 to analyse the PET data. SPM represents Statistical Parametric Mapping, and is the basis of this imaging technology. Rather simplistically one may consider this 'map' as a series of comparative statistical significance tests between voxels in different conditions. Each voxel is subjected to a standard statistical test, such as a t-test (giving rise to 'T contrasts'), and the resulting statistical parameters are assembled into an image, the SPM (Figure 7a). This can then

Figure 7a
Schematic summarising the transformation of imaging data into a statistical parametric map (adapted from Statistical Parametric Mapping, Friston K)

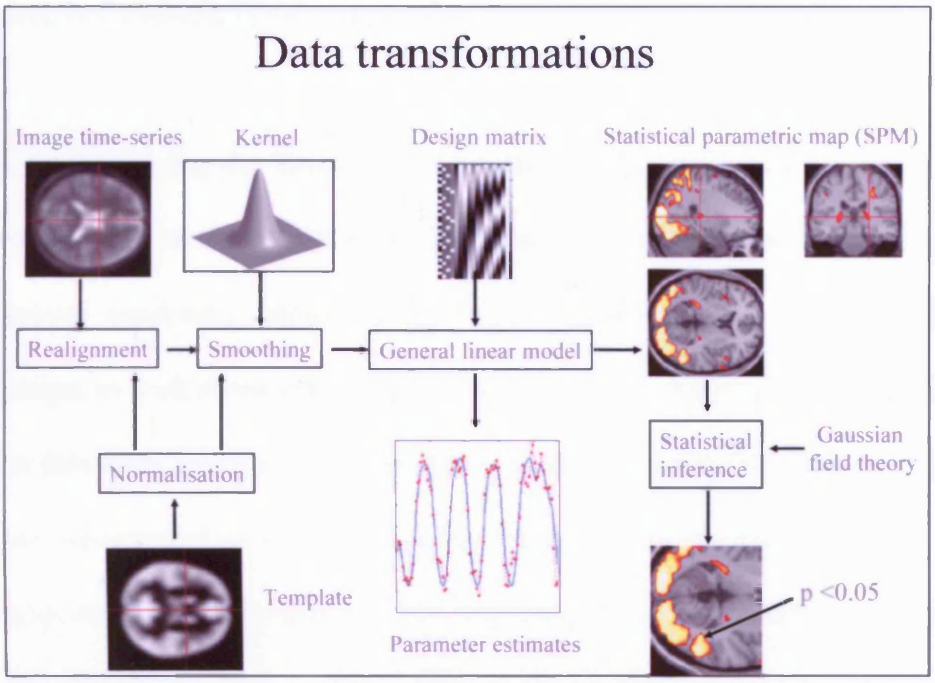
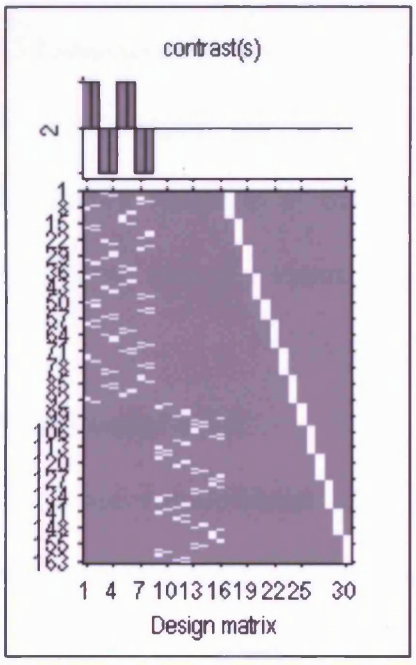


Figure 7b
Pictorial representation of a design matrix, for comparison of full versus empty bladder



be plotted in a standardised anatomical format (eg stereotactic space). Discussion of the basis for the statistics, namely the *General Linear Model* and *Gaussian Random Field* theory, is beyond the scope of this thesis, except to point out that these allow statistical analysis of continuous data sets as produced in images.

After processing the imaging data by registration, normalization and smoothing, the imaging data were entered into a 2x2 design matrix using t-contrasts (Figure 7b). The various conditions compared full versus empty bladder for the different subject groups, as well as the effects of pelvic contraction. After setting up the design matrix, the data were analysed with threshold corrected for $p<0.001$ and $p<0.05$. Images were then represented on a template MRI brain for pictorial representation. We noted the areas of greatest neuronal activity, recording the corresponding Talairach coordinates and identifiable brain centre. Other types of analysis include an effect of interest analysis, to help identify underlying trends, and interaction analysis to investigate effect of stimulation specifically.

7.3 Long-term review

We reviewed the case records of all patients implanted with a sacral nerve stimulator for urinary retention at our centre between 1996-2002. The length of follow-up, number and type of revision procedures, and complications were all noted.

7.4 Sphincter MRI

Ultrasonic measurement of sphincter volume is an ancillary investigation with inherent subjectivity in its estimation of possible sphincter hypertrophy; the greater

resolution and better reproducibility of magnetic resonance imaging was therefore assessed in a pilot feasibility study.

Four patients with retention and four age-matched controls were recruited for three-dimensional imaging of the urethral sphincter using MRI. The patients had been diagnosed with sphincter overactivity (abnormal EMG) causing their retention, and were scanned prior to neuromodulation. The control subjects had no urinary symptoms and in general good health.

All subjects underwent a pelvic MRI scan (1.5T, Siemens Magnetom Vision). The MR images were converted into the MGI format (MedPhys, UCL), enabling volumetric measurement by voxel summation and diameter measurement on reformatted cross-sectional images. Total sphincter volume and volume of the inner components (smooth muscle and lumen) were measured and that of the outer component (striated muscle) derived from their difference. The transverse outer and inner diameters were measured in two different axes (right-left, posterior-anterior) and at two different levels (proximal 1/3 and middle 1/3). The measurements were recorded by two investigators independently.

CHAPTER EIGHT

URODYNAMIC STUDY

A total of 30 women were recruited (aged 19-52 years, mean 36years); 21 had an IPG and 9 were undergoing PNE. Of these 21/30 agreed to have UPP performed before and after neuromodulation, and 25/30 had cystometry following successful restoration of voiding after neuromodulation. Furthermore 10/30 patients agreed to undergo EMG during stimulation.

8.1 Urethral pressure profiles

An example of a UPP produced is shown in Figure 8a, illustrating the repeated measurements used to calculate a mean value. Figure 8b shows the mean MUCP before and after neuromodulation for 21 patients (14 permanent stimulators and 7 temporary PNE), alongside the predicted MUCP estimation. The mean pre-neuromodulation MUCP was 92.9cmH_20, compared to a mean of 84.9 cmH_20 after stimulation; no significant difference was demonstrated ($p=0.06$, paired t-tests). Both values were higher than the mean expected MUCP of 70.3 cmH_20 for this population, as determined by the formula proposed by Edwards and Malvern (Expected MUCP = 92-age) (Edwards and Malvern 1974).

We also calculated the MUCP for patients who were instructed to contract their pelvic muscles during the UPP, before and after neuromodulation. Again no difference was demonstrated at the 0.05 significance level between the MUCP before (105.7 cmH_20) and after (97.3cmH_20) neuromodulation, with the pelvic muscles contracted. These values were higher than the respective measurements with the pelvic muscles relaxed,

Figure 8a: Example of UPP, with mean MUCP calculated from averaging the respective measurements.

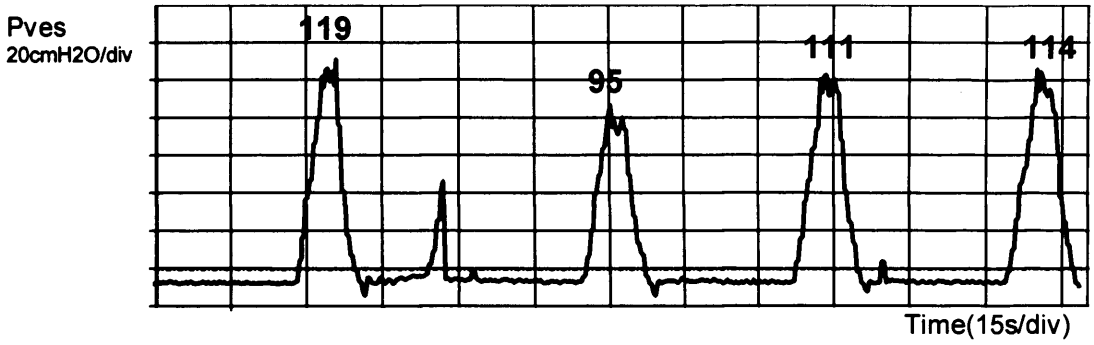
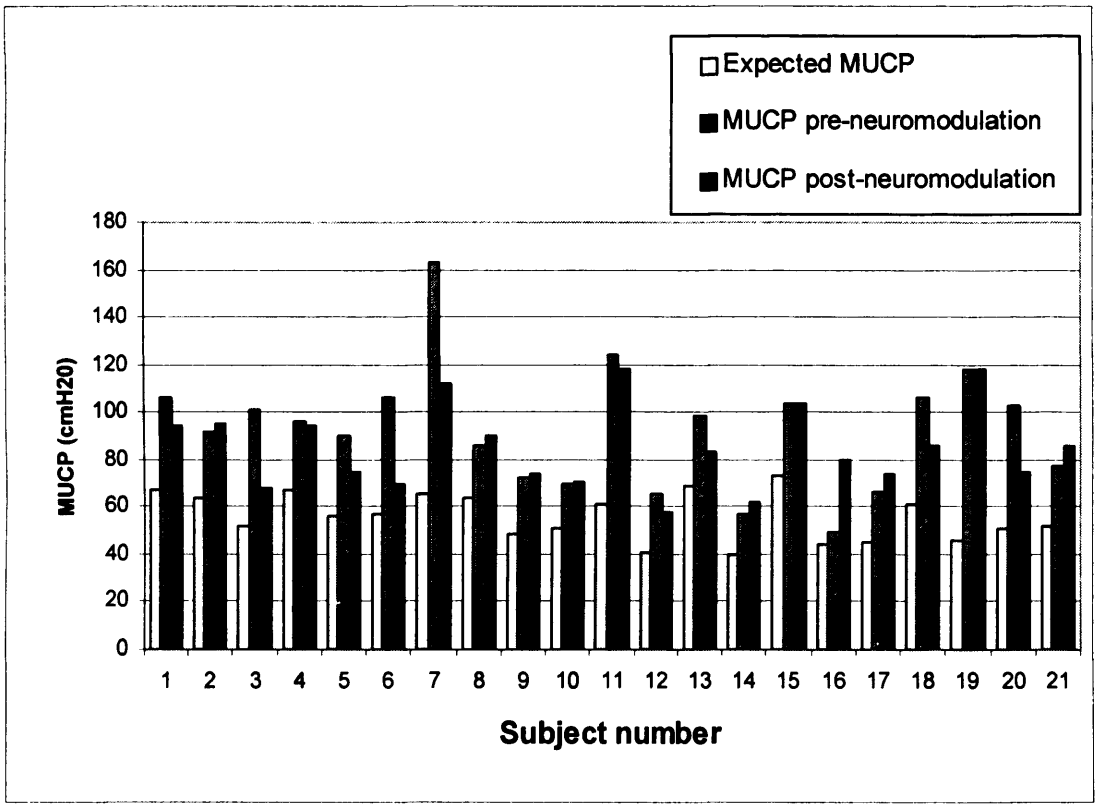


Figure 8b: Mean maximum urethral closure pressure for 21 patients (1-14 IPG, 15-21 PNE), showing expected value (92-age), MUCP before neuromodulation and MUCP after neuromodulation (with pelvic muscles relaxed).



and interestingly there was again a slight trend (but no significant change) towards a lower value following neuromodulation.

8.2 Cystometry

Of the 25 patients (IPG 19, PNE 6) who had a cystometrogram after neuromodulation, 19 had evaluable traces (the pressure lines fell out in 3 patients, and 3 were unable to pass urine with lines in-situ).

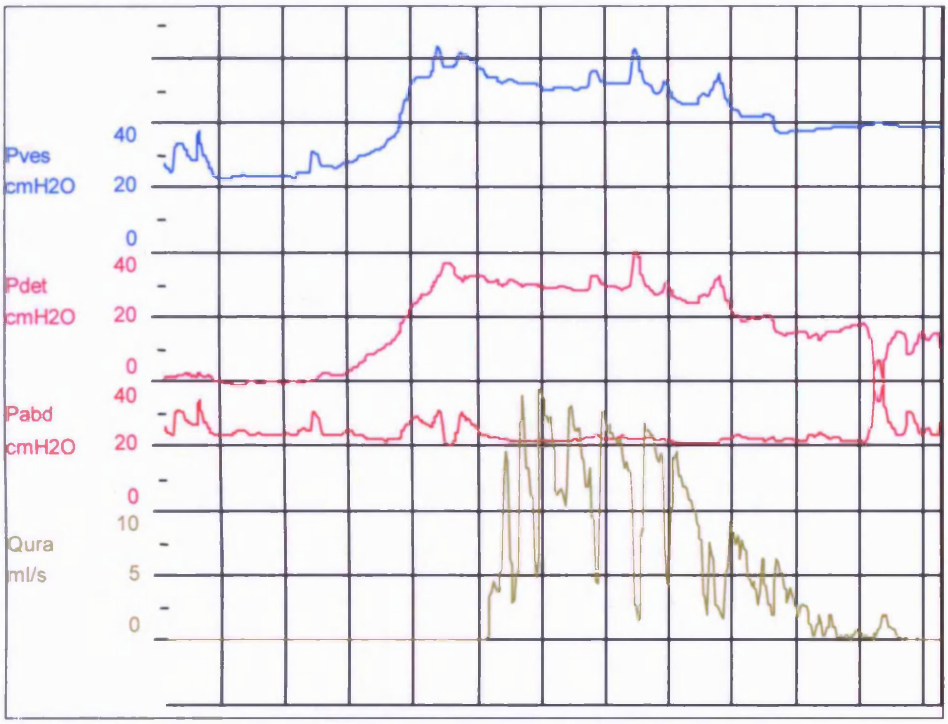
The flow pattern was variable, with most demonstrating an intermittent stream as exemplified by Figure 8c. This trace is a good example of how the detrusor pressure remains fairly constant although the stream is evidently intermittent. However other patients appear to void in different ways, as also shown in Figure 8c, such as the smoother 'normal' voiding pattern and the oscillating stream. The latter example seems to be related to the fluctuations of the detrusor pressure, which could be a reflection of the electrical stimulation frequency. However, this is difficult to prove, and is certainly not a uniform finding.

The mean MCC was 691mls (range 416-1349mls) and the mean volume voided was 433mls (range 170-809mls), and Table 8i is a chart of the individual voided and residual volumes.

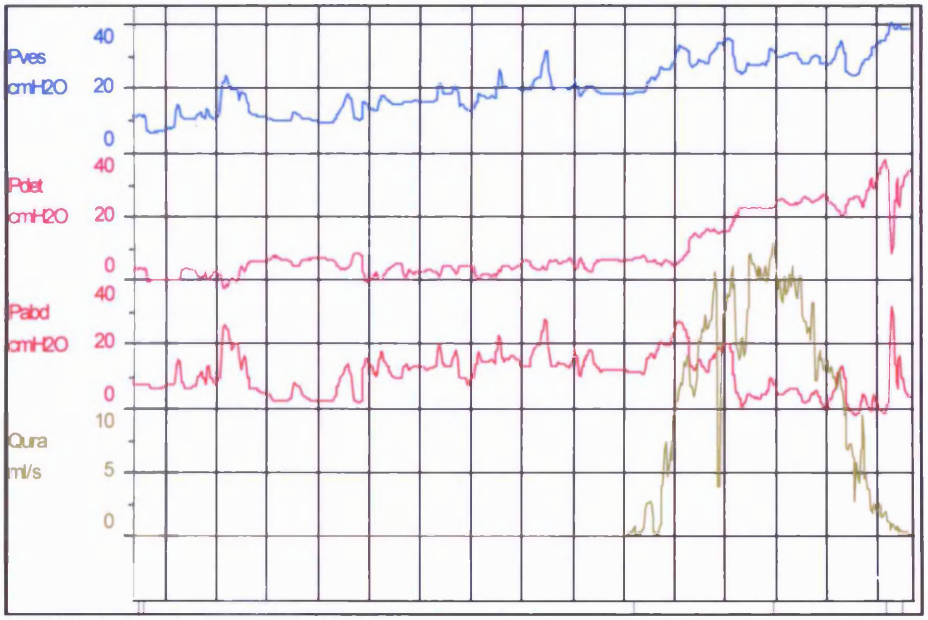
Figure 8d demonstrates the maximum flow rate plotted against the pressure at maximal flow. When the criteria for the various suggested female normograms are applied these results show that after neuromodulation the urinary flow is typically mildly obstructed. An alternative representation of this data, plotting detrusor pressure

Figure 8c: Example of flow patterns, as seen after restoration of voiding by neuromodulation.

Intermittent flow pattern



Flow pattern resembling 'normal' bell-shaped curve



An ‘oscillating’ pattern, reflecting the fluctuation of Pdet.

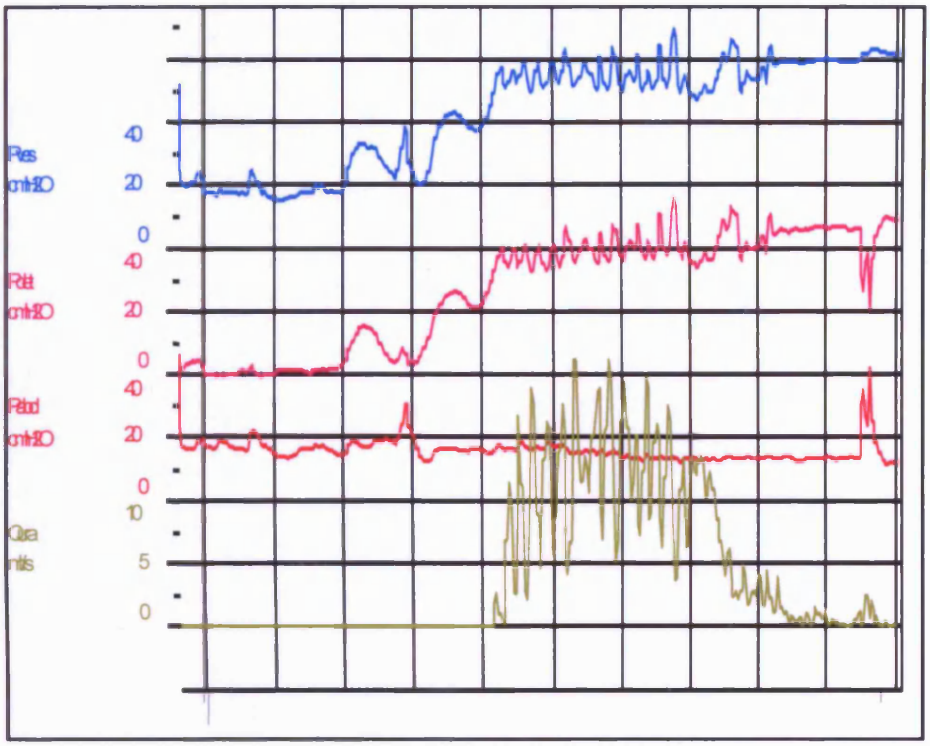


Table 8i

Patient	Vol voided	Residual
1	0	440
2	205	350
3	478	200
4	419	0
5	450	0
6	574	100
7	554	0
8	172	580
9	809	0
10	278	479
11	620	0
12	549	20
13	599	0
14	760	20
15	279	220
16	501	350
17	170	800
18	37	800
19	349	1000
20	409	60
21	466	0
22	593	330
23	252	620

Figure 8d Plot of flow rate versus detrusor pressure at maximal flow in patients who were able to void after neuromodulation; the majority fall within the criteria for obstructed flow.

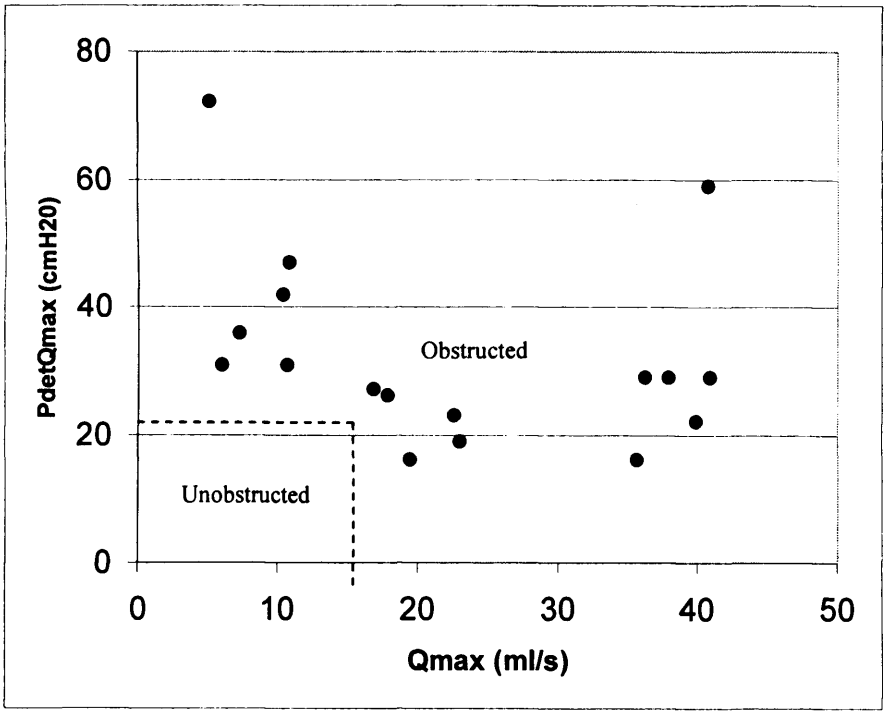


Figure 8e Plot of maximum flow during free void (without urethral pressure line in-situ) versus maximum detrusor pressure, in accordance with the measurements proposed by Blaivas et al. The dotted line demarcates patients with unobstructed voiding from those with mildly obstructed voiding.

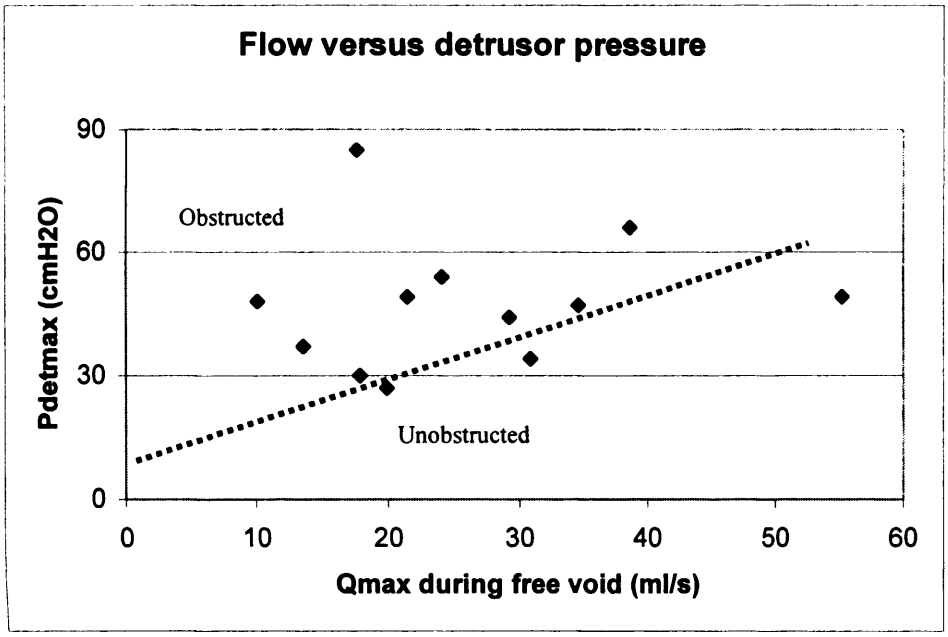


Table 8ii Parameters for bladder function representing different measures of bladder outflow obstruction ([1]derived from values described by Cormier et al, 2002); these are consistent with a picture of either obstructed (or equivocal) bladder emptying.

	Mean area under curve ($cmH_20.sec$)	*Mean area under curve/ voided volume* ($cmH_20.sec/ml$)	*Mean urethral resistance* ($cmH_20/(ml/sec)^2$)	*Mean PdetQmax* (cmH_20)
Patients post neuromodulation	2541.7	7.3	0.30	32.2
Normative [1]				
- unobstructed	627.0	1.6	0.12	21.8
- equivocal	1304.5	3.5	0.30	28.8
- obstructed	2510.7	8.2	1.50	37.7

at maximal flow versus *free flow rate* is illustrated in Figure 8e, again confirming that the majority of patients were voiding in a somewhat obstructed fashion.

Other parameters for bladder outflow obstruction are shown in Table 8ii. These values include the *area under the pressure-flow curve*, which has been proposed as a measure of the work done by the detrusor in order to void. While it does not correspond exactly to contractility, the recently described criteria for obstructed voiding may prove helpful in interpreting ambiguous pressure-flow results. The mean area under curve value of 2541.7cmH_20.sec in patients with voiding restored approximates to the value associated with obstructed voiding of 2510.7cmH_20.sec. Similarly, when this value is adjusted for voided volume it still approaches the obstructed voiding value of 8.2cmH_20.sec/ml. The other two parameters are slightly more equivocal, namely the estimation of urethral resistance and the mean detrusor pressure at maximal flow, though both are outside the range for unobstructed flow.

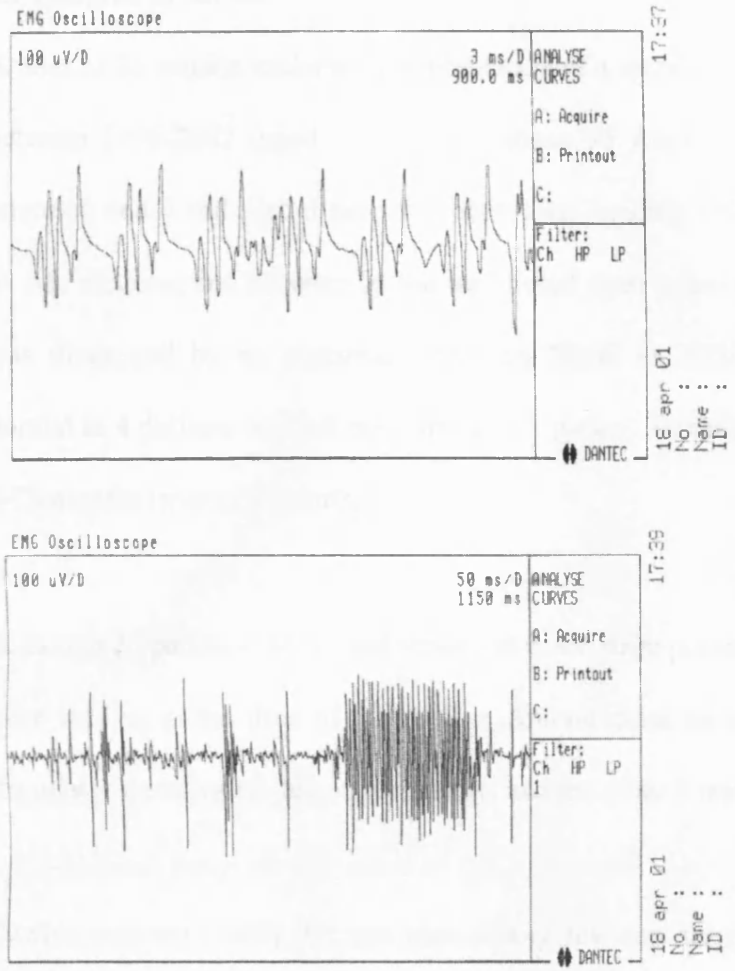
8.3 Electromyography

The characteristic features of complex repetitive discharges (CRD) and decelerating bursts (DB) described previously were identified in the patients undergoing sacral neuromodulation, as represented in Figure 8f. The identification of this abnormality is based on the recognition of these waveforms along with the typical sounds of 'helicopters' (CRDs) and 'whale noises' (DBs); the latter sounds arise from a volley of CRDs in which the terminal components fire at a steadily decreasing rate.

Ten patients with an abnormal sphincter EMG agreed to have the EMG when neuromodulation had restored ability to void. The abnormal signal was still present in

all cases, and unaffected by whether neuromodulation was switched on or off. Ideally, a quantification of the 'amount' of sphincter overactivity would have enabled a statistically valid comparison between states, but was not technically feasible.

Figure 8f Examples of EMG traces with complex repetitive discharges.



CHAPTER NINE

9.1 Long-term review

A total of 26 women underwent implantation of a sacral nerve stimulator at our centre between 1996-2002 (aged 22-52 years, mean 35 years), of whom 22 had complete retention and 4 had partial retention/obstructed voiding. Of these, 20 were performed by one surgeon, and all were by the traditional open technique. Sphincter overactivity was diagnosed by an abnormal sphincter EMG in 21/26 patients; the EMG was normal in 4 patients and not performed in 1 patient. Length of follow-up ranged from 2-73 months (mean 37 months).

Although 25 patients (96%) had voided at some stage post-operatively, only 20 (77%) were voiding at the time of the review. Among those no longer voiding, 2 had their stimulator deactivated due to pregnancy, and the other 3 reported loss of efficacy.

Twelve patients (46%) did not require any revision surgery, but the remaining 14 women (54%) had a total of 21 revision procedures as shown in the table below. The commonest problem was loss of efficacy which developed from 2 weeks to over a year post-operatively. Another previously reported side-effect was pain, either related to the site of the box or due to ipsilateral leg pain. Box discomfort was more commonly noted with the buttock position (4/9 patients) rather than the abdominal position (2/17 patients) in our series. The leg pain resembled sciatica, and required repositioning of the electrode if not controlled well with analgesia.

Of those patients with complete retention in whom voiding was restored, the mean maximum flow rate was 20.8ml/s (6.2-50.8ml/s), voided volume 385mls (96-901mls)

and post-void residual 75mls (0-479mls). The flow pattern ranged from a normal smooth flow curve to an interrupted stream.

Complication	*Number of episodes*
Loss of efficacy	7
Pain/discomfort (box)	6
Pain (leg)	6
Bowel disturbance	2
Infected implant	2
Lead migration	1

9.2 Sphincter MRI

A total of 4 retention patients (aged 23-41 years, mean 34 years) and 4 age-matched controls (aged 24-40 years, mean 34 years) were recruited. Figure 9a illustrates the images obtained by MRI scanning, for reconstruction into 3D format, and figure 9b shows the actual measurements taken. The table below includes the measurements of the outer and inner muscle volumes for the patients according to the two observers, and their comparison with the control measurements. While the sample size was too small to make any meaningful statistical comparison, all 4 patients had greater sphincter volumes than their age-matched controls, and results were broadly similar for both observers.

Sphincter volume (cm^3)		Patient 1	Patient 2	Patient 3	Patient 4
Outer Volume	Observer 1	**2.0**	**2.9**	**1.6**	**2.0**
(striated muscle)	Observer 2	**2.4**	**3.2**	**2.5**	**2.2**
Inner Volume	Observer 1	**1.8**	**2.4**	**1.8**	**2.1**
(smooth muscle)	Observer 2	**2.0**	**2.7**	**1.6**	**2.0**
Total volume	Observer 1	**3.8**	**5.3**	**3.4**	**4.1**
	Observer 2	**4.4**	**5.9**	**4.1**	**4.0**
Controls		Control 1	Control 2	Control 3	Control 4
		2.9	**2.5**	**3.3**	**2.3**

Figure 9a MRI images of the urethral sphincter in sagittal, transverse and coronal sections, subsequently converted into 3D format.

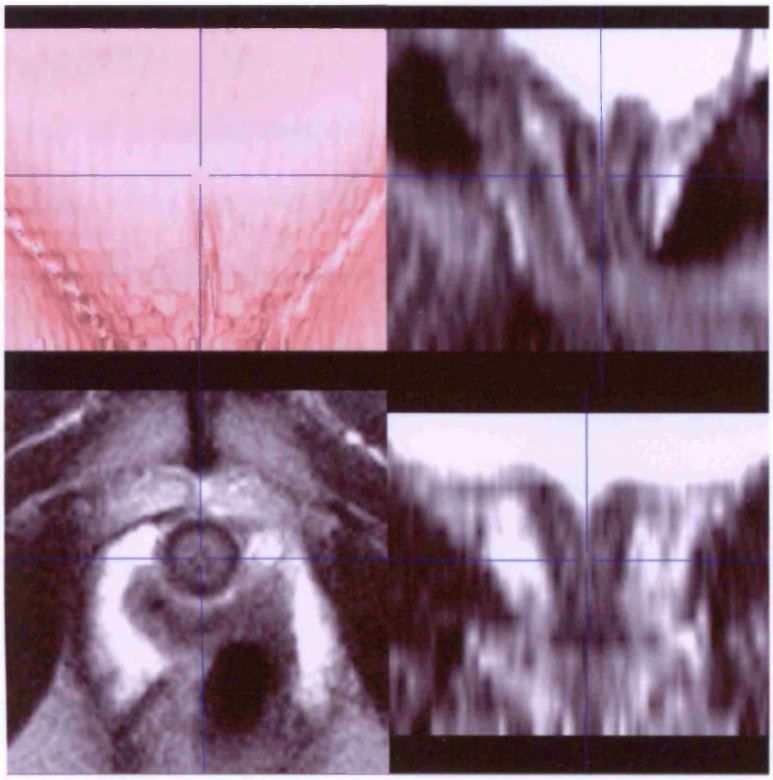
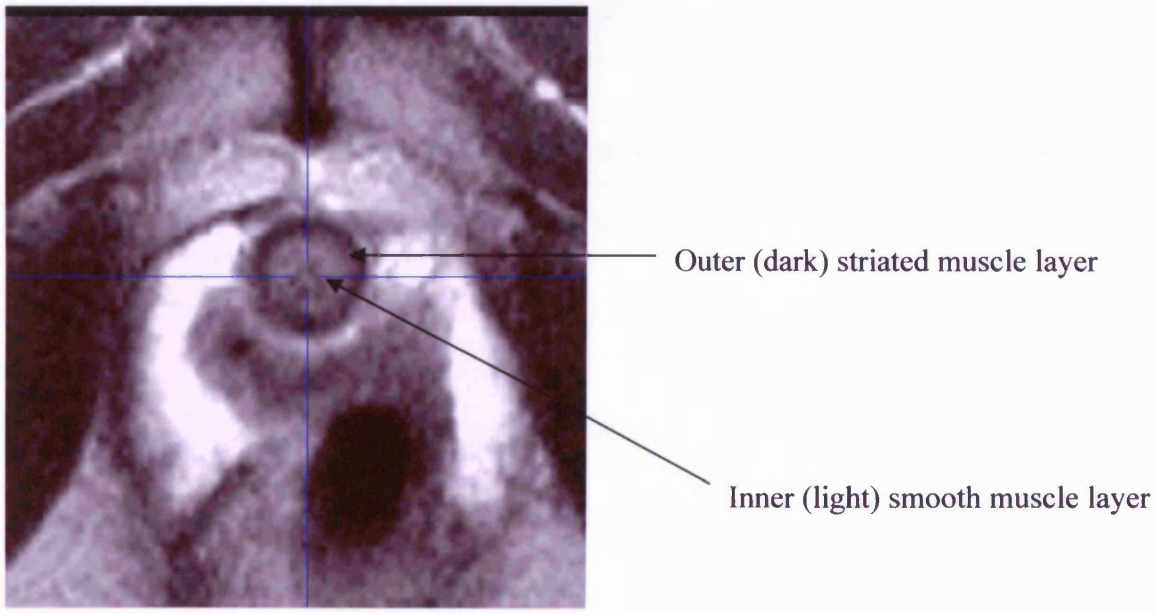


Figure 9b Example of measurements made from transverse sections of the sphincter



CHAPTER TEN

FUNCTIONAL BRAIN IMAGING

10.1 Healthy controls

A total of 8 healthy controls with no history of urinary problems underwent PET scanning. No adverse effects of radioisotope injection were reported, and all the controls completed all sessions, which were counterbalanced as described.

The design matrix for the healthy controls aimed to demonstrate any differences in brain activity between the states of a healthy and full bladder in these subjects. A second issue was of determining whether pelvic floor contraction had any effects on brain activity.

Having a full bladder was associated with enhanced activity in brainstem regions (at the junction of pons and medulla) and in the midbrain (adjacent to but slightly anterior to the periaqueductal grey, PAG). Cortical centres activated during a full bladder state included anterior and posterior regions of the cingulate cortex. These are shown in Figures 10a and 10b.

Conversely, areas activated with an empty (as opposed to full) bladder are shown in Figure 10c. These are therefore areas that are *deactivated* in healthy controls with a full bladder, namely the pons and frontal cortex.

The sensation of urge was clearly distinguished between these bladder states using the scoring system for desire to void, as shown in Figure 10d, whereby the empty bladder generally correlated with a score of 0-1, and a full bladder with a score of 3-4.

Sub-analysis of scans during which subjects contracted their pelvic floor failed to identify any central effects of this action. This was the same whether the bladder was empty or full.

10.2 Retention patients

Of the 8 patients recruited, 2 were excluded from the analysis as they did not complete all the scanning sessions: one suffered a relapse of polymyalgia rheumatica during the study, and another underwent admission to hospital for surgery during this time. The remaining 6 all completed the sessions as planned, enabling SPM analysis as above.

Stimulator off

This served as the baseline retention condition, and group analysis found the patients to have activity in the cingulate cortex, hypothalamus and cerebellum with a full compared to an empty bladder (Figure 10e). The region of cingulate activity was slightly posterior to previous studies. There was no brainstem activity, unlike the control subjects.

Stimulator on

When the stimulator was activated, the full bladder state was associated with an increase in activity in the brainstem, mainly in the midbrain, similar to healthy controls (Figure 10f), but no activation of the cingulate cortex. The effect of activating the stimulator was specifically addressed by an interaction analysis, comparing stimulator on and off in the patient group, with the bladder full. This confirmed activation in the midbrain and also cerebellum (Figure 10g).

The midbrain was further examined in the Effects of Interest analysis demonstrated in Figure 10h. This shows the relative *extent* of activation of the midbrain, based on the region activated by the stimulator with the bladder full. The first 8 scans are those with the stimulator switched off, and the second 8 with the stimulator on. The scans are paired into full or empty conditions. The height of the bars in the bar chart reflects the 'size of the (activation) effect', and therefore the difference between the full and empty states is an indication of the difference in degree of activation of the midbrain for these states. As seen in Fig 10h, this difference is exaggerated when the stimulator is switched on (for example, the difference between scans 9-10 and 11-12 is far greater than between 1-2 and 3-4). This may represent the midbrain being a better discriminator of bladder fullness when the stimulator is activated in retention patients.

Figure 10a

Brain activation in healthy female volunteers with a full bladder (compared to empty bladder) ($p<0.001$, uncorrected height threshold)

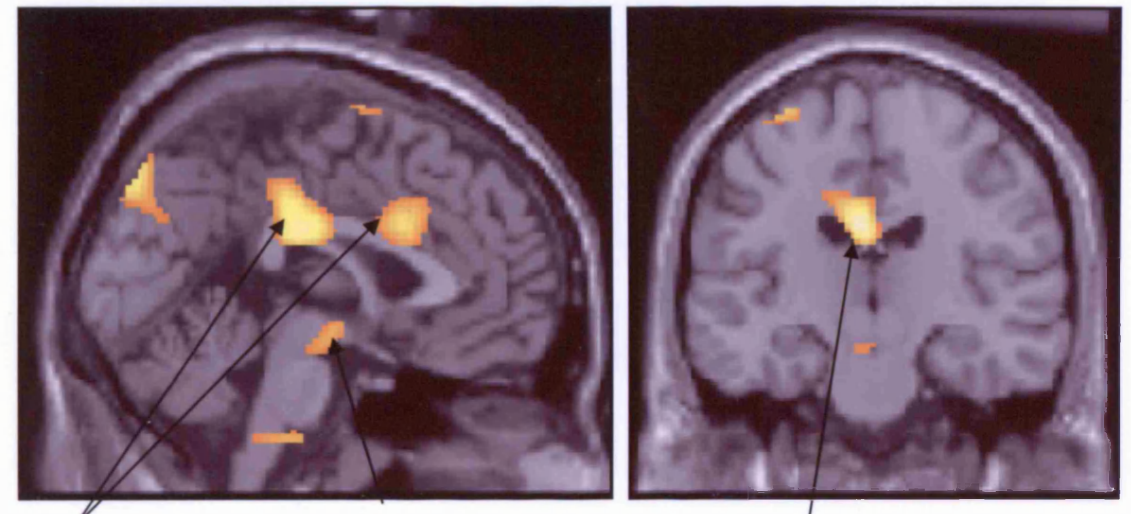


Figure 10b

Brain activation in healthy female volunteers with a full bladder (compared to empty bladder) ($p<0.05$, corrected height threshold)

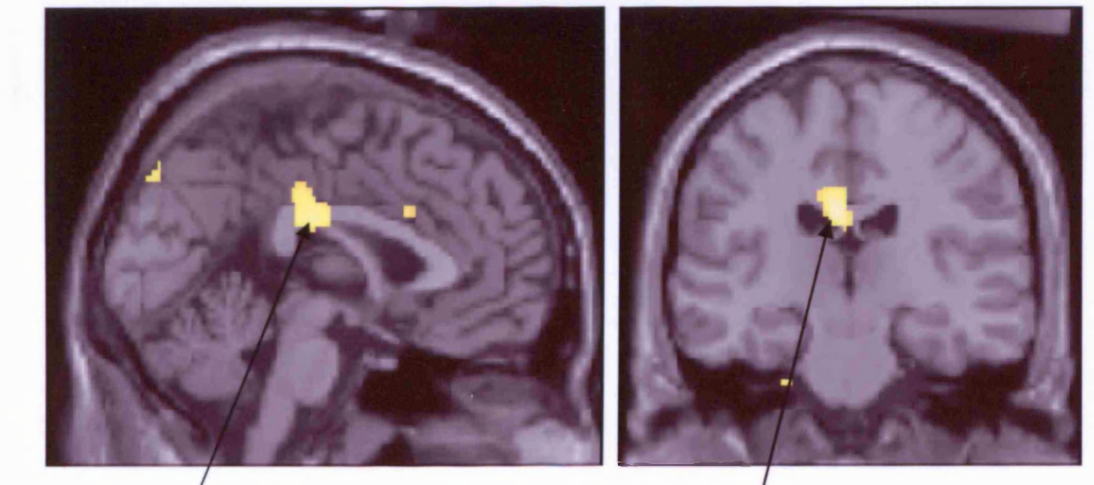


Figure 10c Areas deactivated in healthy females with a full bladder

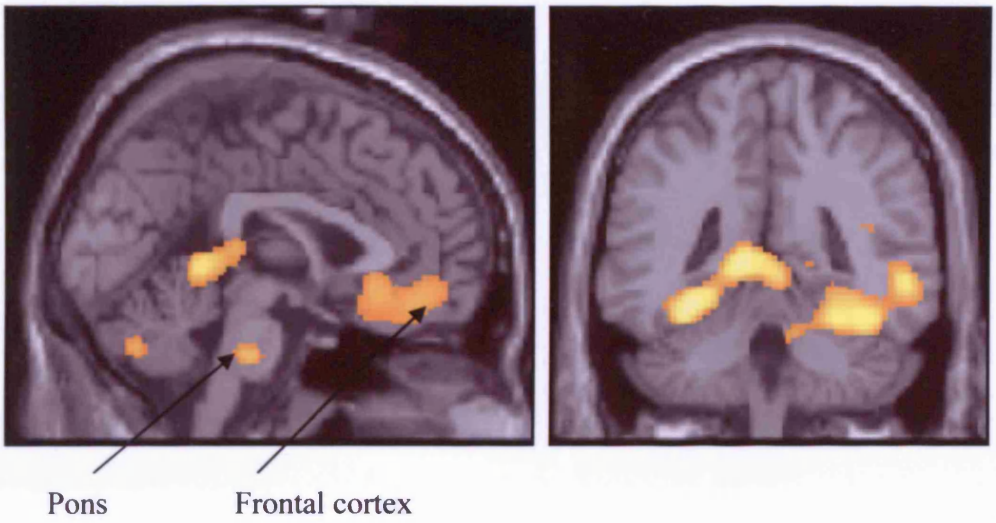


Figure 10d Urge sensation (0-4) versus bladder volume

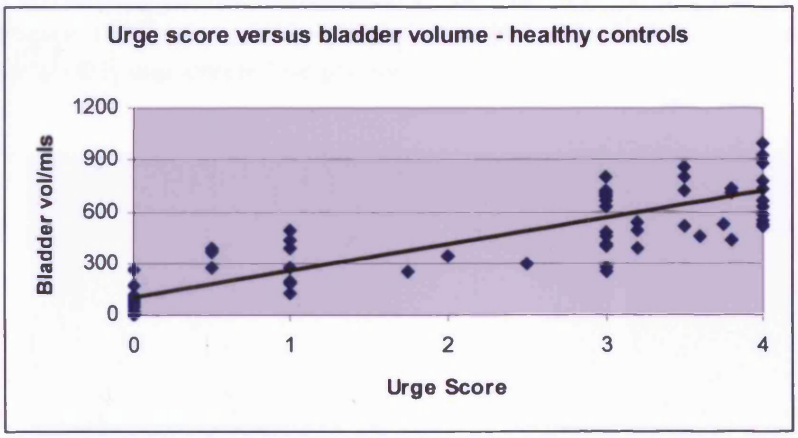


Figure 10e Brain activation in women with Fowler's Syndrome at baseline (with stimulator off) ($p<0.001$, uncorrected height threshold)

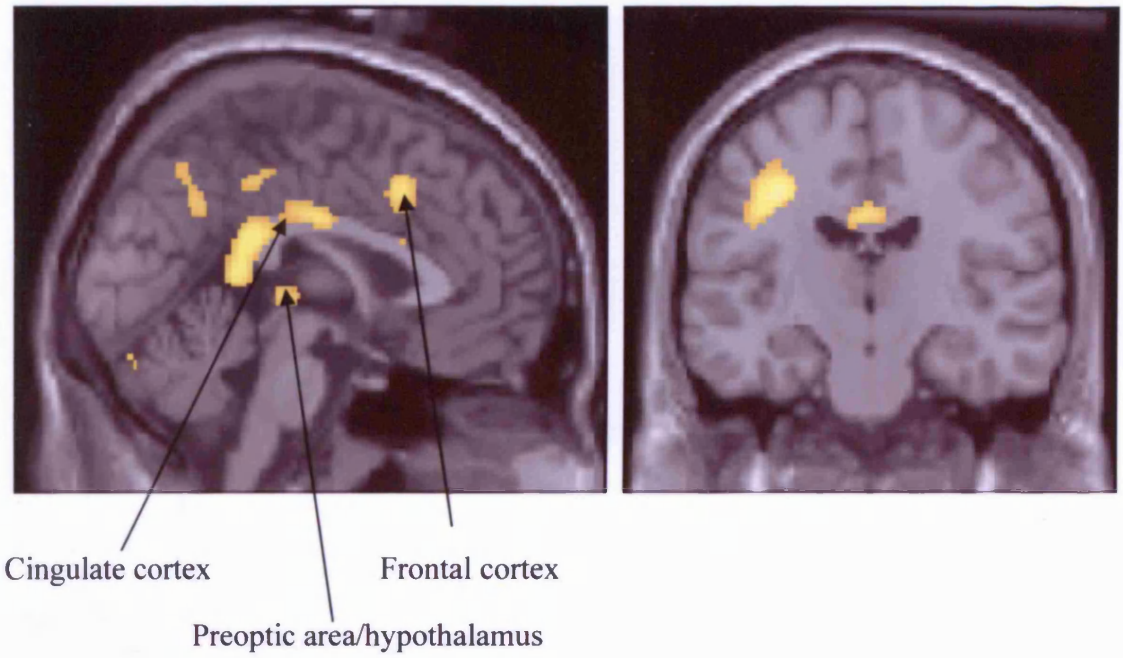


Figure 10f Brain activity in women with Fowler's Syndrome and stimulator activated ($p<0.001$, uncorrected height threshold).

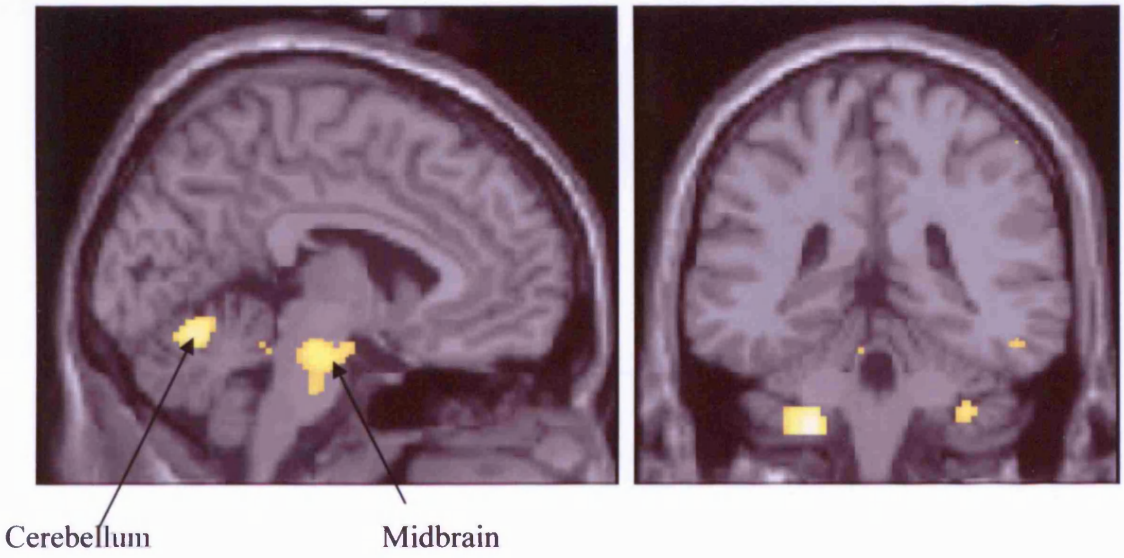


Figure 10g
Interaction analysis to assess specifically the effect of stimulation, by comparison of scans with stimulator on versus off (with the bladder full) in retention patients

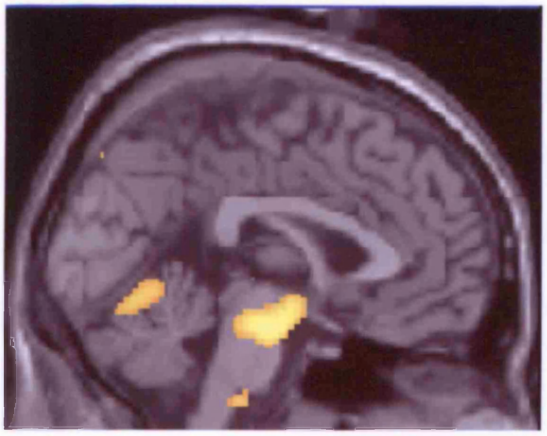
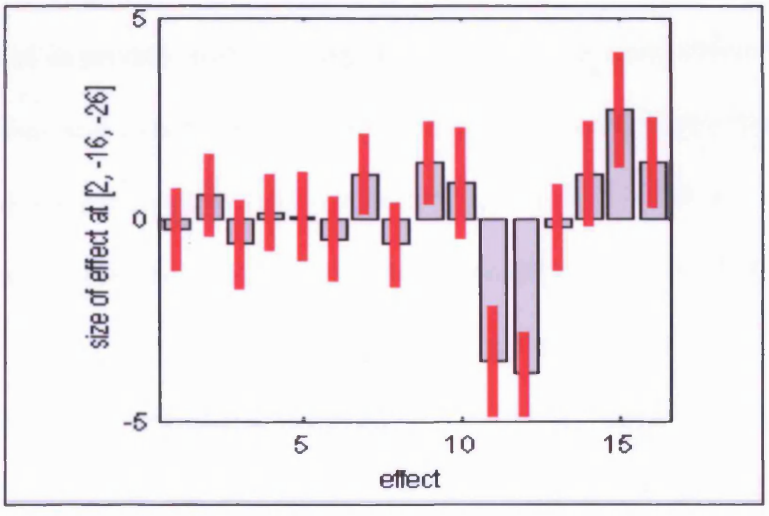


Figure 10h
Effects of interest analysis, illustrating the discriminatory potential of the midbrain with the stimulator activated.

Scans 1-8 Stimulator off; Scans 9-16 Stimulator on
Bladder Full (Scans 1-2, 7-8, 9-10, 15-16)
Bladder Empty (Scans 3-4, 5-6, 11-12, 13-14)



CHAPTER ELEVEN

BLADDER OUTLET OBSTRUCTION

11.1 Causes

There are numerous causes of acute and chronic urinary retention in women, as listed in the Table below; though not exhaustive, this covers the majority of aetiologies for retention. The neurological diseases include cerebrovascular disease, Parkinson's disease, multiple sclerosis, spinal cord injury, neoplasia, Guillain-Barré syndrome, and autonomic neuropathy.

The prevalence of reported bladder outlet obstruction in women is far lower than in men, though estimated figures range from 2%-29% (Blaivas and Groutz 2000). There are several possible reasons for under-diagnosis of this condition in women. They complain of irritative symptoms (frequency, urgency, urge incontinence) and recurrent urinary tract infections (UTI) rather than classically obstructive symptoms (hesitancy, poor stream, straining to void) (Massey and Abrams 1988). Also, women void in private, with less opportunity for direct comparison with others, unlike men (Bass and Leach 1991). In the case of functional obstruction, a more sophisticated understanding of voiding dysfunction is required (Patel and Nitti 2001). And finally, there are no standardised urodynamic criteria for outlet obstruction in women, unlike in men. The clinical significance of recognising the condition is to improve symptoms as well as preventing recurrence of UTIs and their associated long-term sequelae. Furthermore, correct diagnosis can help patients avoid being mislabelled as having a psychological disease (Fowler 2003).

The anatomical causes for bladder outlet obstruction (eg pelvic organ prolapse or anti-incontinence surgery) and neurological causes (eg detrusor-sphincter dyssynergia) will not be discussed further. Instead we will focus on functional obstruction. In the absence of neurological disease, inappropriate sphincter activity during voiding results in functional outlet obstruction, or 'non-neurogenic neurogenic bladder' (sometimes referred to as Hinman's Syndrome). This is proposed to be a learned behavioural disturbance, and therefore is suitable for 'unlearning' or re-education by feedback therapies (Hinman 1986). This type of dysfunctional voiding was described in children and adolescents who presented with enuresis and recurrent UTIs.

A constellation of symptoms including frequency, urgency, dysuria and suprapubic discomfort has been called the 'urethral syndrome'. There are numerous theories regarding its underlying pathophysiology, such as chronic inflammation of the paraurethral glands, strictures at the external urethral meatus, collagen deposition in the distal urethra. Despite the controversial nature of the condition, a significant number of urologists continue to believe in an associated obstruction at the bladder outlet and continue to perform urethral recalibration or dilatation in this group (Lemack, Foster et al. 1999). There is no clear evidence of the efficacy of this treatment in this group, though the subjective improvement in symptoms, albeit short-lived, is held by some as justification of its practice.

Fowler's Syndrome

A unique cause for retention was reported by Fowler et al (Fowler, Christmas et al. 1988), who described an abnormality of the urethral sphincter EMG, leading to a conclusion that the sphincter was over-contracted. Although the prevalence of this

particular type of EMG activity has been estimated as 8-10% in the general population, its expression as urinary retention is far less common (Jensen and Stien 1996) (FitzGerald, Blazek et al. 2000). A study of asymptomatic female volunteers identified the presence of decelerating bursts and complex repetitive discharges in the urethral sphincter of young women with normal bladder emptying, and a possible relationship to the menstrual cycle (Kujawa, Reid et al. 2001). Raz and Smith had previously described an 'external sphincter spasticity syndrome' in women, with complete or partial urinary retention and elevated urethral closure pressures (Raz and Smith 1976). They also described the limited benefit of urethral dilatation in their patient series. An earlier report by Tanagho et al had found a group of children with recurrent UTIs to have high urethral pressure profiles secondary to external sphincter spasticity (Tanagho, Miller et al. 1971). There may be overlap between the types of functional overactivity of the sphincter described in these reports and that outlined by Fowler.

Pathophysiology

The underlying sphincter overactivity in Fowler's syndrome has been attributed to muscle-to-muscle transmission of electrical activity. This is based on single-fibre EMG analysis which shows that when the complex repetitive discharges are firing steadily, the low jitter of component potentials is explained by direct muscle-to-muscle 'ephaptic' transmission, resulting in a continuous state of contraction of the sphincter. Muscle hyperactivity can be classified according to whether the hyperactivity originates in the muscle fibre (or motor end-plate), in the axon, or in the motoneuronal cell body, each with a distinct EMG pattern (Valls-Sole and Montero 2004).

It is postulated that the predisposition to ephaptic transmission is a hyperexcitable state, as seen in neurological 'channelopathies'. A channelopathy refers to a defect in either a ligand- or voltage-gated ion channel. Voltage-gated channelopathies can be further subdivided into skeletal muscle disorders and central nervous system disorders. Examples of the former are periodic paralyses (eg paramyotonia) and myotonia. These conditions are characterised by repetitive discharges due to changes in membrane stability. However, whether this is applicable to the female urethral sphincter remains to be proved.

Finally, recent work has identified the presence of neuronal nitric oxide synthase (nNOS) in the urethral striated sphincter (Ho, Borja et al. 2003). The role of nitric oxide in normal sphincter function, and during disease, is being explored, which may in turn lead to effective therapies.

11.2 Assessment

The clinical history given by the patient is an important part of the assessment. Patients report a lack of normal sensation of bladder filling until a late stage, when they experience discomfort or heaviness due to a very full bladder; they are then unable to void at all or to empty completely. The co-occurrence of polycystic ovaries has been noted but not fully explained yet (Swinn, Wiseman et al. 2002). Another feature is that of there being difficulty withdrawing a catheter, possibly due to tightening of the spastic sphincter around it (Fowler 2003); interestingly Raz and Smith described a similar phenomenon in their earlier paper, whereby removal of urethral catheter had proved difficult (Raz and Smith 1976).

Sphincter EMG

The central investigation in the diagnosis of the condition is the sphincter EMG, with a characteristic pattern described in the Introduction. Interpretation of this neurophysiological investigation requires considerable experience because of the nature of sphincter muscle, which tends to fire continuously unlike the pattern seen in skeletal muscle. Techniques such as asking the patient to perform a Valsalva manoeuvre or to cough can help to 'quieten' the voluntary activity, and thereby unmask any underlying spontaneous sphincteric activity. Some advocate a simultaneous EMG recording during voiding, though in practice this remains technically difficult. A hook electrode may minimise the chance of displacing the recording EMG signal, but the very presence of the probe makes micturition more artificial than the natural state. Also, the lack of quantification of the EMG signal makes it difficult to establish clear diagnostic guidelines, and perpetuates the subjective nature of this test. Nevertheless, without further technological advances in this field, the current recording technique serves its purposes at identifying abnormalities of the sphincter.

Our observations have shown that the EMG abnormality is unaffected by neuromodulation, which therefore does not appear to have a direct relaxant effect on the sphincter. This appears to be corroborated by the urodynamic findings discussed below, as well as the clinical finding of restored voiding with an obstructed flow pattern.

MRI sphincter

The work of Wiseman et al (Wiseman, Swinn et al. 2002) has demonstrated the role of transvaginal ultrasound estimation of sphincter volume as an ancillary investigation. Although ultrasound confers certain advantages, such as being low cost, free of radiation risk, and easy to apply, there are also limitations with regard to resolution, reproducibility and type of ultrasound used. Different sonographic techniques have been described for imaging the female urethral sphincter, including transvaginal (Quinn, Beynon et al. 1988) (Khullar, Salvatore et al. 1994) (Kondo, Homma et al. 2001) (Umek, Obermair et al. 2001), perineal (Koelbl, Bernaschek et al. 1988), intraurethral (Kirschner-Hermanns, Klein et al. 1994) (Frauscher, Helweg et al. 1998) (Schaer, Schmid et al. 1998), and transrectal (Richmond and Sutherst 1989) (Kuo, Chang et al. 1994) approaches. But the possibility of distortion of lower urinary tract anatomy by an intravaginal probe should be considered, as suggested by Wise et al (Wise, Burton et al. 1992).

We investigated the feasibility of using MRI to estimate sphincter volume in order to improve accuracy of measurement. The role of MRI in imaging the urethral sphincter is well documented (Hricak, Secaf et al. 1991) (Klutke, Golomb et al. 1990). The higher resolution of this modality enables distinction between discrete tissue types, and as in our study, this is usually most easily seen in the T2-weighted images.

Histology of the female urethra reveals the lumen to be surrounded by an inner layer of longitudinal and thin circular fibres, and an outer layer of striated muscle. Our images confirm the circumferential surroundings of the urethra, with the dark lumen encircled by a bright layer (incorporating submucosa and smooth muscle) and then an

outer dark layer of striated muscle. In our limited study of 4 patients and 4 age-matched controls, we illustrate the use of MRI to estimate sphincter volumes. Furthermore these results indicate a relative sphincter hypertrophy in retention patients consistent with earlier findings. Of course, further measurements are needed in a far larger cohort in order to validate these results.

Urodynamic criteria

The lack of standardised urodynamic criteria for female bladder outlet obstruction has been briefly mentioned above. Various different criteria have been described.

Massey & Abrams suggested that two of the following 4 conditions needed to be met for a diagnosis of bladder outflow obstruction: Qmax<12ml/s, urethral resistance>0.2cmH_20/ml/s^2, PdetQmax>50cmH_20, and no significant post-void residual (Massey and Abrams 1988). Farrar el al proposed a cut-off of Qmax<15ml/s and Pdetmax>50cmH_20 (Farrar, Osborne et al. 1975), while Salvatore et al's values were Qmax<15ml/s and Pdetmax>60cmH_20 (Salvatore, Khullar et al. 2000). Chassagne et al studied a group of 35 clinically obstructed women (and 124 controls), concluding that thresholds of Qmax<15ml/s and PdetQmax>20cmH_20 had the highest sensitivity and specificity for predicting obstruction (Chassagne, Bernier et al. 1998). Cut-off values of Qmax<11ml/s and PdetQmax>21 cmH_20 were suggested by Lemack and Zimmern on the basis of their urodynamic study of 87 women with obstructive symptoms and 124 controls (Lemack and Zimmern 2000).

Blaivas and Groutz have recently proposed a normogram for women based on free Qmax (no effect of intraurethral catheter) and Pdetmax (rather than PdetQmax,

producing a figure even in cases where the patient cannot produce a flow) (Blaivas and Groutz 2000). Patients with Pdetmax>57cmH_20 were classified as being either moderately or severely obstructed; if the Pdetmax<57cmH_20, then the classification is either mildly obstructed or unobstructed depending on the value of Qmax. According to these criteria, most of our patients tend to fall within the "mildly obstructed" range following neuromodulation. However, one criticism of this normogram is that the two parameters are based on two independent voids.

The importance of videourodynamics in the assessment of female bladder outlet obstruction has been highlighted (Nitti, Tu et al. 1999) (Blaivas, Flisser et al. 2004). Along with the cystometric data acquired, these authors point out that the video helps identify the site of obstruction as well as excluding other potential causes for retention. Incorporating videourodynamic studies would strengthen future studies of Fowler's syndrome. Alternatively, the use of EMG during the voiding phase of pressure-flow studies could confirm the presence of sphincter overactivity when voiding is restored.

At first it may be somewhat surprising that cystometry does not show a particularly high detrusor pressure despite evidence of obstructive voiding. One might expect the PdetQmax to be higher generally to overcome the elevated urethral pressure. However, it is possible that the generation of even a limited detrusor pressure rise represents a sufficient contraction in patients with no previous detrusor contraction, enough to enable micturition. Nitti et al pointed out that many women are able to void with low detrusor pressures (less than 10-15 cmH_20) and achieve bladder emptying with normal urinary flow rates, and that even a mild degree of urethral resistance can

prevent voiding (Nitti, Tu et al. 1999). Hence for this functional obstruction, a modest increase in detrusor pressure may be adequate to overcome the urethral resistance, particularly in this group of patients whose baseline detrusor pressures are very low. The proposed mechanism for this is through modulation of presumed urethral afferent activity.

Another concept that has gained attention recently is that of "work done" by the detrusor, based on cystometric findings, calculating the area under the pressure-flow curve (Cormier, Ferchaud et al. 2002) or other measurements of bladder contractility (Kranse and van Mastrigt 2002). The area under the pressure-flow curve develops the parameter defined as 'bladder work' by Abrams et al, which was calculated as vesical pressure x volume voided (Abrams, Skidmore et al. 1977), and Cormier et al draw a parallel with the estimation of respiratory effort from the area under the curve of respiratory contraction. Their study categorized 85 women with lower urinary tract symptoms as being obstructed, unobstructed or equivocal; they proposed a table of quantifiable parameters and ranges for each group (including area under the curve). The area under the curve adjusted for voided volume may represent the voiding efficiency. Our estimation of the area under the curve suggests that although neuromodulation restores voiding, extra work has to be done by the detrusor to overcome the outlet resistance.

Kranse and Mastrigt also highlight the importance of accounting for bladder contractility in assessing female bladder outflow obstruction (Kranse and van Mastrigt 2002). They attempted to incorporate the post-void residual, which is of clinical relevance, into this assessment, and comment on relating the measurement of outflow

resistance to bladder contractility rather than simply using an absolute measure of outlet resistance. By including the post-void residual in the assessment, this approach may have an advantage over methods which measure urodynamic parameters without necessarily correlating with the clinical picture.

Urethral pressure profiles

The terms *urethral pressure* and *urethral closure pressure* are aimed at reflecting the pressure required to maintain continence. Griffiths defined urethral pressure as "fluid pressure needed to just open a closed (collapsed) tube" (Griffiths 1985). The urethral closure pressure is the difference between the intravesical and the urethral pressure.

The main application of measuring urethral pressures has been in the setting of stress urinary incontinence. In 1923 Bonney found that the crude measure of bladder pressure exceeded intraurethral pressure in women suffering from incontinence (Bonney 1923). Brown and Wickham described the UPP being measured by a catheter-mounted pressure transducer recording the urethral pressure along the length of the urethra, as the catheter was slowly withdrawn (Brown and Wickham 1969). Others have since adapted the technique further (Asmussen and Ulmsten 1976) (Hilton and Stanton 1983). The three main methods available are by perfusion (based on the fluid pressure require to just 'hold open' the urethra), catheter-mounted microtransducer, or a balloon attached to an external transducer.

However, these techniques are all subject to different artefacts. For example it is known that the pressure recorded is greater if the transducer faces anteriorly compared

to posteriorly, and therefore side-holes and transducers are generally placed at the 3 and 9 o'clock positions. Also, error can be reduced by using catheters with more side-holes and not particularly stiff. Balloon techniques avoid any orientational dependence, though in the past distension of the urethra led to over-estimation of the true pressure. The urethral pressure also depends on the position of the patient, and uniformity of recording position is essential. As a result of this variability, there are no standardized values that serve as a cut-off threshold for normality, as demonstrated in the table by Lose (Lose 2001). We have taken care to use exactly the same technique for all values, and the same as that used in the previous description by Wiseman et al (Wiseman, Swinn et al. 2002).

The MUCP is typically elevated in women with idiopathic retention (Wiseman, Swinn et al. 2002), and our study has shown the MUCP remains elevated even when neuromodulation has restored the ability to void in these patients. This supports the finding that the sphincter EMG abnormality persists despite successful neuromodulation, implying that the sphincter remains over-contracted. Hence neuromodulation does not appear to have a direct relaxant effect on the sphincter. Furthermore, no difference was found when the patients were asked to contract their pelvic muscles while the catheter was being withdrawn (a 'stop-test'), so the pressure could not be increased any further.

There is little known about the effect of sacral neuromodulation on urethral function in humans. Bhadra et al performed sacral anterior nerve root stimulation in 4 adult female dogs, recording the effect on UPP and MUCP (Bhadra, Grunewald et al. 2001). They acknowledged the differences between the canine and human urethra, but

used their model to specifically address the effect of electrical stimulation on urethral pressures and function. Overall they showed no significant differences in urethral closure pressure after stimulation of sacral nerve roots, even with selective stimulation of nerve fibres.

In addition to the MUCP and EMG findings, the cystometric data showing 'obstructed voiding' also imply that neuromodulation enables the bladder to overcome a persistently contracted sphincter. Upregulation of the putative 'procontinence reflex' results in urethral afferent activity inhibiting detrusor contraction. Neuromodulation may modify this signal, thereby allowing a degree of detrusor contraction. This concept of 'unmasking' detrusor contractility has also been reported in magnetic stimulation of the sacral nerve roots in healthy males and patients with complete spinal cord injury (Bycroft, Craggs et al. 2004).

Cause of retention	Examples
Neurological	Brain lesions Spinal cord lesions Peripheral/autonomic lesions
Pharmacological	Anti-depressants, anti-psychotics, anti-cholinergics, adrenergic agonists, anti-spasmodics
Infection/inflammation	Urethritis Vulvovaginitis
Mechanical obstruction	Bladder/urethra: neoplasm, stricture, diverticulum, caruncle, stone, absecess Extra-urinary: pelvic or vaginal mass, retroverted uterus, constipation, pelvic organ prolapse Functional: detrusor-sphincter dyssynergia, Fowler's Syndrome, non-neurogenic neurogenic bladder
Medical	Diabetes Mellitus Hypothyroidism Porphyria Scleroderma
Psychogenic	Hysteria Schizophrenia Depression
Post-operative voiding dysfunction	Over-correction during anti-continence procedures
Others	Retroperitoneal masses Post-partum Post-operative

CHAPTER TWELVE

PET IMAGING

12.1 Findings of PET study of cerebral response to neuromodulation

Our findings during bladder filling in healthy females broadly corroborate the results of previous functional imaging studies. The cingulate cortex, midbrain and pons were activated when the bladder was full in these subjects (compared to when their bladders were empty). This is similar to Athwal et al's report of bladder filling in healthy male volunteers in their PET study (Athwal, Berkley et al. 2001), though unlike this study, we did not use an indwelling catheter, with the aim of reducing artefact.

These findings can be contrasted with the patient group, whose clinical symptoms are characterised by a large capacity bladder and a reduced sensation of filling. Different explanations may be proferred for this reduced sensation, including possible inhibitory feedback from urethral overactivity. An alternative would be for some type of afferent desensitisation as seen with hydrodistension, although this tends to produce transient symptoms as opposed to the indefinite symptoms in the retenton patients. In contrast to healthy controls, the patients showed no brainstem activity with a full versus empty bladder (but did show activity in the cerebellum and cingulate). The various brain areas discussed in greater detail in the following section include the midbrain, which may therefore be exemplifying a switch-like role in flow of afferent information. When the stimulator was activated in these patients, and capacity to void was restored, the striking finding was the activation of the midbrain, thus 'normalizing' activity to that of healthy controls.

Different types of functional imaging studies have addressed the functional divisions in cerebral interoception, and the discrete areas are now discussed. It should be remembered, though, that such perception relies on the neural network connections as much as the individual brain centre functions.

12.2 Functional divisions in the cerebral perception of visceral stimuli

The recent interest and developments in functional imaging have provided an insight into what roles different brain centres may have in the control of bladder function. These are discussed both in the context of our study and with reference to other published data.

Midbrain

A key finding in our study was midbrain activation in the healthy controls with a full versus empty bladder. This activity was notably absent in the patient group until the stimulator was switched on, when the activity was restored. This is the *first time a key brain region has shown such a clear response to sacral neuromodulation* for urinary retention. Our hypothesis had been that neuromodulation 'normalizes' this switch mechanism in the patient group, and underlies the restoration of voiding capacity. However, although brainstem (specifically midbrain) activation is restored, the site of activation is marginally different for the 2 groups (healthy controls and patients with stimulator on), with the former being slightly more dorsal. Our findings also raise the possibility that midbrain activation may include centres other than solely PAG. Although 'normalization' of brainstem activity may play a central part in restoring voiding function, the mechanism of action of neuromodulation is likely to be more

complex given the other differences in cortical activity induced, namely the absence of cingulate activity with the neuromodulator on.

The PAG is considered to act as a relay centre in the control of micturition, receiving afferent input from the spinal cord and thereby communicating with the PMC. Whereas the PMC in the rat receives afferent input from the lumbosacral spinal cord, in the cat there are direct projections from the sacral spinal cord to the PAG, which in turn projects to the PMC (Abrams, Cardozo et al. 2002). The general view now, supported by functional imaging evidence, is that the PAG receives information about the state of bladder fullness, and then facilitates initiation of micturition via the pons. However another view is that afferent information from pelvic viscera is integrated through 'cross-talk' between PAG and PMC, in light of reciprocal connections between both nuclei and parallel spinal projections to both (Valentino, Miselis et al. 1999).

Our study shows there to be activation of the midbrain following sacral neuromodulation. Previous PET studies of urinary storage in men have demonstrated PAG activation in the full bladder state (Athwal, Berkley et al. 2001) (Matsuura, Kakizaki et al. 2002); in their studies of micturition, Blok et al reported on such activation during the urine-withholding phase in men but not women (Blok, Willemsen et al. 1997) (Blok, Sturms et al. 1998). The first (control) part of our study also showed activation in the midbrain, though slightly anterior to the PAG previously described in the studies mentioned. This degree of discrepancy was also acknowledged by Matsuura who commented on their PAG activation site being more ventrolateral to other reports (Matsuura, Kakizaki et al. 2002). In another study of

micturition in men, Nour et al reported on lack of activation of the PAG for the condition of urine withholding versus empty bladder, and concluded that there were factors other than simply bladder distension that resulted in PAG activation (Nour, Svarer et al. 2000). In particular, their suggestion was that the PAG was subject to influence from other brain centres such as the hypothalamus.

Earlier work by Blok et al had established the anatomical basis underlying the role of the PAG (Blok, de Weerd et al. 1995) which was then evaluated using functional imaging techniques. Electrical stimulation of the PAG has also been shown to evoke complete micturition in cats (Skultety 1959) (Taniguchi, Miyata et al. 2002). In the latter study electrical stimulation of the PAG induced increase in detrusor pressure and decrease in urethral sphincter EMG activity.

The substantia nigra together with the ventral tegmental area (VTA) in anterior midbrain are the origin of dopaminergic projections to the striatum and cortex. Functionally these pathways facilitate motor behaviour (via extra pyramidal pathways) and drive motivational behaviours. Dysfunction of these dopaminergic pathways manifests as motor abnormalities (bradykinesia, dytonia – as seen in Parkinson's disease) or motivational disturbances (avolitional states, obsessionality or even drug-seeking behaviour). Effective micturition requires both a motivational aspect (desire to void) and volitional relaxation of sphincter muscular tonicity. Neurones in the substantia nigra and ventral tegmentum are believed to play a role in suprapontine bladder control (Sakakibara, Nakazawa et al. 2002) (Winge and Fowler 2005). Further functional imaging evidence is still required to corroborate this view that midbrain activation may not be restricted solely to the PAG.

A further attribute of the midbrain may be its increased discriminatory potential when the stimulator is switched on. The effects of interest analysis illustrated the exaggerated difference in activity between empty and full bladder states for the retention patients following neuromodulation. One may speculate that the midbrain, including the PAG, may be more than a simple switch, but instead it may also have a regulatory role depending on afferent stimuli. In the presence of sacral nerve stimulation, its ability to distinguish states of bladder fullness may be enhanced. It is difficult to see how this regulatory aspect of midbrain activity could explain the discrepancy in PAG activity described by Athwal et al (increased activation with increased bladder volume but not urge to void) (Athwal, Berkley et al. 2001), but raises interesting questions about the functioning of the midbrain as a relay centre.

Cingulate cortex

Broca described the cingulate cortex, the medial convolution adjacent to either side of the corpus callosum, as being part of the 'limbic' system. Further research on the function of the limbic system led to establishing its role in the subjective experience of emotions. The functional subdivisions within the cingulate cortex are still debated, with the anterior cingulate cortex (ACC) being distinguished from posterior cingulate cortex (PCC) on the basis of cytoarchitecture and connectivity. The ACC may have an 'executive' role in contrast to the PCC's more 'evaluative' role (Bush, Luu et al. 2000).

The work of Ward in the 1940s described the two main functions of the ACC as the "most powerful of the cortical suppressor areas and also a potent autonomic effector region" (Luu and Posner 2003). Further attempts to parcellate the ACC have resulted

in the concept of a cognitive dorsal ACC as distinct from an emotional perigenual (anterior) ACC. The dorsal ACC has strong interconnections with the lateral prefrontal cortex, parietal cortex, premotor cortex and supplementary motor areas; the connections from the perigenual ACC, in contrast, include the PAG, amygdala, anterior insula, and hypothalamus. However, the different functions of the ACC can be reconciled without necessarily following anatomical subdivisions, as demonstrated recently by Critchley et al in an fMRI study (Critchley, Mathias et al. 2003). They studied regional brain activity associated with autonomic cardiovascular control during cognitive and motor tasks, and concluded that the ACC has an integrative role: ACC activity is linked to autonomic function (eg cardiac function, via sympathetic output), integrating effortful cognitive and motor behaviour. Their findings supported the role of the ACC in "context-dependent modulation of bodily arousal via autonomic activity", with contributions from somatic and visceral afferents.

The role of the PCC is less clear, though it has been found to display increased activity with neuropathic pain (Hsieh, Belfrage et al. 1995) and emotional processing (Vogt, Abscher et al. 2000) (Maddock, Garrett et al. 2003). Micturition is interrupted in cats following stimulation of the PCC (Gjone 1966). Neural connections between genual ACC and caudal PCC exist, thus ultimately connecting the PCC with other cortical areas. In our study, the patients with a full bladder and the stimulator switched off appeared to show increased activity in the PCC as well as more anteriorly located cingulate cortex. The interconnections may adopt a greater significance in such situations.

Both upper and lower GI stimulation are associated with cingulate activation (Aziz, Andersson et al. 1997) (Hobday, Aziz et al. 2001), as are urine storage (Athwal, Berkley et al. 2001) (Matsuura, Kakizaki et al. 2002) and micturition (Nour, Svarer et al. 2000). The involvement of the cingulate in voiding function has been known since anatomical description of lesions in this region associated with urge incontinence (Andrew and Nathan 1964). In their PET studies of both men and women, Blok et al commented on the *decrease* in activity of the ACC during urine withholding (Blok, Willemsen et al. 1997) (Blok, Sturms et al. 1998), with a resultant reduction in urge to void, and concluded that this decrease reflected a general suppression of the sensation of urge to void. Interestingly, Athwal et al found differential changes in ACC activity in association with increased bladder volume as opposed to urge. Whereas there was increased ACC activity with increasing bladder volumes in their PET study in males, there was in*creased* activity in a different mid-cingulate region with *decreasing* desire to void (Athwal, Berkley et al. 2001). The authors explained this increased activity as related to the suppression of the urge to void, which would seem to be at odds with Blok's finding that the cingulate activity *decreased* with subsequent reduction in urgency (though it was Athwal et al who formally assessed urgency using a validated urge score). However, the context of urine withholding was different for the two experiments, with Blok's patients trained to micturate within the scanner (after the urine storage condition), whereas Athwal's study was purely focussed on urinary storage; the contextual basis of ACC activity described by Critchley may therefore have implications on its function. It remains unclear, however, whether the changes in cingulate activity *drive* the reduction in urgency, or whether these changes are *responsive* to other signals that have reduced urgency in a particular context.

Our study in healthy controls would appear to confirm Athwal's findings in that there is increased cingulate activity in the full compared to empty bladder condition in healthy females. This is also seen in the patients in their baseline state (with stimulators switched off), whereby the cingulate is activated when their bladders are full, albeit in a slightly more caudal position. The patient group generally reported a sensation of suprapubic 'fullness or discomfort' rather than urgency, supporting the notion that the cingulate receives and processes afferent input based on the extent of bladder filling. However, one might also expect there to be cingulate activation with a full bladder when the stimulator is switched on; however this is not the case, a finding which seems to conflict with our understanding of its function. It may be that the stimulator's activation of the brainstem in these patients has a secondary effect on the higher cortical centres (including the cingulate), suppressing possible inhibitory descending cortical control.

Insula cortex

The insula is widely considered to have a visceral sensory function, and some have labelled it the 'limbic sensory cortex' in contrast to the anterior cingulate acting as the 'limbic motor cortex' (Craig 2002). Electrical stimulation of the insula in animal and human studies has shown changes in autonomic function (heart rate, blood pressure), peristaltic activity and adrenaline secretion. Painful somatic sensation also consistently activates this region, which is the site of convergence of somatic and visceral sensory input. Further functional subdivisions have been outlined, with the anterior insula being activated during rectal stimulation while posterior insula is activated during esophageal stimulation (Derbyshire 2003). Whereas anterior insula

tends to receive projections from the perigenual cingulate cortex, the posterior insula is connected to the more posterior mid-cingulate.

There is limited data available at present on the involvement of the insula in bladder control. With reference to urine storage, Blok et al's PET study in female volunteers found there to be right anterior insula activation in the full bladder (compared to empty bladder and micturition conditions) (Blok, Sturms et al. 1998); they commented retrospectively on similar findings in their male study, but acknowledged that this activation was not significant for multiple comparisons. Urine storage was associated with left anterior insula activation in Matsuura's study (Matsuura, Kakizaki et al. 2002). The right insula was also significantly activated by micturition (compared to rest) in one study (Nour, Svarer et al. 2000). No such activation was detected in any of the conditions in our study (in either controls or patients), reflecting the previous findings in Athwal's study which did not report any insula activation (Athwal, Berkley et al. 2001). Whether this signifies a difference in central processing or is a reflection of the technique used may become apparent after further research.

Pons

As outlined earlier, the pons is believed to act as a switch in the control of micturition, with activation of the PMC as the signal for initiating micturition. There are excitatory projections from the PMC to the sacral bladder motoneurones, and also projections to interneurones in the dorsal grey commissure (intermediomedial cell column), which in turn inhibit urethral sphincter motoneurones in Onuf's nucleus. This enables appropriate synergistic contraction and relaxation respectively. Bilateral lesions in this region in cat and rat experiments abolish micturition, while electrical or chemical

stimulation of the PMC produces a bladder contraction and coordinated relaxation of the urethra (Yoshimura 1999). The projections from the PMC to the sacral cord overlap with projections here of primary bladder afferents; this overlap could provide an anatomical substrate for a feed-forward mechanism to continue the voiding reflex, overcoming the effects of the decreasing pontine activity as the bladder empties.

Valentino et al have also proposed that this pontine region may have a role beyond simply micturition control (Valentino, Miselis et al. 1999). Tracer studies of its efferent projections, several containing the neurotransmitter corticotropin-releasing factor, may allude to the pontine regulation of multiple pelvic visceral functions and parasympathetic activity; these efferents also include projection to the PAG. This pontine regulation is also influenced by the afferent projections into the PMC, such as from the PAG and hypothalamus. Whether the direct parasympathetic input into the PMC seen in animal studies has a similar impact in human micturition control remains to be established.

In anatomical studies, Holstege's group commented on the proposition of a distinct lateral region in the pontine tegmentum that is relevant for continence as opposed to micturition. They termed this the 'L-region', in contrast to the 'M-region'; bilateral lesions of this pontine continence centre produce urge incontinence (Holstege, Griffiths et al. 1986). One model of urinary control has been that during urine storage, there is tonic activation of the L-region, and when appropriate signals indicate the bladder is full and the subject needs to void, projections from the PAG stimulate the M-region; there is thus a switch of activity from the L- to the M-region. As Griffiths points out in his subsequent review of the subject, the M-region does not receive

afferent signals directly from the lower urinary tract but via the PAG, as well as from the preoptic area of the hypothalamus, structures which are subject to modulation by various emotional states (Griffiths 2002). Therefore the discrete divide between these two pontine centres may not be so apparent.

Previous PET studies have noted pontine activation (Blok, Willemsen et al. 1997) (Blok and Holstege 1999) (Athwal, Berkley et al. 2001) (Matsuura, Kakizaki et al. 2002), albeit with slight differences regarding exact location. Some of these differences may be due to methodology as the brainstem has sometimes proven to be difficult to represent accurately in imaging studies. In this study, however, there was activation of the pons in healthy controls with an empty compared to full bladder, or in other words a pontine *deactivation* when the bladder was full. This would appear to be at odds with the findings of Athwal's study in men, where activation was associated with increasing bladder volume. It should be noted that in our study design the full bladder state was generally at maximal capacity (compared to the states of filling in Athwal's study), and therefore it could be that at such an extreme, higher cortical centres become more relevant (and active) in order to suppress the urge to void.

There was no activation in this region among the patient group, either before or after stimulation; the reason for this discrepancy is not clear. We cannot confirm therefore what effects sacral neuromodulation may have at a pontine level. One might have expected the pontine continence centre (L-region) to be activated in patients when they were aware of bladder fullness (ie when the activated stimulator had restored this

sensation among the patients). An extension of this study could then explore whether there was activation of the PMC in patients with a stimulator during micturition.

Cerebellum

The cerebellum was traditionally thought to be important in motor control only, mainly based on the observation that motor problems predominate in most patients with cerebellar disease. However, there is increasing evidence of the modulatory role of this brain region, including an influence on visceral sensation and interconnections with other brain areas (eg cerebral cortex, hypothalamus, PAG, pons) (Dietrichs and Haines 2002). Brain imaging experiments have indicated a motor role for the cerebellum in micturition (Blok, Willemsen et al. 1997) (Nour, Svarer et al. 2000), as well as a sensory function during urine storage (Athwal, Berkley et al. 2001) (Matsuura, Kakizaki et al. 2002). Lesional studies of cerebellar function have previously shown effects on both urine storage and micturition (Dietrichs and Haines 2002). The work of Aziz et al also described cerebellar involvement in the processing of visceral sensation, during stimulation of proximal and distal oesophagus (Aziz, Thompson et al. 2000).

In our study we observed stronger activation in the cerebellum in patients with the stimulator switched on versus off (with full bladders). Unlike Athwal's findings, there was little cerebellar activation in healthy controls. One may speculate that restoration of voiding by sacral nerve stimulation may involve the modulatory role of the cerebellum; although a distinct but sparse connection with the PAG has been reported in a cat study, the function of this pathway remains to be elucidated (Dietrichs and

Haines 2002), further imaging studies should help advance our understanding of this brain region.

Hypothalamus

The hypothalamus appears to play a central role, with interconnections between a number of brain centres. Research in the cat has shown projections from the medial preoptic area (MPOA) of the hypothalamus to the PAG and PMC (Holstege, Griffiths et al. 1986), and there is also evidence of connection between hypothalamus and cerebellum (Dietrichs and Haines 2002) (Supple 1993). Ongur et al reported on the projection from the cingulate cortex to the hypothalamus in the macaque monkey (Ongur, An et al. 1998).

The images from our study show activation in the region of the hypothalamus in retention patients with a full bladder (with stimulator off), and no such activation after switching on the stimulator. Athwal et al found increased activity in the hypothalamus with *decreasing* urge to void (Athwal, Berkley et al. 2001); the retention group typically have reduced sensation of fullness in the baseline state, and therefore the activity seen in our study may correlate with the finding reported by Athwal et al. Nor was there increased activity during bladder filling in the study by Matsuura et al (Matsuura, Kakizaki et al. 2002). However, during *micturition*, there is evidence of increased activity in the hypothalamus in PET studies (Blok, Willemsen et al. 1997) (Nour, Svarer et al. 2000). The function of the hypothalamus may therefore be more related to micturition than urinary storage, and the possible neural matrix showing its projection to the pons (PMC) illustrates a possible pathway for this.

Frontal cortex

In 1960 Ueki concluded that the frontal lobe has an inhibitory effect on micturition based on 462 neurosurgical cases (Ueki 1960). A subsequent observational study in 38 stroke patients by Andrew and Nathan found that lesions in the anterior frontal lobe were associated with disturbances of micturition (Andrew and Nathan 1964), with further evidence for this association reported by Maurice-Williams (Maurice-Williams 1974). Similarly in stroke patients, urinary symptoms are reported with frontal lobe lesions (Sakakibara, Hattori et al. 1996), and frontal cortex underperfusion is associated with urge incontinence and reduced bladder sensation (Griffiths 1998).

Our imaging shows a lack of frontal activation in the both controls and patients when the bladder is full, though in the case of the controls there is increased frontal activation when the bladder is empty (ie deactivated when the bladder is full). If frontal lobe activity is associated with inhibition of micturition, then one might expect there to be to greater activity in the bladder full state (when the patient is suppressing the urge to void in the scanner); however, if this inhibitory role relates specifically to the act of micturition, then during urinary storage conditions (as in our study) the frontal lobe may be quiescent as observed.

There is therefore a discrepancy with the findings of Athwal et al, who reported bilateral frontal activation with increasing bladder volume, proposing a connection with the PAG. In their similar study, however, Matsuura et al found frontal activation after ice water instillation but not bladder distension. Nour et al found bilateral activation of the inferior frontal gyrus during micturition (compared to rest), confirming similar findings by Fukuyama et al and Blok et al. Their conclusion was

that the frontal (or prefrontal) lobes might be involved in deciding whether to intitiate micturition. The lack of frontal activation in our storage study therefore does not clarify this process any further,

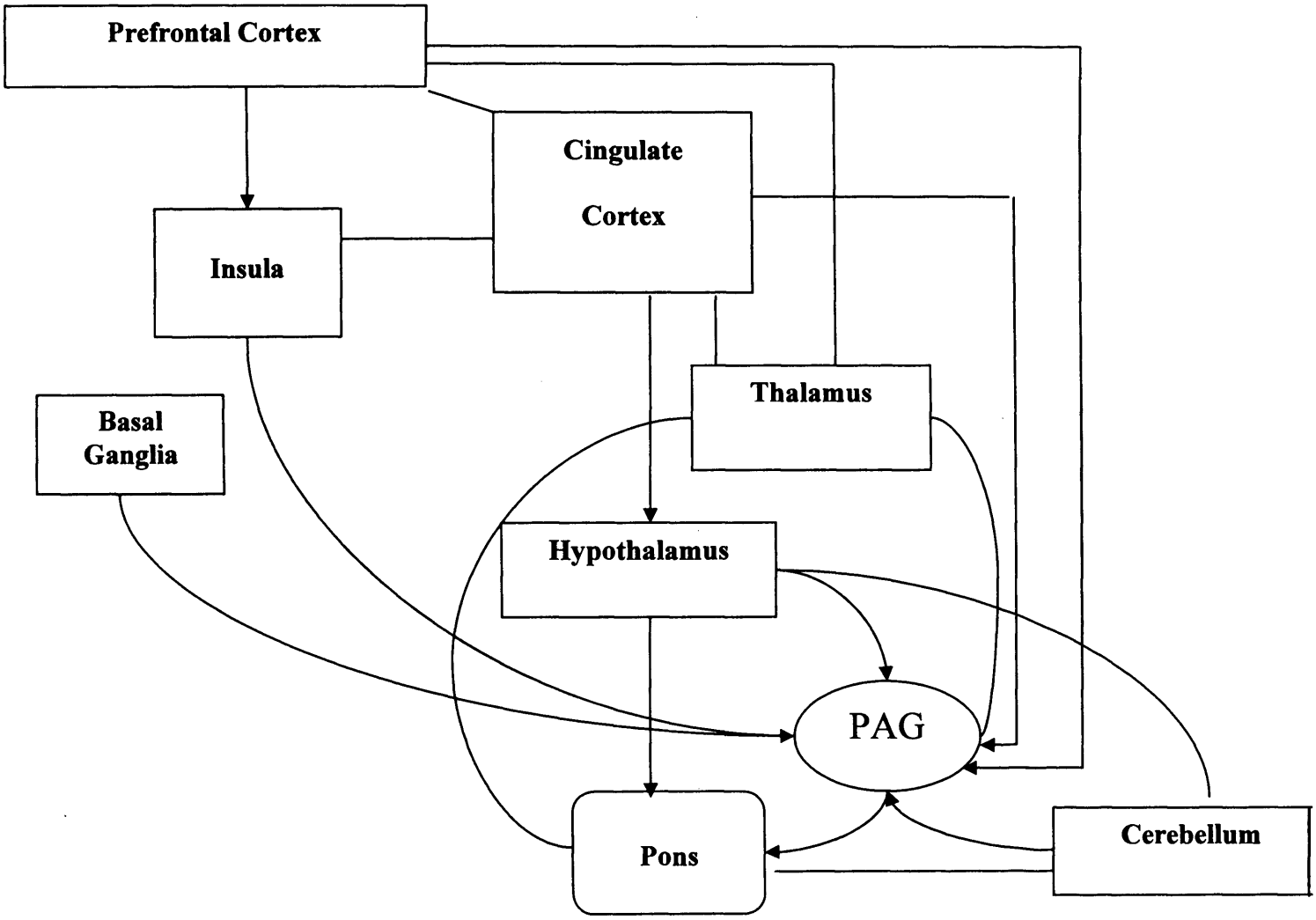
12.3 Functional connectivity

Most studies of the cerebral control of voiding function have concentrated so far on identifying the brain centres involved. This can then be interpreted within a functional framework based on our understanding of interoception in general. The next stage would be to establish a degree of *functional connectivity* or *effective connectivity* between brain centres. These two terms refer to the patterns of information flow between brain centres, pertaining to different physical conditions.

The diagram in Figure 12a is a theoretical representation of how the brain centres may be related. It is important to highlight the difficulty in establishing a hierarchy of centres with limited data on connectivity, and that it is based on information from both urinary storage and voiding studies. Another issue not addressed is that of laterality, which seems to vary between the limited studies available, or its significance.

The majority of interconnections in the network diagram do not specify which brain centre is upstream and which downstream, as this information is still not truly understood. It is known that the PAG is an important relay centre for afferent neural input, but it would appear to be equally important as a relay centre for higher brain structures. The cingulate also has important connections with insula and prefrontal cortex, as well as more 'downstream' regions such as the hypothalamus and thalamus,

Figure 12a Speculative network of brain centres involved in urinary control



which in turn interact with the PAG and pons. The 'evaluative' role of the cingulate may be reflected in its connections with the 'higher' centres, while its 'executive' influence could be mediated through downstream pathways including the PAG and pons; the context-dependent activation described by Critchley et al may be realised through these different pathways. Kershen et al attempted to simplify the functional subdivisions in their review by stating that the prefrontal cortex helps to decide whether it is appropriate to void, the hypothalamus whether it is safe to inititate voiding, the cingulate cortex to process the stimuli affecting desire to void; and thereby the PAG can stimulate the PMC to produce coordinated relaxation of the urethral sphincter and contraction of the detrusor (Kershen, Kalisvaart et al. 2003).

Summary of cerebral control of urinary storage

Women with urinary retention and sphincter overactivity characteristically have a reduced perception of bladder filling, resulting in them retaining large volumes, sometimes over a litre. As well as restoring the ability to void, sacral neuromodulation also improves the sensation of bladder fullness. We have demonstrated that this effect may be mediated by changes in midbrain activity, which acts as a relay centre for afferent signals from the lower urinary tract. The overall effect may thus *include* 'normalizing' the activity of the brainstem towards that seen in scans of healthy females with a full bladder (DasGupta, Critchley et al. 2005). The activity of this control centre is likely to be modulated by higher cortical centres such as the cingulate cortex. We have shown cingulate activity in the control subjects with a full bladder

and also in the patients with the stimulators switched off; the absence of cingulate activity when the stimulators are switched on indicates that the mechanism of sacral neuromodulation is more complex than simply 'normalization'. Most of our understanding of the role of the cingulate cortex as an integrative centre concentrates on the ACC, whereas the cingulate activated in our study was more dorsal than previous studies.

CHAPTER THIRTEEN

MECHANISM OF NEUROMODULATION

The preceding chapters have shown that, in women with retention, neuromodulation does not have a direct relaxant effect on the urethral sphincter, and secondly that it induces changes in activity in different brain centres involved in voiding control. However, other functional aspects of its mechanism of action remain unexplained, such as the relationship with spinal cord neurotransmitters, long-term efficacy (and possible carry-over effect), and action on spinal level reflexes.

13.1 Neurotransmitter Effects

Neuromodulation is believed to act on afferent innervation as described above. The two main types of bladder afferent fibre are Aδ and C-fibres. The Aδ fibres are finely myelinated axons which act as tension receptors (mechanoceptors) sensing bladder fullness. The C-fibres are unmyelinated axons, some of which respond to stretch (volume receptors) and others to nociceptive stimuli. After exposure to irritative substances, such as capsaicin, the 'silent C-fibres' may become mechanosensitive and unmask new afferent pathways.

Pharmacological studies have provided information on the range of neurotransmitters involved in the neural pathways, whether peripherally in the bladder or urethra, or centrally (spinally or supraspinally). For instance, the external urethral sphincter is under the influence of glutamate (excitatory), GABA (inhibitory) and glycine (inhibitory) transmitters (Chancellor and Yoshimura 2003). These substances are released by neurons and interneurones in the reflex pathways described in the

introduction, and the (neuro)modulation of these pathways may actually modify the release of these neurotransmitters.

The different transmitters studied include:

Acetylcholine

The role of cholinergic mechanisms is well established, and anti-cholinergic medication is the mainstay of medication to treat detrusor overactivity.

ATP

Purinergic pathways have been documented in rat, rabbit and guinea pig studies, though their role in human bladder control is less clear at this stage. The P2X receptor (P2X3 in particular) has been studied extensively and is currently under investigation as a possible therapeutic target in detrusor overactivity (Rapp, Lyon et al. 2005).

Adrenergic

The presence of α receptors, α1 in particular, in the urethra is a reflection of the role of this adrenergic subtype in maintaining urethral tone. Both hypogastric nerve stimulation and α-agonists produce a rise in intraurethral pressure, which is blocked by α1-antagonists. In contrast, stimulation of β-receptors (mainly β2 and β3) which are present in human detrusor produce direct relaxation of detrusor smooth muscle.
In experiments where stimulation of sacral motor roots caused a reduction of urethral pressure, propanolol (β-antagonist) prevented this decrease (McGuire and Herlihy 1978).

Nitric oxide

There is evidence that nitric oxide (NO) is an inhibitory transmitter, enabling relaxation of the urethral smooth muscle during micturition. Studies in female rats showed that electrical stimulation of the lumbosacral (L6–S1) spinal roots elicits simultaneous bladder contractions and urethral relaxation (Fraser, Flood et al. 1995). The urethral relaxation was inhibited by NO-synthase (NOS) inhibitors, which did not alter the bladder responses. The inhibition was reversed by administration of L-arginine, a precursor of NO. Recent work by Ho et al has confirmed the presence of nitric oxide synthase in the human female striated urethral sphincter (Ho, Borja et al. 2003). There also seems to be a role for NO in bladder afferent activity: the inhibition of detrusor contraction resulting from electrical stimulation of the tibial nerve is reduced by NOS inhibition.

GABA

Animal studies have indicated a role for the inhibitory neurotransmitter GABA in the relaxation of the urethral sphincter seen during micturition. The neurons in the sacral spinal cord that receive the projections from Barrington's nucleus have been shown to contain GABA. A subset of neurons active during micturition are GABAergic, some of which are in contact with external sphincter motoneurons (Jezernik, Craggs et al. 2002). GABA and glycine are sometimes co-localized in the same neurons.

C-fibre neuropeptides

A subpopulation of c-fibre afferent nerve fibres has been implicated in the pathogenesis of detrusor overactivity; this is distinct from the Aδ-fibres which provide afferent input in normal micturition. These c-fibres release certain neuropeptides

including Substance P (SP), neurokinin A (NKA), vasoactive intestinal peptide (VIP) and calcitonin-gene related peptide (CGRP). Shaker et al investigated the effect of electrical sacral nerve stimulation on neuropeptide levels in spinally transacted Sprague Dawley rats with detrusor hyperreflexia (Shaker, Wang et al. 2000). They showed that the neuropeptide content of dorsal root ganglia increased after spinal transection, coincident with increased urinary bladder activity. Chronic S1 electrostimulation for 3 weeks resulted in a significant decrease in neuropeptide levels back towards baseline levels. Although these findings relate to detrusor overactivity rather than retention, it is conceivable that electrical stimulation for the latter condition may also affect levels of neuropeptides (albeit different ones).

Another marker of afferent c-fibre activity is the product of the proto-oncogene c-fos. C-fos is not expressed in the spinal cord under normal physiological conditions, and is only activated when the sensory cells are exposed to transmembrane stimulation, conveyed mainly by afferent c-fibres. Wang and Hassouna performed sacral nerve stimulation in spinalized rats, and found reduction in c-fos gene expression as well as reduced hyperreflexia (Wang and Hassouna 2000). They compared their findings to that of Chang et al, who also described decreased c-fos expression in rat spinal cord, this time following electroacupuncture in rat hind legs (Chang, Huang et al. 1998).

Nerve growth factor (NGF) is a trophic factor that animal studies have shown to be elevated in dorsal root ganglia and the spinal cord in hyperreflexic bladders following spinal cord injury (Seki, Sasaki et al. 2002). This group showed that neutralization of NGF using intrathecal NGF antibodies reduced the spinal levels of NGF and bladder

contractions. One can speculate as to whether electrical stimulation could also modulate NGF levels, and thereby affect detrusor contractility.

Transmitters acting in the spinal cord

Glutamate: Intrathecal administration of glutamatergic antagonists is known to reduce bladder contractions as well as urethral sphincter EMG activity in rats. There may be differential expression of glutamate receptors in the bladder and urethra, accounting for their different sensitivities to glutamate antagonists.

GABA/Glycine: These inhibitory amino acids also have effects in the spinal cord. Animal studies have implicated baclofen (a GABA agonist) in the suppression of detrusor contraction.

Serotonergic transmitters (5-HT): The raphe nucleus in the caudal brainstem projects 5-HT containing neurons to the dorsal horn and lumbosacral cord. Activation of the raphe neurons or 5-HT receptors in the spinal cord inhibits reflex bladder contractions and sacral efferents to the bladder.

Adrenergic transmitters: The spinal noradrenergic system has a modulatory role, by inhibiting afferent inputs from the bladder and facilitating the descending part of the micturition reflex to increase bladder contractility.

Opioid peptides: These have an inhibitory action on spinal cord reflexes, again with different receptor subtypes acting on bladder and urethra. Their role in the mechanism of acupuncture is described earlier.

To summarise, a key action of glutamate is on spinal efferents enabling micturition. The spinal noradrenergic system (mainly α1) inhibits bladder afferents and facilitates an increase in bladder contractility via the descending limb of the spinal micturition reflex. Neurotransmitters such as GABA, 5HT, and purines may act in the sacral spinal cord by modulating the bladder volume threshold.

Evidence for electrical-neurochemical mechanism

It is attractive to consider that neuromodulation has an effect on the balance (or imbalance) of neurotransmitters, either at the level of the bladder, spinal cord or supraspinally. One could then propose a mechanism by which this therapy could influence conditions as clinically disparate as detrusor overactivity and urinary retention.

We have alluded to the animal experiments showing changes in gene expression and neuropeptide levels following electrical stimulation. Furthermore, women with urinary retention do not show a response to stimulation immediately, as one might expect if it were simply 'resetting a switch' by redirecting a neuronal impulse. Instead, there is a lag time, after which the patient gradually experiences a return of bladder filling sensation, and then a return of ability to void. This period can be upto a few days (Swinn, Kitchen et al. 2000). Similarly, the return of symptoms to baseline

takes a few days after the stimulator is switched off, a 'carry-over' effect which is discussed further below.

Also, we have indicated that the other forms of stimulation, whether electrical, magnetic or acupuncture, may have similar effects on micturition and therefore may involve common underlying mechanisms of action.

13.2 Long-term effects

The retrospective survey of patients implanted with a stimulator between 1996 and 2002 showed that the vast majority still reported adequate voiding at a mean follow-up of 3 years. Whereas most of these patients find that their symptoms (retention or dysfunctional voiding) recur if stimulation is stopped (eg battery expires), a few patients have reported continued resolution of symptoms long after discontinuation of neuromodulation. A limited number of other centres have also described similar findings (DasGupta, Wiseman et al. 2003). However, the more common clinical finding in patients with detrusor overactivity is that when the stimulator is deactivated, the symptoms recur within a hours to days.

The concept of a 'carry-over' effect of neuromodulation is recognised clinically. In the case of anogenital stimulation for urge incontinence, it has been proposed that a prolonged increase in the micturition threshold volume is produced by modulating the synaptic transmission in the central micturition reflex pathway (Jiang and Lindstrom 1998). Repetitive stimulation has been reported to have effects lasting several months in human studies (Gladh, Mattsson et al. 2001). Generally, however, neuronal

plasticity in retention is not sufficient to allow permanent 'resetting' of the pathways as seen, for example, in electrical cardioversion. Another example of this is the use of deep brain stimulation in movement disorders (eg. Stimulation of thalamus for essential tremor, subthalamic nucleus or globus pallidus for Parkinson's disease, and globus pallidus or thalamus for myotonia) (Lozano, Dostrovsky et al. 2002).

13.3 Spinal level reflexes

This thesis has not explored the possibility of neuromodulation having an effect at a spinal level, which is most clearly studied in patients with spinal cord injuries (and disconnection of cerebral and peripheral centres). Such effects could have a bearing on the activity seen during functional brain imaging, and complete theories of mechanism of action should therefore address changes observed at a spinal level.

CHAPTER FOURTEEN

SUMMARY

This thesis has demonstrated changes in brain activity following sacral neuromodulation in women with urinary retention for the first time, using PET functional imaging. The role of the midbrain and cortical areas such as the cingulate are discussed with respect to bladder interoception. The urodynamic study of women with retention undergoing neuromodulation reveals that the stimulation does not restore voiding by a direct relaxant effect. And finally, we have reported on the long-term efficacy of this technique, speculating on the 'resetting' of neuronal circuitry and restoration of the balance of neurotransmitters.

Sacral neuromodulation has gained popularity in recent years, particularly as another treatment option for patients with detrusor overactivity. Further research into its mechanism of action, possibly using functional brain imaging techniques, may enhance our understanding of neuromodulation and of perception of bladder sensation in general.

FIGURES

Appendix A

Permission of the Ethics Committee for this study

University College London Hospitals NHS

NHS Trust

Dr N Hirsch - *Chairman*

Please address all correspondence to:
Ms Doreen Sharpe - *Ethics Administrator*
Email: doreen.sharpe@uclh.org

The National Hospital for Neurology and
Neurosurgery and the Institute of Neurology
Joint Research Ethics Committee
Research & Development
1st Floor, Vezey Strong Wing
112 Hampstead Road
London NW1 2LT

21 June 2002

Our Ref:

Professor Clare Fowler
Department of Uro-Neorology
NHNN
Queen Square

Dear Clare

Study Ref:
Title: **Functional imaging and urodynamic investigation of women in health and disease, and the effect of sacral neuromodulation**

Your application was again reconsidered at the June meeting the Ethics Committee.

I am pleased to say the Committee was satisfied that all issues had been addressed and approved the study.

Please ensure that you have obtained final approval from the Trust (via the R&D office) before proceeding with your research.

Please note that it is important that you notify the Committee of any adverse events or changes (name of investigator etc) relating to this project. You should also notify the Committee on completion of the project, or indeed if the project is abandoned. **Please remember to quote the above number in any correspondence.**

With best wishes.

Yours sincerely

Dr N Hirsch
Chairman

University College London Hospitals NHS
NHS Trust

NHNN Research Director:
Professor Alan Thompson

UCLH Trust R&D Director:
Professor Allyson Pollock

Research & Development
1st Floor, Vezey Strong Wing
112 Hampstead Road
London NW1 2LT

6th September 2002

Professor Fowler
Department of Uro-Neurology
NHNN

Dear ~~Professor Fowler~~ Clare,

Ref:

Title: **Function imaging and urodynamic investigation of women in health and disease and the effect of sacral neuromodulation**

Thank you for registering the above study with the R&D Directorate.

I am pleased to give Trust approval for the study to commence. Please ensure you have addressed any outstanding issues raised by the ethics committee.

Yours sincerely

Professor Alan Thompson
Director of Research, NHNN

Appendix B

The Department of Uro-Neurology

Patient Information Sheet

Brain imaging and urodynamic study of bladder function, and the effects of sacral neuromodulation.

We would like to invite you to participate in a study of how sacral neuromodulation may affect bladder function and the brain's perception of bladder fullness. As you know, a condition has been described that affects primarily young women who are unable to empty their bladders. This has been attributed to an abnormality of the urethral sphincter, at the outlet of the bladder. Until recently the only method of managing this condition was by "intermittent self-catheterisation". It has subsequently been found that electrical stimulation of the nerves involved in bladder control restores normal sensation of bladder filling (previously absent) and the ability to void.

This technique of neuromodulation, or sacral nerve stimulation, also helps patients at the other end of the spectrum, by reducing their urinary urgency, frequency and leakage. It is unclear how the therapy can help such very different conditions. A number of patients have now had stimulators implanted for urinary retention at the National Hospital for Neurology & Neurosurgery, and are able to void successfully as a result.

A previous brain scanning study by our group focussed on brain regions activated in *men* with different degrees of bladder filling. It is important to understand the underlying mechanisms involved in the storage of urine in *women* and the effect of neuromodulation on these mechanisms. We are proposing to use brain scanning and routine bladder tests to examine these effects. We are inviting you to participate because you are in a unique group of patients with a sacral nerve stimulator implanted successfully for an unusual condition.

Tests involved

Brain scans

We will perform a series of PET (positron emission tomography) scans; this is a safe, non-invasive method of scanning, where the subject lies on her back, with a large "polo-mint" around the head effectively taking a series of pictures. Every scan lasts up to 90 seconds, with 8 mins interval between each of 6 scans (the stimulator may be switched on/off for different scans). The entire session is repeated once. The technique involves a very small dose of radiation (about the same as an intravenous urogram, a kidney function test, but less than that for a barium enema), and is equivalent to living in London for two years. Further details can be found in the attached "Volunteer's guide to a PET scan" booklet. Even if you are not eligible for a PET scan (eg if under 40 years old), you may still be included in the trial for the bladder tests only.

Bladder tests
These are standard bladder function tests that are performed routinely in the department on an almost daily basis. These include:

- cystometry : filling the bladder with water through a fine catheter (and placing another pressure-recording line in the rectum), and thereby measuring pressure changes; you will be asked to empty your bladder at the end of filling;
- urethral pressure profile : a catheter is slowly withdrawn from the bladder, measuring the pressure at the urethra as it is pulled out.
- intravaginal ultrasound scan : a small probe is inserted into the vagina to visualise the urethra (similar to ultrasound for ovaries)
- needle electromyography test of the urethral sphincter (unless you have already had this repeated since after your implant): after injection of local anaesthetic into the urethra, a fine needle is inserted into the urethra to record activity in this muscle.

As a patient with an implanted stimulator, you are likely to be familiar with the above tests, having undergone these at an earlier date during your clinical care. They are all safe although there may be slight discomfort in the case of needle electromyography (for which we use local anaesthetic). The risk of urinary infection is minimal, so prophylactic antibiotics are not routinely prescribed.

Urethral sphincter MRI
If you have not yet been implanted with a stimulator, but have had the diagnostic tests suggesting the urethral abnormality, you may be suitable for a Magnetic Resonance Imaging (MRI) scan of the pelvic region, which will allow us to better visualise this abnormality. This is a painless, non-invasive investigation with no significant side-effects.

Subjects
As a patient with a sacral nerve stimulator implanted, you are eligible to take part if you are over the age of 40 years, have no other major medical problems, and are not pregnant (we will perform a pregnancy test before you are enrolled in the study). The whole study will require up to 4 visits to the department, 2 for bladder tests (cystometry, urethral pressure profile, ultrasound on day 1, sphincter EMG on day 2) and 2 separate sessions for brain scanning (with bladder full/empty; randomised order for sequence of bladder fullness for different patients).

Your participation is entirely voluntary; you are free to enter or withdraw from the study at any time, without giving a reason. If you choose not to enter the study, this will in no way affect your future medical care. All information will remain strictly confidential, and will only be used for medical purposes. Your medical records may be inspected only by competent authorities and properly authorised persons. Participation in this study will in no way affect your legal rights. The study has been reviewed by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.
Please contact any of the staff below if you have any queries regarding any aspect of the study, on the following telephone number:

The Department of Uro-Neurology

Healthy Volunteer Information Sheet

Brain imaging and urodynamic study of bladder function,

We would like to invite you to participate in a study of how bladder function is controlled in women, particularly during *storage* of urine, and how the brain processes the sensation of bladder fullness. Previous studies by our group and in other centres have concentrated on activation of brain regions in healthy *men*. It is important now to examine the mechanisms involved in *women*, as some women may have specific abnormalities of their bladder function. For this, we need the help of selected female volunteers with normal urinary function. The study will involve scanning the brain and also a series of bladder tests, as discussed below. This knowledge will allow comparison with results from patients with specific urinary problems.

Tests involved

Brain scans

We will perform a series of PET (positron emission tomography) scans in volunteers; this is a safe, non-invasive method of scanning, where the subject lies on her back, with a large "polo-mint" around the head effectively taking a series of pictures. Every scan lasts upto 90 seconds, with 8 mins interval between each of 6 scans. The entire session is repeated once. The technique involves a very small dose of radiation (about the same as an intravenous urogram, a kidney function test, but less than that for a barium enema), and is equivalent to living in London for two years. Further details can be found in the attached "Volunteer's guide to a PET scan" booklet.

Bladder tests

You will undergo a cystometry and a urethral pressure profile, which are routine bladder tests. Cystometry involves filling the bladder with water through a fine catheter (and placing another pressure-recording line in the rectum) and measuring the pressure changes in the bladder; during the urethral pressure profile a fine catheter is slowly withdrawn from the bladder, measuring the pressure at the urethra as it is pulled out. There is only a small chance of urinary infection (<4%), for which antibiotics are not routinely prescribed but will be available if necessary.

Urethral sphincter MRI

You may also be eligible for a Magnetic Resonance Imaging (MRI) scan of the pelvic region, which will allow us to better visualise the urethral sphincter than current diagnostic ultrasound tests. This is a painless, non-invasive investigation with no significant side-effects.

Subjects
You are eligible to take part if you are a female over the age of 40 years, with no kidney or bladder disorders, no neurological conditions and are not pregnant (we will perform a pregnancy test before you are enrolled in the study).

The whole study will require 3 or 4 visits to the department, 1 or 2 visits for the bladder tests, and 2 separate sessions for brain scanning (with bladder full/empty; randomised order for sequence of bladder fullness for different patients). At the end of this, you will receive a T-shirt with a unique anatomical image of your brain, and expenses as agreed.

Your participation is entirely voluntary; you are free to enter or withdraw from the study at any time, without giving a reason. If you choose not to enter the study, this will in no way affect your future medical care. All information will remain strictly confidential, and will only be used for medical purposes. Your medical records may be inspected only by competent authorities and properly authorised persons. Participation in this study will in no way affect your legal rights. The study has been reviewed by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

Please contact any of the staff below if you have any queries regarding any aspect of the study, on the following telephone number:

Contact Tel No : [redacted]

Mr Ranan DasGupta	Research Registrar]
Professor Clare J Fowler	Professor of Uro-Neurology]
Mrs Collette Haslam	Continence Nurse Specialist]

Appendix C

CONSENT FORM

Study: Brain imaging and urodynamic study of bladder function, and the effects of sacral neuromodulation.

Investigators: Professor Clare Fowler, Professor of Uro-Neurology
Mr Ranan DasGupta, Research Registrar
Department of Uro-Neurology, Tel 0207-837-3611 ext 3418

1. Have you read the information sheets? Yes No

2. Have you had an opportunity to ask questions? Yes No

3. If so, have you received satisfactory answers to your questions? Yes No

4. Which doctor have you spoken to about this study? .....

5. Do you understand that you are free to withdraw from this study:

at any time	Yes	No
without giving a reason	Yes	No
without affecting your future medical care	Yes	No

6. Do you agree to take part in this study? Yes No

Subject name (print): .....

Subject signature: .....

Date: .....

Doctor: .....

Signed Print name

BIBLIOGRAPHY

Published articles

DasGupta R, Critchley HD, Dolan RJ, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention.
J Urol 2005 (In Press)

DasGupta R, Fowler CJ. Urodynamic study of women with urinary retention treated using sacral neuromodulation.
J Urol 2004; 171(3): 1161-1164

DasGupta R, Wiseman OJ, Kitchen N, Fowler CJ. Long-term results of sacral neuromodulation for women with urinary retention.
BJUI 2004; 94(3): 335-337

DasGupta R, Fowler CJ. The management of female voiding dysfunction: Fowler's Syndrome – a contemporary update.
Current Opin Urology 2003; 13: 293-299

DasGupta R. Sacral neuromodulation.
Urology News 2002; 6(6): 18-20

Other presented works

DasGupta R, Deng J, Rockall A, Hall-Craggs M, Fowler CJ. Three-dimensional MRI of the urethra in women with urinary retention.
Institute of Physics and Engineering in Medicine 2002 (London)

Andrich DE, Oliver, SE, DasGupta R, Fowler CJ, Craggs MD, Mundy AR. Acute effect of sacral nerve stimulation on patients with urinary retention.
EAU 2002 (Birmingham)

DasGupta R. Fowler's Syndrome (Invited lecture)
BAUN 2002 (Coventry)

DasGupta R, Wiseman OJ, van den Hombergh U, Siegel S, Edlund C. Spontaneous resolution of urinary symptoms following neuromodulation.
International Society for Pelvic Neuromodulation 2003 (Arizona)

DasGupta R. Neurophysiology and Neuromodulation. (Invited lecture)
ICS Workshop 2003 (Heidelberg)

REFERENCES

Abosief, S., K. Tamaddon, et al. (2002). "Sacral neuromodulation in functional urinary retention: an effective way to restore voiding." BJUI **90**: 662-665.

Abrams, P. H., J. G. Blaivas, et al. (2003). "The role of neuromodulation in the management of urinary urge incontinence." BJUI **91**(4): 355-359.

Abrams, P. H., L. Cardozo, et al. (2002). Incontinence.

Abrams, P. H., R. Skidmore, et al. (1977). "The concept and measurement of bladder work." BJU **49**: 133-.

Agnew, W., D. McCreery, et al. (2002). Principles for safe and effective nerve stimulation. New perspectives in sacral nerve stimulation. U. Jonas and V. Grunewald. London, Martin Dunitz Ltd. **1**: 29-41.

Amarenco, G., S. Sheikh Ismael, et al. (2003). "Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder." J Urol **169**: 2210-2215.

Andrew, J. and P. Nathan (1964). "Lesions of the anterior frontal lobes and disturbances of micturition and defecation." Brain **87**: 233-262.

Andrich, D. E., D. Rickards, et al. (2005). "Structural assessment of the urethral sphincter in women with urinary retention." J Urol **173**(4): 1246-1251.

Asmussen, M. and U. Ulmsten (1976). "A new technique for measurements of the urethral pressure profile." Acta Obstet Gynaecol Scand **55**: 167-173.

Athwal, B. S., K. J. Berkley, et al. (2001). "Brain responses to changes in bladder volume and urge to void in healthy men." Brain **124**(Pt 2): 369-77.

Aziz, Q., J. Andersson, et al. (1997). "Identification of human brain loci processing esophageal sensation using positron emission tomography." Gastroenterology **113**: 50-59.

Aziz, Q., D. G. Thompson, et al. (2000). "Cortical processing of human somatic and visceral sensation." J Neurosci **20**: 2657-2663.

Bass, J. and G. Leach (1991). "Bladder outlet obstruction in women." Prob in Urology **5**: 141-154.

Beleggia, F., E. Beccia, et al. (1997). "The use of type A botulinum toxin in the treatment of detrusor-sphincter dyssynergia." Arch Ital Urol Androl **69**(Suppl 1): 61-63.

Bemelmans, B. L. H., A. R. Mundy, et al. (1999). "Neuromodulation by implant for treating lower urinary tract symptoms and dysfunction." Eur Urol **36**: 81-91.

Bhadra, N., V. Grunewald, et al. (2001). "Urethral pressure profiles in the female canine implanted with sacral anterior nerve root electrodes." World J Urol **19**(4): 272-7.

Blaivas, J. G., A. Flisser, et al. (2004). "Treatment of primary bladder neck obstruction in women with transurethral resection of the bladder neck." J Urol **171**: 1172-1175.

Blaivas, J. G. and A. Groutz (2000). "Bladder outlet obstruction nomogram for women with lower urinary tract symptomatology." Neurourol Urodyn **19**(5): 553-64.

Blaivas, J. G., J. P. Weiss, et al. (2005). "Long-term follow-up of augmentation enterocystoplasty and continent diversion in patients with benign disease." J Urol **173**(5): 1631-1634.

Blok, B., H. de Weerd, et al. (1995). "Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition centre or M-

region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay." J Comp Neurol **359**: 300-309.
Blok, B. F., J. Groen, et al. (2002). "Brain activation during sacral neuromodulation in urge incontinence: a combined PET and MRI study." Neurourol Urodyn: 86.
Blok, B. F., J. Groen, et al. (2003). "Brain plasticity and urge incontinence: PET studies during the first hours of sacral neuromodulation." Neurourol Urodyn **22**(5): 490-491.
Blok, B. F. and G. Holstege (1994). "Direct projections from the periaqueductal gray to the pontine micturition center (M-region): an anterograde and retrograde tracing study in the cat." Neurosci Lett **166**: 93-96.
Blok, B. F. and G. Holstege (1996). "The neuronal control of micturition and its relation to the emotional motor system." Prog Brain Res **107**: 113-126.
Blok, B. F. and G. Holstege (1999). "The central control of micturition and continence: implications for urology." BJUI **83**(Suppl 2): 1-6.
Blok, B. F., L. M. Sturms, et al. (1997). "A PET study on cortical and subcortical control of pelvic floor musculature in women." J Comp Neurol **389**(3): 535-544.
Blok, B. F., L. M. Sturms, et al. (1998). "Brain activation during micturition in women." Brain **121**(Pt 11): 2033-42.
Blok, B. F., A. T. Willemsen, et al. (1997). "A PET study on brain control of micturition in humans." Brain **120**(Pt 1): 111-121.
Bonney, V. (1923). "On diurnal incontinence of urine in women." J Obstet Gynae **30**: 358-365.
Bosch, R. and J. Groen (2000). "Sacral neuromodulation in the treatment of patients with refractory motor urge incontinence: long-term results of a prospective longitudinal study." J Urol **163**: 1219-1222.
Boyce, W., J. Lathem, et al. (1964). "Research related to the development of an artificial electrical stimulator for the paralyzed human bladder: a review." J Urol **91**: 41-51.
Bratt, H., K. Salvesen, et al. (1998). "Long-term effects ten years after maximal electrostimulation of the pelvic floor in women with unstable detrusor and urge incontinence." Acta Obstet Gynaecol Scand **77 (suppl 168)**: 22-24.
Braun, P. M., H. Baezner, et al. (2002). "Alterations of cortical electrical activity in patients with sacral neuromodulator." Eur Urol **41**(5): 562-566; discussion 566-7.
Brindley, G., C. Polkey, et al. (1982). "Sacral anterior root stimulators for bladder control in paraplegia." Paraplegia **20**: 365-381.
Brodak, P., M. Bidair, et al. (1993). "Magnetic stimulation of the sacral roots." Neurourol Urodyn **12**(6): 533-540.
Brown, M. and J. Wickham (1969). "The urethral pressure profile." BJU **41**: 211-217.
Bush, G., P. Luu, et al. (2000). "Cognitive and emotional influences in anterior cingulate cortex." Trends Cogn Sci **4**(6): 215-222.
Bycroft, J., M. Craggs, et al. (2004). "Does magnetic stimulation of sacral nerve roots cause contraction or suppression of the bladder?" Neurourol Urodyn **23**: 241-245.
Caldwell, K. (1963). "The electrical control of sphincter incompetence." Lancet **2**: 174.
Carey, M., M. Fynes, et al. (2001). "Sacral nerve root stimulation for lower urinary tract dysfunction: overcoming the problem of lead migration." BJU Int **87**(1): 15-18.

Chai, T. C. and G. J. Mamo (2001). "Modified techniques of S3 foramen localization and lead implantation in S3 neuromodulation." Urology **58**(5): 786-90.

Chancellor, M. B. and N. Yoshimura (2003). Physiology and Pharmacology of the bladder and urethra. Campbell's Urology. P. Walsh, A. Retik, D. Vaughan and A. Wein. Philadelphia, Elsevier Science. **2**.

Chang, C., S. Huang, et al. (1998). "Electroacupuncture decreases c-fos expression in the spinal cord induced by noxious stimulation of the rat bladder." J Urol **160**: 2274-.

Chang, P. (1988). "Urodynamic studies in acupuncture for women with frequency, urgency and dysuria." J Urol **140**(3): 563-566.

Chartier-Kastler, E., R. Bosch, et al. (2000). "Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia." J Urol **164**: 1476-1480.

Chassagne, S., P. A. Bernier, et al. (1998). "Proposed cutoff values to define bladder outlet obstruction in women." Urology **51**(3): 408-411.

Chen, Y. H. and H. Kuo (2004). "Botulinum A toxin treatment of urethral sphincter pseudodyssynergia in patients with cerebrovascular accidents or intracranial lesions." Urol Int **73**(2): 156-161.

Cheng, P., M. Wong, et al. (1998). "A therapeutic trial of acupuncture in neurogenic bladder of spinal cord injured patients - a preliminary report." Spinal Cord **36**: 476-480.

Cormier, L., J. Ferchaud, et al. (2002). "Diagnosis of female bladder outlet obstruction and relevance of the parameter area under the curve of detrusor pressure during voiding: preliminary results." J Urol **167**(5): 2083-2087.

Craig, A. D. (2002). "How do you feel? Interoception: the sense of the physiological condition of the body." Nat Rev Neurosci **3**(8): 655-66.

Critchley, H. D., C. J. Mathias, et al. (2003). "Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence." Brain **126**: 2139-2152.

DasGupta, R., H. D. Critchley, et al. (2005). "Changes in brain activity following sacral neuromodulation for urinary retention." J Urol **In Press**.

DasGupta, R. and C. J. Fowler (2004). "Urodynamic study of women in urinary retention treated with sacral neuromodulation." J Urol **171**(3): 1161-1164.

DasGupta, R., O. J. Wiseman, et al. (2004). "Long-term results of sacral neuromodulation for women with urinary retention." BJUI **94**(3): 335-337.

DasGupta, R., O. J. Wiseman, et al. (2003). Spontaneous resolution of urinary symptoms following neuromodulation. ISPiN, Jacksonville, Florida, USA.

de Groat, W. C., M. O. Fraser, et al. (2001). "Neural control of the urethra." Scand J Urol Nephrol Suppl(207): 35-43; discussion 106-25.

De Ridder, D., S. Sunaert, et al. (2003). "Functional MRI during percutaneous sacral nerve stimulation of female patients shows central differences between Fowler and non-Fowler patients." J Urol **169**(Suppl 4): 172A.

Decter, R. (2000). "Intravesical electrical stimulation: con." Urology **56**: 5-8.

Deindl, F., D. Vodusek, et al. (1998). "Dysfunctional voiding in women: which muscles are responsible?" BJU **82**: 814-819.

Derbyshire, S. (2003). "A systematic review of neuroimaging data during visceral stimulation." Am J Gastroenterol **98**: 12-20.

Dietrichs, E. and D. Haines (2002). "Possible pathways for cerebellar modulation of autonomic responses: micturition." Scand J Urol Nephrol **210**(Supp): 16-20.

Dykstra, D. and A. Sidi (1990). "Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double blind study." Arch Phys Med Rehabil **71**: 24-.

Dykstra, D., A. Sidi, et al. (1988). "Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients." J Urol **139**: 919-.

Edwards, L. and J. Malvern (1974). "Proceedings: studies of intra-urethral pressures in normal and incontinent women." Urol Int **29**: 205.

Eriksen, B., S. Bergmann, et al. (1989). "Maximal electro-stimulation of the pelvic floor in female idiopahtic detrusor instability and urge incontinence." Neurourol Urodyn **8**: 219-230.

Farrar, D. J., J. L. Osborne, et al. (1975). "A urodynamic view of bladder outflow obstruction in the female: factors influencing the results of treatment." BJU **47**(7): 815-22.

FitzGerald, M., B. Blazek, et al. (2000). "Complex repetitive discharges during urethral sphincter EMG: clinical correlates." Neurourol Urodyn **19**: 577.

Fowler, C.J. (2003). "Urinary retention in women - comments." BJUI **91**: 463-468.

Fowler, C. J., C. D. Betts, et al. (1992). "Botulinum toxin in the treatment of chronic urinary retention in women." BJU **70**(4): 387-9.

Fowler, C. J., T. J. Christmas, et al. (1988). "Abnormal electromyographic activity of the urethral sphincter, voiding dysfunction, and polycystic ovaries: a new syndrome?" BMJ **297**(6661): 1436-8.

Fowler, C. J. and R. S. Kirby (1985). "Abnormal electromyographic activity (decelerating burst and complex repetitive discharges) in the striated muscle of the urethral sphincter in 5 women with persisting urinary retention." BJU **57**(1): 67-70.

Fowler, C. J. and R. S. Kirby (1986). "Electromyography of urethral sphincter in women with urinary retention." Lancet **1**(8496): 1455-7.

Fowler, C. J., M. J. Swinn, et al. (2000). "Studies of the latency of pelvic floor contraction during peripheral nerve evaluation show that the muscle response is reflexly mediated." J Urol **163**(3): 881-3.

Fraser, M. O., H. Flood, et al. (1995). "Urethral smooth muscle relaxation is mediated by nitric oxide (NO) released from parasympathetic postganglionic neurons." J Urol **153**: 461A.

Frauscher, F., G. Helweg, et al. (1998). "Intraurethral ultrasound: diagnostic evaluation of the striated urethral sphincter in incontinent females." Eur Radiol **8**: 50-53.

Fujishoro, T., S. Takahashi, et al. (2002). "Magnetic stimulation of the sacral roots for the treatment of urinary frequency and urge incontinence: an investigational study and placebo controlled trial." J Urol **168**: 1036-1039.

Fukuyama, H., S. Matsuzaki, et al. (1996). "Neural control of micturition in man examined with single photon emission computed tomography using 99mTc-HMPAO." Neuroreport **7**: 3009-3012.

Gallien, P., S. Robineau, et al. (1998). "Treatment of detrusor sphincter dyssynergia by transperineal injection of botulinum toxin." Arch Phys Med Rehabil **79**(6): 715-717.

Gjone, R. (1966). "Excitatory and inhibitory bladder responses to stimulation of 'limbic', diencephalic and mesencephalic structures in the cat." Acta Physiol Scand **66**: 91-102.

Gladh, G., S. Mattsson, et al. (2001). "Anogenital electrical stimulation as treatment of urge incontinence in children." BJUI **87**(4): 366-71.

Glass, H. I. and A. M. Harper (1963). "Measurement of regional blood flow in cerebral cortex of man through intact skull." BMJ **1**: 593.

Goode, P., J. Locher, et al. (2000). "Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization." Int Urogynecol J **11**: 296-300.

Govier, F., S. Litwiller, et al. (2001). "Percutaneous afferent neuromodulation for the refractory overactive bladder: results of a multicentre study." J Urol **165**: 1193-1198.

Griffiths, D. (1985). "The pressure within a collapsed tube, with special reference to urethral pressure." Phys Med Biol **30**(9): 951-63.

Griffiths, D. (1998). "Clinical studies of cerebral and urinary tract function in elderly people with urinary incontinence." Behav Brain Res **92**: 151-155.

Griffiths, D. (2002). "The Pontine Micturition Centres." Scand J Urol Nephrol **Suppl 210**: 21-26.

Griffiths, D., S. Derbyshire, et al. (2003). "Cerebral control of bladder function: the brain-bladder connection." Neurourol Urodyn: 65.

Hassouna, M. M., S. W. Siegel, et al. (2000). "Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety." J Urol **163**(6): 1849-1854.

Hilton, P. and S. Stanton (1983). "Urethral pressure measurement by microtransducer: the results in symptom-free women and in those with genuine stress incontinence." BJOG **90**: 919-933.

Hinman, F. J. (1986). "Nonneurogenic neurogenic bladder (the Hinman syndrome) - 15 years later." J Urol **136**: 769-777.

Ho, K., M. Borja, et al. (2003). "Expression of nitric oxide synthase immunoreactivity in the human female intramural striated urethral sphincter." J Urol **169**: 2407-2411.

Hobday, D. I., Q. Aziz, et al. (2001). "A study of the cortical processing of ano-rectal sensation using functional MRI." Brain **124**(Pt 2): 361-368.

Hohenfellner, M., D. Schultz-Lampel, et al. (1998). "Bilateral chronic sacral neuromodulation for treatment of lower urinary tract dysfunction." J Urol **160**(3 Pt 1): 821-824.

Holstege, G., D. Griffiths, et al. (1986). "Anatomical and physiological observations on supraspinal control of bladder and urethral sphincter muscles in cat." J Comp Neurol **250**: 449-461.

Hricak, H., E. Secaf, et al. (1991). "Female urethra: MR Imaging." Radiology **178**: 527-535.

Hsieh, J., M. Belfrage, et al. (1995). "Central representation of chronic ongoing neuropathic pain studied by positron emission tomography." Pain **63**: 225-236.

Janknegt, R., E. Weil, et al. (1997). "Improving neuromodulation: technique for refractory voiding dysfunctions: two-stage implant." Urology **49**: 358-362.

Janknegt, R. A., M. M. Hassouna, et al. (2001). "Long-term effectiveness of sacral nerve stimulation for refractory urge incontinence." Eur Urol **39**(1): 101-106.

Jensen, D. and R. Stien (1996). "The importance of complex repetitive discharges in the striated female urethral sphincter and male bulbocavernosus muscle." Scand J Urol Nephrol **179**: 69-73.

Jezernik, S., M. Craggs, et al. (2002). "Electrical stimulation for the treatment of bladder dysfunction: current status and future possibilities." Neurol Res **24**(5): 413-30.

Jiang, C. H. and S. Lindstrom (1998). "Prolonged increase in micturition threshold volume by anogenital afferent stimulation in the rat." BJU **82**(3): 398-403.
Jonas, U., C. J. Fowler, et al. (2001). "Efficacy of sacral nerve stimulation for urinary retention: results 18 months after implantation." J Urol **165**(1): 15-9.
Jones, A., B. Kulkarni, et al. (2003). "Pain mechanisms and their disorders." Brit Med Bull **65**: 83-93.
Kaplan, W. (2000). "Intravesical electrical stimulation of the bladder: pro." Urology **56**: 2-4.
Kaplan, W., C. Firlit, et al. (1980). "The female urethral syndrome: external sphincter spasticity as an etiology." J Urol **124**: 43-46.
Kawabe, K. and T. Niijima (1987). "Use of an alpha-1 blocker, YM-12617, in micturition difficulty." Urol Int **42**: 280-284.
Kershen, R., J. Kalisvaart, et al. (2003). "Functional brain imaging and the bladder: new insights into cerebral control over micturition." Curr Opin Rep **4**: 344-349.
Kety, S. S. and C. F. Schmidt (1948). "The nitrous oxide method for the quantitative determination of cerebral blood flow: theory, procedure and normal values." J Clin Invest **27**: 476-483.
Khullar, V., S. Salvatore, et al. (1994). "Three dimensional ultrasound of the urethra and urethral sphincter - a new diagnostic technique." Neurourol Urodynam **13**: 337-344.
Kirschner-Hermanns, R., H. Klein, et al. (1994). "Intra-urethral ultrasound in women with stress incontinence." BJU **74**: 315-318.
Klinger, H., A. Pycha, et al. (2000). "Use of peripheral neuromodulation of the S3 region for treatment of detrusor overactivity: a urodynamic-based study." Urology **56**: 766-771.
Klutke, C., J. Golomb, et al. (1990). "The anatomy of stress incontinence: magnetic resonance imaging of the female bladder neck and urethra." J Urol **143**: 563-566.
Koelbl, H., G. Bernaschek, et al. (1988). "A comparative study of perineal ultrasound scanning and urethrocystography in ptients with genuine stress incontinence." Arch Gynecol Obstet **244**: 39-45.
Kondo, Y., Y. Homma, et al. (2001). "Transvaginal ultrasound of urethral sphincter at the mid urethra in continent and incontinent women." J Urol **165**: 149-152.
Kranse, R. and R. van Mastrigt (2002). "Relative bladder outlet obstruction." J Urol **168**(2): 565-70.
Kujawa, M. L., F. Reid, et al. (2001). "Are 'whaling' women normal?" BJUI **88**(Suppl 1): 82.
Kumar, A., A. Mandhani, et al. (1999). "Management of functional bladder neck obstruction in women: use of alpha-blockers and pediatric resectoscope for bladder neck incision." J Urol **162**: 2061-2065.
Kuo, H., S. Chang, et al. (1994). "Application of transrectal sonography in the diagnosis and treatment of female stress urinary incontinence." Eur Urol **26**: 77-.
Lemack, G. E., B. Foster, et al. (1999). "Urethral dilation in women: a questionnaire-based analysis of practice patterns." Urology **54**(1): 37-43.
Lemack, G. E. and P. E. Zimmern (2000). "Pressure flow analysis may aid in identifying women with outflow obstruction." J Urol **163**(6): 1823-1828.

Lindstrom, S., M. Fall, et al. (1983). "The neurophysiological basis of bladder inhibition in response to intravaginal electrical stimulation." J Urol **129**: 405-410.

Lose, G. (2001). "Urethral pressure measurement--problems and clinical value." Scand J Urol Nephrol Suppl(207): 61-66; discussion 106-125.

Lose, G., D. Griffiths, et al. (2002). "Standardisation of urethral pressure measurement: report from the Standardisation Sub-Committee of the International Continence Society." Neurourol Urodyn **21**(3): 258-60.

Lozano, A., J. Dostrovsky, et al. (2002). "Deep brain stimulation for Parkinson's disease: disrupting the disruption." Lancet (Neurol) **1**: 225-231.

Luu, P. and M. Posner (2003). "Anterior cingulate cortex regulation of sympathetic activity (Editorial)." Brain **126**: 2119-2120.

Maddock, R., A. Garrett, et al. (2003). "Posterior Cingulate Cortex Activation by Emotional Words: fMRI Evidence From a Valence Decision Task." Hum Br Map **18**: 30-41.

Madersbacher, H. (1990). "Intravesical electrical stimulation for the rehabilitation of the neuropathic bladder." Paraplegia **28**: 349-352.

Mahony, D. T., R. O. Laferte, et al. (1977). "Integral storage and voiding reflexes. Neurophysiologic concept of continence and micturition." Urology **9**(1): 95-106.

Massey, J. A. and P. H. Abrams (1988). "Obstructed voiding in the female." BJU **61**(1): 36-9.

Matsuura, S., H. Kakizaki, et al. (2002). "Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study." J Urol **168**(5): 2035-9.

Maurice-Williams, R. (1974). "Micturition symptoms in frontal tumours." JNNP **37**(431-436).

McFarlane, J., S. Foley, et al. (1997). "Acute suppression of idiopathic detrusor instability with magnetic stimulation of the sacral nerve roots." BJU **80**: 734-741.

McGuire, E. and E. Herlihy (1978). "Bladder and urethral responses to isolated sacral motor root stimulation." Invest Urol **16**: 219-.

McGuire, E., S. Zhang, et al. (1983). "Treatment of motor and sensory detrusor instability by electrical stimulation." J Urol **129**(78-79).

McGuire, W. (1955). Response of the neurogenic bladder to various electrical stimuli. Dept of Surgery, Bowman Gray School of Medicine.

Mundy, A. (1999). Structure and function of the lower urinary tract. The Scientific Basis of Urology. A. Mundy, J. Fitzpatrick, D. Neal and N. George. Oxford, ISIS: 217-242.

Murray, K. and R. Feneley (1982). "Endorphins - a role in lower urinary tract function? The effect of opioid blockade on the detrusor and urethral sphincter mechanisms." BJU **54**(6): 638-640.

Nashold, B., H. Friedman, et al. (1971). "Electrical activation of micturition by spinal cord stimulation." J Surg Res **11**: 144-147.

Nathan, P. (1976). The central nervous connections of the bladder. Scientific foundations of Urology. D. J. Williams and G. D. Chisholm. London, Heinemann. **2**.

Nitti, V. W., L. M. Tu, et al. (1999). "Diagnosing bladder outlet obstruction in women." J Urol **161**(5): 1535-40.

Noble, J. G., P. J. Dixon, et al. (1995). "Urethral sphincter volumes in women with obstructed voiding and abnormal sphincter electromyographic activity." BJU **76**(6): 741-6.

Nour, S., C. Svarer, et al. (2000). "Cerebral activation during micturition in normal men." Brain **123**(Pt 4): 781-9.

Oliver, S., C. Fowler, et al. (2003). "Measuring the sensations of urge and bladder filling during cystometry in urge incontinence and the effects of neuromodulation." Neurourol Urodyn **22**(1): 7-15.

Ongur, D., X. An, et al. (1998). "Prefrontal cortical projections to the hypothalamus in macaque monkeys." J Comp Neurol **401**(4): 480-505.

Patel, R. and V. Nitti (2001). "Bladder outlet obstruction in women: prevalence, recognition, and management." Curr Urol Rep **2**(5): 379-87.

Petit, H., L. Wiart, et al. (1998). "Botulinum A toxin treatment for detrusor-sphincter dyssynergia in spinal cord disease." Spinal Cord **36**(2): 91-94.

Phelan, M., M. Franks, et al. (2001). "Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction." J Urol **165**: 1107-1110.

Philp, T., P. Shah, et al. (1988). "Acupuncture in the treatment of bladder instability." BJU **61**: 490-493.

Primus, G. and G. Kramer (1996). "Maximal external electrical stimulation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence." Neurourol Urodyn **15**: 187-194.

Quinn, M., J. Beynon, et al. (1988). "Transvaginal endosonography: a new method to study the anatomy of the lower urinary tract in urinary stress incontinence." BJU **62**: 414-418.

Rainville, P. (2002). "Brain mechanisms of pain affect and pain modulation." Curr Opin Neurobiol **12**(2): 195-204.

Rapp, D. E., M. B. Lyon, et al. (2005). "A role for the P2X receptor in urinary tract physiology and in the pathophysiology of urinary dysfunction." Eur Urol **In Press**.

Raz, S. and R. Smith (1976). "External sphincter spasticity syndrome in female patients." J Urol **115**: 443-446.

Reitz, A., D. M. Schmid, et al. (2003). "Electrophysiological assessment of sensations arising from the bladder: are there objective criteria for subjective perceptions?" J Urol **169**(1): 190-4.

Richmond, D. and J. Sutherst (1989). "Clinical application of transrectal ultrasound for the investigation of the incontinent patient." BJU **63**: 605-.

Riedl, C. R., R. L. Stephen, et al. (2000). "Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test." J Urol **164**(6): 2108-11.

Rodic, B., A. Schlapfer, et al. (2002). "Magnetic stimulation of sacral roots for assessing the efferent neuronal pathways of lower urinary tract." Muscle Nerve **26**: 486-491.

Sakakibara, R., T. Hattori, et al. (1996). "Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI." J Neurol Sci **137**: 47-56.

Sakakibara, R., K. Nakazawa, et al. (2002). "Micturition-related electrophysiological properties in the substantia nigra pars compacta and ventral tegmental area in cats." Auton Neurosci **102**(1-2): 30-38.

Salvatore, S., V. Khullar, et al. (2000). "Urodynamic parameters in obstructed women." Neurourol Urodyn **19**: 480.

Schaer, G., T. Schmid, et al. (1998). "Intraurethral ultrasound correlated with urethral histology." Obstet Gynecol **91**: 60-64.

Scheepens, W. A., R. A. de Bie, et al. (2002). "Unilateral versus bilateral sacral neuromodulation in patients with chronic voiding dysfunction." J Urol **168**(5): 2046-50.

Scheepens, W. A., G. A. van Koeveringe, et al. (2002). "Long-term efficacy and safety results of the two-stage implantation technique in sacral neuromodulation." BJUI **90**(9): 840-845.

Scheepens, W. A., E. H. Weil, et al. (2001). "Buttock placement of the implantable pulse generator: a new implantation technique for sacral neuromodulation - a multicenter study." Eur Urol **40**(4): 434-438.

Schmidt, R. A., U. Jonas, et al. (1999). "Sacral nerve stimulation for treatment of refractory urinary urge incontinence." J Urol **162**(2): 352-357.

Schurch, B., D. Hauri, et al. (1996). "Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients." J Urol **155**(3): 1023-1029.

Seki, S., K. Sasaki, et al. (2002). "Immunoneutralization of nerve growth factor in the lumbosacral spinal cord reduces bladder hyperreflexia in spinal cord injured rats." J Urol **168**: 2269-2274.

Shafik, A. and O. El-Sibai (2001). "Effect of pelvic floor muscle contraction on vesical and rectal function with identification of puborectalis-rectovesical inhibitory reflex and levator-rectovesical excitatory reflex." World J Urol **19**(4): 278-84.

Shaker, H., Y. Wang, et al. (2000). "Role of C-afferent fibres in the mechanism of action of sacral nerve root neuromodulation in chronic spinal cord injury." BJU Int **85**(7): 905-10.

Shaker, H. S. and M. Hassouna (1998). "Sacral root neuromodulation in idiopathic nonobstructive chronic urinary retention." J Urol **159**(5): 1476-8.

Sheriff, M., P. Shah, et al. (1996). "Neuromodulation of detrusor hyper-reflexia by functional magnetic stimulation of the sacral roots." BJU **78**: 39-46.

Skultety, F. (1959). "Relation to periaqueductal gray matter to stomach and bladder motility." Neurology **9**(3): 190-198.

Spinelli, M., P. Bertapelle, et al. (2001). "Chronic sacral neuromodulation in patients with lower urinary tract symptoms: results from a national register." J Urol **166**(2): 541-5.

Spinelli, M., G. Giardiello, et al. (2003). "New percutaneous technique of sacral nerve stimulation has high initial success rate: preliminary results." Eur Urol **43**: 70-74.

Spinelli, M., G. Giardiello, et al. (2003). "New Sacral Neuromodulation lead for percutaneous implantation using local anaesthesia: description and first experience." J Urol **170**(5): 1905-1907.

Stoller, M. (2000). "Afferent nerve stimulation for pelvic floor dysfunction." Eur Urol **37 (suppl 2)**: 33.

Supple, W. J. (1993). "Hypothalamic modulation of Purkinje cell activity in the anterior cerebellar vermis." Neuroreport **4**: 979-982.

Swinn, M. J., N. D. Kitchen, et al. (2000). "Sacral neuromodulation for women with Fowler's syndrome." Eur Urol **38**(4): 439-43.

Swinn, M. J., O. J. Wiseman, et al. (2002). "The cause and natural history of isolated urinary retention in young women." J Urol **167**(1): 151-6.

Takahashi, S. and T. Kitamura (2003). "Overactive bladder; magnetic versus electrical stimulation." Curr Opin Obstet Gynecol **15**: 429-433.

Tanagho, E., E. Miller, et al. (1971). "Spastic striated external sphincter and urinary tract infection in girls." BJU **43**: 69-82.

Tanagho, E. and R. Schmidt (1988). "Electrical stimulation in the clinical management of the neurogenic bladder." J Urol **140**: 1331-1339.

Tanaka, Y., Y. Koyama, et al. (2002). "Effects of acupuncture to the sacral segment on the bladder activity and electroencephalogram." Psych Clin Neurosci **56**: 249-250.

Taniguchi, N., M. Miyata, et al. (2002). "A study of micturition inducing sites in the periaqueductal gray of the mesencephalon." J Urol **168**(4 Pt 1): 1626-31.

Trisnar, B. and B. Kralji (1996). "Maximal electrical stimulation in children with unstable bladder and nocturnal enuresis and/or daytime incontinence." Neurourol Urodyn **15**: 133-142.

Ueki, K. (1960). "Disturbances of micturition observed in some patients with brain tumour." Neurol Med Chir **2**: 25-33.

Umek, W., A. Obermair, et al. (2001). "Three-dimensional ultrasound of the female urethra: comparing transvaginal and transrectal scanning." Ultrasound Obstet Gynecol **17**: 425-430.

Valentino, R. J., R. R. Miselis, et al. (1999). "Pontine regulation of pelvic viscera: pharmacological target for pelvic visceral dysfunctions." Trends Pharmacol Sci **20**(6): 253-260.

Valls-Sole, J. and J. Montero (2004). "Role of EMG evaluation in muscle hyperactivity syndromes." JNNP **251**(3): 251-260.

van Balken, M., V. Vandoninck, et al. (2001). "Posterior tibial nerve stimulation as neuromodulative treatment of lower urinary tract dysfunction." J Urol **166**: 914-918.

van Balken, M., H. Vergunst, et al. (2004). "The use of electrical devices for the treatment of bladder dysfunction: a review of methods." J Urol **172**(3): 846-851.

Vandoninck, V., M. van Balken, et al. (2003). "Posterior tibial nerve stimulation in the treatment of idiopathic nonobstructive voiding dysfunction." Urology **61**: 567-572.

Vodusek, D., J. Light, et al. (1986). "Detrusor inhibition induced by stimulation of pudendal nerve afferents." Neurourol Urodyn **5**: 381-389.

Vogt, B., J. Abscher, et al. (2000). "Human retrosplenial cortex: where is it and is it involved in emotion?" TINS **23**: 195-196.

Wang, Y. and M. M. Hassouna (2000). "Neuromodulation reduces c-fos gene expression in spinalized rats: a double-blind randomized study." J Urol **163**(6): 1966-70.

Wheeler, J. S., Jr., D. J. Culkin, et al. (1990). "Female urinary retention." Urology **35**(5): 428-432.

Williams, A., K. Taylor, et al. (2003). "Knowledge of female bladder care among medical staff, nurses and midwives: results of a questionnaire survey." BJUI **91**(3): 208-210.

Winge, K. and C. J. Fowler (2005). "Bladder dysfunction in Parkinsonian Disease and parkinsonian syndromes." Mov Disord **(In Press)**.

Wise, B., G. Burton, et al. (1992). "Effect of vaginal ultrasound probe on lower urinary tract function." BJU **70**: 12-16.

Wiseman, O. J., M. J. Swinn, et al. (2002). "Maximum urethral closure pressure and sphincter volume in women with urinary retention." J Urol **167**(3): 1348-51; discussion 1351-2.

Wiseman, O. J., U. van den Hombergh, et al. (2002). "Sacral neuromodulation and pregnancy." J Urol **167**(1): 165-8.

Wyndaele, J., D. Michielsen, et al. (2000). "Influence of sacral neuromodulation on electrosensation of the lower urinary tract." J Urol **163**: 221-224.

Yamanishi, T., R. Sakakibara, et al. (2000). "Comparative study of the effects of magnetic versus electrical stimulation on inhibition of detrusor overactivity." Urology **56**: 777-781.

Yamanishi, T., S. Yasuda, et al. (2000). "Effect of functional continuous magnetic stimulation for urinary incontinence." J Urol **163**: 456-459.

Yoshimura, N. (1999). "Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder." Prog Neurobiol **57**: 583-606.

Yoshimura, N. and W. C. de Groat (1997). "Neural control of the lower urinary tract." Int J Urol **4**: 111-125.

Zhang, H., A. Reitz, et al. (2005). "An fMRI study of the role of suprapontine brain structures in the voluntary voiding control induced by pelvic floor contraction." Neuroimage **24**: 174-180.

Zhou, Y., Y. Wang, et al. (2002). "Change of vanilloid receptor 1 following neuromodulation in rats with spinal cord injury." J Surg Res **107**(1): 140-4.