Pathophysiology of Bowel Dysfunction in Multiple Sclerosis and the potential for targeted treatment

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Declaration

I, Giuseppe Preziosi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. The Ethics Committee of University College of London granted ethical approval (REC reference number: 08/h07164/7) for the study.

Signed: Date:

Abstract

Bowel symptoms (constipation and/or faecal incontinence) affect the vast majority of patients with multiple sclerosis (MS), but the pathophysiology is unclear and treatment remains empirical.

The primary hypothesis of this thesis is that involvement of the spinal cord by the disease is central to the development of bowel symptoms, and this is tested in the first two studies:

1. A study of the overlap in prevalence of bladder symptoms in patients with MS and bowel symptoms.
2. A study of rectal compliance, as an important reflection of both the gut's neural tone and its ability to hold content, in comparison to patients with supraconal spinal cord injury and normal controls.

The secondary hypothesis is that residual spinal cord function can represent a potential target of treatment, and this is tested in studies 3 and 4:

3. A prospective observational study of bowel biofeedback in symptomatic MS patients.
4. A prospective observational study of transanal irrigation in symptomatic MS patients.

Study 1 shows that the prevalence of bladder symptoms – determined by spinal cord disease - is higher in patients with bowel symptoms than in the general population of MS sufferers.

The second study shows that rectal compliance - as an index of the spinal reflex activity regulating autonomic rectal function – is altered in patients with MS according to the clinical degree of spinal cord involvement by the disease. A similar pattern is followed for symptoms of constipation, but not faecal incontinence.

The two treatment studies showed that:

- Biofeedback improves bowel symptoms and 5-seconds-endurance squeeze pressure. Improvement of sphincter pressure could be the result of behavioural changes, inducing physiological changes through residual efferent pathways in the spinal cord.
- Transanal irrigation is effective to treat bowel symptoms in patients who fail biofeedback.

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Glossary of Abbreviations

ACE	Antegrade Continence Enema
ARP	Ano-Rectal Physiology
ASIA	American Spinal Injury Association
BOP	Basal Operating Pressure
CNS	Central Nervous System
EDSS	Expanded Disability Status Scale
ENS	Enteric Nervous System
IBS	Irritable Bowel Syndrome
MDP	Minimal Distending Pressure
MS	Multiple Sclerosis
MUCCA	Mean Upper Cervical Cord Area
NBD	Neurogenic Bowel Dysfunction
PD	Parkinson's Disease
PEC	Percutaneus Endoscopic Colostomy
PTNS	Posterior Tibial Nerve Stimulation
RAIR	Recto-Anal Inhibitory Reflex
SCI	Spinal Cord Injury
SNM	Sacral Neuromodulation
TAI	Transanal Irrigation

Communications Arising from this Thesis

Published papers

1. Autonomic rectal dysfunction in patients with multiple sclerosis and bowel symptoms is secondary to spinal cord disease.
   G.Preziosi, D. Raptis, A. Raeburn, J. Panicker, A.V. Emmanuel.
   Disease of Colon and Rectum, April 2014 - Volume 57 - Issue 4 - pp 514-521

2. Peristeen transanal irrigation in patients with Multiple Sclerosis.
   G.Preziosi, J. Gosling, A. Raeburn, J. Storrie, J. Panicker, A.V. Emmanuel.
   Diseases of the Colon and Rectum 2012: 55(10), 1066-73

3. Bowel biofeedback treatment for patients with multiple sclerosis and bowel symptoms.
   G.Preziosi, D. Raptis, J. Storrie, A. Raeburn, C.J. Fowler, A. Emmanuel,
   Diseases of the Colon and Rectum 2011: 54(9), 1114–1121

4. Neurogenic bowel dysfunction: pathophysiology, clinical manifestations and treatment.

   Preziosi G., Emmanuel A.V. Expert Review in Gastroeneterology and Hepatology 2009: 3(4), 417-23

5. Gut dysfunction in patients with Multiple Sclerosis and the role of spinal cord involvement by the disease
   G. Preziosi, D. Raptis, A.Raeburn, K. Thirrupathy, J. Panicker, P. Boulos, A.V. Emmanuel.
   Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1044-50

Book Chapters:

Bowel dysfunction in MS, book chapter in Fowler, Panicker & Emmanuel: Pelvic Organ Dysfunction in Neurological Disease & Rehabilitation, pp 220-237

Presentations:

1. The relationship between bowel and uro-genital dysfunction in Multiple Sclerosis
    - Digestive Disease Week, Chicago, (USA), 30/5 - 4/6 2009 (poster)

2. The role of the spinal cord in bowel dysfunction secondary to Multiple Sclerosis: a comparison with Supra-conal Spinal cord injury
    - British Society of Gastroenterology, 16/3/2011, Birmingham (oral)
    - European Federation of Gastroenterology, Barcelona Oct 23 - 27, 2010 (poster)
    - ECTRIMS, Gothenburg 13-16 Oct 2010 (poster)

3. Bowel biofeedback in patients with Multiple Sclerosis and bowel dysfunction
    - Society for Academic and Research Surgery meeting, Dublin 4-5 Jan 2011 (oral)
    - ECTRIMS, Gothenburg 13-16 Oct 2010 (poster)

4. Peristeen transanal irrigation in patients with Multiple Sclerosis
    - British Society of Gastroenterology, 16/3/2011, Birmingham (oral)
    - Society for Academic and Research Surgery meeting, Dublin 4-5 Jan 2011 (oral)
    - ECTRIMS, Gothenburg 13-16 Oct 2010 (poster)

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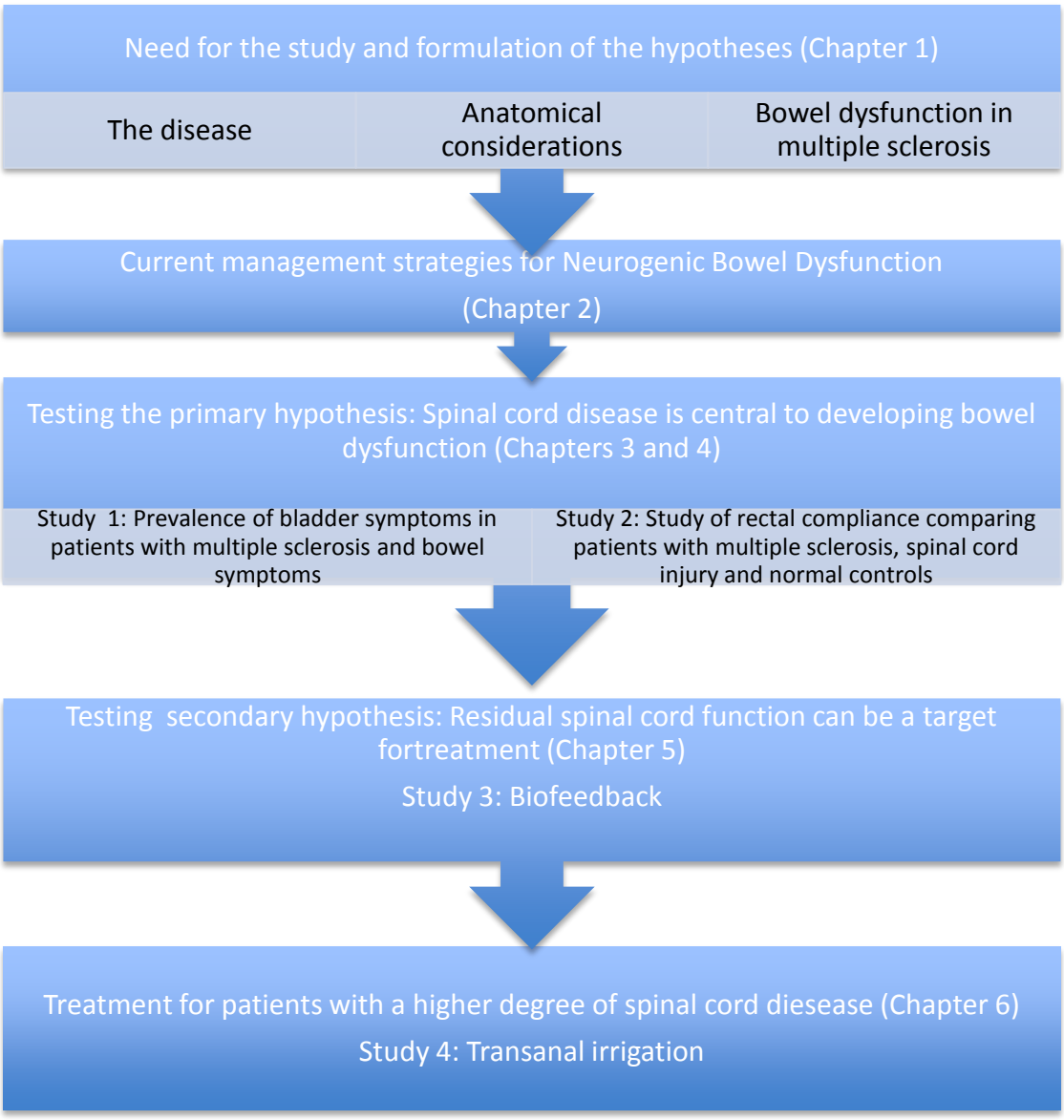
Last but not least, I would like to mention all the members of the GI Physiology Unit, above all Amanda Raeburn who works tirelessly to make the Unit function, and Julie Storrie the clinical specialist nurse of the Unit. She trained patients in biofeedback and transanal irrigation, so I owe a great part of the success of my studies to her.

To my father Ettore

Synopsis

The thesis is structured in a logical manner:



CHAPTER 1: INTRODUCTION

Chapter overview:

- The disease
- Relevant anatomical considerations
- Bowel dysfunction in multiple sclerosis, detailing alteration of physiological process of defecation
- Possible mechanism of constipation in multiple sclerosis
- Possible mechanism of faecal incontinence in multiple sclerosis
- Primary and secondary hypotheses

1.1 The Disease

Multiple Sclerosis (MS) is the most common neurological disorder in young adults, and affects around 100,000 people in the UK (Sara L Thomas, 2009; World Health Organization, 2008), with a worldwide peak of recorded prevalence in Scotland of 193 per 100,000 inhabitants (Pugliatti *et al*, 2002) and an average of 1 per 1000 in the Western world (Williams *et al*, 1995).

The disease is characterised by an autoimmune response that results in the disruption of the myelin sheath in the central nervous system (CNS), (demyelination), and the subsequent gliosis leads to the widespread occurrence of plaques in the white matter of the CNS (Figure 1.1). These plaques affect signal transmission in the CNS, and the wide spectrum of symptoms reflects the variety of neurological pathways affected. The aetiology is unknown and currently there is no

treatment that can affect the natural history of the disease, which is of a progressive accumulation of neurological symptoms leading to severe disability.

Eighty per cent of patients present with relapsing remitting symptoms and only in a minority (5-37%) of cases is the disease progressive from the beginning (Compston, 2006). Based on clinical course MS is classified as: relapsing remitting, secondary progressive, primary progressive and progressive relapsing. Although most present with relapsing remitting disease, the median time to secondary progression using survival techniques is 11 years (Confavreux *et al*, 1980).

There are significant pathological differences between relapsing remitting MS and progressive MS, with more new and active focal inflammatory demyelinating lesions in the white matter of patients with relapsing disease. In contrast, diffuse injuries of the normal appearing white matter were observed in primary and secondary progressive multiple sclerosis (Kutzelnigg *et al*, 2005). Axonal loss resulting in atrophy of both the brain and spinal cord is of critical importance in determining permanent clinical disability, particularly in patients with progressive disease (Furby *et al*, 2008). Recent studies have suggested that inflammation is the driving force for brain injury in progressive MS, but anti-inflammatory and immunomodulatory therapies do not have a significant effect (Bradl & Lassmann, 2009).

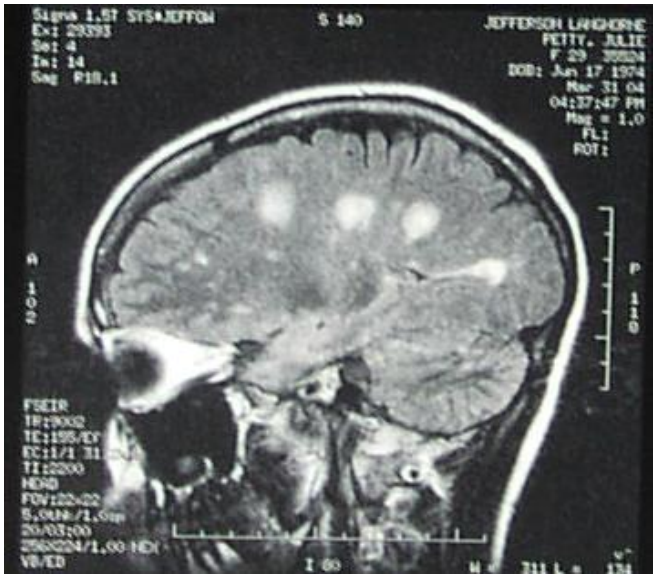


Figure 1.1: Sagittal MRI brain scan demonstrating sclerotic plaques in the white matter in a patient with MS.

1.2 Anatomical Considerations

The voluntary voiding of faeces, faecal continence and the ability to delay defecation rely on the integrity of several neuro-muscular structures, the influx of hormones and luminal content, stool consistency as well as psychological factors and the ability to access the toilet.

Schematically normal colonic transit will allow stools to reach the rectum; in the presence of a normal rectal reservoir and preserved rectal sensation, an urge to defecate will arise, and the recto-anal inhibitory reflex (RAIR, also called the sampling reflex, Figure 1.2) will allow rectal content to come in contact with the anal epithelium. This event has the dual function of both distinguishing the nature of the rectal content (solid, liquid or gas) to allow selective voiding and also to signal to the brain to take a conscious decision if defecation has to be delayed.

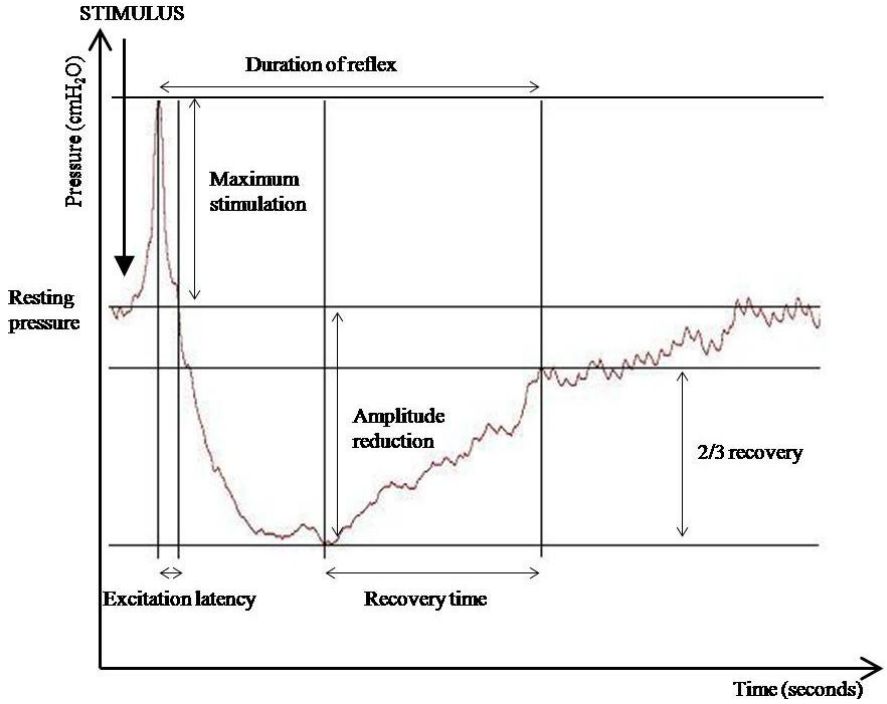


Figure 1.2: The various components of RAIR wave on a manometry trace

- Excitation peak: initial increase in the resting pressure associated with the sudden rectal distension.
- Excitation Latency: duration from the point of excitation peak back to the baseline pressure.
- Point of maximum relaxation: lowest point of resting pressure secondary to reflex IAS relaxation.
- Recovery time: the duration between maximum relaxation and the point at which the resting pressure recovers to two-thirds its baseline.
- Total reflex duration: calculated as the duration from the point of the Excitation Peak to the point two thirds' the recovery.

In the presence of normal anal sensation voluntary contraction of the external anal sphincter will allow deferment to a time that is deemed appropriate. The tonic contraction of the internal anal sphincter (with the contribution of the external anal sphincter and vascular haemorrhoidal cushions) stops seepage of rectal content (Figure 1.3).

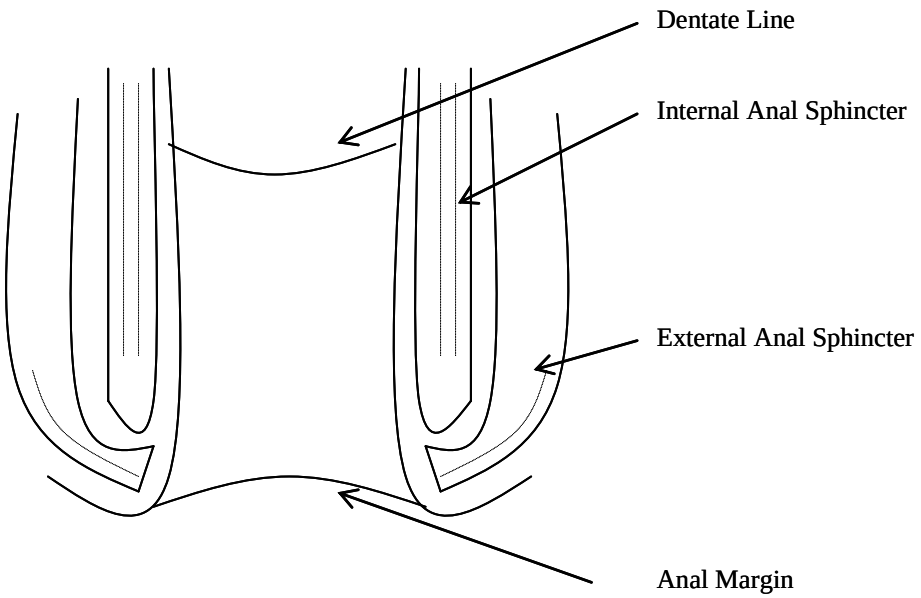


Figure 1.3: The anal sphincter complex

Defecation is initiated by assuming an appropriate toileting position, and increasing abdominal pressure by the action of the abdominal muscles, in synchrony with the coordinated relaxation of the pelvic floor muscles (Figure 1.4).

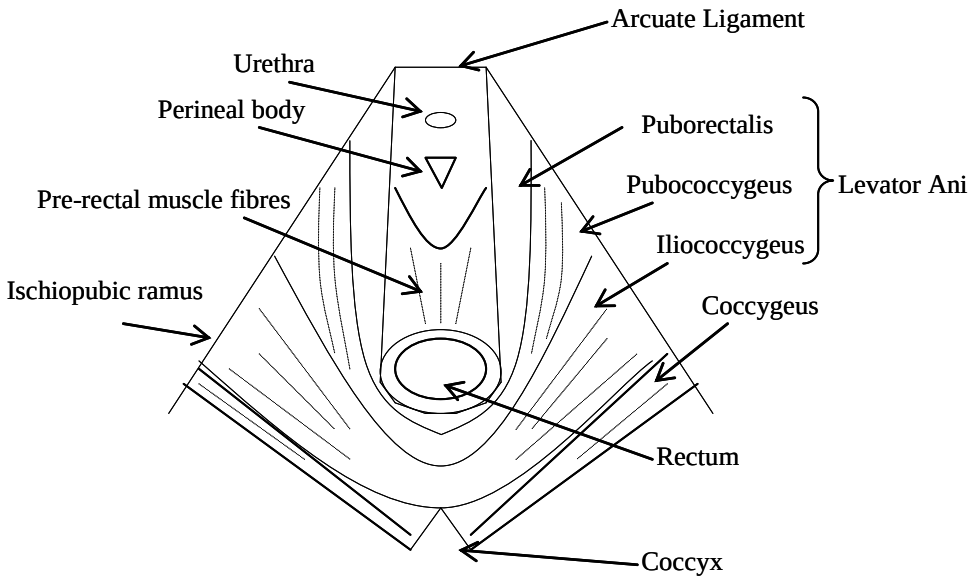


Figure 1.4: The male pelvic floor

1.2.1 Extrinsic Innervation of the Gut

Somatic and visceral sensation from the ano-rectum is conveyed through afferent fibres to the cortex via the sacral segments. The pudendal nerve is responsible for the anal sensation, whilst parasympathetic fibres from the sacral segments S2-S4 cover sensation from the rectum. Proximal colonic innervation is from the vagus nerve for the parasympathetic stimulating and sensorial component, whilst the inhibitory sympathetic fibres arise from the thoracic spinal cord (T5-L2) to the colon and rectum (Figure 1.5).

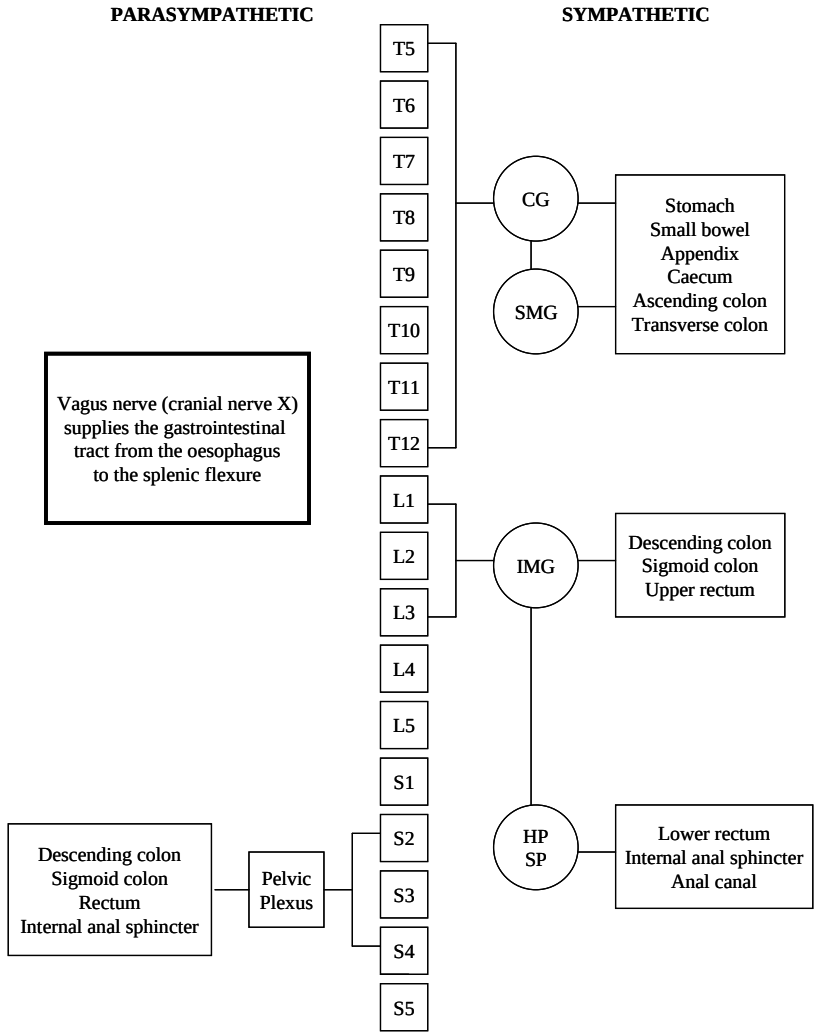


Figure 1.5: Autonomic innervation of the bowel

CG, coeliac ganglion; SMG, superior mesenteric ganglion; IMG, inferior mesenteric ganglion; HP, hypogastric plexus; SP, sacral plexus

The internal anal sphincter is a continuation of the circular muscle layer of the bowel, and its slow-twitch, fatigue-resistant smooth muscle is responsible for 80% of resting anal pressure (Schweiger, 1979). This is maintained by tonic sympathetic discharge (Frenckner & Ihre, 1976). The external anal sphincter is a striated muscle under voluntary control from Onuf´s nucleus in the ventral horn of the sacral spinal cord via the pudendal nerve (S2-S3).

1.2.2 Intrinsic Innervation of the Gut

As I will discuss in Chapter 4, the bowel and the bladder share many similar anatomical and functional features. However, their specialisation is related to crucial structural differences. One of these is the presence in the bowel wall of the enteric nervous system (ENS), which is represented by two ganglionated plexuses, the myenteric and submucosal plexus, located within the bowel wall. The ENS, through a variety of neuropeptides, coordinates peristalsis as well as the secretive and absorptive function of the colo-rectum that is only modulated by the extrinsic innervation (Goyal & Hirano, 1996).

The myenteric plexus is primarily concerned with the control of the smooth muscles in the longitudinal and circular layers of the bowel wall, whilst the submucosal plexus is mainly secretomotor and has a sensory component.

1.2.3 Cerebral Control of Defecation

The higher defecation centres are not well anatomically defined, but sensorial information are integrated at cortical level to generate appropriate responses. The sensation from the gut is conveyed via the spinal cord to the periaqueductal grey

matter and thalamus. The cortex is then reached through the insula and limbic system (Mayer *et al*, 2006). It has been suggested that a defecation centre exists within the brainstem (Weber *et al*, 1985).

In the last two decades, functional brain imaging – notably positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – has allowed us to gain more insight in our knowledge of the brain control of defecation.

Sensory pathways are clearly crucial to brain-gut interactions, and maintaining anorectal function. Visceral sensation is conveyed via spinal and vagal afferents. The latter projects to the brainstem nucleus of the solitary tract (Andrews, 1986), at which level reflex control of gut function is integrated (Sawchenko, 1983). Spinal afferents are mainly through the spinothalamic tract and the dorsal columns.

A sequence of PET, fMRI (Aziz *et al*, 1997), electro-encephalography (EEG) and magneto-encephalography studies have allowed us to identify cortical activation with visceral stimulation.

Most of these studies have focused on oesophageal sensation, because of the feature of this organ of both a somatic (upper third) and visceral (lower part) innervation. Nevertheless, cortical activation patterns of the anorectum appear to be similar to that of the oesophagus (Mertz *et al*, 2000; Silverman *et al*, 1997). A consistent finding seems to be activation of the cingulate cortex, the insula, the prefrontal cortex, the primary and secondary somatosensory cortex and the thalamus (Rapps *et al*, 2008). In the primary somatosensitive cortex representation of visceral sensation is less defined. The involvement of limbic and para-lymbic

structures, such as the cingulate, the insula and the prefrontal cortices (Bittorf *et al*, 2006) might explain how psychological factors also can play an important role in the elaboration of rectal visceral sensation, as demonstrated in patients with Irritable Bowel syndrome (IBS) (Mertz *et al*, 2000).

The importance of the cerebral control of anorectal function is also demonstrated in patients with stroke of the frontal lobes, who develop fecal incontinence (Nakayama *et al*, 1997; Weber *et al*, 1990). This has raised the possibility of a frontal lobe "defecation center" analogous to the micturition control locus in the midline frontal lobe.

Trans-cranial magnetic stimulation offers the possibility of evaluating brain-gut efferent signals. In this technique, a "figure-of-8-shape" coil is placed on the scalp, and a magnetic stimulator discharges a high-current magnetic pulse that focally stimulates the underlying motor cortex. Gut electromyographic (EMG) activity is then measured in response to direct stimulation of the cerebral cortex (Rothwell *et al*, 1991). Using this technique, it has been shown that there is bilateral cortical representation of the anal, and pelvic floor muscles within the primary motor cortex (Turnbull *et al*, 1999). Trans cranial magnetic stimulation has also been used to induce changes in anorectal functions that may be important in maintaining continence (Hendermann J, 1995), demonstrating the cortical influences on the gut. This has confirmed that although autonomic nervous reflexes primarily control gut motor activity, it can also be influenced by cortical activity, and autonomic colonic motility is modulated by cortical influxes.

Essentially, from the neural point of view, the act of defecation is a reflex arch controlled and modulated by cortical efferents, and MS can disrupt this at several levels of the neural hierarchy, sometimes at different levels at the same time; damage can fluctuate according to disease progression.

1.3 Bowel Dysfunction in Multiple Sclerosis

Faecal incontinence occurs in 1-2% of the general adult population (Nelson *et al*, 1995), while the prevalence of constipation varies between 2% to 20% (Heaton *et al*, 1992). Bowel dysfunction, manifest as constipation and/or incontinence, often co-existing and alternating, affects between 39 and 73% of patients with MS (Bakke *et al*, 1996; Hinds *et al*, 1990; Hinds & Wald, 1989; Munteis *et al*, 2006; Nordenbo *et al*, 1996).

The pattern of bowel dysfunction is variable, with constipation being the more prevalent symptom. Around half of MS patients experience some degree of faecal incontinence during the course of the disease and for 25% of the patients it represent a permanent feature (Hinds & Wald, 1989). Quality of life is greatly reduced because of these symptoms (Norton & Chelvanayagam, 2010) which limit patients' ability to work – the third cause of inability to work after spasticity and incoordination- (Bauer *et al*, 1965) and cause them great psychosocial disability (Hornby, 1978). Furthermore, these symptoms are frequently under-reported and underestimated (Trezza *et al*, 1999).

1.4 Multiple Sclerosis and Bowel Physiology

The genesis of bowel symptoms as a consequence of MS can be attributed to disturbances of neurological pathways, disability and behavioural alterations. There are also factors with a high impact on the gastrointestinal tract, which are not directly related to the disease, but rather are a consequence, such as the effect of certain drugs and diet-modifications induced symptoms (restriction of fluid or food intake). Very little evidence is available on the pathophysiology of bowel dysfunction. I will discuss both potential mechanisms and what evidence is available in the literature, considering the different level of neural hierarchy and the effect of MS on the end organ.

1.4.1 Cortex

It can be speculated that at the cortical level the voluntary control of bowel function could be lost as the result of the involvement of the frontal lobe; this can cause psychosocial behavioural disturbances, resulting in the loss of voluntary control of stools or failure of relaxation of the pelvic floor and obstructed defecation. Emotional factors and behavioural changes may influence toileting habits directly, or via altered autonomic control of gut function (i.e. loss of supraspinal modulation of spinal reflexes) (Wiesel *et al*, 2001).

1.4.2 The Spinal Cord

The spinal cord seems to have a crucial causative role in bowel dysfunction. Disturbances in the spinal cord control of colonic motility are a relevant factor in determining bowel dysfunction and this has been widely demonstrated in patients

with spinal cord injury (SCI) (Aaronson *et al*, 1985; Glick *et al*, 1984; Gore *et al*, 1981; Sun *et al*, 1990a). In MS, the role of the spinal cord is based only on indirect and inconclusive evidence. Conduction in the central motor pathways to the sphincteric sacral neurons is delayed in MS (Snooks & Swash, 1985).

Patients with MS and bowel dysfunction have showed delayed somato-sensory evoked potentials from the spinal cord to the brain, with normal potentials recorded at the lumbar spine (Haldeman *et al*, 1982). There is also evidence for the involvement of motor spinal pathways, as conduction times between cortex to lumbar spine and cortex to pelvic floor striated muscle conduct were prolonged in some patients with MS and bowel symptoms (Mathers *et al*, 1990).

1.4.3 Pelvic Floor Dyssynergia

Another phenomenon described is pelvic floor incoordination, resulting from the loss of cortical modulation of spinal reflexes that causes the pelvic organs to function automatically, and this is the explanation of the bladder detrusor dyssynergia (Betts *et al*, 1993). A similar mechanism might occur with MS patients, with the generation of uncoordinated pelvic floor contractions responsible for the genesis of outlet obstruction (pelvic floor dyssynergia) (Chia *et al*, 1996). These abnormalities have been well documented with proctography in patients with MS and intractable constipation (Gill *et al*, 1994) and paradoxical contraction of puborectalis on straining have been found on electro-myography (Mathers *et al*, 1990).

1.4.4 Colonic Transit

Another shared feature between SCI and MS patients is delayed colonic transit time, particularly in the left colon (Chia *et al*, 1996; Nicoletti *et al*, 1992; Waldron *et al*, 1993; Weber *et al*, 1987). This could be the result of reduced parasympathetic outflow or be secondary to obstructed defecation (Chia *et al*, 1996), but it has also been suggested that slow transit could be secondary to a dampened gastro-colic reflex (Glick *et al*, 1982). On the other hand, increased motility through the generation of intracolonic pressures has been observed and can be related to the interruption of the normal cortical inhibition of colonic motor activity (Glick *et al*, 1982).

1.4.5 Ano-Rectal Unit Alterations

Rectal hyposensitivity is another of the features of MS and sensory thresholds have been found to be altered, with reduced sensitivity of rectal fullness (Glick *et al*, 1982; Nordenbo *et al*, 1996). Associated attenuated anal sensation has also been associated with the onset of bowel symptoms (Munteis *et al*, 2006; Nordenbo *et al*, 1996).

Studies looking at the rectal properties in patients with MS have shown that the basal tone of the rectal wall is increased (Glick *et al*, 1982; Haldeman *et al*, 1982; Weber *et al*, 1987), and compliance reduced (Nordenbo *et al*, 1996). I will discuss rectal compliance in more detail in Chapter 5.

Finally, another possible and recurrent finding is weakness of the external sphincter (Chia *et al*, 1996; Jameson *et al*, 1994b; Nordenbo *et al*, 1996; Swash *et al*, 1987;

Weber *et al*, 1987). This could be the result of impaired function of the striated muscle that is ubiquitous in MS or as the result of alterations in motor pathways as discussed above (Mathers *et al*, 1990; Snooks & Swash, 1985). The hypothetical mechanism underlying it could therefore be a reduction in conduction of the motor pathways extending from the motor cortex to synapse with neurons in Onuf's nucleus in the anterior horn of the sacral spinal cord segments. Sphincter weakness could also be due to coexisting pathologies (parity, diabetes, lumbar disc prolapse) (Swash *et al*, 1987).

1.5 Symptoms and Physiological Correlation

In the evaluation of patients with MS and bowel symptoms, both pre-existing and co-existing factors should be considered and this will be discussed in more detail in Chapter 2. I will now describe the physiological alteration within the context of the symptoms.

1.5.1 Constipation

Overall it appears that constipation is related to disability, disease duration, presence of bladder dysfunction and the use of medications (Hinds & Wald, 1989). A recurrent finding is increased colonic transit, which can result in a loss of supraspinal modulation of the spinal reflex activity, and unopposed the sacral sympathetic outflow to the large bowel. Other factors might be represented by reduced mobility, dampened gastro-colic reflex and the retrograde effect of pelvic floor dyssynergia. In fact spastic contraction of the external anal sphincter might generate an increase in transit time in subjects with idiopathic constipation (Klauser *et al*, 1990).

Pelvic floor incoordination has a definite role in the genesis of obstructed defecation, resulting from the lack of relaxation of the puborectalis muscle and of the anal sphincter, or from the generation of inadequate expulsive forces (rectal contraction and increase in intra-abdominal pressure). This has been shown to determine constipation in the general female population (Read *et al*, 1986) and has been documented with radiological evidence (Halligan *et al*, 1995).

This phenomenon of incoordination of pelvic floor muscles could be parallel to bladder detrusor dyssynergia and be manifested by a pelvic level of spasticity and incoordination, a result of the loss of modulation of the spinal activity. However, the recto-anal incoordination seen in some MS patients may be a behavioural phenomenon, as in non-neurologically impaired patients (Halligan *et al*, 1995), particularly those who have experienced incontinence or have difficulty accessing the toilet through disability.

Blunting of rectal sensation can be the cause of constipation by reducing the urge to defecate, but could also contribute to the genesis of outlet obstruction with two possible mechanisms. In fact reduced sensation could result in a sensory-motor alteration of the rectum and in the genesis of inadequate rectal contraction. Also, blunting in the urge to defecate in patients with reduced rectal sensation could result in a failure of relaxation of the pelvic floor on straining (Gladman *et al*, 2006). A further possible cause of failure of relaxation of the external anal sphincter could be a disturbance of the RAIR (Thiruppathy *et al*, 2012). Fatigue and weakness of the abdominal wall are a contributing factor to a functionally altered defecation, through the production of inadequate expulsive forces.

It has been observed that constipation in MS patients is associated with decreased rectal compliance, accompanied by reduced rectal and anal sensation (Nordenbo *et al*, 1996). This could result in reduced awareness of rectal content due to a lack of rectal wall distension, and is reflected in the reduction or loss of normal desire to defecate; at the same time this explains the associated urgency and urge incontinence, with the sudden generation of contraction of the rectal wall, and late awareness of the initiation of defecation due to reduced anal sensation.

The co-existence of bladder dysfunction and the distress resulting from urinary urgency and incontinence induces patients to reduce fluid intake, which in turn dehydrates the stools, making their progress and expulsion difficult. In parallel, patients with faecal urgency and incontinence drastically reduce their food intake in an attempt to constipate themselves. Sometimes the quality of diet might be poor as a consequence of unemployment, where patients tend to prefer cheap high calorie-low fibre food.

Drugs are certainly relevant, in particular medication for spasticity (gabapentin) and antidepressants (tryciclic and amytriptiline), as well as anti-cholinergic drugs used for bladder dysfunction.

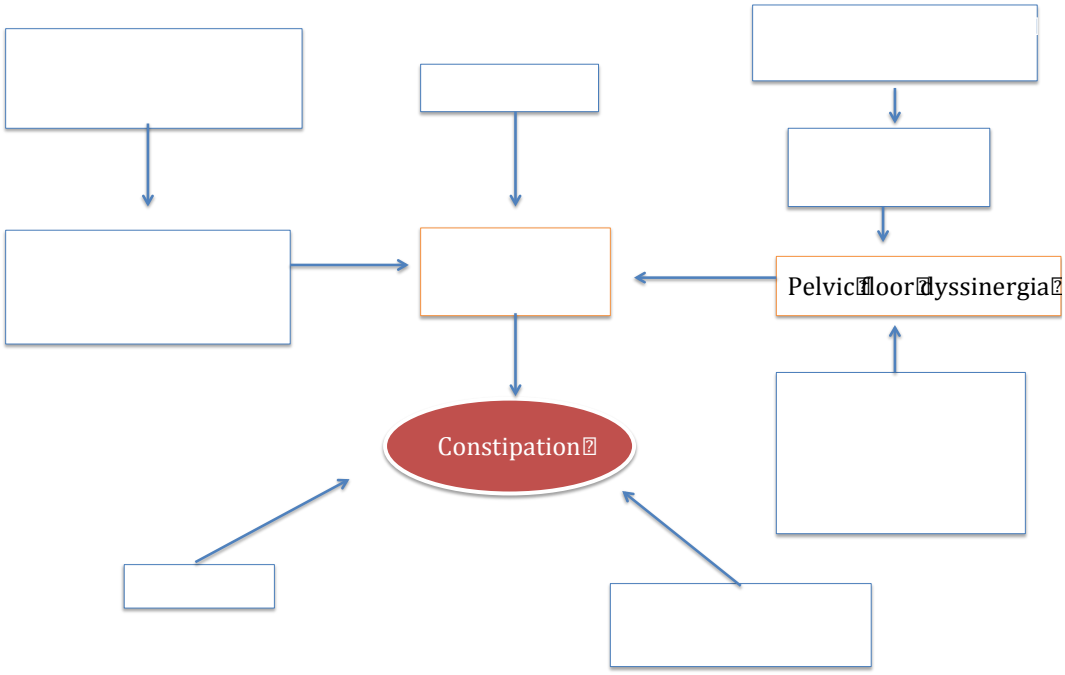


Figure 1.6: Potential mechanisms underlying constipation in MS patients

1.5.2 Incontinence

Faecal incontinence is an on-going complaint in about 25 % of patients, whilst 50% of patients will have been affected at some point (Hinds *et al*, 1990). The involuntary loss of stools is critically related to the lack of ano-rectal sensation and anal sphincter weakness (Speakman & Kamm, 1993). Hyposensitivity is a potential cause of incontinence on its own, even in the presence of a normal sphincter. The reduced rectal sensation is responsible for a delay or absence of the perception of rectal fullness; this afferent component is essential to trigger voluntary contraction of the anal sphincter once the RAIR has been activated by rectal distension, particularly as this occurs at a lower threshold in patients with reduced rectal sensation (Sun *et al*, 1990b).

Rectal compliance and sensation interact as crucial elements of the reservoir function of the rectum, and their alteration is frequently combined in MS. Rectal compliance was found to be reduced in a small study that employed an out-dated technique of measurement (Nordenbo *et al*, 1996). Still it can be speculated that this has the dual effect of making the patient constipated, and with the build-up of faeces, can generate a sudden uncontrollable rectal contraction. The mechanisms described above are also the basis of faecal urgency.

Sphincter weakness is also a potential feature in MS as discussed earlier, and childbirth could be an aggravating factor contributing by direct sphincter damage, or by damaging the pudendal nerve (Swash *et al*, 1987).

Often the presence of loose or liquid stool will be the cause of incontinence, and the underlying dysfunction might be the generation of high intracolonic pressures and uncontrolled peristalsis, a phenomenon that has been observed in patients with a SCI (Glick *et al*, 1984). As the external sphincter contributes to the resting anal pressure, its weakness, in the presence of loose stools, might cause seepage of rectal content. A prolonged recovery phase of the RAIR has been found to be correlated to faecal incontinence (Thiruppathy *et al*, 2012).

Rectal impaction of faeces and overflow should also be considered as a cause of incontinence. Dietary irritants such as caffeine and alcohol should be considered as contributing factors, and eliminated when present. In addition, medications that reduce spasticity in striated muscle may be contributing to the problem. These primarily include baclofen and tizanidine, both frequently used in MS, and their

dose or scheduling may need to be adjusted. In Figure 1.7 I relate the potential mechanisms for faecal incontinence.

Rectal compliance, ano-rectal sensation, sphincter control, RAIR and colonic motility are factors involved in a coordinated process, and along with voluntary control of bowel function allow the normal process of defecation. These have been considered separately but they can reciprocally affect one another, contributing to the onset of bowel symptoms in MS.

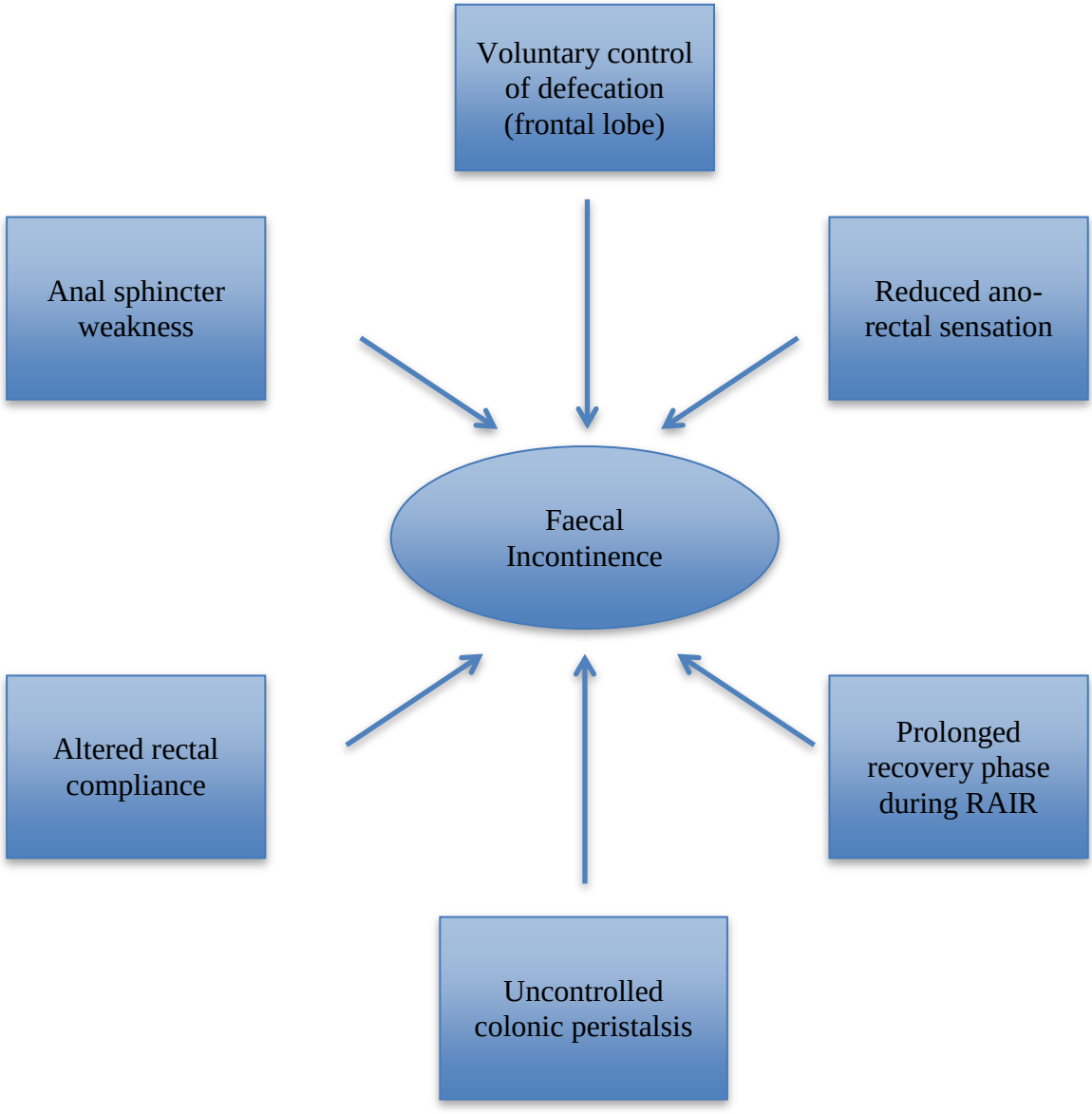


Figure 1.7: Mechanisms underlying faecal incontinence in patients with MS.

1.6 Hypothesis

It appears evident that there is a lack of systematic and hypothesis-driven studies. Most of the literature available is old and either based on retrospective series, small prospective studies without a control group or physiological studies performed with out-dated modalities.

In fact this study is the first that aims to define the pathophysiology of bowel symptoms on the basis of a hypothesis and to lay the foundation for future systematic studies and randomised controlled trials in the area of neurogenic bowel dysfunction secondary to MS.

1.6.1 Primary Hypothesis

I hypothesise that bowel dysfunction in MS is secondary to extent of spinal cord involvement by the disease, assessed clinically with the Expanded Disability Status Scale (which I will describe in chapter 3.5). From this hypothesis we developed 2 studies:

Study 1: Relationship between bowel and bladder dysfunction

Study 2: The role of the spinal cord in bowel dysfunction secondary to MS: a comparison with SCI

1.6.2 Secondary Hypothesis

My secondary hypothesis is that the treatment strategies should target residual spinal cord function. This hypothesis was tested in a prospective observational study:

Study 3: Bowel biofeedback treatment in patients with MS and bowel symptoms (pilot study)

For patients that do respond to biofeedback or are too disabled for this treatment, mechanical bowel emptying should be considered as an option. We therefore carried out the fourth study:

Study 4: *Transanal Irrigation for bowel symptoms in patients with MS*

I will next discuss neurogenic bowel dysfunction in the most common neurological diseases, and available treatment strategies.

The Ethics Committee of University College of London granted ethical approval (REC reference number: 08/h07164/7) for the study.

CHAPTER 2: NEUROGENIC BOWEL DYSFUNCTION: PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS AND TREATMENT

Neurogenic bowel dysfunction: pathophysiology, clinical manifestations and treatment.
Preziosi G., Emmanuel A.V.
Expert Review in Gastroeneterology and Hepatology 2009 Aug;3(4):417-23.

Chapter overview:

- Neurogenic bowel dysfunction, introduction
- Neurophysiology of bowel dysfunction in SCI and MS
- Neurophysiology of bowel dysfunction in Parkinson's Disease
- Management

2.1 Introduction

Bowel symptoms (faecal incontinence, infrequent or difficult defecation) are both common and severely troubling problems for patients with SCI, MS and Parkinson´s Disease (PD). The aetiology of these symptoms is complex: there may be autonomic and pelvic nerve dysfunction (with attenuation of voluntary motor function, and impaired ano-rectal sensation and ano-rectal reflexes), or generalised systemic factors (altered diet and behaviour, impaired mobility, psychological disturbance or drug adverse effects). The mainstay of current treatment is adapting a conservative approach towards reversing the systemic effects and optimising the mechanics of defecation through the use of laxatives and irrigation approaches. When successful,

this approach improves both evacuation and incontinence symptoms, with associated improvements in quality of life and independence. Future therapies may be directed at modulating pelvic innervation through electrical stimulation. Stoma formation remains an option for patients refractory to other approaches.

2.1.1 Overview

Disorders of the CNS are common, with worldwide estimates of the prevalence of SCI at over 2.5 million, MS considerably greater than 1.5 million and PD approximately 3 million (Lang & Lozano, 1998a; Lang & Lozano, 1998b; Saunders *et al*, 2009; Williams *et al*, 1995). Whilst mobility, pain and bladder dysfunction has been relatively well studied, bowel and pelvic floor dysfunction has been comparatively, something of a Cinderella subject. This is doubly unfortunate, as a large proportion of patients with CNS dysfunction experience frequent bowel symptoms, and these symptoms are amongst the most physically, socially and emotionally disabling (Edwards *et al*, 1992; Glickman & Kamm, 1996; Hinds *et al*, 1990). In this chapter I will deal primarily with the bowel dysfunction associated with three common CNS diseases – SCI, MS and PD. The literature on the most common of all CNS diseases – stroke – is patchier and is often directed towards acute post-stroke problems as opposed to chronic neurogenic bowel dysfunction. With rapid advances in rehabilitation medicine resulting in increased survival of patients, these individuals are experiencing bowel symptoms for ever longer periods.

2.1.2 The Scale of the Problem

Spinal cord injuries are common, with an estimated 50 people per million sustaining a traumatic spinal injury every year in the Western world (De Vivo, 2002). Non-traumatic injury (vascular, infection, tumour) is even more common, and cancer alone is estimated to cause more SCI than trauma (Avery & Avery, 2008). Traumatic injuries mostly affect young men, and advances in rehabilitation medicine mean that the longevity of paraplegics is similar to the general population, while that of tetraplegics is 10 years shorter (Biering-Sorensen *et al*, 1990). Bowel dysfunction affects almost all patients with a chronic SCI – up to 95% report constipation, faecal incontinence is experienced at least once per year by 75% and daily by 5%, with 33% experiencing regular abdominal pain (Finnerup *et al*, 2008; Glickman & Kamm, 1996; Krogh *et al*, 1997). Inevitably, given the nature and chronicity of the bowel symptoms, this represents a significant contributor to reduced quality of life in SCI individuals (Glickman & Kamm, 1996). Patients with SCI reported bowel dysfunction as more problematic than bladder dysfunction, pain, fatigue and body image (Glickman & Kamm, 1996).

Bowel dysfunction in MS is less well studied, but almost as prevalent as in other neurological conditions. The prevalence of MS is approximately 1 per 1 000 (Williams *et al*, 1995). As discussed in Chapter 1, about one-third of MS patients suffer from constipation and one-quarter are incontinent at least once per week (Bakke *et al*, 1996; Hinds *et al*, 1990). In patients with PD, constipation, in particular difficulty with defecation occurs in 37% (Krogh *et al*, 2008). One quarter of stroke

survivors experience constipation, and 15% suffer with faecal incontinence (Doshi *et al*, 2003).

2.2 Neurophysiology of Bowel Dysfunction in Spinal Cord Injury and Multiple Sclerosis

The pathophysiology of pelvic floor and colorectal dysfunction is broadly similar in patients with both SCI and MS. The extent of injury is the most important factor in determining bowel symptoms in both SCI and MS. However, whereas in chronic SCI patients the lesion is usually sharply defined and unchanging, in patients with MS the lesions typically occur at multiple levels within the CNS and tend to vary with time. Pathophysiology of MS-related bowel dysfunction has already been discussed in detail, so I will now focus on alterations observed in SCI, highlighting any similarity.

Standard clinical classification of SCI relates to the level of injury and completeness. The International Standards for Neurologic and functional classification of SCI classifies it according to neurologic level (the most caudal segment of the spinal cord with minimal sensory or motor function in both sides of the body). The severity of damaged is assessed by the American Spinal Injury Association (ASIA) Impairment Scale (Marino *et al*, 2003).

Table 2.1: American Spinal Injury Association impairment scale

A	complete	No sensory or motor function preserved in sacral segments S4 to S5
B	incomplete	Sensory but no motor function preserved below the neurologic level, including S4 to S5 sacral segments
C	incomplete	Motor function preserved below the neurologic level and more than half of key muscles below the neurologic level have a muscle grade below 3 (useless)
D	incomplete	Motor function preserved below the neurologic level and more than half of key muscles below the neurologic level have a muscle grade of 3 or higher (useful) (incomplete)

Depending on the level involved in the spinal cord they are divided in:

- Supraconal or suprasacral (lesion above the conus medullaris – T5, conventionally termed upper motoneuron lesions) interrupting modulatory pathways that normally coordinate bowel and sphincter function.
- Lesions of the sacral cord or nerve roots (cauda equina type injury -lumbar–sacral nerve roots damage or disease) conventionally termed lower motor neuron lesions as they disconnect part of the bowel and sphincters from their source of innervation in the spinal cord.

In supraconal SCI, an 'upper motor neurone' type injury of the bowel results in slowed whole gut transit (Lynch *et al*, 2000; Sun *et al*, 1995) and hypertonia and hyperreflexia of the hindgut (i.e. distal to the splenic flexure) (Krogh *et al*, 2000; Lynch *et al*, 2000). The slowing of transit is autonomic-mediated, but also contributed to by reduced mobility and attenuation of the gastro-colic response (Aaronson *et al*, 1985). The rectal hypertonia results in reduced rectal compliance and predisposes to reflex defecation and incontinence. In cauda equina lesions the

efferent limb of the reflex arc to the hindgut is interrupted, resulting in a 'lower motor neurone' type bowel dysfunction with hypotonia and hyporeflexia (Krogh *et al*, 2003).

Supraconal injury tends not to alter anal tone, whilst the reduced tone of cauda equina lesions may relate to faecal bilus impaction as much as loss of parasympatehtic input. Thus, in motor complete SCI the voluntary control of the external anal sphincter is lost (Craggs *et al*, 2006). Completeness of the SCI according to the ASIA criteria can be confounded when looking at function of the ano-rectum. For example, in clinical practice a patient with a motor incomplete SCI might not have voluntary contraction of the external anal sphincter. It appears in fact that both patients with complete and incomplete SCI have similar symptoms, and that the level of injury might be more relevant (Valles & Mearin, 2009).

Rectal hyposensitivity occurs in both supraconal and cauda equina lesions, and predisposes to faecal impaction (especially in the flaccid rectum of patients with cauda equina lesions) (Krogh *et al*, 2003).

2.3 Neurophysiology of Bowel Dysfunction in Parkinson's Disease

The pathophysiology of bowel dysfunction in patients with PD is quite different from that of SCI or MS. Dystonia of the striated muscles of the pelvic floor and external anal sphincter explains the defecatory dysfunction (Ashraf *et al*, 1995); this aetiological factor is supported by the observation that pelvic floor dysfunction is alleviated with l-Dopa (Singaram *et al*, 1995).

In addition to the pelvic dysfunction, colonic transit time is usually prolonged in patients with idiopathic PD (Ashraf *et al*, 1995). Two important pathopysiological factors contribute to this: firstly, the number of dopamine producing cells in the colonic wall is reduced in idiopathic PD (Edwards *et al*, 1994); and secondly, Lewy bodies, typical of PD, form in the enteric ganglia (Kupsky *et al*, 1987). Recent observations have identified that men with a bowel opening frequency less than every 24 hours have an almost threefold risk of developing PD in later life compared to men with a daily or more often bowel frequency (Abbott *et al*, 2001), suggesting that PD is not just a degenerative disorder of the CNS but also of the ENS. It has been proposed that bowel symptoms may permit early identification of PD.

2.4 Management

2.4.1 Assessment

The critical first step in managing most patients with neurogenic bowel dysfunction is to define the patient's prior bowel pattern. Current bowel symptomatology is next assessed, and this is in relation to bowel frequency, stool consistency, faecal incontinence and manoeuvres needed to achieve bowel management. This information is usually gathered from standard patient and carer history, but scoring systems exist which may supplement this. There are standard instruments (St Mark's incontinence score (Maeda *et al*, 2007), Wexner-Constipation (Agachan *et al*, 1996) and Wexner-Incontinence score (Jorge & Wexner, 1993), and recently a condition specific score has been developed for neurologic patients (Krogh *et al*,

2006b). This Neurogenic Bowel Dysfunction (NBD) Score is validated in SCI, but not PD. I will assess the NBD in patients with MS in Chapter 4.

Digital rectal examination is an essential component, allowing assessment of rectal filling, resting anal tone, ability to generate a voluntary contraction and it also gives a crude assessment of anal sensitivity. The place of more interventional physiological or radiological transit investigations is not established, but may be appropriate if there is any co-morbidity (prior anal surgery, obstetric history, pelvic organ prolapse). Plainly, patients with alarm symptoms should have the necessary colonic imaging performed. Other causes of bowel symptoms should be ruled-out in individual cases by means of laboratory tests (thyroid function, electrolytes imbalance, coeliac disease, etc.), radiological or endoscopical investigations (i.e. inflammatory bowel disease).

2.4.2 Basic Management

Treatment is usually empirical, with an escalating step-wise approach usually being adopted. There is little formal clinical trial evidence for this, and no consensus on the basic data set required, the decision-making strategy or the components of the management algorithm.

The basic management intention for all patients is to establish a pattern of scheduled defecation in a comfortable position, exploiting any easily implementable manipulations of diet and lifestyle before considering laxatives, suppositories or constipating agents (1998). Despite the absence of a strong evidence base, these conservative interventions are helpful in the vast majority of neurogenic bowel patients (Krogh *et al*, 1997). In the absence of any consensus, this

needs to be empirical and flexible to accommodate the patient's realistic ability to comply, recognising that there is huge individual variation both in bowel pattern and in response to modifications. Components of this aspect of care may include the following:

- simplifying drug regime to minimise use of any constipating medication (anti-cholinergics, muscle relaxants, diuretics, etc)
- rationalising fibre intake (recognising that patients may be taking too much dietary fibre which is both unhelpful and exacerbates abdominal bloating)
- optimising fluid intake to ideally more than 1.5l per day (within the balance of what is practical given the bladder regime)
- avoiding excess caffeine, sorbitol or artificial sweetener intake (which can promote stool looseness and soiling)
- timing regular mealtimes
- attempting the bowel evacuation regime in the mornings after a warm drink and small meal in order to optimise the gastro-colic response
- abdominal massage may accelerate gut transit and ease bowel management (Ayas *et al*, 2006).

The patient or carer often needs to undertake digital examination to check that there is rectal content. If there is no spontaneous defecation, rotatory digital stimulation of the ano-rectum will provoke reflex rectal contraction and may allow bowel emptying. If such digital stimulation is insufficient, stimulation of these same rectal contractions with suppositories (glycerine or bisacodyl) is preferred to manual extraction of stool. A recent study has suggested that docusate mini-

enemas and PEG-base bisacodyl suppositories are more effective than standard oil-base bisacodyl suppositories (Ayas *et al*, 2006). If there is no response to suppositories, a mini-enema may be required (Ayas *et al*, 2006). Commercially sponsored trials of the macrogol osmotic agents have established a place for these compounds (Movicol®) in patients with PD (Zangaglia *et al*, 2007) and faecal impaction (Chen *et al*, 2005), but it is likely that other osmotic agents would be equally effective. Fibre supplements are generally unhelpful (as discussed above), but stimulant laxatives are sometimes helpful when taken in the evening to optimise the opportunity for a morning bowel action (1998).

Recently, an innovative prokinetic agent, Prucalopride, has been introduced onto the market. Prucalopride is a highly selective, high-affinity 5-HT_4 receptor agonist with prokinetic properties (Emmanuel *et al*, 1998). The 5-HT4 receptor has a particularly important role, both physiologically and pathophysiologically, in the regulation of gut function (Kim & Camilleri, 2000). Activation of neuronal 5-HT4 receptors results in prokinetic activity throughout the GI tract, and triggers the release of neurotransmitters from the enteric nerves resulting in increased contractility and stimulation of the peristaltic reflex (Gershon, 2005). *In vivo* studies have shown that prucalopride increases the velocity of coordinated colonic propulsion (Jin *et al*, 1999) and enhances colonic motility and transit (Emmanuel *et al*, 2002).

There are no studies of prucalopride in neurological patients, but three large clinical trials of prucalopride have been undertaken in patients with laxative refractory constipation (Camilleri *et al*, 2008; Quigley *et al*, 2009; Tack *et al*, 2009). All three

studies showed that prucalopride increased the number of bowel movements and reduced the severity of symptoms. These three studies enrolled almost 2000 patients. The most frequently reported adverse events of prucalopride were headache, nausea, abdominal pain and diarrhoea, which were mainly reported on the first day of treatment. There were no clinically relevant adverse events reported on prucalopride. The majority of patients recruited to these studies (85%) were female, but the magnitude of effect was similar in both men and women.

Prucalopride is particularly promising for patients with MS and SCI, particularly in the acute phase of symptoms where there are no primary abnormalities in the bowel wall, which can sometimes be observed in chronic idiopathic constipation (Lyford *et al*, 2002). In a study of patients with a chronic SCI prucalopride was both effective and safe, with only 2 out 11 patients discontinuing the drug because of abdominal pain (Krogh *et al*, 2002a).

Loperamide (rather than codeine or lomotil) is the first line treatment for patients with faecal incontinence (Norton *et al*, 2007). The alternative, or additional, strategy to reduce faecal incontinence in this group is to optimise rectal clearance with suppositories or small volume enemas, on the principle that an empty rectum cannot cause incontinence.

Bowel biofeedback treatment has a well-established role in the treatment of functional constipation and faecal incontinence (Enck *et al*, 2009), and has been proposed for MS patients with lower disability and lesser alterations in standard ano-rectal physiology (ARP) tests (anal sphincter manometry and ano-rectal sensation) (Munteis *et al*, 2008; Wiesel *et al*, 2000). These studies though had the

limitation of having a small number of patients (Wiesel *et al*, 2000) and of being retrospective (Munteis *et al*, 2008). I will discuss biofeedback further in Chapter 6.

2.5 Mechanical Bowel Emptying

2.5.1 Retrograde Irrigation

When lifestyle and laxative approaches cannot achieve satisfactory bowel management, the next step is to attempt irrigation of the colon. The least invasive method of undertaking this is with transanal irrigation (TAI), which will be discussed in more depth in Chapter 7. This has been shown to successfully empty the rectum and often the left colon too, thus helping neurogenic patients with both constipation and faecal incontinence (Christensen *et al*, 2003). A major improvement in this technique came from the commercial development of Peristeen®, which replaced earlier ad hoc (frequently uncomfortable) devices (Shandling & Gilmour, 1987). This system, consists of a reservoir, hand control and single-use catheter, and allows variable volumes of liquid to be instilled, up to 4000 ml.

An important randomised trial among SCI subjects with bowel dysfunction showed that TAI reduced constipation symptoms and episodes of faecal incontinence compared to standard bowel management without irrigation (39). There were associated improvements in symptom-related quality of life, and subsequent studies have shown that the system is cost effective compared to standard supportive bowel management (40). These observations complemented the classical findings in children with NBD that demonstrated the efficacy of TAI

(Christensen *et al*, 2006). With careful patient selection (those able to tolerate rectal instillation, potentially independent of carers, able to transfer to a toilet or commode), this technique represents an important addition to the therapeutic options for this patient group. Whilst MS patient were included in studies on TAI, and the largest contained 25 (Faaborg *et al*, 2009a), no study has evaluated its efficacy in a selected group of MS patients.

2.5.2 Antegrade Irrigation

Following the initial reports of TAI, Malone and colleagues undertook a novel procedure of antegrade irrigation via an appendicostomy (as the conduit for instillation of tap water or osmotic agent) (Malone *et al*, 1990). Commonly known as the antegrade continence enema (ACE) procedure it has been especially used in children with constipation and faecal incontinence due to NBD, especially myelomeningocoele (Koyle *et al*, 1995). In adults, long-term satisfaction with ACE is reported in over 80% of patients (Worsoe *et al*, 2008). ACE achieves near total colonic clearance, the chief drawback being that the appendicostomy may stenose with time (Gerharz *et al*, 1997). In fact, a recent decision analysis model (which did not include TAI) suggested that ACE is the optimal long-term option for NBD (Furlan *et al*, 2007). An alternative to the surgical creation of an irrigation port is the formation of a percutaneous endoscopic colostomy (PEC), whereby an enterostomy tube is endoscopically located in (usually) the left colon. A single retrospective publication of PEC showed that over 80% of adults with NBD reported symptom improvement with such management (Cowlam *et al*, 2007). It must be remembered that the technique is not without complications (sepsis, tube displacement,

haemorrhage, pain) that can ultimately be fatal, and the technique needs a greater evidence base before its potential role is identified.

2.6 Surgical Intervention

2.6.1 Neuromodulation

Sacral nerve stimulation, or sacral neuromodulation (SNM), is an emerging minimally invasive technique for patients with idiopathic faecal incontinence and constipation refractory to standard treatments (Furlan *et al*, 2007). In brief, the technique involves the insertion of a stimulating electrode via the sacral foramina onto the anterior (efferent) roots of the S2 or S3 roots (Kenefick & Christiansen, 2004). A temporary electrode connected to an external battery is inserted for a two to three week trial period. If there is a satisfactory response, then a permanent electrode and implantable pulse generator is placed, although there is a question about whether this trial period is actually an accurate predictor of response to a permanent electrode (Mowatt *et al*, 2007). Overall, 41-75% of patients achieved complete faecal continence, and smaller studies in patients with constipation suggest similar rates of response for this too (Thomas *et al*, 2013). The mechanism of action is unknown, but is thought to involve afferent neuromodulation as much as efferent neurostimulation (Kenefick *et al*, 2003). Two recent small studies on patients with spinal and cauda equina injury have suggested that the technique may help in selected patients with incomplete neurological lesions (Gstaltner *et al*, 2008; Jarrett *et al*, 2005). Nevertheless, anxieties remain about the durability of effect in this group, and especially about the potential risks of autonomic dysreflexia.

A non-invasive option of nerve stimulation is offered by Posterior tibial nerve stimulation (PTNS). Originally used in chronic pelvic pain and sexual dysfunction, it is a relatively newer neuromodulation modality to treat faecal incontinence, first employed for (Shafik *et al*, 2003). There have since been eight studies, with a total of 129 patients, including two prospective controlled studies, with a success rate of between 30% to 83.3% and without major complications (Findlay & Maxwell-Armstrong, 2011).

The mechanisms by which PTNS improves faecal incontinence is not clear, but may be similar to sacral nerve stimulation. What is known is that it improves anal squeeze pressure (Findlay & Maxwell-Armstrong, 2011). There is an ongoing multicentre randomised-controlled trial to define its role in idopathic faecal incontinence. This modality of treatment will also merit further evaluation for the treatment of NBD.

2.6.2 Formation of a Stoma

An option for patients with NBD is the formation of a colostomy or ileostomy. However, this should not be considered a last ditch option of desperation, as the procedure reduces time spent with bowel care and can provide independence, improving quality of life for patients (Randell *et al*, 2001; Safadi *et al*, 2003; Stone *et al*, 1990). A questionnaire study on patients with a colostomy for neurogenic bowel revealed that the overwhelming majority of patients would undergo the procedure again and wished they had been operated on earlier (Norton *et al*, 2005). However, the caveat is that patients with neurological diseases experience greater complications with their stoma than neurologically intact patients (Randell *et al*,

2001; Stone *et al*, 1990), relating in part, at least, to body habitus and wheelchair use. Furthermore, whilst incontinence and independence of bowel management are often greatly enhanced by stoma formation, impairment of colonic transit is not altered by the procedure, so stoma irrigation or laxative use may continue to be required. In this regard, some surgeons prefer the formation of a laporoscopic loop ileostomy.

2.7 Summary

Patients with CNS diseases frequently experience socially restricting bowel dysfunction. The causation of these symptoms is multifactorial, and our understanding of bowel transit and the pelvic reflexes in these patients has increased in recent years.

A logical step-wise approach can improve bowel symptoms and includes:

- Conservative interventions (position of toileting, meal timing, minimising constipating medication, use of suppositories), which can improve function in many patients.
- Antegrade irrigation via an appendicostomy may benefit some patients with NBD; it is especially effective in children.
- An alternative for antegrade colorectal irrigation is via an endoscopically placed colostomy; however this is limited by a high incidence of adverse affects.
- TAI using a novel system of single use rectal catheters offers a well tolerated approach for patients with NBD.

- Formation of a colostomy or ileostomy is the last option – but a reasonably successful one – for some refractory patients.

Three-quarters of these patients can be managed conservatively, but these simple steps need to be applied systematically. Only a minority of patients need to undergo more complex procedures (irrigation, electrical stimulation or surgical).

It appears clear that there is almost a complete lack of evidence on the efficacy of treatment for bowel symptoms in MS, and that most of our experience in managing NBD is based on evidence accumulated in patients with SCI.

As MS, like SCI, is at present incurable and a sizable social issue, greater emphasis should be given to the management of symptoms.

The aim of my study is to lay the foundations to a rationalised – targeted approach to bowel symptoms in MS, in order to develop a treatment algorithm and identify new treatment strategies.

As stated in section 1.6.1, my primary hypothesis is that bowel dysfunction in patients with MS is secondary to the extent of spinal cord involvement by the disease. A key element in the development of my hypothesis is that patients with MS show similar end organ alteration to patients with a supraconal-SCI, and the degree of measurable dysfunction could also follow a pattern. I will develop this further in Chapter 5.

I have so far discussed NBD in MS and other common neurological disorders, outlining the rationale of my studies. In the next chapter I will illustrate the

assessment tools I have employed in my studies, including questionnaires, disability scales and tests of ARP.

CHAPTER 3: METHODS

Chapter overview:

- Assessment of ano-rectal physiology
- Measurement of rectal compliance
- Assessment of bowel symptoms and general health status
- Assessment of disability and MS impact

3.1 Introduction

The experimental part of this thesis is composed of four studies.

1. A study of prevalence of bladder symptoms in patients with MS and bowel symptoms involving 71 patients.
2. A study of rectal compliance through the comparison of patients with supraconal SCI and normal controls, involving 46 patients with MS, 23 patients with a supraconal-SCI (SCI, above T-5 level) and 25 healthy individuals without bowel symptoms.
3. A prospective observational study of bowel biofeedback involving 39 patients.
4. A prospective observational study of TAI involving 29 patients.

Whilst the thesis is conducted on the basis of a unified hypothesis, each individual study has its own specific hypothesis and aims. Therefore the study design is described in each individual chapter. Patients in study 1 (correlation of bowel and bladder symptoms, chapter 4) and 3 (biofeedback study, chapter 6) are

independent cohorts, whilst all the patients in the transanal irrigation study (chapter 7) had been also included in the rectal compliance study (chapter 5).

In this chapter the tests and questionnaire employed are described, highlighting in which study they have been used.

3.2 Ano-Rectal Physiology Tests

In all studies except study 1 all patients underwent baseline standard ARP tests (measurement of anal sphincters pressure and ano-rectal sensation). In the biofeedback study (study 3) these tests were repeated after treatment. In studies 2 and 4 patients also had measurements of baseline rectal compliance. I performed all the measurements according to standardised criteria (Diamant *et al*, 1999) (Diamant *et al*, 1999).

Given that our cohort was predominately female patients, normal values for this gender, currently used at our Unit, are reported (Jameson *et al*, 1994a). In brief, resting anal pressure (internal anal sphincter function), squeeze and endurance squeeze pressure (external sphincter function) were measured using an 8-channel water-perfused catheter (Ardmore Healthcare Limited, External Diameter 3.9mm with Mui pump, using Medical Measurement System software) and a 'station pull-through' method.

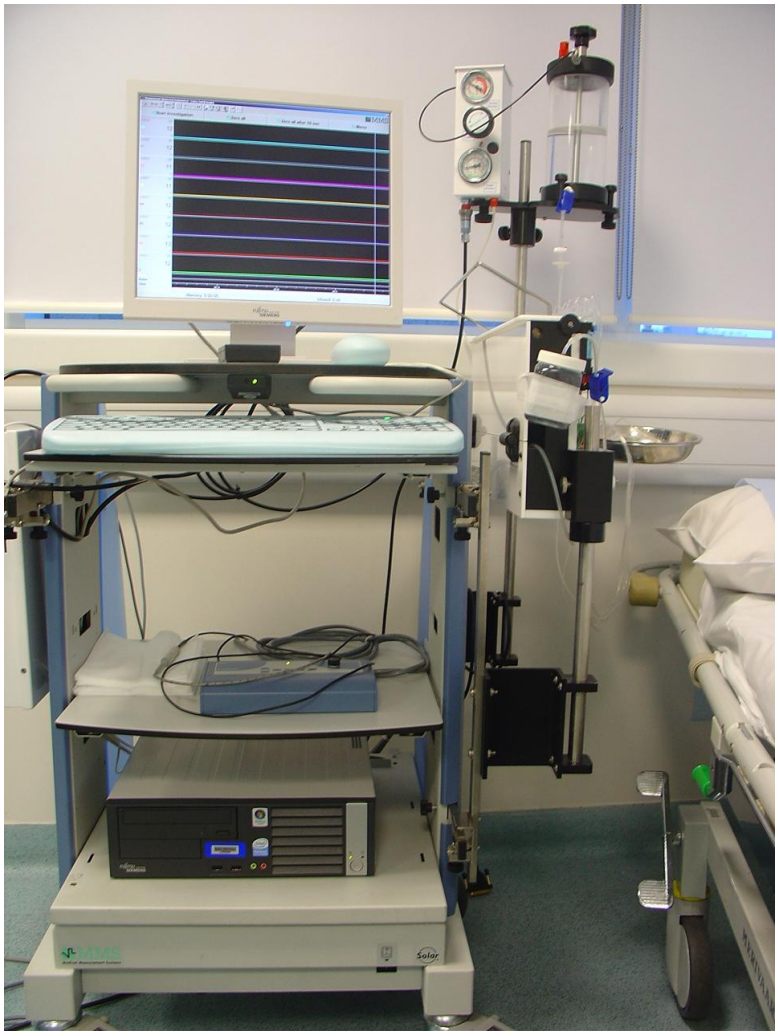


Figure 3.1: The manometry stack

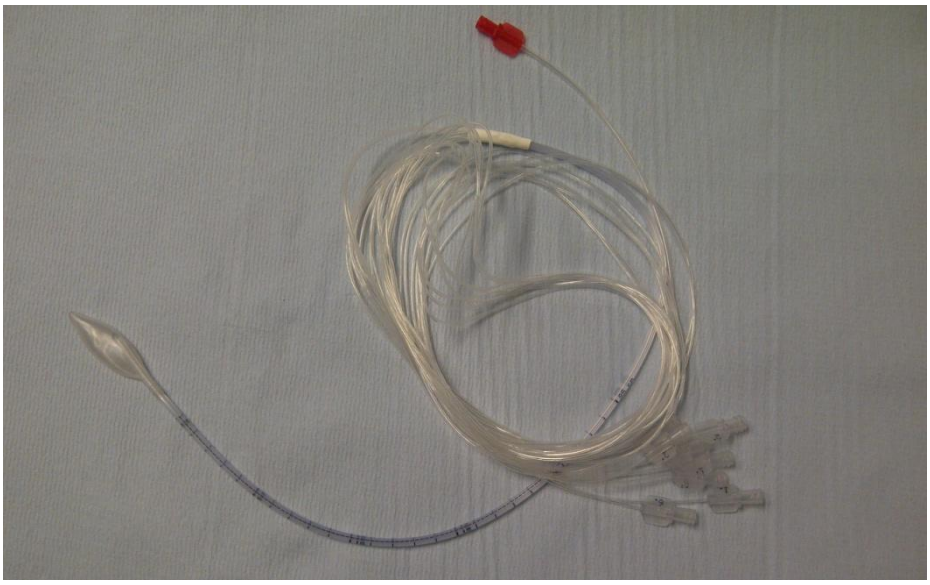


Figure 3.2: Manometry catheter

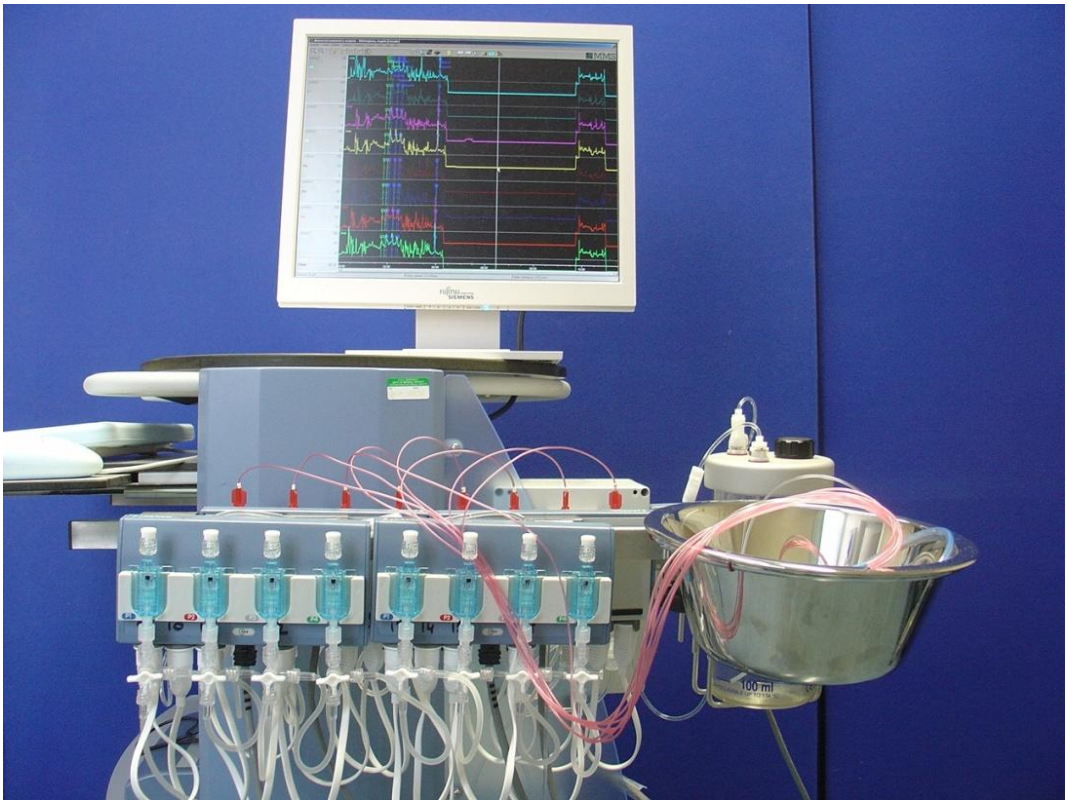


Figure 3.3: Manometry sensors

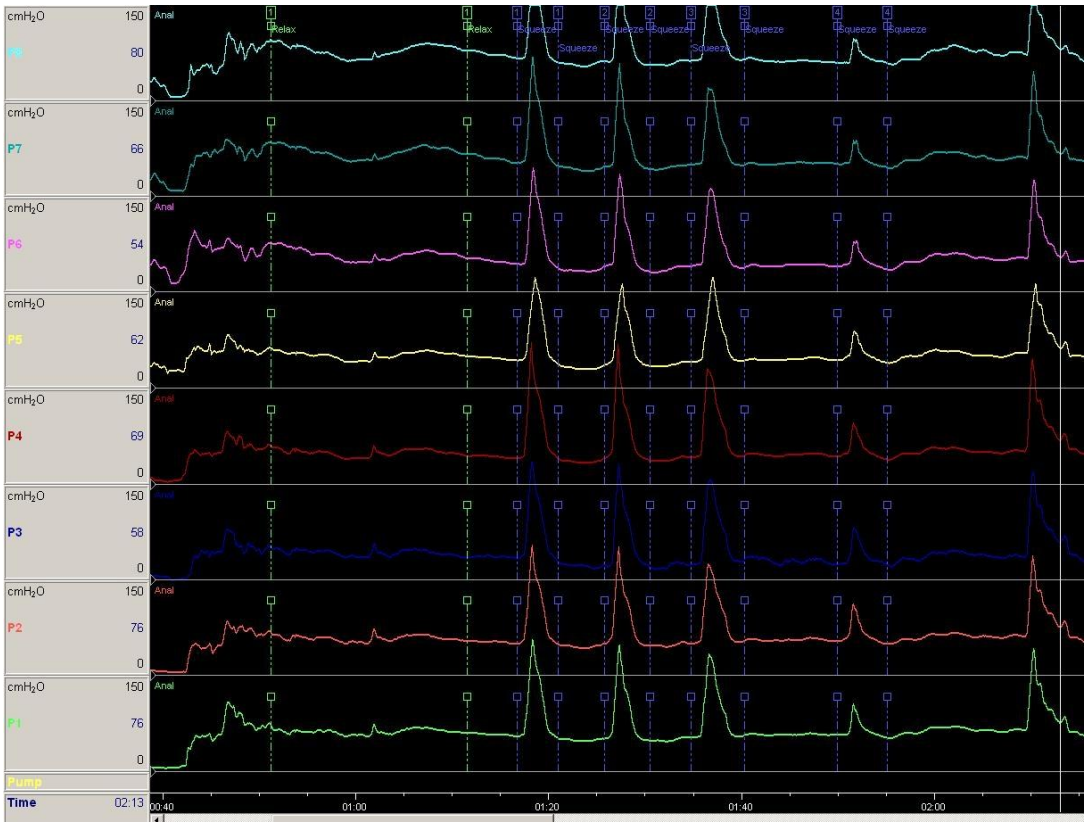


Figure 3.4: Manometry trace

The lower limit for normal anal resting and squeeze pressures at our unit is 60 cmH_2O. Rectal sensitivity to balloon distension was measured by continuous inflation of a latex balloon placed in the rectum, 6 cm above the anal verge: threshold volume of first sensation (normal range 20–60 ml), urge volume at which urge to defecate is first perceived (normal range 35-120 ml) and maximum tolerated volume (normal range 100-260 ml) were recorded.

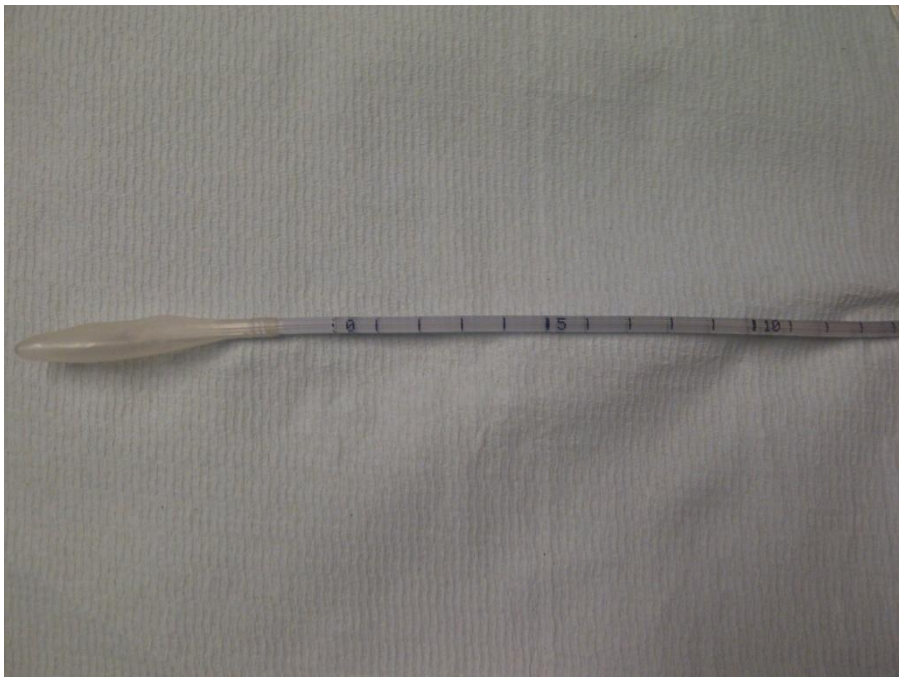


Figure 3.5: Tip of the manometry catheter demonstrating the mounted balloon. This was used to elicit the RAIR.

Finally, anal and rectal electro-sensitivity was measured with a bipolar electrode catheter (Gaeltec Ltd., using Medical Measurement System software) placed in the anal canal and then in the rectum.

Anal electric-stimulation was applied at 1cm from the anal verge at 5Hz with a pulse width of 0.1msec; the current was then incrementally increased up to 20mA until the patient reported their first sensation (normal range 2-9 mA). In the rectum, at 6cm from the anal verge, electrical stimulation was applied at 10 Hz with a width of

0.5msec and increased up to 50mA until the patient reported their first sensation (normal range 14-38 mA).

3.3 Measurement of Rectal Compliance

3.3.1 Rectal Compliance

In the normal subject the colon propels the stools in the rectum, and subsequent rectal distension has the dual effect of generating a sense of rectal fullness and of activating the RAIR. Their transmission to the cortex clearly depends on an intact spinal cord. The integration of these two physiological mechanisms at the supraspinal level generates a desire to defecate and a decision of whether it is an appropriate time to void the rectum. This simplistic and schematic view makes evident the importance of the distensibility of the rectum in response to pressure, rectal compliance.

Measurement of rectal compliance is calculated as the average changes in volume determined by changes in pressure. The distensibility of the rectum depends on the various structures composing its wall, namely the mucosa, connective tissue and the smooth muscle. As expected, physical alteration of the rectal wall can alter rectal compliance, like for example in ulcerative colitis and radiation proctitis (Bajwa A., 2009; Farthing & Lennard-jones, 1978; Rao *et al*, 1987; Varma *et al*, 1985). Alteration of rectal compliance in neurological diseases suggests instead that changes in rectal stiffness and tone can be secondary to modification of the autonomic outflow and its effect on smooth muscle in the rectal wall.

3.3.2 Measurement of Rectal Compliance – Instruments

The measurement of rectal compliance has been the subject of debate, but minimum standards have been agreed (Whitehead & Delvaux, 1997).

Rectal compliance was measured with a mechanical barostat (Distender II, G & J Electronics, On, Canada, Figure 3.6) and a 20cm x 15cm polyethylene, over-sized, non-compliant bag (maximum volume 600ml) tied to ridges 10cm apart to a dual lumen silicon catheter (Mui Scientific Inc., Ontario, Canada, Figure 3.7), and placed into the rectum at 6 cm from the anal verge.

The barostat bag has to have specific properties so that whilst it is distended and in contact with the rectal wall, the pressure measured within the bag equates to the pressure exerted on the bag by the rectum. For this to occur, the bag itself had to be infinitely compliant exerting no force of its own.

This means that polyethylene rather than latex (which has the problem of requiring a large initial pressure to stretch but then stretches very easily) had to be used. There are two ways of designing an infinitely compliant bag. Either a balloon that is infinitely compliant up to its maximum volume, or a fixed, large-volume non-compliant bag which has a maximum volume greater than the maximum volume of the rectum. Krogh *et al* demonstrated that results using the 'oversized bag' are more reproducible (Krogh *et al*, 2001a), so for this study a 20 x 15 cm polyethylene, over-sized, non-compliant bag with a maximum volume of 600ml (CT-BP500R bag, Mui Scientific, Ontario, Canada) was used to measure compliance (Figure 3.7).

Figure 3.6: The barostat machine

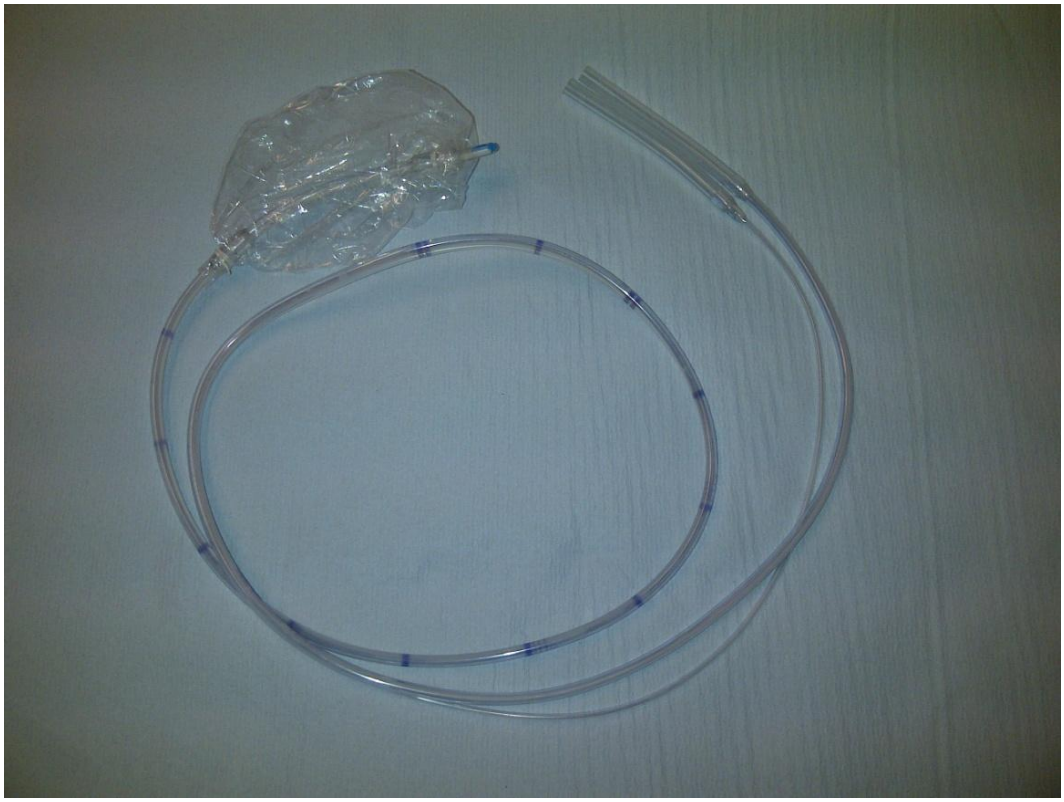


Figure 3.7: The barostat catheter

3.3.3 Measurement of Rectal Compliance - Distension Protocol

We employed a distension protocol (Fox *et al*, 2006), which reduces variability of measurement due to variation in rectal capacity. Initially a minimal distending pressure (MDP) is calculated as the pressure at which respiratory excursions are regularly recorded as changes in barostat volume. This is the minimal level of pressure required for the barostat bag to be adherent to the rectal wall without distending it. (Bell *et al*, 1991). The basal operating pressure (BOP) was set at MDP + 2mmHg (Bharucha *et al*, 1997). In order to make measurement reproducible it is required that the rectal wall basal tone is stabilised though repeated and equilibrated distensions, a phenomenon called tissue pre-conditioning (Bharucha *et al*, 2004; Hammer *et al*, 1998), and this also has the function of familiarising the individual to the barostat assembly. So by using the BOP as a baseline, the conditioning distension sequence was performed; this consisted of sequential 4mmHg staircase distensions up to 20mmHg. Each step was maintained for 15 seconds. Subsequently, the index distension was performed and sequential 4mmHg stepwise distensions were attained up to a maximum of BOP + 40mmHg or a patient's tolerance. Each distension step was maintained for 1 minute.

3.3.4 Calculation of Compliance: Analysis of the Pressure-Volume Data

Special software (Protocol Plus) provided by the barostat manufacturer (G&J Electronics, Ontario, Canada) was used to analyse the raw data recorded during distension sequences (Figure 3.8).

The software was utilised to average the volume of air within the bag over the last 10 seconds of the each distension step. This usually reflected the volume of the bag in a stable stage of the corresponding pressure increment phase (Figure 3.8). This volume was then plotted against the pressure of correspondent distension, to produce a pressure-volume curve.

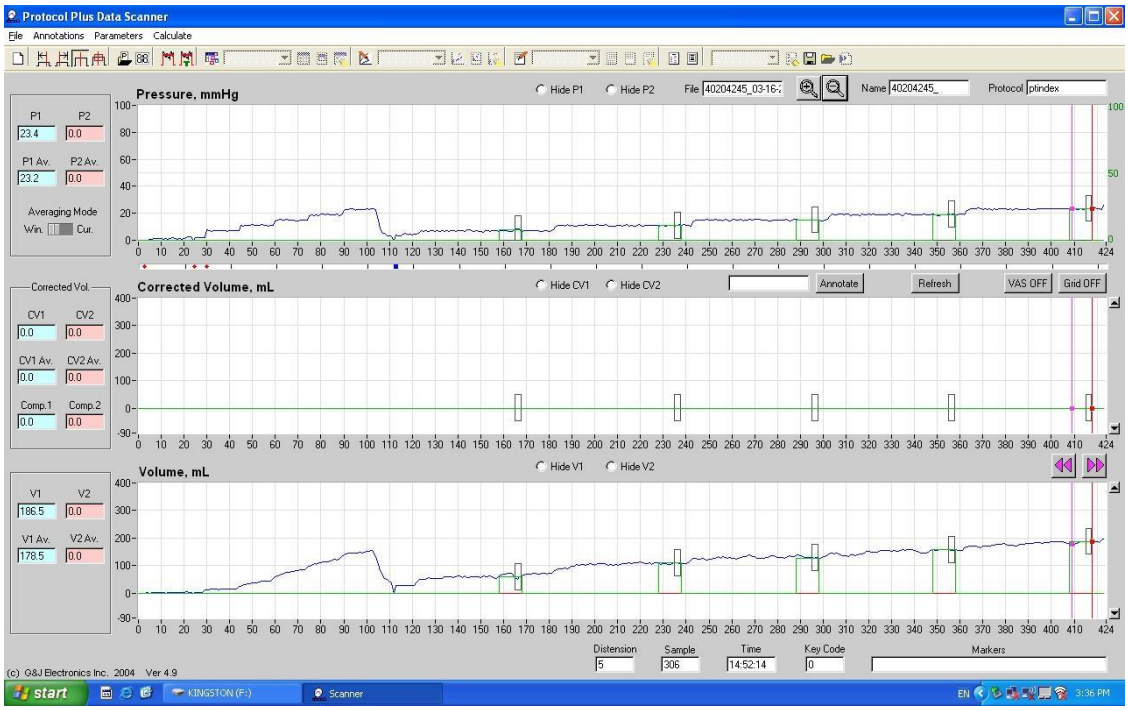


Figure 3.8: The software used for analysis of volume-pressure data

The pressure-volume values were entered into Prism 4.0 (GraphPad Software Inc, CA, USA) to create a graphical representation of the values.

a) Sigmoidal relationship observed:

If a sigmoidal relationship was observed, a best-fit curve was computed and a tangent was then drawn to the steepest part of the curve. The gradient of this line was considered as the compliance of the rectum (measured in ml*/mmHg*) (Figure 3.9)(Varma & Smith, 1986).

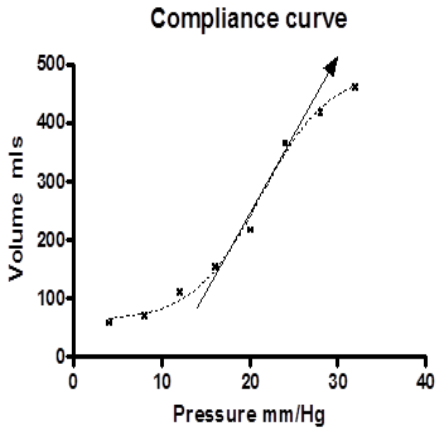


Figure 3.9: Typical sigmoidal pressure-volume curve

b) Sigmoidal relationship not observed:

A linear relationship was sometimes identified between the pressure-volume values. On these occasions, a best-fit line was computed and its gradient was taken to be the compliance value (Figure 3.10) (Bharucha *et al*, 2004).

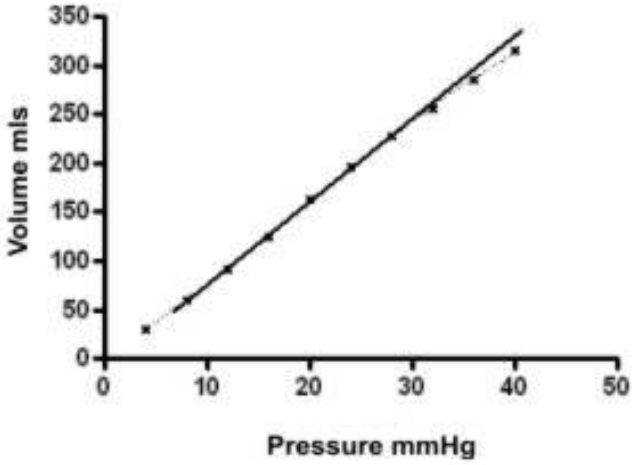


Figure 3.10: Linear pressure-volume relationship curve

Normal values for rectal compliance were obtained by applying this protocol in normal controls and the normal range at our Unit is 11-15 ml/mmHg.

3.4 Symptoms Assessment

No bowel questionnaire has been validated to measure bowel symptoms in patients with MS. We employed different questionnaires depending on the type of study, and the reasons for specific choices are given in the individual chapters.

In study 1 we used the NBD questionnaire and patient-reported symptoms of bowel and bladder dysfunction. In the other studies we employed the Wexner-Constipation and Wexner-Incontinence questionnaires.

3.4.1 Neurogenic Bowel Dysfunction Questionnaire

This questionnaire was employed in Study 1. The NBD questionnaire has been designed and validated in patients with SCI (Krogh *et al*, 2006a), and includes questions about background parameters (n=8), faecal incontinence (n=10), constipation (n=10), obstructed defecation (n=8), and impact on quality of life (QOL) (n=3). The NBD score weights each symptom of bowel dysfunction in relation to its impact on quality of life, and scores are categorised as follows: 0-6 very minor dysfunction, 7-9 minor dysfunction, 10-13 moderate dysfunction and 14-47 severe dysfunction. The use of this questionnaire in study 1 was dictated by the need to have an instrument that quantifies constipation and faecal incontinence as well as impact on quality of life.

The number of points for each possible answer is given in parenthesis

	Points
(1) Frequency of defecation Daily ☐(0) 2–6 times every week ☐(1) Less than once a week ☐(6)	____
(2) Time used for each defecation 0–30 min ☐(0) 31–60 min ☐(3) More than one hour ☐(7)	____
(3) Uneasiness, headache or perspiration during defecation No ☐(0) Yes ☐(2)	____
(4) Regular use of tablets against constipation No ☐(0) Yes ☐(2)	____
(5) Regular use of drops against constipation No ☐(0) Yes ☐(2)	____
(6) Digital stimulation or evacuation of the anorectum Less than once every week ☐(0) Once or more every week ☐(6)	____
(7) Frequency of faecal incontinence Less than once every month ☐(0) 1–4 times every month ☐(6) 1–6 times every week ☐(7) Daily ☐(13)	____
(8) Medication against faecal incontinence No ☐(0) Yes ☐(4)	____
(9) Flatus incontinence No ☐(0) Yes ☐(2)	____
(10) Perianal skin problems No ☐(0) Yes ☐(3)	____

NBD score	Bowel dysfunction
0–6	Very minor
7–9	Minor
10–13	Moderate
14 or more	Severe

Figure 3.11: The NBD score

3.4.2 Patient-Reported Symptoms of Bowel and Bladder Dysfunction

This modality of symptoms assessment was employed in Study 1. Patient-reported outcome measures are increasingly used in medical studies (Ang *et al*, 2011; Paterson, 1996; Rahimi *et al*, 2010) and were assessed within a structured interview, conducted in the outpatient clinic. The alternating and fluctuating pattern of bowel habit in MS patients is similar to that of irritable bowel syndrome. In patients with this condition, the product of frequency and severity of symptoms

has been employed to quantify bowel function (Talley *et al*, 1989; Talley *et al*, 1990). So each patient was asked what proportion of time of his or her life was affected by constipation and/or faecal incontinence, with five possible answers (0%, 25%, 50%, 75% or 100% of the time). We then assessed severity by asking patients to use a visual analogue scale (VAS) from 0 to 100, with 0 representing absence of symptoms, and 100 if the patient thought that bowel symptoms were the worst possible.

The presence of bladder symptoms and on-going treatment (anti-muscarinic agents, use of intermittent self-catheterisation, permanent catheter) was ascertained from the patient's history and clinical notes. Urgency was defined as a sudden compelling desire to pass urine that is difficult to defer (Abrams *et al*, 2002); urge urinary incontinence was defined as incontinence accompanied by or immediately preceded by urgency. The patient was also asked about difficulty of initiating bladder voiding (hesitancy), interruption of flow, sense of incomplete bladder emptying and use of pads.

We wished to quantify bladder and bowel dysfunction uniformly. Therefore we asked the proportion of time a patient perceived bladder symptoms affected his or her life, with five possible answers (0%, 25%, 50%, 75% or 100% of the time). Severity was assessed on a VAS from 0 to 100, similarly to bowel symptoms.

This modality of assessment is not validated, and their limitations are acknowledged in the discussion.

3.4.3 Wexner Constipation and Incontinence Scores

The Wexner-Constipation (Agachan *et al*, 1996) and Wexner-Incontinence (Jorge & Wexner, 1993) questionnaires provide a validated and reproducible quantitative assessment of bowel symptoms (Holzer *et al*, 2008; Vaizey *et al*, 1999). The incontinence score ranges between 0-20, and the constipation score between 0-30, with 0 representing absence of symptoms, and 20 or 30 the most burdensome level of symptoms.

Wexner Constipation Score

Please answer the following questions that relate to the emptying of your bowels. Circle the most appropriate number that applies to you.

1). Typically how often do you empty your bowels?	**Score**
1-2 Times per 1-2 days	0
2 times per week	1
Once per week	2
Less than once per week	3
Less than once per month	4
2). How often do you have to strain to empty your bowels?	
Never	0
Rarely	1
Sometimes	2
Usually	3
Always	4
3). How often do you feel you have not fully evacuated your rectum when you empty your bowels?	
Never (always feel empty)	0
Rarely	1
Sometimes	2
Usually	3
Always (never feel empty)	4
4). How often do you suffer with abdominal pains due to your bowel evacuation problem?	
Never	0
Rarely	1
Sometimes	2
Usually	3
Always	4
5). Typically how long do you spend in the lavatory per attempt?	
Less than 5 minutes	0
5 – 10 minutes	1
10 – 20 minutes	2
20 – 30 minutes	3
More than 30 minutes	4
6). Which of the following do you need, to help with the emptying of your bowel?	
No help	0
Laxatives	1
Digital assistance, suppositories, or enema	2
7). Typically how often do you attempt to empty your bowels WITHOUT a result in a 24hr period?	
Never	0
1-3	1
3-6	2
6-9	3
More than 9	4

8). How long have you had these bowel symptoms?	
0 Years	0
1-5 Years	1
5-10 Years	2
10-20 Years	3
More than 20 Years	4
Total score	

Figure 3.12: Wexner Constipation questionnaire

Type of incontinence	Frequency				
	Never	Less than once per month	Greater than once per month, Less than once per week	Greater than once per week, Less than once per day	Greater than or equal to once per day
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Requires pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

0 = normal continence
20 = total incontinence

Figure 3.13: Wexner faecal incontinence questionnaire

3.4.4 Assessment of Anxiety and Depression

Anxiety and depression were evaluated in study 3 before and after treatment with the Hospital Anxiety and Depression Scale (HADS)[22]. This is a widely used instrument of self-assessment of psychological state in non-psychiatric patients, both in the hospital and primary care setting.[23] It is composed of 7 questions for each domain, and scores of 0-7 in respective sub-scales are considered normal, with 8-10 borderline, and 11 or over suggesting the presence of a clinical syndrome.

I feel tense or wound up:			**I feel as if I am slowed down:**		
Most of the time		■	Nearly all the time	■	
A lot of the time		■	Very often	■	
Occasionally		■	Sometimes	■	
Not at all		■	Not at all	■	
I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like "butterflies" in the stomach:**		
Definitely as much	■		Not at all		■
Not quite as much	■		Occasionally		■
Only a little	■		Quite often		■
Hardly at all	■		Very often		■
I get a sort of frightened feeling as if something awful is going to happen:			**I have lost interest in my appearance:**		
Very definitely and quite badly		■	Definitely	■	
Yes, but not badly		■	I don't take as much care as I should	■	
A little, but it doesn't worry me		■	I may not take quite as much care	■	
Not at all		■	I take as much care as ever	■	
I can laugh and see the funny side of things:			**I feel restless as if I have to be on the move:**		
As much as I always could	■		Very much indeed		■
Not quite as much now	■		Quite a lot		■
Definitely not so much now	■		Not very much		■
Not at all	■		Not at all		■
Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**		
A great deal of the time		■	As much as I ever did	■	
A lot of the time		■	Rather less than I used to	■	
From time to time, but not too often		■	Definitely less than I used to	■	
Only occasionally		■	Hardly at all	■	
I feel cheerful:			**I get sudden feelings of panic:**		
Not at all	■		Very often indeed		■
Not often	■		Quite often		■
Sometimes	■		Not very often		■
Most of the time	■		Not at all		■
I can sit at ease and feel relaxed:			**I can enjoy a good book or television programme:**		
Definitely		■	Often	■	
Usually		■	Sometimes	■	
Not often		■	Not often	■	
Not at all		■	Very seldom	■	

Figure 3.14: Hospital anxiety and depression questionnaire

3.4.5 Assessment of General Health Status

General health status was measured in study 4 with the widely used 36-item short form health survey (SF-36) (McHorney *et al*, 1993). The modified version including specific MS items did not show any advantage in comparison with the shorter original SF-36 (Freeman *et al*, 2001), which was therefore used for this study. The values range between 36 and 149 which are then converted into a scale of 0-100 so that each domain has the same impact on the final score; the higher the score the better the health status.

SF-36 HEALTH SURVEY

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one number **only**)

Excellent ……1
Very good……2
Good……..3
Fair……4
Poor……..5

2. Compared to one week ago, how would you rate your health in general now?

(circle one number **only**)

Much better now than one week ago 1
Somewhat better now than one week ago 2
About the same as one week ago 3
Somewhat worse now than one week ago 4
Much worse now than one week ago 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited** At All
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing **several** flights of stairs	1	2	3
Climbing **one** flight of stairs	1	2	3
Bending, kneeling, or stooping	1	2	3
Walking **more than a mile**	1	2	3
Walking **half a mile**	1	2	3
Walking **one hundred yards**	1	2	3
Bathing or dressing yourself	1	2	3

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

circle one number on each line)

	YES	**NO**
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the **kind** of work or other activities	1	2
Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as **carefully** as usual	1	2

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one number **only**)

Not at all ……1
Slightly ……2
Moderately ……3
Quite a bit ……4
Extremely ……5

7. How much bodily pain have you had during the past week?

(circle one number **only**)

None ……1
Very mild ……2
Mild ……3
Moderate ……4
Severe ……5
Very severe ……6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one number **only**)

Not at all ……1
A little bit ……2
Moderately ……3
Quite a bit ……4
Extremely ……5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week.
(circle one number on each line)

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
Did you feel full of life?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time ……1
Most of the time ……2
Some of the time ……3
A little of the time ……4
None of the time ……5

11. How TRUE or FALSE is each of the following statements for you?
(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
I seem to get ill a little easier than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

Thank you

Figure 3.15: SF-36 questionnaire

3.5 Assessment of Specific Aspects of MS

3.5.1 Disability

Disability was measured with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), which is commonly used in patients with MS both in research and clinical practice. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability and is principally based on ambulatory ability of the patient. For scores between 1 and 4.5 the patient is able to walk, and the score is mainly based on evaluation of 8 functional system: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual function, cerebral and mental function and lastly any other system.

With an EDSS above 5 mobility is impaired, at 7 the patient is wheelchair-bound, and for scores above 8 the patient is bed-bound.

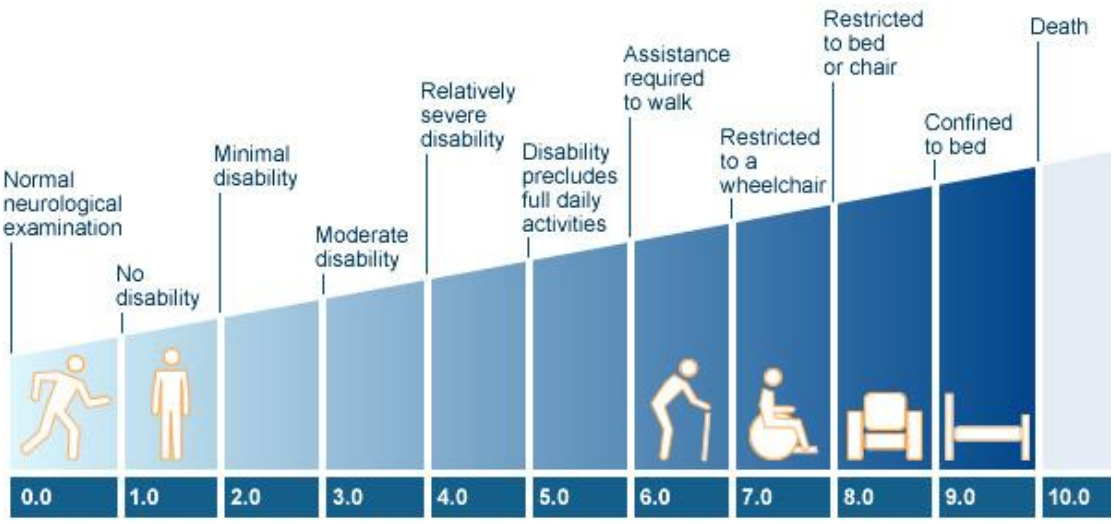


Figure 3.16: Rating neurologic impairment in MS: an expanded disability status scale (EDSS).

Disability is thought to be dependent on spinal cord involvement by MS, a common site of demyelinating lesions (Oppenheimer, 1978). About 90% of patients with MS have spinal cord lesions, and most will have them at presentation, whether diffuse or localized. The use of MRI using multi-array coils and fast spin echo has allowed to study in vivo the load, site and characteristics of lesions, and to correlate these factors with clinical features. In a seminal study, scans of the brain and the spinal cord of 80 MS patients, and it was observed that whilst there is no correlation between load of cord lesions on imaging and MS symptoms, it appears that spinal cord atrophy (signifying axonal loss) is a good radiological marker that correlates with clinical disability as measured with EDSS (Kidd *et al*, 1996; Kidd *et al*, 1993). In this study patients with MS who had cord atrophy at one or more of four spinal cord levels (C5, T2, T7 and T11), had significantly higher scores on the EDSS than those who did not have atrophy. The lack of correlation between symptoms and spinal cord load might be the consequence of limitations in MRI resolution, and this aspect was further highlighted in a study of serial MRIs, where in the presence of

increased disability there was no evidence of new appearing active lesions (Kidd *et al*, 1996). This could be the result the inability of MRI to detect new small but clinically relevant lesions or the result of axonal loss within pre-existing lesions. In fact pathological heterogeneity of the lesions cannot be differentiated with conventional T2-weighted MRI. This study further confirmed that the most reliable marker that is detectable on MRI is cord atrophy, which correlates with EDSS (Kidd *et al*, 1996; Kidd *et al*, 1993; Losseff *et al*, 1996) and is a reflection of diffusion of spinal cord disease (Lycklama a Nijeholt *et al*, 2000).

Spinal cord atrophy is measured as Mean Upper Cervical Cord Area (MUCCA) on magnetic resonance imaging (MRI). Usually the area imaged is at the level of C1-C2 (13,14) and measurements in this region are thought to be more accurate. Moreover, lower regions are commonly affected by movement artifacts due to breathing and swallowing.

A very recent, study measured MUCCA in 196 MS patients and 55 healthy controls, and confirmed that cervical cord atrophy is independently associated with clinical disability, as well as reduced mobility. The authors concluded that MUCCA is a relevant marker for clinical disability in long-standing disease, independent of other MRI measures. Finally MUCCA is also associated with the number of spinal cord lesions (Daams *et al*, 2014). This in line with a previous multicenter study (Losseff *et al*, 1996) that employed different image acquisition protocol. Losef et al. measured normalized cross-sectional area at the C2-C5 level in 212 MS patients in 3 European centers.

From appraisal of this evidence it appears that EDSS is a good surrogate marker of spinal cord atrophy at cervical level. This is in relation with extent of spinal cord

disease and therefore we elected to employ EDSS to clinically quantify spinal cord disease in our cohort.

On the basis of these considerations we judged that employing a clinical surrogate of spinal cord disease we could avoid costly, time-consuming and possibly inaccurate imaging.

Table 3.1: Expanded disability status scale (EDSS)

EDSS score	CHAPTER 4: **Description**
0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting
7	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10	Death due to MS

FS = functional system

3.5.2 MS impact

The impact of MS on patients' lives was recorded in study 4 with the MSIS-29 questionnaire (Hobart *et al*, 2001), which is a validated instrument to evaluate both the physical and psychological impact of the disease (Hobart *et al*, 2005; Hoogervorst *et al*, 2004). The MSIS-29 scores range between 29 and 145 and indicating respectively 'no impact at all' and life 'extremely affected' by MS.

Multiple Sclerosis Impact Scale (MSIS-29)

- The following questions ask for your views about the impact of MS on your day-to-day life **during the past two weeks**
- For each statement, please **circle** the **one** number that **best** describes your situation
- Please answer **all** questions

In the past two weeks, how much has your MS limited your ability to...	Not at all	A little	Moderately	Quite a bit	Extremely
1. Do physically demanding tasks?	1	2	3	4	5
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4	5
3. Carry things?	1	2	3	4	5

In the past two weeks, how much have you been bothered by...	Not at all	A little	Moderately	Quite a bit	Extremely
4. Problems with your balance?	1	2	3	4	5
5. Difficulties moving about indoors?	1	2	3	4	5
6. Being clumsy?	1	2	3	4	5
7. Stiffness?	1	2	3	4	5
8. Heavy arms and/or legs?	1	2	3	4	5

9.	**Tremor of your arms or legs?**	1	2	3	4	5
10.	**Spasms in your limbs?**	1	2	3	4	5
11.	**Your body not doing what you want it to do?**	1	2	3	4	5
12.	**Having to depend on others to do things for you?**	1	2	3	4	5

In the past two weeks, how much have you been bothered by...		Not at all	A little	Moderately	Quite a bit	Extremely
13.	**Limitations in your social and leisure activities at home?**	1	2	3	4	5
14.	**Being stuck at home more than you would like to be?**	1	2	3	4	5
15.	**Difficulties using your hands in everyday tasks?**	1	2	3	4	5
16.	**Having to cut down the amount of time you spent on work or other daily activities?**	1	2	3	4	5
17.	**Problems using transport (e.g. car, bus, train, taxi, etc.)?**	1	2	3	4	5
18.	**Taking longer to do things?**	1	2	3	4	5
19.	**Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?**	1	2	3	4	5
20.	**Needing to go to the toilet urgently?**	1	2	3	4	5
21.	**Feeling unwell?**	1	2	3	4	5
22.	**Problems sleeping?**	1	2	3	4	5
23.	**Feeling mentally fatigued?**	1	2	3	4	5
24.	**Worries related to your MS?**	1	2	3	4	5
25.	**Feeling anxious or tense?**	1	2	3	4	5
26.	**Feeling irritable,**	1	2	3	4	5

	impatient, or short tempered?					
27.	**Problems concentrating?**	1	2	3	4	5
28	**Lack of confidence?**	1	2	3	4	5
29.	**Feeling depressed**	1	2	3	4	5

Figure 3.17: Multiple Sclerosis Impact Scale (MSIS-29)

CHAPTER 4: PREVALENCE OF BLADDER AND BOWEL SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS

Gut dysfunction in patients with Multiple Sclerosis and the role of spinal cord involvement by the disease

G. Preziosi, D. Raptis, A.Raeburn, K. Thirrupathy, J. Panicker, P. Boulos, A.V. Emmanuel.

Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1044-50

4.1 Chapter Layout

Having discussed the rationale for this thesis, and the background of cortical and spinal involvement, I will describe my first study. Since bladder dysfunction has been studied for longer and in more detail, it has become clear that selective plaque involvement in the spinal cord can predict symptom pattern with bladder dysfunction. To understand the landscape better, I undertook this initial study to look at the overlap prevalence of bladder and bowel symptoms in MS.

4.2 Abstract

Background: Bowel and bladder symptoms are both highly prevalent in patients with MS. Bladder dysfunction (affecting 75% of these patients) is caused by disease in the spinal cord, whilst the neural alteration causing bowel dysfunction is unknown.

Hypothesis: My primary hypothesis is that bowel dysfunction in MS is secondary to extent of spinal cord involvement by the disease, assessed clinically with the Expanded Disability Status Scale. Pathways regulating bowel and bladder lie in close

proximity within the spinal cord, and co-existence of their dysfunction might be the result of common pathophysiology, and prevalence of bladder symptoms should be greater in patients with MS and bowel symptoms.

Objective: To evaluate prevalence of bladder symptoms in patients with MS and bowel symptoms. We also evaluated how patient-reported symptoms quantify bowel dysfunction, and any correlation between patient-reported bowel and bladder symptoms.

Design: The NBD questionnaire results and the presence of bladder symptoms were recorded. Both bowel and bladder symptoms were quantified by patient-reported frequency, expressed as a time percentage (0%, 25%, 50%, 75%, 100% of the time the symptom was perceived), and patient-reported severity on a VAS between 0-100. Correlation analysis was performed.

Settings: Specialist neurogastroenterology clinic, tertiary referrals centre.

Patients: Seventy-one patients with MS and bowel symptoms (55 female, age 43±9, median disease duration 78±43 months)

Results: Prevalence of bladder symptoms was 85%. The NBD score was significantly correlated with both patient-reported frequency ($r=0.860$, $p<0.0001$) and severity of bowel symptoms ($r=0.659$, $p=<0.0001$). Patient-reported frequency and severity of bowel and bladder symptoms were also correlated ($r=0.367$, $p=0.002$ and $r=0.463$, $p<0.0001$ respectively).

Conclusions: Prevalence of bladder symptoms is higher than expected in patients with MS and bowel symptoms, suggesting a common pathophysiology of bowel and

bladder dysfunction. Patient-reported bowel symptoms quantified well bowel dysfunction, and are correlated with patient-reported bladder symptoms.

4.3 Introduction

The primary hypothesis of my thesis is that spinal cord disease in patients with MS is central to developing bowel symptoms. In this study I attempt to demonstrate this through a prevalence study. I also analysed how well bowel dysfunction is assessed by patient-reported bowel symptoms, and any correlations between patient-reported bowel and bladder symptoms.

4.4 Formulation of the Hypothesis for a Prevalence Study

Bladder dysfunction, affecting around 75% of MS patients (DasGupta & Fowler, 2003), has been well characterised. It is established that MS plaques in the spinal cord are central in causing urinary symptoms (Betts *et al*, 1993), and their treatment has been rationalised and standardised (Gilman *et al*, 1998). Neurological pathways regulating pelvic organs are in close proximity within the spinal cord. The spinal pathway for defecation, operating through the sacral roots S2-S4, lies in the lateral column of the cord, in close proximity to the pathways important for bladder control (Nathan & Smith, 1951; Nathan & Smith, 1953; Nathan & Smith, 1958).

The neural pathways concerned with physiological bladder control operate through complex bulbo-spinal-bulbar pathways, in close proximity to the lateral pyramidal tracts, and are mediated peripherally through the sacral roots S2 to S4 (Bradley *et al*, 1974; De Groat, 1979). Cortical voluntary control of micturition is established by

connection of the frontal cortex to the micturition centre in the pons (McLellan, 1939).

So it is unsurprising bowel and bladder symptoms often co-exist in MS patients (Hinds *et al*, 1990; Munteis *et al*, 2006; Nordenbo *et al*, 1996). When this is the case, it could be that demyelinating lesions in the spinal cord simultaneously affect bladder and bowel function. However in a study of MS patients with bladder dysfunction (Chia *et al*, 1995), the prevalence of bowel symptoms was only around 50%. This apparent discrepancy could be explained by the presence of the gut's ENS, which would allow preservation of some bowel function in the presence of altered extrinsic hindgut modulation; this compensatory mechanism is not available to the bladder. My primary hypothesis is that bowel dysfunction in MS is secondary to extent of spinal cord involvement by the disease, assessed clinically with the Expanded Disability Status Scale. To test this in a prevalence study, I hypothesised that if bowel and bladder dysfunction can be caused by the same MS-related neurological alteration, in a selected population of MS patients with bowel symptoms a higher prevalence of bladder symptoms should be observed than in the general MS population. The aim of this study is to test this hypothesis. I also analysed how well bowel dysfunction is assessed by patient-reported bowel symptoms, and any correlations between patient-reported bowel and bladder symptoms.

4.5 Patients and Methods

Entry criteria were a definite diagnosis of MS and normal bowel function prior to onset of MS. Exclusion criteria included: concomitant primary bowel pathology, co-

morbidities (i.e. diabetes, thyroid dysfunction, coeliac disease, prostate hypertrophy, etc.) and sphincter injury. These were ruled out in all patients by means of a negative investigation (colonoscopy, radiological or laboratory test) as appropriate. We recruited to the study 71 consecutive patients with MS referred for bowel symptoms to a specialist neuro-gastroenterology clinic, in a tertiary referrals unit. None of the patients met any of the exclusion criteria. Disability was measured with the EDSS (Kurtzke, 1983).

4.6 Symptoms Assessments

In this study I adopted the NBD questionnaire and patient-reported symptoms of bowel and bladder dysfunction, which were described in Chapter 3.

4.7 Study Design and Statistical Analysis

Scores from questionnaires and outcome of outpatient interviews were prospectively collected. Prevalence of bladder dysfunction was established as the presence of at least one urinary symptom at least 25% of the time. Data were either ordinal or not normally distributed (according to Kolmogorov-Smirnov test), so are expressed as median and inter-quartile ranges and non-parametric tests were employed. Correlations between our parameters (EDSS, MS type and duration, NBD and patient-reported bowel and bladder symptoms) were evaluated with the Spearman's Rank test.

To evaluate how patient-reported symptoms quantified bowel dysfunction, we analysed correlations between NBD scores and patient-reported bowel symptoms with the Spearman's rank test (r= correlation coefficient). The values of the NBD

score for each of the four different categories of patient-reported frequency of bowel symptoms (25%, 50%, 75%, 100%) were compared with the Kruskal-Wallis test. Statistical significance was two-sided, and declared for p values ≤ 0.05.

4.8 RESULTS

Patient's characteristics are reported in Table 4.1. Of the interviewed patients, 85% had some degree of urinary symptoms.

Table 4.1: Patients' baseline characteristics

	All cohort (n=71, 55 female)	**Primary progressive MS** (n=16, 13 female)	**Secondary progressive MS** (n=30 23 female)	**Relapsing remittimg MS** (n=25, 19 female)
Age	43±9	39±10	44±8	45±8
Disease duration (months)	78±43	58 (33.5 – 107.5)	84.5 (55-104)	67 (45-89)
EDSS	3 (1-4)	1.5 (0.5-3)	3.5 (1-4.5)	3.5 (1.75-4)
NBD score	8 (6-13)	5.5 (4-8)	10.5 (6-14)	8 (7-18)

4.8.1 Correlation Analysis

Correlation of EDSS, MS type and duration, NBD and patient-reported bowel symptoms is summarised in Table 4.2. Figure 4.1 shows graphically the correlation between EDSS and NBD.

Table 4.2: Correlation analysis of bowel symptoms and patients' characteristics

	Relapsing Remitting MS (25)	**Primary Progressive** MS (16)	**Secondary Progressive** MS (20)	**Disease Duration** (70, 47-100)	**EDSS** (3, 1-4)
NBD score	r= 0.168 p= 0.161	**r= -0.355** **p= 0.002**	r= 0.137 p= 0.253	r= 0.125 P= 0.297	**r= 0.526** **p<0.0001**
Bowel symptoms patient-reported frequency	r= 0.168 p= 0.161	**r= -351** **p= 0.003**	r= 0.153 p= 0.203	r= 0.169 p= 0.160	**r= 0.645** **p<0.0001**
Bowel symptoms patient-reported severity	r= 0.21 p= 0.873	r= -0.120 p= 0.318	r= 0.81 p= 0.500	r= 0.79 p= 0.512	r= 0.112 p= 0.352

Data are reported with median and range; Spearman's Rank correlation coefficients (r) are given along with p value. Disease duration is in months. Statistically significant correlations are showed in bold.

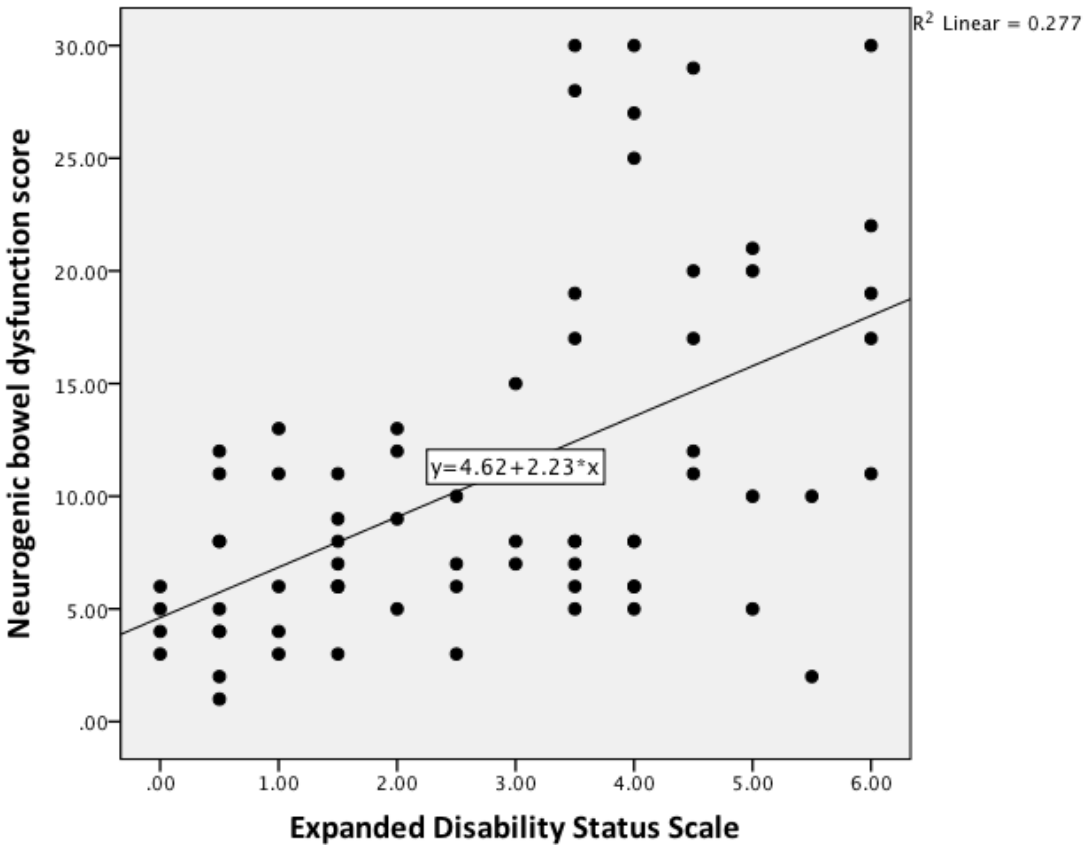


Figure 4.1: Correlation between EDSS and NBD (Spearman's rank test)

The correlation between bowel and bladder patient-reported symptoms is summarised in Table 4.3 and shown graphically in Figure 4.2.

Table 4.3: Correlation analysis of bowel and bladder symptoms

		Bladder symptoms	
		Patient- reported frequency (50%, 0-100%)	Patient-reported severity (41, 0-93)
Bowel symptoms	NBD (median 8, range 1-30)	r=0.342 p= 0.003	r= 0.659 p<0.001
	Patient reported frequency (50%, 25-100%)	r= 0.367 p= 0.002	r= 0.300 p= 0.011
	Patient -reported severity (median 58, range 11-96)	r= 0.300 p= 0.011	r=0.463 p<0.0001

Spearman's Rank correlation coefficient and p values are given for correlation analysis of variable of bowel and urinary dysfunction. All correlations were statistically significant.

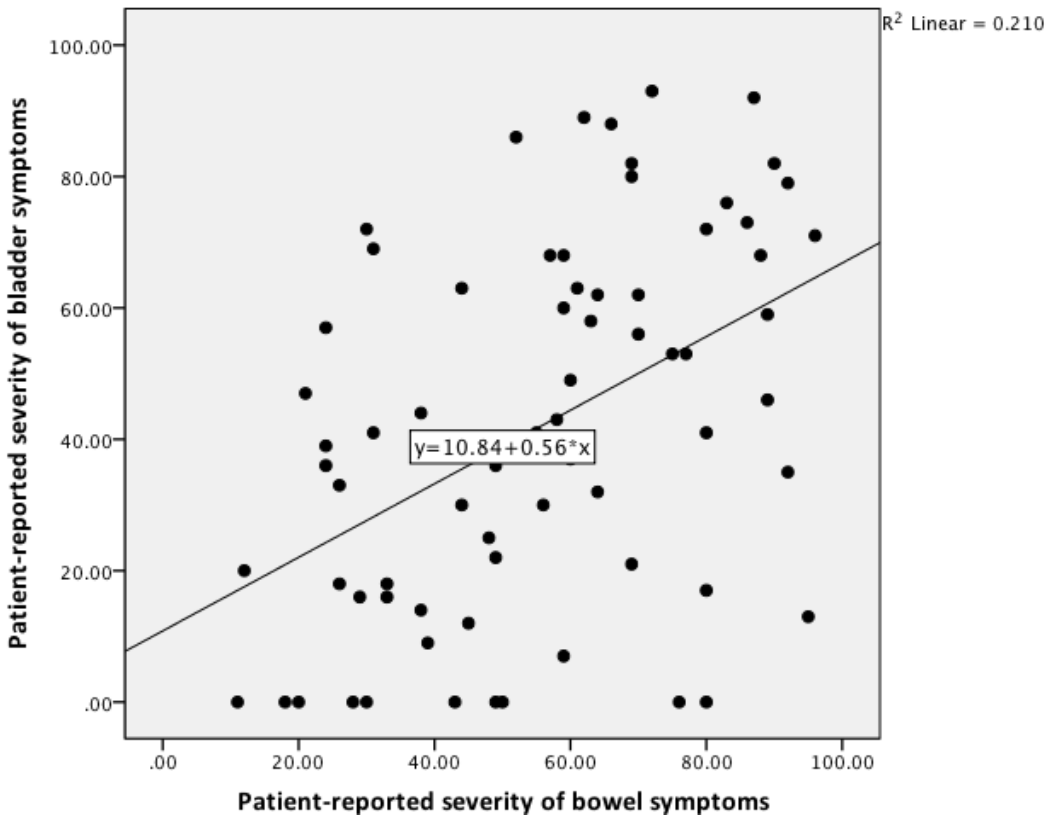


Figure 4.2: Scatter plot showing correlation between patient-reported bowel and bladder patient-reported severity of symptoms.

4.8.2 Evaluation of Patient-Reported Symptoms

NBD scores were correlated with patient-reported frequency (r=0.860, p<0.0001) and severity (r=0.659, p<0.0001) of bowel symptoms. There was a significant difference between the values of NBD scores in the four categories of patient-reported frequency of bowel symptoms (Table 4.4 and Figure 4.3). EDSS was positively correlated with patient-reported frequency (r=0.645, p<0.0001) but not with patient-reported severity (r=0.112, p=0.352) (figures 4.4 and 4.5)

Table 4.4: Comparison of NBD scores between the four categories of bowel symptoms patient reported frequency

Bowel symptoms patient-reported frequency	Neurogenic Bowel Dysfunction score	Kruskal-Wallis test
25%	4 (3-5.5)	p <0.001
50%	8 (6-9.5)	
75%	17 (11-20)	
100%	26.5 (21-29.5)	

In this table values of NBD scores for each group of bowel symptoms patient-reported frequency are shown.

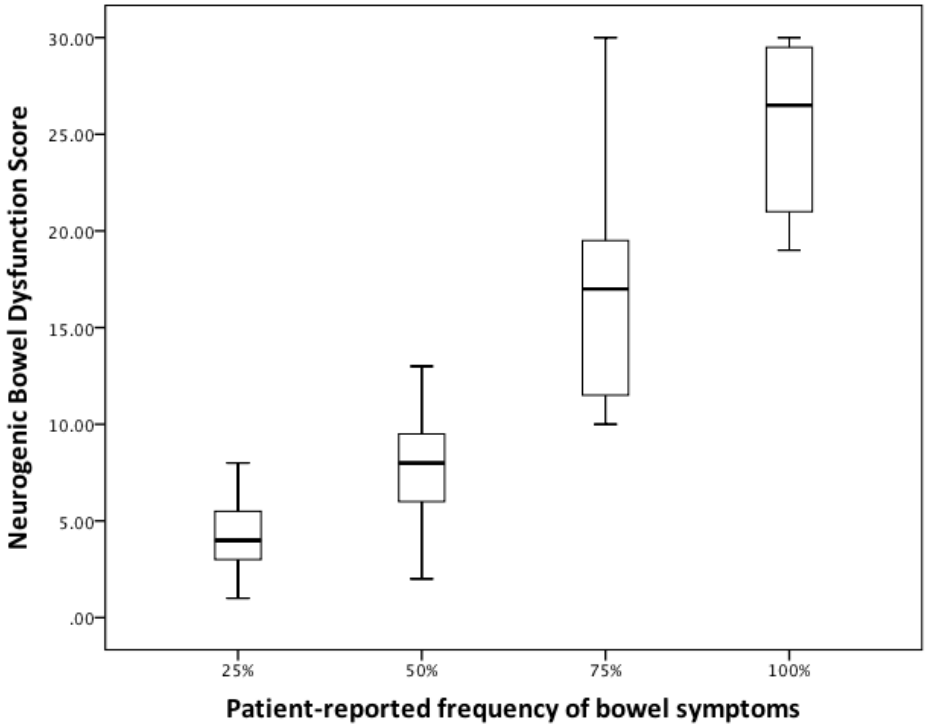


Figure 4.3: Comparison of NBD scores between the four categories of patient-reported frequency of bowel symptoms.

P value of Kruskal-Wallis test was <0.001 for all comparisons.

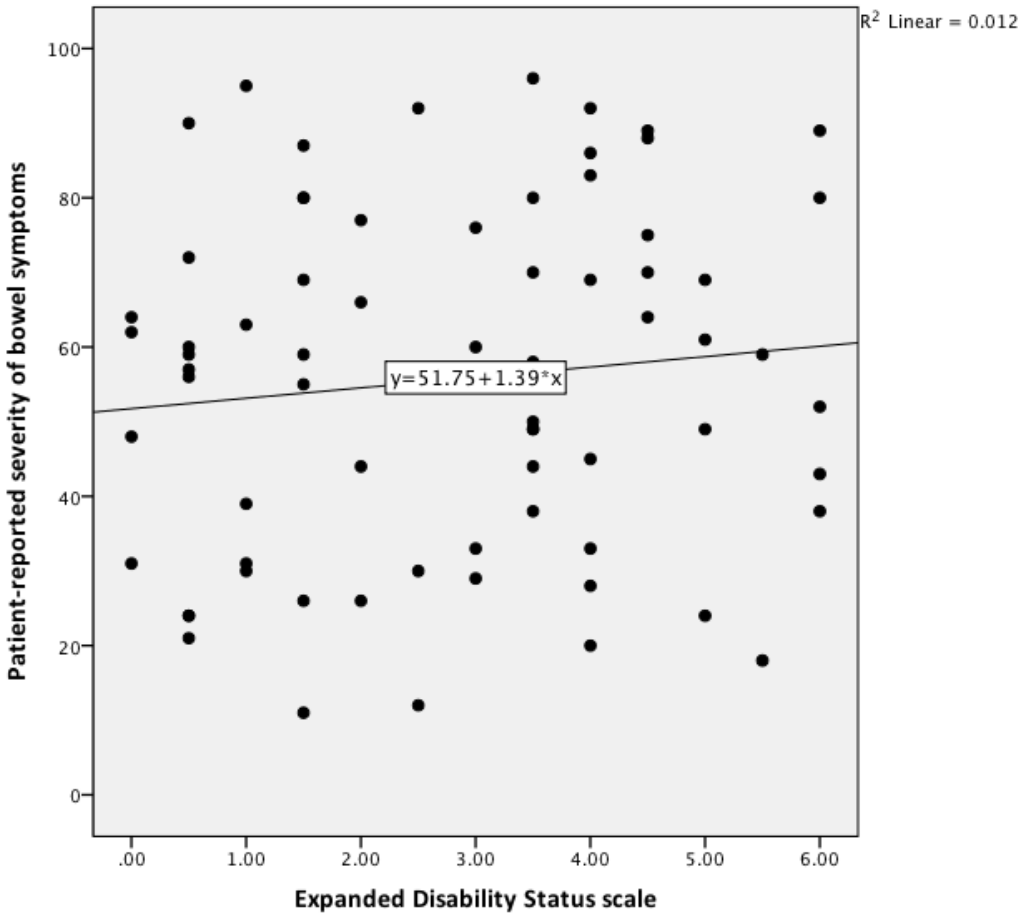


Figure 4.4: Scatter plot showing correlation between EDSS and patient-reported severity of bowel symptoms.

4.9 Discussion

In this study I have showed that the NBD score was strongly correlated with disability (EDSS). As discussed in section 3.5.1, EDSS is a clinical indicator of spinal cord involvement by MS. Also the prevalence of bladder dysfunction in our cohort was very high.

These findings suggests that gut dysfunction in patients with MS is secondary to spinal cord involvement by the disease.

In patients with primary progressive disease there was an inverse relationship with bowel symptoms (i.e. the higher the EDSS the lower the level of symptoms). The lower level of disability of this sub-group might explain this, but it might just indicate that patients with other MS types have more bowel symptoms.

- Patient-reported frequency and severity of bowel and bladder symptoms were correlated.
- With regards to bowel symptoms evaluation, simple questioning of patient-reported frequency and severity of bowel symptoms is as accurate as a validated questionnaire.

Therefore physicians in the clinical setting would be able to assess the impact of bowel dysfunction by asking the percentage of time these symptoms are perceived. On the other hand, the NBD score could be employed to improve quality of bowel studies in patients with MS.

4.9.1 Strengths

The main strength of this study is the methodology used to evaluate our hypothesis, which is supported by anatomical considerations and supportive evidence (Section 1.4.2). Also the low level of disability in this cohort reduced the effect of confounders such as reduced mobility and polypharmacy.

4.9.2 Limitations

- A relevant limitation is the lack of a control group without bowel symptoms. Unfortunately, bowel symptoms are so prevalent that it is very difficult to recruit into a study such a reference population.

- It is well know that anti-muscarinic drugs used for urological symptoms can cause constipation, and this could be a confounding factor affecting our findings. Still in one study (Chia *et al*, 1995), where patients were receiving pharmacological treatment for bladder dysfunction, no higher occurrence of bowel symptoms was observed. Unfortunately we did not record drugs taken at the time. Antimuscarinic could hypothetically mask symptoms of faecal incontinence, ultimately making patients overall more constipated. Nevertheless patients with higher disability had high scores in both constipation and incontinence, suggesting that the confounder effect of drugs, if present was minimal. In some of our male patients the presence of undetected prostate hypertrophy might also have contributed to bladder symptoms.
- A high prevalence of bladder symptoms in our cohort could have been related to small sample size.
- Another limitation of this study is that bladder symptoms were not quantified using a standard questionnaire. The correlation of patient-reported bowel and bladder symptoms merits further evaluation, employing a validated urological questionnaire.
- An element that requires further discussion is the low level of disability in our cohort. In fact for an EDSS of less than 5, other functional systems other than the spinal cord are relevant.

- Our correlation analysis does not constitute a formal validation of the NBD in MS patients; however it shows a good correlation between a formal questionnaire and simple questioning of patient symptoms.

I have so far discussed the anatomical basis for my hypothesis and the indirect evidence that is available in the literature. This study of prevalence is a step further to proving the role of the spinal cord in determining bowel dysfunction in MS patients. I will describe next the physiology study.

CHAPTER 5: STUDY OF AUTONOMIC RECTAL ALTERATIONS IN PATIENTS WITH MULTIPLE SCLEROSIS AND BOWEL SYMPTOMS: A COMPARISON WITH SPINAL CORD INJURY AND NORMAL CONTROLS

Autonomic rectal dysfunction in patients with multiple sclerosis and bowel symptoms is secondary to spinal cord disease
G.Preziosi, D. Raptis, A. Raeburn, J. Panicker, A.V. Emmanuel.
Disease of Colon and Rectum, April 2014 - Volume 57 - Issue 4 - pp 514-521

5.1 Chapter Overview

The content of this chapter represents the key physiological study of this thesis. Below I summarise the hypothesis, methods and the results in an abstract format, and then I will discuss the study in details.

5.2 Abstract

Background: Most patients with MS complain of bowel symptoms, but the underlying pathophysiology is unclear.

Hypothesis: My primary hypothesis is that bowel dysfunction in MS is secondary to extent of spinal cord involvement by the disease, assessed clinically with the Expanded Disability Status Scale. So a similar disturbance to the one described for a SCI above T5 should observed in patients with MS and extensive spinal cord disease.

Objective: To evaluate autonomic rectal dysfunction in patients with MS

Design: case-control study

Settings: Neurogastroenetrology clinic, tertiary referrals centre

Patients: 45 patients with MS, 19 with a SCI above T5 and 25 normal controls. Patients with MS were sub-divided into two groups according to an EDSS below 5 (MS-minor-disability, n=25) or above 5 (MS-major-disability, n=20), as a reflection of spinal cord involvement.

Main Outcome Measures: Rectal compliance, Wexner-constipation and Wexner-incontinence scores.

Results: Data are presented as means and standard deviation. EDSS (4 ± 2) correlated with rectal compliance (12.7±5.4mls/mmHg, r=0.410, p=0.005) but not with Wexner-Constipation (11±4.7, r=0.075, p=0.626) or Wexner-Incontinence scores (8±5.8, r=0.185, p=0.223).

Rectal compliance (mls/mmHg): Normal controls (11±3.1) vs. MS-minor-disability (10.5±4.3) vs. MS-major-disability (15.4±5.6) vs. SCI (18 ± 5.8), p<0.0001. Post-hoc analysis: MS-major-disability = SCI > MS-minor-disability = normal controls

Wexner-constipation: MS-minor-disability (10.8±5.3) vs. MS-major-disability (11.3±4.3) vs SCI (15.4±5.8) p=0.037.

Wexner-incontinence: MS-minor-disability (6.12±4.72) vs. MS-major-disability (9.8±6.4) vs SCI (18±5.8) p=0.031.

Post-hoc analysis showed no significant difference in Wexner-Constipation and Wexner-Incontience between the two MS groups.

Limitations: Lack of an asymptomatic group with MS and small sample size to evaluate bowel symptoms.

Conclusions: Rectal compliance correlates with disability and observed alterations in the rectal properties are secondary to spinal cord involvement. Therefore, in neurological patients, rectal compliance is a surrogate of reflex activity of the spinal cord regulating rectal function, and both a potential predictor of outcome and target for treatment. MS patient sub-groups had similar symptom burden, arguing that bowel dysfunction is multifactorial.

5.3 Introduction

5.3.1 Background

I discussed in Chapter 1 how previous studies of hindgut physiology in patients with MS have focused on motor and sensitive alterations of the colon and ano-rectum, showing delayed bowel transit, anal sphincter weakness and reduced ano-rectal sensation. (Wiesel *et al*, 2001). These alterations though are non-specific and do not correlate to a specific neuro-pathophysiological alteration. The demyelinating plaques of MS, are ubiquitous in the CNS but plaques in the spinal cord appear to be crucial to developing bladder symptoms, and in the previous chapter I discussed the evidence that this might also be the case for bowel symptoms (Preziosi *et al*, 2013). Furthermore our group have shown that specific symptom patterns correlate with alteration of the RAIR (Thiruppathy *et al*, 2012), suggesting a primary role of spinal cord alteration.

I wished to test my primary hypothesis, that NBD in MS is secondary to extent of

spinal cord disease as assessed clinically by EDSS, with a physiological study.

Existing evidence in SCI research suggests that rectal compliance can be regarded as a marker of autonomic dysfunction, and that its changes can be correlated to the level of injury (Trivedi P, 2009). In this study patients with a supraconal SCI were found to have a higher rectal compliance than those with a lower motoneurone injury and normal controls. SCI patients represent an ideal control group, as the neurological damage is well defined, and therefore it is clear that in the absence of other factors (parity, drugs or co-morbidities) the observed ano-rectal physiological alteration can be attributed to a primary spinal cord damage.

5.3.2 Anatomical Considerations

The sympathetic supply to the large bowel arises from the T5-L3 nerve roots. The vagus nerve supplies parasympathetic fibres up to the splenic flexure. The parasympathetic supply to the left colon and rectum arises from the sacral nerve roots S2-4 synapsing in the pelvic plexus. As discussed in section 2.4 the pathophysiology of bowel dysfunction in a SCI is essentially related to the loss of the supraspinal modulation of sympathetic and/or parasympathetic efferents.

NBD in SCI can be related precisely to the injury level, and so if the alteration is above the T5 level, the supra-spinal modulation of the autonomic outflow to the large bowel and rectum is lost and rectal compliance is increased, regardless of completeness of injury (Trivedi P, 2009).

5.3.3 Rectal Compliance

I have discussed in detail the determinant of rectal compliance and its measurement in section 3.3. I will now discuss why I think it can represent a marker of autonomic dysfunction of the rectum in MS patients. In the colon the loss of supraspinal modulation of autonomic efferents can result in an alteration of transit times (Krogh *et al*, 2000; Krogh *et al*, 1997; Krogh *et al*, 2003). Similar alterations of motility can occur in the rectum, and are measured as altered rectal compliance (Craggs *et al*, 2006; Trivedi P, 2009), though with conflicting results. Inconsistencies might be related to sample size, heterogeneous patient's cohort or methodology of measurement.

Rectal compliance has been studied in MS patients before and was found to be reduced (Nordenbo *et al*, 1996). That study though had a small sample formed of a heterogeneous group of MS-patients, and compliance was measured with a surpassed technique.

5.3.4 Hypothesis and Aims

My primary hypothesis is that bowel dysfunction in MS is secondary to extent of spinal cord involvement by the disease, assessed clinically with the Expanded Disability Status Scale. So a similar disturbance to the one described for a SCI above T5 should observed in patients with MS and extensive spinal cord disease. The resultant autonomic dysfunction of the rectum should be measurable as increased rectal compliance. We therefore analysed rectal compliance and its relationship with disability (as a surrogate of spinal cord disease) and bowel symptoms in MS

and in comparison with patients with a supraconal-SCI and normal controls. We also compared symptoms burden and standard ARP tests between MS patients.

5.4 Patients and Methods

Patients were recruited at a neuro-gastroenterology clinic at a tertiary referral centre, and both verbal and written information were given prior to the patient agreeing to sign a consent form. Patients included were aged 18 or over and had bowel symptoms for at least 6 months, post-dating a diagnosis of MS or supraconal-SCI.

Exclusion criteria were:

- Concomitant primary bowel pathology
- Previous colorectal surgery (including haemorrhoidectomy and fistulotomy)
- Previous sphincter injury, perianal sepsis, rectal prolapse
- Diabetes

These were ruled out in all patients by means of a negative investigation (colonoscopy, radiological or laboratory test) as appropriate and as part of their clinical assessment.

Normal controls were enrolled by advertisement within the institution. No reimbursement was offered for participation. All controls underwent clinical assessment to exclude use of any medication or presence of any intestinal or chronic illness.

Between February 2008 and Sept 2010 we recruited to the study 45 patients with MS (age 48±10.5 years, 21 females, mean parity 0.8±1) and 23 patients with a

supraconal-SCI. We also recruited 25 healthy individuals (14 females, age 54±18) without bowel symptoms.

5.4.1 Disability

Disability was measured with EDSS. As stated before, the EDSS is an established clinical measure of the degree of spinal cord involvement by MS (Kidd *et al*, 1996; Kidd *et al*, 1993; Losseff *et al*, 1996). In summary, for values between 1 and 4.5 the patient is fully ambulant, between 5 and 7.5 the patient is wheelchair-bound and for scores above the patient bed-bound. The first category (1 to 4.5) has less spinal cord involvement than those with a score of 5 and above, as manifested by impaired mobility.

5.4.2 Measurement of Rectal Compliance

Patients were asked to discontinue anti-muscarinic medications for at least one week before their appointment. Rectal compliance was measured with the methodology described in section 3.3.

Normal values for rectal compliance varies widely amongst different GI physiology units, and ours were obtained by applying this protocol in normal controls where the range was 11-15ml/mmHg (Bajwa *et al*, 2011).

5.4.3 Bowel Symptoms

To assess bowel symptoms we adopted the Wexner-constipation (Agachan *et al*, 1996) and incontinence (Jorge & Wexner, 1993) questionnaires (Section 3.4.3). The incontinence score ranges between 0-20, and the constipation score between 0-30,

with 0 representing an absence of symptoms, and 20 or 30 the most burdensome level of symptoms.

5.4.4 Standard Tests of Ano-Rectal Physiology

Standards test for ARP were performed according to the standardised criteria described earlier.

In summary I measured in all patients with MS:

- Anal manometry (resting and squeeze pressure)
- Rectal sensation to balloon distension (threshold, urge and maximum tolerated volume)
- Anal and rectal electro-sensitivity

5.4.5 Study design

I firstly evaluated if there was any relationship between disability (EDSS) and rectal compliance.

Patients with MS were divided into two subgroups according to the clinical extent of spinal cord disease as evaluated with EDSS. So MS patients with a clinically low degree of involvement (EDSS<5) formed the MS-minor disability group (n=25), and those with clinically significant spinal cord disease (EDSS≥5) formed the MS-major disability group (n=20).

Rectal compliance (primary outcome measure) was compared amongst the four groups. Wexner-constipation and Wexner-incontinence scores (secondary outcome measures) were compared between the MS-minor, MS-major disability and SCI

groups. Standard ARP parameters (anal manometry and ano-rectal sensation measurements) were compared between MS-minor and MS-major disability groups.

5.4.6 Sample Size Calculation

Rectal compliance in normal controls was normally distributed, and mean and standard deviation (RC: 11 ± 3 mls/mmHg), was similar to the values found in other studies employing the same distension protocol (Fox *et al*, 2006). Sample size calculation were performed to have 5% overall two-sided significance and 80% power to detect a difference of 3 ml/mmHg or greater between any two of the four groups. The Bonferroni correction was applied to allow for multiple testing. There are six possible comparisons between any two of the four groups so the sample size was calculated at the 0.83% significance level in order to retain overall 5% two-sided significance. In total, 17 individuals were required in each group for the equal size group comparisons with 25 healthy controls, and 13 patients for each of the comparisons with healthy controls. Thus the study required 25 healthy controls, and 17 in each of the patient groups. Dropouts were not considered as only patients with completed tests and questionnaires were included in the study.

5.4.7 Statistical Analysis

As distributions of the physiological parameters were approximately bell-shaped, results are expressed as means and standard deviations, and the t-test and one-way analysis of variance with the Bonferroni correction were used for comparisons between groups. The Pearson correlation coefficient was used to assess correlations between EDSS, rectal compliance and Wexner scores. Comparability

between groups with respect to gender was assessed with the chi-squared test. Significance tests were two-tailed and the level of significance was set at less than or equal to 0.05.

5.5 Results

Baseline characteristics of study participants are shown in Table 5.1.

Table 5.1: Participants' baseline characteristics

	MS (whole cohort)	**MS-Minor disability group**	**MS-Major disability group**	**Supraconal-SCI** (9 complete – 10 incomplete)	**Normal Controls**
Age (years)	48±10	45±11	51±9	46±12	54±18
Gender (male/female)	24/31	8/17	6/14	6/13	11/14
Disease duration (years)	13±8	12±8	14±9	9±6	
EDSS	4 ± 2	2.6 ± 1.3	6 ± 1	/	/

Of the SCI group, nine had a cervical injury, and ten a thoracic injury level above T5. In terms of aetiology, 14 had a traumatic injury, two a vascular accident and three a cord tumour. The four study groups were checked for comparability with respect to age, parity (one-way Anova) and sex (chi-squared test), and no statistical difference was identified.

5.5.1 Correlation between EDSS and Rectal Compliance

There was a positive and statistically significant correlation between EDSS (4 ± 2) and rectal compliance (12.7 ± 5.4 mls/mmHg, r=0.410, p=0.005) (Figure 5.1), but no such correlation with Wexner-constipation (11 ± 4.7, r=0.075, p=0.626) or Wexner-incontinence scores (8 ± 5.8, r=0.185, p=0.223).

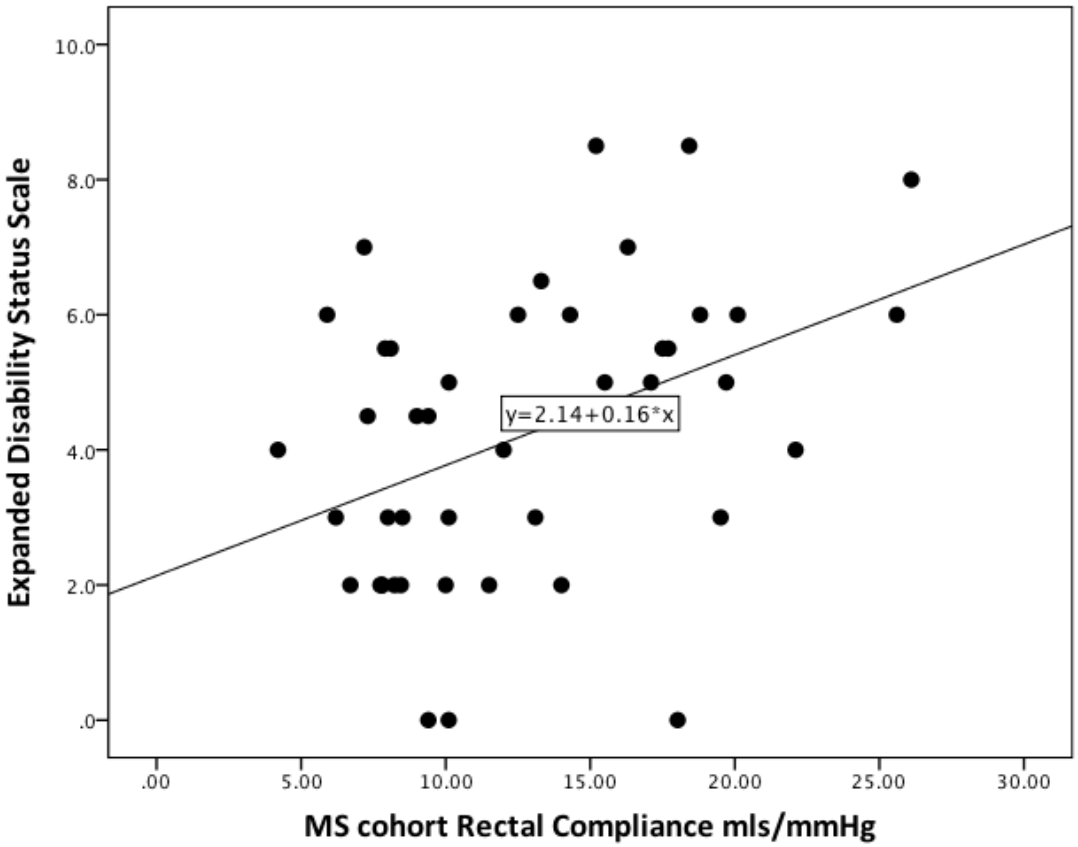


Figure 5.1: Scatter plot showing quadratic correlation between EDSS and Rectal compliance.

5.5.2 Rectal Compliance

There was a statistically significant difference in rectal compliance between the four groups ($p<0.001$) (Figure 5.2).

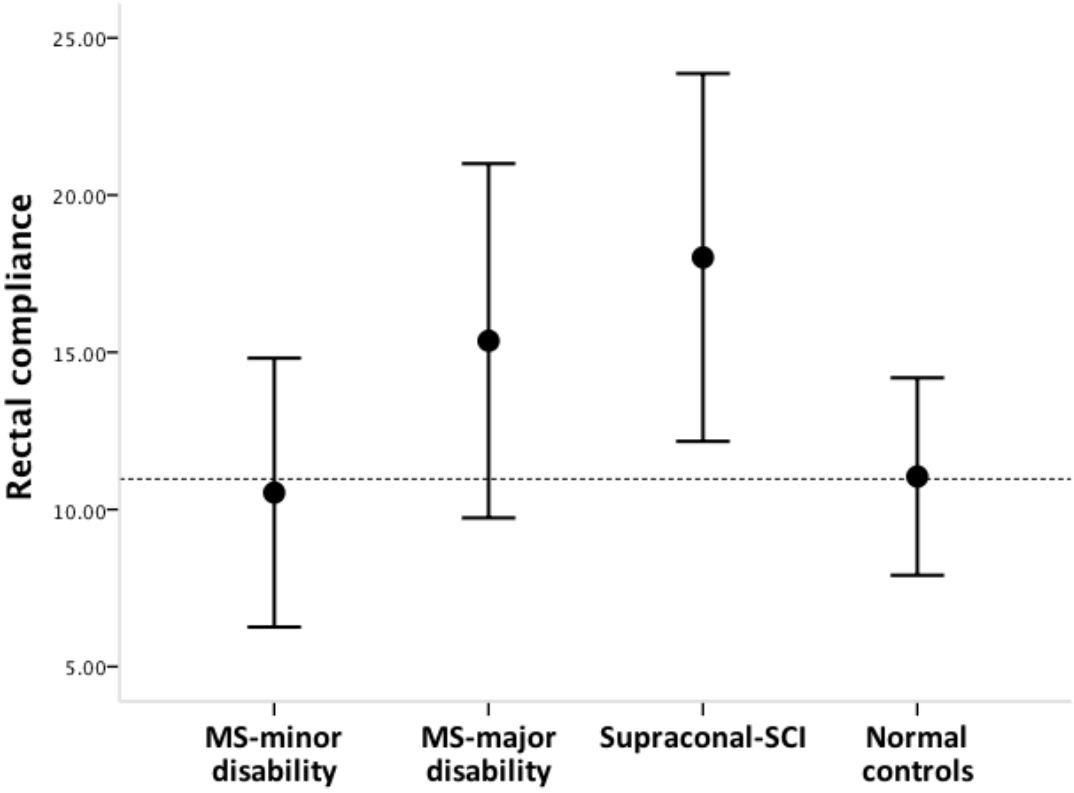


Figure 5.2: Comparison of rectal compliance between the 4 groups

In summary, rectal compliance was higher in patients with SCI and MS-major disability group than in the other two groups. Bonferroni correction data are shown in Tables 5.2 and 5.3.

Table 5.2: Comparison of rectal compliance of symptomatic groups vs. normal controls

	Rectal compliance mls/mmHg	**Mean difference**	**p-value**	**Confidence interval**
MS-minor disability vs. Normal controls	10.5 ± 4.3 vs. 11 ± 3.1	-0.5	1	-4.1 / 3.1
MS-major disability vs. Normal controls	15.4 ± 5.6 vs. 11 ± 3.1	4.3	**0.018**	0.5 / 8.1
Supraconal-SCI vs. Normal controls	18 ± 5.8 vs. 11 ± 3.1	7	**<0.0001**	3.1 / 10.8

Table 5.3: Comparison of rectal compliance between symptomatic groups

	Rectal compliance mls/mmHg	**Mean difference**	**p-value**	**Confidence interval**
MS-minor disability vs. MS-major	10.5 ± 4.3 vs. 15.4 ± 5.6	-4.8	**0.006**	-8.6 /-1
MS-minor disability vs. Supraconal-SCI	10.5 ± 4.3 vs. 18 ± 5.8	-7.5	**<0.0001**	-11.3 / -3.6
MS-major disability vs. Supraconal-SCI	15.4 ± 5.6 vs. 18 ± 5.8	-2.65	0.499	-6.7 / 1.43

Rectal compliance was similar between normal controls and MS-minor disability patients, and was also similar between MS-major disability and the SCI groups. Rectal compliance was higher in the latter two groups than the normal controls and the MS-minor group. In summary: MS-major = SCI > MS-minor and Normal controls.

5.5.3 Wexner-Constipation and Incontinence Scores

A one-way Anova test comparing the Wexner-constipation score amongst the symptomatic groups was statistically significant with a p= 0.020 (Figure 5.3).

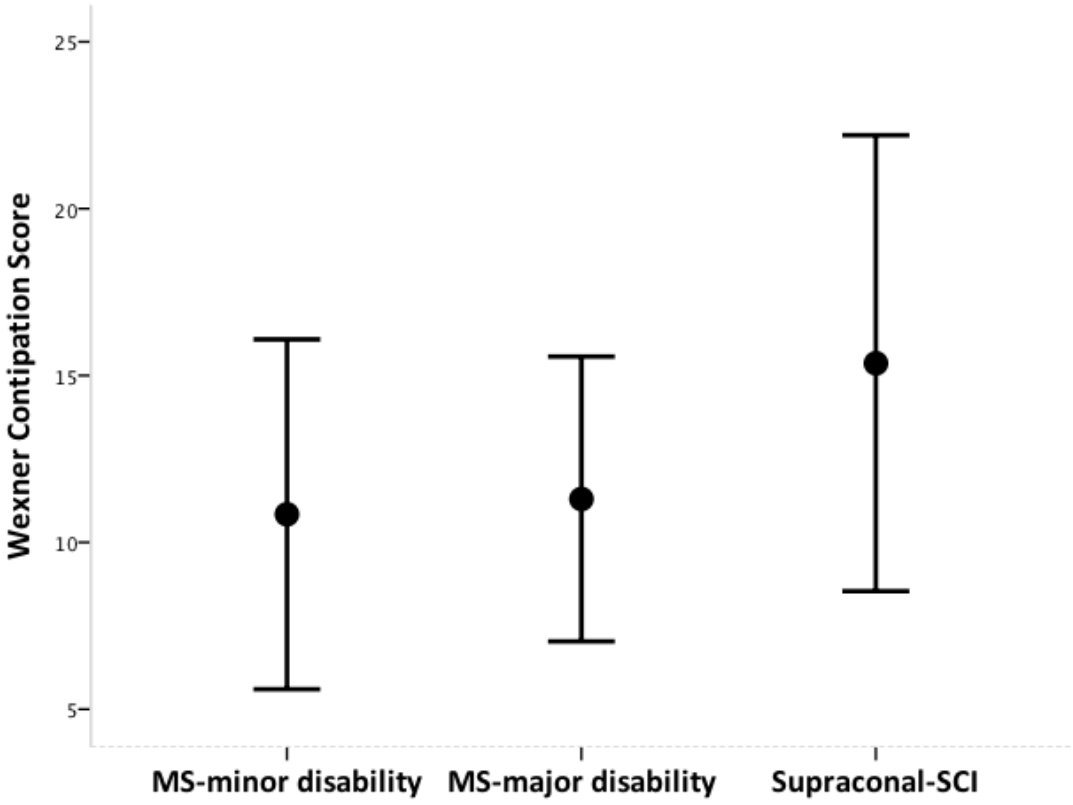


Figure 5.3: Comparison of Wexner-Constipation scores

Results of the Bonferroni's test are shown in Table 5.4.

Table 5.4: Comparison of Wexner-constipation scores

	Wexner Constipation	Mean difference	p value	Confidence interval
MS-minor disability vs. MS-major	10.8 ± 5.3 vs. 11.3±4.3	-0.460	1	-4.5 / 3.6
MS-minor disability vs. Supraconal-SCI	10.8 ± 5.3 vs. 15.4 ± 5.8	-4.5	**0.027**	-8.65 / -0.41
MS-major disability vs. Supraconal-SCI	11.3±4.3 vs. 15.4 ± 5.8	-4	0.073	-8.41 / 0.27

SCI patients had higher Wexner-constipation scores compared to MS-minor disability patients, but similar to MS-major disability patients. However, there was no difference between the two MS groups.

A one-way Anova test comparing Wexner-incontinence scores amongst the symptomatic groups also showed statistically significant differences amongst the three groups with a p= 0.048 (Figure 5.4), but the Bonferroni's test showed no significant differences in the coupled comparisons (Table 5.5).

In summary, there was no difference in symptom burden between the two MS groups.

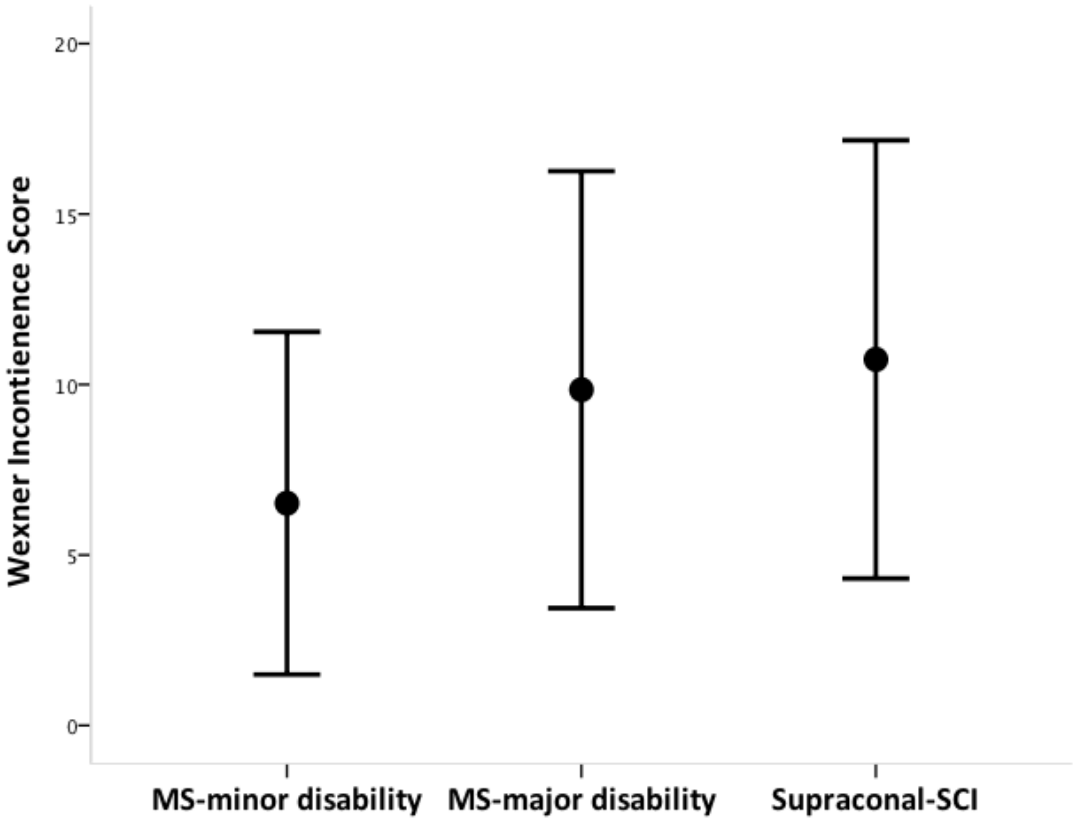


Figure 5.4: Comparison of Wexner-incontinence scores

Table 5.5: Comparison of Wexner-incontinence scores

	Wexner Incontinence	Mean difference	p value	Confidence interval
MS-minor disability vs. MS-major disability	6.12 ± 4.72 vs. 9.8 ± 6.4	-3.3	0.195	-7.7 / 1
MS-minor disability vs. Supraconal-SCI	6.12 ± 4.72 vs. 18 ± 5.8	-4.217	0.067	-0.8 / 0.2
MS-major disability vs. Supraconal-SCI	9.8 ± 6.4 vs. 18 ± 5.8	-0.887	1	-5.55 / 3.77

5.5.3 Comparison of baseline ano-rectal physiology between MS groups

The t-test was used to compare baseline ARP tests between the two MS groups (Table 5.6), and it showed that urge volume of rectal sensation was higher and anal electro-sensitivity was reduced in the MS-major disability group.

Table 5.6: Comparison of ano-rectal physiology tests MS-minor vs. MS-major disability

	MS minor disability	MS major disability	p-value
Resting Pressure mmHg	67 ± 23	59 ± 27	0.259
Squeeze Pressure mmHg	86 ± 74	60 ± 47	0.155
Threshold volume mls	79 ±75	118±101	0.146
Urge Volume mls	127 ± 62	194 ± 102	**0.015**
Maximum Tolerated Volume mls	208 ± 71	249 ± 81	0.083
Anal-electrosensitivity mAmp	24.6 ± 10.9	27.0 ± 15.5	**0.028**
Rectal-electrosensitivity mAmp	10.5 ± 4.2	15.3 ± 5.6	0.555

5.6 Discussion

Our hypothesis of a correlation between spinal cord disease, measured as disability (EDSS), and rectal compliance is confirmed by our findings. Evaluation of the rectal properties showed that rectal compliance is higher in patients with SCI above T5 and those MS patients with severe disability than in either MS patients with minor disability or healthy volunteers. These findings though were not reflected in differences in bowel symptoms, as MS patients with minor and major disabilities had similar constipation and incontinence symptom burden. This is at least partly explained by the multifactorial nature of bowel dysfunction in MS.

Comparison of baseline ARP revealed that MS patients with a major disability have higher urge volumes for sensitivity to rectal distension and higher threshold for anal electrosensitivity, even though the differences measured are small and probably not clinically relevant. This suggests mixed somatic and autonomic dysfunction, and also that the observed changes in rectal compliance are independent from sensory deficit.

5.6.1 Strengths

- This is a controlled study that was adequately powered to test our hypothesis.
- Findings add to our theoretical knowledge of rectal physiology and to the understanding of MS-related bowel dysfunction.

5.6.2 Limitations

- We employed a surrogate of spinal cord disease, EDSS, and our threshold to divide patients as MS-minor or MS-major disability has never been employed before. Nevertheless our choice takes into account the well-described observation that EDSS correlates well with degree of spinal cord atrophy (Kidd *et al*, 1996; Kidd *et al*, 1993; Losseff *et al*, 1996); for an EDSS of less than 5 the degree of spinal cord atrophy is negligible, whilst for an EDSS of above 5 it is considerable. (Kurtzke, 1983).

MS causes a progressive accumulation of cord lesions scattered at different levels, as opposed to the clearly defined level in SCI patients. However the acquisition of accurate MRI imaging of the entire spinal cord, to quantify MS lesions, is technically challenging and potentially highly inaccurate. We therefore used a surrogate clinical parameter of spinal cord involvement by MS (EDSS) that quantified extent, rather than level of disease. Most of the cord anatomically lies above T5, and therefore it can be assumed that patients with extensive spinal cord disease (EDSS≥5) have disease above T5. This explains our choice of a symptomatic control group. As the rectum is not under influence of the vagus nerve, the observed alterations of rectal compliance are likely to represent the result of loss of supra-spinal modulation of the spinal cord reflex activity, and the effect of un-opposed sympathetic outflow from the thoraco-lumbar segment. This could be a parallel phenomenon that leads to slow colonic transit, commonly observed in MS patients.

- A limitation of motility studies is usually the lack of reproducibility. Three main factors we believe make our measurement reproducible and reliable.

Firstly we employed polyethylene bags with infinite compliance (Krogh *et al*, 2001b), an electronic barostat was used for measurements (Diamant *et al*, 1999), and our distension protocol has been shown to obtain a reproducible measurement of rectal compliance (Bharucha *et al*, 2004; Fox *et al*, 2006; Hammer *et al*, 1998).

- MS patients without bowel symptoms would have constituted an ideal control group, but we employed healthy controls for two reasons. One was ethical, as we had this data already available questioning whether it would have been reasonable to put gut-asymptomatic MS patients through these tests. Secondly, given the high prevalence of bowel symptoms in MS, it would have been difficult to recruit an asymptomatic MS group.

5.6.3 Rectal Compliance in Health and Disease

The importance of coordination of the anal and rectal components of bowel evacuation and continence has been demonstrated in healthy subjects (Fox *et al*, 2011). It is established that alteration of rectal compliance can play a role in both constipation and incontinence in functional bowel disorders. In idiopathic faecal incontinence there is reduced rectal compliance that can result in hypersensitivity and faecal urgency, which in the presence of a weak anal sphincter can precipitate faecal incontinence (Steens *et al*, 2002). This can be corrected with pharmacological manipulation with clonidine, where increasing rectal compliance results in amelioration of symptoms (Bharucha *et al*, 2010).

In idiopathic constipation there is increased rectal compliance, hyposensitivity to rectal filling and hence difficulty with evacuation (Gladman *et al*, 2006). However

some studies in patients with obstructed defecation have shown normal rectal compliance (Gosselink *et al*, 2001).

Rectal alterations can also occur as the result of primary anatomical damage, and rectal compliance is correlated with disease activity in ulcerative colitis (Farthing & Lennard-jones, 1978; Rao *et al*, 1987) and radiation proctitis (Varma *et al*, 1985). After anterior resection of the rectum for cancer, reduced rectal compliance is correlated with faecal incontinence, regardless of sphincter function (anterior resection syndrome) (Rasmussen *et al*, 2003). Whilst these changes in rectal properties are the consequence of a mechanical damage (radiation, inflammation or surgery), in neurological patients, such as those with MS, changes in rectal compliance are the result of changes in the tone of the smooth muscle as a consequence of altered autonomic function. This has been shown in SCI patients,(Craggs *et al*, 2006; Trivedi P, 2009) though with conflicting results, but inconsistencies might have been related to sample size, heterogeneous patient's cohort or methodology of measurement.

However MS patients present unique features, such as the alternating and fluctuating patterns of bowel symptoms. So it is not surprising that in our cohort we observed increased rectal compliance in the presence of both constipation and faecal incontinence.

Although ano-rectal alterations are associated with the presence of bowel symptoms, we could not demonstrate any specific symptom relationship. It should be observed that this study did not address other aspects of gut motility, and has been powered to look primarily at rectal properties.

Bowel symptoms in MS are likely multi-factorial in aetiology. Disability itself can limit the ability to access the toilet and cause behavioural modifications. So patients could either 'learn' to be constipated (Klauser *et al*, 1990), to avoid a trip to the lavatory, or might be unable to access the toilet in time, hence manifesting faecal incontinence (particularly in the presence of a full rectum). This might explain why trans-anal irrigation is effective in patients with high disability (Preziosi *et al*, 2012). The proof that behavioural factors come into play is demonstrated, indirectly, by improvement with biofeedback (Preziosi *et al*, 2011), even though pelvic floor incoordination might be a primary neurological symptom (Chia *et al*, 1996). Polypharmacy certainly has a role; antimuscarinic and anti-spasticity drugs in particular are powerful constipating agents. The latter were discontinued prior to testing of rectal compliance, but there is no evidence available to suggest that they might have contributed to compliance alterations.

5.6.4 Future Studies and Wider Implications of our Findings

What this study showed is that the observed alteration in rectal wall properties in MS patients is likely to be the consequence of spinal cord involvement, such that severe disability is associated with greater rectal compliance. Further confirmation might come from studies that correlate degree of spinal cord atrophy on MRI scans with ARP. Adequately powered studies, comparing patients with MS and bowel symptoms with a group of MS patients without bowel symptoms, extracted from the general MS population, could evaluate the significance of alterations in rectal compliance to determine bowel symptoms.

Our findings also have wider implications. It is accepted that standard tests of ARP

(testing of ano-rectal sensation and sphincter pressures) are not specific, and their alteration cannot identify a specific underlying neurological abnormality (Diamant *et al*, 1999). This study shows that rectal compliance is a surrogate of reflex activity of the spinal cord regulating rectal function. Residual spinal cord function represents a potential treatment target, and the usefulness of our finding is that this can be clinically assessed with EDSS and measured with rectal compliance. Whilst the role of altered rectal compliance in determining bowel symptoms needs further evaluation, future studies should assess efficacy of physiotherapy or neuromodulation, and whether their effects are associated with modification of rectal compliance. Pharmacological modulation of compliance, and hence symptoms, could also represent an innovative treatment strategy.

5.7 Conclusions

In conclusion, we have shown that ano-rectal properties in MS patients with bowel symptoms are altered in predictable fashion, according to degree of disability. Symptom burden was very high in both MS groups, suggesting the presence of multiple causative factors.

5.8 Summary of Main Findings

With this study we have shown that:

- Rectal compliance correlates positively with the extent of spinal cord disease
- Patients with higher disability have greater threshold for urge sensation at rectal balloon distension and reduced ano-rectal electrosensitivity.

- Symptoms burden is very high in both MS groups, suggesting the presence of multiple causative factors including medications and behavioral factors.

This has wider implications:

- With the development of techniques of nerve stimulation, residual spinal cord function might represent a target for treatment, and rectal compliance might represent a predictive factor of response.
- Pharmacological modulation of rectal compliance could be a therapeutic strategy for the treatment of constipation and incontinence.
- Furthermore this study has shown that rectal compliance is a good surrogate measure of altered reflex activity secondary to spinal cord disease.

In summary, I have discussed so far:

- Potential pathophysiology of bowel dysfunction in MS.
- Tested my primary hypothesis with a prevalence and a physiology study.

I am now going to test my secondary hypothesis, which is that residual spinal cord function can be a target of treatment for bowel symptoms in MS. In the next chapter I will evaluate bowel biofeedback treatment in patients with MS and bowel dysfunction.

CHAPTER 6: BOWEL BIOFEEDBACK TREATMENT IN PATIENTS WITH MULTIPLE SCLEROSIS AND BOWEL SYMPTOMS

Bowel biofeedback treatment for patients with multiple sclerosis and bowel symptoms.
G.Preziosi, D. Raptis, J. Storrie, A. Raeburn, C.J. Fowler, A. Emmanuel,
Diseases of the Colon and Rectum 2011: 54(9), 1114–1121

6.1 Chapter Layout

Below I provide a summary of the next chapter in the form of an abstract. I then discuss in detail the biofeedback study.

6.2 Abstract

Background: Bowel biofeedback treatment has a well-established role in the treatment of functional constipation and faecal incontinence.

Objective: This study aimed to identify the effect of biofeedback on bowel symptoms, mood and ARP in patients with MS.

Hypothesis: My secondary hypothesis is that the treatment strategies should target residual spinal cord function. The effect of bowel biofeedback treatment is thought be mediated by the extrinsic autonomic nervous system, with spinal efferents playing a key part. This biofeedback-induced modulation of gut autonomic function may be impeded by the underlying neural dysfunction secondary to MS. If this was

the case, then successful biofeedback could depend on secondary behavioural alterations and/or residual spinal cord function (lower disability).

Design: This is a prospective observational study: we compared and analysed the amount of change between pre- and post-treatment values of outcome measures. Responders were considered to be patients who demonstrated an improvement greater than or equal to the 25th percentile of the change in bowel score. We then compared baseline characteristics between responders and non-responders.

Settings: Neurogastroenterology clinic, tertiary referrals centre.

Patients: Thirty-nine patients with MS and constipation and/or faecal incontinence

Intervention: Bowel biofeedback.

Main Outcome Measures: *Primary*: Wexner-constipation and Wexner-incontinence scores. *Secondary*: HADS, ARP parameters.

Results: Data are reported as median and interquartile ranges. After biofeedback there was significant improvement in Wexner-constipation [12(5-19) pre-treatment vs. 8(4-14) post-treatment, p=0.001], Wexner-incontinence [12(3-15) pre-treatment vs. 4(2-10) post-treatment, p<0.001)] and HADS [7(3-11) pre-treatment vs. 5(3-10) post-treatment, p=0.015)]. The 5-seconds-endurance squeeze pressure was also improved [21(11-54)mmHg pre-treatment vs. 43(26-59)mmHg post-treatment, p=0.001]. Post-treatment change of Wexner-Constipation was -2(-5/0), and of Wexner-Incontinence was -3(-9/0) ('-' indicates improvement). Therefore those patients who had a reduction of at least 5 points in Wexner-constipation and/or of at least 9 points in Wexner-incontinence scores were considered responders (18

patients, 46%). They showed a greater improvement of only 5-seconds-endurance squeeze pressure [23.5(7.5/32.75)mmHg responders vs. 4(-6/20)mmHg non-responders, p=0.008]; comparing baseline variables with non-responders no difference was observed. Significant negative relationship existed between change in Wexner-constipation [-2(-5/0)] and pre-treatment Wexner-constipation score [12(5/19), β= -0.463, p<0.001)], and change in Wexner-incontinence [-3(-9/0)] with pre-treatment Wexner-incontinence score [12(3/15), β= -0.590, p<0.001). So the higher the initial bowel symptom score the greater the improvement.

Limitations: Lack of a control group.

Conclusions: Biofeedback improves bowel symptoms, depression and 5-seconds-endurance squeeze pressure in patients with MS.

6.3 Introduction

Bowel biofeedback treatment has a well-established role in the treatment of functional constipation and faecal incontinence, improving bowel symptoms, pelvic floor coordination, ano-rectal sensation and transit time (Enck *et al*, 2009).
As discussed in section 1.4, the pathophysiology of bowel dysfunction in MS is multifactorial and partly common to both constipation and faecal incontinence (Wiesel *et al*, 2001). Some of the alteration observed represents the potential target of bowel biofeedback behavioural treatment. More specifically pelvic floor dyssynergia and slow bowel transit, which have been observed in association with constipation (Chia *et al*, 1996; Nicoletti *et al*, 1992), and anal sphincter weakness and rectal hyposensitivity, frequently associated to faecal incontinence (Nordenbo

et al, 1996). Pelvic floor dyssynergia could be a behavioural phenomenon as in non-neurological patients (Halligan *et al*, 1995) or neurological in origin and parallel to bladder neck dyssynergia in MS (Betts *et al*, 1993).

In fact it has been proposed for MS patients with lower disability and lesser alterations in standard ARP tests (Munteis *et al*, 2008; Wiesel *et al*, 2000) (anal sphincter manometry and ano-rectal sensation). These studies were limited by the small number of patients (Wiesel *et al*, 2000) and of being retrospective (Munteis *et al*, 2008).

In patients with bowel disorders, depression and anxiety are classically observed traits associated with symptom burden, although it is not known if bowel symptoms are the cause or the effect of this (Burnett C, 1998; Nehra *et al*, 2000). Either way they also appear to improve after biofeedback therapy (Mason *et al*, 2002). The role of anxiety and depression in MS related bowel dysfunction, and the effect of biofeedback on these, has not been addressed before.

Along with mood improvement, in non-neurogenic patients biofeedback has been shown to induce gut-specific changes in autonomic outflow to the large bowel (Emmanuel & Kamm, 2001). These are thought to be mediated by the extrinsic autonomic nervous system, with spinal efferents playing a key part (Emmanuel & Kamm, 2001). This biofeedback-induced modulation of gut autonomic function may be impeded by the underlying neural dysfunction secondary to MS. If this was the case, then successful biofeedback could depend on secondary behavioural alterations and residual spinal cord function (lower disability).

ARP tests can measure anal sphincter pressure and ano-rectal sensation, which can both be abnormal in MS (Nordenbo *et al*, 1996), and it is unclear if these tests can provide information on which patients are suitable for biofeedback or if this would modify the physiological test outcomes.

The aim of the study is to evaluate prospectively the effect of biofeedback on bowel symptoms, mood and ARP variables in MS and to identify specific characteristics of the patients who had greater improvement.

6.4 Patients and Methods

Forty-four consecutive patients with bowel dysfunction and MS, seen by a consultant (Dr Anton Emmanuel) or myself in a neurogastroenterology clinic at a specialist tertiary referral centre and referred for biofeedback, were recruited to the study and signed a consent form.

Entry criteria were:

- definite diagnosis of MS
- failure to respond to changes in diet, lifestyle and at least two forms of maximal dose laxative therapy
- bowel symptoms onset post-dating the diagnosis of MS.

Exclusion criteria were:

- complete lack of sensation and squeeze at ARP
- concomitant primary bowel pathology, co-morbidities (i.e. diabetes, thyroid dysfunction, coeliac disease, etc.)

- sphincter injury

These were excluded in all patients by means of a negative investigation (colonoscopy, radiological or laboratory test) as appropriate. Two patients with complete lack of sensation and anal squeeze pressure, two who had relapses of their MS and one patient lost to follow up, were all excluded from the study.

Therefore 39 patients [30 females] with constipation and/or faecal incontinence were included for analysis.

6.4.1 Disability

Disability was measured with EDSS, as discussed in the section 3.5.1.

6.4.2 Outcome Measures

Primary outcome measures were the Wexner-constipation (Agachan *et al*, 1996) and Wexner-incontinence (Jorge & Wexner, 1993) scores (section 3.4.3), assessing bowel symptoms. Secondary outcome measures were assesses using the HADS (Zigmond & Snaith, 1983) (section 3.4.4) to ascertain psychological state, and ARP tests. I collected the questionnaires and performed the ARP tests. In order to be blinded to questionnaire outcomes, the scores were calculated after all the tests had been performed.

6.4.3 Ano-Rectal Physiology Tests

Measurements were performed according to standardised criteria, which were discussed in section 3.2.

In brief, we measured resting anal pressures (resting, squeeze and endurance squeeze pressure). Ano-rectal sensation was measured as rectal sensitivity to balloon distension (threshold volume of first sensation, urge volume at which urge to defecate is first perceived and maximum tolerated volume) and as anal and rectal electro-sensitivity.

6.4.4 Biofeedback

Biofeedback is based on the theory of operant conditioning behavioural therapy, and teaches patients to focus on conscious modification of organic function, hence altering behaviour more permanently. According to its original definition, information about a physiological process is converted into a simple visual or auditory signal to enable the patient to learn to control the disordered function (Engel *et al*, 1974). Since then the technique has been bedevilled by the absence of a general consensus on the protocol to be used (Enck *et al*, 2009; Norton *et al*, 2003), and the use of an external device, to feed the physiological information back to the patient has also been questioned (Koutsomanis *et al*, 1995; Norton *et al*, 2003; Solomon *et al*, 2003).

Biofeedback offered at our Unit is not computer assisted, and has been described previously (Chiotakakou-Faliakou *et al*, 1998; Koutsomanis *et al*, 1995; Norton *et al*, 2003). It is a 'package of care' including toileting advice, optimising use of laxatives and constipating agents, defecatory habit conditioning and pelvic floor retraining.

At the first appointment the patient was fully assessed, and toileting advice given. At this stage the patient's test results were explained and he or she was then

educated about normal gut function and correct toilet position through the use of standardised diagrams.

Given the mixed nature of symptoms there was some overlap in biofeedback strategies, and manoeuvres aimed to improve recto-anal coordination, sensory training and improving evacuation were adopted in all patients. For constipation, with the patient lying on his or her side a rectal balloon was inserted, and pelvic floor dyssynergia was addressed with balloon assisted defecatory coordination (Koutsomanis *et al*, 1995). With the balloon inflated in the rectum, the nurse would encourage the patient to recognise progressively lower balloon distensions, to improve awareness of rectal content (Rao *et al*, 1997). The balloon was then removed and in the sitting position the patient was taught how to utilise diaphragmatic and abdominal musculature ('brace technique') to optimise evacuation, improving abdominal and pelvic floor coordination.

If faecal incontinence was present, the difference from the above described protocol was that biofeedback strategies included techniques for delaying defecation: with the rectal balloon inflated, the patient was encouraged to recognise urgency, resist it (if faecal urgency was present) and coordinate rectal distension with sphincter contraction (Miner *et al*, 1990). If hyposensitivity was present, lowering distensions were performed for sensory training (Chiarioni *et al*, 2002). At the second appointment sphincter exercises to improve voluntary anal squeeze were taught (Norton *et al*, 2003). Crucially treatment was focused, in all patients, on reducing the number of inappropriate visits to the toilet and maximising rectal emptying.

All patients entered in the analysis had completed their treatment, which continued over a median period of 11 weeks (range 8-16), and were encouraged to implement learned manoeuvres and toileting advice by integrating them into their routine. Sessions were spaced four weeks apart, and a median of three sessions (range 2-4) comprised the course of treatment, all undertaken by the same therapist (Mrs Julie Storrie). The number of sessions was determined by agreeing with the patient if maximum success was achieved or no further progress was possible (Chiotakakou-Faliakou *et al*, 1998). Two weeks after the final direct visit, the therapist made telephone contact with the patient to check on progress and give advice.

Because of the underlying neurological cause for bowel symptoms and polypharmacy, laxatives and constipating agents were not always discontinued, but instead reduced or optimised as appropriate.

6.5 Study Design

Given the presence of mixed symptoms and overlapping biofeedback strategies, all patients were considered as one cohort. Questionnaires and ARP tests were undertaken before and after treatment, and values were compared; the degree of change occurring in outcome measures was also analysed.

We wished to identify as responders those patients who had the highest improvement in bowel symptoms. So the responders group was formed of patients who demonstrated a reduction greater than or equal to the 25^{th} percentile of the change in Wexner-constipation and/or Wexner-incontinence scores. Patients whose improvement was less than these values formed the non-responders group.

The amount of change in secondary outcome measures (HADS and ARP values) after treatment was compared between responders and non-responders. To identify characteristics of responders we compared baseline variables between the two groups. Linear regression analysis was performed to identify what could predict successful treatment.

6.5.1 Statistical Analysis

Given that the data, based on the Kolmogorov-Smirnov test, were not normally distributed, we used non-parametric tests: the Wilcoxon test to compare pre- and post-treatment values, and the Mann-Whitney U test to compare values between responders and non-responders. Data are expressed as medians and interquartile ranges. All calculated p values were two-sided and p values ≤ 0.05 were considered statistically significant. Linear regression analysis (β = standardised partial regression coefficient) evaluated relationship between change in Wexner-constipation and Wexner-incontinence scores as dependent variables with respectively pre-treatment Wexner-constipation and Wexner-incontinence scores, and EDSS, HADS-anxiety and HADS-depression. Statistical analysis was performed using the statistical software package SPSS statistics v19 for Mac.

6.6 Results

Patient's characteristics are summarised in table 6.1.

Table 6.1: Patients' characteristics

	All cohort (n=39)	**MS-C**[1] (n=14)	**MS-I**[2] (n=12)	**MS-CI**[3] (n=13)
Age	38 (31-50)	38 (34-51)	34 (26-49)	38 (36-53)
Disease Duration (in years)	9 (5-24)	7 (3-23)	11 (7-25)	8 (5-23)

Expanded Disability Status Scale	5 (3-7)	4 (2-6)	5 (4-8)	4 (3-7)
Wexner-Constipation score	12 (5-19)	14 (11-22)	3 (2-5)	18 (12-24)
Wexner-Incontinence score	12 (3-15)	2 (1-4)	15 (13-18)	14 (12-16)
HADS*-Anxiety	3 (2-7)	2 (1-4)	4 (2-5)	6 (3-11)
HADS*-Depression	7 (3-11)	5 (2-10)	7 (3-12)	8 (5-15)

1= MS Patients with prevalent constipation symptoms, 2=MS patients with prevalent incontinence symptoms, 3= MS patients with constipation and faecal incontinence, *= Hospital Anxiety and Depression Score.

6.6.1 Wexner Scores

After biofeedback there was a significant improvement in Wexner-constipation scores [12 (5-19) pre-treatment vs. 8 (4-14) post-treatment, p=0.001, Wilcoxon test] and Wexner-incontinence scores [12 (3-15) pre-treatment vs. 4 (2-10) post-treatment, p<0.001, Wilcoxon test] (Figure 6.1).

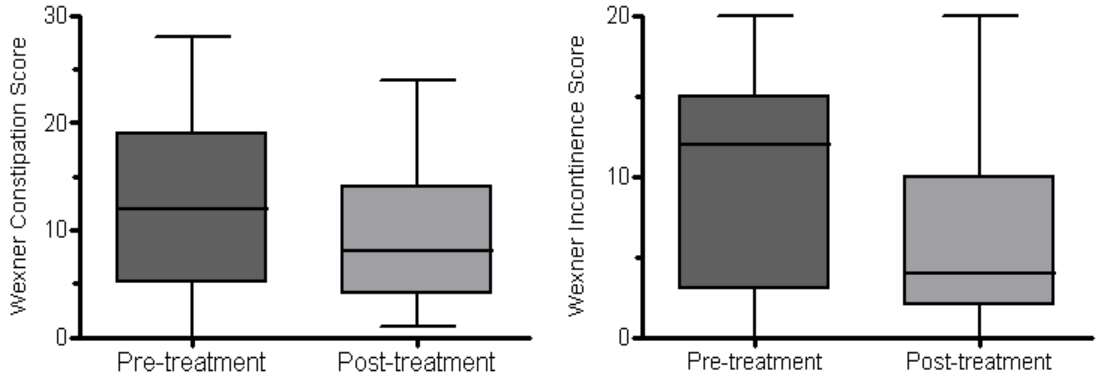


Figure 6.1: Pre and post-treatment Wexner-constipation (left) and Wexner-incontinence (right)

6.6.2 Hospital Anxiety and Depression Scores

After treatment, HADS-anxiety remained unchanged [3 (2-7) pre-treatment vs. 3 (2-6) post-treatment, p=0.067, Wilcoxon test], whilst HADS-depression scores significantly improved [median 7 (3-11) pre-treatment vs. 5 (3-10) post-treatment, p= 0.015, Wilcoxon test].

6.6.3 Ano-Rectal Physiology Tests

The only physiological parameter to improve after biofeedback (Table 6.2) was the 5-seconds-endurance squeeze pressure [21 (11-54) mmHg vs. 43 (26-59) mmHg, p=0.001, Wilcoxon test].

Table 6.2: ARP parameters

	Pre-treatment	Post-Treatment	P-value
Resting Pressure (mmHg)	53 (34-76)	57 (41-77)	0.525
Squeeze Pressure (mmHg)	53 (35-76)	60 (45-85)	0.152
5 seconds endurance pressure (mmHg)	21 (11-54)	43 (26-59)	0.001
Threshold Volume (mls)	55 (40-85)	55 (40-75)	0.182
Urge Volume (mls)	110 (80-170)	120 (90-150)	0.523
Maximum Tolerated Volume	225 (150-295)	210 (145-290)	0.816
Anal Electro-sensitivity (mAmp)	8.5 (6.5-12)	8.4 (6.3-10.9)	0.402
Rectal Electro-sensitivity (mAmp)	24.4 (18.3-31)	24.0 (17.0-30.0)	0.701

6.6.4 Responders vs. Non-Responders Analysis

Changes after treatment in individual Wexner-constipation and Wexner-incontinence are shown in Figure 6.2.

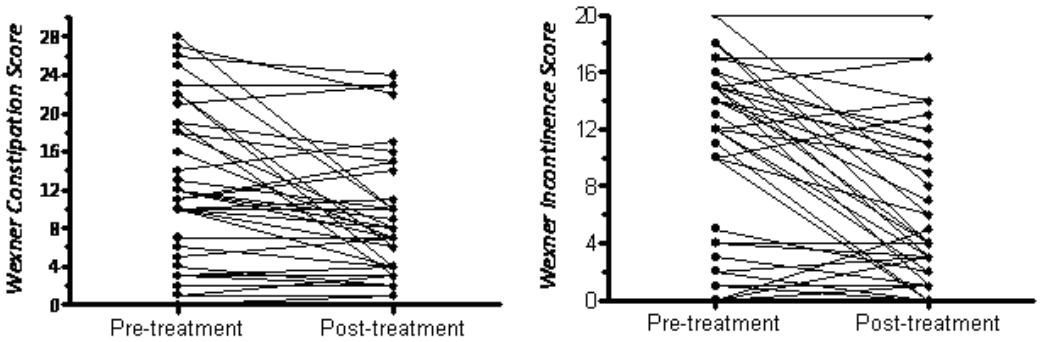


Figure 6.2: Ladder plots of pre- and post-treatment Wexner-constipation (left) and Wexner-incontinence (right)

The median amount of change in Wexner-constipation was -2 (-5/0), and for Wexner-incontinence was -3 (-9/0) ('-' indicates improvement, i.e. reduction, while positive values a worsening score), so the 25th percentile of the change in Wexner-constipation was -5 and for Wexner-incontinence was -9. Therefore the threshold to declare a patient as a responder was an improvement of at least 5 points in the Wexner-constipation score and/or of at least 9 points in the Wexner-incontinence score. According to this criterion 18 patients (46%) formed the responders group (Figure 6.3).

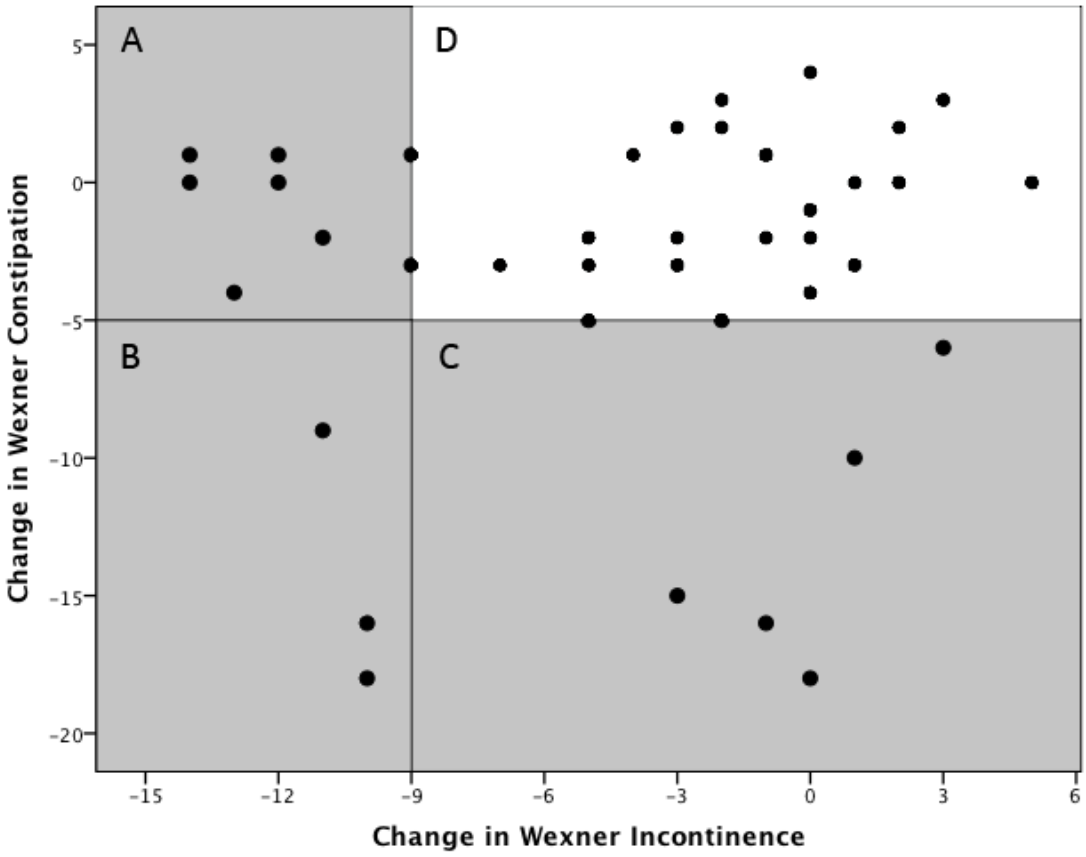


Figure 6.3: Changes in Wexner scores

Comparing the amount of change in secondary outcome measures with non-responders, it appeared that responders had a significantly higher improvement in

5-seconds-endurance squeeze pressure [23.5 (7.5/32.75) mmHg responders vs. 4 (-6/20) mmHg non-responders, p= 0.008, Mann-Witney U test] (Table 6.3).

Table 6.3:Responders vs. non-responders following biofeedback

	Responders	Non-responders	p-value
Change in HADS*- Anxiety	0 (-3.25/0.25)	0 (-1.5/1)	0.269
Change in HADS*- Depression	-1 (-3.25/0)	0 (-2/0.5)	0.443
Change in Resting Pressure (mmHg)	3 (-6 /13.25)	-3 (-12/13.5)	0.321
Change in Squeeze Pressure (mmHg)	12.5 (-5/29.25)	3 (-15.5/11.5)	0.60
Change in 5 sec. endurance pressure (mmHg)	23.5 (7.5/32.75)	4 (-6/20)	0.008
Change in Threshold Volume (mls)	-2.50 (-10/15)	-10 (-17.5/2.5)	0.245
Change in Urge Volume (mls)	7.5 (-6.25/21.25)	0 (-15/12.5)	0.460
Change in Maximum Tolerated Volume (mls)	-10 (-27.5/30)	10 (-20/40)	0.245
Change in Anal Electro-sensitivity (mAmp)	-1.3 (-2.45/0.725)	0.7 (-1.4/1.6)	0.223
Change in Rectal Electro-sensitivity (mAmp)	-1 (-4 /2.85)	1.5 (-1.65/3)	0.223

Comparing baseline variables between responders and non-responders no difference was observed (Table 6.4).

Table 6.4: Responders vs. non-responders baseline values

	Responders	Non-responders	p-value
Age	40.5 (33-53)	37 (30-47)	0.335
EDSS	4 (3-5)	6 (3.5-8.0)	0.94
Disease Duration	10.5 (4.8-24.8)	8 (4.5-19.0)	0.364
HADS*- Anxiety	3 (1.8-5.5)	4 (2.5-8.5)	0.234
HADS*- Depression	4.5 (2.7-8.3)	8 (4-13)	0.1
Wexner Incontinence	12 (3.7-10)	12 (2-15)	0.512
Wexner Constipation	12.5 (6-22)	11 (4.5-8.5)	0.530
Resting Pressure (mmHg)	49 (40-73)	58 (33-82)	0.989
Squeeze Pressure (mmHg)	55 (50-75)	53 (32-81)	0.707
5 seconds endurance pressure (mmHg)	22 (15-51)	20 (6.5-6.3)	0.626
Threshold Volume (mls)	52 (40-79)	60 (33-88)	0.945
Urge Volume (mls)	105 (80-155)	120 (93-200)	0.364
Maximum Tolerated Volume (mls)	170 (150-282)	250 (148-303)	0.379
Anal Electro-sensitivity (mAmp)	7.6 (6.2-18.8)	9.4 (6.8-12.5)	0.512
Rectal Electro-sensitivity (mAmp)	25.2 (18.8-30.4)	22.0 (15.5-32)	0.587

6.6.5 Linear Regression Analysis

There was a significant negative relationship between the amount of change in Wexner-constipation score and pre-treatment Wexner-constipation score (β= -0.463, p<0.001), but not with EDSS (β=0.316, p=0.537), pre-treatment HAD-anxiety (β=0.326, p=0.219) and HADS-depression score (β=-0.129, p= 0.613).

Similarly, amount of change in Wexner-incontinence score showed a significant negative relationship with pre-treatment Wexner-incontinence score (β= -0.590, p<0.001), but not with EDSS (β=0.698, p=0.97), pre-treatment HAD-anxiety (β= -0.48, p=0.819) or HAD-depression score (β=0.206, p=0.317).

The value of change in Wexner scores is negative (indicating a symptom burden reduction) as well as the direction of the relationship with initial Wexner scores. So the higher the initial bowel symptom score the greater the improvement.

6.7 Conclusions

This study suggests that:

- Biofeedback behavioural therapy can improve bowel symptoms, refractory to standard medical treatment, in patients with MS in the short term.
- According to our definition, about half of the patients were responders.
- Bowel scores improved as well as depression score, which suggests the presence of a psychological component associated with bowel symptoms that is reversible with biofeedback, as in non-neurological patients (Burnett C, 1998; Nehra *et al*, 2000). Nevertheless the amount of improvement was

similar in responders and non-responders.

- Responders had a median EDSS of 4 (low level of spinal cord disease, mobility not compromised).
- Non-responders had a median EDSS of 6 (high level of spinal cord disease, mobility severely restricted).
- High score on the initial bowel symptoms questionnaires predicted a more successful treatment, suggesting that biofeedback is also suitable for the more symptomatic patients.
- Incontinence scores had the greatest improvement. This might be the result of improved squeeze pressure, but also of better rectal emptying.

The only physiological parameter that improved was 5-seconds-endurance squeeze pressure, and improvement was higher in responders; this suggests that amelioration of symptoms was more related to improved toilet-behaviour, including improvement of pelvic floor dyssynergia and improved evacuation technique, than to changes in physiological parameters. The overall lack of significant improvement in physiological variables might be related to the presence of a fixed underlying neurological deficit, and may also explain why these tests did not have a predictive value in identifying responders. Overall improvement of bowel symptoms might be related to secondary physiological changes that were not measured in this study. Improvement of 5-seconds-endurance squeeze pressure could have been also due to recruitment of residual spinal function, secondary to implemented behavioural changes.

Responders had a median EDSS of 4 of and non-responders of 6. EDSS values and individual changes in Wexner Scores are graphically represented in figure 6.4 and 6.5.

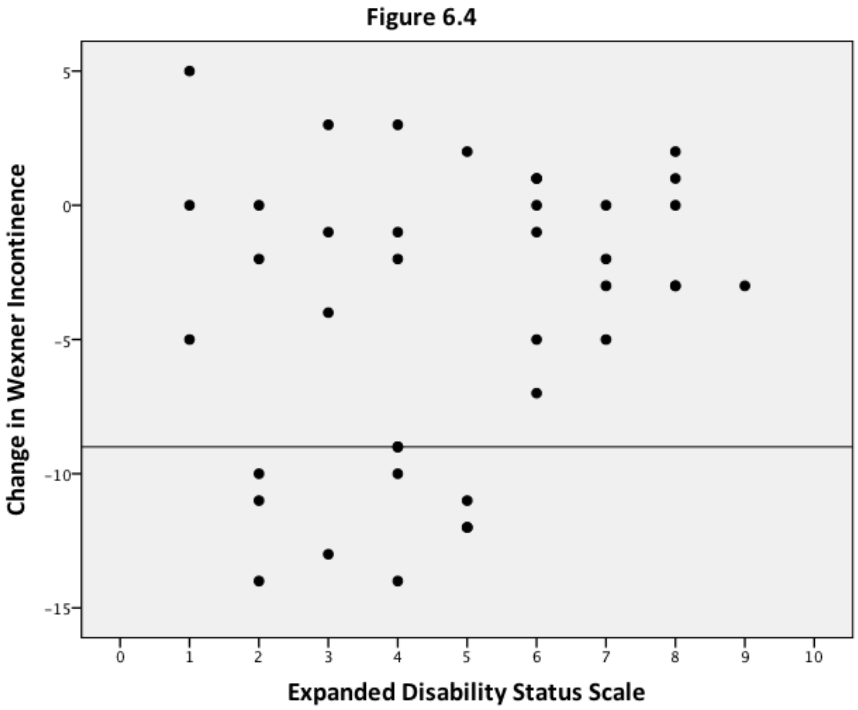


Figure 6.4: A line is drawn at -9, which was the cut-off to declare a patient a responder.

Please note that 2 responders with EDSS of 5 and 2 with EDSS of 4 had the same change in Wexner-Incontinence scores (-12 and -9 respectively).

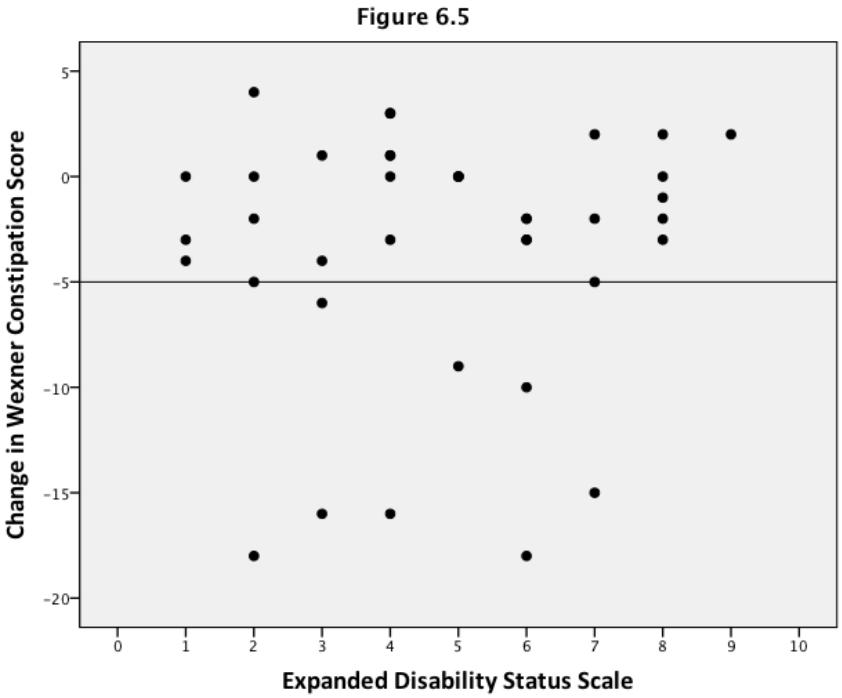


Figure 6.5: A line is drawn at -5, which was the cut-off to declare a patient a responder.

It interesting to note that the EDSS of patients who had the most significant improvement in Wexner-Incontinence scores was 5 or less. These patients had less clinically significant spinal cord disease, and possibly their symptomatic improvement might have been related to their ability to improve anal sphincter function by recruiting residual spinal cord function. This pattern is not observed for changes in constipation scores. If we included also patients with no ano-rectal sensation and no anal squeeze, this difference in EDSS might have become significant as well as baseline ARP values, but we judged it unethical for patients with these characteristics to undergo biofeedback.

6.7.1 Strength

This is the largest series in the literature and its results will assist in any power calculations necessary for future case-control or randomised studies.

6.7.2 Limitations

This is an observational study, without a control group with alternative treatment. Patients with constipation and incontinence were pooled in consideration that bowel dysfunction in MS is mixed (as reflected in our cohort) and multifactorial, and as a consequence, biofeedback strategies were largely overlapping. Whilst this might bring in confounding factors, it is the consequence of inherent characteristics of this patients group.

Laxatives and constipating agents were not discontinued, given the presence of irreversible factors such as the underlying neurological condition, and the presence of polypharmacy in these patients. On the other hand biofeedback is a 'package of care' that includes advising patients on drug titration and optimisation by a dedicated nurse specialist. Whilst this might means that improvement was partly caused by a better use of drugs, this falls within the aims of biofeedback in these patients.

These limitations in our study reflect the lack of - and need for- an agreed instrument to measure bowel symptoms, and their impact on quality of life, in patients with ano-rectal symptoms and MS.

We excluded patients with a complete lack of ano-rectal sensation and anal squeeze pressure, and this clearly introduced a selection bias. This might explain

why we didn't show a statistically significant difference in EDSS and baseline ARP tests, as we might have excluded patients with higher disability who were highly unlikely to respond.

There is an important limitation of our definition of responders, which was based on the amount of change in symptoms scores. This might have been greater in patients with a higher initial score. However, some of the non-responders, with a lower initial score, still had a significant benefit from the treatment.

It is clear that the patient-therapist interaction is a key factor in defining outcomes of biofeedback (Norton *et al*, 2003), and the cost implications of this form of intensive therapy restricts its wider availability (Enck *et al*, 2009). Identifying prognostic criteria could render the treatment more cost-efficient, and available. This study however does not reveal any characteristic useful to identify which MS patient is suitable for biofeedback. In fact there was no statistically significant difference between responders and non-responders, but this can be explained by the selection bias.

Finally, a reason for a lack of treatment response might have been cognitive impairment that was not evaluated in this study

In summary, we have shown that biofeedback is an effective option to treat bowel symptoms in patients with MS. Depression and 5-seconds endurance squeeze pressure can also be improved.

The variety of biofeedback strategies on one hand, and the specific characteristics of MS patients on the other, makes comparison of our results with general

literature on biofeedback very difficult. With regards to the effect of biofeedback on mood, it appear that our results are in keeping with those observed in idiopathic patients (Mason *et al*, 2002). It is not clear if this is a consequence of symptoms improvement or if the mood improvement causes bowel symptoms to be better.

Pelvic floor coordination, measured as the ability to expel a rectal balloon, improves in idiopathic patients (Rao *et al*, 2010), and it might be that the improved sphincter function we have observed is a surrogate of this. In our patients pelvic floor coordination was assessed subjectively only by the trainer, Julie Storrie. The improvement of colonic transit time (Rao *et al*, 2010) is probably also an epiphenomenon of improve rectal expulsion ability. Sphincter pressure has been observed to improve with biofeedback (Rao *et al*, 1996), but not consistently (Boselli *et al*, 2010), possibly reflecting different strategies of biofeedback. Rectal sensation can also be improved with exercises involving lowering distensions (Rao *et al*, 1996), but this was not the case in our cohort.

Building on these observations future randomised controlled studies should clarify criteria for patient's selection for this therapist-intensive treatment. Clearly patients who are refractory to standard treatment and fail to improve with biofeedback are left with a considerable symptom burden. I therefore wished also to study a mechanical means to achieving bowel emptying, and I discuss this in the next chapter.

CHAPTER 7: TRANSANAL IRRIGATION FOR BOWEL SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS

Peristeen transanal irrigation in patients with Multiple Sclerosis.
G.Preziosi, J. Gosling, A. Raeburn, J. Storrie, J. Panicker, A.V. Emmanuel.
Diseases of the Colon and Rectum 2012: 55(10), 1066-73

7.1 Chapter Layout

I have shown in the previous chapter that patients who fail to improve with laxatives and changes in lifestyle regimes might benefit from biofeedback (Munteis *et al*, 2008; Preziosi *et al*, 2011; Wiesel *et al*, 2000). This treatment though is not widely available and is not suitable for more disabled patients (Munteis *et al*, 2008; Preziosi *et al*, 2011; Wiesel *et al*, 2000) who are left with a considerable symptom burden. Furthermore, response to biofeedback may diminish in the long-term if MS progresses. Therefore for these patients a suitable option could be TAI.

My findings are summarised in an abstract format, and then the study is discussed in detail.

7.2 Abstract

Background: Constipation and faecal incontinence affect 68% of patients with MS, but management is empirical. TAI has been employed successfully in patients with NBD.

Objective: To evaluate the effect of TAI on bowel symptoms and general health status in these patients, characteristics of those that had successful treatment, and to obtain data for power calculations necessary for future randomised-controlled studies.

Hypothesis: My secondary hypothesis is that the treatment strategies should target residual spinal cord function, and this was evaluated by the biofeedback study. For patients that do respond to biofeedback or are too disabled for this treatment, mechanical bowel emptying should be considered as an option.

Design: Prospective observational study: comparison between pre- and post-treatment questionnaires (bowel symptoms and health status). Patients that received treatment had at least a 50% improvement in bowel symptoms were considered responders. Baseline variables including ARP tests and rectal compliance were compared between responders and non-responders.

Settings: Specialist neurogastroenterology clinic, tertiary referrals centre.

Patients: Thirty patients with MS and constipation, faecal incontinence or both.

Intervention: TAI.

Main Outcome Measures: Primary: Wexner-constipation and Wexner-incontinence scores. Secondary: SF-36 health survey. All recorded before and after 6 weeks of treatment

Results: At 6 weeks post-treatment the Wexner-constipation score significantly improved [12(8.75/16) pre-treatment vs. 8(4/12.5) post-treatment, p=0.001] as

well as the Wexner-incontinence score [12(4.75/16) pre-treatment vs. 4(2/8) post-treatment, $p<0.001$]. The SF-36 score did not improve significantly (51.3±7.8 pre-treatment vs. 50.4±7.8 post-treatment, $p= 0.051$). Sixteen patients were responders, and had higher baseline Wexner-incontinence scores [14(11/20) responders vs. 9(4/15) non-responders, $p= 0.038$] and SF-36 (53.9±6.3 responders vs. 47.9±7.8 non-responders, $p=0.027$) as well as greater maximum tolerated volume to rectal balloon distension [310(220/320) ml responders vs. 168(108/305) ml non-responders, $p= 0.017$] and rectal compliance [15.2(14.5/17.2) ml/mmHg responders vs. 9.2(7.2/15.3) ml/mmHg non-responders, $p=0.019$].

Limitations: Small sample size and lack of control group with alternative treatment.

Conclusions: TAI is effective to treat bowel symptoms in patients with MS. Responders (53%) had higher baseline incontinence symptoms and better perception of their health as well as a more capacious and compliant rectum.

7.3 Introduction

TAI is a means to achieve mechanical bowel emptying and has been proved to be effective and safe in the treatment of NBD (Emmanuel, 2010). Its use has been extensively studied in adult patients with SCI, where it has been shown to be more effective than conservative bowel management. The time spent for bowel toileting and the incidence of urinary tract infections are reduced (Christensen *et al*, 2006) improving both symptoms (Christensen *et al*, 2008; Del Popolo *et al*, 2008) and quality of life (Del Popolo *et al*, 2008). Its long-term use does not alter parameters

of ano-rectal function (Faaborg *et al*, 2010); however no predictive factor of successful treatment has been identified (Christensen *et al*, 2008).

While previous studies on TAI included patients with MS, and the largest had 25 (Faaborg *et al*, 2009a), no study has evaluated its efficacy in a selected group of MS patients.

I therefore wished to evaluate the effects of TAI on bowel symptoms and general health status in patients with MS. In addition, we investigated whether initial ARP tests could characterise patients who responded to treatment.

7.4 Patients and Methods

Patients recruited to the study were seen in a neurogastroenetrology clinic at a tertiary referral centre, and signed a consent form after verbal and written explanations were given.

We offered TAI to:

- Patients with a definite diagnosis of MS and bowel symptoms onset postdating the diagnosis of MS.
- All patients who had failed bowel biofeedback, or that were considered too disabled (severely impaired mobility) to undergo biofeedback, and failed to respond to changes in diet, lifestyle and at least two forms of maximal dose laxatives.

Exclusion criteria were:

- Concomitant primary bowel pathology and previous colorectal surgery, including haemorrhoidectomy, fistulotomy and sphincter injury. These were excluded in all patients by means of a negative investigation (colonoscopy, radiological or laboratory test) as appropriate and as part of their assessment.

Over a period of 2 years between August 2008 and August 2010, we recruited 37 MS patients with constipation and/or faecal incontinence. None of the patients met any exclusion criteria.

7.4.1 Disability and Impact of MS

Disability was measured with the EDSS (section 3.5.1)(Kurtzke, 1983) and impact of MS on patient's life was recorded with the MSIS-29 questionnaire (section 3.5.2,) (Hobart *et al*, 2001), which evaluates both the physical and psychological impact of the disease (Hobart *et al*, 2005; Hoogervorst *et al*, 2004). The MSIS-29 scores range between 29 and 145 and indicate respectively 'no impact at all' and life 'extremely affected' by MS.

7.4.2 Outcome Measures

As in the Biofeedback study I employed the Wexner-constipation (Agachan *et al*, 1996) and Wexner-incontinence (Jorge & Wexner, 1993) questionnaires (section 3.4.3) as primary outcome measures. The secondary measure was general health status, as measured with the widely used 36-item short form health survey (SF-36, (section 3.4.5) (McHorney *et al*, 1993). The scores range between 0 and 100, and the higher the score the better the health status.

7.4.3 Ano-rectal Physiology Tests

I performed baseline measurements of standard rectal compliance according to standardised criteria (sections 3.2 and 3.3).

7.4.4 Transanal Irrigation

There are two commercially available TAI systems: the Enema Continence Catheter (Cardiomed Supplies, Ontario, Canada) and Peristeen (Coloplast A/S, Humlebaek, Denmark). The latter was employed, as it was the only irrigation system reimbursed by the National Health Service at the time of the study. Peristeen is made of a rubber catheter with an inflatable cuff connected to a water bag and a dial switch with a hand-held pump. The bag is filled with lukewarm tap water. With the patient on the toilet the rubber catheter is inserted in the rectum, and is held in place by inflating the cuff with air. Water is then flushed with the pump from the bag in the bowel. When the catheter is removed the irrigation water and bowel content are voided.

The patients were referred to a nurse specialist (Mrs Julie Storrie) to be trained in a one-to-one session in the use of the device. If the patient was unable to perform irrigation independently, the caregiver was trained in the presence of the patient.

There is no standardised protocol to perform TAI. The frequency and volume of water used are established empirically through trial and error. We usually suggest starting with a volume of 500 ml, to be increased up to 1.5 lt. This is then titrated to obtain the best response with the least volume. Initially, the recommended frequency is every third day, and is adjusted according to response.

Laxatives and constipating agents were not discontinued. After the initial appointment, patients were given direct phone access to a nurse specialist (JS) for advice.

7.4.5 Study Design

This is a prospective observational study. Given the significant overlap of bowel symptoms in MS, patients were pooled into one cohort.

We recorded baseline demographic data, disability, rectal compliance, and questionnaire scores. Wexner-constipation and Wexner-incontinence scores (primary end point) and the SF-36 questionnaire (secondary end point) were repeated 6 weeks after treatment had been commenced, as this is the time required to adapt to TAI (Christensen *et al*, 2008). The pre- and post-treatment values were compared. I collected the questionnaires to avoid treatment bias. Correlations were evaluated between rectal wall properties and changes in Wexner-constipation and Wexner-incontinence scores.

Responders were considered to be those patients who had, after treatment, an improvement of at least 50% in Wexner-constipation and/or Wexner-incontinence scores. Baseline variables were compared between responders and non-responders.

A telephone interview was conducted with all patients after 3 months to ask if the treatment was still being carried out. Patients who were still performing irrigation at that point were then interviewed again at 6 months.

7.4.6 Statistical Analysis

Data from the SF-36 questionnaires were normally distributed and analysed with the t-test. Other data were not-normally distributed and were analysed with the Wilcoxon or the Mann-Whitney U test. The Spearman test was used to evaluate correlations (r= correlation coefficient). Data are expressed as medians and interquartile ranges, except SF-36 data which is presented as mean and standard deviation. All calculated p values were two-sided and *p* values ≤ 0.05 were considered statistically significant.

Statistical analysis was performed using the statistical software package SPSS statistics v19 for Mac.

7.5 Results

Four patients after the training session, did not wish to start treatment, and one had worsening of MS and discontinued rectal irrigation before follow-up was arranged. Two patients were lost to follow-up before training started. These 7 patients were excluded from the analysis.

Thirty patients were therefore entered in the study [27 females, age 49 (42/56) years]. MS duration was 8 (5/13) years, while bowel symptoms duration was 5 (2/9) years; EDSS was 5 (4/7) and MSIS-29 was 88 (104/75). Baseline bowel symptoms scores are shown in Figure 7.1.

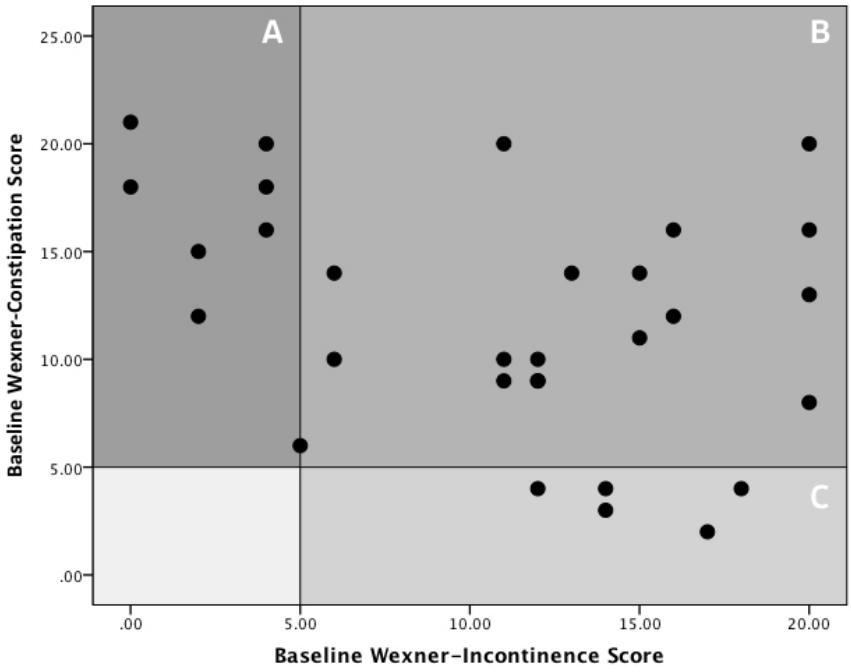


Figure 7.1: Scatter plot distribution of baseline bowel symptoms scores.
In the top-left quadrant (A) are patients who had prevalent constipation symptoms; the top-right (B) quadrant represents patients with mixed symptoms, and the bottom-right quadrant (C) those with prevalent symptoms of faecal incontinence.

Patients who discontinued TAI before the assessment at 6 weeks (due to difficulty handling the device, lack of results or worsening of incontinence) were still included in order to make a valid comparison of pre- and post-treatment scores using the principle of 'intention to treat'.

7.5.1 Comparison of Pre- and Post-Treatment Questionnaires

After treatment the Wexner-constipation score significantly improved [12 (8.75/16) pre-treatment vs. 8 (4/12.5) post-treatment, p=0.001 – Wilcoxon test] as well as the Wexner-incontinence score [12 (4.75/16) pre-treatment vs. 4 (2/8) post-treatment, p<0.001 – Wilcoxon test] (Figure 7.2).

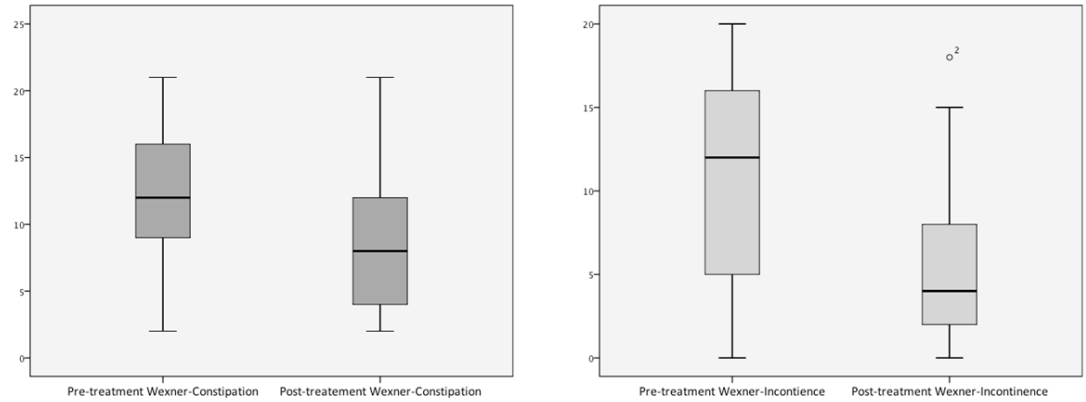


Figure 7.2: Boxplots showing comparison between pre and post-treatment of Wexner-constipation (right) and Wexner-incontinence score (left).

There was no significant change in the value of SF-36 (51.3±7.8 pre-treatment vs. 50.4±7.8 post-treatment, *p*= 0.051– paired t-test).

Median change in Wexner-constipation was 0 (-6/0) and for Wexner-incontinence was -3.5 (-10/0) ('-' indicates improvement, i.e. reduction, while positive values a worsening score, and '0' indicates no change) (Figures 7.3 and 7.4).

Figure 7.3: Ladder plots of individual changes in Wexner-constipation (right) and Wexner-incontience score (left).

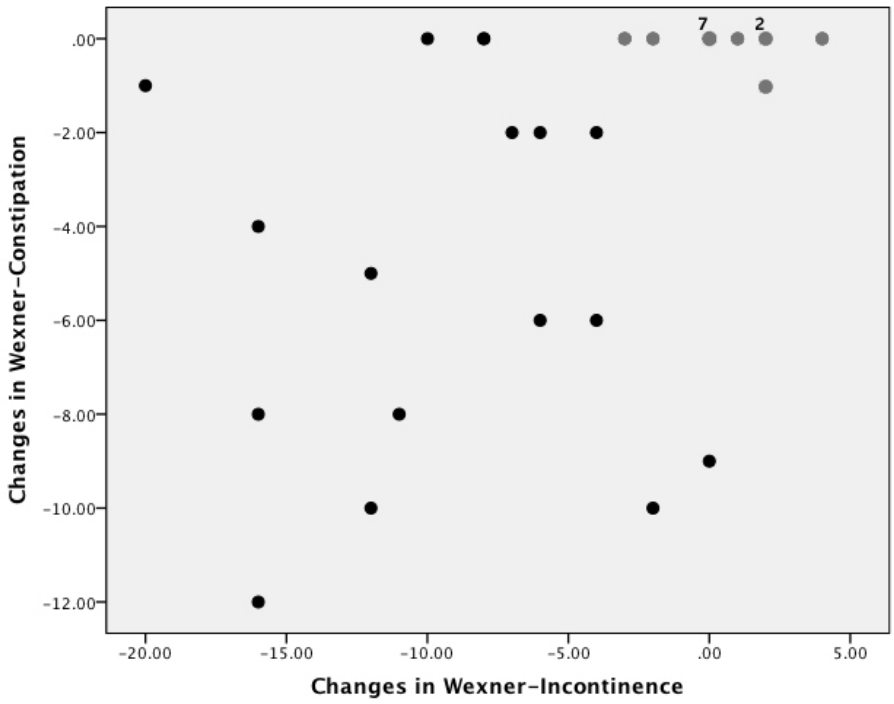


Figure 7.4: Scatter plot of individual changes of Wexner-constipation (y axis) and Wexner-incontinence (x axis) after treatment.

Responders are represented by the black dots, and non-responders are in grey. The numbers 7 and 2 indicate overlapping patients.

7.5.2 Correlation Analysis

Correlations are shown in Table 7.1.

Table 7.1: Correlation between changes in Wexner scores and rectal properties

	Change in Wexner-Constipation	Change in Wexner-Incontinence
Threshold volume	r= -215, p= 0.254	r= -0.321, *p*= 0.254
Urge Volume	r= -0.176, p=0.351	r= -0.310, *p*= 0.095
Maximum Tolerated Volume	r= -0.318, p= 0.087	r= -0.536, *p*= 0.002
Rectal Compliance	r= -0.317, p= 0.088	r= -0.463, *p*= 0.010
Change in Wexner-Constipation	1	r= 0.630, *p*< 0.001
Change in Wexner-Incontinence	r= 0.630, p< 0.001	1

7.5.3 Responders vs. Non-Responders Analysis

At 6 weeks follow-up 16 patients (53%) were considered responders. A caregiver performed the irrigation for two of our patients, and one was a responder. Of the non-responders 7 had no change in either Wexner scores, 4 had an increase between 1 and 4 in the Wexner-incontinence and 3 had a reduction of between 2 and 4 in the Wexner-incontinence score, with lesser changes in the Wexner-constipation score. Responders had a reduction of at least 6 points in one of the 2 Wexner scores (Figure 7.3). Comparison of baseline variables between responders and non-responders is shown in Table 7.2.

Table 7.2: Comparison of baseline variables between responders and non-responders

	Responders (n=16)	**Non-responders** (n=14)	**p-value**
Age (years)	48 (36/55)	53 (45/55)	0.423
MS duration (years)	9 (4/15)	10 (6/17)	0.423
Symptoms duration (years)	7 (2/10)	5 (4/17)	0.759
Baseline Wexner-Constipation	12 (5/16)	12 (9/13)	0.697
Baseline Wexner-Incontinence	14 (11/20)	9 (4/15)	0.038
SF-36	53.9±6.3	47.9±7.8	0.027
MSI-29	81 (71/123)	96 (80/105)	0.608
EDSS	5 (4/7)	6 (3/7)	0.984
Resting pressure (mmHg)	54 (47/70)	55 (37/78)	0.951
Squeeze Pressure (mmHg)	43 (21/58)	30 (11/68)	0.552
Threshold Volume (ml)	60 (55/120)	40 (32/171)	0.179
Urge Volume (ml)	130 (100/285)	105 (60/290)	0.355
Maximum tolerated volume (ml)	310 (220/320)	168 (108/305)	0.017
Anal Electrosensitivity (mAmp)	10.1 (8/13.8)	7.7 (6.4/19.3)	0.208
Rectal Electrosensitivity (mAmp)	22.0 (15.7/31.7)	17.3 (12.5/50.0)	0.697
Rectal Compliance ml/mmHg	15.2 (14.5/17.2)	9 (7.2/15.3)	0.019
Change in Wexner-Constipation	-6 (-9/-1.25)	0 (0/0)	n/a
Change in Wexner-Incontinence	-9(-15/-6)	0 (-5/1)	n/a

All data, with the exception of the SF-36, are presented as median and interquartile range and the p value for the Mann-Whitney U test is given. Data of the SF-36 are presented as mean and standard deviation and the p value given is for the independent-samples t-test.

7.5.4 Follow-up

All of the responders were using the Peristeen at the 3 months. At 6 months follow-up all except two responders were continuing to use the irrigation: one patient reported no more response, and the other had severe deterioration of MS. Three of the responders who were still using the irrigation at 6 months, would do so on average once a week (particularly when going out or attending a public occasion), while the rest required 2 to 7 irrigations per week.

7.6 Conclusions

The principal findings are:

- Peristeen TAI is an effective option to treat bowel symptoms in patients with MS.
- Greater tolerance to rectal balloon distension and rectal compliance correlated with greater improvement in symptoms of faecal incontinence, but not of constipation. Both symptoms improved in tandem.
- Fifty-three percent of the patients in our study were considered responders. They were characterised, in comparison to non-responders, by higher initial incontinence scores, better perception of their health, greater tolerance to rectal balloon distension and greater rectal compliance.

7.6.1 Strengths

This is the largest of the series in the literature of studies including patients with MS, and the only one to address this patient's group separately. It is also the first study that showed factors that might predict response to Peristeen (more capacious rectum and better perception of own health). Expulsion of the catheter in response to inflation of the irrigation catheter cuff is a common cause of unsuccessful treatment, and may be related to reflex contraction of the rectum, a phenomenon that has been observed in patients with SCI (Krogh *et al*, 2002b). Therefore responders, given their rectal properties, might have been able to better tolerate the irrigation catheter with the cuff inflated. In patients complaining of catheter expulsion it might be helpful to regulate the amount of air inflated in the cuff.

7.6.2 Limitations

This study does have limitations, such as the absence of a control group with an alternative treatment and the small sample size, which might have lead to a type 2 error.

The threshold of 50% improvement of Wexner score to identify responders had an inherent potential pitfall. In fact a responder could have been a patient with low initial Wexner score and subsequent small change, or vice-versa, we could have identified as a non-responder a patient who had a big drop (but not halving) from a high initial score. This was not the case, as non-responders had no change, worsening or minimal reduction in Wexner scores. Responders instead had an improvement of at least 6 points in at least one of the 2 Wexner scores.

Furthermore, all but two responders were still using rectal irrigation after 6 months. Consequently, our chosen threshold was arbitrary, but effective. That said it is of note that some of the most recent studies of faecal incontinence outcomes with neuromodulation have used a 50% reduction in incontinence symptoms to define responders (Boyle *et al*, 2010; Govaert *et al*, 2010).

Another limitation of this study is the lack of an optimal measure of quality of life, as the SF-36 questionnaire failed to demonstrate an improvement with treatment. It should be noted that MS is a complex disease, so the SF-36 may fail to address clinically important aspects of the impact of specific symptoms (Riazi *et al*, 2003). Responders had a better perception of their health, despite a similar high disability and impact of MS on their lives. We speculate that this, and an almost 'all or nothing' response observed, suggest that in at least some patients lack of motivation was a factor in failing to implement a bowel regime with TAI. A variety of factors such as manual dexterity, vision and cognition are also likely to influence compliance. Furthermore, it could be that TAI itself affects some MS symptoms (such as spasticity or mobility). These elements were not addressed in this study and require further evaluation.

As in the biofeedback study, laxatives and constipating agents were not discontinued, and their optimisation could improve efficacy of TAI.

7.6.3 Further Considerations

Incontinence symptoms showed a greater improvement than constipation, and responders had higher baseline incontinence scores. This might reflect the inability of the water enema to reach and mobilise the stools in constipated patients

(Christensen *et al*, 2003). Another theoretical explanation could be that a bowel peristaltic wave, stimulated by irrigating water, is required to produce an effect. This mechanism of action could be less effective in patients with reduced colonic motility. This is in keeping with literature of employment of transanal irrigation in a range of disorders. An heterogeneous study, including patients with a diverse range of pathophysiological conditions, used multivariate regression analysis to show that patients with NBD or faecal incontinence did better than patients with idiopathic constipation or patients with sequelae to anorectal surgery (Christensen *et al*, 2009). This study showed that 'Low rectal volume at urge to defecate' and 'low maximal rectal capacity' were significantly associated with a successful outcome. Our study suggests that increased rectal compliance is associated with better outcomes. Increased rectal compliance can be associated with a rectum that accumulates faeces in the absence of rectal sensation, and in this group of patients urge incontinence arises when the rectum is full, rather than in a rectum with reduced compliance, as in a rectum subjected to irradiation injury (Bajwa A., 2009). Another study on NBD patients found successful outcome to be related to male gender, mixed constipation and faecal incontinence symptoms, and prolonged colonic transit time (Faaborg *et al*, 2009b).

Overall NBD patients seem to do better than those with functional disorders (Emmanuel *et al*, 2013).

The worsening of faecal incontinence seen in four of the non-responders (Figure 7.3, right) was related to an inability to eliminate all the irrigation water in one setting. Fine-tuning the amount of irrigation required and implementing

manoeuvres of manual abdominal compression while on the toilet can improve post-irrigation leakage.

Frequency of irrigation varies; if the patient is occasionally having no result with irrigation we suggest reducing the frequency, if there are episodes of incontinence in-between irrigations, we advise increasing the frequency.

During the study no adverse effect was recorded. The risk of perforation with TAI is very low (2 non-fatal bowel perforation reported for 110,000 irrigation) (Christensen *et al*, 2009), and this treatment modality has been employed in patients after low anterior resection (Koch *et al*, 2009) with no anastomotic leak reported. Nevertheless, we routinely perform a flexible sigmoidoscopy in patients who are above the age of 45 to rule out a potential risk factor for perforation such as diverticular disease. In the presence of previous colonic surgery or diverticulosis, the patient is counselled about a theoretical increased risk of bowel perforation, and if he or she wishes to go ahead, the irrigation is initiated with smaller volumes.

CHAPTER 8: CONCLUSIONS

8.1 Main Findings

My studies testing the primary hypothesis, that the involvement of the spinal cord by the disease is central to the development of bowel symptoms, have shown that:

- Prevalence of bladder symptoms is higher than expected in patients with MS and bowel symptoms.
- Patients with MS and clinically significant spinal cord disease have similar alterations of the rectal wall properties as measured by increased rectal compliance to patients with a SCI above T5.

I have also concluded that:

1. Patient-reported bowel symptoms quantify well bowel dysfunction, and are correlated with patient-reported bladder symptoms.
2. The cause of bowel symptoms in MS is multifactorial.

The secondary hypothesis, residual spinal cord function is a target for treatment of bowel symptoms, was tested with the biofeedback study which concluded that:

- Biofeedback improves bowel symptoms, depression and 5-seconds-endurance squeeze pressure in patients with MS. There was no significant difference between responders and non-responders, yet responders had a median EDSS of 4 and non-responders of 6. This is clinically relevant, particularly in the light of the compliance study.

Finally I showed that:

- TAI is effective to treat bowel symptoms in patients with MS who fail to respond to biofeedback. Responders (53%) had higher baseline incontinence symptoms and a better perception of their health, as well as a more capacious and compliant rectum. Incidentally, we have shown in study 2 that rectal compliance is higher in subjects with a higher disability. These are the patients that are less likely to respond to biofeedback, and this consideration allows a treatment algorithm to be constructed to rationalise bowel dysfunction in MS.

These findings are interwoven and support our central hypothesis that bowel dysfunction in MS is secondary to spinal cord involvement by the disease.

Therefore I conclude that:

- While the cause of bowel symptoms in patients with MS is multifactorial, the extent of spinal cord disease is a critical factor.
- The actual burden of bowel symptoms depends on the extent of spinal cord disease, and the natural history of bowel dysfunction follows disability.
- That this can be measured clinically with the EDSS and with rectal compliance.

This in turn has wider implications.

- With rapid development of techniques of nerve stimulation, residual spinal cord function might represent a target of treatment, and rectal compliance might represent a predictive factor of response.

- Pharmacological modulation of rectal compliance could be a therapeutic strategy for the treatment of constipation and incontinence.
- Furthermore this study has shown that rectal compliance is a good measure of altered reflex activity secondary to spinal cord disease, where other symptoms of autonomic dysfunction are absent. The initial study by Trivedi (Trivedi P, 2009) in patients with spinal cord injury showed that there is a pattern of compliance alterations depending on injury level. This study confirms that rectal compliance, when measured according to a physiological protocol employing an electronic barostat, a polyethelene bag with infinite compliance and a standard distension protocol, is a reliable indicator of autonomic rectal dysfunction. This has implication beyond patients with neurological disorders, given that most tests of ARP are non-specific for the underlying neurological dysfunction.

8.2 Strengths

The strengths of these studies are that:

- They are hypothesis driven, and are tightly interconnected.
- Study design was rigorous and reflected the research questions.
- It is the first sequence of studies to address the subject of MS guts pathophysiology systematically.
- The results demonstrate that we have made a significant contribution to the knowledge in this area of research and in the understanding of the natural history of bowel dysfunction in MS.
- A potential new target of treatment has been identified.

- I have also tried to identify clearly what the challenges for future studies are and how to overcome some of them. Consequently, future studies of NBD will be of higher quality.

8.3 Limitations

There are limitations that I had to accept when designing the studies, some which emerged whilst carrying out the studies and other that became apparent at their conclusion. Some of them are inherent to the population studied, some are inherent to the test we employed, and some will aid better studies in the future.

A major limitation is the absence of imaging regarding the brain and spinal cord lesions. We didn't set out to obtain imaging at the start, and the imaging available was not sufficiently specific or most of the times not close enough temporally to when the physiological measurements were taken. Given that MS is a fluctuating and often progressive disease, it made any available imaging unreliable to draw any conclusion. I attach an appendix (appendix 5) with available imaging of 16 patients who were in the rectal compliance study (chapter 5).

The cut off we used in the biofeedback and TAI studies, were empirical, but another study has used a percentage improvement of the Werner score reduction to measure response: good response= 90% of the pretreatment score or absence of fecal incontinence symptoms, partial response= reduction of 50– 89% of the pretreatment score), and no response= reduction of less than 50% of the pretreatment score or no alleviation of the symptoms (Boselli *et al*, 2010).

In the biofeedback study we were directed by the reviewers' comments. Overall they do help to separate patients who had a good response from those who didn't. We initially considered as responders for the biofeedback study all patients whose Wexner score had gone below 10, but it was pointed out by the reviewers of the biofeedback study that many patients with great improvement, but not to below 10, would have erroneously considered non responders. On the base of this experience we decided to employ a percentage reduction in score for the TAI study. The different type of intervention employed dictated the different strategy in selecting responders. In fact in the majority of cases response to TAI was more of a dualistic nature: it either worked very well or it didn't work at all. It should finally observed that our strategy to identify responders is rather unorthodox, as in the literature questionnaire based response is usually measured either by comparing pre- and post-treatment scores or in comparison to a control group (NICE, 2007).

Limitations Inherent to an MS Population

Patients with MS are a challenging group to study, as many confounding factors come into play:

- Multiple neurological lesions in the CNS, not necessarily correlating to neurological symptoms. I have tried to overcome this using a clinical index of spinal cord disease, the EDSS.
- Multiple neurological symptoms, compounding perception of bowel symptoms. To overcome this I employed two different questionnaires in the TAI study: the SF-36 and the MSI-29.
- Potential presence of cognitive impairment.

- Significant psychosocial impairment.
- Multiple bowel symptoms, which are alternating and fluctuating.
- Polypharmacy.

8.3.1 Limitations Related to the Tests Employed

- There are no validated instruments that take into account the above-mentioned specific traits to measure bowel symptoms in MS
- It is difficult to ensure reproducibility in tests of gut motility (rectal compliance). I have tried to overcome this by employing an electronic barostat, polyethylene bags with infinite compliance and a tested distension protocol.
- Current imaging modalities do not help to identify clinically significant disease. Again to this end I used a clinical indicator of spinal cord disease (the EDSS).

8.3.2 Limitations of our Study

- I didn't evaluate cognitive function; this would have been highly relevant in the biofeedback study.
- I didn't perform tests of autonomic dysfunction, which might have helped to distinguish the cause of autonomic dysfunction (spinal cord vs. higher centres). This would have been highly relevant in the rectal compliance study.

- Treatment studies 3 and 4 did not have a control group. They were pilot studies and the results will be employed for the power calculations in future studies.
- I didn't employ any measure of bowel-related quality of life

8.4 Future Studies

Further evaluation of the physiological alteration might be of interest, and to this end in the future it would be helpful to try to correlate:

1. Alterations of rectal compliance with MRI findings, comparing number, size and volume of sclerotic plaques above and below the T5 level.
2. Rectal compliance with RAIR. It has been shown that specific alterations of the RAIR occur. It could be that modification of rectal wall properties might be responsible for these alterations, or it could be that alteration of the RAIR and of rectal compliance are both manifestations of altered reflex activity in the spinal cord. In the latter, there might be specific patterns of alterations of rectal compliance and of specific component of the RAIR.

What we have found is that physiological bowel studies in patients with MS present significant challenges, the principal being the multiplicity of patterns affected.

Certainly from the patient's perspective, in the absence of a cure for the neurological disorder, symptoms relief is paramount, and we believe that future efforts should focus in this direction.

1. *Biofeedback vs. Transanal irrigation*

Biofeedback and TAI both better improve symptoms of incontinence than constipation. Even though they are completely different approaches to treat bowel symptoms, they might achieve this improvement through a common mechanism, which is to optimise rectal emptying. Biofeedback has the great limitation of not being widely available, and results are dependent strongly on the patient-therapist interaction. Instead, Peristeen is a mechanical means to achieve bowel emptying, and even if it requires training and encouragement, this might be achieved through a single training session, and a lot of issues related to its use can be dealt with over the phone. It might be that Peristeen is equally or more effective than biofeedback, even in the less disabled patient, and therefore might represent a better treatment if laxatives fail. In my studies both biofeedback and TAI have proved to be more effective for incontinence symptoms rather than constipation. Another consideration to take into account is that all our patients who had transanal irrigation had failed biofeedback in the past. Therefore a randomised controlled trial based on my data should compare biofeedback (group A) versus biofeedback and TAI in combination (group B). A sample size calculation was performed with the available data from our existing study. With a alpha of 0.05 and power of 0.80, a mean difference in the Wexner score of -3.95 for group A and standard deviation of 3.56 and a mean difference in the Wexner score of -5.13 for group B and standard deviation of 6.45 using the Student t tests comparing the mean of difference between two dependent means (matched pairs), we would need to recruit 179 patients for a well powered study. Other power calculations are reported in Appendix 6.

2. *Prokinetic study*

As discussed above, we have shown that biofeedback and TAI treat more effectively incontinence symptoms. However, constipation, whilst less socially embarrassing than incontinence, is a more prevalent bowel symptom. Prucalopride is a highly selective 5-HT_4 agonist that has a pro-peristaltic effect in the gut. Linaclotide is a 14 amino-acid peptide that activates the guanylate-cyclase pathway in colonic and small intestine enterocytes, resulting in luminal chloride secretion, and hence acts as a prokinetic. In MS slow bowel transit is related to disturbances in the CNS, but the bowel itself is actually normal (with the exception of the effects of certain drugs).

We therefore speculate that patient with MS might respond even better to one or other of these prokinetics, and therefore studies should compare the use of these drugs with a placebo and/or other treatment modality (laxatives, biofeedback, TAI).

3. *Surgery for constipation*

As discussed above, we still have difficulty treating constipation in patients with MS, and efforts should be made in this direction. The Malone procedure (antegrade enema) has been successfully employed in paediatric patients, and should certainly be evaluated in patients with MS.

4. *Nerve modulation*

We believe that there is enough evidence to suggest a central role of spinal cord disease in determining bowel symptoms, and therefore future studies should focus on how to target residual spinal cord function. This might be achieved with sacral nerve stimulation or PTNS.

- A randomised clinical trial of interventions (stratified by extent and site of nerve lesion) would help optimise the currently available modalities of bowel management.
- Specific instruments, tailored to assess NBD, should be developed to help monitor progress with interventions, from both a clinical and a research standpoint.
- Understanding of the gut pathophysiology of each individual patient may permit tailoring of a specific bowel regime. Specifically, tailored electrical or magnetic stimulation may influence the specific pathophysiology, and hence improve symptoms.

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Appendix 1 – Supporting data for Chapter 4

Sex	Type of MS	Duration MS	EDSS	NBD score	Transit	Paradox Contr	Bowel Time Proptn	VAS Severity	bladder Time Proptn	VAS Severity	Sex Time Proptn	VAS Severity
f	rr	48	2.5	3	slow	0	25	30	0	0	0	0
f	rr	63	0.5	11	slow	0	50	90	75	82	25	12
f	rr	57	1.5	6	slow	0	25	55	25	40	0	0
f	rr	10	3.5	7	slow	0	25	50	0	0	0	0
f	rr	29	3	15	slow	0	75	33	50	18	50	67
f	rr	36	4	8	slow	0	50	28	0	0	0	0
f	rr	144	3.5	6	slow	0	50	44	25	63	0	0
f	rr	69	5	20	slow	0	100	69	25	21	0	0
f	rr	168	1.5	7	slow	0	50	59	50	68	25	49
f	rr	192	3.5	19	slow	0	100	80	100	72	50	83
f	sp	67	0	4	slow	0	25	64	50	32	100	100
f	sp	120	2	13	slow	0	75	66	75	88	25	12
f	sp	96	2	12	slow	0	50	77	25	53	0	0
f	sp	31	4.5	17	slow	0	75	70	25	56	0	0
f	sp	89	3	11	slow	0	50	60	25	37	0	0
f	sp	94	6	22	slow	0	100	43	0	0	0	0
f	sp	112	0	5	slow	0	50	31	75	69	25	13
f	sp	27	5.5	2	slow	0	50	18	0	0	0	0
f	sp	85	4	6	slow	0	50	45	25	12	25	9
f	sp	44	5	21	slow	0	75	61	50	63	0	0
f	sp	58	0.5	1	slow	0	25	24	75	36	0	0
f	pp	41	0	3	slow	0	25	48	25	25	0	0
f	pp	110	2.5	7	slow	0	50	55	25	41	25	69
f	pp	146	0.5	5	slow	0	25	60	50	49	50	21
f	pp	31	4.5	20	slow	0	75	88	50	68	50	33
f	pp	152	3.5	8	slow	0	50	49	25	22	0	0
f	pp	20	0.5	8	slow	0	50	56	50	30	0	0
m	rr	30	1	6	slow	0	50	39	25	9	50	38
m	rr	74	3	8	slow	0	25	76	0	0	0	0
m	rr	180	3.5	5	slow	0	50	49	25	36	25	47
m	sp	42	4	5	slow	0	50	20	0	0	0	0
m	sp	80	1	4	slow	0	25	31	25	41	0	0
m	sp	76	1.5	11	slow	0	50	80	50	17	50	26
m	sp	132	5	10	slow	0	75	24	75	57	25	32
m	pp	100	2.5	6	slow	0	50	12	50	20	75	59

Sex	Type of MS	Duration MS	EDSS	NBD score	Transit	Paradox Contr	Bowel Time Proptn	VAS Severity	bladder Time Proptn	VAS Severity	Sex Time Proptn	VAS Severity
m	pp	53	1.5	3	slow	0	25	11	0	0	25	20
m	pp	20	6	17	slow	1	75	89	25	46	25	32
f	rr	42	3.5	30	slow	1	100	96	100	71	50	33
f	rr	67	4	27	slow	1	75	92	50	35	0	0
f	rr	16	4	8	slow	1	50	83	25	76	0	0
f	rr	88	6	11	slow	1	75	52	50	86	25	69
f	rr	72	3.5	17	slow	1	75	58	100	43	0	0
f	sp	36	1.5	9	slow	1	50	87	25	92	25	16
f	sp	89	4.5	29	slow	1	100	89	100	59	100	89
f	sp	94	2.5	10	slow	1	50	92	50	79	0	0
f	sp	60	4.5	12	slow	1	75	75	50	53	25	88
f	sp	84	3.5	28	slow	1	100	70	100	62	25	90
f	sp	126	4.5	11	slow	1	50	64	25	62	0	0
f	pp	84	1.5	6	slow	1	25	80	50	41	0	0
f	pp	48	5	5	slow	1	50	49	0	0	0	0
m	rr	88	1.5	8	slow	1	50	69	75	82	75	36
m	sp	70	1	13	slow	1	50	95	25	13	75	88
m	sp	116	0.5	12	slow	1	50	72	100	93	100	100
f	rr	55	2	9	normal	1	50	26	50	18	0	0
f	rr	90	4	25	normal	1	100	69	100	80	0	0
f	rr	53	3.5	8	normal	1	50	38	25	44	0	0
f	rr	100	1	11	normal	1	75	63	100	58	25	90
f	sp	103	4	30	normal	1	100	86	100	73	50	67
f	sp	47	5.5	10	normal	1	75	59	25	60	25	33
f	sp	69	0.5	8	normal	1	50	57	75	68	0	0
f	sp	192	4	6	normal	1	50	33	25	16	0	0
f	sp	40	0.5	2	normal	1	25	24	25	39	50	90
f	sp	87	6	30	normal	1	75	80	0	0	0	0
f	pp	63	1	3	normal	1	25	30	50	72	25	86
f	pp	66	0.5	4	normal	1	25	21	50	47	25	79
f	pp	22	0.5	4	normal	1	25	59	50	7	0	0
f	pp	150	0	6	normal	1	50	62	75	89	0	0
f	pp	49	2	5	normal	1	25	44	25	30	25	64
m	rr	70	6	19	normal	1	75	38	50	14	25	80
m	rr	58	3	7	normal	1	50	29	25	16	0	0
m	sp	106	1.5	6	normal	1	50	26	75	33	50	22

Appendix 2a – Supporting data for Chapter 5

MS patients

Symp Dur.	Dis.Duration	MS Type	EDSS	Wexner-I	Wexner-C	RP	SP	TV	UV	MTV	AE	RE	Compliance
2	4	rr	4.5	16	17	71	52	50	110	270	10.2	23	9.4
1	5	rr	2	8	7	69	66	30	90	150	7	31.8	7.74
>20	1	pp	5	17	16	73	38	60	320	320	7.8	22	17.1
3	6	rr	6	0	13	34	102	20	60	90	7.2	17	25.6
3	7	pp	4	16		70	0	120	160	320	7.4	35.5	18.02
1		?rr?sp	5	0	16	47	161	140	200	220	10.2	19.5	10.11
3	5	rr	5	20	0	51	12	320	320	320	20	50	15.5
13	16	sp	5.5	16	8	59	43	45	75	200	10.2	14	7.9
3	33	rr	3	4	2	55	188	300	320	320	8.4	23	19.51
1	25	sp	7	11	10	109	0	120	320	320	9.2	25	16.3
5	6	pp	3	0	8	100	136	30	60	200	10.4	25.5	13.1
3	15	pp	2	9	14	104	70	180	220	240	7.8	42.5	9.4
4	4	rr	2	7	9	62	124	45	105	160	9.2	33.5	10.1
3	6years	rr	2	0	21	50	36	170	220	270	5.6	17.5	7.8
3	5	sp	2	2	2	29	279	170	180	320	4.8	19.5	11.5
1	21	sp	2	2	15	53	58	100	140	220	12.6	21	6.7
3	4	rr	6	4	16	78	94	120	140	300	19	50	20.1
1	9	rr	2	13	14	69	56	40	80	200	9	27	7.8
4	31	rr	3	0	7	22	18	60	140	280	11.2	18.5	8.5
4	15	rr	7	15	14	67	26	40	100	130	6.4	39	7.18
1	7	rr	2	6	4	50	24	40	160	210	7.8	17	10
5	14	rr	2	0	13	64	62	80	140	200	14.6	39	8.45
1	1	rr	2	9	19	106	54	40	80	110	7.2	11.5	8.23
2	17	rr	3	8	7	65	122	20	35	60	3.4	11.5	10.1
1	16	sp	6	8	10	64	74	20	60	150	8.6	19.5	5.9
2	20	rr/sp	2	11	11	53	42	40	90	140	6.8	41	14
3	16	sp	8.5	4	18	76	0	55	110	130	14.2	32.5	15.2
2	22	sp	8	15	11	20	0	320	320	320	20	50	26.1
1	26	rr	5	20	15	31	106	200	320	320	9.4	6.5	19.7
2	10	rr	6	12	7	109	93	150	240	320	7.6	12	14.3
15	24	sp	5.5	0	13	26	85	160	230	320	10	50	8.1
2	9	sp	3	5	6	97	34	50	110	160	7.2	15	6.2
1	12	rr	3	0	17	72	285	80	104	180	3.7	10.8	8

1	11	rr	5.5	12	9	73	59	80	280	320	9.4	5.5	17.7
1	12	atipical	8.5	10	12	86	43	320	320	320	20	50	18.42
Symp Dur.	**Dis.Duration**	**MS Type**	**EDSS**	**Wexner-I**	**Wexner-C**	**RP**	**SP**	**TV**	**UV**	**MTV**	**AE**	**RE**	**Compliance**
3	17	sp	4.5	7	14	76	39	80	150	200	11.6	50	14.25
1	11	sp	4.5	1	4	117	130	70	120	180	11	25.5	7.3
1	15	sp	4.5	8	12	50	133	70	130	280	14	29	9
2	6	sp	6	4	8	73	62	40	100	160	8.6	20	18.8
4	5	rr	4	12	9	54	41	20	40	80	6.2	7.5	22.1
1	16	rr	4	11	16	67	92	50	80	210	7.8	18	4.2
2	36	rr	5.5	13	7	32	36	50	110	220	7.8	22.5	17.5
7	15	pp	6	10	9	59	152	60	160	220	13	22.5	12.5
1	7	pp	6.5	6	14	12	16	35	110	280	6.4	14	13.3
4	8	rr	4	8	11	67	25	40	120	240	6.2	21.5	12

Appendix 2b– Supporting data for Chapter 5

SCI patients

Sex	Level	Complete	Age	Dis. Duration	Sf36	Wexner-I	Wexner-C	Compliance
F	T11	n	38	6	95	18	15	16.7
M	C3	n	54	1	109	3	12	9.7
F	C5	n	76	2	83	11	21	7.8
M	T3/T7	n	40	2	101	13	12	20.2
M	C2-C3	n	58	4	66	18	17	15
M	C2-T10	n	39	3	95	3	16	21.8
M	c5	y	48	7	114	18	23	12
M	T5	n	51		90	16	5	22.5
F	C6	y	26	21		1	22	19
M	T3	y	33	6		13	12	17.8
M	T2	y	24	9		3	20	29.7
M	C8	y	49	16		2	23	13.6
F	C6	y	38	19		17	16	24.5
F	C5	n	41	14		13	8	8.9
M	T1	y	47	11		2	24	18.7
F	T2	y	59	20		8	21	22.5
M	C7	n	56	8		17	2	24.9
M	T3	y	40	10		12	19	20.2
M	T4	n	49	7		16	4	16.8

Appendix 2c– Supporting data for Chapter 5

Sex	Age	TV	UV	MTV	Compliance
f	45	25	55	115	8.7
m	76	60	160	220	11.3
m	63	35	100	175	11.5
f	42	40	150	215	12.7
f	37	50	95	170	7.3
f	74	60	110	200	9
m	69	35	70	115	15.4
f	71	40	110	160	10.4
m	79	40	75	130	9
m	66	50	145	210	9.1
m	46	60	180	240	16.5
f	73	30	105	150	11.3
f	58	50	90	135	7
f	70	40	85	160	17.2
f	63	55	100	180	13.3
f	44	50	115	205	12.1
f	37	25	75	180	10.7
m	58	20	40	90	5.7
m	22	45	70	210	14.6
f	24	40	70	160	8.2
m	39	35	80	155	10.4
m	62	40	65	120	9.2
f	41	60	120	220	15.8
f	72	45	110	195	12.5
m	21	65	115	200	7.3

Appendix 3– Supporting data for Chapter 6

	Gender	Age	DSS	Duration	Pre-HAD-A	Pre-HAD-D	Pre-Wex-i	Pre-Wex-c	Pre-RP	Pre-SP	Pre-CP	Pre-5sec Endur	Pre-TV	Pre-UV	Pre-MTV	Pre-AE	Pre-RE	Post-HAD-A	Post-HAD-D	Post-Wex-i	Post-Wex-c	Post-RP	Post-SP	post-CP	Post-5sec Endur	Post-TV	Post-UV	Post-MTV	Post-AE	Post-RE
FI	**f**	**26**	**2**	**8**	**5**	**3**	**15**	**2**	**70**	**48**	**41**	**12**	**20**	**80**	**150**	**9.8**	**22**	**0**	**3**	**1**	**2**	**64**	**63**	**57**	**47**	**35**	**90**	**135**	**9**	**21.5**
FI	**f**	**28**	**4**	**11**	**2**	**5**	**12**	**3**	**62**	**76**	**46**	**30**	**180**	**220**	**290**	**5.6**	**31.5**	**2**	**5**	**3**	**4**	**79**	**71**	**50**	**60**	**105**	**160**	**200**	**5**	**30**
FI	**f**	**26**	**5**	**10**	**3**	**2**	**18**	**1**	**32**	**52**	**46**	**21**	**55**	**80**	**150**	**3.8**	**24.5**	**2**	**4**	**6**	**1**	**68**	**47**	**72**	**38**	**60**	**80**	**140**	**4**	**22**
FI	**f**	**44**	**3**	**24**	**4**	**12**	**10**	**0**	**142**	**65**	**66**	**20**	**70**	**190**	**250**	**4.8**	**35.5**	**2**	**5**	**6**	**1**	**120**	**77**	**53**	**58**	**50**	**150**	**230**	**5.6**	**31**
FI	**f**	**51**	**5**	**40**	**0**	**4**	**20**	**7**	**45**	**51**	**26**	**11**	**45**	**50**	**110**	**18.6**	**28**	**1**	**4**	**8**	**7**	**41**	**58**	**47**	**52**	**55**	**90**	**160**	**16**	**20**
FI	**f**	**52**	**6**	**25**	**2**	**7**	**14**	**4**	**32**	**121**	**166**	**106**	**35**	**95**	**220**	**5.2**	**11.5**	**1**	**3**	**9**	**2**	**38**	**111**	**169**	**102**	**50**	**110**	**210**	**8**	**13**
FI	**f**	**40**	**4**	**4**	**1**	**2**	**18**	**3**	**44**	**52**	**40**	**23**	**35**	**80**	**155**	**6.7**	**18.3**	**1**	**2**	**4**	**3**	**39**	**63**	**62**	**50**	**50**	**90**	**120**	**9**	**19**
FI	*m*	*59*	*5*	*29*	*4*	*6*	*12*	*2*	*32*	*68*	*55*	*30*	*40*	*105*	*150*	*4*	*16*	*4*	*6*	*14*	*2*	*47*	*44*	*51*	*27*	*35*	*95*	*180*	*5*	*19.6*
FI	*f*	*31*	*9*	*10*	*16*	*19*	*14*	*5*	*27*	*30*	*49*	*0*	*20*	*100*	*145*	*6.5*	*33*	*16*	*19*	*11*	*7*	*15*	*37*	*45*	*7*	*45*	*115*	*130*	*7.5*	*35*
FI	*f*	*26*	*8*	*5*	*12*	*15*	*20*	*3*	*68*	*53*	*70*	*13*	*15*	*55*	*90*	*11*	*41*	*12*	*15*	*20*	*2*	*54*	*46*	*54*	*7*	*20*	*65*	*100*	*10*	*37*
FI	*f*	*28*	*7*	*7*	*3*	*11*	*17*	*6*	*59*	*44*	*47*	*0*	*30*	*50*	*65*	*12*	*27*	*3*	*11*	*17*	*4*	*62*	*55*	*63*	*0*	*20*	*50*	*75*	*14.8*	*30*
FI	*m*	*37*	*8*	*14*	*5*	*7*	*15*	*1*	*70*	*36*	*79*	*21*	*25*	*35*	*75*	*9.1*	*22*	*5*	*7*	*17*	*3*	*54*	*21*	*45*	*20*	*25*	*45*	*70*	*10.8*	*26*
C	**m**	**37**	**1**	**4**	**0**	**3**	**1**	**12**	**42**	**26**	**26**	**8**	**25**	**50**	**90**	**7**	**9**	**0**	**1**	**1**	**8**	**40**	**41**	**38**	**28**	**35**	**50**	**100**	**5.6**	**10.2**
C	**m**	**47**	**6**	**5**	**2**	**9**	**1**	**22**	**63**	**53**	**56**	**50**	**40**	**100**	**160**	**6.3**	**30**	**2**	**5**	**1**	**4**	**55**	**82**	**47**	**46**	**40**	**95**	**155**	**7.4**	**14.9**
C	**f**	**39**	**3**	**3**	**2**	**4**	**4**	**19**	**42**	**142**	**60**	**23**	**60**	**100**	**140**	**6.6**	**26**	**2**	**2**	**3**	**3**	**45**	**109**	**63**	**59**	**55**	**110**	**175**	**6.8**	**17**
C	**f**	**41**	**3**	**9**	**3**	**2**	**0**	**10**	**53**	**61**	**36**	**17**	**50**	**180**	**450**	**17.4**	**50**	**3**	**5**	**3**	**4**	**57**	**56**	**32**	**41**	**45**	**150**	**390**	**15**	**50**
C	**f**	**48**	**6**	**22**	**10**	**15**	**2**	**18**	**45**	**57**	**62**	**54**	**50**	**110**	**160**	**8.2**	**7.5**	**2**	**11**	**3**	**8**	**58**	**72**	**69**	**66**	**40**	**110**	**145**	**6.4**	**9.2**
C	**f**	**59**	**2**	**30**	**1**	**6**	**3**	**12**	**32**	**173**	**107**	**63**	**40**	**80**	**170**	**16.6**	**27.5**	**2**	**3**	**1**	**7**	**30**	**194**	**126**	**116**	**60**	**90**	**150**	**13.7**	**30**
C	**f**	**34**	**1**	**2**	**0**	**0**	**0**	**10**	**88**	**125**	**111**	**93**	**80**	**210**	**260**	**9.4**	**31**	**1**	**3**	**5**	**10**	**74**	**89**	**106**	**69**	**55**	**155**	**210**	**8**	**24**

Gender	Age	DSS	Duration	Pre-HAD-A	Pre-HAD-D	Pre-Wex-i	Pre-Wex-c	Pre-RP	Pre-SP	Pre-CP	Pre-5sec Endur	Pre-TV	Pre-UV	Pre-MTV	Pre-AE	Pre-RE	Post-HAD-A	Post-HAD-D	Post-Wex-i	Post-Wex-c	Post-RP	Post-SP	post-CP	Post-5sec Endur	Post-TV	Post-UV	Post-MTV	Post-AE	Post-RE	
C	**f**	**61**	**7**	**24**	**2**	**7**	**5**	**25**	**96**	**79**	**48**	**20**	**95**	**120**	**300**	**10**	**27**	**2**	**4**	**2**	**10**	**90**	**71**	**46**	**47**	**60**	**140**	**350**	**8**	**25**
C	*f*	*36*	*2*	*2*	*0*	*2*	*4*	*11*	*33*	*59*	*40*	*21*	*85*	*160*	*300*	*14*	*21*	*1*	*5*	*4*	*15*	*40*	*50*	*43*	*13*	*60*	*135*	*280*	*10.9*	*30*
C	*f*	*64*	*6*	*32*	*8*	*11*	*0*	*13*	*89*	*43*	*33*	*16*	*90*	*100*	*250*	*7.8*	*18.9*	*8*	*10*	*1*	*10*	*77*	*44*	*46*	*32*	*85*	*105*	*320*	*5*	*23.1*
C	*f*	*27*	*4*	*6*	*2*	*5*	*1*	*10*	*122*	*76*	*80*	*72*	*75*	*90*	*350*	*4.6*	*24.4*	*6*	*4*	*0*	*11*	*134*	*60*	*75*	*45*	*65*	*90*	*410*	*6.3*	*22.3*
C	*f*	*33*	*4*	*8*	*3*	*3*	*2*	*14*	*106*	*85*	*35*	*75*	*60*	*110*	*225*	*13*	*12*	*5*	*4*	*0*	*17*	*100*	*96*	*41*	*100*	*50*	*120*	*275*	*17*	*13.4*
C	*f*	*29*	*6*	*3*	*4*	*2*	*4*	*26*	*76*	*142*	*110*	*68*	*55*	*135*	*305*	*10.5*	*21.7*	*3*	*4*	*3*	*24*	*65*	*159*	*98*	*43*	*55*	*130*	*250*	*11*	*24*
C	*m*	*34*	*8*	*10*	*5*	*12*	*2*	*23*	*58*	*128*	*108*	*57*	*85*	*155*	*295*	*16*	*39*	*7*	*14*	*3*	*23*	*74*	*112*	*103*	*51*	*70*	*135*	*245*	*12*	*42*
CFI	**m**	**35**	**5**	**4**	**5**	**4**	**15**	**16**	**94**	**16**	**44**	**16**	**90**	**120**	**170**	**7.6**	**16**	**3**	**0**	**4**	**7**	**88**	**46**	**52**	**39**	**80**	**120**	**145**	**5.3**	**14.2**
CFI	**f**	**64**	**2**	**19**	**3**	**0**	**12**	**28**	**71**	**72**	**74**	**70**	**50**	**90**	**120**	**7.4**	**19**	**0**	**0**	**2**	**10**	**74**	**85**	**65**	**76**	**30**	**115**	**150**	**8**	**13**
CFI	**f**	**56**	**1**	**31**	**5**	**6**	**15**	**12**	**31**	**20**	**76**	**20**	**50**	**120**	**200**	**16**	**15**	**2**	**2**	**10**	**9**	**28**	**49**	**58**	**40**	**40**	**130**	**220**	**9.3**	**11.7**
CFI	**f**	**50**	**3**	**27**	**3**	**8**	**16**	**10**	**44**	**51**	**31**	**38**	**55**	**115**	**245**	**6**	**18**	**4**	**5**	**3**	**6**	**53**	**86**	**42**	**60**	**75**	**120**	**240**	**9.2**	**24.2**
CFI	**f**	**38**	**4**	**19**	**7**	**9**	**10**	**22**	**97**	**19**	**26**	**18**	**120**	**170**	**270**	**4.9**	**20**	**2**	**5**	**0**	**6**	**78**	**67**	**48**	**50**	**110**	**150**	**235**	**9.7**	**25.5**
CFI	**f**	**25**	**2**	**3**	**1**	**3**	**11**	**10**	**80**	**75**	**44**	**70**	**60**	**180**	**290**	**7.6**	**23**	**3**	**3**	**0**	**8**	**96**	**114**	**39**	**59**	**50**	**170**	**290**	**4.2**	**26.9**
CFI	**f**	**59**	**4**	**33**	**10**	**8**	**13**	**13**	**21**	**14**	**37**	**0**	**40**	**80**	**220**	**9.6**	**32**	**6**	**9**	**4**	**10**	**35**	**26**	**51**	**8**	**55**	**110**	**210**	**5.1**	**28.6**
CFI	*f*	*27*	*6*	*1*	*6*	*14*	*14*	*18*	*52*	*35*	*26*	*11*	*45*	*140*	*255*	*7.7*	*28.7*	*4*	*12*	*7*	*15*	*47*	*61*	*42*	*18*	*65*	*160*	*310*	*8.4*	*30.4*
CFI	*f*	*44*	*4*	*7*	*3*	*9*	*10*	*11*	*61*	*68*	*34*	*5*	*100*	*260*	*300*	*8.5*	*19.9*	*5*	*9*	*13*	*14*	*87*	*47*	*34*	*28*	*75*	*260*	*280*	*7.6*	*21.4*
CFI	*f*	*37*	*8*	*8*	*9*	*17*	*15*	*19*	*24*	*16*	*47*	*0*	*95*	*255*	*315*	*9.4*	*33*	*7*	*16*	*12*	*16*	*42*	*19*	*35*	*6*	*80*	*280*	*335*	*10.9*	*31.8*
CFI	*f*	*36*	*7*	*5*	*16*	*15*	*16*	*27*	*34*	*75*	*60*	*10*	*75*	*150*	*280*	*12*	*41*	*14*	*13*	*11*	*22*	*47*	*45*	*38*	*0*	*90*	*190*	*310*	*9.8*	*50*
CFI	*m*	*50*	*7*	*6*	*17*	*8*	*12*	*21*	*50*	*27*	*14*	*22*	*150*	*310*	*400*	*13*	*25*	*12*	*7*	*10*	*23*	*39*	*35*	*31*	*26*	*120*	*260*	*420*	*14*	*26*
CFI	*m*	*38*	*8*	*10*	*11*	*18*	*17*	*26*	*42*	*33*	*31*	*3*	*145*	*285*	*350*	*10.4*	*12.7*	*11*	*15*	*14*	*24*	*58*	*40*	*27*	*28*	*135*	*310*	*450*	*11*	*15.3*

Appendix 4– Supporting data for Chapter 7

Gender	Age	Dis. Duration	Symp Dur.	MS Type	EDSS	SF36	Pre-wexner-i	Post-we-i	Δ-Wex-i	Pre-wex-c	Post-wex-c	Δ-wex-c	MSIS 29	RP	SP	TV	UV	MTV	AE	RE	Compliance
f	55	22	14	pp	6	103	20	4	-16	16	8	-8	50	73	38	60	320	320	7.8	22	17.1
f	61	2	1	pp	6.5	83	16	4	-12	16	6	-10	80	70	0	120	160	320	7.4	35.5	18.02
f	54	25	12	sp	7	89	11	8	-3	10	10	0	85	109	0	120	320	320	9.2	25	16.3
f	47	9	7	rr	4	101	13	2	-11	14	6	-8	130	69	56	40	80	200	9	27	10.7
f	45	16	8	sp	8.5	94	4	2	-2	18	8	-10	103	76	0	55	110	130	14.2	32.5	15.2
f	46	21	14	sp	2	95	2	2	0	15	6	-9	81	53	58	100	140	220	12.6	21	6.7
f	33	5	2	rr	4	105	12	0	-12	9	4	-5	49	54	41	200	320	320	6.2	7.5	22.1
m	30	12	7	sp	8.5	89	20	0	-20	13	12	-1	135	46	22	320	320	320	20	50	15.2
f	53	4	3	sp	4	101	12	4	-8	4	4	0	69	62	58	60	120	200	9.4	14.6	15.2
f	58	5	4	sp	7	99	18	8	-10	4	4	0	130	23	20	55	100	320	14.2	22.1	17.4
f	60	12	11	pp	4	98	20	4	-16	8	4	-4	78	69	89	80	100	260	8.9	11.9	14.8
f	31	2	1	rr	5	102	14	6	-8	3	3	0	90	52	43	45	90	220	10.1	19	14.5
f	54	16	12	sp	4.5	105	14	8	-6	4	2	-2	55	48	58	45	80	240	11.8	24.6	16.4
f	48	12	6	sp	7	84	20	4	-16	20	8	-12	130	18	13	320	320	320	20	50	17.2
f	50	9	7	sp	5.5	89	6	0	-6	10	4	-6	80	54	56	120	160	320	10.2	29.3	16.2
f	45	3	2	rr	4	101	12	8	-4	10	4	-6	76	34	42	60	120	320	7.8	14.3	14.7

Gender	Age	Dis. Duration	Symp Dur.	MS Type	EDSS	SF36	Pre-wexner-i	Post-we-i	Δ-Wex-i	Pre-wex-c	Post-wex-c	Δ-wex-c	MSIS 29	RP	SP	TV	UV	MTV	AE	RE	Compliance
f	40	5	4	rr	5	98	17	18	1	2	2	0	83	51	12	320	320	320	20	50	15.5
f	46	4	3	rr	6	84	4	4	0	16	16	0	134	78	94	40	60	120	19	50	10.1
m	31	15	6	rr	7	90	15	15	0	14	14	0	90	67	26	40	100	130	6.4	39	7.18
f	65	22	13	sp	8	78	15	15	0	11	11	0	102	20	0	320	320	320	20	50	16.1
f	43	9	4	sp	3	92	5	5	0	6	6	0	104	97	34	20	40	90	7.2	15	6.2
f	50	11	2	rr	3	90	12	10	-2	9	9	0	102	73	59	80	280	320	9.4	5.5	7.7
f	52	7	7	pp	6.5	98	6	8	2	14	14	0	86	12	16	35	110	280	6.4	14	12.3
f	53	11	4	sp	7	86	16	12	-4	12	10	-2	106	38	7	20	60	95	6.4	17	7.2
f	21	5	2	rr	6	102	11	4	-7	20	18	-2	103	80	56	60	180	300	10.6	20	4.8
f	54	34	20	sp	7	92	0	0	0	18	18	0	104	32	201	22	94	237	20	50	20.8
f	55	12	8	sp	7.5	95	11	11	0	9	9	0	106	46	22	175	175	175	6.3		5.8
f	45	6	5	rr	2	85	0	0	0	21	21	0	50	50	36	170	220	270	5.6	17.5	7.8
f	67	7	3	rr	2	75	2	4	2	12	12	0	68	59	39	40	60	110	8.2	12.5	8.9
m	55	5	4	rr	2	110	4	8	4	20	20	0	49	78	189	40	60	100	6.9	12.5	9.2

Appendix 5 – Available Radiology data

ARP Date	MRI Date	Neuroradiology Report	Lesion No.	Cord Atrophy
6/7/2008	23/12/2008	• **C1-2:** Large central ventral lesion involving grey and white matter, sparing the dorsal columns, tapering and fading away to mid **C2** • **Craniocaudal distance:** 11mm • No significant cord atrophy at this level • **C4-5:** Small right lateral lesion (possibly) • **C5-6** lesion most likely due to cord compression • **April 2009** – no change	**2**	No significant atrophy
17/9/2008	11/1/2010	• **C2:** Large central dorsal lesion • **Craniocaudal distance:** 29mm • Cord atrophy at this level (mild) • **C4:** Small central dorsal lesion • **T1-2:** Left lateral dorsal lesion • **Craniocaudal distance**: 10mm • Local mild atrophy at this level • Lesions do not enhance with gadolinium	**3**	**Mild** cord atrophy at the segmental level of the lesions

		• **12/11/2010** No change • **March 2012** – Cord • Conus looks normal • No enhancement		
21/10/2008	8/3/2010	• **C2-3:** Right lateral lesion • **Craniocaudal distance**: 10mm • **C2-3:** Left paramedian dorsal lesion • **Craniocaudal distance**: 7-8mm • **C2-3:** Left lateral lesion • All the above C2-3 lesions are associated with mild volume loss of the cord • **C3-4:** Mild volume loss of the cord • **C4-5:** Left lateral lesion • **C7:** Dorsal • **T1:** Central diffuse lesion • The lesions from **C3-C7** are small in size	**7**	**Mild** volume loss (cord) at the segmental level of the lesions
7/9/2009	19/1/2011	**Jan 2008**: • **C4-5**: Midline dorsal lesion • **Craniocaudal distance**: 14mm • No enhancement with contrast **6/2008:**	1/2	No cord atrophy

		• **C4-5:** Lesion (described above) much smaller, much less T2 hyperintense • **Craniocaudal distance:** 12mm • Normal conus region **Jan 2011** • **C7-T1**: Possible new lesion on axial slices, at edge of field of view • No cord atrophy		
11/12/2008	29/12/2009	• **C3:** Left hemicord lesion • **C4-5:** • **C5-6:** Cord appears flattened (mild atrophy) • **C6-7**: Right ventral lesion	2	Patchy mild cord atrophy
29/10/2008	25/2/2009	• Extensive patchy signal change in cervical spinal cord **C1-7** • **C2**: Bilateral signal changes – right and left lateral regions, also dorsolateral region (3 lesions) • **C7**: Large lesion • **Craniocaudal distance**: 17.5mm • **T1-2:** Hyperintense region (lesion) • **T6-7:** Small right lateral lesion and left anterolateral lesion • **T8:** Diffuse lesion	8	Very mild atrophy of the cervical spinal cord

		• **T9-10** Signal change (lesion)		
ARP Date	**MRI Date**	**Neuroradiology Report**	**Lesion No.**	**Cord Atrophy**
02/07/2008	05/04/2005	**C4-5:** ?thinning of cord, but at edge of field of view so difficult to be sure **T11-12:** lesion (Suggestion of two lesions)	2	Segmental volume loss
16/12/2008	02/07/2008	*Spinal cord:* **C3**: small left lateral lesion **C3-4**: right dorsolateral lesion, central lesion • **Craniocaudal distance:** 1.3 cm • No convincing volume loss **C5:** right lateral lesion **C5:** left lateral lesion **C5-6:** left lateral lesion (3 small lesions that coalesce) *Brain:* • Large lesion load >20 • Supratentorial cerebral volume loss • Frontal lobe involvement; left paracentral lobule and precentral gyrus • Left cerebral hemisphere more affected •	5	No atrophy
28/05/2008	22/05/2008	(Poor quality images) *Spinal cord:*	2	

		• **T10-11**: possible lesion (no axial image, ?truncation artefact) • **L1/conus:** 3 cm craniocaudal distance *Brain:* • Saggital T2 2002 • Lesion load > 20 (all small in size) ~35 • No paracentral lobule involvement • Normal posterior fossa • No volume loss		
09/07/2008	01/07/2009	*Brain* • V. Atrophic, brainstem involvement • Extensive intracranial lesion load • **4 (severe)** brain volume loss • Significant frontal lobe involvement • Left paracentral lobule involvement • Right paracentral lobule involvement (less compared to left)		
19/11/2008	14/07/2008	*Brain* • Large discrete intracranial lesions • Lesion load 24 (20-30) • Frontal lobe involvement • No significant volume loss • Periventricular enhancing lesion in splenium of corpus callosum **(1 active lesion** – faint enhancement)		
19/11/2008	24/06/2008	*Brain* • Lesion load 20-30 • Right precentral gyrus lesion – subcortical • Mild volume loss		

		• Large right frontal lobe lesion		
16/04/2008	12/06/2006	*Spinal cord* • **C1-2**: Suggestion of a lesion, volume loss *Brain* • Frontal periventricular lesions + smaller peripheral lesions		
27/08/2008	13/04/2006, 19/07/2007	*Brain* • **2006:** extensive pontine and midbrain involvement • No paracentral lobule involvement • Lesion load > 20 • **2007:** Progession of brainstem disease • Supratentorial lesions unchanged • Cerebellar lesions unchanged		
17/09/2008	3/2009	*Brain* • Right paracentral lobule – cortical and subcortical • Left frontal meningioma • Faintly enhancing lesions: Right trigone, right centrum semiovale (frontal) • Volume loss mild • Brainstem and pontine involvement **11/2010** • Lesion load – 19 (cerebral hemispheres), 1 pons, 1 cerebellar **2012**		

		• Enhancement even fainter		
07/09/2009	19/1/2011	*Brain* **18/1/2008** • 2 large frontal lesions • No volume loss, posterior fossa normal (no contrast given) **5/6/2008** • Frontal lesions smaller, but new periventricular lesion superiorly • 3 lesions in 2008 • No paracentral lobule involvement **19/1/2011** • 8 lesions in total		

Appendix 6 – Power Calculations

Sample Size Calculation – Biofeedback vs. Transanal Irrigation - Constipation

Available data

A. Non-paired:

Biofeedback:
Δ Wexner Constipation -3.41 (sd 5.95)
Δ Wexner Incontinence -3.95 (sd 3.56)

Transanal irrigation
Δ Wexner Constipation -2.83 (sd 3.88)
Δ Wexner Incontinence -5.13 (sd 6.45)

B. Paired:

Biofeebdack:

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
preWex-i	39	0	20	10.00	6.517
preWex-c	**39**	**0**	**28**	**12.69**	**8.339**
postWex-i	39	0	20	6.05	5.448
postWex-c	**39**	**1**	**24**	**9.28**	**6.875**
Valid N (listwise)	39				

Transanal irrigation

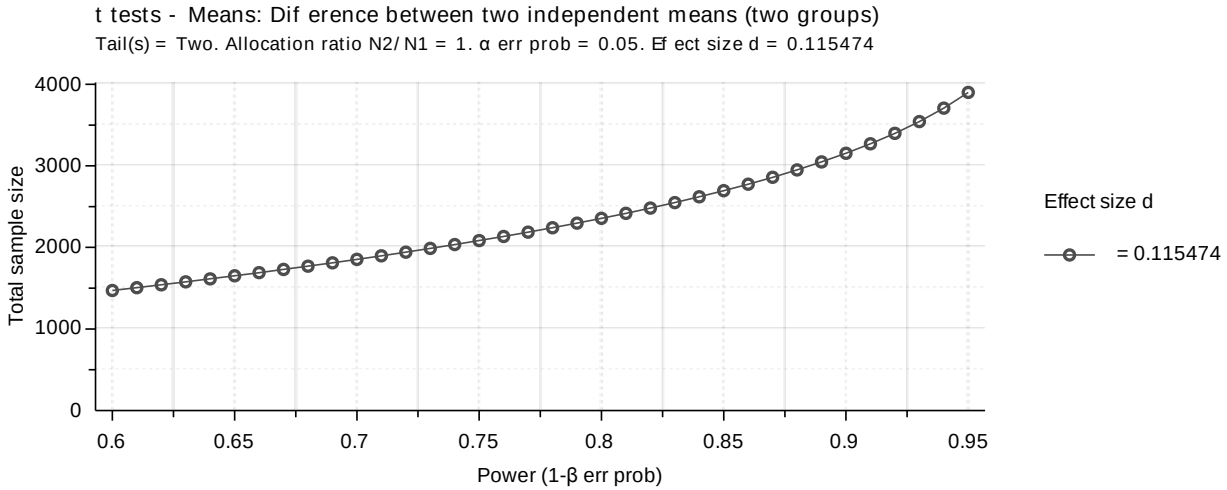
Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
PreWexInc	30	.00	20.00	11.0667	6.30781
PostWexInc	30	.00	18.00	5.9333	4.79895
PreWexnConst	**30**	**2.00**	**21.00**	**11.9333**	**5.50820**
PostWexnConst	**30**	**2.00**	**21.00**	**9.1000**	**5.48572**
Valid N (listwise)	30				

A. Non-paired - Constipation:

t tests - Means: Difference between two independent means (two groups)

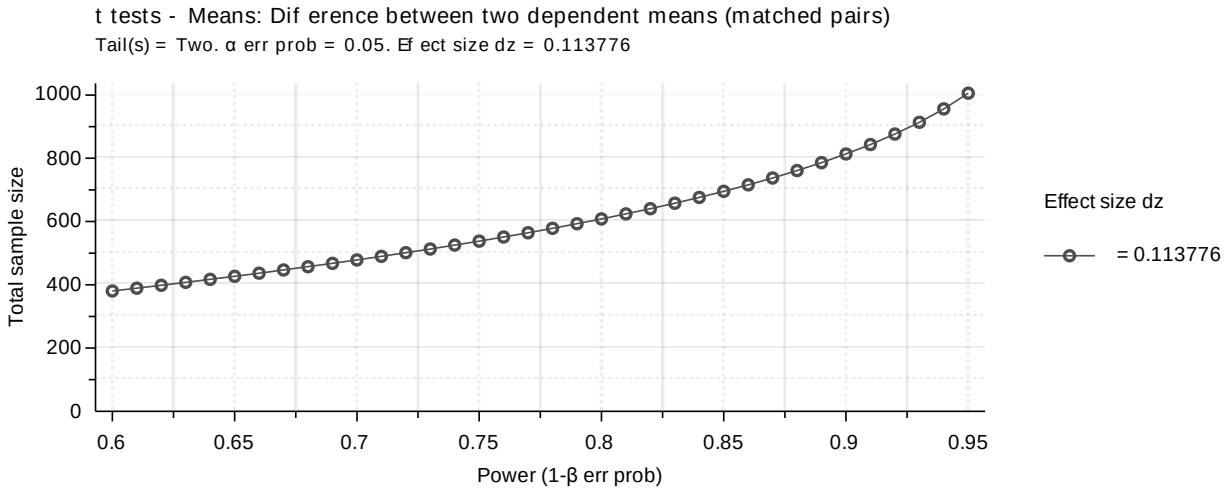
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0.1154736
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	2.8036553
	Critical t	=	1.9609714
	Df	=	2356
	Sample size group 1	=	1179
	Sample size group 2	=	1179
	Total sample size	**=**	**2358**
	Actual power	=	0.8002604


t tests - Means: Dif erence between two independent means (two groups)
Tail(s) = Two. Allocation ratio N2/ N1 = 1. α err prob = 0.05. Ef ect size d = 0.115474
Total sample size
4000
3000
2000
1000
0
0.6
0.65
0.7
0.75
0.8
0.85
0.9
0.95
Power (1-β err prob)
Effect size d
= 0.115474

B. Paired - Constipation:

t tests - Means: Difference between two dependent means (matched pairs)

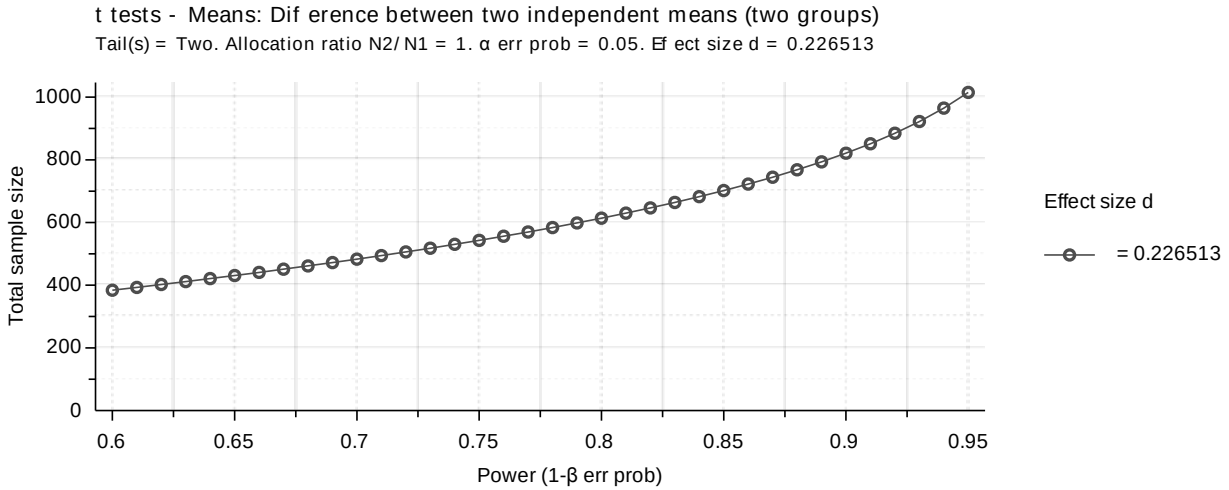
Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size dz	=	0.113776
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
Output:	Noncentrality parameter δ	=	2.8077556
	Critical t	=	1.9638734
	Df	=	608
	Total sample size	**=**	**609**
	Actual power	=	0.8004857



C. Non-paired - Incontinence:

t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	0.2265128
	α err prob	=	0.05
	Power (1-β err prob)	=	0.8
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	2.8063830
	Critical t	=	1.9638478
	Df	=	612
	Sample size group 1	=	307
	Sample size group 2	=	307
	Total sample size	**=**	**614**
	Actual power	=	0.8001105


t tests - Means: Dif erence between two independent means (two groups)
Tail(s) = Two. Allocation ratio N2/ N1 = 1. α err prob = 0.05. Ef ect size d = 0.226513
Total sample size
1000
800
600
400
200
0
0.6
0.65
0.7
0.75
0.8
0.85
0.9
0.95
Power (1-β err prob)
Effect size d
= 0.226513

D. Paired - Incontinence:

t tests - Means: Difference between two dependent means (matched pairs)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size dz	=	0.2108687
	α err prob	=	0.05
	Power (1-β err prob)	=	0.8
Output:	Noncentrality parameter δ	=	2.8212309
	Critical t	=	1.9733809
	Df	=	178
	Total sample size	=	179
	Actual power	=	0.8012286