Motor Evoked Potentials From the Pelvic Floor

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Aims: Proper function of the lower urinary tract depends on the integrity of the central and peripheral nervous pathways on multiple levels, and the complexity of this system leaves it susceptible to even minor lesions. While dysfunction of the lower urinary tract is prevalent amongst patients with nervous system disease, e.g., multiple sclerosis (MS), most women with lower urinary tract dysfunction (LUTD) have no overt neurological cause. Refined neuro-diagnostic approaches are needed to reveal neurogenicity in these patients. A potential method is transcranial magnetic stimulation (TMS), which is used routinely to test the motor innervation of limb muscles, but also can be applied to test pelvic floor efferents. To resolve the lack of methodological clarity and the need for normative values for the use of pelvic floor motor evoked potentials (MEPs), 30 healthy women and 16 women with MS were studied. Methods: The healthy women underwent MEP studies with various stimulus and recording modalities, and, to test reproducibility, 18 of them were retested at a separate session. The women with MS underwent MEP testing as well as urodynamic studies. Results: From the methodological studies of healthy women, the use of invasive concentric needle electrodes was found to be superior to surface electrodes. When applying magnetic stimuli over the sacral region, various methodological problems were encountered. In the healthy women, a large variability of responses was noted, the long-term reproducibility of pelvic floor MEP latencies was poor, and in some cases responses could not be obtained. In the study of women with MS, prolonged central conduction times were found, along with many cases of unevokable responses, and a poor correlation of MEPs to urodynamic findings. The problems of obtaining selective recordings from the inaccessible pelvic floor musculature are discussed, and possible sources of variability in MEPs from the pelvic floor are considered. By relating the findings in the present studies to those of others using different modalities, some reflections are presented on the nature of the neural pathways to the pelvic floor activated by magnetic stimulation. As unevokable responses from the pelvic floor were an occasional finding among the healthy women, it is argued that a pelvic floor non-response in a patient with suspected corticospinal lesion should be interpreted with care, and should not carry the same clinical significance as an absent limb response. Conclusions: The inherent limitations of pelvic floor MEPs are discussed, and it is concluded that while there seems to be only limited clinical value of pelvic floor MEP testing, there might be some interesting scientific perspectives in studies that aim to control and explain the variability of responses. Neurol. Urodynam. 22:620–637, 2003. © 2003 Wiley-Liss, Inc.

INTRODUCTION

Continence and coordinated micturition, as well as defecation, sexual arousal, and orgasm, are dependent on the integrity of the central and peripheral nervous pathways to the sacral region. While lower urinary tract dysfunction (LUTD) is prevalent amongst patients with nervous system diseases, e.g., multiple sclerosis (MS), apoplexy, or spinal cord trauma, most women with LUTD have no overt neurological disease. Defects in the supportive structures of muscle and connective tissue are probably more important in the latter, though in some ‘idiopathic’ cases of LUTD, neurogenicity is suspected. Refined neuro-diagnostic approaches are needed, both in clinical work and in research. Revealing neurogenicity in a patient with LUTD may alter the choice of therapy. In patients with established neurological disease, testing of sacral functions could be used to assess severity and monitor disease progression. In research, investigations of sub-groups of patients can shed light on the pathophysiology of pelvic floor dysfunction.

Abbreviations: CMAP, compound muscle action potential; CMCT, central motor conduction time; EAS, external (striated) anal sphincter; EUS, external (striated) urethral sphincter; LUTD, lower urinary tract dysfunction; MEP, motor evoked potential; MS, multiple sclerosis; PR, puborectalis muscle; TMS, transcutaneous magnetic stimulation.

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Received 31 March 2003; Accepted 18 June 2003
Published online in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/nau.10151
The pelvic floor musculature and sacral nerves are not easily accessible, and thus difficult to test. While most diagnostic principles of clinical neuropathophysiology have been applied to test sacral functions, the methodological literature is sparse, and there is no consensus on their use. Transcranial magnetic stimulation (TMS) is one potential approach in the assessment of the corticospinal pathways. TMS has less discomfort for the patient than electric stimulation. Though mostly used to study the innervation of limb muscles, the method can also be applied to the motor efferents of striated sphincters and associated pelvic floor musculature. In this article, the background and principles of the use of TMS and motor evoked potentials (MEPs) to test sacral motor innervation are described. The literature on pelvic floor MEPs is critically reviewed, and the methodological problems of pelvic floor MEPs are discussed, with specific reference to our own studies.

NEUROPATHOPHYSIOLOGY OF LOWER URINARY TRACT DISORDERS

Neural Circuitry in Storage and Voiding

The neural pathways controlling storage and voiding of urine, function as simple 'on/off' circuits, coordinating the activity of the visceral smooth muscle in the bladder and bladder outlet with the activity of the striated external urethral sphincter [Chai and Steers, 1997; Morrison et al., 2002]. In contrast to other visceral systems, such as the cardiovascular system, the lower urinary tract is subject to voluntary control. However, voluntary control matures late: the child learns to walk before being continent. Proper function of the lower urinary tract is determined by norms of social behavior. Uninhibited voiding is acceptable in the infant; but from early childhood onwards, the bladder should be quiescent, and when voiding is desired, emptying should be instant and complete. Proper continence and voiding operates on both conscious and subconscious levels, by interplay of autonomic and somatic neural pathways. Thus, lower urinary functions are dependent on the integrity of central and peripheral nervous systems on multiple levels, and the complexity of these pathways leaves the central control of continence and voiding susceptible to even minor lesions.

Neurogenic LUTD

The prevalence of LUTD amongst patients with nervous system disease has long been recognized. In his original description from 1817 of 'the shaking palsy', James Parkinson noted as a characteristic of the disease, that 'urine and faeces are passed involuntarily' [Parkinson, 1817]. Studies of head injured soldiers from the wars of the early 20th century promoted an understanding of the cerebral control of voiding [Pfeifer, 1918]; later neurosurgical experiences expanded the knowledge [Andrew and Nathan, 1964]. On disruption of central control of storage and voiding, aberrant reflexes predomi-

nate, causing an uncoordinated function of bladder and bladder outlet, resulting in voiding dysfunction, irritative symptoms, or incontinence.

LUTD is common in women, the majority having no recognized neurological diseases. One study found that 16% of women between 40 and 60 years had experienced a more than weekly occurrence of any type of urinary incontinence; a further proportion of them had lower urinary tract symptoms without incontinence [Moller et al., 2000]. In the urological or gynecological care for patients with LUTD, defects of structural support are often evident, and underlying neurological diseases are usually excluded by coarse clinical routines, such as testing of vulvar sensitivity and sacral cutaneous reflexes. But unrecognized neurological disease is rarely revealed.

However, there is evidence that more cases of LUTD than previously recognized are neurogenic. Griffiths et al. [1994] reported a finding of reduced cortical perfusion and impaired cognitive function in elderly patients with urge urinary incontinence. By careful and extensive neurological workup in 45 cases of idiopathic overactive bladder, Ahlberg et al. [2002] uncovered subclinical neurological disease in 82% of the patients. Fall et al. [1989] provided similar evidence of underlying neurological disease in patients with overactive bladder, by utilizing the ice-water test of urothelial hypersensitivity, and Wyndaele [1993], testing electrosensitivity in the lower urinary tract, revealed abnormal innervation in 29% of patients with no previous evidence of neuropathy. Several studies have described electrophysiological evidence of pudendal nerve damage in stress urinary incontinent women, presumably related to obstetric injury [Anderson, 1984; Snooks and Swash, 1984a; Snooks et al., 1984a, 1985; Barnick and Cardozo, 1993; Aanestad and Flink, 1999; Weidner et al., 2000]. Fidas et al. [1988] used electrophysiological and radiological approaches to reveal neurogenic defects in every other case of female genuine stress incontinence, while Hale et al. [1999], focusing on the striated urethral sphincter, presented both electrophysiological and histological evidence of a neurogenic contribution to genuine stress incontinence. Vereecken and Grisar [1986] described EMG abnormalities of the urethral sphincter consistent with a central nervous system pathology in urge incontinent patients.

Principles of Neuourological Diagnosis

Patterns of symptoms may indicate neurogenicity of LUTD, e.g., by a spontaneous onset of emptying problems, or by concomitant lower extremity symptoms. But the relation of specific lower urinary tract symptoms to neurogenic lesions is weak. Routine clinical examination of a female patient with LUTD may include testing of sensitivity in the perineum, testing of pelvic floor muscle strength, and testing of sacral reflexes. However, the diagnostic validity of these tests is poor; an absent sacral reflex does not imply a neurogenic lesion, and its presence does not exclude a partial lesion [Vodusek, 2000]. Urodynamic tests are routinely used in the investigation of
LUTD, to reproduce symptoms while carrying out measurements that can reveal the causes of these symptoms [Schafer et al., 2002]. The addition of kinesiological EMG-recordings of sphincter activity during voiding has been suggested as a tool in neurourological differential diagnosis [Blavas et al., 1977; Blavas, 1982]. The testing of the bladder cooling reflex by rapid infusion of ice-water during urodynamics is another such test [Geirsson et al., 1993]. But urodynamic tests generally have a poor diagnostic validity [Abrams, 1999].

Most of the routine diagnostic principles of clinical neurophysiology have been applied to test sacral functions, even coining the phrase 'uroneurophysiology' to describe this field of interest [Vodusek et al., 2000]. Fifty years ago needle EMG studies were applied to the striated urethral sphincter [Franksson and Petersén, 1953]. MEPs with recordings from the pelvic floor muscles were first described in 1975 [Jelasic et al., 1975]. Initially, electric scalp and root stimulations were used; after the introduction of magnetic coils for transcranial stimulation in the 1980s, this technique was quickly employed to test pelvic floor efferents [Barker et al., 1985; Opsomer et al., 1989]. In the 1980s, evoked potentials produced by stimulation of pelvic sensory nerves were described, and in 1984, British investigators described the use of transrectal stimulation of the pudendal nerve with recordings from the pelvic floor musculature to test the pudendal nerve terminal motor latency [Kiff and Swash, 1984; Snooks and Swash, 1984b; Snooks et al., 1984a,b]. For most of these tests, there is no consensus on the clinical applicability [Fowler et al., 2002]. Though measurements of pudendal latency are widely used by gynecologists, urologists, and proctologists, the use is controversial. Concentric needle EMG of the striated sphincters is best supported by evidence, and recommended as a first-line investigation of peripheral lesions in selected patient groups (e.g., suspected cauda equina disease) [Podnar and Vodusek, 2001; Fowler et al., 2002].

MEPs

Nerve Conduction and Evoked Potential Testing

The velocity of a signal along a nerve is primarily determined by thickness of axon, quality of myelin sheath, and temperature. Both sensory and motor nerve conduction can be tested by applying non-physiological stimuli, producing self-propagating nerve action potentials in either physiological (orthodromic) or reverse (antidromic) directions. Stimulating and recording electrodes can be applied directly to the nerve in experimental settings, but this is impractical in clinical practice, where surface electrodes are placed at a distance from the nerve.

In motor conduction studies, responses arise from depolarized muscle fibers, and are termed compound muscle action potentials or CMAPs. As responses are triggered by external stimuli, recordings are also called motor evoked potentials or MEPs. CMAPs can be recorded distantly using surface electrodes, or invasively through concentric needle electrodes. The latency is measured as the time from stimulus to the first negative deflection of the CMAP. As the CMAP may be a summation of responses from several motor units with different conductional properties, the latency represents only the quality of the fastest of these. It should also be noted that the latency of the CMAP quantifies not only the neural conduction, but also the transmission across the neuromuscular junction. The amplitude is measured as the voltage of the deflections of the CMAP. In principle, the size of the amplitude should correspond to the number of motor units activated, but in practice this correlation is weak due to many factors, such as recording-electrode configuration and lack of synchronicity of motor units leading to phase cancellation.

TMS

Initially, high-voltage electrical stimulators were used for transcranial stimulation of the motor cortex, but scalp pain and discomfort limited its clinical applicability [Merton and Morton, 1980]. Barker et al. [1985] described the use of a magnetic coil to stimulate the human motor cortex with only minor discomfort. TMS made clinical studies of central motor conduction possible on a wide scale [Rossini and Rossi, 1998]. TMS is based on Faraday’s principle of induction. A short and large current is passed through a metal coil, producing a strong, time-varying magnetic field. The magnetic field passes unattenuated through scalp and skull, inducing an electrical field in the underlying cortical tissue. The induced current runs counter to the inducing current, and various coil configurations can be employed to achieve different shapes of magnetic fields, e.g., to achieve a focal strength.

In clinical studies, latencies of CMAPs produced with electrical stimulation tend to be around 2 msec shorter than similar responses to magnetic stimulation, indicating that the two modes of stimulation excite the motor pathways at different sites. While electrical stimulation is believed to excite the large corticospinal motor neurons directly at the axon hillocks or proximal nodes of Ranvier, the increase in latency seen with magnetic stimulation is believed to be due to synaptic delay in intracortical neural elements. However, with an increased intensity of magnetic stimulation and a magnetic field perpendicular to the neural structures, it is possible to achieve latencies comparable to electrical stimulation, suggesting a direct activation [Cracco and Cracco, 1999].

The technique of TMS can be used for both transcranial stimulation of the motor cortex and stimulation of the ventral spinal roots. By subtracting the latencies of the responses to cortical and spinal stimulation, the central motor conduction time (CMCT) can be calculated (Fig. 1). When CMCT is calculated in this way, it may include a peripheral component of the proximal part of the spinal root, as well as a synaptic delay. If a target muscle is voluntarily contracted concomitantly with cortical stimulation, amplitudes of CMAPs increase and latencies shorten in a phenomenon known as facilitation,
probably reflecting an increased excitability of spinal motor neurons due to voluntary descending input.

**Pelvic Floor MEPs**

Transcutaneous electrical stimulation of spinal roots with recordings from the striated urethral sphincter was applied as early as 1984, by Snooks and Swash [1984b]. Thiry and Deltenre [1989] used transcranial electrical stimulation of the motor cortex to assess the motor pathways controlling the striated urethral sphincter in incontinent patients. However, their study had to be discontinued because of the patients’ poor tolerance of repeated scalp shocks. That same year, Opsomer et al. [1989] reported a more successful use of TMS. They recorded responses with needle electrodes in the bulbocavernous muscle and the external (striated) anal sphincter (EAS) in 15 men. Subsequently, others reported the use of TMS to produce MEPs in the external (striated) urethral sphincter (EUS) of both men and women [Eardley et al., 1990]. MEPs recorded with anal, perineal, or vaginal surface electrodes were also reported [Mathers et al., 1990; Ghezzi et al., 1991; Gunnarsson et al., 1999]. There have been no reports of TMS with selective recordings from the puborectalis muscle (PR).

Several reports have described methodological problems with TMS and pelvic floor recordings. Some centers have reported problems with stimulus artifacts from high-output sacral stimulation [Eardley et al., 1990; Jost and Schimrigk, 1994a; Maccabee et al., 1996]. Ghezzi et al. [1991] found that MEP waveforms were barely perceptible when TMS was applied over the upper lumbar area. Eardley et al. [1991] reported that responses from the striated urethral sphincter were only obtainable in a few patients with MS.

Most TMS studies on anogenital motor efferents have targeted the EAS or bulbocavernous [Opsomer et al., 1989; Dressler et al., 1990; Ghezzi et al., 1991; Herdmann et al., 1991; Bemelmans et al., 1992; Brodak et al., 1993; Del Carro et al., 1993; Jost and Schimrigk, 1994a; Loening-Baucke et al., 1994; Pelliccioni et al., 1997; Hamdy et al., 1998; Jennum et al., 2001]. Only some of them reported control data, and populations were small (from 6 to 12 participants). Reported mean latencies to cortical stimulation of non-facilitated responses from the EAS range from 25.1 msec [Loening-Baucke et al., 1994] to 30.0 msec [Thiry and Deltenre, 1989]; facilitated latencies range from 19.4 msec [Jost and Schimrigk, 1994b] to 29.0 msec [Del Carro et al., 1993]. The only published study of latencies to the EUS has non-facilitated responses at 29.0 msec and facilitated at 26.4 msec [Eardley et al., 1990]. In the literature, mean values of anogenital sacral latencies in healthy subjects range from 2.5 to 6.1 msec [Ghezzi et al., 1991, 1992; Brodak et al., 1993; Jost and Schimrigk, 1994a,b; Pelliccioni et al., 1997; Hamdy et al., 1998; Jennum et al., 2001]. The published studies report varying levels of stimulation, anywhere from ‘L1’ to ‘S2–S3.’ In a careful study, Maccabee et al. [1996] reported both proximal and distal ‘hot-spots’ for spinal stimulation, and described the calculation of segmental conduction times of the cauda equina. Their study comprised only very few participants, and there have been no reports replicating their findings.

The literature is sparse on reports of the relationship between abnormalities of pelvic floor MEPs and clinical disease. Eardley et al. [1991] used TMS to investigate a group of 10 patients with MS and lower urinary tract disorders, with recordings through needle electrodes in the EUS. While they report abnormal motor conduction in 82% of the patients studied, they only obtained responses in five of ten patients, and in three of these five cases responses could only be detected with concomitant voluntary contraction of the sphincter. In a
To assess the clinical value in well-defined patient groups;

- To assess the long-term test-retest reproducibility;

- To present normative data for cortical and spinal latencies of pelvic floor MEPs to the motor pathways to the pelvic floor musculature, with subsequent application of a tailored investigation program to selected patient groups. The Regional Scientific Ethical Committee approved the protocol, and we obtained informed consent from all participants. All investigations were carried out by me in the period May 2000 to January 2002 at the Department of Obstetrics and Gynecology of the Glostrup County Hospital in Copenhagen, Denmark.

Thirty female volunteers without symptoms or signs of nervous system or lower urinary tract disorders were investigated, to determine stimulus and recording parameters and to establish reference values [Appendix A: I, II] (Table I). We recruited the women through community advertising because we wanted healthy women, not patients with other conditions. Conversely, we did not want a super-normal reference group, so we enrolled only women over 40, and allowed for parity, hysterectomy, and menopause. Eighteen of these healthy women later volunteered to undergo re-testing of pelvic floor MEPs to assess the test-retest reliability [Appendix A: III].

A further 16 women were recruited amongst the patients with MS attending a large university clinic [Appendix A: IV] (Table II). All patients had relapsing-remitting MS, received β-interferon, and had clinical definite disease according to the Poser criteria [Poser et al., 1983]. None of the patients had clinical signs of peripheral neuropathies.

We used an adapted and validated Danish-language version of the Bristol Female Lower Urinary Tract Symptoms questionnaire [Bernstein et al., 1996]. Patients were scored as

### Materials and Methods

### Aims

Our studies of pelvic floor MEPs in women had the following aims:

- To validate the use of various electrodes in TMS-studies of the pelvic floor musculature;
- To determine the optimal stimulus and recording parameters;
- To present normative data for cortical and spinal latencies of the motor pathways to the pelvic floor musculature, with comparative data from limb muscles;
- To assess the long-term test-retest reproducibility;
- To assess the clinical value in well-defined patient groups (i.e., MS), by comparing pelvic floor MEPs to limb responses, and to data from urodynamic investigations.

Our initial working hypotheses were:

- TMS with surface recordings from the pelvic floor musculature is an advantageous supplement to commonly used investigations of suspected lesions of the anogenital innervation in women;
- the method has good reproducibility and validity, allowing comparative studies of various corticospinal and peripheral neural lesions.

### METHODOLOGICAL ASPECTS OF PELVIC FLOOR MEPs

When we started our studies, TMS with recordings from striated limb muscles had become a routine investigation in clinical neurophysiology to demonstrate the integrity of the corticospinal motor pathways, but its role in the study of pelvic floor innervation was unresolved due to methodological problems and a lack of normative data. Specifically, there was controversy regarding the use of surface or needle electrodes, and questions regarding the control of stimulus artifacts. Furthermore, there was a need for reference values based on larger populations of healthy women, and targeting the EUS and the PR.

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### Materials and Methods

A protocol was developed for this prospective study, detailing the investigations to be carried out on both healthy women and patient groups. A step-wise approach was taken, where stimulus and recording parameters and reference values were determined first, on healthy women in a comprehensive setup, with subsequent application of a tailored investigation program to selected patient groups. The Regional Scientific Ethical Committee approved the protocol, and we obtained informed consent from all participants. All investigations were carried out by me in the period May 2000 to January 2002 at the Department of Obstetrics and Gynecology of the Glostrup County Hospital in Copenhagen, Denmark.

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### TABLE I. Details of the 30 Healthy Women

| Age (years) | 52 (range: 39–72) |
| Parity      | 1.7 (range: 0–3)  |
| Height (cm) | 166 (range: 151–183) |
| BMI         | 25 (range: 17–35)  |
| Postmenopausal | 16               |
| Hysterectomized | 5                |
| Hormone replacement therapy | 8               |
symptomatic if they had any lower urinary complaint more often than weekly [Moller et al., 2000]. In the control group of healthy women, symptomatic women were excluded. As urodynamic abnormalities have been described in patients with MS without lower urinary complaints [Bemelmans et al., 1991], we performed urodynamics on all patients to reveal subclinical LUTD. Medium-fill 37°C saline water cystometry with pressure-flow micturition studies were performed with patients in a sitting position. Kinesiological EMGs were recorded through hook-wire electrodes in the EUS. Urodynamic procedures and definitions conform to the standards recommended by the International Continence Society [Abrams et al., 1988].

In the investigations of the healthy women, three different electrodes were tested: a vaginal sponge with two surface-mounted electrodes, with the sponge placed in the vagina vis-à-vis the mid-urethra; an intraurethral ring-electrode mounted on a Foley catheter; and a concentric needle electrode inserted in the EUS and in the right PR by transvaginal routes. Correct placement of the needle electrodes was confirmed by the audio-visual output of the spontaneous EMG signal. Based on the initial experiences with surface electrodes, we only used concentric needle electrodes in the reproducibility studies and in the patients with MS. MEPs were recorded with standard EMG equipment and conventional settings.

Supramaximal magnetic stimuli were delivered with a round coil as monophasic, single pulses. Stimulations were applied at three different sites: (a) over the vertex corresponding to the primary motor center in the precentral gyrus, (b) over the upper lumbar spine corresponding to the exit of the sacral roots from the conus medullaris, and (c) dorso-laterally over the right sacrum corresponding to the exit of the sacral nerves from the sacral bone. For cortical stimulation, we recorded MEPs in each of two conditions: with the target muscle relaxed and with moderate to maximum contraction (facilitation). The ability to voluntarily contract the pelvic floor muscles was assessed by digital palpation.

Normality was confirmed with the Kolmogorov–Smirnov test. The success-rates of the different electrodes were calculated as the ratio between acceptable curves and expected responses. A two-sided analysis of variance was used to test the effect of electrode type on recorded latencies. To compare electrodes and to assess reproducibility we used difference versus means plots with calculations of limits of agreement [Bland and Altman, 1986]. Pearson’s chi-square test with Yates’ continuity correction was used to test for equality of success rates of different electrodes. In the analysis of reference values, Students’ t-test for paired data was used to assess the effect of facilitation, and stepwise multiple regression analysis was performed to test for the effect of other variables. A two-tailed t-test was used to compare patients with healthy women. For all tests a value of $P < 0.05$ was regarded as significant.

### Results

In the initial studies, we saw that recordings from the PR had a better signal-to-noise relationship than recordings from the EUS [Appendix A: I] (Fig. 2). Recordings through a needle electrode were superior to surface recordings, as were facilitated responses versus non-facilitated responses (Fig. 3). The latencies of MEPs from the EUS and PR were similar. In some patients, only facilitated responses were observed, and in

| Table II. Details of the 16 Women With Multiple Sclerosis (MS) |
|--------------------|------------------|
| Age (years)        | 43 (range: 31–56) |
| Disease duration (years) | 6.6 (range: 1.2–15.6) |
| Parity             | 1.6 (range: 0–3)  |
| Height (cm)        | 168 (range: 159–178) |
| BMI                | 24 (range: 18–35)  |
| Postmenopausal     | 8                 |
| Hysterectomized    | 1                 |
| Hormone replacement therapy | 7              |
others, responses were discarded due to a poor signal-to-noise relationship or artifacts. We experienced only minor difficulties in using the concentric needle electrodes in the genital area, and the women reported only slight discomfort from the examinations. As the needle electrodes also had better success-rates, we chose them for further studies.

When determining the reference values, we found a statistical significant shortening of latencies (facilitation) of responses to cortical stimulation with concomitant voluntary contraction of the pelvic floor [Appendix A: II] (Fig. 2; Table III). It should be noted that the limb responses were also facilitated with pelvic floor contraction, even though the target muscle itself was relaxed. In some participants, despite maximal output of the stimulator, we could only record cortical MEPs with facilitation. We had the best results with stimulations over the left hemisphere with a counter-clockwise coil current.

It was difficult to elicit responses to lumbar stimulation. Maximal output of the stimulator was often required, and the curves were poor. In some cases we saw contamination of lumbar MEPs with sacral signals (Fig. 4). Carefully repositioning the coil and decreasing the output of the stimulator could often overcome this. The best spot to stimulate was over the L₁–L₂ region, slightly off-center and with a counter-clockwise coil current.

On sacral stimulation, lower outputs were used, typically 30–40%. Initially, we had problems in identifying the take-off of the MEPs because of large stimulus artifacts (Fig. 5). We tried several different remedies for this problem, including placing the ground electrode intra-vaginally (with no noticeable improvement). We also tried using a small, “focal” figure-of-eight coil without resolving the problem. Finally, we found that careful attention to the following factors could avoid the problem: (1) a large ground electrode on the proximal right thigh; (2) keeping the patient and the couch dry; (3) keeping all electrode cables in a direction away from the magnetic field; and (4) carefully adjusting stimulus intensity and coil

![Fig. 3. Non-facilitated responses to cortical TMS in a 65-year-old healthy woman. Concomitant responses were recorded with a concentric needle electrode in the EUS (a) and PR (d), with a vaginal sponge electrode (b) and a Foley-mounted intra-urethral electrode (c).](image)

![Fig. 4. MEPs recorded by concentric needle in the EUS of a 51-year-old healthy woman after lumbar (a) and sacral (b) stimulation. Some responses to high-output lumbar stimulation (c) were contaminated by sacral responses.](image)

<table>
<thead>
<tr>
<th>Electrode type</th>
<th>Non-facilitated responses (msec)</th>
<th>Facilitated responses (msec)</th>
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<tr>
<td></td>
<td>Means (95% CI)</td>
<td>Means (95% CI)</td>
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<tr>
<td>EUS concentric needle</td>
<td>20.3 (19.6–21.0)</td>
<td>17.8 (17.1–18.4)</td>
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<tr>
<td>PR concentric needle</td>
<td>20.3 (14.7–21.0)</td>
<td>18.1 (17.4–18.9)</td>
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<td>Urethral ring electrode</td>
<td>20.3 (19.8–20.8)</td>
<td>17.8 (17.1–18.6)</td>
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<tr>
<td>Vaginal sponge</td>
<td>20.7 (20.1–21.3)</td>
<td>18.6 (17.8–19.4)</td>
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position. We found the best spot to stimulate was over the right side of the sacrum (2nd to 3rd sacral foramen) with a clockwise coil current.

Eighteen of the healthy women were re-tested after a mean of 39 weeks (range: 24–47) [Appendix A: III]. The means of differences between latencies in the two trials were not statistically significant from zero, despite large variations in recorded amplitudes (Fig. 6; Table IV). The means versus differences plots had no skewness, indicating that biases were not related to the magnitudes of latencies (Fig. 7). However, there was large intra-individual test–retest variability. This poor reproducibility seemed to be common for all tested pelvic floor muscles and modalities, though, as the limits of agreement are smaller, facilitated responses are slightly more reliable.

In the study of women with MS, we found prolonged corticosacral CMCTs compared to reference values (Table V). But in many cases, especially when recording from the EUS, we did not obtain responses from the pelvic floor muscles (Fig. 8). Consequently, CMCTs could only be calculated from EUS responses in every fourth patient, and this variable was therefore excluded from further analyses. Sixty-three percent of the patients complained of frequency-urgency, 56% had voiding difficulties, and 31% were incontinent. Urodynamic studies were abnormal in 82% of symptomatic cases, and in none of the asymptomatic cases. There was no correlation between neurophysiological and urodynamic abnormalities.

**DISCUSSION**

While we managed to achieve the aims and objectives of the present study, our initial working hypotheses were refuted early in the process. The use of patient-friendly surface recordings did not appear to be a viable alternative to more invasive methods, and the validity and reliability of the method seemed poor. Consequently, we desisted from doing comparative studies of further patient groups, e.g., women with stress urinary incontinence or idiopathic overactive bladder. However, our studies have revealed some original findings, and we believe the work has contributed to a clarification of the problems of pelvic floor evoked potential testing.
Selectivity of Pelvic Floor MEPs

TMS is non-selective. On both cortical and spinal stimulation, multiple neural elements are stimulated, resulting in concomitant bioelectric activity in adjacent muscle groups. The selectivity of the method, therefore, depends on the quality of the recording of responses. Inaccessibility of the target musculature constitutes a specific problem in pelvic floor MEP testing. The EUS in women is a small striated muscle, and decreases in size with age [Perucchini et al., 2002]. Signals recorded from the EUS with surface electrodes could easily be contaminated by volume conduction from concomitant activity in larger, surrounding muscles, e.g., PR or gluteals.

We found similar latencies of MEPs from the EUS and PR. This confounded data analysis, as we had hoped to test PR as a possible contaminator of surface electrode recordings from the EUS through a larger discrepancy in the conduction in the motor pathways of these two muscles. In women, the EUS and the PR are intimately related. It has been conclusively shown, however, that the EUS is anatomically discontinuous with the surrounding pelvic floor muscle [Gosling et al., 1981]. The peripheral motor innervations of the two muscles are also distinct: the EUS is innervated by the pudendal nerve, while the PR seems to be innervated only by branches directly from the sacral plexus [Tanagho et al., 1982; Barber et al., 2002]. However, the physical distance and other properties of neural elements might be similar, which could explain our findings of similar conduction. While this might not be surprising in healthy women with intact pathways, similar findings should not be expected in patients with neurological

<table>
<thead>
<tr>
<th>Striated urethral sphincter</th>
<th>1st test (msec)</th>
<th>2nd test (msec)</th>
<th>Mean (95% CI)</th>
<th>Bias</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR contracted</td>
<td>18.2 (17.4—19.0)</td>
<td>18.9 (17.9—19.8)</td>
<td>0.4</td>
<td>±1.3—2.1</td>
<td></td>
</tr>
<tr>
<td>PR relaxed</td>
<td>20.6 (19.5—21.8)</td>
<td>20.9 (19.8—22.1)</td>
<td>0.3</td>
<td>±1.7—2.3</td>
<td></td>
</tr>
<tr>
<td>Sacral stimulus</td>
<td>4.3 (3.9—4.6)</td>
<td>4.4 (4.0—4.7)</td>
<td>0.3</td>
<td>±1.5—2.0</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical stimulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR contracted</td>
<td>18.4 (17.4—19.3)</td>
<td>18.5 (17.8—19.2)</td>
<td>0.1</td>
<td>±2.0—2.2</td>
<td></td>
</tr>
<tr>
<td>PR relaxed</td>
<td>20.7 (19.7—21.7)</td>
<td>20.0 (19.3—20.6)</td>
<td>0.6</td>
<td>±3.8—2.5</td>
<td></td>
</tr>
<tr>
<td>Sacral stimulus</td>
<td>4.1 (3.7—4.6)</td>
<td>4.3 (3.8—4.8)</td>
<td>0.1</td>
<td>±1.8—2.1</td>
<td></td>
</tr>
<tr>
<td>Abductor hallucis muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical stimulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR contracted</td>
<td>39.8 (37.8—41.8)</td>
<td>39.4 (37.6—41.2)</td>
<td>0.7</td>
<td>±2.5—1.1</td>
<td></td>
</tr>
<tr>
<td>PR relaxed</td>
<td>41.0 (39.2—42.7)</td>
<td>41.4 (39.5—43.3)</td>
<td>0.8</td>
<td>±3.1—4.8</td>
<td></td>
</tr>
<tr>
<td>Sacral stimulus</td>
<td>24.7 (23.3—26.2)</td>
<td>24.8 (23.1—26.5)</td>
<td>0.01</td>
<td>±6.6—6.6</td>
<td></td>
</tr>
</tbody>
</table>

All means of differences between 1st and 2nd measurement were not statistically different from zero.
or lower urinary tract disorders: a functional dissociation of the urethral and anal branches of the pudendal nerve has been shown in several studies of patients with LUTD disease [Vereecken and Verduyn, 1970; Doyle et al., 1975; Sundin and Petersen, 1975; Blaivas et al., 1977, 1979; Nordling and Meyho¡, 1979; Perkash, 1980; Snooks and Swash, 1985a]. Therefore, if peripheral neuropathy is suspected, differential testing of target muscles should be done. If the patency of the central pathways were in question, it would probably be enough to resort to testing the most accessible muscle with the best responses, i.e., the anal sphincter.

Another possible explanation of our finding is that our recordings from both the EUS and from the PR are contaminants from a third, unrecognized source, e.g., the gluteals. Vodusek and Zidar [1988] compared surface and needle recordings from the bulbocavernosus or the anal sphincter and the gluteus medius muscle. Applying electrical stimuli over the lumbar spine, they found that simultaneous recordings from perineal muscles consistently showed longer latencies for responses obtained with needles, as compared to surface electrodes, and that individual surface-recorded perineal MEPs closely resembled gluteal responses. Like them, we used simultaneous recordings through separate electrodes. Jost et al. [1994] argued in favor of surface electrodes for recording perineal MEPs, but we believe their conclusion is weakened by their comparison of results from two different patient groups. In an early study, Snooks and Swash [1984b] validated the urethral ring electrode by comparison with concentric needle electrode responses, but we believe their conclusion is weakened by the same reasons as ours: they used healthy women.

Sources of Variability

When looking at our data, and those of other studies, the large variability of pelvic floor MEPs is striking. This variability is reflected by both the broad confidence intervals of the reference values, and the wide limits of agreement in the comparison of electrodes supposedly measuring responses from the same muscle. However, the most striking finding is the large test–retest variability in the reproducibility study. While there were no statistical differences between mean latencies of the two trials, which could indicate systematic effects of time or other variables that might differ between trials for all participants, the differences versus means plots revealed wide limits of agreements. Limits of agreement can easily be translated into clinical relevance. For example, for PR responses to sacral stimulation (Fig. 7) the interpretation would be: ‘in a given patient the 2nd trial would be expected to reveal a response anywhere from 1.8 msec lower to 2.1 msec higher than the result of the 1st trial.’ Thus the method is unreliable, given the fact that the mean latency is in the neighborhood of 4 msec!

The large variability is also reflected in the discrepancies of the findings of the different published studies of pelvic MEPs in healthy controls (Tables VI and VII). The variability applies to MEPs produced by both cortical and spinal stimulations. Factors such as age, sex, and height should be considered when comparing results of groups. We found an effect of height on latencies; our data was not suited to an assessment of the effect of age or sex. Age and sex have been shown by others to affect results of conduction studies of limb innervation [Tobimatsu et al., 1998]. Interestingly, shorter latencies have been observed in women, and this effect of female sex seems to be independent of height. But there are several other possible sources of variability.

The central motor control of the lower urinary tract is a complex system, involving at least one center in the pons beside Barrington’s nucleus, as well as other cerebral centers

### TABLE V. Central Motor Conduction Times (CMCTs) in Patients With MS

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Non-facilitated (msec)</th>
<th>Facilitated (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means (95% CI)</td>
<td>Means (95% CI)</td>
</tr>
<tr>
<td>Puborectalis</td>
<td>19.3 (14.2–24.4)</td>
<td>18.4 (13.3–23.5)</td>
</tr>
<tr>
<td>Abductor hallucis</td>
<td>25.8 (20.6–30.9)</td>
<td>23.1 (16.9–29.2)</td>
</tr>
</tbody>
</table>

The central conduction times in the MS patients were delayed compared to findings in normal healthy female controls. All differences were statistically significant ($P < 0.01$).
[Blok et al., 1997a]. The corticospinal pathways in this system are probably indirect, and their activity is modulated by several sources. Fluctuations in motoneuronal excitability are bound to affect artificially induced measurements of conduction in these systems, due to poorly controlled delays in synaptic and neuromuscular transmission. This variability in excitability is exemplified by the effect on measurements of the state of voluntarily induced contraction of the target muscle (or adjacent muscles), i.e., facilitation. There is a correlation between the increase in voluntary contraction of the target muscle and the reduction in latency, until a certain level of around 10–15% of maximal contraction [Ravnborg, 1996]. It could be assumed that it would be sufficient, as we did in our studies, to instruct patients to deliver a moderate to maximum contraction of the pelvic floor. Properly facilitated measurements should thus be expected to exhibit less variability.

### TABLE VI. Studies of Pelvic Floor MEPs Produced by Cortical Magnetic Stimulation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Target muscle</th>
<th>Electrode type</th>
<th>Facilitation</th>
<th>Latencies</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsomer et al. [1989]</td>
<td>15 men</td>
<td>EAS</td>
<td>Needle</td>
<td>Non-facilitated</td>
<td>Mean 30.0</td>
<td>SD 4.4</td>
<td></td>
</tr>
<tr>
<td>Eardley et al. [1990, 1991]</td>
<td>8 men, 3 women; 22–74 years</td>
<td>EUS</td>
<td>Needle</td>
<td>Non-facilitated</td>
<td>Mean 29</td>
<td>SD 2.3</td>
<td></td>
</tr>
<tr>
<td>Dressler et al. [1990]</td>
<td>6 volunteers; 22–68 years</td>
<td>Bulbocavernosus</td>
<td>Needle</td>
<td>Facilitated</td>
<td>Mean 27.3</td>
<td>SD 3.5</td>
<td></td>
</tr>
<tr>
<td>Herdmann et al. [1991]</td>
<td>10 volunteers; 18–51 years</td>
<td>EAS</td>
<td>Surface</td>
<td>Facilitated</td>
<td>Mean 24.5</td>
<td>SD 2.1</td>
<td></td>
</tr>
<tr>
<td>Ghezzi et al. [1991]</td>
<td>17 volunteers</td>
<td>Bulbocavernosus</td>
<td>Surface</td>
<td>Facilitated</td>
<td>Mean 22.9</td>
<td>SD 1.8</td>
<td></td>
</tr>
<tr>
<td>Ghezzi et al. [1992]</td>
<td>14 women; 21–63 years</td>
<td>Perineum</td>
<td>Surface</td>
<td>Facilitated</td>
<td>Mean 20.2</td>
<td>SD 1.3</td>
<td></td>
</tr>
<tr>
<td>Del Carro et al. [1993]</td>
<td>13 women; 44–70 years</td>
<td>EAS</td>
<td>Needle</td>
<td>Facilitated</td>
<td>Mean 29.0</td>
<td>SD 1.8</td>
<td></td>
</tr>
<tr>
<td>Loening-Baucke et al. [1994]</td>
<td>13 men and 14 women</td>
<td>EAS</td>
<td>Surface</td>
<td>Non-facilitated</td>
<td>Mean 25.1</td>
<td>SD 2.9</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>7 men and 11 women; 19–55 years</td>
<td>EAS</td>
<td>Surface</td>
<td>Facilitation?</td>
<td>Mean 19.4</td>
<td>SD 1.7</td>
<td></td>
</tr>
<tr>
<td>Pelliccioni et al. [1997]</td>
<td>7 men and 9 women; 9–80 years</td>
<td>EAS</td>
<td>Needle</td>
<td>Non-facilitated</td>
<td>Mean 26.9</td>
<td>SD 3.0</td>
<td></td>
</tr>
<tr>
<td>Hamdy et al. [1998]</td>
<td>8 men and 3 women; 26–45 years</td>
<td>EAS</td>
<td>Surface</td>
<td>Facilitation?</td>
<td>Mean 20.9</td>
<td>SD 1.1</td>
<td></td>
</tr>
<tr>
<td>Hamdy et al. [1999]</td>
<td>7 men and 1 woman; 23–45 years</td>
<td>EAS</td>
<td>Surface</td>
<td>Facilitation?</td>
<td>Mean 22.1</td>
<td>SD 1.0</td>
<td></td>
</tr>
<tr>
<td>Ghezzi et al. [1991]</td>
<td>12 volunteers; 26–64 years</td>
<td>Vagina</td>
<td>Surface</td>
<td>Facilitated</td>
<td>Mean 20.6</td>
<td>SD 2.0</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>12 men and 11 women; 19–55 years</td>
<td>EAS</td>
<td>Surface</td>
<td>Facilitation?</td>
<td>Mean 24.6</td>
<td>SD 2.3</td>
<td></td>
</tr>
<tr>
<td>[Appendix A: III]</td>
<td>30 women; 39–72 years</td>
<td>EUS</td>
<td>Needle</td>
<td>Non-facilitated</td>
<td>Mean 20.3</td>
<td>SD 1.7</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>30 women; 39–72 years</td>
<td>PR</td>
<td>Surface</td>
<td>Non-facilitated</td>
<td>Mean 17.8</td>
<td>SD 1.8</td>
<td></td>
</tr>
<tr>
<td>Pelliccioni et al. [1997]</td>
<td>30 women; 39–72 years</td>
<td>PR</td>
<td>Surface</td>
<td>Non-facilitated</td>
<td>Mean 20.3</td>
<td>SD 1.6</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>30 women; 39–72 years</td>
<td>PR</td>
<td>Surface</td>
<td>Non-facilitated</td>
<td>Mean 18.1</td>
<td>SD 1.8</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE VII. Studies of Pelvic Floor MEPs Produced by Spinal Magnetic Stimulation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Stimulus site</th>
<th>Target muscle</th>
<th>Electrode type</th>
<th>Latencies</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsomer et al. [1989]</td>
<td>15 men</td>
<td>Right iliac crest</td>
<td>EAS</td>
<td>Needle</td>
<td>Mean 7.9</td>
<td>SD 2.1</td>
<td></td>
</tr>
<tr>
<td>Eardley et al. [1990]</td>
<td>8 men, 3 women; 22–74 years</td>
<td>Lumbosacral column</td>
<td>EUS</td>
<td>Needle</td>
<td>Mean 8.2</td>
<td>SD 1.8</td>
<td></td>
</tr>
<tr>
<td>Herdmann et al. [1993]</td>
<td>10 volunteers; 18–51 years</td>
<td>L4–S3</td>
<td>EAS</td>
<td>Surface</td>
<td>Mean 3.5</td>
<td>SD 0.8</td>
<td></td>
</tr>
<tr>
<td>Ghezzi et al. [1991]</td>
<td>17 volunteers</td>
<td>LI</td>
<td>Bulbocavernosus</td>
<td>Surface</td>
<td>Mean 5.9</td>
<td>SD 0.4</td>
<td></td>
</tr>
<tr>
<td>Ghezzi et al. [1992]</td>
<td>14 women; 21–63 years</td>
<td>LI</td>
<td>Perineum</td>
<td>Surface</td>
<td>Mean 5.1</td>
<td>SD 0.8</td>
<td></td>
</tr>
<tr>
<td>Loening-Baucke et al. [1994]</td>
<td>13 men and 14 women</td>
<td>Right iliac crest</td>
<td>EAS</td>
<td>Surface</td>
<td>Mean 3.7</td>
<td>SD 1</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>7 men and 11 women; 19–55 years</td>
<td>S3</td>
<td>EAS</td>
<td>Surface</td>
<td>Mean 5.6</td>
<td>SD 0.7</td>
<td></td>
</tr>
<tr>
<td>Pelliccioni et al. [1997]</td>
<td>7 men and 9 women; 9–80 years</td>
<td>L3–L4</td>
<td>EAS</td>
<td>Needle</td>
<td>Mean 6.1</td>
<td>SD 1.4</td>
<td></td>
</tr>
<tr>
<td>Hamdy et al. [1998]</td>
<td>8 men and 3 women; 26–45 years</td>
<td>L3–L5</td>
<td>EAS</td>
<td>Surface</td>
<td>Mean 3.2</td>
<td>SD 1.1</td>
<td></td>
</tr>
<tr>
<td>Jost and Schimrigk [1994a,b]</td>
<td>12 volunteers 20–64 years</td>
<td>S2–S4</td>
<td>EAS</td>
<td>Surface</td>
<td>Mean 4.8</td>
<td>SD 1.4</td>
<td></td>
</tr>
<tr>
<td>[Appendix A: III]</td>
<td>30 women; 39–72 years</td>
<td>Upper lumbar spine</td>
<td>EAS</td>
<td>Needle</td>
<td>Mean 8.6</td>
<td>SD 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right sacrum</td>
<td></td>
<td></td>
<td>Mean 4.7</td>
<td>SD 1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper lumbar spine</td>
<td>PR</td>
<td></td>
<td>Mean 8.6</td>
<td>SD 1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right sacrum</td>
<td>PR</td>
<td></td>
<td>Mean 4.1</td>
<td>SD 0.8</td>
<td></td>
</tr>
</tbody>
</table>
However, pelvic floor contraction is difficult to verify and quantify, and the ability to voluntarily contract the pelvic floor on simple instructions is not present in many healthy women [Bump et al., 1991]. We believe these factors explain a large part of the intra- and inter-individual variability observed in studies of pelvic floor MEPs, though other factors should also be considered: fluctuations in the bioactivity of neuroendocrine substances, or preactivation of spinal reflexes (e.g., through variations in bladder filling). These factors are probably not unique to pelvic floor MEP testing, as a substantial inter-individual variability has also been noted on limb responses [Wassermann, 2002].

It is controversial whether facilitation is a cortical or subcortical phenomenon. One explanation is that the preactivation of spinal α-motoneurons results in an upregulation of their excitability by lowering the threshold for depolarization, thus requiring fewer descending volleys (and excitatory postsynaptic potentials) to fire [Cracco and Cracco, 1999]. This would also explain why the greatest effect of facilitation is seen on the amplitude of MEPs, which is thought to reflect the number of axons activated. If facilitation is a spinal phenomenon, it is interesting to consider why this is observed in equal measure when investigating the striated sphincters, which exhibit a constant tone due to perpetual spinal activity. Another possible explanation of the observed variability is the uncertainty as to which neural elements are stimulated. The orientation of the magnetic coil over the scalp has been shown to be important in this respect [Cracco and Cracco, 1999]. With a lateral-sagittally oriented magnetic coil, corticospinal neurons are exited directly, and at lower intensities, than is required for indirect, transsynaptic excitation via cortical interneurons [Amassian et al., 1996]. As electrical stimulation, TMS of the cortex with this coil orientation produces MEPs with latencies several milliseconds shorter than those evoked by a horizontal coil orientation. These latency differences are probably related to differences in the direction of current-flow induced in the brain tissue, where the horizontally oriented coil preferentially excites horizontally oriented cortical elements, e.g., interneurons. Whereas most studies of pelvic MEPs describe a horizontal coil orientation centered over the vertex, we stimulated with a lateral-sagittally oriented coil over the left hemisphere. We did this mostly for pragmatic reasons: this was an easier set-up with the patient in lateral decubitus, and consistently produced the best results; but this factor may in part explain why we found considerably shorter cortical latencies than most other published studies.

The short latencies found in our study raise interesting questions on the nature of the pathways activated by cortical TMS. Presumably, the predominant pathways of central control of storage and micturition are indirect, with a prominent modulatory role of pontine centers. In the dorsal pontine tegmentum, the pontine micturition center (Barrington’s nucleus) is an essential center for the control of micturition, with connections to sacral afferent and parasympathetic centers as well as to the periaqueductal grey, a cortical area involved in the regulation of many visceral and pain pathways [Barrington, 1925; Loewy et al., 1979]. Just lateral to the pontine micturition center is a group of neurons called the ‘L-region’ or the pontine storage center, with connections to EUS motoneurons in Onuf’s nucleus and to sympathetic neurons in the thoraco-lumbar spinal cord. Imaging studies of cerebral blood flow in humans have confirmed increased activity of the pontine micturition center during void, and increased activity of the L-region during withholding of urine [Blok et al., 1997a,b, 1998].

However, the short latencies we found could be the result of an activation of direct corticospinal pathways, without polysynaptic delay. In a study of voluntary control of pelvic floor muscle contraction, Blok et al. [1997a] revealed the supramedial precentral gyrus as responsible, effectively confirming previous findings from animal studies of a cortical pelvic floor motor center. Utilizing imaging of cerebral perfusion, they found that this small center in the most medial portion of the primary motor cortex was activated during ‘on command’ pelvic floor contractions, as opposed to the activation of pontine centers in the subconscious withholding of urine. With the coil placement we used, we believe our responses are the result of a stimulation of this center in the primary motor cortex, with spinal projections bypassing the pontine relay. However, others, placing the coil centrally over the vertex, might inadvertently have activated other indirect pathways, e.g., through stimulation of centers in the frontal lobe that have also been shown to be involved in pelvic floor contraction [Andrew and Nathan, 1964; Blok et al., 1997a].

Regarding spinal stimulation, it is also unresolved at which points the motor efferents are excited. In a careful study of cauda equina conduction, Maccabee et al. [1996] found two fixed low-threshold sites or ‘hot-spots’ along the lumbo-sacral spine. Possible anatomical correlates for these ‘hot-spots’ are: proximally the exit of cauda equina rootlets from the spinal cord; and distally the transit of nerve rootlets through the osseous foramina [Ugawa et al., 1989; Maccabee et al., 1996]. However, they also observed responses with intermediate latency on stimulation between the proximal and distal ‘hot-spots,’ showing that excitation is not restricted to these sites. This implies a need for great precision in choosing stimulus site, and could be one explanation of the poor test–retest variability found in our study.

Coil orientation is important for the configuration and quantification of the waveforms produced on spinal stimulation [Ugawa et al., 1989; Maccabee et al., 1996]. We replicated the findings of Maccabee and co-workers, and also noted the importance of coil orientation, though, as others, we encountered difficulty in obtaining the responses to stimulation of the proximal ‘hot-spot,’ and sometimes found it difficult to separate responses (Fig. 4) [Ghezzi et al., 1991]. Most published studies have been indiscriminate in their choice of spinal stimulation sites, and the published data vary greatly (Table VII). It would be commendable if spinal stimulation sites were carefully chosen, and reported, in future studies.
Inherent problems with the methods for recording and measuring pelvic floor MEPs are probably also a large contributing factor to the variability. The problem of electrode selectivity was discussed above. Favoring surface electrodes, Jost et al. [1994] argued that this electrode-type would pick up signals from a greater number of motor units compared with needle electrodes, ensuring that the signals traveling in the fastest fibers (i.e., with shortest latency) would be captured. If this argument is correct, this could definitely invalidate our reproducibility study. However, we do not agree with them. A concentric needle electrode records activity from muscle fibers within a hemisphere of around 0.5 mm radius [Stalberg et al., 1996]. With muscle fibers in the EUS of only 15–20 \( \mu \)m in diameter, the needle should detect activity of many different fibers on a single insertion. The signal-to-noise relationship constitutes another problem. Both the PR muscle, and especially the EUS, exhibit a constant tone. MEPs from the striated sphincters also lack the silent period observed when evoking responses in limb muscles [Ertekin et al., 1990]. These factors, along with the need for high amplification and the great variability of amplitudes, result in a noisy and unstable baseline of the MEP waveforms, making it difficult to demarcate the take off of the shortest latency.

The proximity of stimulus and recording electrodes on spinal stimulation can introduce several different artifacts that contribute to the great variability of measurements. As others, we noted the problems of stimulus artifacts, and the importance of the placement of the ground electrode in this respect [Eardley et al., 1990; Jost and Schimrigk, 1994a,b; Maccabee et al., 1996]. However, we believe there is also the risk of another, more overlooked, type of artifact in studies of sacral conduction. Figure 9 illustrates serial measurements of sacral MEPs in two different women. In one woman, the two recorded waveforms are substantially different. The second test was made 39 weeks after the first, and the investigator was blinded to the results of the examination. While the waveforms of the second examination were accepted in the clinical situation, on comparison a large discrepancy in measured values was noted. The latency of the second was also unbelievably short. Considering the physical length of nerve fibers from stimulus to target muscle, and allowing for the delay of neuromuscular transmission, individual latencies much shorter than 3.5–4.0 msec are implausible. However, several publications report such short latencies, and produce waveforms—similar to our Figure 9—to show. We believe these waveforms could very well be artifactual, as a result of a direct stimulation of excitable muscular tissue, bypassing the neural pathways. As the waveforms are deceptively similar to CMAPs, this artifact is difficult to control.

**Significance of Unevokable Responses**

A striking finding in our study of pelvic floor MEPs in women with MS is the low success rate. This concurs with the findings in two previously published, smaller studies. Earlier studies at St. Mark’s Hospital in London used electrical scalp stimulation, with recording of responses from the EAS [Snooks and Swash, 1985b; Mathers et al., 1990]. They noted unrecordable responses in 38% of patients with MS and sacral dysfunction, probably reflecting the greater difficulty in recording low-amplitude potentials from relatively small striated muscles. Another British group used TMS to investigate a group of 10 MS patients with LUTD, with recordings...
through needle electrodes in the EUS [Eardley et al., 1991]. They obtained responses in five of ten patients, and in three of these five cases responses could be detected only with concomitant voluntary contraction of the sphincter.

Unevokable lower extremity responses to cortical stimulation is a well-known problem in patients with MS; the proportion of unevokable abductor hallucis responses in our study is similar to other published findings [Ingram et al., 1988; Ravnborg et al., 1992]. Absent responses in patients with MS are probably due to extensive demyelination and subsequent axonal loss, as well as a raised threshold of depolarization. Intracerebral reorganization due to plaques affecting the complex central pathways of lower urinary control might further contribute to the difficulties in obtaining MEP responses from the pelvic floor in patients with MS. The success rate was increased with facilitation in our group of healthy women, where we also verified the ability to contract the pelvic floor in all. However, not all of our patients with MS could voluntarily contract the pelvic floor, a factor that might have affected the lack of increase in success rate with facilitation.

While non-responses in lower limbs are rare in healthy test persons, we found it in up to 16% cases when examining pelvic floor muscles [Appendix A: II]. We assume the occurrence of unevokable pelvic floor responses in healthy women was due primarily to the small volume and deep inferomedial location of the cortical motor center. Since unevokable responses from the pelvic floor are not uncommon in healthy women, we believe a non-response in a patient with suspected corticospinal lesions should be interpreted with care, and should not carry the same clinical significance as an absent limb response.

**Inherent Limitations of MEP Testing**

Evoked potentials are compound responses that express the artificially induced activity of several motor units and their associated components: neurons, axons, synapses, and muscle fibers. The shortest latency of this compound potential reflects the conductional properties of the fastest unit. Conduction is primarily dependent on the quality of the myelin sheath. Thus, latency may be normal, despite a substantial loss of motor units, if the myelin sheaths of the fastest fibers are intact. The size of the amplitude of the compound responses should in principle better reflect a loss of motor units, or their parts, e.g., axonal damage. However, amplitudes are much more variable than latencies; they depend on many biological and technical variables, and have a poor reproducibility. For these reasons, MEP testing is weak in revealing partial lesions, and thus obtaining a normal MEP in a patient helps only to demonstrate the patency, but not the integrity, of a particular pathway.

The difficulties in measuring segmental conductional properties also limit the use of pelvic floor MEPs. Ideally, conductional properties should be expressed as velocities, requiring simultaneous measurements of time and distance. While TMS may exhibit cortical or spinal low-threshold hot spots, the exact neuroanatomical correlation of these hot spots are obscure. In contrast to the routinely used electrical stimulation of peripheral nerves, the precise measurement of nerve distances is impractical with TMS. This problem is exacerbated in pelvic floor MEPs by the intrapelvic location of peripheral branches. The calculation of CMCT is also affected by the prevalence of uninterpretable spinal MEPs. We found these problems to be similar in healthy women and in women with MS. In our study of women with MS, we attempted to remedy the problem by scoring MEPs as abnormal based on cortical latencies, where CMCT could not be calculated. Others have done likewise [Ravnborg et al., 1992]. However, this approach is questionable. Peripheral latencies, also for pelvic floor muscles, are dependent on the height of the patient; this possible bias should be controlled. Furthermore, peripheral neuropathies should be excluded, which in practice would be difficult.

Another inherent problem with cortically evoked pelvic floor MEPs relates to the role of the primary motor cortex in disorders of continence and micturition. While cortical centers, and the corresponding fast corticospinal fibers, are undoubtedly involved in the voluntary withholding of urine, lesions of sub-cortical and spinal neuronal tissue are probably more predominant in patients with neurogenic LUTD, but not elucidated in a cortically targeted diagnostic approach. Finally, an obvious limitation in MEP testing is the fact that only somatic motor pathways are tested. Lesions of autonomic and sensory pathways could play a prominent role in many types of LUTD, but escapes detection by MEP testing.

**Validity of Pelvic Floor MEPs**

The diagnostic value of limb MEPs has been investigated in several studies of patients with MS. Hess and co-workers studied responses from the abductor muscle of the little finger in 62 patients with definite or probable MS according to the Poser criteria, and found abnormal CMCTs in 79% [Poser et al., 1983; Hess et al., 1987]. Ravnborg et al. [1992] found abnormal responses from various limb muscles in 83% of patients with definite or probable MS. Beer et al. [1995] found abnormal limb MEPs in only 68% of 142 patients with definite or probable MS, and saw that MEPs contributed only little to improve diagnosis compared to magnetic resonance imaging, and other routine diagnostic instruments. Mayr et al. [1991] showed a poor diagnostic value of lower, compared to upper, limb responses, with only 61% abnormal abductor hallucis MEPs in 44 patients with MS.

In our study of women with MS, we tried to correlate pelvic floor MEPs to LUTD. We assumed urodynamic abnormalities could represent corticospinal lesions, but found only abnormal PR CMCTs in 66% of patients with abnormal urodynamics. Our results contradict earlier findings of Eardley et al. [1991]. In a small study of patients with MS, they invariably found normal EUS MEPs in patients with normal urodynamics, and abnormal MEPs in patients with abnormal
urodynamics. Their study population differs from ours by including men, and their patients generally had longer disease durations.

Our results indicate a poor diagnostic value of pelvic floor MEPs. We chose to study a population of women with MS where we expected a high incidence of neurogenic LUTD. Despite this, the diagnostic yield was poor. Maybe our initial assumption—that all cases of LUTD in MS patients are neurogenic—was wrong. LUTD is common in women without MS of comparable age, and it would seem logical that some women with MS also have LUTD on a non-neurogenic basis. Our study was thus hampered by the lack of a golden standard for demonstrating lesions of the motor pathways to the lower urinary tract and pelvic floor.

Perspectives

At present, there seems to be only a very limited clinical use of MEPs from the pelvic floor; perhaps the only good indication is the demonstration of patency of a specific neural pathway, where a total lesion needs to be ruled out. In research, the method seems ill suited to investigate the neurogenic hypothesis of idiopathic LUTD in women. To contribute with original results, I believe future research using pelvic floor MEPs should focus on explaining or controlling the variability of responses, instead of carrying out simple comparative studies. The literature has some relevant studies exemplifying alternative approaches.

Gunnarsson et al. [1999] studied a group of women with genuine stress incontinence after completion of pelvic floor training. Those women who had regained continence after training, had fewer non-responses to cortical stimulation, and had higher amplitudes of responses. The authors conclude that the women who benefit from pelvic floor training have a higher degree of corticofugal control of their pelvic floor. The study is a novel use of pelvic floor MEPs, in that it utilizes the variability of responses to firmly place the central nervous system as a target of pelvic floor retraining.

Sato et al. [2001] did a meticulous study of responses to sacral stimuli, recorded through a concentric needle at various levels of the striated anal sphincter system. Interestingly, they demonstrated significant variations in motor latencies depending on the depth of insertion of the needle, with latencies recorded in the subcutaneous part of the sphincter having more than twice the duration of latencies recorded in the deepest part, i.e., the puborectalis. The strength of the study is that it utilizes the variability of responses to show that the anal sphincter system is not electrophysiologically homogenous.

Herdmann et al. [1995] made simultaneous measurements of evoked potentials and similarly evoked contractions in the anal sphincter. By calculating the difference between electrical and mechanical latencies, they presented a quantitative measure of the electromechanical coupling, which might be relevant in the study of myopathies. Welter et al. [2000] essentially did the same, but they utilized the sequential measurements of mechanical responses to cortical and spinal stimulation to measure central conduction, thus overcoming the difficulties of stimulus artifact when recording electrical responses to spinal stimulation. These studies are interesting, in that they utilize technical variations of the method to gain new insight. Perhaps the same approach could be used to control the sources of artifacts to spinal stimulation, i.e., to test the hypothesis of direct muscle activation (see “Significance of Un-evokable Responses”).

Turnbull et al. [1999] used the difficulties of localizing cortical sites of stimulation to map the cortical motor representations of the anorectal musculature. Compared to lower limb responses, the anorectal responses were bilaterally represented on the superomedial cortex, though subtle differences in this bilaterality were apparent between individuals. Hamdy et al. [1999] also studied laterality differences in anal sphincter responses to cortical TMS. By applying conditioning stimuli to the sacral motor nerve branches on each side prior to cortical stimulation, they found evidence of a functional asymmetry in the varying degrees of facilitation obtained.

An exciting approach to control and investigate the variability of intracerebral modulation of motor responses, as expressed in the varying degrees of facilitation on cortical stimulation, is the use of paired cortical magnetic stimuli. MEPs can be modulated by a preceding conditioning pulse delivered with an intensity below the motor threshold [Kujirai et al., 1993]. Apparently through activation of different intracerebral pathways, MEPs are inhibited with interstimulus intervals of 1–4 msec, and facilitated with intervals of 8–12 msec, with no inter-hemispheric asymmetry, and a good reproducibility [Ziemann, 1999; Maeda et al., 2002]. Paired-pulse TMS has been used to study the effects of drugs and diseases on the human brain. Using this approach, Smith et al. [1999, 2002] were the first to give direct electrophysiological evidence of a neuronal effect of ovarian hormones on the human brain. Studying limb muscle responses to paired cortical stimuli in women in different phases of their normal menstrual cycle, they found an excitatory neuronal effect associated with estradiol, and an inhibitory effect associated with progesterone. It would be interesting to use the same approach to study the effect of hormones or pharmacological substances on the cortical control of sacral functions.

CONCLUSIONS

Since its introduction in the late 1980s, several studies of pelvic floor MEPs have attested to the great variability of responses. There is mounting evidence of fundamental methodological difficulties, primarily due to the difficulties of stimulating the small and deeply located cortical motor representations of the pelvic floor musculature, and to the difficulties of selective recordings from the small and inaccessible target muscles. Additionally, the poorly controlled inter- and intra-individual variability, and the limited inherent qualities of evoked potential testing in revealing partial neuronal
ACKNOWLEDGMENTS

This article was accepted as a Ph.D. Thesis by the University of Copenhagen. It was defended on 22 August 2003, with a most qualified review panel, whom I deeply respect. Professors Jørgen Nording, Anders Fuglsang-Frederiksen, and Anders Mattiason.

The studies were done from 2000 to 2002, during my employment as a Research Fellow in the Department of Obstetrics and Gynecology at Glostrup County Hospital, University of Copenhagen, Denmark. I am deeply grateful for the privileged working conditions I had in the department. I am especially grateful to my principal supervisor, Professor Gunnar Lose, for his perpetual enthusiasm and encouragement, for his precise guidance, and for his diligent and thoughtful review of all my writings. The supervision of Dr. Poul Jennum was also invaluable to me; he was a great inspiration in the conception of this project, and he carefully guided my entry into the world of electrophysiology.

I thank all the doctors and nurses of the Department of Obstetrics and Gynecology for their help, and for their patience with my doings. I am also grateful to Professor Martin Lauritzen and his staff at the Department of Clinical Neurophysiology for lending me the equipment to carry out my studies, and to Dr. Jette L. Frederiksen of the Department of Neurology for her cooperation in the study of women with MS.

The principal sponsor of this project was the University of Copenhagen, whose Fund for Clinical Research paid my salary. I received further financial support from The Hospital Research Fund of Greater Copenhagen, Hørslev-Fonden and the Danish Medical Research Council.

REFERENCES


APPENDIX A

This Ph.D. thesis is based on the following articles:


