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The Pontine Micturition Centres

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Objective: To review recent literature on the function of the two postulated pontine regions (the M- and L-regions) concerned with lower urinary tract control.
Material and Methods: The work reviewed is based on stimulation and lesion experiments and post-operative follow-up in the cat, supported by acute chemical stimulation and blocking experiments in the rat and PET functional brain scanning in humans.
Results and Conclusions: The M-region in the cat, homologous to Barrington's micturition centre and to a similar area in humans, is a small region both specific and necessary to voiding, the origin of the final common pathway to bladder and urethra, and the locus of co-ordination of the bladder and the striated sphincter. The L-region in the cat is part of a larger, less specific area that probably serves sphincter control in various circumstances, not exclusively micturition. The homolog of this region in the human or in the rat has not been adequately established.

Key words: urodynamics, brainstem, pontine micturition centre, voiding reflex.

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INTRODUCTION

Normal micturition takes place in two phases. During storage, the bladder (the detrusor muscle) is relaxed and muscles of the urethra and pelvic floor contract tonically. This phase typically lasts about three hours. During emptying, the bladder contracts and the urethral and pelvic floor muscles are relaxed. This phase may only last about 20 seconds. The switching between the two phases appears to be automatic in infants but is normally under learned voluntary control in older children and adults.

It is believed that voluntary control originates in the cerebral cortex, while the switch is operated from the brainstem via neurons that run to the sacral cord segments S2–S3, where they synapse on neurons of the main bladder (pelvic) and urethral (pudendal) nerves. The basic circuit that operates the bladder and urethra thus includes both parasympathetic and somatic components. The co-ordination of these two branches of the nervous system occurs in the brainstem. Sympathetic innervation of the bladder and urethra, originating from the spinal cord segments T11–L1, is believed to modulate rather than determine this basic behaviour.

Retrograde tracing of nervous pathways back from the sacral cord to the brain shows that efferent projections come mainly from two separate bilateral regions in the pons (1). Anterograde tracing (2) shows that a more medial region in the pontine reticular formation (the M-region) projects to the intermediolateral cell group of the sacral cord, which gives rise to the parasympathetic bladder innervation. A more lateral L-region projects to Onuf's nucleus in the sacral cord, which gives rise to the somatic innervation of the urethral and anal striated sphincters (Fig. 1).

The M-region is homologous to a region in the pons identified in various species, which has long been known to be concerned with micturition (3). The L-region is a newer concept (2). Thus there are apparently two regions in the pons that are related to LUT

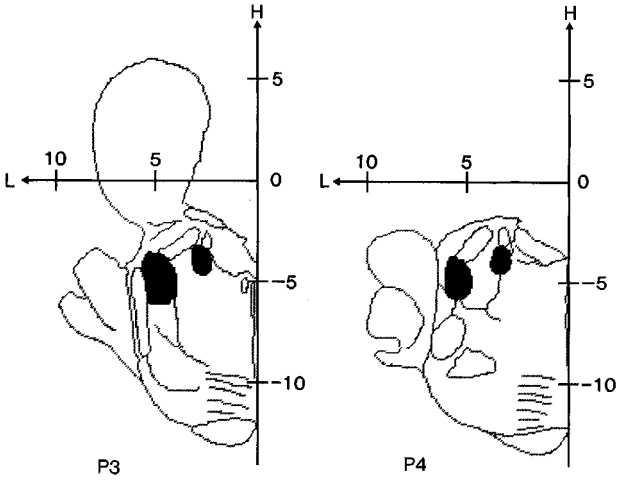

Fig. 1. Location of M- and L-regions in the cat as determined by neuroanatomic track-tracing methods. The M-region is the more medial and the L-region the more lateral of the two regions shown in black. P, H, L = standard stereotaxic co-ordinates (in mm). Reproduced from reference (8).

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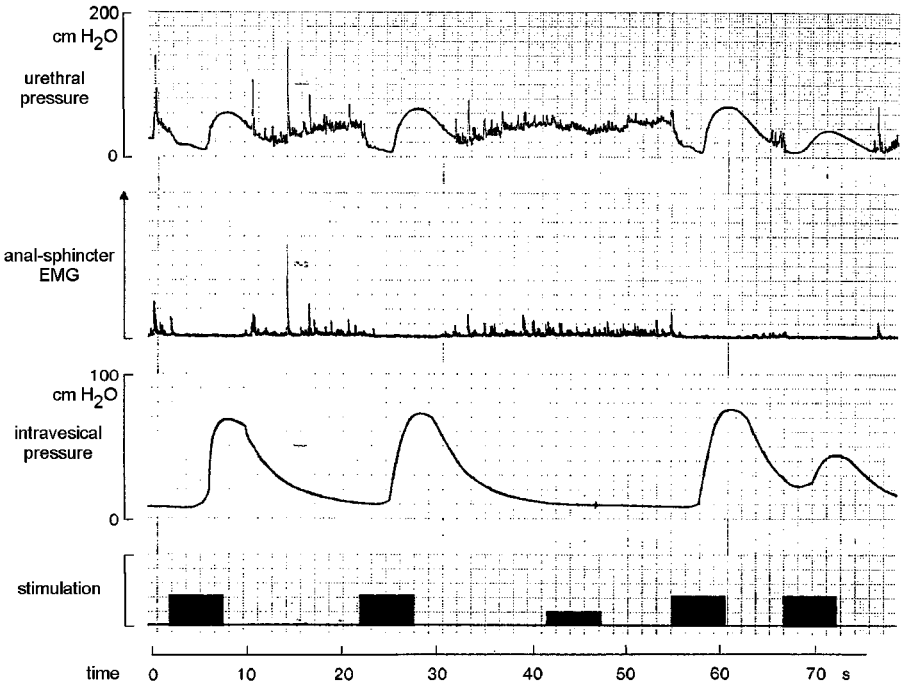

Fig. 2. Effect of electrical stimulation of the M-region in the cat (50–100 μA). On stimulation (black bars, bottom trace), urethral pressure and EMG decrease. After 2–3 s a bladder contraction causes the intravesical pressure to rise; the pressure increase forces open the urethra and is visible there also. Reproduced from reference (8).

function. This review is concerned with recent evidence for them and for what they do. A previous review in this symposium series (4) identified the locus coeruleus alpha, the locus subcoeruleus and the nucleus reticularis pontis oralis as important brainstem micturition centres. The first two of these lie very close to the M-region and L-region respectively and appear functionally to behave similarly, suggesting that perhaps the same structures are involved. No further evidence is presented in this review for a role of the nucleus reticularis pontis oralis in urinary tract control.

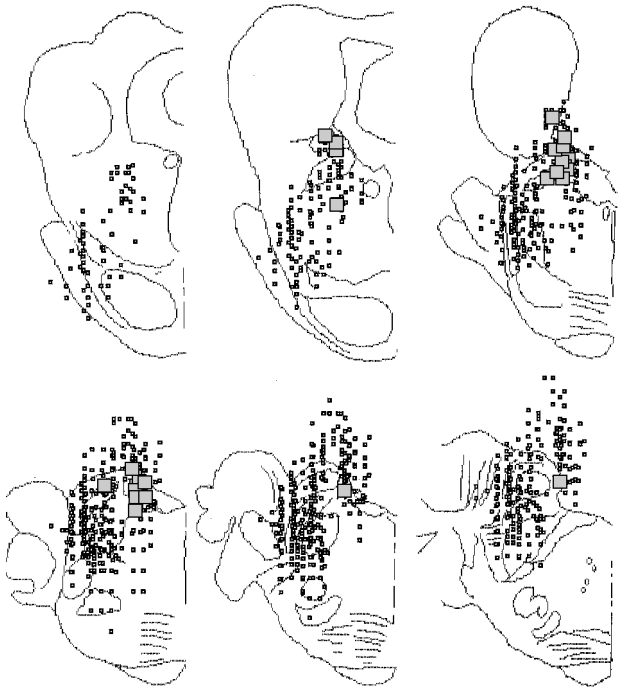

Fig. 3. Locations in which electrical stimulation caused the effect shown in Fig. 2 (large squares) or did not do so (small squares). Diagrams show levels P1 (top left) to P6 (bottom right). Reproduced from reference (8).

MATERIAL AND METHODS

The results reviewed here were obtained by simultaneous electrical stimulation and urodynamic measurement in 34 cats under ketamine anesthesia (5). Stimulation currents were kept as low as possible in an attempt to avoid stimulating fibres of passage. Lesions were made by much larger currents at points where a bladder or urethral response to stimulation was obtained, and the cats were followed with regular urodynamics after recovery. After sacrifice some months later, the locations of the lesions were studied. More recent work is based on functional brain scanning by PET in human volunteers, and observations in rats.

RESULTS

Cat: effects of stimulation

The effect of electrical stimulation in the M-region or pontine micturition centre is shown Fig. 2. The sphincter relaxes, as shown both by EMG and urethral pressure measurement, and—after a short delay—the detrusor contracts. This pattern mimics co-ordinated

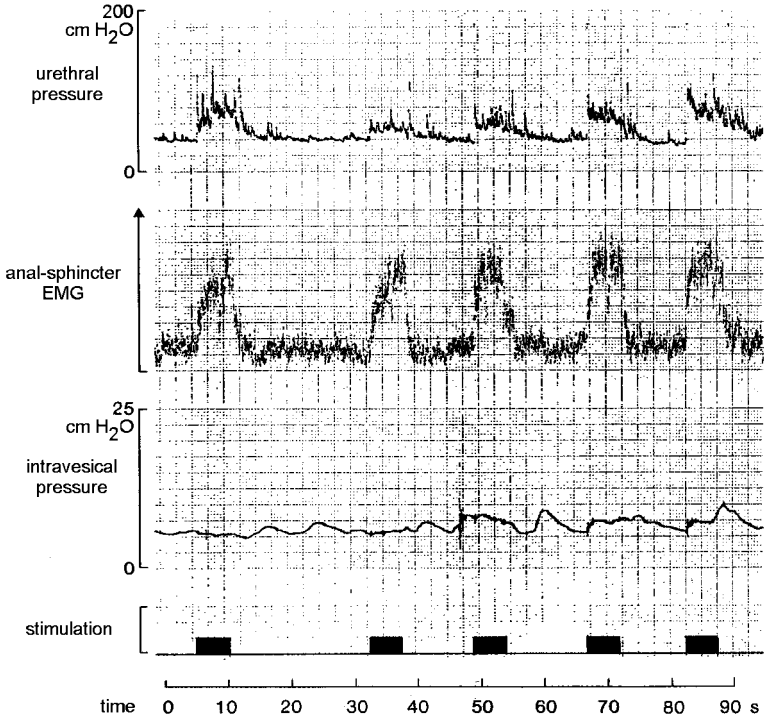

Fig. 4. Expected effect of electrical stimulation of the L-region (50 μA). On stimulation (black bars, bottom trace), urethral pressure and EMG increase. Stimulation does not cause bladder contraction (although occasionally a presumed abdominal contraction occurs, raising the bladder pressure abruptly). In a few cases a small, spontaneous bladder contraction appears to be inhibited by the stimulation. Reproduced from reference (8).

(synergistic) voiding. Fig. 3 shows where in the brain stem this pattern of responses was evoked.

In other parts of the brainstem, stimulation had a different effect: contraction of the urethra with increased pelvic floor (anal sphincter) EMG, together with possibly some inhibition of detrusor contraction (Fig. 4). This pattern, which corresponds to storage rather than emptying, was evoked in the locations shown in Fig. 5.

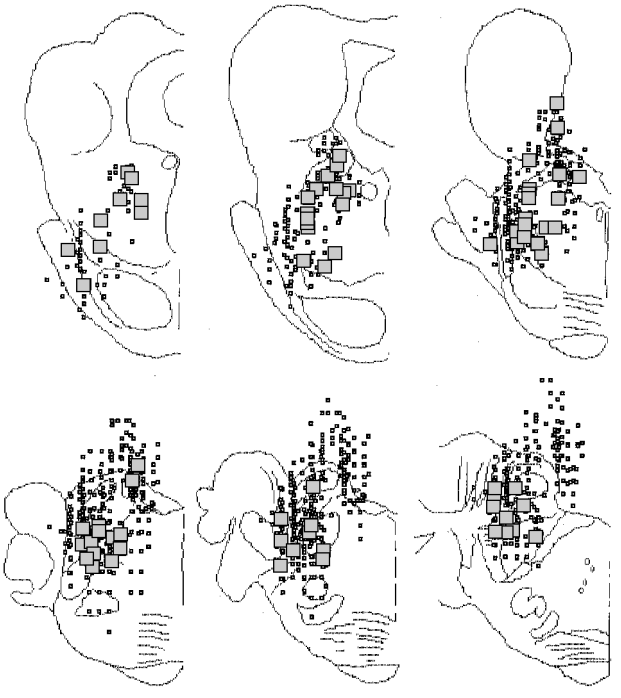

Fig. 5. Locations in which electrical stimulation caused the effect shown in Fig. 4 (large squares) or did not do so (small squares). Reproduced from reference (8).

However, electrical stimulation sometimes had other effects: for example, a combination of increased EMG with decrease of urethral pressure, but without any evoked detrusor contraction. The locations where such mixed sphincter response patterns were evoked are shown in Fig. 6.

Comparison of the three maps (Figs. 3, 5, 6) shows that simulated micturition (urethral relaxation with detrusor contraction) was evoked only by stimulation in or very near the anatomic M-region, whereas the storage pattern (urethral contraction with possible detrusor inhibition) and mixed combinations of sphincter response, without detrusor contraction, were seen over a wide area that included, but was not limited to, the L-region.

Cat: effects of ablation

Predominantly unilateral ablation of either the M- or the L-region had no clear effect on the voiding pattern or the urodynamic findings after recovery. In contrast, the effect of bilateral M-region ablation was dramatic. For example, the cat with the lesions shown in Fig. 7A was in clinical retention for three weeks post-surgery and had to be emptied by expression. Measurement of the volume in the bladder by catheterisation on the 5th

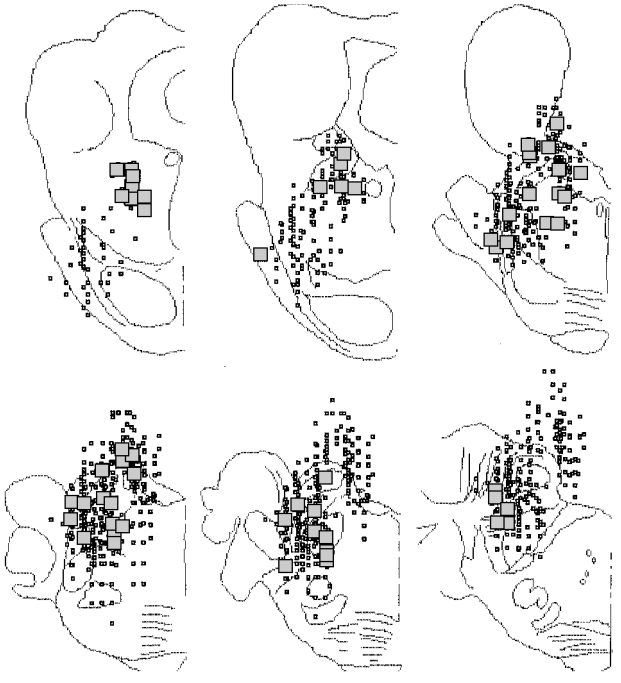

Fig. 6. Locations in which electrical stimulation led to a mixed pattern of EMG increase, together with urethral pressure decrease, without detrusor contraction (large squares). Reproduced from reference (8).

post-operative day gave a value of 180 ml. On urodynamics, a greatly enlarged cystometric capacity (5 times greater than the pre-operative value) was maintained for a month after surgery, and no detrusor contraction at all could be observed during the first two weeks. Thus, bilateral M-region ablation abolished both detrusor contraction and voiding.

Bilateral ablation of the L-region sometimes prevented survival, presumably because of damage to nearby respiratory centres. One cat with bilateral L-region lesions (Fig. 7B) survived and developed clinical incontinence after only three days' retention, leaking continually on the floor of the cage instead of voiding in its tray. The volume in the bladder on the 5th post-operative day was only 12 ml. On urodynamics, there were frequent large-amplitude detrusor contractions, which limited the cystometric capacity to only 10% of the pre-operative value. Thus bilateral L-region ablation caused severe detrusor overactivity and incontinence.

Rat: chemical stimulation and blocking

Chemical stimulation of the homolog of the M-region in the rat (6) has confirmed that it causes co-ordinated voiding, although the pattern of co-ordination of bladder and sphincter activity in rats is different from that in humans. Chemical stimulation revealed no homolog of the L-region. However, the area investigated was not particularly extensive.

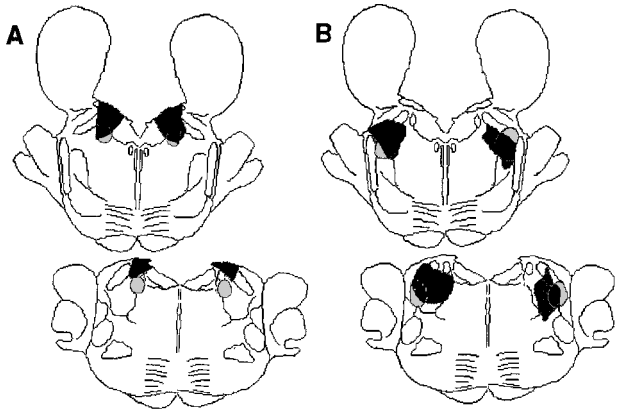

Fig. 7. A: Example of bilateral lesions (shown in black) near M-region (shaded); this cat was in retention for several weeks post-operatively. B: Example of bilateral lesions near L-region; this cat was severely incontinent with pronounced detrusor overactivity post-operatively. Reproduced from reference (8).

Human: functional brain scans during voiding and storage

PET brain scans in human volunteers (7) suggest that the homolog of the M-region becomes active during voiding (Fig. 8, left panel). There is some indication that the right side may be more important than the left. Similar, though more complex, results have been obtained by others (8).

PET scans made during storage by another group (9) show that a region in the pons becomes progressively more active as the bladder is filled, and sensation becomes stronger—as one would expect for a continence centre such as the postulated the L-region. However, the location is more medial and more caudal than that expected for the L-region.

Some subjects are unable to void in the PET scanner when requested and may be presumed to be contracting their sphincter involuntarily, so suppressing voiding. When this occurs, an area in the pons becomes active (7). It has been suggested that this area corresponds to the L-region (Fig. 8, right panel).

Neural efferent and afferent pathways

Ten years ago, it was suggested that the stimulation results in the cat (the large squares in Figs. 3, 5, and 6) might trace out a connecting pathway from the M-region to the L-region, perhaps by stimulation of fibres of passage (5). Later investigations (10, 11) disproved this hypothesis and showed that, in the cat, there is a direct descending pathway from the M-region to the sacral parasympathetic region, which stimulates bladder contraction. Correspondingly, other descending

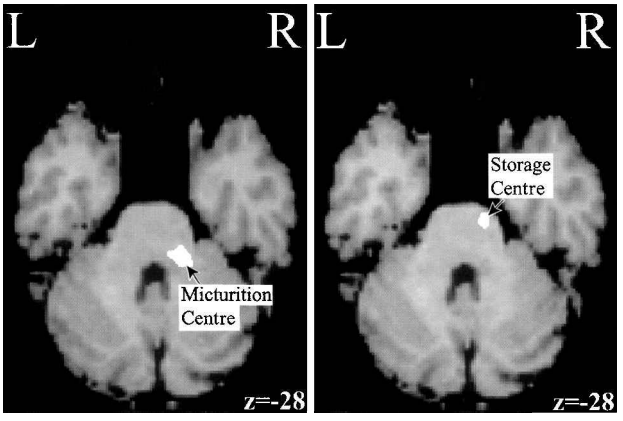

Fig. 8. Left panel: region with significant changes in regional cerebral blood flow during voiding, as shown by PET scans in humans. The region labelled "micturition centre" appears to correspond to the M-region in the cat (see Fig. 1). Right panel: region showing significant changes in regional cerebral blood flow in human volunteers attempting but unable to void while undergoing PET scan. Although this region, labeled "storage centre", may be the homolog of the L-region in the cat, interspecies differences make it difficult to judge whether its location is plausible (compare with Fig. 1). Reproduced from reference (6).

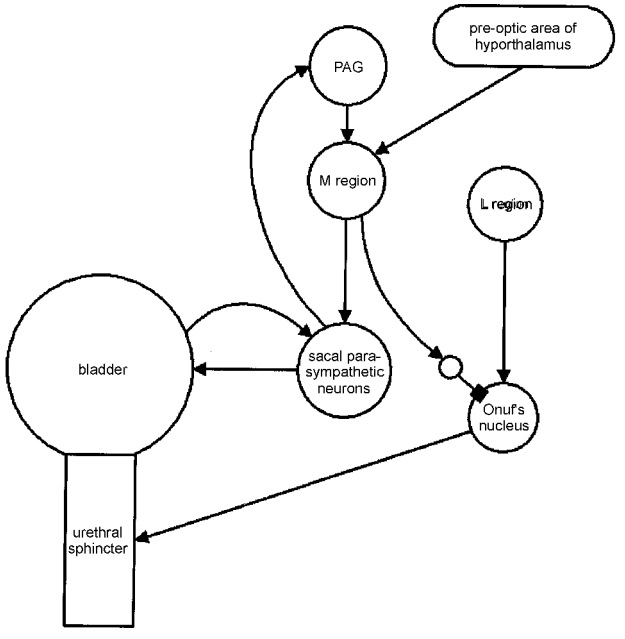

Fig. 9. Schematic organisation of micturition reflex suggested by the work reviewed here. The M-region innervates the nucleus of Onuf via an inhibitory interneuron (shown by ■) in the sacral spinal cord. Other synapses (□) are probably excitatory. Clearly this scheme is incomplete: there is no afferent signal from the urethra, no input to the L-region, and no input from the superior parts of the brain to the periaqueductal grey or the hypothalamus.

fibres synapse on interneurons at the sacral level, which in turn inhibit the outflow from the nucleus of Onuf to the urethral sphincter (Fig. 9). Thus the signals from the pontine M-region ensure the co-ordination of bladder and sphincter that is seen in normal voiding, but do not do so via a connection to the L-region, the role of which remains unclear.

The voiding reflex requires a return pathway from the bladder back to the brain. This afferent pathway appears to follow a similar course to the efferent pathway, with one important exception. In the brainstem it bypasses the M-region and synapses more cranially in the periaqueductal grey matter (PAG) (12). From the PAG there is strong innervation back to the M-region (Fig. 9). Consistent with this anatomical picture, PET scans in human volunteers show that the activity in the PAG increases as the bladder is filled, suggesting a response to input from increasing afferent signals from the bladder (9). The role of the PAG in the voiding reflex, and the fact that it acts via the M-region, have been confirmed in the rat (6): chemical stimulation of the PAG provokes co-ordinated voiding, but voiding is prevented if synapses in the M-region have been blocked prior to stimulation of the PAG.

DISCUSSION

The results presented in this review reveal the neural organisation sketched in Fig. 9. A small, highly specific region of the pontine reticular formation—the M-region—regulates co-ordinated voiding via descending pathways that when activated both stimulate the detrusor and inhibit the urethral striated muscles. Destruction of the M-region on both sides abolishes voiding. The M-region is thus the origin of the final common efferent pathway for voiding. However, it does not receive afferent signals directly from the lower urinary tract, but only via the PAG. It also receives input from the pre-optic area of the hypothalamus (11). In both of these regions, the reflex is presumably subject to modulation associated with various emotional states. Conscious control of voiding, probably arising in the frontal cortex, may also be exerted via pathways from one or both of these areas.

The L-region, in contrast, is part of a larger, more diffuse and less specific area of the pontine reticular formation in which varying sphincter responses—but not detrusor contraction—can be elicited by stimulation. This author's memory of the experiments in which the L-region was stimulated is that there was a good deal of ancillary muscle contraction, like a poorly performed Kegel exercise. Although the place of the L-region in the organisation shown in Fig. 9 is not entirely clear, bilateral destruction probably does lead to marked incontinence associated with detrusor overactivity. Interestingly, recent human data also show that poor sphincter control is associated with worsened urge incontinence (13). If one supposes that the L-region is responsible for organising the response of the

urethral sphincter and the pelvic floor to events such as respiration, sneezing, coughing, vomiting, and sexual activity, as well as threatened incontinence, then one would expect a much less specific, more varied response to stimulation, depending on which particular part of the L-region was stimulated, and involving the sphincter and various ancillary muscles, exactly as is observed. None of these events is usually associated with detrusor contraction, and some may actually inhibit contraction, again as observed. Viewed in this light, the L-region is not so much a continence or storage centre as a pelvic floor/sphincter centre governed by a complex set of connections that remain to be unravelled.

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