Neural control of micturition in humans: a working model

Derek Griffiths

Abstract | Results from functional brain scanning have shown that neural control of the bladder involves many different regions. Yet, many aspects of this complex system can be simplified to a working model in which a few forebrain circuits, acting mainly on the midbrain periaqueductal grey (PAG), advance or delay the triggering of the voiding reflex and generate bladder sensations according to the volume of urine in the bladder, the safety of voiding and the emotional and social propriety of doing so. Understanding these circuits seems to offer a route to treatment of conditions, such as urgency incontinence or overactive bladder, in patients without overt neurological disease. Two of these circuits include, respectively, the medial prefrontal cortex and the parahippocampal complex, as well as the PAG. These circuits belong to a well-known network that is active at rest and deactivated when attention is required. Another circuit, comprising the insula and the midcingulate or dorsal anterior cingulate cortex, is activated by bladder filling and belongs to a salience network that generates sensations such as the desire to void. Behavioural treatments of urgency incontinence lead to changes in brain function that support the working model and suggest the mechanism of this type of treatment.

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Introduction

In the past few decades, a general consensus has been reached that brain activity is organized into a series of networks ('circuits') in which different grey matter regions of the brain (the nodes of the network) are linked together by white matter pathways. In this period, our expanding knowledge of the central control of the lower urinary tract (LUT) has enabled development of a working model based on such a framework (Figure 1), which comprises a few cortical and subcortical circuits that act to control voiding mainly by inhibiting the voiding reflex. Such a model enables testable hypotheses regarding brain function to be suggested and tested; indeed, this model has been repeatedly revised to account, in a simple way, for new knowledge as knowledge has accumulated.[1–6] This process will continue; consequently, the model should be regarded as a plausible but somewhat speculative interpretation of the data, based upon current knowledge.

The working model is based largely on findings from functional brain imaging in humans with no overt neurological pathology, including some whose impaired bladder control illuminates key features of normal control. Descriptions of a few animal studies are included in this Review because they are the only available way to investigate some aspects of function and pathology (Box 1). The knowledge of central control and dysfunction gained in this way might suggest mechanisms of continence or incontinence that enable the development of more effective therapies for patients with LUT dysfunction, although therapy is not the focus of this Review.

Function of the LUT

The function of the LUT is to allow urine to accumulate in the bladder and periodically discharge it through the urethra, an action resembling that of a simple on–off switch.[1,2] This apparent simplicity raises the question why neural control of this system is necessary. To answer this question, remembering what happens when control is impaired by neurological disease is helpful: not only can voiding occur involuntarily, implying incontinence, but a risk of continual failure to empty the bladder also exists, with potentially life-threatening consequences. Even in apparently healthy individuals, impaired control of LUT function is common, although the cause of this impaired control is less obvious. Among middle-aged women, for example, the symptom complex known as overactive bladder (OAB, consisting of urgency and frequency of micturition with or without urgency urinary incontinence [UUI]) is highly prevalent,[7,8] but its cause is not clearly established. Similarly, among elderly people, UUI is one of the most bothersome and common conditions: prevalence is approximately 30–40% among community-dwelling women >70 years of age, rising to approximately 60% in those of a similar age living in nursing homes.[9] Indeed, OAB symptoms are so common in older people that they can be difficult to distinguish from normal aging. In the absence of overt neurological alterations, such conditions are typically described as 'non-neurogenic',

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Key points

- Neural control of the bladder is complex, but many aspects can be accounted for by a simple working model
- In this model, a few forebrain circuits, acting on the midbrain, can advance or delay the triggering of the voiding reflex and generate bladder sensations, such as desire to void
- Understanding these circuits might, in the future, offer a new route to more effective treatments of urgency incontinence or overactive bladder
- This new knowledge might shift clinical attention toward behavioural and/or electrophysiological treatments, or even direct stimulation of the deep brain

but the research reviewed in this article is aimed not only at understanding the normal working of the neural control system but also at identifying abnormal brain functioning that might provide a neuropathological basis of UUI, thus, reclassifying these symptoms as 'neurogenic'.

Returning to the question posed above, the function of neural control of the bladder and urethra is ultimately homeostatic: to maintain continence during urine storage and to enable voiding to completion if, and only if, appropriate. To this end, voiding should occur only if certain criteria are satisfied (Box 2).

Whatever the circumstances, urine storage cannot be maintained indefinitely: the bladder must ultimately be emptied. This process is initiated by the propagation of a series of signals in the brain, whose frequency, intensity and unpleasantness increases as the bladder fills, until the individual is driven to void in a more or less suitable place. The standard names for these sensations, as recorded during urodynamic testing, are first sensation of filling, first desire to void, strong desire to void and urgency.[10] All of these signals help to maintain homeostasis by promoting regular voiding, and the first three are entirely normal. However, urgency (a sudden compelling desire to void during urodynamic testing)[10] is also one of the symptoms of the OAB complex: those who experience urgency might be considered abnormal in terms of their control of bladder function.

The ability to remain continent during urine storage is a defining characteristic of normal LUT function. UUI, the type of incontinence considered here, is associated with involuntary or premature triggering of the voiding reflex, resulting in involuntary bladder contraction (detrusor overactivity)[10] and urethral relaxation.

Innervation from brain to bladder

As shown schematically in the working model (Figure 1), a few neural circuits in the forebrain together with parts of the brainstem seem to form the foundation of the neural control of the LUT. The real brain control network is undoubtedly highly complex,[11] although the convergence of several important pathways on the midbrain periaqueductal grey (PAG) enables some simplification (Figure 1a). The PAG is also the rostral terminus of the voiding reflex (Figure 1b);[12] therefore, it acts as a pivotal region that distributes incoming spinal afferents to many regions of the forebrain, where they generate sensations such as the desire to void or motor output to avert leakage. The PAG receives descending signals from forebrain structures concerned with control of the LUT and other systems;[13] it 'decides' on this basis whether or not the voiding reflex should be triggered.

Thus, the control system can be broken down into two parts: the long-loop, spinobulbospinal voiding reflex (Figure 1b); and the forebrain circuits that modulate this reflex, mostly via the PAG (Figure 1a). As well as the LUT, the PAG controls other activities and systems that are essential to life, such as cardiovascular function, bowel function and, more generally, pain and emotion.[13] Thus, the PAG can coordinate the function of all these organ systems to maintain homeostasis.

This simple picture of the primacy of the PAG, however, is confounded by certain observations. Monosynaptic projections exist, which convey signals from the hypothalamus to the pontine micturition centre (PMC, Figure 1a). These projections are believed to send a 'safe-to-void' or 'unsafe-to-void' signal directly to the PMC, thus, bypassing the PAG.[14] In addition to the parasympathetic input provided by the voiding reflex, the detrusor and the urethral sphincter receive sympathetic innervation that, bypassing the PAG, follows a pathway from the brain to the LUT via sympathetic outflow at the T10–L2 level of the spinal cord (Figure 1b). This innervation is provided through release of noradrenaline onto inhibitory β-adrenergic receptors on the bladder body and excitatory α-adrenergic receptors on the urethral sphincter and bladder neck.[1] Thus, sympathetic activation, should it occur, enhances urine storage and suppresses voiding.

The voiding reflex occurs via innervation of parasympathetic ganglia in the sacral parasympathetic region. Projections from these ganglia then directly innervate the urinary bladder (Figure 1b). When the switch in the PAG is triggered, a small nucleus in the brainstem (the pontine micturition centre, PMC or M-region) is activated, setting off a chain of events that initiate micturition. The voiding reflex also includes an ascending arm, which carries sensory signals generated by receptors in the bladder and urethra, via afferent neurons in the sacral spinal cord,[15] up to the PAG (bypassing the PMC).

Sympathetic control of the LUT operates in parallel with the voiding reflex. In addition, interconnections between nerves supporting ascending and descending signals at the thoracolumbar and sacral levels of the nervous system support sympathetic and parasympathetic spinal reflexes that might help maintain continence.[1,16] Spinal reflexes are important when the volume of urine in the bladder is small, before the first sensation of filling. Once sensations of bladder filling occur, however, the supraspinal mechanism (Figure 1) takes over control of the LUT.

Regulation of micturition

As was shown by Barrington nearly a century ago in the cat,[17,18] the PAG, making use of the voiding reflex, is capable of controlling micturition in a rudimentary way, even without neural input from the forebrain. In this situation, as the bladder fills with urine during

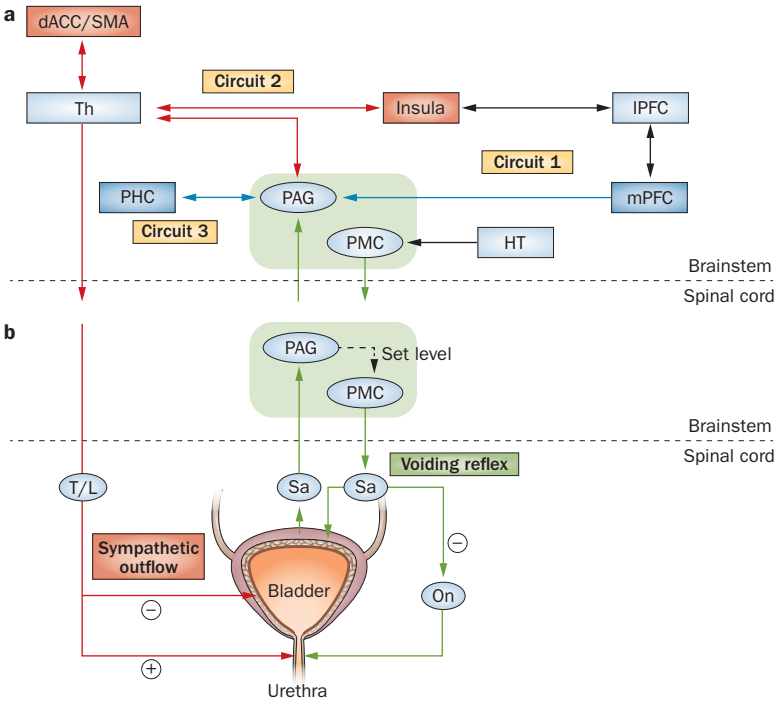

Figure 1 | Simple working model of LUT control. **a** | Brainstem and forebrain circuits one, two and three that act on the LUT. **b** | Brainstem and spinal connections that make up the voiding reflex. Circuits one and three form part of the default mode network (blue) that is active at rest but deactivated when attention is required. Circuit two is the salience network (red): activation is associated with sensation. In circuit one, mPFC deactivation tends to suppress voiding via a return pathway to the PAG. In circuit two, activation of insula and dACC/SMA evokes strong desire to void or urgency as well as sympathetic motor output to the LUT. In circuit three, deactivation of parahippocampal regions tends to suppress voiding at the PAG. The hypothalamus might be part of this subcortical circuit, sending a 'safe' or 'unsafe' signal to the pontine micturition centre. PAG activation is driven by afferent input from the sacral spinal cord and inhibitory or excitatory inputs from circuits one, two and three. The voiding reflex (green) is triggered if PAG activity reaches a certain set level. The PAG then activates the pontine micturition centre, which in turn contracts the bladder and relaxes the urethral sphincter mechanism. Abbreviations: dACC, dorsal anterior cingulate or midcingulate; HT, hypothalamus; lPFC, lateral prefrontal cortex; mPFC, medial prefrontal cortex; On, nucleus of Onuf; PAG, periaqueductal grey; PHC, parahippocampal complex; PMC, pontine micturition centre; Sa, sacral parasympathetic region; SMA, supplementary motor area; Th, thalamus; T/L, thoracolumbar sympathetic outflow. Adapted from W. C. de Groat *et al*. Neural control of the lower urinary tract. *Compr. Physiol.* **5**, 327–396 (2015) © American Physiological Society.

the storage phase, the (detrusor) pressure, bladder volume and wall tension all increase; correspondingly the afferent signals from receptors in the urothelium and bladder wall, which are propagated upward to the PAG, also become stronger.[1] If these afferent signals reach a sufficiently high intensity (above a certain set level), a switching action is triggered, giving rise to efferent signals that descend through the spinal cord and activate sacral regions of the peripheral nervous system. This activation stimulates the smooth muscle of the bladder, thus causing detrusor contraction, and also promotes relaxation of the urethral sphincter via activation of sacral inhibitory interneurons.[6,14] Thus, micturition is initiated. As long as the bladder is not empty, bladder afferents continue to fire and voiding is maintained.

Forebrain regulation of micturition can be accomplished by altering the input to the PAG so as to manipulate the strength of its activation. If activation of the PAG increases and approaches the set level, the switch to voiding is advanced, and *vice versa*. Thus, the decision to void or to postpone voiding depends on forebrain processing of signals transmitted by bladder afferents, together with information from other organ systems and circumstances that might influence the desirability of voiding. In healthy people, the usual outcome of this decision is to temporarily postpone voiding, but to create a desire to void. When eventually the decision to empty the bladder is made, the immediate result is to seek a toilet or washroom, but ultimately suppression of the voiding reflex will cease and voluntary voiding will take place.

Findings from studies using functional brain scanning show that processing of signals from the urinary bladder in the forebrain involves many different brain regions. The working model suggests, however, that much of the processing, at least in the storage phase, can be simplified to the operation of a few neural circuits, each of which is able to delay or suppress voiding at the level of the PAG or elsewhere.[1]

The voiding reflex and three forebrain circuits ensure that the four criteria for voiding (Box 2) are satisfied, by addressing the four corresponding questions (Box 3). Further details on these circuits, their place in bladder control and their relation to established brain networks, such as the salience network[19] and the default mode network,[20] are provided in the following section.

Urine storage (the filling phase)

Monitoring brain activity

Investigations performed using functional brain scans, such as PET, functional MRI (fMRI) or single-photon emission computed tomography (SPECT, now largely superseded by fMRI or PET), provide much of the information presented in this Review. Evidence provided by another modality, near-infrared spectroscopy, has also been described occasionally.[21–23] All these imaging techniques provide information regarding variations in regional blood perfusion, which are assumed to correspond with local changes in neuronal activity. PET and SPECT provide 3D snapshots of brain activity, so that, for example, the effect of filling the bladder can be investigated by subtracting an empty-bladder snapshot from a full-bladder snapshot made minutes apart.[24–26] By contrast, fMRI yields a 3D movie showing more rapid (~1–100 s) changes than PET (but still much slower than the real underlying neuronal activity). In most published work, variations on two 'paradigms' have been used to generate relevant, measurable brain activity. In one paradigm, a small quantity of liquid is rapidly and repeatedly infused into and withdrawn from the bladder to stimulate bladder mechanoreceptors. In the other paradigm, the patient performs repeated contraction and relaxation of the pelvic floor muscles to increase the desire to void.[27] In either paradigm, the effect of filling the bladder can be assessed with either a full, or near-empty

Box 1 | Limitations of animal models of LUT function and dysfunction

In humans, a critical distinction exists between voluntary voiding and involuntary leakage of urine (urgency incontinence), which depends on the intention of the individual—whether or not to void. In animals this distinction is hard to make because their intention is not known. Under anaesthesia especially it is not clear that there exists any intention at all. Consequently, animal models intended to represent voiding might in fact model urgency incontinence, and vice versa. This makes the type of research discussed in this Review difficult to carry out in animal models.

bladder and examining the differences in brain activity.[27,28] In addition, correlations between the signals in different brain regions provide information about their interconnections,[11,29–32] although precise interpretation is often hampered by the multiplicity of paradigms and methods of analysis. Together, findings of these connectivity studies suggest the existence of a large number of connections, which, inevitably, cannot be accurately represented in any simple model. However, some of the regions of the simple working model (Figure 1) appear again in the results of studies investigating connectivity—for example, the dorsal anterior cingulate (dACC),[30] insula,[32] medial prefrontal cortex (mPFC) (Box 4),[29] parahippocampal complex[30] and, surprisingly, the PMC[11]—lending some support to the working model.

Contractions during the filling phase

Voluntary control of pelvic floor contraction, together with contraction of the urethral sphincter, is an integral part of LUT control. Accordingly, pelvic floor muscle training is a recommended treatment of both stress and urgency incontinence.[33] Most PET and fMRI studies of repetitive pelvic floor contraction concur that contractions are associated with activation of the supplementary motor area (SMA) or a nearby brain region (Figure 2).[27,34–36] These contractions activate the dACC, (also known as midcingulate) and the insula,[37] as well as the SMA. All are regions of circuit two and together they make up the salience network (Figure 1a).[19] The pattern of cingulate and insular activation (Figure 2) is a defining feature of this network.

Functional brain scans with near-empty bladder

If the bladder is empty or almost empty, neither repetitive activation of pelvic floor muscles (in men)[27] nor rapid infusion and withdrawal of liquid (in women)[38] generates any significant brain activity in adults with strictly normal urological function. This observation suggests that in the near-empty bladder only weak afferent (sensory) signals are generated, presumably because bladder mechanoreceptors are only weakly stimulated. In one study, nonetheless, a trend towards activation of PAG and parahippocampal regions was observed, implying that subcortical circuit three (Figure 1a) is slightly activated by rapid infusion into the bladder.[38] A reported trend towards SMA activation during pelvic floor muscle contraction[27] is consistent with weak bladder sensation.

Box 2 | Criteria for voiding

Voiding should be:

- Mechanically appropriate (specifically, with enough urine initially in the bladder)
- Safe (for example, safe from predators, as learnt during evolutionary history)
- Emotionally appropriate (with regard to secondary emotions such as embarrassment)
- Socially appropriate (voiding must take place in the right place at the right time, learnt as a toddler during toilet training)

Cerebral effects of bladder filling

Brain responses to rapid infusion and/or withdrawal are generally stronger with a full, rather than an empty bladder[28,30] and some regions or circuits are revealed only after substantial bladder filling has generated strong bladder sensations.

PAG

Bladder filling is expected to generate or reinforce the afferent signals that activate the PAG. Indeed, in healthy men, PAG activity increases when the bladder is filled,[25,39] although in unselected patients and healthy individuals, rapid infusion and withdrawal activates the PAG more strongly with a full, rather than with a near-empty bladder.[28] This observed activation is located in the ventrolateral PAG,[39] at the origin of the pathway descending to the PMC (Figure 1).[14] In healthy individuals this pathway is not active during urine storage but only during micturition, when it activates the PMC and, thus, the voiding reflex. However, the PAG is connected via ascending pathways to many other parts of the brain,[40] including the dACC and anterior insula. Thus, PAG activation can have widespread effects on brain activity, enabling generation of bladder sensation and engagement of mechanisms of continence.

Pons

In women with UUI, use of the infusion–withdrawal paradigm suggests that the PMC is activated at large bladder volumes (that is, with strong sensation),[3] apparently implying incipient firing of the voiding reflex. Normally, however, the PMC is inactive during urine storage,[28,41] signifying that the voiding reflex has not been triggered. Instead, a more ventrolateral region of the pons is activated. This pattern of activation might be a human homologue of the L-region in the cat,[42] a continence centre that controls contraction of pelvic floor muscles and the urethral sphincter. This L-region homologue is also activated in humans who try to void but are unsuccessful.[17] A slightly different pontine region is activated by alternating contraction and relaxation of pelvic floor muscles with a full bladder.[35,43] Together these observations from animals and humans confirm that regions in the pons have a critical role in LUT control.

Circuit two: insula

The insula, placed in circuit two (Figure 1a), is part of the salience network, which is activated in many conditions

Box 3 | The main neural circuits of the working model

Circuit zero: Is there enough urine in the bladder? This circuit is the ascending limb of the voiding reflex, which provides afferent information regarding the state of the bladder. These signals might be modified by spinal processing.

Circuit three: Is voiding safe? This subcortical circuit includes the parahippocampal complex as well as the PAG and probably the hypothalamus. This circuit might be involved in subconscious monitoring of bladder events.

Circuit two: Is voluntary voiding emotionally appropriate? This limbic circuit includes the dACC and the nearby SMA. It probably includes the anterior insula also (previously assigned to circuit 1).[1] The dACC might be involved in generating the desire to void and urinary urgency, and the insula in registering the degree of bladder filling.

Circuit one: Is voiding socially appropriate? Social aspects are primarily dealt with in the prefrontal cortex, especially the medial prefrontal cortex (mPFC), which appears to maintain a direct pathway back to the PAG.[69]

This working model does not imply that these circuits operate entirely independently. For example, if a conscious sense of lack of safety exists, cortical activity must be involved, not just the subcortical circuit three.

Abbreviations: dACC, dorsal anterior cingulate or midcingulate; mPFC, medial prefrontal cortex; PAG, periaqueductal grey; SMA, supplementary motor area.

involving sensation. The anterior insula is considered to be the autonomic sensory cortex,[44] and is the seat of visceral sensation.[45] In normal, continent women the anterior insula becomes activated as the bladder fills,[3,46] especially on the right side of the brain. This progressively increasing activation might correspond with the normal series of sensations: first sensation of filling, first desire to void and strong desire to void.[10] When healthy men withhold urine with a full bladder, a trend towards insular activation on the right[46] and left[26,39] is again observed. In women with urgency, activation of the right insula (Figure 3) is part of the salience network pattern (Figure 2).

Circuit two: dACC/SMA

Like the insula, the dACC and nearby SMA in circuit two form part of the salience network (Figure 1a) and respond similarly to bladder filling—with activation (Figure 3). Findings of many studies attest to the role of the dACC and SMA in the response to changes in bladder volume: repetitive pelvic floor muscle contractions provoke stronger sensations and greater SMA responses when the bladder is full than when it is empty;[27] in women, rapid infusion generates stronger sensation with increasing bladder volume, as well as activation of the dACC and SMA;[3] in men, dACC activity increases with a full bladder, after adjusting for sensation.[25] In women with UUI, both sensation and dACC and SMA activation are particularly strong at maximum bladder capacity (Figure 3) and this pattern might be the neural substrate of the abnormal sensation of urgency.[47] The coexistence of SMA and dACC activation presumably leads to motor output that promotes tightening of both the striated and the smooth muscle elements of the urethral sphincter and suppression of detrusor contraction (Figure 1).

Box 4 | Lateral prefrontal cortex

The lateral parts of the prefrontal cortex (lPFC in Figure 1a, also called in part the inferior frontal gyrus) are activated by bladder filling,[24] and also by rapid infusion or withdrawal if the dACC and SMA and insula are also strongly activated.[29,48] The lPFC might, therefore, belong to circuit two although this option has been left open in Figure 1a owing to a lack of conclusive evidence.

Abbreviations: dACC, dorsal anterior cingulate or midcingulate; lPFC, lateral prefrontal cortex; SMA, supplementary motor area.

Circuit one: medial prefrontal cortex

Some women with UUI respond to bladder filling with activation of circuit two and a strong sensation of urgency. Others, however, respond quite differently: a marked deactivation[48] (initially incorrectly classified as a deficit in activation)[28] occurs in the mPFC, part of circuit one. Similarly, in adult men, a region close to the mPFC is deactivated while withholding urine.[24] The concept of deactivation has caused some perplexity but, as pointed out previously,[30] circuit one is part of the widely recognized default mode network (DMN), which is active at rest and deactivated whenever conscious attention to a task is required.[20] mPFC deactivation can result in suppression of voiding at the PAG (circuit one, Box 5).

Circuit three: parahippocampal complex

Relative to the other circuits, little is known about subcortical circuit three, which includes regions such as the temporal and parahippocampal complex. These tend to be deactivated in parallel with the mPFC (Figure 3),[48,49] and might suppress voiding at the PAG in a similar way. The parahippocampal complex, which surrounds the hippocampus, is known to be involved in the retrieval of episodic memories and the recognition of scenes and social context. Circuit three is one of the most speculative areas of the working model that clearly requires more work.

Hypothalamus

The hypothalamus can sometimes be activated by bladder infusion and/or withdrawal in healthy individuals or those with incontinence at large bladder volumes,[3,28] and is believed to provide a 'safe' or 'not safe' signal directly to the PMC (as well as to the PAG). Tentatively, this activation might belong to circuit three (but this is left open in Figure 1a).

Thalamus, basal ganglia and midbrain nuclei

The thalamus is included in the working model as a relay station *en route* to the cortex (Figure 1a) but its role in micturition has not been fully established. The arrangement of thalamic connections is analogous to that observed in heart rate control.[50] Findings of several brain scanning studies, especially studies of connectivity, have shown that the putamen is involved in brain–bladder control,[27,31,39] and that deep brain stimulation of midbrain nuclei (such as the subthalamic nucleus) affects bladder control mechanisms in patients with neurological disease.[51,52] Both are omitted from the working model.

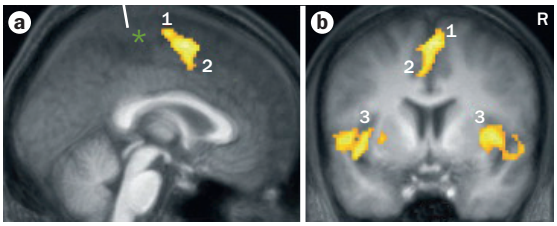

Figure 2 | Brain activity during pelvic floor muscle contractions. **a** | Sagittal and **b** | coronal fMRI images showing an increase in brain activity in the SMA (1) and dACC (2). Another region (asterisk) is activated during toe movement, suggesting functional localization in these brain regions. Bilateral activation of the insula (3) suggests that bladder or urethral sensation is evoked. Data represent a group analysis of fMRI scans from 17 healthy males aged between 21–47 years of age, examined with an empty bladder. Abbreviations: dACC, dorsal anterior cingulate or midcingulate; fMRI, functional magnetic resonance imaging; R, right side; SMA, supplementary motor area. Reprinted from *J. Urol.* Schrum, A. *et al.* Motor cortical representation of the pelvic floor muscles. **186**, 185–190, (2011) with permission from Elsevier Ltd.

Comparison with heart rate variability

Urinary urgency has a strong social and emotional content—fear of embarrassment by leaking urine in public. A similar fear is evoked by the prospect of ill-prepared public speaking and is associated with autonomic changes such as increased heart rate. These changes are mediated by signals in two distinct brain regions: the rostral dACC and ventromedial PFC,[50,53] which strongly resemble those of the dACC and mPFC. These signals affect the heart via activation of two different pathways: the dACC provides sympathetic outflow that increases heart rate on a long-term basis; mPFC provides parasympathetic input via the PAG that decreases the heart rate on a beat-to-beat basis. These two mechanisms are strikingly similar to neural circuits one and two involved in LUT control (Figure 1a and Figure 2). These mechanisms reflect a common pattern of response to fear of embarrassment that utilizes a sympathetic mechanism based on the dACC/SMA (circuit two) and a parasympathetic mechanism based on the mPFC (circuit one). Increased heart rate and increased sphincter contraction (with bladder inhibition) are both mediated by increased dACC/SMA signal or by decreased signals from the mPFC.

Forebrain circuits reinterpreted

Current knowledge of neural circuits involved in control of continence has emerged *ad hoc* from a series of observations made over several years. The plausibility of such circuits is heightened because, as we have seen, similar circuits are employed in other situations, such as control of heart rate. Indeed, circuit one is part of the well-known DMN, which is active in the resting state and deactivated when conscious attention to a cognitive task is required.[20] As well as the mPFC, the DMN includes the parahippocampal and middle temporal cortices (in circuit three) and the posterior cingulate and lateral occipital cortices (not so far ascribed to any circuit).[54] In the case of the LUT, these regions tend to be co-deactivated with the mPFC (Figure 3),[49] confirming that they belong to the same network. Presumably, the unusual sensation of rapid infusion into a full bladder demands increased attention, resulting in deactivation of the DMN (Figure 2). How deactivation might help to maintain homeostasis can be understood by considering how the working model, and especially mPFC deactivation, could operate (Box 5).

Circuit two corresponds with another established brain network. Activation of the midline dACC together with the insula bilaterally forms the pattern that is typical of the salience network (Figures 2 and 3a).[54] The insula is the seat of interoception,[55] and the salience network is associated more generally with emotion processing and autonomic regulation, as well as interoceptive awareness.[54] Consequently, the insula is ideally placed to register the degree of bladder filling, whereas the dACC can create the associated emotion—desire to void or urgency, the 'salience' of the bladder filling sensation. The dACC might also provide sympathetic motor output to the LUT to temporarily inhibit voiding until the urgency can be relieved.

Speculatively, homeostasis (continence) seems to be maintained by two mechanisms that are driven by two well-known neural networks. One of these networks (the DMN) is composed of the *ad hoc* circuits one and three (Figure 1a), but without the insula or the lateral PFC. This network provides parasympathetic output to the LUT via the voiding reflex. The other network, the salience network, corresponds with circuit two, including the insula, and provides bladder sensation and sympathetic output. Which of these mechanisms is chosen, and whether they can be harnessed for effective treatment of incontinence are problems examined in the next section.

Treatment and the working model

Stress incontinence

Treatment of stress incontinence using pelvic floor muscle training is accompanied by more focused activity near the dACC and SMA with less emotional arousal.[56] As the working model predicts, therefore, successful treatment results in a reduction in salience that reflects a diminished fear of leakage.

Urgency incontinence

Treatment of urgency incontinence or overactive bladder typically involves antimuscarinic medication, but behavioural treatment, such as pelvic floor muscle training, is also recommended.[7] Other, newer therapies[57–59] are not being considered here owing to lack of data on relevant neurological effects. Both types of treatment lead to changes in brain activation that can be used to probe the working model and illuminate the mechanism of action of these therapies.[8,60]

Antimuscarinic treatment

In adult women with overactive bladder, treatment with an antimuscarinic agent (tolterodine) reduced brain

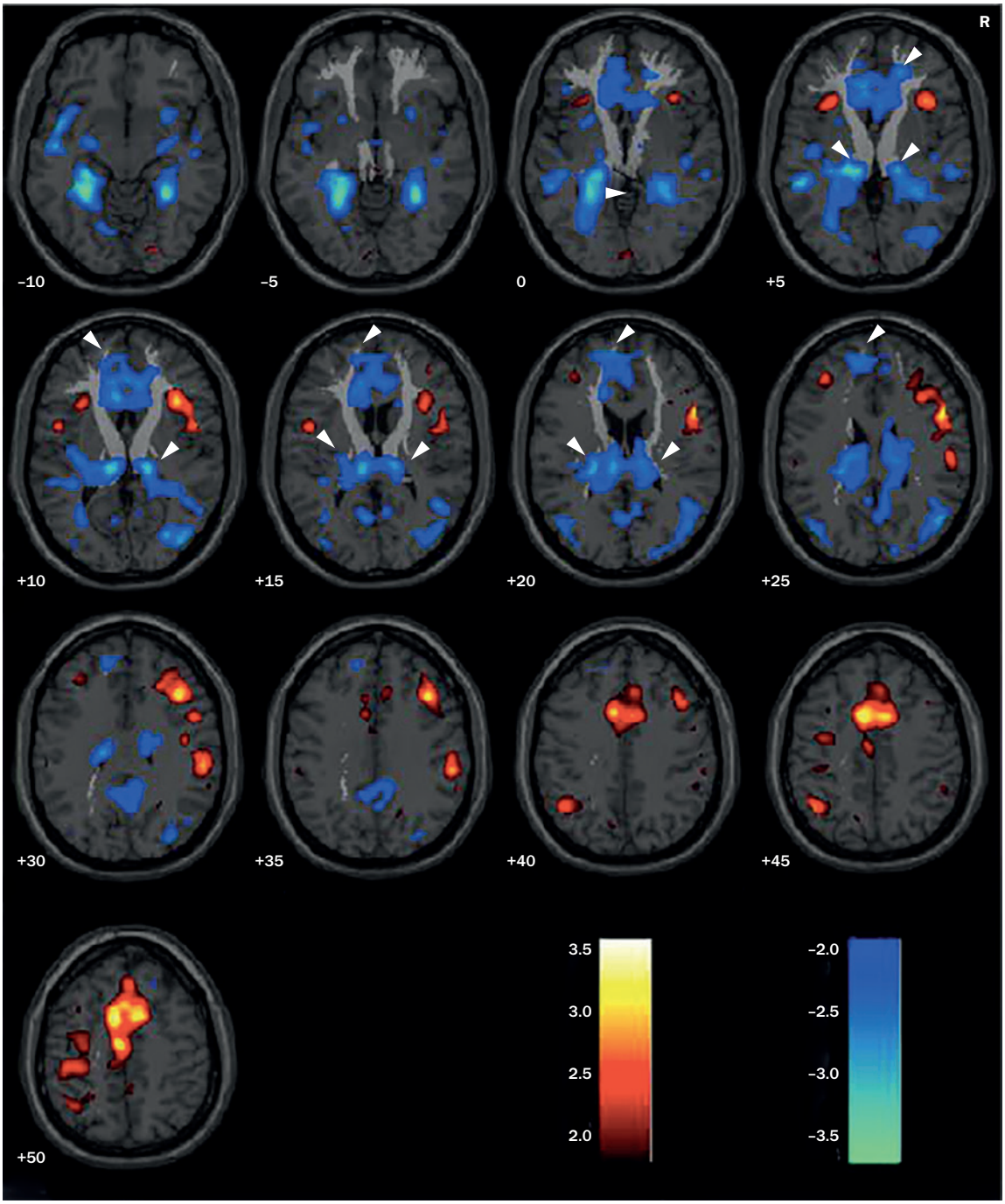

Figure 3 | Brain responses to bladder filling. Axial fMRI sections at 5 mm intervals are superimposed on a prominent white-matter tract (light grey) called the ATR. Numbers indicate the axial coordinate of the z-dimension for each slice. From z = 50 (near the top of the brain) to 40, a medial red/yellow blob shows activation of the dACC/SMA. From z = 40 to z = 25, scattered red/yellow blobs on the right side suggest right insular activation, thus completing circuit two and the salience network. From z = 25 to z = 0 a medial blue blob near the front of the brain indicates deactivation of the mPFC and there is also deactivation of a bilateral region in the middle of the brain (in blue) that becomes stronger (lighter blue) in the hippocampus (at z = 10 to –10). Deactivation in the right posterior brain at z = 25 to 10 completes the default mode network and circuit three. The ATR appears to connect numerous sites on circuit three (white arrowheads) and might carry the return signal from the mPFC to PAG shown in Figure 1a. It does not contact dACC/SMA. fMRI data represent a group analysis of 25 women >60 years of age with UUI, who were examined with a full bladder and urinary urgency, but without concurrent detrusor overactivity. Colour bars show t-values. Abbreviations: ATR, anterior thalamic radiation; dACC, dorsal anterior cingulate or midcingulate; fMRI, functional magnetic resonance imaging; mPFC, medial frontal cortex; PAG, periaqueductal grey; R, right side; SMA, supplementary motor area; UUI, urgency urinary incontinence. Reprinted from *Neuroimage*, Tadic, S. D. *et al.* Brain activity during bladder filling is related to white matter structural changes in older women with urinary incontinence. **51**, 1294–1302 © (2010) with permission from Elsevier Ltd.

Box 5 | How the PAG switch can delay or advance voiding

The operation of the PAG switch and the meaning and effect of deactivation of the mPFC might be understood by an analogy between neuronal excitation and flow of water. Speculatively, one might think of the PAG as a leaky bucket partly filled with water. The level of water in the bucket represents PAG activity. This activity is maintained by inflow of excitation from the bladder (bladder afferent signals) and also by inflow from the mPFC and elsewhere. During bladder filling bladder afferents, and therefore, excitatory inflow into the PAG increase and the water level in the bucket begins to rise. Provided that the water level remains below a certain 'set level' nothing more happens. If, however, the water level rises as far as the set level, it trips a switch and voiding occurs. After voiding, the bladder is empty, bladder afferent signals are much reduced and the water level (PAG activity) has fallen.

In the normal situation, voiding can be initiated voluntarily by exciting the mPFC so that its inflow into the PAG increases. PAG activity then increases until it reaches the set level and the voiding reflex is triggered.

In the UUI or OAB situation, if the water level approaches the set level when voiding is not desired, a sensation of urgency might be generated. Moreover, voiding might be suppressed by deactivating the mPFC so as to reduce its inflow into the PAG, allowing the water level to fall below the set level. This putative continence mechanism stops working once the inflow from circuit 1 has been reduced to zero (a ceiling effect corresponding to the maximum mPFC deactivation). If undesired voiding still threatens, then nothing further can be done by the mPFC.

Thus, the mPFC, the seat of executive control, can either delay or advance voiding by reducing (deactivating) or increasing (activating) the flow of excitation along the pathway from the mPFC to PAG.

Abbreviations: mPFC, medial prefrontal cortex; OAB, overactive bladder; PAG, periaqueductal grey; UUI, urgency urinary incontinence

activation in an extensive area including the dACC and SMA.[61] This finding suggests reduced salience (indicating reduced urgency), as one would expect, but the cogency of this finding was undermined, owing to a similar reduction of activity after placebo 'treatment' in the control group of patients with overactive bladder. Moreover the tolterodine and placebo groups were not well matched in terms of brain activity before treatment.

Biofeedback-assisted pelvic floor training

In elderly females with UUI, treatment using biofeedback-assisted pelvic floor training (BFB) followed by fMRI confirmed that two mechanisms of response to bladder infusion exist, based upon circuits one and three and on circuit two,[49] respectively. Patients were found to have either deactivation of circuits one and three or activation of circuit two, but rarely both. Remarkably, the mechanism of the response to bladder infusion predicted the subsequent response to therapy: those who would later respond well to BFB (>50% reduction in incontinence episodes) used predominantly circuit two before treatment, activating the dACC and SMA, and insula; those who would later fail to respond used circuits one and three before treatment, thus, deactivating the mPFC together with limbic and subcortical regions. In these nonresponders, strong deactivation of the mPFC, which was present before treatment, was essentially unchanged after unsuccessful treatment (Figure 4) This finding suggests that a ceiling effect (complete mPFC deactivation) prevents any improvement in therapeutic outcome. Supposing, therefore, that the choice of circuit is variable from individual to individual, depending on learned experience, those whose response to infusion involves deactivation of circuits one and three inevitably fail to respond well to behavioural treatment. Thus, use of BFB therapy as a probe reveals the differing brain responses to bladder filling of women with incontinence.[49]

On the other hand, evidence from responders to BFB provides information on the mechanism of this type of behavioural therapy. Successful treatment is associated with changes in circuit two: reduction in dACC and SMA activation (Figure 4) shows that urgency (salience) has been reduced in reaction to a diminished risk of UUI.[49] Thus, this change is not a cause, but a consequence of treatment success. The actual cause of therapeutic improvement is suggested speculatively by the observation that, in responders to BFB, mPFC deactivation tends to appear *de novo* after successful treatment (Figure 4), implying that the mechanism of improvement in response to behavioural therapy involves strengthening of the deactivation of circuits one and three, with correspondingly enhanced suppression of reflex voiding at the PAG.

These observations confirm that activation of circuit two is a marker of urgency (salience) but not an effective continence mechanism that could be harnessed for treatment of UUI. On the other hand, deactivation of circuits one and three is not only a mechanism of therapy but might also be a mechanism for maintaining continence by directing conscious attention to the LUT. Impairment of this mechanism, as a consequence of age-related deterioration of connectivity,[54,62] might contribute to the high prevalence of UUI in older people. Restoration of the integrity of connecting pathways, for example by more effective behavioural treatment, is a possible goal of therapy, although the effectiveness of this approach will probably be limited by the ceiling effect just described.

Brain activity related to voiding

The working model (Figure 1) was developed to describe the storage phase, but it can also plausibly account for aspects of voiding. According to the model, voluntary voiding should occur when suppression of the voiding reflex by the forebrain circuits is consciously turned off. The contribution of the mPFC to this process is particularly important, as this part of the brain is concerned with executive function—thus, with voluntary control—and also has a direct connection with the voiding and/or storage switch at the PAG.

Imagined voiding

Imagined voiding without actual flow has been studied by several authors,[32,35,43] although its relationship to real voiding is unclear. Findings of their studies[32,35,43] show activation of the salience network without notable activation of the PMC, indicating that the voiding reflex is not triggered. Activation of other regions also occurs, including a medial pontine region that seems to be distinct from the PMC and the L-region;[35] this brain region might be another pontine continence centre.

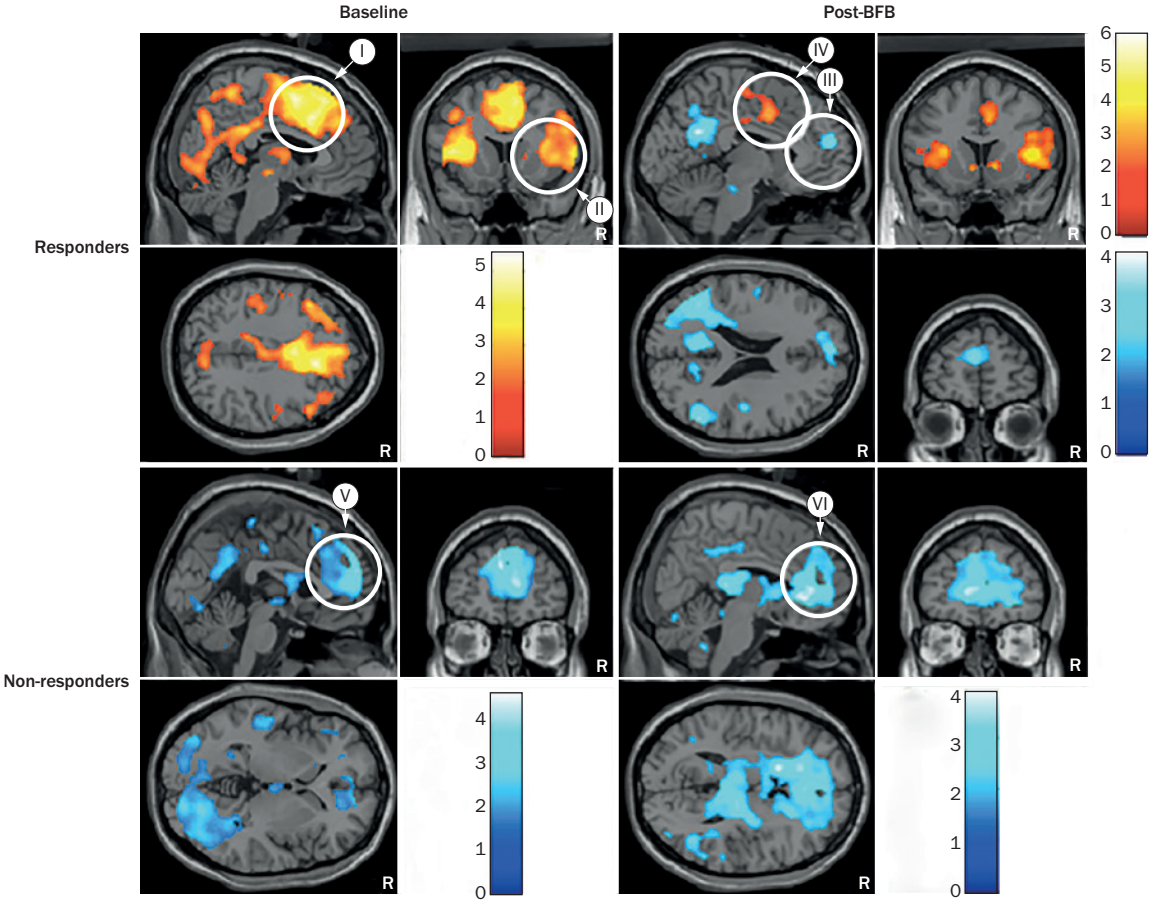

Figure 4 | Responses to bladder filling in women with UUI. Sagittal, coronal and axial fMRI images showing brain responses to bladder filling in 62 women >60 years of age with UUI, treated using conservative BFB. Prior to BFB, those whose incontinence will later respond to treatment show activation (yellow or orange blobs) in dACC and SMA (I) and right insula (II) (circuit two). Those who will later fail to respond show deactivation (blue blobs) in the mPFC (V, circuit one). After BFB, those whose symptoms have improved >50% have evidence of *de novo* mPFC deactivation (III) and reduced dACC and SMA activation (IV). This finding suggests that mPFC deactivation is the mechanism of successful therapy, which leads to reduced dACC and SMA activation (reduced urgency). By contrast, those who have failed to respond to treatment have an almost unchanged mPFC deactivation (VI), perhaps because it is already at its maximum extent. These fMRI data are the results of group analyses obtained from individuals with a full bladder and urinary urgency, but without concurrent detrusor overactivity. Coloured blobs indicate locations where the mean response of the group of subjects is significantly greater than zero. Coloured bars indicate corresponding values of Student's T. Note that not all axial sections are displayed at the same axial coordinates. Abbreviations: BFB, biofeedback-assisted pelvic floor training; dACC, dorsal anterior cingulate or midcingulate; fMRI, functional magnetic resonance imaging; mPFC, medial frontal cortex; R, right side; SMA, supplementary motor area; UUI, urgency urinary incontinence. Adapted from *J. Urol.* Griffiths, D. *et al.* Brain mechanisms underlying urge incontinence and its response to pelvic floor muscle training. **194**, 708–715 © (2015) with permission from Elsevier Ltd.

Initiation of voiding

Since the initiation of voiding is the critical event, most scanning studies of voiding have been designed to include this aspect of continence in the scanning window. Early studies were carried out using natural urine production to fill the bladder followed by PET scanning.[24,46] Those who could successfully initiate voiding in the scanner within a 90 second window of opportunity (voiders), were included in the main analysis; nonvoiders were analysed separately. In men,[24] successful micturition was associated with activation of the rostral anterior cingulate (part of the mPFC), suggesting that mPFC deactivation had been abolished and replaced by activation. Voiding was also associated with activation of the PAG—suggesting that the set level for voiding had been exceeded—and with activation of the right PMC, indicating that voiding had been triggered. The right inferior frontal gyrus (lateral PFC) was also activated. A similar pattern emerged in woman voiders.[46] Nonvoiders of either sex failed to show activation of the PMC, confirming that the voiding reflex had not been triggered. Instead, activation was observed in a more lateral pontine location, believed to correspond with a pontine continence region (the L-region); and, mPFC activation was much reduced compared with that observed in voiders, suggesting weaker suppression of PAG activation, and hence, of voiding.

Findings of another PET study not only demonstrated the expected activation of the PMC during voiding,[26] but also activation of an extensive network of cortical and

subcortical regions that included the right insula and dACC/SMA. This unexpected observation might reflect activation of the salience network during initiation, rather than during the course of bladder emptying. In an fMRI study of a small number of female voiders, using bladder pressure measurements to identify the initiation of voiding, investigators found activation of the mPFC and parahippocampal gyrus,[63] thus confirming that suppression of voiding by circuits one and three had been turned off, or indeed reversed. Moreover, findings of another study of healthy females confirmed that initiation of micturition was associated with activation of numerous regions, including the parahippocampal gyrus, caudate nucleus, lentiform nucleus and pons.[11]

Maintenance of voiding

Among healthy male voiders, using a flow detector to establish initiation of voiding, supraspinal activity was prominent just before the onset of micturition (during initiation), and subsided once actual urine flow had started, allowing the voiding reflex to run its course without further interference from cortical and/or subcortical circuits.[64] Of course, other spinal reflexes that maintain flow once it has been initiated might also exist.[1]

The switch between filling and voiding

The operation of the switch and the role of deactivation can be illustrated by an analogy (Box 5). In the ongoing discussion of the nature and site of the brainstem micturition switch,[4] I have here taken the view that the PAG receives bladder afferent information, compares it with a set level that determines the firing of the voiding reflex, and passes this information to the PMC. Furthermore, PAG activity can be altered by inputs from the forebrain, which are thus able to advance or delay voiding according to the influence of certain social and emotional factors. On this view, the PAG acts as the switch and the PMC is a simple pattern generator that—via its projections to the sacral cord and thence to bladder and urethra—ensures synergistic voiding. An alternative view exists that the PAG is just one of a series of locations in the ascending sensory limb of the micturition pathway, where modulation of afferent activity can occur. In this alternative view, the PAG sends output to the PMC during both storage and voiding, where comparison with a set level takes place. The PMC activity (or the set level) can be influenced by input from the hypothalamus (Figure 1), which is thus the final arbiter of whether voiding shall take place. In this view, the PAG acts as a relay (with processing ability) and the PMC as the switch.

Findings of animal experiments show that, whereas stimulation from the PMC excites the voiding reflex, stimulation from the PAG has more variable effects, which can alternatively be inhibitory or excitatory,[13,42,65–67] and this might be one of the reasons why activity in the PAG has been difficult to observe in humans. However, the working of the switch has been further elucidated in an fMRI study of anaesthetized rats.[68] After a resting period, the bladder was slowly filled while scanning, until a voiding contraction was triggered. Scanning continued so as to obtain 'voiding' data (the penis was ligated to prevent actual flow). Ultimately the bladder was drained and brain activity during another resting period was recorded. The switching action was clear: during storage, the PAG was activated but the PMC was not; during voiding the PMC became activated while activation of the PAG increased further, signifying that it had reached the set level, thus triggering voiding. Together these observations support the first of these two views, that the PAG is the switch and the PMC is the pattern generator.

Conclusion

Data from the brain imaging studies reviewed here have led us to a credible—but highly simplified—picture of how the LUT is controlled in healthy humans, and of functional brain abnormalities that are associated with conditions such as overactive bladder and urgency incontinence. This new knowledge of the mechanisms underlying incontinence and responses to therapy might help to shift clinical attention away from the peripheral organs and focus it on cerebral control, with greater emphasis on behavioural and electrophysiological treatments, and on treatments involving direct brain interventions such as deep brain stimulation. This process has already begun.[49,52,57]

The model, and the observations presented in this Review suggest, nonetheless, that there might be certain limitations to the improvements in incontinence that can be brought about by therapy-induced changes in forebrain processing. Consequently, treatments intended to improve this processing, for example exercises or electrical stimulation to reinforce white matter integrity, are likely to remain only modestly successful. New and more effective therapeutic approaches might have to be targeted at the PAG switch itself, which might well become unreliable in old age.

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