

Brain responses to changes in bladder volume and urge to void in healthy men

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Summary

Knowledge of how changes in bladder volume and the urge to void affect brain activity is important for understanding brain mechanisms that control urinary continence and micturition. This study used PET to evaluate brain activity associated with different levels of passive bladder filling and the urge to void. Eleven healthy male subjects (three left- and eight right-handed) aged 19–54 years were catheterized and the bladder filled retrogradely *per urethra*. Twelve PET scans were obtained during two repetitions of each of six bladder volumes, with the subjects rating their perception of urge to void prior to and after each scan. Increased brain activity related to increasing bladder volume was seen in the periaqueductal grey matter (PAG), in the midline pons, in the mid-cingulate cortex and bilaterally in the frontal lobe area. Increased brain activity relating to decreased urge to void

was seen in a different portion of the cingulate cortex, in premotor cortex and in the hypothalamus. Both activation patterns were predominantly bilaterally symmetric and none of the effects could be attributed to the presence of the catheter. However, in some subjects, mostly those reporting intrusive sensations from the urethral catheter, there was a discrepancy between filling volume and urge so that they reported high urge with low volumes. As this ‘mismatch’ decreased, activation increased bilaterally in the somatosensory cortex. Our findings support the hypothesis that the PAG receives information about bladder fullness and relays this information to areas involved in the control of bladder storage. Our results also show that the network of brain regions involved in modulating the perception of the urge to void is distinct from that associated with the appreciation of bladder fullness.

Keywords: bladder filling; urinary urgency; periaqueductal grey; pons; cingulate cortex

Abbreviations: PAG = periaqueductal grey matter; SPM = statistical parametric mapping

Introduction

The lower urinary tract serves two functions: the storage of urine and its periodic elimination through micturition. Most of the time, the bladder is held in storage mode, with a switch to micturition when the bladder is full. The complex processes of storage and voiding of urine are strongly influenced by social and environmental factors and are intricately associated with the subject's perception of urge to void. Although the dominant initiator of micturition is the sensation of urinary urgency derived from bladder fullness, in health it is usually only in the appropriate environmental circumstances that bladder activity is switched to voiding. When micturition is initiated, it proceeds through a bulbo-spinal reflex thought to be influenced by processes under higher cerebral control. Following initiation, attempts to halt micturition usually serve at best only to limit the volume of urine passed. Strategies for the treatment of incontinence

should, therefore, focus on modifying the initiation process by modulating the sensory input from the bladder.

It is generally assumed that, in health, the degree of bladder filling influences the urge to void, but there have only been a few detailed studies of this relationship. Everyday experience and available evidence suggest that although at low volumes the relationship between filling and the urge to void is simple, at bladder capacity the relationship may be more complex (Yarnitsky and Vardi, 1993). Furthermore, we may manage to endure periods with a full bladder without troublesome intrusions of sensations of urinary urgency but, at other times and particularly when anxious, the desire to micturate may be strong even though there may be little urine to pass.

A substantive understanding of the coordination of the act of micturition has emerged from animal studies and from

clinical observation in humans (de Groat, 1997, 1998; Blok and Holstege, 1999; Fowler, 1999). Since the 1920s, it has been known that motor control of the bladder arises within the pons (Barrington, 1925; Kuru, 1965; Griffiths *et al.*, 1990) and that electrical stimulation of the pontine micturition centre, 'Barrington's nucleus,' gives rise to coordinated micturition. Holstege's group refined this knowledge of the brainstem activity involved in bladder storage and voiding in animals by showing that stimulation of a medial region in the dorsum of the pons causes a decrease in urethral pressure and silence of the pelvic floor EMG signal, followed by a rise in detrusor pressure. They termed this area the medial or 'M-region' (Holstege *et al.*, 1979, 1986; Griffiths *et al.*, 1990), and tracing studies in the cat demonstrate direct projections from the M-region to the intermediolateral cell column of the sacral cord. The intermediolateral cell group contains parasympathetic bladder motor neurones; the intermediomedial cell group contains inhibitory interneurons for the pelvic floor motor neurones in Onuf's nucleus. Via direct excitatory projections to these two regions, the M-region produces micturition by stimulating the detrusor muscle of the bladder and, at the same time, inhibiting Onuf's nucleus motor neurones, resulting in relaxation of the urethral sphincter (Holstege *et al.*, 1986). Injection of radioactive leucine into the L-region labels fibres in Onuf's nucleus (Holstege *et al.*, 1986), the motor nucleus that innervates the sphincters. Thus it has been proposed that the M-region be regarded as the site for micturition (Griffiths *et al.*, 1990) and the L-region be regarded as being important in the maintenance of continence.

Despite their role in the control of both micturition and continence, these two pontine centres seem to receive few if any direct projections conveying sensory information from the lower urinary tract. For example, there are few sacral projections to the M-region (Blok *et al.*, 1995). A rich direct sacral projection does however pass to the mesencephalic periaqueductal grey matter (PAG) (Vanderhorst *et al.*, 1996) and, in turn, there are direct projections from the PAG to the M-region of the pontine micturition complex (Noto *et al.*, 1991; Blok and Holstege, 1994). This connectivity suggests that the PAG receives information concerning the state of bladder fullness and then influences the M-region to set in motion the neuronal events that result in micturition. Thus one current model of bladder control holds that during urine storage there is a tonic influence of PAG upon the 'continence' neurones of the L-regions. However, when bladder afferent activity indicates a state of bladder fullness and the situation is appropriate, there is a switch of activity within the pons from the L-region to the M-region. The result is an inhibition of spinal somatic outflow to the urethral sphincter, resulting in relaxation of the striated muscle, followed by activation of lumbosacral spinal parasympathetic fibres to the detrusor causing a contraction resulting in bladder emptying.

That forebrain structures have a role in the control of micturition in humans is evident from patients with anterior cortical lesions. Thus, anterior cerebral artery aneurysms,

tumours or cerebrovascular accidents affecting the mesial frontal lobes disrupt bladder control by symptoms of unsuppressed initiation of micturition, although voiding itself may be coordinated normally (Ueki, 1960; Andrew and Nathan, 1964; Maurice-Williams, 1974; Mochizuki and Saito, 1990; Sakakibara *et al.*, 1996).

The control of micturition has been investigated by recent human functional brain imaging studies that demonstrate cerebral cortical and subcortical activity associated with voiding. Fukuyama and colleagues using SPECT throughout voiding showed activity in the upper pons, left sensorimotor and right frontal cortex, as well as bilaterally in supplementary motor areas (Fukuyama *et al.*, 1966). PET studies from Groningen showed that micturition in healthy right-handed females and males is associated with alterations in blood flow within areas in the pons, PAG, pre-optic area, hypothalamus, right anterior cingulate gyrus, insula and right inferior frontal gyrus (Blok *et al.*, 1997b, 1998). A PET study of repeated voiding monitored cystometrically by catheterization showed activity in areas similar to those shown by the Dutch group with additional activity bilaterally in the inferior frontal gyrus, globus pallidus and cerebellum (Nour *et al.*, 2000). There were laterality differences, with activation of the left thalamus, caudal cingulate, and right mesencephalon and insula. What remain unclear, however, are the specific roles of the various portions of this cortico-subcortical network in micturition control.

So far, human brain imaging studies have focused on the act of micturition itself, specifically comparing the maintained state of voiding with resting bladder states. Little is yet known of how the brain regulates the initiation and cessation of micturition, maintains continence or gives rise to perceptions of bladder fullness and urge to void. This study was designed to begin to address these issues by investigating the brain activity that is associated with differing amounts of non-painful bladder filling and levels of the urge to void. On the basis of previous studies, we expected a number of regions to exhibit activity, including the pons, PAG, frontal cortex, parietal somatosensory cortex, hypothalamus and cingulate cortex. We hypothesized that brain regions exhibiting activity related to the state of fullness would not necessarily coincide with those related to the urge to void. Some of these data have been reported in abstract form (Athwal *et al.*, 1999).

Methods

Eleven healthy, male volunteers, aged 19–54 years, were catheterized with a 10F urethral catheter. Three of the subjects were left-handed, eight right-handed. The study was approved by the Joint Medical Ethics committee of the National Hospital for Neurology and Neurosurgery, and the Institute of Neurology. Subjects were recruited by advertisement. Written informed consent was given prior to entry.

Immediately prior to the scanning session, the subjects were instructed in the use of a 0–4 perceptual scale (0 = no

sensation; 1 = first sensation; 2 = first urge to void; 3 = strong urge; 4 = uncomfortable urge). This scale is similar to that commonly used in clinical investigations and research studies of the urinary system (Bradley *et al.*, 1975; Wyndaele, 1990; Creighton *et al.*, 1991). Following catheterization with a 10F catheter *per urethra*, each subject's bladder capacity (level 3, non-painful) was established by slow infusion of warm saline through the catheter. Six volumes were chosen as regular fractions of this capacity. Each subject was then given several practice trials of two or three of these volumes until he reported that he understood how to assess his perception. None of the chosen volumes was reported as painful.

The experimental session consisted of a series of 12 PET scans at intervals of 8–10 min. Just before the beginning of each scan, one of the six volumes of saline (warmed to body temperature) was instilled slowly into the bladder through the catheter (~200 ml/min). This volume was maintained in the bladder for the duration of the PET scan. During each scan, the subject lay quietly with eyes closed, having been instructed to attend to sensations of urge to void. The subject's reported perception of his urge to void was recorded immediately before and after each scan. Between scans and before filling the bladder to the next volume, the bladder was emptied completely by gentle suction through the catheter using a syringe. The six different volumes were delivered in pseudo-random order for the first six scans, and in the opposite order for the last six scans (to control for the effects of experimental duration and stimulus order). Stimulus order was counterbalanced across subjects.

PET scanning utilized the standard oxygen-15 water bolus technique on a Siemens ECAT PET scanner operating in 3D mode with septa retracted and with a 15 cm axial field of view. The resulting PET images were reconstructed to yield 63 axial planes with in-plane resolution of 6 mm at full-width-half-maximum. The images were co-registered to the subject's own MRI scan, spatially normalized to a standard brain in Talairach space, and smoothed using a 14 mm isotropic Gaussian kernel. These data were then analysed using Statistical Parametric Mapping (SPM99b, <http://www.fil.ion.ucl.ac.uk/spm>, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Data analysis fitted values derived from the bladder fill volume, and the subjects' perception of urge to void, to the PET data using least squares linear regression. Because volume and urge scores were correlated to some extent (see Results), orthogonalization of urge scores with respect to volume score was performed using Gram–Schmidt orthogonalization. This procedure allowed for the effect of volume or urge to be addressed separately and in isolation from the other, thus allowing for full evaluation of all experimental effects (Andrade *et al.*, 1999). Subject- and scan-dependent influences were co-varied out using ANOVA (analysis of variance).

Some subjects reported a periodic mild discomfort or conflicting sensations from the catheter during the scanning

session. Although there were no statistically significant inter-subject effects associated with these reports, co-variables corresponding to these influences nevertheless were modelled at subject level as confounding factors for data analysis. To control for the effect of possible sensitization or tolerance to either the presence of the urinary catheter or the successive fill/empty cycles (see Discussion), the statistical model included a linear time parameter as a further confound. Voxel-level parameter estimates for each regression were then obtained and linear contrasts of these estimates tested for significance using multiple independent *t* tests applied at voxel level. The resulting *t* statistics were transformed to the corresponding *Z* score and displayed in three dimensions as a statistical parametric map (SPM) of spatially distributed voxel-level activity. In the light of our prior, anatomically specified, hypotheses concerning regions of expected brain activity, the statistics so obtained were interpreted such that activations in pre-specified regions were considered significant at $P < 0.05$ without whole-brain correction for multiple comparisons. For the activation in the PAG, our principle area of interest, we corrected for multiple comparisons in a volume of interest (Worsley *et al.*, 1996) defined as a region of the brainstem estimated from the standard MRI to contain this structure.

Outside of regions anatomically specified *a priori*, we applied a significance threshold of $P < 0.05$ with correction for multiple whole-brain comparisons. No voxels reached this threshold in any comparisons, and we report activations in these areas only as trends, for descriptive purposes.

To characterize further the pattern of brain activity in those conditions where reported urge was inconsistent with volume, the volume score related to each scan was subtracted from the corresponding urge score. The resulting value represented a measure of the 'mismatch' between volume and urge for each scan and was maximal primarily for those scans where there was low volume and high urge. These values were regressed onto the PET data and the observed activations again considered in terms of anatomically defined regions specified *a priori* as above.

Results

Bladder fill volume and perception of urge to void

In general, perceptions of the urge correlated positively with bladder fill volume (Fig. 1). There were no significant differences in ratings of urge either before and after each scan or between the first and second sets of trials. However, there were individual variations in the relationship between volume and urge. Whilst all subjects gave their urge to void high values when their bladder was filled close to its capacity, urge values given when the bladder was empty or filled to a low volume differed between subjects. Those reporting some interference in urge sensation related to the presence of the catheter (six out of 11 subjects) reported higher urinary urge at low bladder volumes. Despite these differences, comparison

of brain activation between these two subject groups revealed no significant group-related effect in either effect of urge or effect of bladder filling.

Changes in brain activity with increasing volume and not with urge to void

Brain regions showing activity related to increases in bladder volume are listed in Table 1. Increases in activation were seen in the PAG and a central region of mid-pons (Fig. 2A and B). There was also activation bilaterally in the cingulate cortex and frontal lobes (Fig. 2) and an additional focus of activation in the right inferior frontal gyrus. There were *trends* to activation with increasing bladder volume in bilaterally symmetrical portions of the parietal lobes and the right and left cerebellum.

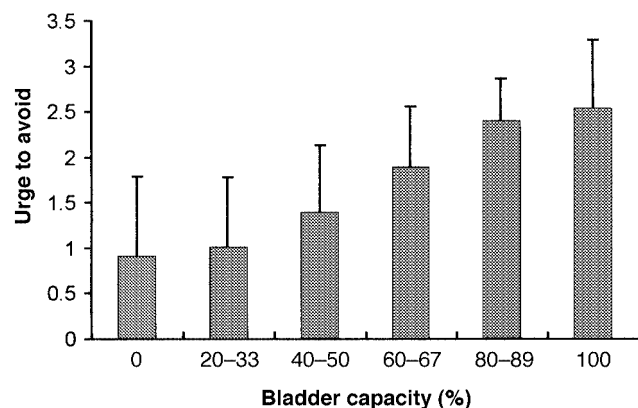


Fig. 1 Relationship between urge (perceptual scale 0–4, see Methods) to void and bladder capacity (correlation coefficient $\rho = 0.65$). Urge scores are those reported immediately after each PET measurement and bladder capacity is expressed as a percentage of total (see Methods). The error bars are standard deviation.

Changes in brain activity with urge and not with bladder volume

Increases in the urge to void were associated only with *deactivations* (Table 2). Thus, significant deactivation with increases in urge to void (alternatively increased activation with decreased urge to void) were seen in a central brain area in the region of the hypothalamus, peaking to the right of the midline. Similar changes in brain activity were seen bilaterally in the premotor regions, as well as bilaterally in the cingulate gyrus (Fig. 3).

Mismatch between urge and bladder volume

Deactivation was observed bilaterally in somatosensory cortex as the ‘mismatch’ between bladder volume and urge to void increased (Table 3).

Discussion

The inconsistent relationship between bladder volume and urge to void observed here is a well-known phenomenon. The functional imaging data reflected this mismatch to some extent. Increases in the volume of bladder fullness, regardless of the subjects’ perception of urge, activated a set of areas that previously have been associated with the control of bladder function (PAG, pons, cingulate and frontal cortices). In contrast, changes in urge were associated with brain activity decreases in a distinct set of regions (right and left premotor cortex, hypothalamus and cingulate cortex). ‘Mismatches’ between the degree of bladder fullness and urge (primarily high urge, low volume) deactivated the somatosensory cortex bilaterally.

Possible confounding influences

It is important to consider two factors other than fill volume or urge that could have influenced the results. One factor is

Table 1 Regions where increases in blood flow were significantly correlated with increasing bladder volume and not with the urge to void

	x	y	z	Z score	P value (uncorrected)
Periaqueductal grey matter	4	–24	–12	2.83	<0.001*
Mid-pons	4	–22	–32	2.07	<0.005
Cingulate cortex	–2	18	22	3.27	<0.001
Left middle frontal gyrus	–36	38	44	3.43	<0.001
Right middle frontal gyrus	46	48	26	3.52	<0.001
Right inferior frontal gyrus	56	40	16	3.36	<0.001
Left parietal cortex	–56	48	52	3.12 [†]	<0.001
Right parietal cortex	58	–28	56	2.70 [†]	<0.005
Cerebellar left lateral lobe	–12	–48	–20	2.79 [†]	<0.005
Cerebellar right lateral lobe	24	–52	–30	2.72 [†]	<0.005

*Small volume correction (cluster) for a sphere 2.5 cm diameter centred at cluster peak = 0.039. [†]Activations in areas outside those specified by prior hypotheses, here considered only as trends to activate.

that repeated presentations of bladder stimuli might have provoked successively greater perceptual responses, in a process of sensitization. Ness and colleagues have reported such sensitization in the context of repeated filling of the urinary bladder *per urethra*, but only within the first few in a series of stimuli (Ness *et al.*, 1998). Our experimental paradigm included several bladder fills prior to the scanning session, so it appears unlikely that such sensitization influenced urge ratings here. In fact, urge ratings for the first six stimuli did not differ significantly from those for the second six. Furthermore, the statistical model included a term considering activations related to scan order-dependent effects of bladder filling as effects to be excluded from the analysis.

Another potentially confounding factor is the urethral catheter. The fact that the catheter was present throughout the experiment would have minimized its influence on measurements of brain activity unless its effect was in some way changing systematically with bladder volume or urge to void. More than half the subjects reported that the catheter affected their ratings of urge, primarily at low volumes of

bladder filling. A comparison of brain activity between those who did and did not report this catheter effect revealed no significant catheter-related activity *per se* nor a catheter-related interaction of the effects of volume upon urge. However, when the interference of the catheter with the perceptions of urge was assessed (low volume, high urge), the interference or 'mismatch' was reflected by decreased activity in primary somatosensory cortex (see below).

Periaqueductal grey

The PAG receives bladder-related sensory input from the sacral spinal cord (Blok *et al.*, 1995). Our observation here that brain activity in PAG increases as bladder volume increases supports this finding and suggests that the PAG plays a critical role in the control of urinary events, serving as an interface between the afferent and efferent arms of the bladder control system. Interestingly, in studies of micturition, Blok and colleagues reported PAG activation with micturition in men (Blok *et al.*, 1997b) but not in women (Blok *et al.*, 1998), indicating variation in the association of this region with the act of micturition. Of relevance is that activity in PAG in the present study did *not* correlate with sensations of urgency, suggesting that the influence of bladder sensory information on the PAG is unlikely to be the only determinant of voiding behaviour. Particularly in humans, the initiation of voiding is a complex process, and factors other than bladder fullness are critical.

Pons

In their studies in male and female volunteers, Blok and colleagues (Blok *et al.*, 1997b, 1999) found activation in a

Table 2 Regions where increases in blood flow were significantly correlated with decreased urge to void and not with bladder volume*

	x	y	z	Z score	P value
Left cingulate cortex	-2	-4	36	2.94	<0.005
Right cingulate cortex	10	6	36	2.62	<0.005
Right premotor cortex	50	2	28	4.34	<0.001
Left premotor cortex	-62	6	12	3.11	<0.001
Hypothalamus	4	-12	-6	3.25	<0.001

*No significant increases in blood flow were observed.

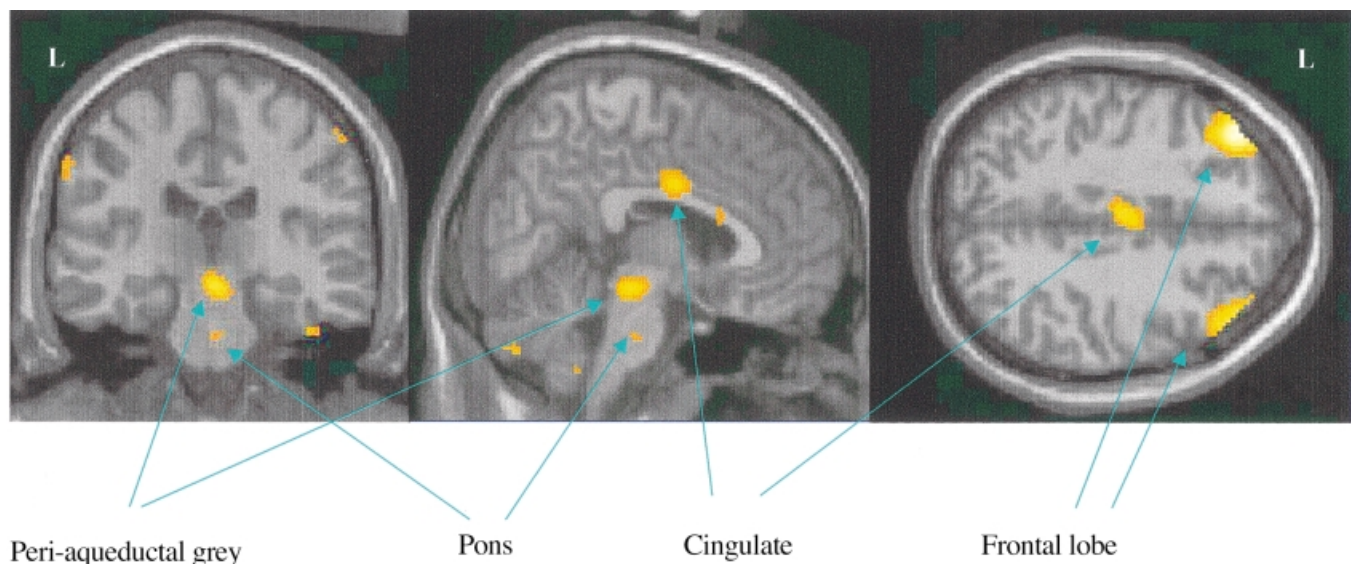


Fig. 2 Increases in brain activity with increasing volume. Activations are shown superimposed on three orthogonal sections of normalized brain (see Methods). Increases in brain activity with increases in bladder volume are seen in the PAG, pons, cingulate and also in frontal lobes. SPM *t*, *P* < 0.05 uncorrected.

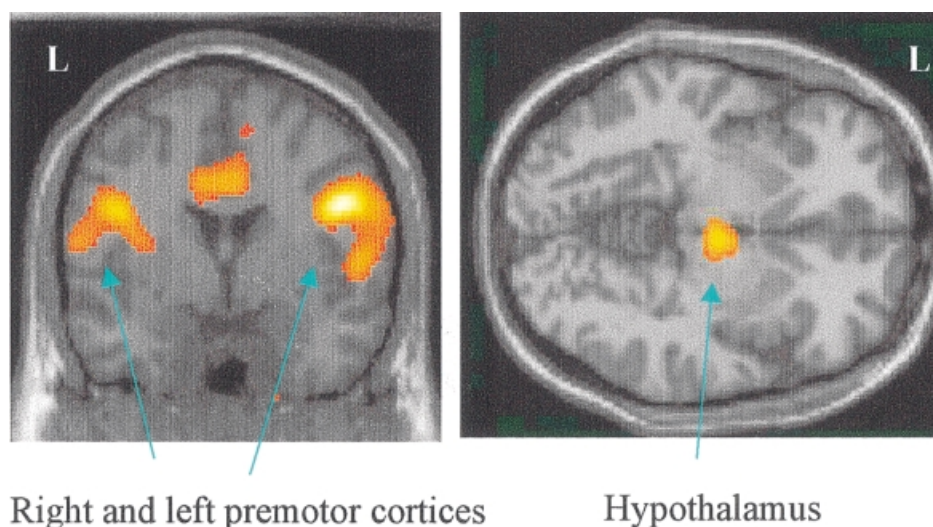


Fig. 3 Decreases in brain activity with increasing urge. Areas of brain showing decreases in activity with increasing urge to void. Activity changes are shown superimposed on sections of normalized brain. SPM t , $P < 0.05$ uncorrected.

Table 3 Regions where decreases in blood flow occurred with mismatches between reported urge to void and bladder fill volume*

	x	y	z	Z score	P value
Right primary somatosensory cortex	30	-24	50	2.99	<0.001
Left primary somatosensory cortex	-38	-22	60	2.78	<0.005

*No significant increases in blood flow were observed.

dorsolateral region of the pons in those subjects unable to void and proposed this region as the human homologue of the L-region of the cat which exerts a continuous excitatory effect on Onuf's nucleus resulting in inhibition of urethral relaxation and detrusor contraction (Griffiths *et al.*, 1990). Such a mechanism would be likely to become increasingly engaged during progressively increased bladder filling in a situation inappropriate for voiding such as in the present study. However, the peak of the activation we observed was situated 4 mm more medial and 4 mm more caudal to that previously reported.

Cerebellum

A recent study that compared the cortical processing of human somatic and visceral sensation by stimulating the proximal and distal oesophagus found the greatest difference in stimulation-evoked brain responses to be in the cerebellum (Aziz *et al.*, 2000), with activation most marked with the more distal visceral stimulation. It is of interest that here we found a trend for bilateral activation of the cerebellar lateral lobes with increasing bladder filling, but not urge. Cerebellar activation is thought to be brought about by activation of C fibres but not A-delta fibres (Aziz *et al.*, 2000). The sensation of non-painful distension of the bladder is thought also to have a significant C fibre-mediated component, as evidenced

by recent studies on the rat (Morrison, 1999), and previous PET studies of the act of micturition micturition also showed cerebellar activation (Blok *et al.*, 1997b; Nour *et al.*, 2000). We suggest therefore that, in addition to a probable motor role in micturition, the cerebellum processes sensory information from the bladder during urine storage. This conclusion is consistent with earlier animal studies showing that stimulation or lesions within the cerebellum affect both urine storage and micturition (Bradley and Teague, 1969; Nishizawa *et al.*, 1989).

Frontal lobes

In a series of papers in the mid 1960s, Nathan and Andrew described bladder dysfunction in a group of patients produced by aneurysms, tumours, gunshot wounds or leucotomies that had disrupted portions of the anterior part of the frontal lobe (Nathan, 1963; Andrew and Nathan, 1964, 1965; Andrew *et al.*, 1966). They reported a syndrome of urinary urge, frequency and urge incontinence: 'the feeling of gradual distension of the bladder is lost and the only warning that the patient has that his bladder is full is the sensation associated with the imminence of micturition'. The patients had problems in sensing bladder fullness and experienced incontinence, nocturnal enuresis and an inability to suppress the micturition reflex once it had begun. Characteristically,

detrusor–sphincter coordination required for the act of micturition itself was normal. Similar observations reported in stroke are of the association of urinary symptoms with frontal cortex brain lesions (Sakakibara *et al.*, 1996) and of frontal cortex underperfusion with urge incontinence and reduced bladder sensation (Griffiths *et al.*, 1994). The results of brain imaging studies of micturition in right-handed men and women support these findings, showing increased activity in the right frontal regions both during micturition and during unsuccessful attempts to micturate (Fukuyama *et al.*, 1996; Blok *et al.*, 1997b, 1998), although Nour and colleagues did not find frontal cortex activity in voiding studies (Nour *et al.*, 2000).

The findings reported here extend these observations to show that the frontal lobes are also involved in the storage mode of bladder function. Activation was mostly bilateral in our group of mixed left- and right-handed men, and how these regions are involved in storage is difficult to specify, but one possibility is that there is interaction with other brain regions such as the PAG. In support of this hypothesis is evidence from lesion studies and, in a case series of frontal lobe tumours, Maurice-Williams reported improvement in bladder symptoms upon excision of the frontal lobes, suggesting a role for these areas in the modulation of urinary control (Maurice-Williams, 1974). Similarly, in another series of nearly 500 patients who had had surgery for brain tumour, frontal lobectomy or bilateral anterior cingulectomy, Ueki concluded that, in the normal course of events, the frontal lobes inhibited a micturition-promoting centre in the pons (Ueki, 1960).

Cingulate gyrus, hypothalamus, and premotor cortex

Activity in the cingulate gyrus has been reported in a number of brain imaging studies of visceral sensation, particularly visceral pain (Jones *et al.*, 1991; Aziz *et al.*, 1997; Derbyshire *et al.*, 1997). This area functions as a part of the limbic system (Devinsky *et al.*, 1995) and in the context of pain may constitute part of a system that participates in the affective, motivating component of the pain experience. However, lesions in the cingulate gyrus are also associated with bladder disturbances of various types, especially urge incontinence (Andrew and Nathan, 1964; Maurice-Williams, 1974). Furthermore, stimulation of a posterior part of the cingulate gyrus in cats interrupts micturition when the bladder is filled rapidly (Gjone, 1966). Blok and colleagues found that brain activity decreases in anterior cingulate have been related to urine withholding and also presumably urgency when the bladder was full, compared with either micturition or an empty bladder condition (Blok *et al.*, 1997b).

Here, we observed that activity in a portion of the cingulate gyrus increased as bladder volume increased, while activity in a different, mid-portion of the cingulate increased as urge to void decreased. Although some of this activity conceivably

could have been related to the nociceptive functions of the cingulate cortex mentioned above, our subjects never reported pain. Activity in the cingulate relating to non-painful visceral stimulation has been observed in a study of proximal and distal oesophageal distension (Aziz *et al.*, 2000). In that study, activity occurred during stimulation of the proximal (but not distal) oesophagus in a part of the cingulate gyrus similar to that which was activated here as urge to void decreased (compare Fig. 2 here with Fig. 1D in Aziz *et al.*, 2000). The cingulate gyrus is known to have direct connections with brainstem nuclei and to be involved in regulation of autonomic and emotional responses to external stimuli (Devinsky *et al.*, 1995; Vogt *et al.*, 1996; Aziz *et al.*, 2000). It has reciprocal connections with a number of brain regions including the PAG (Hardy and Leichnetz, 1981) and projects to, among other regions, the motor and premotor cortices (Devinsky *et al.*, 1995.) It is possible, therefore, that the responses observed here in two parts of the cingulate gyrus reflect its complex role in using information arising from the bladder to influence the urge to void as well as the maintenance of continence.

What is particularly interesting here was the observation that activity in the mid-cingulate gyrus, hypothalamus and premotor cortex increased as urge to void *decreased*. Similar regions were activated in a study by Nour and colleagues at the onset of micturition in catheterized subjects (Nour *et al.*, 2000). Voiding in the scanner in our study would have been inappropriate, and thus one way to interpret these activity patterns is that they are associated with suppression of the urge to void and with control of the initiation of voiding. In support of this conclusion are two disparate findings. First, recent evidence suggests that the portion of the premotor cortex activated here and the cingulate gyrus have important functions in modulating selective attention under conditions of task conflict (Cohen *et al.*, 2000) and interact in ‘monitoring behavior and guiding compensatory systems’ (Gehrig and Knight, 2000). Secondly, earlier evidence derived from patients with various disruptions to the anterior midline region of the frontal lobe which led Andrew and Nathan to conclude that this region controls the septal and hypothalamic nuclei to ‘integrate micturition and defaecation into our normal daily activities with our environment’ (Andrew and Nathan, 1965).

Somatosensory cortex

There was a notable lack of any activation in regions of primary somatosensory cortex associated with changes in either bladder volume or the urge to void. Other studies have reported conflicting results with respect to activation of these areas by visceral stimulation. For example, PET studies of gastrointestinal distension report finding either the presence (Silverman *et al.*, 1997) or absence (Rothstein *et al.*, 1996) of somatosensory cortex activation. Consistent neuronal responses to visceral stimuli have, however, been demonstrated in these areas in experimental animals

(Bruggemann *et al.*, 1994, 1997). Here we observed *decreased* activity bilaterally in the post-central gyri with greater degrees of mismatch, or discrepancy, between the bladder fill level and urge to void. In other words, at low volumes, when the urge to void was low (less mismatch), somatosensory cortical activation was greater than at low volumes when the urge to void was high (more mismatch). Because the phenomenon of 'mismatch' was most marked in those subjects who reported that the catheter interfered with their ratings of urge, the results here suggest that activity in primary somatosensory cortex and parietal operculum does indeed relate to some aspect of somatic perception produced by the urethral catheter. In support of this conclusion are results from a recent PET study of micturition in catheterized subjects, in which sensorimotor activity observed during voiding was attributed to an increased resistance to voiding due to the presence of the catheter (Nour *et al.*, 2000).

Conclusion

These findings underscore the complexity of neural processing associated with the control of storage and elimination of urine, and support our hypothesis that the network of brain regions associated with the recognition of bladder fullness is distinct from that associated with the perception of the urge to void.

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