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Cerebral activation during micturition in normal men

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Summary

Specific cerebral lesions have shown the crucial role of the brain in the control of micturition. The precise identification of the anatomical cerebral structures involved in micturition can contribute to a better understanding of the control of micturition and the development of therapeutic models. Various neuropathological and animal studies have referred to the medulla oblongata, pons, limbic system, superior frontal lobe and premotor cortical regions as areas implicated in micturition control. The aim of this study was to investigate whether the activity of these areas during micturition can be confirmed by PET in normal men. The distribution of the regional cerebral blood flow after bolus injection of ^{15}O water was used as an indirect measure of cerebral activation. PET scans were performed during the following three conditions: (i) at rest with the bladder empty; (ii) during simulated micturition after instillation of isotonic saline into the urinary bladder; and (iii) the withholding of urine (saline). Normal micturition using this model was achieved in eight out of 12 right-handed normal subjects. The changes in bladder contraction, bladder pressure and intra-abdominal pressure were monitored on-line during the whole scanning session by a cystometry device. The images were analysed using statistical parametric mapping at a significance threshold of $P < 0.05$ with correction for multiple independent comparisons. Micturition versus rest was associated with bilateral activation of areas close to the postcentral gyrus, inferior frontal gyrus, globus pallidus, cortex cerebelli, vermis and midbrain. On the left side, activation of the middle frontal gyrus, superior frontal gyrus, superior precentral gyrus, thalamus and the caudal part of the anterior cingulate gyrus was seen, while on the right side we found activation in the supramarginal gyrus, mesencephalon and insula. When the threshold value was lowered to $P < 0.001$ ($Z > 3.09$) without correction for multiple comparisons, we found additional activation in the medial pontine tegmentum, mesencephalon, right thalamus, right middle frontal gyrus and left insula. When urine-withholding was compared with rest, the left insula showed a tendency to activate. We conclude from this study, in which urinary bladder contraction was verified cystometrically, that the onset and maintenance of micturition in normal men is associated with a vast network of cortical and subcortical regions, confirming observations from clinical and animal studies.

Keywords: PET; brain mapping; micturition; insula; frontal lobe

Abbreviations: FD = first desire to void; ND = normal desire to void; PAG = periaqueductal grey matter; PMC = pontine micturition centre; SD = strong desire to void; SMA = supplementary motor area; SPECT = single photon emission computed tomography; SPM = statistical parametric mapping

Introduction

Micturition is a complex process involving the coordination of functions that are under both voluntary and involuntary control. Thus, in spite of many clinical and animal studies and recent functional imaging studies there is still very little known about the central pathways and mechanisms behind the control of micturition.

Urinary incontinence is a common deficit associated with stroke (Kamouchi *et al.*, 1995; Sakakibara *et al.*, 1996*a*, *b*), multiple sclerosis (Barbalias *et al.*, 1998), Alzheimer's disease (Del-Ser *et al.*, 1996), multiple system atrophy (Chandiramani *et al.*, 1997), traumatic brain lesion (Kuru 1965), brain tumours (Yamagushi 1959), normal pressure hydrocephalus, Parkinson's disease (Jost *et al.*, 1996) and other cerebral disorders.

Incontinence-provoking lesions can be located in the motor cortex (Kuru, 1965), the anterior and medial surfaces of the frontal lobe, the anterior edge of the paraventricular white matter, the genu of the internal capsule, the putamen, the thalamus (Sakakibara *et al.*, 1996*a*) and the brainstem (Sakakibara *et al.*, 1996*b*). Disorders located rostral to the pons almost always result in urge incontinence, while total disruption of the spinal cord always results in bladder–sphincter dyssynergia (an uncoordinated contraction of bladder and sphincter) (Schurch *et al.*, 1994). Micturition must therefore be controlled by some region rostral to the pons and not by the spinal cord.

Earlier animal studies (Langworthy *et al.*, 1936; Tang, 1955; Tang and Ruch, 1956; Mukai, 1959; Gjone *et al.*, 1963; Yeates, 1974) have revealed that the motor cortex, the superomedial part of the frontal lobe, the anterior part of the cingulate gyrus and the genu of the corpus callosum have an inhibitory effect on two centres responsible for the initiation and coordination of micturition, viz. the hypothalamus and the pontine micturition centre (PMC). The physiology of micturition has been further elucidated by a more recent animal study (Fukuda *et al.*, 1992) using somatosensory evoked potentials and electrocortical stimulation in dogs. This study suggests involvement of the sacral, hind leg and abdominal motor areas in the interruption of micturition through inhibition of the PMC and contraction of the external urethral sphincter.

Brain imaging studies of regional cerebral blood flow during behavioural activation offers a powerful tool for the non-invasive localization of sensorimotor and psychological functions. Two previous brain imaging studies of micturition (Fukuyama *et al.*, 1996; Blok *et al.*, 1997*a*) have confirmed the crucial role of frontal lobe and subcortical structures during micturition. A study by Fukuyama and colleagues using single photon emission computed tomography (SPECT) showed bilateral activation in the supplementary motor areas (SMA), the left sensorimotor area, the right frontal lobe, the pons and the midbrain during micturition (Fukuyama *et al.*, 1996). Some of these results were confirmed by Blok and colleagues, who found significant activation in the right PMC, the periaqueductal grey (PAG), the hypothalamus and the right inferior frontal gyrus when comparing successful micturition with rest with the bladder empty (Blok *et al.*, 1997*a*). These studies were performed without behavioural observation by cystometric recording and with the use of the subject's own urine production, which limited the number of scans performed per subject to one. Based on these considerations, we designed an experimental setup involving catheterization of subjects for cystometry, which allowed on-line recording of the pressure changes resulting from detrusor muscle activity during scanning. These recordings were used in further qualitative evaluation of the PET images. By infusion of isotonic saline, we were able to repeat conditions for each subject two to four times, producing a better foundation for the statistical analysis.

Methods

Subjects

Twelve strongly right-handed (Oldfield, 1971) healthy male volunteers were recruited (mean age 23.4 $\pm$ 1.1 years, range 22–25 years). No subject had a reported history of urological, psychiatric or neurological disease and all gave written informed consent according to the Helsinki II declaration, and the study was approved by the local ethics committee [J.nr. (KF) 01–406/96]. Two of the subjects were unable to void during scanning and an additional two subjects had delayed micturition; all four of these subjects were excluded from further analysis.

Activation paradigm

A few days before the scanning sessions the subjects were instructed to practise voiding in a horizontal position at home. None reported difficulty voiding in this position. Ten to twelve PET scans were completed under five conditions in a randomized order (at least two scans in each condition). All scans were performed with the eyes closed and covered, in a dim room. Only results from the comparisons of three of these conditions will be reported.

The three conditions were: (i) two scans at rest with the bladder empty; (ii) two to four scans during micturition after the bladder had been filled to the normal desire to void (ND); (iii) two scans during the withholding of urine (isotonic saline) after the bladder had been filled to ND.

The conditions not discussed in this paper are (i) interrupted micturition every third second cued by a metronome, and (ii) contractions of the urethral sphincter muscles at rest with the bladder empty every third second. These conditions will be published soon as a complementary part of the present study.

The subject's bladder was catheterized with two feeding tubes (100 cm, no. 5; Pharma-Plast International, Lynge, Denmark) and the bladder was emptied. The two intravesical catheters were connected to a cystometry device (Menuet; Dantec Medical, Skovlunde, Denmark) and used to fill the bladder with isotonic saline (temperature 37°C, infusion velocity 50 ml/min) and to monitor intravesical pressure, respectively. Voiding was possible without removing the catheters. A feeding tube (100 cm, no. 8; Pharma-Plast International) was placed in the rectum to monitor intra-abdominal pressure. After the initiation of isotonic saline infusion into the bladder, the subjects were asked to report the first sensation of bladder filling (FD, first desire to void) and, after further filling, to report ND. The water volumes infused at these points corresponded to the bladder volumes at FD and ND, respectively. The sensation at ND is normally stronger and of a longer duration than that at FD. A strong desire to void (SD) can be accomplished by further instillation of saline. Strong pain and sometimes the involuntary initiation of micturition characterize SD; therefore, ND was used in conditions (ii) and (iii). It should be noted that the FD, ND

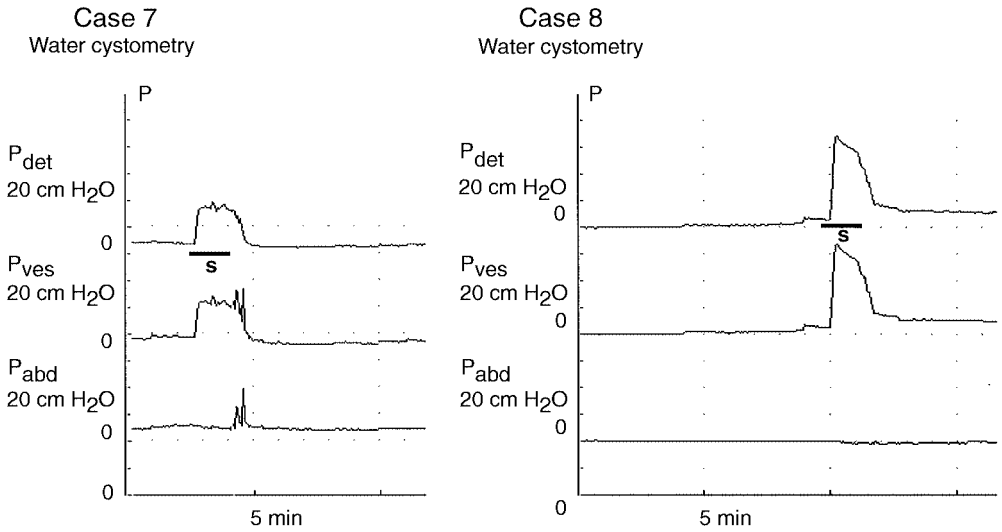

Fig. 1 Cystometry pressure curves. Two examples of pressure curves obtained during micturition PET scanning. The variations in intra-abdominal, vesical and detrusor pressures are illustrated. The intra-abdominal (P_{abd}) and intravesical (P_{ves}) values were measured directly by pressure transducers while detrusor pressure (P_{det}, the pressure resulting from bladder muscle activity) was calculated as $P_{ves} - P_{abd}$. The bar with the letter S illustrates the scanning period. P = pressure (cm H_2O).

and SD are used in clinical cystometric evaluation of bladder capacity and are not constant between or within subjects; these definitions are therefore subjective and represent an attempt to standardize bladder stimulation to some degree.

During the whole scanning session, the cystometry device performed on-line analysis of detrusor pressure, measured by subtraction of the intra-abdominal from the intravesical pressure. The pressure was plotted against time (Fig. 1), and the increase in the detrusor pressure was used to confirm bladder contraction during scanning.

Data acquisition

PET scanning

PET scans were obtained with an 18-ring GE-Advance scanner operating in 3D acquisition mode, producing 35 image slices with an interslice distance of 4.25 mm. The total axial field of view was 15.2 cm, with an in-plane resolution of ~5 mm. The technical specifications have been described elsewhere (DeGrado *et al.*, 1994). Every subject received 10–12 slow intravenous bolus injections of 400 MBq (11.4 mCi) of $H_2{}^{15}O$ with an interscan interval of 15 min. The isotope was administered through an antecubital intravenous catheter over 30 s (16 ml/min) by an automatic injection device. Head movement was limited by a head-holder constructed of thermally moulded foam. Before the activation session, a 10 min transmission scan was performed for attenuation correction. At the time of arrival of the bolus in the brain (~30 s after injection), the subjects were verbally instructed to void. The acquisition period was 90 s (Kanno *et al.*, 1991). Images were reconstructed with a 4.0 mm Hanning filter transaxially and an 8.5 mm Ramp filter axially. The resulting distribution images of time-integrated counts were used as indirect measurements of the regional neural activity (Fox *et al.*, 1989).

MRI scanning

Structural MRI scanning was performed with a 1.5 T Vision scanner (Siemens, Erlangen, Germany) using a 3D MPRAGE sequence (TR = 11 ms, TE = 4 ms, TI = 100 ms, flip angle = 15°). The images were acquired in the sagittal plane with an in-plane resolution of 0.98 mm and a slice thickness of 1.0 mm. The number of planes was 170 and the in-plane matrix dimensions were 256 × 256 voxels.

Image analysis

The complete brain volume was sampled for all subjects. Image analysis was performed using statistical parametric mapping software (SPM96; Wellcome Department of Cognitive Neurology, London, UK) (Frackowiak *et al.*, 1994).

All intrasubject PET images were aligned using a 3D six-parameter rigid body transformation. The MRI image from each subject was co-registered to the corresponding average PET image and both image modalities were transformed into the standard stereotaxic atlas of Talairach and Tournoux (Talairach and Tournoux, 1988; Friston, 1994). The inter-subject MRI average image was used for the anatomical localization of the activated areas. PET images were then smoothed with a 10 mm isotropic Gaussian filter to increase the signal-to-noise ratio and accommodate residual variability in morphological and topographical anatomy that was not accounted for by the stereotaxic normalization process (Friston *et al.*, 1995). Differences in global activity were

Table 1 *Data from cystometric recordings during scanning*

Subject	Successful recordings*	Micturition			Mean bladder volume at ND (ml)		
		Maximum detrusor pressure (cm H_2O)	Mean detrusor pressure (cm H_2O)	Mean detrusor contraction time (s)	Urine withholding scans	Micturition scans	Mean total volume
1	3/4	46 ± 4	26 ± 4	104 ± 45	569 ± 15	521 ± 36	545 ± 34
2	3/4	67 ± 4	47 ± 5	105 ± 2	317 ± 54	331 ± 27	324 ± 10
3	3/4	31 ± 2	18 ± 1	173 ± 94	351 ± 148	394 ± 54	373 ± 30
4	1/2	36	16	153	496 ± 6	643 ± 223	570 ± 104
5	3/4	38 ± 5	27 ± 5	134 ± 5	510 ± 98	577 ± 93	544 ± 47
6	3/4	93 ± 4	39 ± 2	79 ± 15	467 ± 47	413 ± 80	440 ± 38
7	3/4	30 ± 1	25 ± 4	167 ± 77	359 ± 34	460 ± 76	410 ± 71
8	2/2	61 ± 2	42 ± 40	143 ± 11	288 ± 1	358 ± 72	323 ± 49
Mean ± SD		50 ± 22	30 ± 11	132 ± 33	419 ± 103	462 ± 109	441 ± 30

*Number of successful cystometric recordings/total number of micturition PET scans.

removed by proportional normalization of global brain counts to a value of 50.

The resulting set of voxel values constituted a statistical parametric map of the t statistic, SPM{t}. By transforming values from the SPM{t} into the unit Gaussian distribution using a probability integral transform, changes could be reported in Z scores (SPM{Z}). Voxels were considered significant if their Z score exceed a threshold of $P < 0.05$ with correction for multiple comparisons. The threshold value was subsequently dropped to $P < 0.001$ ($Z > 3.09$) without correction for multiple comparisons in order to detect activation tendencies. This threshold has also been used in a previous PET study reporting data on the activation pattern during micturition (Blok *et al.*, 1997*a*). The resulting foci were then characterized in terms of the number of voxels (k) and peak Z score above this level.

Results

Cystometry

An increase in the average abdominal pressure during scanning was found in only three out of 21 successful cystometric recordings (range 2.3–7.4 cm H_2O). The remaining measurements were all found to be close to the noise level (range 2.1–1.8 cm H_2O).

The detrusor pressure curves (Fig. 1) were analysed to determine mean and maximum detrusor pressure and detrusor contraction time for each subject under the different conditions (Table 1). The mean and maximum detrusor pressures and the detrusor contraction times were used to document bladder contraction throughout the scanning period. Using paired t tests, we found no significant differences at a threshold level of $P < 0.05$ between urine withholding and micturition mean bladder volume at ND. Due to errors in data storage, not all cystometric recordings could be analysed *post hoc*. The numbers of successful recordings compared with the total numbers of micturition PET scans can be seen in Table 1. It should be noted, however, that the pressure changes were monitored on-line and that detrusor pressure changes were observed throughout all micturition scans. The ND volume was recorded before each scan, and thus no data were lost.

PET results

Urine withholding versus rest

When the urine-withholding condition was compared with rest, no areas showed significant activation (with correction for multiple comparison), but there was a tendency to activation (without correction for multiple comparison) in the left insula ($x = –40$, $y = 14$, $z = 2$).

Micturition versus rest

Areas with significant activation. The micturition condition compared with rest was associated with bilateral activation of areas close to the postcentral gyrus, inferior frontal gyrus, globus pallidus, midbrain, vermis and cortex cerebelli. On the left side, additional activation of the superior precentral gyrus, middle frontal gyrus, superior frontal gyrus, thalamus and caudal part of anterior cingulate gyrus was seen, whereas on the right side we found additional activation in the supramarginal gyrus, the central part of the mesencephalon on the right side of aqueductus cerebri and insula (Table 2 and Fig. 2).

Activation tendencies. When the threshold value was dropped to $P < 0.001$ ($Z > 3.09$) without correction for multiple comparisons, we found additional activation in the medial pontine tegmentum, mesencephalon, right thalamus, right middle frontal gyrus and left insula.

Discussion

The cortical structures

It should be noted that micturition is a complex process involving both voluntary and involuntary control and that

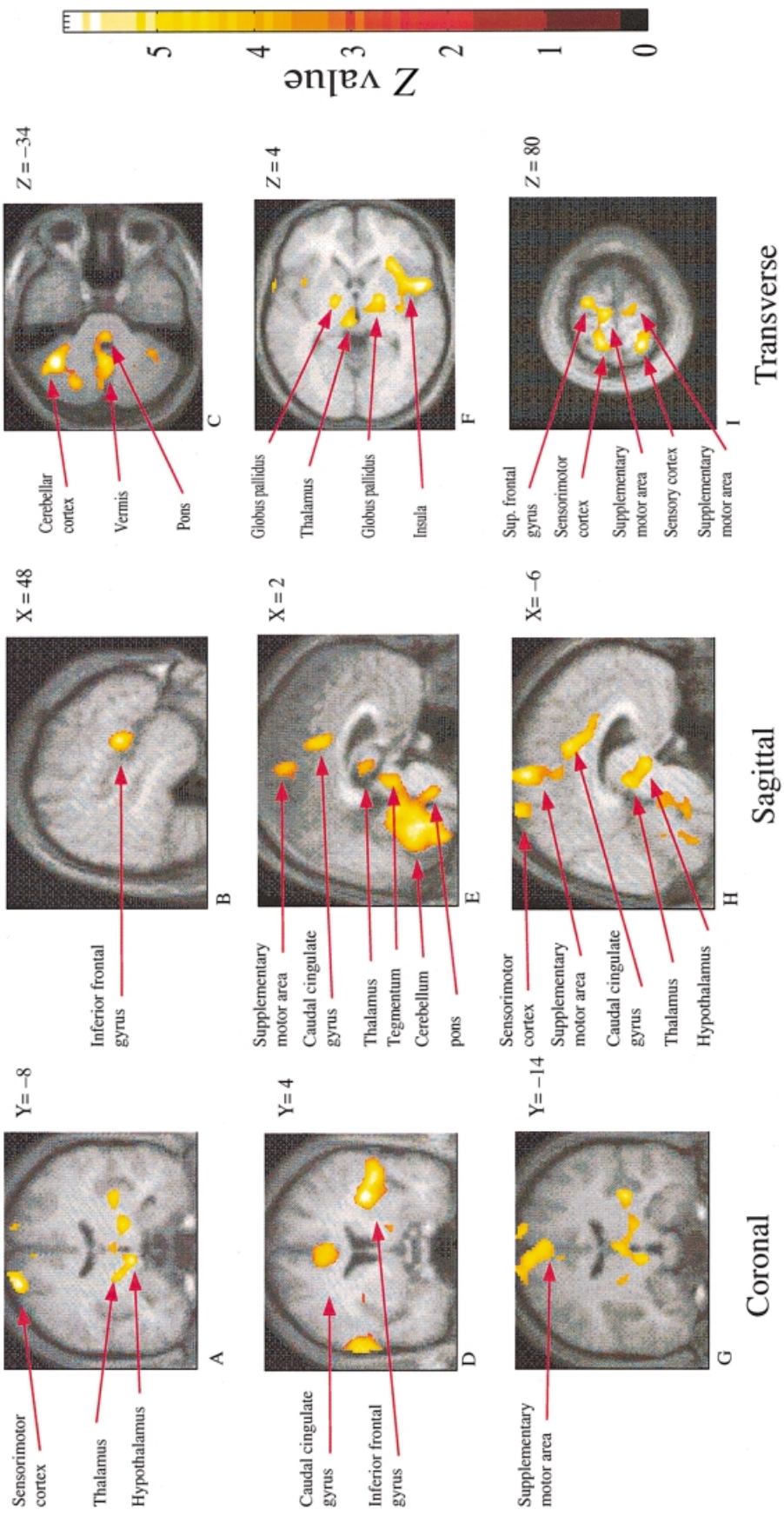

Fig. 2 Activation pattern of micturition versus rest superimposed on the average of the individual structure MRI scans. The activation image is thresholded at $P < 0.001$ uncorrected for multiple comparisons.

the active micturition scans in this study involved both the onset and the maintenance of micturition. The activation in the left pre- and postcentral gyri during micturition probably corresponds to activation of the abdominal sensorimotor region while the activation in the left middle frontal gyrus represents the SMA. A similar pattern has been demonstrated in a SPECT micturition study by Fukuyama and colleagues, who found activation in the left sensorimotor cortex and right lateral frontal cortex and bilateral activation in the SMA when comparing micturition with rest (Fukuyama *et al.*, 1996). Our study is the first to employ cystometric recording in the behavioural characterization of micturition during scanning. Although the catheters are also in place during the resting condition when this technique is used, it is possible that they can lead to micturition-related sensory stimulation. In part, this could be due to increased resistance to urine outflow, which could increase the stimulation of bladder stretch receptors. As these receptors would also be stimulated during normal micturition, it is reasonable to assume that the cerebral areas involved in the sensory perception are unchanged, although the regional activity might be increased. That the activation in this sensorimotor area is not solely an artefact of catheterization is supported by a study performed during normal micturition in which a similar activation was found (Fukuyama *et al.*, 1996). Although the change in abdominal pressure in the present study was modest, the relationship between intra-abdominal pressure and cerebral activation has not been studied in detail. Our activated foci are located close to areas found during the contraction of the pelvic floor and abdominal muscles (Blok *et al.*, 1997*b*), and therefore we cannot exclude this component.

The abdominal sensory motor cortex was not sampled in the study by Blok and colleagues (Blok *et al.*, 1997*a*), in which the actual field of view of the PET scanner used was limited; this restricted sampling to areas below 44 mm in Talairach space.

Sakakibara and colleagues have shown that lesions particularly in the frontal lobe or its descending pathways at the anterior edge of the paraventricular white matter, the genu of the internal capsule, the putamen or the thalamus result in micturitional disturbance (Sakakibara *et al.*, 1996*a*). This suggests that it is mainly lesions in the anteromedial frontal lobe and its descending pathways and the basal ganglia that are responsible for detrusor hyper-reflexia. Additionally, a study of 36 patients suffering from cerebrovascular accidents causing hemiplegia and continence disorders performed by Thiry and colleagues has pointed to the motor cortex as one region that is crucial in the inability to interrupt micturition in patients with continence disorders (Thiry *et al.*, 1989). These authors report that, when the bladder was empty, transcranial stimulation of the vertex resulted in contraction of the external urethral sphincter, whereas during micturition this stimulation had no micturition-interrupting effect. They concluded that, in these patients, either the central motor pathway was inhibited by other central circuits or the central motor volley itself failed to depolarize the inhibited sphincter lower motor neurons above their firing threshold.

During micturition we found bilateral activation in the inferior frontal gyrus as well as a tendency towards activation in the left superior frontal gyrus. Likewise, Fukuyama and colleagues and Blok and colleagues reported activation in the right lateral frontal cortex and the right inferior frontal gyrus when comparing similar conditions (Fukuyama *et al.*, 1996; Blok *et al.*, 1997*a*). The prefrontal lobes possibly play an important role in deciding whether to initiate micturition by direct connections to subcortical regions.

Apart from the motor cortex, the premotor cortex and the medial frontal gyrus, the comparison of micturition and rest demonstrated activation in other areas related to voluntary motor control, such as the anterior cingulate gyrus and the cerebellum. This pattern of activation could reflect the involvement of voluntary motor control over the autonomic nervous system in micturition. In many ways this resembles findings during volitional breathing (Colebatch *et al*., 1991).

Urodynamic evaluation of patients with cerebellar ataxia (Prati *et al.*, 1993) and investigations in animals involving cerebellectomy (Nishizawa *et al.*, 1989) suggest an inhibitory role of the cerebellum in the storage phase and a possible facilitatory role in the emptying phase of micturition. Blok and colleagues also found the cerebellum to be activated significantly during straining of the pelvic muscles in women (Blok *et al.*, 1997*b*). It is possible that the cerebellum regulates detrusor muscle tone during both urine storage and the micturition phase. We also found that the vermis was activated during micturition. Intricate connections exist between the hypothalamus and the anterior cerebellar vermis which could supply the anatomical substrate for the regulation of autonomic responses such as micturition (Supple, 1993).

Subcortical structures

In comparing micturition versus rest, this study showed bilateral activation in the globus pallidus and the cortex cerebelli as well as activation in the anterior and posterior parts of the midbrain and in vermis, left thalamus and right insula (Fig. 2 and Table 2). Activation in the midbrain possibly represents activation in the rostral part of the hypothalamus and the tegmental part of the PAG (Fig. 2E and H). A region in the pons (possibly PMC) and tegmentum (possibly PAG) also showed a tendency to activate (Table 2). Fukuyama and colleagues have reported activation in the midbrain and pons when comparing micturition versus rest (Fukuyama *et al*., 1996). Additionally, Blok and colleagues have demonstrated activation in the hypothalamus, areas close to the PAG, the right dorsomedial pons, the right dorsomedial pontine tegmentum and the rostral hypothalamus when comparing successful micturition with rest with the bladder empty (Blok *et al.*, 1997*a*). None of these authors have reported any activation in the thalamus, insula or globus pallidus; some of these activated areas may therefore reflect stimulation of the bladder and urethra by the catheter. On

Table 2 *Results comparing micturition with rest*

Region	Cluster size *k*	*Talairach coordinates*			Peak activation	
		x	*y*	*z*	*Z* score	*P* value*
R cerebellum &		30	−42	−50	4.92	<0.05
R cerebellum	575	*36*	*−48*	*−40*	*4.26*	*0.283*
L cerebellum &		−24	−66	−48	5.08	<0.05
L cerebellum &		*−32*	*−42*	*−40*	*4.29*	*0.261*
L cerebellum &		−38	−54	−34	6.00	<0.001
L cerebellum &		*−22*	*−72*	*−32*	*4.58*	*0.092*
R cerebellum (vermis) &		2	−56	−24	5.60	<0.001
R cerebellum (vermis) &		2	−44	−8	5.18	<0.05
R cerebellum &		*2*	*−56*	*−6*	*4.47*	*0.135*
R pons (PMC) &		*2*	*−34*	*−32*	*4.63*	*0.074*
Mesencephalon (PAG) &		*0*	*−32*	*−10*	*4.06*	*0.499*
R mesencephalon (PAG)&		4	−26	−6	5.24	<0.05
L anterior mesencephalon &		−6	−10	−4	4.75	<0.05
L thalamus &		−4	−24	6	4.89	<0.05
R thalamus &		*0*	*−16*	*12*	*4.14*	*0.404*
R thalamus &		*10*	*−14*	*4*	*3.59*	*0.963*
R globus pallidus &		16	−4	0	5.35	<0.001
L globus pallidus &		−16	−8	2	4.71	<0.05
R anterior insula &		28	24	4	4.72	<0.05
R anterior insula &		36	4	14	6.17	<0.001
R posterior insula &		36	−14	8	4.74	<0.05
L caudal cingulate gyrus &		*−6*	*16*	*32*	*3.94*	*0.657*
L caudal cingulate gyrus &		*−4*	*6*	*38*	*4.57*	*0.092*
L caudal cingulate gyrus &		−4	0	46	4.95	<0.05
R inferior frontal gyrus	7484	48	4	10	5.67	<0.001
L superior frontal gyrus &		−22	−8	72	4.95	<0.05
L middle frontal gyrus (SMA) &		*−8*	*−20*	*54*	*3.74*	*0.867*
R middle frontal gyrus (SMA) &		*4*	*−16*	*64*	*4.24*	*0.305*
L middle frontal gyrus (SMA) &		−6	−18	74	5.09	<0.05
L post- and precentral gyrus	2187	−10	−40	76	5.11	<0.05
R middle frontal gyrus (SMA) &		*10*	*−18*	*80*	*3.99*	*0.595*
R postcentral gyrus	469	20	−44	74	5.45	<0.001
R supramarginal gyrus	379	56	−30	24	5.09	<0.05
L inferior frontal gyrus	338	−66	4	14	5.30	<0.01
L frontal insula	**93**	40	10	0	3.79	0.828

Results of comparisons of micturition with rest. Coordinates are given in standard stereotaxic space (Talairach and Tournoux, 1988) as defined by the Montreal Neurological Institute (MNI) in millimetres for the maximally significant pixel in each area in the order *x*, *y*, *z*; *x* is the lateral displacement from the midline (− for the left hemisphere and + for the right hemisphere); *y* is the anterior–posterior displacement relative to the anterior commissure (– for positions posterior to this); *z* is the vertical displacement relative to the anterior–posterior commissure line (– below this line). Interconnected foci are indicated by an ampersand (&) and the total cluster size *k* above a threshold of $P < 0.001$ is given. The *Z* scores at the peak increase and the corresponding corrected *P* values are quoted. The foci activated above a threshold of $P < 0.05$ corrected are in bold characters and the foci above $P < 0.001$ uncorrected are in italic.
*Corrected for multiple comparisons.

the other hand, activity of these structures could be due to the involvement of a complex network of cortical and subcortical structures during the onset and maintenance of micturition.

The most recent model of the control of micturition is based on studies performed by Blok and Holstege (Blok and Holstege, 1994) and Blok and colleagues (Blok *et al.*, 1995, 1997*a*). According to this model, information about the degree of bladder-filling is sent from neurons in the lumbosacral cord to the PAG, an area known for its involvement in nociception (Mantyh 1982), micturition and many other vital functions. When the bladder is filled near to its capacity and voiding is appropriate, the PAG activates an area in the dorsomedial pontine tegmentum referred to as the M region or PMC. The PMC in turn initiates a complete synergic micturition response through the descending parasympathetic bladder motor neurons in the sacral part of the spinal cord. It has been suggested that PAG activation results from bladder stretch receptor activity, which in turn activates the PMC (Vanderhorst *et al.*, 1996). On the other hand, when comparing the withholding of urine with rest with the bladder empty, neither the present study nor previous studies have reported significant activation in the PAG. So either the activation of the PAG in this state is not detectable by PET or the distension of the bladder near to its capacity alone is not what gives rise to PAG activation. Activation of the PAG during

micturition may be responsible for disinhibition of the PMC. The remaining question is how the PAG is controlled. It has been shown that the rostral part of the hypothalamus not only has descending pathways to the PAG (Holstege, 1995) but is also the only region in the midbrain that projects directly to the PMC (Holstege, 1987). Micturition may be initiated through activation of the hypothalamus, which in turn activates the PAG, resulting in disinhibition of the PMC, which in turn coordinates micturition. Inhibition of the PMC, on the other hand, may occur via the descending projections of the abdominal sensorimotor area, also resulting in contraction of the external urethral sphincter (Fukuda *et al.*, 1992). A recent MRI study of patients with urinary disorders after an acute brainstem stroke (Sakakibara *et al.*, 1996*b*) verifies the pons as a region that is crucial in the control of micturition. This study showed correlation between urinary disorders and lesions concentrated in the dorsolateral pons, including the pontine reticular nucleus and the reticular formation adjacent to the medial parabrachial nucleus and the locus coeruleus.

Subtracting urine-withholding scans at ND from rest with the bladder empty, we found a tendency towards activation only in the left anterior insula. Hsieh and colleagues demonstrated that chronic ongoing neuropathic pain in man results in activation of the anterior insula but not activation of the somatosensory areas (Hsieh *et al.*, 1995). It has also been suggested (Saper, 1982) that insular cortex may represent a cortical region for the integration of the limbic and the autonomic response. The activation of the insula during the withholding of urine could be due to visceral sensory feedback from the stretch receptor activity of the bladder, the autonomic regulation of the micturition process or the stimulation of the bladder and urethra by catheters.

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References

Barbalias GA, Nikiforidis G, Liatsikos EN. Vesicourethral dysfunction associated with multiple sclerosis: clinical and urodynamic perspectives. J Urol 1998; 160: 106–11.

Blok BF, Holstege G. Direct projections from the periaqueductal gray to the pontine micturition center (M-region). An anterograde and retrograde tracing study in the cat. Neurosci Lett 1994; 166: 93–6.

Blok BF, De Weerd H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. J Comp Neurol 1995; 359: 300–9.

Blok BF, Willemsen AT, Holstege G. A PET study on brain control of micturition in humans. Brain 1997a; 120: 111–21.

Blok BF, Sturms LM, Holstege G. A PET study on cortical and subcortical control of pelvic floor musculature in women. J Comp Neurol 1997b; 389: 535–44.

Chandiramani VA, Palace J, Fowler CJ. How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol 1997; 80: 100–4.

Colebatch JG, Adams L, Murphy K, Martin AJ, Lammertsma AA, Tochon-Danguy HJ, et al. Regional cerebral blood flow during volitional breathing in man. J Physiol (Lond) 1991; 443: 91–103.

DeGrado TR, Turkington TG, Williams JJ, Stearns CW, Hoffman JM, Coleman RE. Performance characteristics of a whole-body PET scanner. J Nucl Med 1994; 35: 1398–406.

Del-Ser T, Munoz DG, Hachinski V. Temporal pattern of cognitive decline and incontinence is different in Alzheimer's disease and diffuse Lewy body disease. Neurology 1996; 46: 682–6.

Fox PT, Mintun MA. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of H215O tissue activity. J Nucl Med 1989; 30: 141–9.

Frackowiak RS, Friston KJ. Functional neuroanatomy of the human brain: positron emission tomography—a new neuroanatomical technique. [Review]. J Anat 1994; 184: 211–25.

Friston, KJ. Statistical parametric mapping. In: Thatcher RW, Hallett M, Zeffiro T, John ER, Huerta M, editors. Functional neuroimaging: technical foundations. San Diego: Academic Press; 1994. p. 79–93.

Friston KJ Ashburner J, Frith CD, Poline J, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Mapp 1995; 3: 165–89.

Fukuda H, Koga T. Stimulation of three areas of the primary motor cortex interrupts micturition in dogs. J Auton Nerv Syst 1992; 38: 177–90.

Fukuyama H, Matsuzaki S, Ouchi Y, Yamauchi H, Nagahama Y, Kimura J, et al. Neural control of micturition in man examined with single photon emission computed tomography using 99mTc-HMPAO. Neuroreport 1996; 7: 3009–12.

Gjone R, Setekleiv J. Excitatory and inhibitory bladder response to stimulation of the cerebral cortex in the cat. Acta Physiol Scand 1963; 59: 377–48.

Holstege G. Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. J Comp Neurol 1987; 260: 98–126.

Holstege G. The basic, somatic, and emotional components of the motor system in mammals. In: Paxinos G, editor. The rat nervous system. 2nd ed. San Diego: Academic Press; 1995. p. 137–54.

Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 1995; 63: 225–36.

Jost WH, Schimrigk K. Urinary incontinence in patients with Parkinson syndrome. [German]. Wien Klin Wochenschr 1996; 108: 296–302.

Kamouchi M, Ibayashi S, Takaba H, Omae T, Sadoshima S, Yamashita Y, et al. Urinary incontinence in elderly patients in the chronic stage of stroke. [Japanese]. Nippon Ronen Igakkai Zasshi 1995; 32: 741–6.

Kanno I, Iida H, Miura S, Murakami M. Optimal scan time of oxygen-15-labeled water injection method for measurement of cerebral blood flow. J Nucl Med 1991; 32: 1931–4.

Kuru M. Nervous control of micturition. Physiol Rev 1965; 45: 425–94.

Langworthy OR, Kolb LC. An experimental study of micturition released from cerebral control. Am J Physiol 1936; 115: 694–700.

Mantyh PW. The ascending input to the midbrain periaqueductal gray of the primate. J Comp Neurol 1982; 211: 50–64.

Mukai K. Experimental studies on the bladder contraction point in gyrus cinguli and projection fibers from this point. Osaka Diagaku Igaku Zasshi 1959; II: 1645–53.

Nishizawa O, Ebina K, Sugaya K, Noto H, Satoh K, Kohama T, et al. Effect of cerebellectomy on reflex micturition in the decerebrate dog as determined by urodynamic evaluation. Urol Int 1989; 44: 152–6.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.

Prati A, Cantoni C, Pieri L, Sacchini P, Savino A, Arnaudi R, et al. Urodynamic aspects in cerebellar degenerative disease. Acta Urol Ital 1993; 7: 175–6.

Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance after acute hemispheric stroke: analysis of the lesion site by CT and MRI. J Neurol Sci 1996a; 137: 47–56.

Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance and the pontine tegmental lesion: urodynamic and MRI analyses of vascular cases. J Neurol Sci 1996b; 141: 105–10.

Saper CB. Convergence of autonomic and limbic connections in the insular cortex of the rat. J Comp Neurol 1982; 210: 163–73.

Schurch B, Yasuda K, Rossier AB. Detrusor bladder neck dyssynergia revisited. J Urol 1994; 152: 2066–70.

Supple WF Jr. Hypothalamic modulation of Purkinje cell activity in the anterior cerebellar vermis. Neuroreport 1993; 4: 979–82.

Talairach J, Tournoux, P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Tang PC. Levels of brain stem and diencephalon controlling micturition reflex. J Neurophysiol 1955; 18: 583–95.

Tang PC, Ruch TC. Localization of brain stem and diencephalic areas controlling the micturition reflex. J Comp Neurol 1956; 106: 213–31.

Thiry AJ, Deltenre PF. Neurophysiological assessment of the central motor pathway to the external urethral sphincter in man. Br J Urol 1989; 63: 515–9.

Vanderhorst VG, Mouton LJ, Blok BF, Holstege G. Distinct cell groups in the lumbosacral cord of the cat project to different areas in the periaqueductal gray. J Comp Neurol 1996; 376: 361–85.

Yamagushi K. Disturbances of urinary excretion in patients with brain tumor. Seishin Shingeigaku Zasshi 1959; 61: 239–76.

Yeates WK. Neurophysiology of the bladder. Paraplegia 1974; 12: 73–82.

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