A PET study on brain control of micturition in humans

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Summary

Although the brain plays a crucial role in the control of micturition, little is known about the structures involved. Identification of these areas is important, because their dysfunction is thought to cause urge incontinence, a major problem in the elderly. In the cat, three areas in the brainstem and diencephalon are specifically implicated in the control of micturition: the dorsomedial pontine tegmentum, the periaqueductal grey, and the preoptic area of the hypothalamus. PET scans were used to test whether these areas are also involved in human micturition. Seventeen right-handed male volunteers were scanned during the following four conditions: (i) 15 min prior to micturition during urine withholding; (ii) during micturition; (iii) 15 min after micturition; (iv) 30 min after micturition. Ten of the 17 volunteers were able to micturate during scanning. Micturition was associated with increased blood flow in the right dorsomedial pontine tegmentum, the periaqueductal grey, the hypothalamus and the right inferior frontal gyrus. Decreased blood flow was found in the right anterior cingulate gyrus when urine was withheld. The other seven volunteers were not able to micturate during scanning, although they had a full bladder and tried vigorously to do so. In this group, during these unsuccessful attempts to micturate, increased blood flow was found in the right ventral pontine tegmentum, which corresponds with the hypothesis, formulated from results in cats, that this area controls the motor neurons of the pelvic floor. Increased blood flow was also found in the right inferior frontal gyrus during unsuccessful attempts at micturition, and decreased blood flow in the right anterior cingulate gyrus was found during the withholding of urine. The results suggest that, as that of the cat, the human brainstem contains specific nuclei responsible for the control of micturition, and that the cortical and pontine micturition sites are predominantly on the right side.

Key words: right pontine tegmentum; periaqueductal grey; hypothalamus; right anterior cingulate gyrus; right inferior frontal gyrus

Abbreviations: ANCOVA = analysis of covariance; BA = Brodmann area; MPO = medial preoptic area; PAG = periaqueductal grey; PMC = pontine micturition centre; rCBF = regional cerebral blood flow; SPM = statistical parametric mapping

Introduction

It is generally accepted that the brain plays a crucial role in normal micturition, but in humans little is known about which specific brain areas are involved. This lack of knowledge is the more surprising, since it is highly probable that dysfunction of certain brain areas causes incontinence in many elderly people (Andrew and Nathan, 1964; Blaivas, 1982). Incontinence in the elderly is a major social problem. At least 10 million adults in the United States (Consensus Conference, 1989), up to 30% of elderly citizens (age ≥60 years) residing in the community (Teasdale et al., 1988) and over 50% of those living in care (Resnick et al., 1989) suffer from urinary incontinence, in particular urge incontinence (Jewett et al., 1981; Ouslander et al., 1982). In 1987 the direct annual costs for care of patients with incontinence were estimated to exceed $10.3 billion in the United States alone (Consensus Conference, 1989).

Urge incontinence occurs when patients sense the urge to void, but are unable to delay it long enough to reach the toilet (Consensus Conference, 1989). In healthy individuals this ‘urge’ is not immediately followed by micturition and it
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usually disappears when micturition is not appropriate at that particular time and place. Urge incontinence is also frequently found in patients with stroke (Khan et al., 1981) or with CNS diseases, such as multiple sclerosis (Blaivas et al., 1979). Urge incontinence should not be confused with genuine stress incontinence, which is not the result of lesions in the CNS and will not be discussed in this study. In humans, complete interruption of the brainstem–sacral cord pathways always results in unco-ordinated contractions of bladder and sphincter (i.e. bladder–sphincter dyssynergia; Blaivas, 1982). Patients with brain lesions rostral to the pons never show bladder–sphincter dyssynergia, but may suffer from urge incontinence (Blaivas, 1982). Apparently, micturition, as such, is not co-ordinated by regions in the spinal cord, but in the caudal brainstem. The beginning of micturition, however, is determined by regions in the forebrain. Evidence from animal experiments supports this conclusion. The experiments of Blok and Holstege (1994) and Blok et al. (1995) in the cat have led to a concept for the micturition reflex (Fig. 1).

The pelvic nerve conveys information about the degree of bladder filling to neurons in the lumbosacral cord (Morgan et al., 1981), which, in turn, project to the periaqueductal grey (PAG) (Noto et al., 1991; Blok et al., 1995; VanderHorst et al., 1996), a midbrain area known for its role in nociception and emotional responses (Depaulis and Bandler, 1991; Holstege, 1995). When the bladder is filled to such a degree that voiding is appropriate, the PAG, according to this concept, activates an area in the dorsomedial pontine tegmentum, referred to as the pontine micturition centre (PMC) or M-region (Blok and Holstege, 1994), which produces complete (synergic) micturition via long descending pathways to the parasympathetic bladder motor neurons in the sacral cord (Holstege et al., 1979, 1986). In the cat, stimulation of forebrain structures, including the anterior cingulate gyrus, preoptic area of the hypothalamus, amygdala, bed nucleus of the stria terminalis and septal nuclei, have been shown to elicit bladder contractions (Gjone and Setekleiv, 1963; Gjone, 1966). All these structures give rise to descending pathways to the PAG and other regions belonging to the so-called emotional motor system (Holstege, 1995), but only one, the medial preoptic area (MPO), being the rostral part of the hypothalamus, projects directly to the PMC or M-region (Holstege, 1987). Possibly, the MPO plays a role in the start of micturition.

Another pontine area has been implicated in the maintenance of continence. This area, called the L-region, is located more laterally and ventrally than the PMC or M-region, and maintains direct projections to the nucleus of Onuf in the sacral cord (Holstege et al., 1979, 1986). Onuf’s nucleus contains motor neurons innervating the pelvic floor, including the anal and urethral sphincters (Sato et al., 1978). In the cat, bilateral lesions in the L-regions cause an extreme form of ‘urge’ incontinence (Holstege et al., 1986; Griffiths et al., 1990).

PET is a non-invasive technique used to study changes in regional cerebral blood flow (rCBF) in humans performing specific tasks (Fox and Mintun, 1989). The rCBF is used as an index of the presynaptic activity in the area under consideration (Jueptner and Weiller, 1995). In the present PET study we tested the hypothesis that the same brain areas are active in humans during micturition, as those in the cat. Therefore, areas in the brainstem and diencephalon, such as the PMC, PAG and the MPO of the hypothalamus, received special attention. Additional areas, other than those implicated by the cat experiments, were investigated too. However, because of the limitation of the detection field of the camera areas located at the top of the brain were not scanned.

**Methods**

**Subjects**

In all experiments, the volunteers completed a general health questionnaire. No subject reported a history of neurological,
Table 1 Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Micturition initiation, time after start of Scan 2 (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>B</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>C</td>
<td>23</td>
<td>No micturition</td>
</tr>
<tr>
<td>D</td>
<td>46</td>
<td>−2</td>
</tr>
<tr>
<td>E</td>
<td>31</td>
<td>No micturition</td>
</tr>
<tr>
<td>F</td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>G</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>H</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>J</td>
<td>29</td>
<td>No micturition</td>
</tr>
<tr>
<td>K</td>
<td>45</td>
<td>No micturition</td>
</tr>
<tr>
<td>L</td>
<td>26</td>
<td>No micturition</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>N</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>O</td>
<td>41</td>
<td>No micturition</td>
</tr>
<tr>
<td>P</td>
<td>42</td>
<td>−2</td>
</tr>
<tr>
<td>Q</td>
<td>21</td>
<td>No micturition</td>
</tr>
<tr>
<td>Mean</td>
<td>32.3</td>
<td></td>
</tr>
</tbody>
</table>

psychiatric or urologic illnesses. All subjects were exclusively right-handed, and gave their written, informed consent according to the declaration of Helsinki. The protocol of the study was approved by the research-ethics committee of the University Hospital of Groningen.

Data acquisition

The subjects were placed in a horizontal position in the PET camera (Siemens-CTI 951/31, Knoxville, Tenn., USA) parallel to, and 5 cm below, the glabella–inion line as determined by external examination. Because of the technical characteristics of the PET camera, the most caudal limit of the scanned area was the pons, and the most rostral limit was the cingulate gyrus. This resulted in images extending between 28 mm below and 44 mm above the intercommissural plane. This implied, for example, that the motor cortex was not included in the investigated brain regions.

An individually constructed head mould was used to minimize changes in head position from one scan to another. First, a transmission scan of 20 min was made for attenuation correction of the emission scans and then the four main scans were carried out. Before each scan, the subjects were given 1.85 GBq of H$_2$O in saline. The H$_2$O bolus, followed by 40 ml saline, were injected into the right brachial vein from an automatic pump. Data acquisition was initiated 23 s after the beginning of the injection, at which time the peak in radioactivity was assumed to reach the cerebral circulation, and it was continued for 90 s. To allow the radiation to return to background levels, there were 15 min intervals between the injections.

Data analysis

The data were sampled using a voxel size of 2.2×2.2×2.4 mm$^3$. They were analysed using the Statistical Parametric Mapping procedure (SPM95 from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, Mass., USA) on a SPARC workstation (Sun Microsystems Inc., Surrey, UK). The SPM95 software was used for anatomical realignment, normalization and smoothing of the data, and then for statistical analysis.

Anatomical realignment

The rCBF was reconstructed for each scan, using an attenuation correction based on the preliminary transmission scan. Movement-related components between scans were corrected during the realignment, using the first recorded scan from each subject as a reference.

Normalization

Following realignment, all images were transformed into a stereotactic standard space (Talairach and Tournoux, 1988). This normalizing spatial transformation matches each scan to a reference or template image that conforms to the standard space (Friston et al., 1991a). Stereotactic normalization of PET images allows comparison of scan data in identical pixels across different subjects and scans.
Smoothness
Prior to the statistical analysis, the scans were smoothed in order to increase the signal-to-noise ratio and to suppress effects due to residual differences in functional and gyral anatomy between subjects during inter-subject averaging. During smoothing, a Gaussian filter of \(8 \times 8 \times 8\) mm\(^3\) was used (full width, half maximum in the \(x\), \(y\), and \(z\) axes, respectively). This relatively small filter was used because the main part of the study was aimed at the relatively small brainstem and diencephalon.

Statistical analysis
Differences in global activity within and between subjects were removed by analysis of covariance (ANCOVA) on a pixel-by-pixel basis with global counts as covariate. This was done because inter- and intra-subject differences in global activity may obscure regional alterations in activity following cognitive processes (Friston et al., 1990). For each pixel in the stereotactic space, the ANCOVA generated a condition-specific adjusted mean rCBF value (normalized to 50 ml/dl/min) and an associated adjusted error variance. A repeated-measures ANCOVA was used for the comparison of the second micturition scan (Scan 4) with the other scans, each subject being studied under all conditions. The ANCOVA allows comparison of the means across conditions using the \(t\) statistic. The resulting set of \(t\) values constitutes a statistical parametric map \([SPM\{t\}; Friston et al., 1991b]\). During analysis, special attention was put on the expected micturition control areas in the diencephalon and brainstem, i.e. the PMC, PAG and hypothalamus, including the MPO. An uncorrected \(P\) value of 0.001 was used for these areas since the exact location could be predicted on the basis of cat experiments. This (omnibus) approach can be used when the location of the area, in which activation is expected, is known (Friston et al., 1991b). Trends in activation in the expected micturition control areas are reported when they reach a significance level of \(P < 0.005\). This level of significance gives sufficient protection against false positives (Warburton et al., 1996). Other brain areas observed to be activated were considered statistically significant only after a correction for multiple comparisons (corrected threshold \(P < 0.05\)); this is necessary when there is no preconceived hypothesis (Friston et al., 1991b).

Results
Ten of the 17 volunteers were able, as requested, to urinate within 30 s after the beginning of Scan 2, i.e. within 53 s after the injection of \( \text{H}_2^{15}\text{O} \) (Table 1).

The collected urine volume was \(567 \pm 267\) ml (mean\(\pm\)SD). The results obtained in this group will be referred to as ‘Micturition successful’.

The other seven volunteers tried to urinate during scanning, but did not succeed (Tables 1 and 2). However, these seven were able to micturate within 5 min of finishing Scan 2 (mean urine volume = 712\(\pm\)234 ml).

The scanning data from this group were analysed separately and the results are reported under the heading ‘Micturition unsuccessful’.

Micturition successful
The activated brain areas of the 10 subjects of this group are presented in Table 3. The overall activation, revealed by comparing activation during successful micturition (Scan 2) with that recorded during the withholding of urine (Scan 1), is shown in Fig. 2.

During micturition, the rCBF was significantly increased (uncorrected \(P < 0.001\)) in the PAG and hypothalamus and on the right in the dorsomedial pontine tegmentum (Figs 2 and 3). The activation in the hypothalamus appeared to be located predominantly in its rostral part (Fig. 4).

Of the cortex cerebri, only the right inferior frontal gyrus [Brodmann areas (BA) 45 and 47, and the most dorsal tip of BA 44] and the right anterior cingulate gyrus (BA 24 and 32) were significantly more activated during micturition than in the urine withholding phase (corrected \(P < 0.05\)). The right medial temporal gyrus (BA 21) and the rostral striatum were also more active, although not significantly for multiple comparisons.

Comparing successful micturition (Scan 2) with the conditions 15 and 30 min after micturition (Scans 3 and 4), similar results were obtained. During micturition, the rCBF increased (uncorrected \(P < 0.001\)) in the same areas as it did when micturition (Scan 2) was compared with urine withholding (Scan 1). Exceptions were the anterior cingulate gyrus and the rostral striatum, which did not show any statistically significant difference in activity (Table 3).

A significant increase in activity was found in the anterior cingulate gyrus (corrected \(P < 0.05\)) when the bladder was empty (Scans 3 and 4) compared with when the urine was being withheld (Scan 1).

Decreases in rCBF were also found. During micturition (Scan 2) compared with Scan 1 or with Scans 3 or 4, decreased rCBF was found in the left inferior and medial frontal gyri (BA 9 and 44; peak activation –42, +10, +32; \(Z\) score = 3.1) and the left medial temporal gyrus (BA 21; peak activation –56, –48, –8; \(Z\) score = 3.2). However, these differences were not significant after correction for multiple comparisons (corrected \(P < 0.05\)).

Micturition unsuccessful
In the unsuccessful micturition group, increased rCBF was found in distinct brain areas during Scan 2 when the volunteers tried hard to micturate, but failed, compared with the empty-bladder condition (Scans 3 and 4). Prior to the statistical analysis, it was hypothesized that the ventrolateral pons would be activated during the unsuccessful micturition (Scan...
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Table 2 Study design

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Scan 1</th>
<th>Scan 2</th>
<th>Scan 3</th>
<th>Scan 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (10)</td>
<td>Withholding urine</td>
<td>Micturition successful</td>
<td>Empty bladder for 15 min</td>
<td>Empty bladder for 30 min</td>
</tr>
<tr>
<td>Group 2 (7)</td>
<td>Withholding urine</td>
<td>Micturition unsuccessful</td>
<td>Empty bladder for 15 min</td>
<td>Empty bladder for 30 min</td>
</tr>
</tbody>
</table>

All subjects in Group 2 (unable to micturate when requested: micturition unsuccessful) were able to micturate within 5 min of completion of the second scan.

Table 3 Results from Group 1 subjects (successful micturition during Scan 2)

<table>
<thead>
<tr>
<th>Micturition successful—withholding urine (Scan 2 – Scan 1)</th>
<th>Peak position (x, y, z) (mm)</th>
<th>Min/max of ( rCBF )</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus (BA 44, 45, 47)</td>
<td>+52, +16, +4</td>
<td>−8/+12</td>
<td>10.0</td>
</tr>
<tr>
<td>Anterior cingulate gyrus (BA 24, 32)</td>
<td>+12, +32, +16</td>
<td>0/+28</td>
<td>7.9</td>
</tr>
<tr>
<td>Medial temporal gyrus (BA 21)</td>
<td>+50, −2, −12</td>
<td>−24/−4</td>
<td>4.9</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>−22, +22, +4</td>
<td>0/+4</td>
<td>7.3</td>
</tr>
<tr>
<td>Diencephalon and brainstem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>−4, −4, −4</td>
<td>−8/+4</td>
<td>8.2</td>
</tr>
<tr>
<td>Periaqueductal grey</td>
<td>+4, −34, −12</td>
<td>−12/−8</td>
<td>7.1</td>
</tr>
<tr>
<td>Right dorsomedial pons</td>
<td>+10, −42, −24</td>
<td>−28/−24</td>
<td>7.7</td>
</tr>
<tr>
<td>Micturition successful—empty bladder (Scan 2 – Scan 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus (BA 45, 47)</td>
<td>+48, +26, −4</td>
<td>−8/+4</td>
<td>11.9</td>
</tr>
<tr>
<td>Medial temporal gyrus (BA 21)</td>
<td>+50, −2, −12</td>
<td>−28/−4</td>
<td>4.4</td>
</tr>
<tr>
<td>Diencephalon and brainstem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>−4, −4, −4</td>
<td>−8/0</td>
<td>6.5</td>
</tr>
<tr>
<td>Periaqueductal grey</td>
<td>+4, −34, −12</td>
<td>−12/−8</td>
<td>5.5</td>
</tr>
<tr>
<td>Right dorsomedial pons</td>
<td>+10, −42, −24</td>
<td>−24</td>
<td>6.1</td>
</tr>
<tr>
<td>Empty bladder—withholding urine (Scan 3 – Scan 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate gyrus (BA 24, 32)</td>
<td>+8, +36, −4</td>
<td>−8/+20</td>
<td>10.5</td>
</tr>
<tr>
<td>Medial temporal gyrus (BA 21)</td>
<td>+50, −18, 0</td>
<td>0/+4</td>
<td>4.7</td>
</tr>
</tbody>
</table>

The location of the peak activation is indicated by \( x, y \) and \( z \) coordinates, according to the atlas of Talairach and Tournoux (1988). The differences between Scan 2 (micturition successful) and Scan 4 (30 min after bladder emptying) were in the same range as those between Scans 2 and 3 (15 min after emptying bladder), and are not shown. BA = Brodmann area. *Significant after a correction for multiple comparisons with a threshold of \( P < 0.05 \); **significant for an uncorrected threshold of \( P < 0.004 \); ***extent in \( z \)-axis is based on an uncorrected threshold of \( P < 0.001 \), unless otherwise indicated.

2). Previously, this area has been implicated in the process of maintaining continence on the basis of cat experiments. Indeed, increased activation (uncorrected \( P < 0.0001 \)) was found in the right ventral pons (peak activation \( x = +8 \) mm, \( y = −28 \) mm, \( z = −28 \) mm; \( Z \) score = 3.7; extent in \( z \)-axis relative to the AC–PC line (the line between the anterior and posterior commissure): −24 to −28 mm (on the basis of an uncorrected threshold of \( P < 0.001 \)); see Fig. 5, right).

In the right inferior frontal gyrus (BA 45 and 47; peak activation \( x = +50, y = +26, z = 0; Z \) score = 4.3; extent in \( z \)-axis 0 to +4 mm) an activation was found also, but this was not significant after a correction for multiple comparisons (corrected \( P < 0.05 \)).

Comparing Scan 2 with Scan 1, which was carried out during the withholding of urine, a slight increase (uncorrected \( P < 0.002 \)) in the \( rCBF \) was found during Scan 2 in the right ventral pons (peak activation \( x = +8, y = −28, z = −28; Z \) score = 2.9). Furthermore, a significant difference (corrected \( P < 0.05 \)) was observed in the right anterior cingulate gyrus (BA 24 and 32; peak activation \( x = +10, y = +20, z = +24; Z \) score = 4.7; extent in \( z \)-axis +24 to +28 mm). Remarkably, the location of the activated area was more posterior and superior than when successful micturition was compared with withholding of urine (Fig. 6 at the bottom).

In the inferior frontal gyrus (BA 45 and 47; peak activation, \( x = +50, y = +26, z = 0; Z \) score = 3.4; extent in \( z \)-axis 0 to +4 mm) an increase in \( rCBF \) was found, but after
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similar to the organization observed during micturition in the (Holstege et al., 1986; Griffiths et al., 1990). This led us to pay special attention to the brainstem in the present PET study. In general, the results indicate that micturition in the humans seems to be organized in the brainstem in very much the same way as in the cat (Fig. 1). In the following discussion, each of the various brain structures which have been highlighted in this PET study will be discussed separately.

Fig. 2 Differences in rCBF, comparing successful micturition with voluntary withholding of urine (Scan 2–Scan 1; average of 10 subjects). Pixels that are significant at the threshold of an uncorrected \( P < 0.002 \) are displayed on single sagittal, coronal and transverse projections of the brain. The numbers refer to the distance (in mm) relative to the intercommissural plane. The activation of the expected micturition control areas have been indicated by arrows. R = right side of the brain; VAC = vertical line through the anterior commissure; VPC = vertical line through the posterior commissure; PMC = pontine micturition centre; PAG = periaqueductal grey; HT = hypothalamus.

Areas involved in micturition

Dorsomedial pontine tegmentum

A distinct area in the dorsomedial pontine tegmentum was activated during micturition (Scan 2) when compared with the withholding of urine (Scan 1) or an empty bladder (Scans 3 and 4).

Retrograde and anterograde tracing studies have shown that, in the rat and cat, a cell group exists in the dorsomedial pons, which is associated with micturation. This has been referred to as the pontine micturition centre (PMC; Loewy et al., 1979), the M-region (Holstege et al., 1986) and Barrington’s nucleus (Barrington, 1925). Cells in this region project directly to the sacral intermediolateral cell column (Holstege et al., 1979; Loewy et al., 1979; Holstege et al., 1986), which contains the parasympathetic motor neurons innervating the bladder. In the cat, electrical stimulation of the PMC produces an immediate and sharp decrease in urethral pressure and pelvic floor electromyogram, followed in ~2 s by a steep rise in the intravesical pressure, mimicking complete micturition. Bilateral lesions in the PMC result in urinary retention, during which detrusor activity is depressed and bladder capacity increases (Holstege et al., 1986; Griffiths et al., 1990). The present PET results strongly suggest that a similar group of neurons exists in the dorsomedial pons of humans.

Discussion

The present study demonstrates, for the first time, that specific human brain structures have an increased rCBF during micturition. In all likelihood, these areas are involved in micturition control. There are not many studies on the CNS control of micturition in humans. Based on studies on patients with lesions in brain and spinal cord, Blaivas (1982) concluded that the coordination between the bladder (detrusor) and the urethral sphincter takes place in the pons, similar to the organization observed during micturition in the cat (Holstege et al., 1986; Griffiths et al., 1990). This led us to pay special attention to the brainstem in the present PET study. In general, the results indicate that micturition in the humans seems to be organized in the brainstem in very much the same way as in the cat (Fig. 1). In the following discussion, each of the various brain structures which have been highlighted in this PET study will be discussed separately.

The periaqueductal grey

In humans, the midbrain PAG appears to be more active during micturition than when urine is withheld or the when the bladder is empty. In the cat, electrical stimulation of the PAG has been shown to evoke complete micturition (Skultety, 1959), facilitate bladder reflexes and reduce bladder capacity (Kruse et al., 1990). The PAG receives fibres from the sacral cord (Blok et al., 1995; VanderHorst et al., 1996), which possibly conveys information concerning the degree of bladder filling. In turn, the PAG sends fibres to the PMC (Blok and Holstege, 1994).
Fig. 3 Regions with a significantly higher rCBF during successful micturition (Scan 2) than during the withholding of urine (Scan 1). An uncorrected threshold of $P < 0.002$ (micturition, successful minus withholding of urine) was used for display. The differences have been superimposed onto averaged MRI scans which have been transformed stereotactically to fit a standard atlas (Talairach and Tournoux, 1988). The numbers refer to the distance (in mm) relative to the intercommissural plane. Significant activation was observed in the same three areas as have been demonstrated in the cat to be involved in micturition control: the dorsomedial pontine tegmentum (indicated by pmc), the periaqueductal grey (pag), and the hypothalamus (ht). Significant activation was also observed on the right in the anterior cingulate gyrus, inferior frontal gyrus and medial temporal gyrus, and on the left in the rostral striatum. Of these regions, only the anterior cingulate gyrus and the inferior frontal gyrus appeared to be statistically significant after a correction for multiple comparisons (corrected $P < 0.05$). L = left side of the brain; R = right side of the brain.
Hypothalamic involvement in micturition control in humans, as implicated by our results, has also been demonstrated in the cat (Tang and Ruch, 1956). In the cat, stimulation of forebrain structures, including the anterior cingulate gyrus, preoptic area of the hypothalamus, amygdala, bed nucleus of the stria terminalis and septal nuclei, elicits bladder contractions (Gjone and Setekleiv, 1963; Gjone, 1966). All these structures give rise to descending pathways to the PAG and other regions belonging to the so-called ‘emotional motor system’ (Holstege, 1995; Blok and Holstege, 1996). Only the preoptic area, being the rostral part of the hypothalamus, has been shown to project directly onto the PMC (Holstege, 1987).

Although our PET results suggest that the preoptic area also plays an important role in human control of micturition, its exact role is unknown. One might speculate that the direct influence of the preoptic area on the PMC determines the beginning of micturition. Whether or not micturition takes place is always related to the environment in which the individual is situated. In other words, when a full bladder signals, via fibres to the sacral cord and the PAG, that micturition should occur, it only takes place when forebrain structures have ‘decided’ that the situation is safe enough.

**Fig. 4** The activation of the hypothalamus (ht) as seen on the coronal section (y = -4 mm relative to the anterior commissure), comparing successful micturition with voluntary withholding of urine (Scan 2 – Scan 1; average of 10 subjects). The peak activation seems to be located just ventral to the anterior commissure in the preoptic area of the hypothalamus. The activation in the right temporal lobe was not significant after a correction for multiple comparisons. An uncorrected threshold of \( P < 0.002 \) was used for display. For the Z score scale see Fig. 3. ht = hypothalamus.

**Fig. 5** Left: significant differences in rCBF in the right dorsomedial tegmentum (indicated by pmc), comparing successful micturition with voluntary withholding of urine (Scan 2 – Scan 1; average of 10 subjects). Right: significant differences in rCBF in the right ventral tegmentum (indicated by L-region), comparing unsuccessful micturition with an empty bladder, 15 min after micturation (Scan 2–Scan 3; average of seven subjects). Uncorrected threshold of \( P < 0.002 \).
Right inferior frontal gyrus
The present results demonstrate that the right inferior frontal gyrus is significantly activated during micturition. The same region is involved in attention mechanisms (Pardo et al., 1991) and response selection (Jenkins et al., 1994). With respect to micturition, this region might play a role in making the decision as to whether or not micturition should take place at that particular time and place.

Right anterior cingulate gyrus
The rCBF in the right anterior cingulate gyrus was significantly decreased during the withholding of urine (Scan 1) compared with successful micturition (Scan 2) or an empty bladder (Scans 3 and 4). Possibly, this decrease in rCBF in the anterior cingulate gyrus during withholding of urine (Scan 1) reflects a general suppression of sensory input and motor output in order to suppress the sensation of a filled bladder and subsequent urge to void. Additionally, the rCBF during withholding of urine (Scan 1) is also lower in this area than when the bladder is empty (Scans 3 and 4). Apparently, the relatively high rCBF during Scans 2, 3 and 4 was not specific for response selection or attention, because that was only the case during Scan 2 and not during Scans 3 and 4. According to Paus et al. (1993) the anterior cingulate gyrus facilitates possible responses to incoming sensory input (see also Pardo et al., 1990; Jenkins et al., 1994). In other words, it might be considered as a level setting system, facilitating certain blueprints of behaviour. However, whilst urine is withheld, the reverse of facilitation is needed, i.e. the urge of voiding has to be inhibited. This might explain the decreased rCBF in the anterior cingulate gyrus during withholding of urine, even when compared with the empty-bladder condition. On the other hand, lesions in the forebrain including the anterior cingulate gyrus have been reported to cause urge incontinence (Andrew and Nathan, 1964; Maurice-Williams, 1974). This would favour the idea that the anterior cingulate gyrus also plays a specific role in micturition control.

Observations during unsuccessful micturition
Seven of the 17 volunteers were unable to micturate when requested (for Scan 2). In this group the ventral pontine tegmentum showed increased rCBF during Scan 2 in comparison with the other three scans (Scans 1, 3 and 4). During Scan 2, the volunteers who were unsuccessful in
their attempt at micturition, probably for emotional reasons, contracted their urethral sphincter and withheld their urine, although they had a full bladder and tried to urinate. At first glance the condition withholding of urine (Scan 1) is the same as Scan 2, also taken when these volunteers withheld their urine. The difference was that the volunteers, albeit involuntarily, contracted their urethral sphincter much more strongly during Scan 2 than during the withholding of urine condition of Scan 1. From cat experiments, it has been shown that a distinct cell group in the ventrolateral pontine tegmentum is associated with powerful contraction of the bladder sphincter (Holstege et al., 1986). This cell group, located ventrolateral to the PMC, is called the ‘L-region’ and projects to the nucleus of Onuf in the sacral cord (Holstege et al., 1979, 1986). The nucleus of Onuf contains motor neurons of the pelvic floor muscles including the external urethral sphincter. Electrical stimulation of the L-region produces closure of the sphincter, and bilateral lesions in this area result in a condition that can best be explained as an extreme kind of ‘urge’ incontinence (Holstege et al., 1986; Griffiths et al., 1990). The L-region possibly plays an important role in the storage of urine. We predicted that a human homologue of the cat’s L-region in the ventral pontine tegmentum might be activated in the unsuccessful micturition group, and our PET results, described above, corroborate this idea.

The anterior cingulate gyrus showed decreased rCBF during Scan 1, compared with the other three scans, as in the successful micturition group, and the prefrontal cortex showed increased rCBF. The possible involvement of these areas in more general mechanisms, other than in the regulation of micturition itself has been discussed in the previous paragraph.

In summary, the results of this study suggest that, in humans, as in cats, the dorsomedial and ventral pontine areas are involved in micturition and maintaining continence, respectively. The distance between the peak activation of these areas in the pons was >15 mm, well within the resolution of the scanner, which was ~6 mm in the x, y and z directions, and within in the smoothing limits of the applied Gaussian filter of 8 mm in the x, y and z directions.

Lateralized activation

A striking observation was that the micturition-control areas were found predominantly on the right side of the brain (frontal and cingulate cortices) and brainstem (pontine areas). This finding corresponds with studies reporting that urge incontinence is specifically correlated with lesions in the right hemisphere (Maurice-Williams, 1974; Kuroiwa et al., 1987). The importance of the right side of the brain in autonomic behaviour in general was also indicated by a PET study on human respiration by Corfield et al. (1995), who found an increase in rCBF in the anterior cingulate gyrus, predominantly on the right side. In a SPECT (single photon emission computer tomography) study, an increase in the right prefrontal cortex was observed during male orgasm (Tiihonen et al., 1994).

Future studies using dynamic imaging techniques are underway to find out whether the micturition control structures in the brain, as demonstrated in the present study, are dysfunctional in patients with urge incontinence.

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References


Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing


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