An fMRI study of the role of suprapontine brain structures in the voluntary voiding control induced by pelvic floor contraction

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We have learned that micturition is comprised of two basic phases: storage and emptying; during bladder emptying, the pontine and periaqueductal gray (PAG) micturition center ensures coordinated inhibition of striated sphincter and pelvic floor muscles and relaxation of the internal urethral sphincter while the detrusor muscle contracts. Due to several disorders of the brain and spinal cord, the achieved voluntary control of bladder function can be impaired, and involuntary mechanisms of bladder activation again become evident. However, little has been discovered so far how higher brain centers strictly regulate the intricate process of micturition.
The present functional magnetic resonance imaging (fMRI) study attempted to identify brain areas involved in such voluntary control of the micturition reflex by performing functional magnetic resonance imaging during a block design experiment in 12 healthy subjects. The protocol consisted of alternating periods of rest and pelvic muscle contraction during empty-bladder condition (EBC) and full-bladder condition (FBC). Repeated pelvic floor muscle contractions were performed during full bladder to induce a stronger contrast of bladder sensation, desire to void and inhibition of the micturition reflex triggering, since the subjects were asked not to urinate. Empty-bladder conditions were applied as control groups. Activation maps calculated by contrast of subtracting the two different conditions were purposed to disclose these brain areas that are involved during the inhibition of the micturition reflex, in which contrast, the SMA, bilateral putamen, right parietal cortex, right limbic system, and right cerebellum were found activated. The combined activation of basal ganglia, parietal cortex, limbic system, and cerebellum might support the assumption that a complex visceral sensory–motor program is involved during the inhibitory control of the micturition reflex.
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Introduction

Voiding disorders and incontinence are frequently encountered in patients with spinal cord injury (SCI), cerebrovascular accident, traumatic brain injury, multiple sclerosis, dementia, and Parkinson disease (Jost and Schimrigk, 1996; Khan et al., 1989). Incontinence associated with these central nervous system (CNS) diseases usually heralds a poor prognosis (Chua et al., 2003; Gross, 2000; O’Donnell et al., 1992). The high prevalence of incontinence in these populations indicates that the CNS may play an important role in bladder-voiding disorder.

Although the exact neuronal structures involved in micturition and the control of urine storage are still under investigation, it is known that the parasympathetic nervous system controls bladder contraction and micturition, and the sympathetic system becomes especially active during the last part of urine storage when micturition is actively postponed and the striated external urethral sphincter is the main structure responsible for normal urinary continence. Three CNS areas are thought to contribute to bladder functions: the sacral and pontine micturition centers, and the cerebral cortex. Lesions in peripheral nerves or the sacral micturition center cause detrusor areflexia that manifests as a distended bladder with overflow incontinence. Lesions of spinal cord or brainstem between the sacral and pontine micturition centers lead to uninhibited bladder contraction (neurogenic detrusor overactivity) and uncoordinated sphincter activity; so-called detrusor-sphincter dyssynergia. Lesions above the pontine micturition
center result in uninhibited bladder contractions attributed to a lack of inhibition from the cerebral cortex, while leaving relaxation of the urethral sphincter intact (overactive bladder) (de Groat, 1997; Fall et al., 1989; Hampel et al., 1997; Payne, 1998).

So far, animal and human experimental studies have focused on the micturition centers in the pons, periaqueductal gray (PAG), and spinal cord level; little has been done to elucidate the voiding control mechanism in suprapontine structures. Functional magnetic resonance imaging (fMRI) has emerged over the past decade as a powerful tool for the noninvasive study of the brain’s functional localization and connectivity (Ogawa et al., 1990). Based on blood oxygen level-dependent (BOLD) contrast, fMRI takes advantage of the changes in signal intensity which arise due to alterations in the local transverse relaxation times (T2 and T2*) associated with regional changes in cerebral deoxyhemoglobin concentration. Due to the small signal intensity change which results, the correlation between the task activity and the fMRI response must be identified in a statistical manner, using a series of images acquired during alternating periods of activity and rest. After thresholding for a suitable level of statistical significance, the T-map of the correlation is typically displayed as a color-coded image in which the color is indirectly related to in vivo neuronal activation.

Making use of the fMRI technique, the aim of this study was to investigate the brain structures involved in voluntary control of bladder function: in colloquial terms, to answer the question: “Which areas in the brain are involved in the voluntary control of the micturition?” Derived from earlier urology study (Reitz et al., 2003), it is hypothesized that these areas’ activity triggered by pelvic floor muscle contraction will increase when bladder is full, since the filled bladder has almost no room for urine holding; therefore any pelvic floor muscle action would dramatically arouse desire to void and suppression of such desire, since it is not allowed to urinate in the scanner, thereby we have established a nonvoiding model (i.e., active pelvic floor muscle contraction with full bladder to induce stronger desire to void and micturition reflex inhibition, since the subject is not allowed to urinate) of inhibitory bladder control. The model involves the performance of repetitive pelvic floor muscle contraction in alternating with periods of rest under full (FBC)- and empty (EBC)-bladder conditions.

Materials and methods

Experimental conditions

Each subject drank water (range, approximately 1 to 2 l) until they felt their bladder was full and that they had a desire to void before being positioned in the MR scanner and undergoing the imaging protocol described below. During the functional scans, the subjects were instructed via audio headphones to contract their pelvic floor muscles in a repetitive manner and to rest in alternating 15-s intervals. This cycle was repeated eight times over the course of 4 min. The scanner ran continuously over this period to produce a series of 80 image volumes. This series of images constituted the full-bladder pelvic floor contraction condition (FBC condition). The subject was removed from the scanner, allowed to empty their bladder, and then returned to the magnet to undergo a second functional scan during which they repeated the pattern of muscle contraction and rest. Images from this second fMRI scan constituted the empty-bladder pelvic floor contraction condition (EBC condition). The imaging procedure is outlined in Table 1.

Subjects

Between May 2002 to March 2003, 12 right-handed, male medical school students (mean age of 23.8 ± 0.65 years) were recruited for this study. Before scanning, the protocol was explained to each participant, and informed consent was obtained. To achieve comparable levels of motor activity during the fMRI scanning, the performance of pelvic floor contraction was guided and practiced with a biofeedback device (SEDIA Pelvitrain®, Sedia AG, Switzerland) at frequency of 1 Hz, and the average feedback strength was maintained at 20–30% of full scale on the device scale meter; the bladder volume estimation and monitoring were made by means of X-ray during volunteer’s pervious urology study involvement. The timing parameter (15 s, 4 min) of the “Off–On” block design was chosen under consideration of volunteer’s tolerance and BOLD fMRI design convention. The subjects were then entered into the MRI scanner after such training, where planning and functional and anatomical image data sets were acquired according to the experimental and imaging protocol detailed below. The study was covered by a local ethic committee approval.

fMRI scanning

For both the full- and empty-bladder functional studies, an axial, BOLD-sensitive, single-shot gradient-echo echoplanar imaging sequence was used (15 slices, TE/TR/flip angle: 30 ms/2900 ms/75 grad; slice thickness/gap/FOV: 5/0/230 mm; acquisition matrix/reconstruction matrix: 64/128 sq). On average, the time between the bladder-full and bladder-empty scans was 10 min. Following the empty-bladder functional scan, a high-resolution T1-weighted volumetric scan was acquired (TE/TR/flip angle: 5 ms/20

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**Table 1**

Bladder control study design

<table>
<thead>
<tr>
<th>Functional activity</th>
<th>pelvic floor contraction (on)</th>
<th>[Action A] pelvic floor muscle contraction, bladder sensation, desire to void, inhibition of voiding</th>
<th>[Action C] pelvic floor muscle contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic floor (as single subtraction)</td>
<td>rest (off)</td>
<td>[Action B] bladder sensation, desire to void</td>
<td>[Action D] rest</td>
</tr>
<tr>
<td>Double subtraction</td>
<td>net effect between above two groups</td>
<td>![Expression](A − B = (C − D)) inhibitory control of voiding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>![Expression](full bladder condition)</td>
<td>![Expression](empty bladder condition)</td>
</tr>
</tbody>
</table>

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ms, 30 grad; slice thickness/gap/FOV: 4.00/0.40/240 mm; acquisition matrix/reconstruction matrix: 80/180 sq). All imaging was performed on a 3-T MR scanner (Philips Medical Systems, Best, The Netherlands).

Data postprocessing

Following DICOM transfer of the images to an offline workstation and conversion of the image formats, all data subsequent processing was performed with SPM99 (Wellcome Department of Cognitive Neurology, London, England) with Matlab 6.5 (Mathworks Inc., Sherborn, USA) under SuSE 8.0 Linux platform(SuSE Linux AG, Nuernberg, Germany). Before the statistical analysis, the time series were motion-corrected by realigning all the images in each session to the first image using a six-parameter rigid-body transformation. The aligned images were coregistered to T1 anatomical images and then subsequently transformed into the standard stereotactic space (MNI template provided by the Montreal Neurological Institute and bundled with SPM) using linear and nonlinear spatial deformations registration algorithms (Evans et al., 1993; Ashburner and Friston, 1999). This transformation warps all subjects’ brain images into the stereotactic standard space and allows performing group analysis. Each normalized scan was smoothed with a Gaussian kernel full width at half maximum (FWHM 8 × 8 × 8 mm) to reduce residual noise and inhomogeneity between individual brain images.

The statistical analysis of the grouped data consisted of two stages as illustrated in Table 1. First, based on a boxcar function and general linear approach, all the normalized and smoothed single subject brain volume images were computed for each condition, and each subject’s data were convolved with the modeled hemodynamic response delay function (Friston et al., 1995; Poline et al., 1997; Worsley, 1995) implemented in SPM99 on voxel by voxel basis and generated first level analysis T-maps for the contraction versus rest in the full- and empty-bladder conditions (i.e., contrast of \([A – B] – (C – D)]\) to observe the inhibitory event computed by empty-bladder condition contrasted against the full-bladder condition as indicated in Table 2. The second level group analysis was purposed to search for between-conditions difference in the sense of population inference, conjunction group analysis (Ashburner and Friston, 1999) was employed instead of random-effect group analysis for the modest size of the subjects number; the resulted T-map for the conjunction group analysis of double contrast analysis on conditions FBC > EBC was shown in the Figs. 1a, b. For all steps of analysis, the statistical threshold was set to \(P < 0.001\), only activation clusters at \(P < 0.05\) corrected for the entire brain volume (for multiple testing). This groupwise difference map of micturition inhibition was then displayed as color-coded overlays on axial and coronal sections through a representative averaged MNI brain. The resulted MNI coordinates were transformed to Talairach coordinates using Matthew Brett et al.’s (2001) algorithm to derive the anatomical location and Brodmann area labeling in Talairach and Tournoux atlas (Talairach 1988); the anatomical location of these activated areas were consulted and reconfirmed by a neuroradiologist.

Results

All the imaging sessions were performed smoothly for all the volunteers, each session lasted about 1 h for each subject, with the uncomfortable full-bladder condition about 30 min. Despite four scans were discarded later due to various reasons(one needed to go to toilet, three had large motion artifact due to head movement), all the volunteers managed to follow the experimental protocol along the entire study time course.

In the empty-bladder condition, repetitive activation of pelvic floor muscles (group EBC) induced an insignificant activation in SMA only (results not reported here), with no activation of M1 or cerebellum. Under the full-bladder condition (group FBC), double contrast with conjunction group analysis (i.e., group EBC was subtracted) yielded a bilateral activation of SMA (BA6) in medial premotor cortex, bilateral putamen in basal ganglia, right parietal cortex, and right parahippocampal gyrus, as well as the right cerebellum, was found activated as computed by double contrast conjunction group analysis approach employed in the second stage of the data analysis.

The group results for the conjunction double contrast analysis under the FBC and EBC conditions are illustrated in Figs. 1a and b, respectively, to demonstrate three major areas of differential activation, namely, medial premotor cortex, basal ganglia, and cerebellum. The Talairach coordinates, anatomical location, Brodmann area label, cluster size, and statistical scores for each area of activation are detailed in Table 2.

<table>
<thead>
<tr>
<th>Talairach coordinates x, y, z (mm)</th>
<th>Brain lobe</th>
<th>Anatomical position</th>
<th>Brodmann areas</th>
<th>Cluster level</th>
<th>Voxel level</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>–8</td>
<td>62</td>
<td>right frontal lobe</td>
<td>medial frontal gyrus</td>
<td>BA6</td>
</tr>
<tr>
<td>-2</td>
<td>–30</td>
<td>70</td>
<td>left frontal lobe</td>
<td>paracentral lobule</td>
<td>BA6</td>
</tr>
<tr>
<td>4</td>
<td>–78</td>
<td>44</td>
<td>right parietal lobe</td>
<td>precuneus</td>
<td>BA7</td>
</tr>
<tr>
<td>28</td>
<td>6</td>
<td>–2</td>
<td>right basal ganglia</td>
<td>lentiform nucleus, putamen</td>
<td>97</td>
</tr>
<tr>
<td>64</td>
<td>–18</td>
<td>16</td>
<td>right parietal lobe</td>
<td>postcentral gyrus</td>
<td>BA40</td>
</tr>
<tr>
<td>18</td>
<td>–32</td>
<td>–10</td>
<td>right limbic lobe</td>
<td>parahippocampal gyrus</td>
<td>BA35</td>
</tr>
<tr>
<td>–24</td>
<td>10</td>
<td>–6</td>
<td>left sublobar</td>
<td>lentiform nucleus, putamen</td>
<td>32</td>
</tr>
<tr>
<td>–20</td>
<td>18</td>
<td>6</td>
<td>left basal ganglia</td>
<td>lentiform nucleus, putamen</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>–38</td>
<td>68</td>
<td>right parietal lobe</td>
<td>paracentral lobule</td>
<td>BA4</td>
</tr>
<tr>
<td>18</td>
<td>–32</td>
<td>–10</td>
<td>right cerebellum</td>
<td>cerebellum</td>
<td>15</td>
</tr>
</tbody>
</table>

*Transformed from MNI coordinates (\(P < 0.05\) and all survival voxels at \(P\) value of 0.001) at double subtractions (see Table 1) of conditions FBC > EBC, that is, \([A – B] – (C – D)]\) in Table 1.
Discussion

While the involuntary micturition is largely intact at birth, the inhibition of the micturition is achieved during a developmental hierarchy of sensory–motor learning and reinforcement and is not a “built-in” behavior present at birth. As such, it may be a cognitive process that undergoes progressive maturation. While the pontine micturition center is credited with overall control of the micturition as a positive feedback reflex, it is assumed that a CNS network is involved in releasing or inhibiting the micturition reflex. During later stage of bladder filling, any small muscular maneuver of pelvic floor would massively trigger the arousal of bladder sensation and desire to void, hereby pelvic floor contraction was instrumented in present fMRI study to construct a contrast in “off–on” block-design paradigm, with which we have intended to isolate cortical areas associated with the inhibition of the micturition reflex during a strong desire to void. We could show that a complex activation pattern of bilateral SMA, bilateral putamen, and right cerebellum is engaged during the inhibition of the micturition.

Compared to positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies focused on similar bladder neural control issues (Athwal et al., 2001; Blok et al., 1997a,b, 1998; Fukuyama et al., 1996; Matsuura et al., 2002; Nour et al., 2000), our experimental design is significantly different in two respects, namely, bladder voiding did not occur during the scan (a nonvoiding model), and there was no catheter inserted in the lower urethral tract and the bladder volumes remained either full or empty during the scan. Thus, we do not expect to detect CNS structures facilitating the micturition reflex and areas related to urination, nor catheter- or bladder filling-induced sensations. The paradigm is meant to observe the voluntary control of voiding only, although indirectly by pelvic floor contraction.

Cortical and subcortical involvement in voiding control in general

During the urine storage phase, the detrusor is inhibited from contraction, and the striated sphincter is inhibited from relaxation. This negative feedback mechanism ensures intact continence and prevents the release of urine. The micturition reflex is believed to be controlled and coordinated by the pontine micturition center, as a positive feedback reflex, which is excitatory towards micturition phase. It is believed that the suprapontine brain structures are responsible for maintaining “matured” voiding behavior, that is, suppressing the desire for voiding until it is under proper time and occasion.

Despite studies from cat animal model (Edvardsen, 1966, 1968a,b; Edvardsen and Ursin, 1968), previous knowledge of brain involvement in voiding control is mainly derived from clinical reports in stroke and brain tumor patients with urinary functional disorder complications.

Compared with Barrington’s (1921) excellent work on the role of pons in urinary control early in 1920, the first study of cortex and brainstem involvement in voiding control arises over 40 years later. Ueki (1960) pioneer work based on 462 neurosurgical cases concluded that there is a positive influence of pons and an inhibitory influence of frontal lobe on micturition, as illustrated with a relationship diagram. Andrew (1964) described 38 stroke patients with lesions in the anterior frontal lobe that developed disturbances of micturition. This work was followed by another report of 50 frontal lobe tumor patients, seven of them manifested

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Fig. 1. The group results for the conjunction double contrast analysis with conditions FBC > EBC revealed a significant activation of SMA (A) and of bilateral putamen (B) and presented glass brain views (C) (figures are in neurological conventions; right is right, left is left; the cross-hair shows the global maxima).
micturition disturbance syndrome, a condition not found in 100 consecutive nonfrontal intracranial tumors (Maurice-Williams, 1974). Recent animal study (Ding et al., 1997) demonstrated an equally dense projection to the periaqueductal gray (PAG), and Barrington’s nucleus from the rat lumbosacral spinal cord suggested that an important role of this area may play in micturition control, which was also mirrored by human brain PET imaging study (Matsuura et al., 2002). A more recent 452 multiple sclerosis patient MRI images-based, lesion location, and neurological disability relation statistical mapping analysis (Charil et al., 2003) indicated that bowel and bladder scores correlated with lesions in the medial frontal lobes, cerebellum, insula, dorsal midbrain, and pons, areas known to be involved in the control of micturition. A review on stroke patients by Sakakibara et al. (1996a,b) also suggests such an existence of supraspinal inhibitory centers involved in voiding control. It is speculated that two areas in brain are involved in inhibitory bladder control: the “prefrontal cortex” and the “basal ganglia”.

**Supplementary motor area (SMA)**

SPECT (single photon emission computed tomography) and PET (positron emission tomography) studies have shown prefrontal motor cortical activity during pelvic muscle contraction and micturition (Blok et al., 1997a; Fukuyama et al., 1996). Supplementary motor area is considered to be involved in motor timing and inhibition of motor control. A recent fMRI study combined with MMPI (Minnesota Multiphasic Personality Inventory) suggested that self-control including self-inhibition is associated with SMA (Matsui et al., 2002). The activation of SMA in our voluntary voiding control may be interpreted as higher inhibition instrumented for suppressing the voiding desire during full-bladder session compared with empty-bladder session.

It is noteworthy that we did not see any activation in primary motor cortex (M1) during pelvic muscle contraction; it may indicate that pelvic floor muscle is not significantly represented in M1 and much less predominant than abdominal muscle in terms of motor cortical presentation.

**Cerebellum**

The cerebellum has traditionally been considered as a center of secondary motor control and coordination. Nevertheless, a growing body of data starts to shed light on its role as a general modulator of various forms of central neural activity. As regards to the micturition, both facilitatory (Chambers, 1947) and inhibitory (Bradley and Teague, 1969; Martner, 1975) effects have been reported. Studying the effect of cerebellectomy in decerebrate dogs, Nishizawa et al. (1989) suggested that the cerebellum also plays an inhibitory role in the collecting phase of the reflex micturition cycle and a facilitatory role in the emptying phase. Recently, Blok et al.’s (1997a) PET study in humans using pelvic muscle contraction has provided evidence of cerebellar involvement in micturition. Interestingly, we also found predominant activation in right hemisphere which is consistent with Blok’s results.

In spite of these clinical and experimental physiological data, it is still unclear how the cerebellum may participate in autonomic control. It is possible that cerebellar influence on visceral functions is to some extent mediated via the cerebral cortex. Sifert et al. (2000) found that children with postoperative cerebellar mutism (after removal of medulloblastoma) suffered from long-lasting urinary and fecal incontinence. This might indicate that global cerebellar dysfunction also affects bladder function.

**Basal ganglia and limbic system**

Basal ganglia were postulated to be involved in micturition inhibition control from animal studies since early days (Lewin et al., 1965, 1967; Pazo, 1976). Pazo’s rat study showed that electrical stimulation was excitatory on micturition when applied to dorsomedial caudoputamen and inhibitory when applied to nucleus ventromedial caudoputamen. The inhibitory effect from extrapyramidal tract is found in other studies as well (Lewin and Porter, 1965; Lewin et al., 1967). Clinical patient data also strongly indicate the role of the basal ganglia in micturition control. Sakakibara et al. (1996b) found that 9 of 10 patients who had lesions in the putamen showed bladder hyperreflexia. The recent publication of subthalamic nucleus electrical stimulation (Finazzi-Agro et al., 2003) decreasing detrusor hyperreflexia gives additional evidence of the role of basal ganglia in voiding control.

Cingulate cortex and parietal cortex were seen activated in PET bladder studies (Athwal et al., 2001; Blok et al., 1997a,b; 1998; Fukuyama et al., 1996; Matsuura et al., 2002; Nour et al., 2000). In Athwal’s PET study, bilateral parietal cortex was found activated during bladder filling, while in our results, the right side of parietal cortex seems more dominant; these findings indicate the important role parietal cortex may play in bladder control. It was also observed in their study that activity in anterior portion of the cingulate gyrus increased as bladder volume increased. In contrast, the activation at midportion of the cingulate increased as urge to void decreased; therefore cingulate cortex might present a complex role in the control of micturition. There are recent neuroimaging evidence that limbic system is involved in visceral sensation like esophageal dissention, anorectal sensation, and irritable bowel syndrome(Binkofski et al., 1998; Hobday et al., 2001; Verne et al., 2003); limbic structures were found engaged when the visceral sensation is unpleasant or painful(Binkofski et al., 1998), and it is proposed by Aziz et al. (2000) that, unlike somatic sensation, visceral sensation is represented in the paralimbic and limbic structures which are likely to mediate the affective and cognitive components of visceral sensation. As mirrored in our results, parahippocampal gyrus was activated in our bladder voiding control paradigm; this finding extends the evidence that limbic system is highly involved in visceral sensation.

**Developmental neurology**

One disorder that is assumed to be due to dysmaturated neuronal control of micturition is nocturnal enuresis (bed-wetting), which is considered an inhibitory micturition control disorder (Bath et al., 1996; Benjamin et al., 1971; Djurhuus, 2001; Kruse et al., 1999; Rasmussen et al., 1996). It is assumed that an inhibitory mechanism from premotor cortex level for the micturition is an acquired reversible behavioral response (as for nonprimary enuresis) for incentives rather than hereditary delay of maturation of somatosensory system. Wyndaele (1993) found that the sensory threshold of the urethra in bed-wetting children was significantly higher compared to control group. Interestingly, the variables of the bladder filling sensation were not different between the two groups. This finding hinted that bladder and urethra are controlled by separate neuronal pathways.
Conclusion

High-field fMRI on humans provided evidence of suprapontine brain structures involved in inhibitory control of bladder voiding; our study confirmed clinical lesion observation-based assumptions that medial prefrontal cortex, basal ganglia, and cerebellum are involved in the control of micturition, while parietal cortex and limbic system were also found in our study to be involved in inhibitory voiding control mechanism. It seems that right hemisphere is more dominant than left hemisphere in aforementioned control mechanism. The applied nonvoiding model provides a paradigm that might be applicable in the diagnostic assessment of disorders of the central bladder control due to different brain diseases.

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