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Original Article: Clinical Investigation

Brain activity during bladder filling and pelvic floor muscle contractions: A study using functional magnetic resonance imaging and synchronous urodynamics

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Abbreviations & Acronyms
fMRI = functional magnetic resonance imaging
GLM = general linear model
ICA = independent component analysis
LUT = lower urinary tract
MPR = multiplanar reconstruction
PET = positron emission tomography
PF = pelvic floor
PMA = primary motor area
SMA = supplementary motor area

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Objectives: To map the brain activity during bladder filling by functional magnetic resonance imaging using a refined scanning protocol including synchronous urodynamics and pelvic floor muscle contractions.

Methods: A total of 23 healthy female volunteers (age 20–68 years) were enrolled. Participants were asked to contract their pelvic floor muscles. This was followed by a urodynamic examination consisting of repeated filling cycles. Brain activity was measured by functional magnetic resonance imaging using a 3T magnetic resonance system. Measurements of brain activity consisted of 120 functional scans during pelvic floor contractions and 210 scans during bladder filling. Each functional magnetic resonance imaging scan covered the brain with 35 slices. Statistical analyses used the general linear model and independent component analysis. Areas of activation were visualized using group statistics.

Results: The following main clusters of activation were observed during pelvic floor muscle contractions: medial surface of the frontal lobe (primary motor area), bilaterally; supplementary motor area, bilaterally; and left gyrus precentralis. During bladder filling, activation was detected in the inferior frontal lobe bordering the frontal cingulum, left gyrus parietalis superior, left central area, right insula, brainstem and thalamus with subcortical gray matter nuclei.

Conclusions: Our work extends an existing functional magnetic resonance imaging protocol for researching the neural control of the lower urinary tract. The present results are consistent with the available literature and agree with the present hypothetical functional model of lower urinary tract neural control.

Key words: functional magnetic resonance imaging, pelvic floor, urinary bladder, urodynamics.

Introduction

In the past three decades, considerable research attention has been paid to the central neural control of various organs. However, compared with other organs and systems, relatively few studies have addressed neuroregulation of the LUT.

PET and fMRI have implicated the pons, periaqueductal grey, lobus insularis, anterior cingulate gyrus and prefrontal cortex as the structures most involved in the central control of LUT function in the human brain.[1] These findings have led to the development of a hypothetical model of the cerebral control of LUT.[2] However, our understanding of the neuroregulation of LUT and PF muscles is still incomplete, and results of existing studies are inconsistent. During the filling phase of the micturition cycle, PF muscles contribute to maintaining continence by gradually increasing their tone during bladder filling and through reflex contraction during a sudden increase in abdominal pressure.[3] In addition, it has been shown that a contraction of PF muscles inhibits detrusor contraction.[4]

We have previously mapped brain activity during micturition.[5] We observed the activation of several brain regions at the final filling phase, but we were not able to rule out the potential brain co-activations related to the PF muscles contraction. Based on these findings, we decided to carry out a study dedicated to the filling phase with respect to the potential influence of either volition or reflex PF muscles contraction.

In order to further increase precision and better correlate bladder function with central nervous system activity, we used synchronous urodynamic examination and fMRI, together with direct monitoring of the PF muscle activity.

Methods

Participants

A total of 23 right-handed healthy female volunteers aged 20–68 years were enrolled in the study. All participants were informed of the risks associated with the study, and provided written, informed consent. The study protocol was approved by the Ethics Committee of Thomayer Hospital, Prague. The study was designed in accordance with the principles of the Declaration of Helsinki, World Medical Association.

Participants with the following conditions were excluded from participation in the study: urinary infections, any LUT symptoms, significant prolapse of the pelvic organs, dementia, urolithiasis, history of previous malignant disease in the pelvic area, previous irradiation therapy of the pelvis, claustrophobia, use of medications that could influence functions of the brain or the LUT, metallic or electronic implants, or positive pregnancy test. Before enrolment, all participants were examined by a physiotherapist and trained in the use of a perineometer to ensure isolated contraction of the PF muscles.

Study design

Examinations performed on all volunteers were carried out under antibiotic prophylaxis (ofloxacin 200 mg). A Ch6 dual-channel catheter was inserted into the urinary bladder before the start of each examination for bladder filling and measurement of intravesical pressure. A catheter was also inserted into the rectal ampulla for measurement of abdominal pressure for monitoring of PF muscle activity. Both catheters were connected to urodynamic pressure transducers (MMS, Enschede, the Netherlands) located outside the examination room, and then zeroed against atmospheric pressure in the area of the symphysis, according to Good Urodynamic Practices.[6] Before the initial filling, a 10-min rest period was observed to allow catheter-induced irritation to subside.

The filling phase was evaluated by infusing the bladder with a sterile solution of 0.9% NaCl at a rate of 50 mL/min. Subjective parameters (first filling sensation, strong desire to void) were recorded by the participant using a hand-held signaling device. fMRI measurements were initiated after the bladder had been filled with 100 mL of solution. After the initial bladder filling, rapid filling and emptying of the bladder with 25 mL of the infusion solution was initiated in order to strengthen the sensory stimulus. Two trials of rapid filling and emptying were carried out according to the scheme described by Griffiths *et al.*[5] Briefly, the protocol examined the following four sequential phases: resting phase (14 s), filling phase (25 mL over 14 s), resting phase (14 s) and withdrawal phase (25 mL over 14 s). The filling cycle was continued until the participant recorded a strong desire to urinate. Then, four additional cycles of filling and emptying of the bladder were carried out simultaneously with continuous fMRI.

During another fMRI measurement, participants were asked to carry out three to four PF contractions lasting approximately 6 s, followed by a resting phase of 30 s. This procedure was repeated 10 times with 120 simultaneously carried out functional scans. This data was used in the final analysis to differentiate between brain activity that resulted from bladder sensations and activity resulting from voluntary contractions of the PF muscles.

fMRI data acquisition

All data was acquired with a 3T magnetic resonance scanner (Siemens Trio Tim 3T; Siemens, Erlangen, Germany) using a gradient-echo echo-planar imaging sequence (field of view = 192 × 192 mm; voxel size = 3 × 3 × 3 mm; repetition time/echo time = 2000/30 ms; bandwidth = 2790 Hz/pixel; parallel acquisition technique factor = 2). Measurements of brain activity during PF contractions used 120 functional scans. A total of 210 scans were used in the measurement of brain activity during bladder filling. Each fMRI dynamic covered the brain with a total of 35 slices.

Statistical processing

Statistical evaluations were carried out using SPM8 software (Wellcome Trust Center for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm). fMRI data preprocessing consisted of motion correction (realignment), slice timing and smoothing with a Gauss filter (full width at half maximum = 6 × 6 × 6 mm). Data was then normalized to standard Montreal Neurological Institute-152 space (Montreal Neurological Institute, Montreal, Canada, International Consortium for Brain Mapping, http://www.loni.ucla.edu/ICBM). Brain activity due to PF contractions was statistically evaluated using the GLM with a canonical hemodynamic response function convolved with a block scheme describing periods of contractions and rests (6 s of repeated contractions and 30 s of rest). Group level statistical maps were thresholded with an uncorrected P-value of 0.0001.

Both SPM8 and GLM was also used to evaluate brain activity during bladder filling using the following two protocols: (i) step function comparing empty versus full bladder (participant reporting a strong desire to void) – model A; and (ii) cyclic filling and withdrawal of 25 mL of 0.9% NaCl – model B. The procedure used for bladder filling during fMRI is shown in Figure 1. This figure also shows how the estimated brain activity was split into two models for statistical evaluation using GLM. Individual statistical maps were evaluated with a threshold of $P \leq 0.001$ (uncorrected) or $P \leq 0.05$ (adjusted for multiple observations FWE). The resulting statistical maps were included in group statistics (random effect) using a one-sample t-test with an uncorrected threshold of $P = 0.001$. Parallel evaluations used ICA for every measurement, with an identical number (n = 20) of components and the basic initial setup of the group ICA of fMRI toolbox program (version 1.3i, default values of processing parameters, infomax algorithm). This ICA analysis allowed for a comparison at the individual level of components obtained with simultaneously carried out urodynamic recording. The threshold of Z-score ($Z = 1.0$) was used for all components.

In addition to assigning anatomical brain regions to coordinates of activation cluster (position of maximum t-value within the cluster), the software package, Marina (B Walter, University of Giessen, Giessen, Germany), was used.

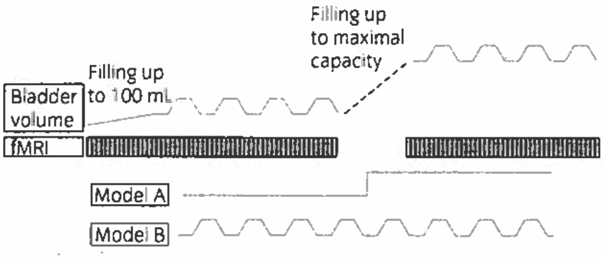

Fig. 1 Schematic summarizing the procedure used for bladder filling and the time course of fMRI. The first line represents how the volume was varied: to begin, the bladder was filled to 100 mL ("empty bladder condition") followed by a cycle of filling and withdrawing 25 mL. Scanning was stopped and the bladder was filled to maximal capacity, which was indicated by each participants ("full bladder condition"). Immediately after maximal bladder capacity was achieved, a second cycle of fMRI recording with simultaneous bladder filling and withdrawing was started. The second line shows when fMRI was carried out simultaneously. The two bottom lines indicate how both models were defined for statistical evaluation after data concatenation.

Table 1 Brain regions activated during PF contractions ($P = 0.0001$, t-test; uncorrected data for nine participants in group statistic using GLM)

Brain region	T	Z	x	y	z
Frontal lobe, medial surface (PMA)	10.12	4.47	±4	−27	65
Frontal lobe, medial surface (SMA)	12.47	4.88	±2	2	50
Central region, left precentral gyrus	8.22	3.62	−43	−13	63

Table 2 Brain regions activated during filling of the urinary bladder, tested using model A ($P = 0.001$, t-test, uncorrected)

Brain region	T	Z	x	y	z
Orbital surface of the inferior frontal lobe, olfactory cortex, bordering the frontal cingulum	5.02	3.38	−5	20	−10
Left gyrus parietalis superior	11.27	4.84	−25	−60	52
Left central area, gyrus postcentralis	6.97	3.99	−5	−35	60

Table 3 Brain regions activated during filling of the urinary bladder, tested using model B ($P = 0.001$, t-test, uncorrected)

Brain region	T	Z	x	y	z
Brain stem bilaterally	4.43	3.49	±14	−20	−9
Subcortical gray matter nuclei of the thalamus bilaterally	6.52	4.42	±10	−16	3
Right insula	5.38	3.95	40	14	3

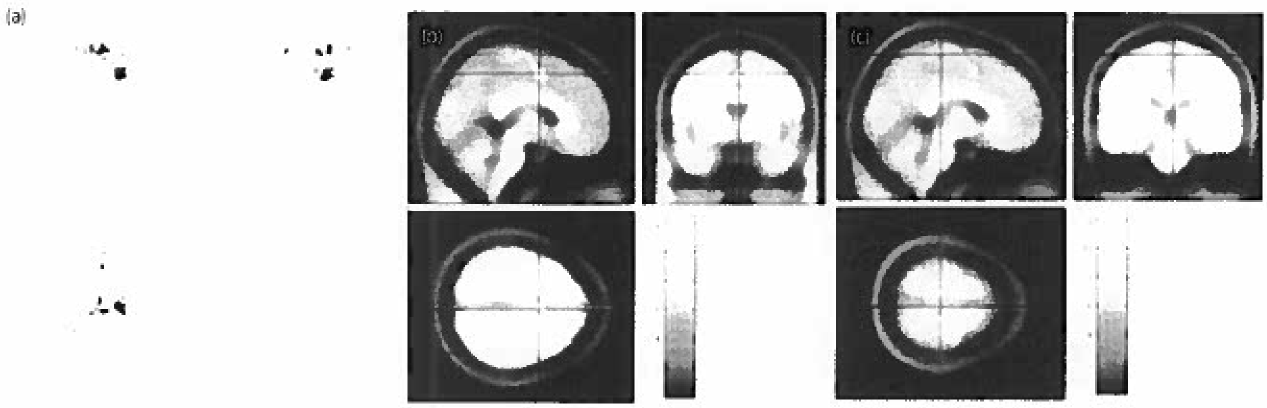

Fig. 2 Activations during PF contraction ($P = 0.0001$, t-test [$n = 9$]; group statistic, uncorrected). (a) 3-D projections showing all activity in sagittal, coronal and axial orientations; (b) MPR in SMA localization (±2, 2, 50); (c) MPR in localization of the primary motor cortex for the pelvic region (±4, −27, 65).

Results

Brain activation during PF contraction

The main clusters of brain activation during PF contractions were observed in the following areas: medial surface of the frontal lobe (primary motor area), bilaterally (±4, −27, 65); SMA, bilaterally (±2, 2, 50); and left gyrus precentralis (−43, −13, 63). Other, less significant, clusters of activation were observed on the left side of the medial frontal gyrus (−38, 36, 32), the right side of the medial frontal gyrus (42, 36, 32) and the right superior temporal gyrus (62, −34, 22; Table 1 and Fig. 2).

Brain activation during bladder filling

A total of 23 participants were evaluated. Meaningful data (evidence of brain activity) was obtained from 19 participants (this means data where any activation could be detected at all). The likely high level of motion could be degraded acquired data in the case of four participants without any activation. Using bladder-filling model A, we detected activations in the frontal lobe, left parietal gyrus and left central area (Table 2 and Fig. 3). Bladder-filling model B triggered activation mainly in the brainstem (7, −10, −10), the subcortical

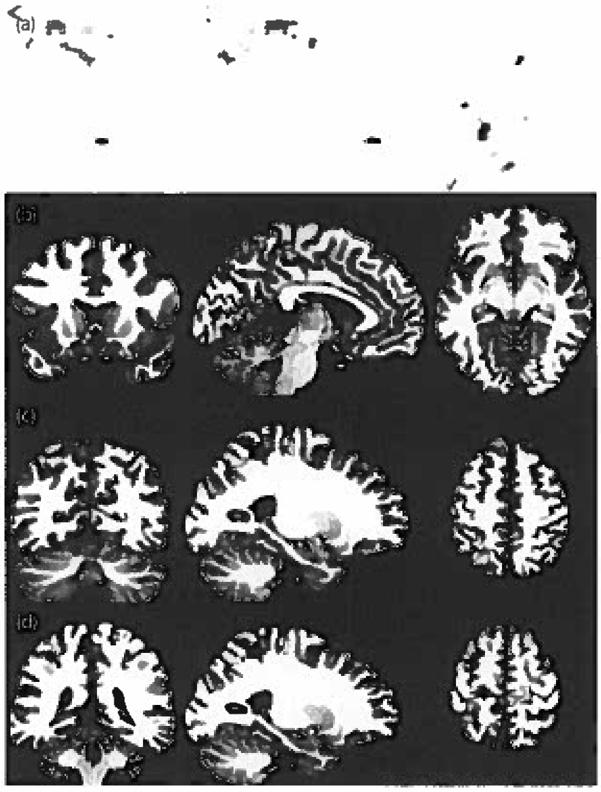

Fig. 3 Final activations stimulated by differences between empty and full bladder, calculated by GLM (model A). (a) Maximal intensity projection (frontal, sagittal, transversal) of group statistical map thresholded with $P = 0.001$ (uncorrected). (b) MPR in three orthogonal orientations centered in position (−5, 20, −10): orbital surface of the inferior frontal lobe, olfactory cortex, bordering the frontal cingulum. (c) MPR in three orthogonal orientations centered in position (−25, −60, 52): left gyrus parietalis superior. (d) MPR in three orthogonal orientations centered in position (−5, −35, 60): left central area, gyrus postcentralis.

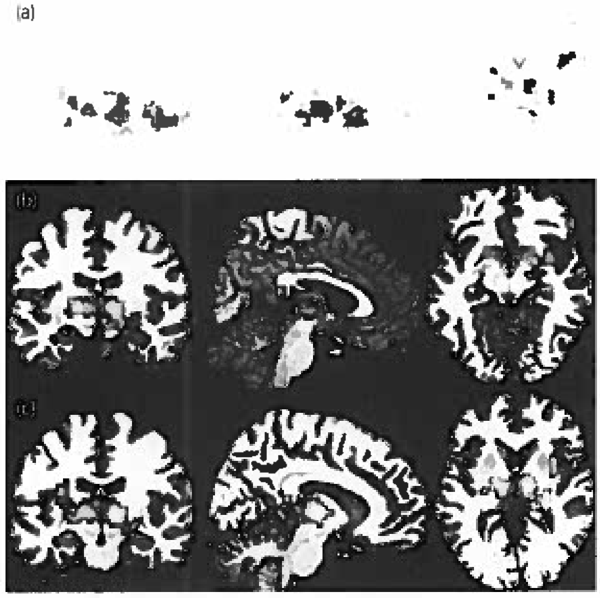

Fig. 4 Final activations stimulated by cyclic bladder filling and withdrawal (model B). (a) Maximal intensity projection (frontal, sagittal, transversal) of group statistical map thresholded with $P = 0.001$ (uncorrected). (b) MPR in three orthogonal orientations centered in position (7, −10, −10): brainstem. (c) MPR in three orthogonal orientations centered in position (10, −15, 0): thalamus with subcortical gray matter nuclei.

gray matter nuclei of the thalamus (10, −15, 0) and right insula (40, 14, 3; Table 3 and Fig. 4). Changes in brain activation during repeated filling and emptying of the bladder were also analyzed using ICA, which was carried out for each of the 23 measurements. One representative component for each of the measurements, which correlated with the simultaneously obtained urodynamic data, was identified by visual comparison (Fig. 5). Four measurements failed to identify a component associated with the change in volume of the urinary bladder. The most frequently identified areas of activation were localized to the right portion of the posterior cingulate gyrus [5, −47, 22], the left thalamus [−9, −10, 11], the middle left frontal gyrus (−36, 33, 45), and the left (−46, 20, −6) and right (47, 30, −14) orbital parts of the inferior frontal gyrus. The brain areas activated by changes in bladder volume and their relative frequencies of occurrence are presented in Table 4.

Discussion

Our understanding of the central neural mechanisms controlling the LUT is incomplete and the reproducibility of previously published data is inconsistent.[7]

The present study confirmed the reproducibility of an infusion/withdrawal protocol and provided further data in support of the feasibility of recording brain activity during bladder filling using fMRI.[8] Adding comprehensive urodynamics and direct recording of the PF muscle contractions to the fMRI scanning protocol allowed for better correlation between the detrusor, PF muscle function and brain activity. Cystometry carried out synchronously with fMRI scanning enabled a detailed visual comparison between brain activation and filling of the bladder, which allowed for selection of relevant components for ICA statistical analysis. Adding PF muscle contraction monitoring to the experimental protocol allowed for separation of brain activity caused by voluntary or reflex PF contractions at the terminal phase of the bladder filling from the activation caused by afferent signaling from mechanoreceptors in the bladder wall. PF contraction is known to cause inhibition of the micturition reflex. Patients suffering from urgency use this maneuver to suppress onset of the micturition phase. It is therefore possible that at least some components of the brain activity, recorded by fMRI during fast bladder filling, which others attributed to a strong urge to urinate, could be caused by contraction of the PF muscles. In order to precisely localize brain activity associated with PF contraction and distinguish it from activation related to bladder filling, we used a series of PF contractions at the beginning of the examination protocol. Using simultaneous urodynamics and direct PF muscle activity recording, we extended the protocol used in experiments by Kuhtz-Buschbeck *et al.*,[9,10] who evaluated the brain centers involved with control of the pelvic floor muscles. Our assessment of brain projections of PF

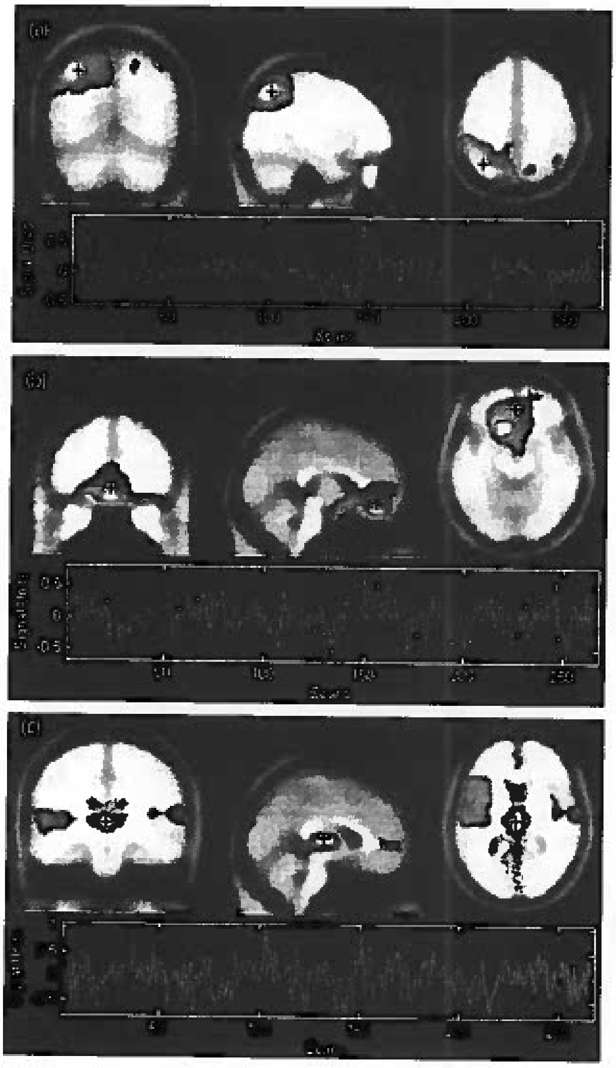

Fig. 5 Activations in the brain during changes in bladder volume recorded using group ICA: (a–c) showing three selected components with the best correlation with the time course of bladder volume changes. Each upper line shows three orthogonal sections (coronal, sagittal and axial) centered in the area marked with the black cross (a) (−34, −55, 49), (b) (−4, 42, −8) and (c) (−3, −15, 4). Corresponding time signal course in this point is shown in the lower line.

muscle activity identified bilateral activation of the SMA together with activation of the primary motor cortex for the PF muscles. This is in accord with previously published data.[10] However, contrary to the report from Di Gangi-Herms,[11] who described activation in the area of the right pre-central gyrus, we observed activation in the medial frontal gyrus. Seseke *et al.* examined activation of the cortex during the contraction of PF muscles with a full bladder. Similar to the present results, they observed activation of primary and SMA without hemispheric predominance. Furthermore, they described activation of numerous subcortical structures (hypothalamus, thalamus, periaqueductal grey) and the cerebellum.[12]

The reason for utilizing rapid filling and withdrawal during the early and final stage of bladder filling (model B) was to augment the afferent signals according to a protocol proposed by Griffith *et al.*[8] Comparison between these two models of

Table 4 Relative frequency of brain activity in nine selected brain regions during bladder volume changes (individual statistics using ICA)

Brain region	Coordinates			Relative frequency of activations in the subject population
	x	y	z	
Middle left frontal gyrus	−36	33	45	47% (9/19)
Inferior frontal gyrus, left orbital part	−46	20	−6	42% (8/19)
Inferior frontal gyrus, right orbital part	47	30	−14	42% (8/19)
Middle frontal gyrus, right orbital part	21	62	−14	26% (5/19)
Middle frontal gyrus, left orbital part	−21	45	−16	26% (5/19)
Left angular gyrus	−41	−59	57	47% (9/19)
Right posterior cingulate gyrus	5	−47	22	58% (11/19)
Anterior cingulate, left paracingulate gyri	−2	46	14	26% (5/19)
Subcortical grey nuclei, left thalamus	−9	−10	11	53% (10/19)

bladder filling allowed us to observe that the slow gradual bladder filling (model A), used in the present study, induced activation solely in the cortical regions of the brain, while the subcortical regions and insula are activated only by rapid filling and withdrawal. We speculate that rapid change in the intravesical volume and pressure triggers micturition reflex mechanisms responsible for maintaining detrusor relaxation during filling (e.g. sympathetic pelvic-to-hypogastric storage reflex or guarding somatic pelvic-to-pudendal reflex). This could possibly imitate the brain response to non-voiding detrusor contractions. In contrast, gradual filling allows time for bladder accommodation, which is predominantly under the control of the cortical centers.

The present findings are generally consistent with results of the initial works of Griffiths *et al.*[13,14] and earlier studies using PET, which describe activation in the area of the insula, cingulum, periaqueductal grey, cerebellum and occipito-parietal area with sensory stimulation during bladder filling in healthy subjects.[15,16] We did not observe any brain activation in the regions related to PF muscle contractions during the filling phase.

The present study further developed a protocol applicable for studying neural control of LUT using fMRI. The results acquired with this refined scanning protocol point to the fact that the thalamus, cingulate gyrus, and especially the lower surface of the frontal lobe play a significant role in sensation and afferent signaling from the LUT, and could therefore represent a potential target for the treatment of the cardinal LUT symptom of urgency. Future studies in this area should focus on comparing central nervous system activity of patients with various LUT dysfunctions with those of healthy controls, together with assessing the influence of pharmacotherapy.

Acknowledgments

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Conflict of interest

None declared.

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Editorial Comment

Editorial Comment to Brain activity during bladder filling and pelvic floor muscle contractions: A study using functional magnetic resonance imaging and synchronous urodynamics

The frontal cortex is regarded as the higher center for micturition, because lesions in the frontal cortex; for example, the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex, insula and supplemental motor area, produce marked lower urinary tract dysfunction in humans. Overactive bladder (urinary urgency and frequency) as a result of detrusor overactivity is a common bladder abnormality in the aforementioned brain areas. Functional neuroimaging in normal volunteers using single-photon emission computed tomography, positron-emission tomography, functional magnetic resonance imaging, and near infrared spectroscopy has been applied to observe brain activation in response to bladder fullness and urination; and the activated areas strikingly overlap the lesions described in clinical studies. Among the brain areas, anterior cingulate cortex and insula are thought to be "primary", and the prefrontal cortex is "secondary" (presumably modulatory) in regulating micturition. The constellation of these cortical areas seem to "switch on and off" the spino–bulbo–spinal micturition reflex involving the midbrain periaqueductal grey and the pontine micturition center.[1-3]

Krhut *et al.* studied 20 healthy female volunteers who participated in bladder push and pull, and pelvic floor contraction paradigm for urodynamics-functional magnetic resonance imaging.[4] The results were in agreement with the previously reported results. In addition, that study successfully highlighted the role of the pelvic floor, though already suggested by others,[5-7] that bilateral primary motor area (midline medial surface), bilateral supplementary motor area (similar) and left precentral gyrus are significantly activated by pelvic floor contraction. In order to manage patients' pelvic floor, for both diagnosis and treatment, the brain is worth looking at.

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Conflict of interest

None declared.

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