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Functional Magnetic Resonance Imaging during Urodynamic Testing Identifies Brain Structures Initiating Micturition

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Abstract

Purpose—Normal voiding in neurologically intact patients is triggered by the release of tonic inhibition from suprapontine centers, allowing the pontine micturition center to trigger the voiding reflex. Supraspinal mechanisms of voluntary voiding in humans are just beginning to be described via functional neuroimaging. We further elucidated brain activity processes during voiding using functional magnetic resonance imaging in normal females to gain better understanding of normal voiding as well as changes that may occur in voiding dysfunction.

Materials and Methods—We screened 13 healthy premenopausal female volunteers using baseline clinic urodynamics to document normal voiding parameters. We then recorded brain activity via functional magnetic resonance imaging and simultaneous urodynamics, including the pressure flow voiding phase. After motion correction of functional magnetic resonance images we performed activation and connectivity analyses in 10 subjects.

Results—Group analysis revealed consistent activation areas, including regions for motor control (cerebellum, thalamus, caudate, lentiform nucleus, red nucleus, supplementary motor area and post-central gyrus), emotion (anterior/posterior cingulate gyrus and insula), executive function (left superior frontal gyrus) and a focal region in the pons. Connectivity analysis demonstrated strong interconnectivity of the pontine micturition center with many short-range and long-range cortical clusters.

Conclusions—Our study is one of the first reports of brain activation centers associated with micturition initiation in normal healthy females. Results show activation of a brain network consisting of regions for motor control, executive function and emotion processing. Further studies are planned to create and validate a model of brain activity during normal voiding in women.

Keywords

urinary tract; urination; brain; central nervous system; magnetic resonance imaging

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The lower urinary tract has 2 functions, that is storage and voluntary elimination of urine. Normal voluntary voiding in neurologically intact patients is triggered by the release of tonic inhibition from suprapontine centers, allowing the PMC to trigger the voiding reflex. Mediated through spinal centers, this reflex initiates relaxation of the pelvic floor musculature and the urethral sphincter. The bladder then contracts and empties.

In the last 2 decades the evolution of neuroimaging modalities applied to the field of neurourology has provided a new frontier of research.[1–4] In 1998 Blok et al studied normal micturition in 10 females using CNS positron emission tomography.[5] Increased blood flow was noted in the right dorsal pontine tegmentum and the right inferior frontal gyrus. Kuhtz-Buschbeck et al incorporated fMRI to examine brain region activation during bladder filling.[6] They studied 33 healthy subjects, including 17 women and 16 men, and noted that supplementary motor areas, the frontal and prefrontal cortex, the insula and the mid cingulate cortex were active during attempted micturition.[7] They observed differences in brain activation between higher and lower volumes of bladder filling and among men and women. They also identified activation of supplementary motor areas during voluntary pelvic floor muscle contractions, which was independent of bladder volumes and gender. Seseke et al reported findings in 11 healthy females during voiding initiation by pelvic floor muscle relaxation and imitation of interrupted voiding by voluntary pelvic floor contraction.[8] They noted that specific locations in the PAG and PMC became activated. Di Gangi Herms et al reported fMRI evidence of cortical neuroplastic changes after pelvic floor muscle training and biofeedback therapy for stress urinary incontinence.[9] In addition, Seseke et al used fMRI with a concurrent urodynamic study to assess brain activation early in the post-prostatectomy period in 22 patients before and after radical retropubic prostatectomy.[10]

Due to technical challenges related to voiding in the scanner most investigators have focused efforts on the storage phase and initiation of micturition.[3,4] However, recently Krhut et al focused on actual micturition in the fMRI machine.[11] They presented preliminarily findings of brain activity during supine bladder emptying in 6 healthy females, localizing areas in the parahippocampal gyrus, anterior cingulate gyrus, inferior temporal gyrus and inferior frontal gyrus during micturition. Our study is the second report of brain activation during micturition using fMRI and concurrent urodynamic testing that focused on initiation of micturition.

The etiology of voiding dysfunction in females is often unknown. We sought to improve our ability to understand CNS regulation of normal voiding using fMRI in healthy normal females. With new discoveries at the level of CNS activity we hope to gain better understanding of normal voiding and changes that occur in voiding dysfunction.

MATERIALS AND METHODS

Subjects

Approval was obtained from the Methodist Hospital institutional review board. A total of 13 subjects were screened by history, physical, urinalysis, urine culture and urine pregnancy test. They were also asked to complete the UDI-6 (Urogenital Distress Inventory), IIQ-7 (Incontinence Impact Questionnaire) and HAM-A (Hamilton Anxiety Rating Scale)

questionnaires, a fMRI safety screening questionnaire and a demographic form. Before fMRI urodynamics were performed in the office to exclude those unable to void under the testing circumstances. Study exclusion criteria included post-menopausal status, positive urine pregnancy test, neurological illness or injury, neurogenic bladder, history of incontinence or prolapse surgery, any lower urinary tract surgery and any lower urinary tract symptom.

fMRI Examination

Double lumen 7Fr magnetic resonance imaging compatible urodynamic bladder and rectal catheters were inserted for fMRI. All fMRI examinations were performed with a Philips® 3.0 Tesla full body scanner using the standard 12-channel head coil. Task instruction consisted of giving subjects directions to perform a quick hand signal to convey the point of fullness, and the initiation and completion of voiding. Patients were instructed to squeeze a bulb in the hand if they experienced claustrophobia or discomfort and wanted to be removed from the scanner.

After standard localizer and a high resolution structural scan (3D T1-weighted fast field echo acquired in the sagittal orientation with a reconstructed isotropic spatial resolution of 0.7 mm) functional images were acquired with the concurrent urodynamic examination (axial echo planer, repetition time 3,000 milliseconds, slice thickness 4 mm, in-plane resolution 3.38 mm and number of slices matched for full coverage of the brain). Total scan duration was limited to about 25 minutes due to the restriction of the scanner software. The bladder was filled with sterile saline and subjects were instructed to signal the point of fullness. After holding for 30 seconds they were allowed to initiate voiding to completion into absorbent pads. After voiding was completed the urodynamic cycle of filling and voiding with concurrent fMRI was repeated up to 4 times.

Analysis

Functional magnetic resonance imaging—In the analysis described we focused on initiation of the voiding event as identified by recordings obtained at the concurrent urodynamic examination. fMRI was analyzed by AFNI (http://afni.nimh.nih.gov/afni/), software to process, analyze and display fMRI data to map human brain activity. As the first step, motion correction was performed to assess the amount of motion during the scan. In 3 subjects motion was large (maximum translation range 4.5 to 14 mm) and they were consequently excluded from further analysis. In the remaining 10 subjects the range of maximum translation due to motion was 0.5 to 2.5 mm, less than the size of 1 voxel and, thus, deemed acceptable. We used the generalized linear model to create individual fMRI activation maps (t-scores) at initiation of voiding. The Student t-test implemented in AFNI was applied to the average fMRI activation in all 10 subjects to determine statistical significance after transformation into Talairach space.

Connectivity—Sensitivity analysis of the activation threshold (t-score 5.761, corresponding to uncorrected $p = 2.7 \times 10^{-4}$, data not shown) was performed to identify areas of pertinent activation in the average fMRI BOLD map. Connectivity between activated brain voxels was defined as the Pearson correlation coefficient calculated from

BOLD signal time courses and used as edge weights in network graphs with voxels as vertices. The 2-dimensional network graphs were displayed using spring embedded network layouts created by force directed algorithms. These algorithms assign forces among the set of edges and the set of nodes of a graph drawing. Springlike attractive forces are typically used to attract pairs of endpoints of graph edges toward each other while repulsive forces are simultaneously used to separate all pairs of nodes. In this study attracting forces were defined by the strength of the Pearson correlation coefficient between BOLD signal time courses of different vertices. Because in the 3D networks vertices are oriented at the anatomical position, edge length did not correspond to the correlation between vertices. Clusters in the networks were identified using the MCODE algorithm in Cytoscape software (http://www.cytoscape.org) as described previously.[12]

The goal of this graph-network connectivity analysis was to identify functional subunits (clusters) in the brain that act together to perform the described task in small world behavior, ie where focal regions of highly interconnected voxels interact with each other through long-range connections.

RESULTS

Patient Demographics and Baseline Urodynamics

Mean age of the 10 subjects was 32.4 years (range 25 to 45). All 10 subjects could void while supine. Each voided at least 3 complete voiding cycles (up to 5) during the fMRI scanning phase with time to voiding initiation and cystometric capacity as factors in the total number of voiding cycles. Mean ± SD cystometric capacity was 242.4 ± 106.5 ml.

Analysis

fMRI activation—Group analysis of the 10 subjects yielded consistent areas of activation during voiding initiation (fig. 1). The areas included regions for motor control (cerebellum, thalamus, caudate, lentiform nucleus, red nucleus, supplementary motor area and postcentral gyrus), emotion (anterior and posterior cingulate gyrus, and insula), executive function (left superior frontal gyrus), parahippocampal gyrus, precuneus, cuneus, occipital lobe (visual stimulus) and a focal region in the pons. The table and figure 2 show coordinates using the MNI (Montreal Neurological Institute) convention of derived clusters, representing regions of highest activation.

Connectivity—Graph-network analysis yielded spring embedded network layouts that for each subject showed a small world structure of focal clusters with short-range interactions connected by long-range edges (fig. 2). A 3D representation of cluster connectivity showed strong PMC interconnectivity with most remaining clusters except the cluster in the frontal lobe (fig. 2). In turn they showed long-range connectivity to other clusters, including those in supplementary and primary motor areas.

DISCUSSION

Our understanding of suprapontine neural control over micturition has evolved significantly in the last 30 years. In the spinal cord the Gert nucleus is responsible for starting the basic

reflex system and eventually relaying it to the PAG.[13] Many researchers have explained an emotional motor system framework for micturition control existing in a cell group with functions similar to those of cardiovascular changes, respiration, vocalization and receptive behavior.[14] In the case of significant bladder filling the PAG activates the PMC, which signals voiding. Many higher cortical centers control the PAG. The strongest influences are from the mediofrontal cortex. In addition the insula, the lateral prefrontal premotor cortex and temporal limbic cortex send moderate to weak signals.[15]

While mapping the brain during filling has been the focus of many researchers using fMRI and positron emission tomography, studying the micturition phase has raised some challenges.[4,8] We sought to contribute to the literature by further mapping the central anatomical locations responsible for micturition initiation in healthy female subjects and develop an initial understanding of functional brain connectivity while performing this study. We believe that this knowledge will be of particular interest for patients with dysfunctional voiding, those with neurological disorders and those without obstruction who cannot initiate urination.

Using simultaneous urodynamic testing with fMRI during voiding in healthy female subjects we defined and analyzed voiding initiation as an entity temporally distinct from other time points. At voiding initiation structures previously implicated in micturition were activated in motor and executive areas that coordinate the voiding phase. Group analysis also revealed activation of a focal region in the midbrain, which may be the region of the PAG and/or PMC. Also, activation of emotion centers (cingulate gyrus and insula), which is known to occur during bladder filling, reflected the sensation of fullness and/or discomfort at the time of voiding as well as a baseline level of anxiety. Network analysis demonstrated the interconnection between these activated brain regions at voiding initiation.

Krhut et al reported preliminary results in 6 subjects with successful micturition using simultaneous urodynamics and fMRI.[11] Results revealed upper pontine region, inferior frontal lobe and thalamic activation in all 6 subjects. In addition, the anterior and posterior cingulate gyrus was activated in 3 and 4 subjects, respectively. These centers were also activated and confirmed in our subjects. Moreover, in the study by Krhut et al analysis of the 4 patients who could not void showed no pons activation, unlike in those who could void. Likewise, all of our voiding subjects showed pons activation, confirming the role of the PMC in voiding initiation. Understanding the role of the PMC is key in further studies of patients with dysfunctional voiding.

Tadic et al described initial fMRI studies of bladder filling and the role of the right insula and anterior cingulate gyrus.[16] Connectivity analysis was done using those baseline regions of interest, delineating areas connected to them during bladder filling. In our micturition studies we generated connectivity networks without previously setting regions of interest in an entirely data driven model. This model yielded significant connections in short-range focal clusters as well as long-range associations.

In this analysis all voxels in the BOLD activation maps were separated into separate subunits that were each highly connected within each other with long-range connections between

each other. The functional implications of these connections have yet to be fully elucidated. These interactions are broader than those previously described for bladder filling since they are independent of any baseline regions. The connectivity strength of a region can provide clues to its functional importance. For example, we noted strong interconnectivity of the PMC with several cortical and subcortical regions. They in turn had long-range interactions with other cortical areas that are important for emotional and executive processing regarding the act of micturition. The connectivity networks provide insight not simply into the discrete regions controlling micturition but also into their interdependence. Understanding this will be critical in future studies of subjects with neurological disease. Lesions compromising hubs may have a higher impact on voiding than lesions affecting other poorly connected regions. This hypothesis must be tested in patients with lesions and compromised voiding.

A limitation of this study is that only healthy female subjects were evaluated. Because we initially verified normal voiding parameters in clinic, all subjects could void in the scanner while supine. Voiding while supine may pose a challenge to many individuals who can void normally while seated. Thus, by analyzing only voiding while supine, there may have been selection bias compared to the general population. In addition, the circumstances of being secured to the scanner could have affected brain activation and cystometrogram parameters. Nonetheless, this feasibility study presents invaluable information on brain regions involved in the initiation of micturition. Further studies are undoubtedly needed in a larger population of healthy males and females to further characterize normal anatomical centers.

CONCLUSIONS

Concurrent urodynamic testing and fMRI have allowed greater insight into central control of normal voiding. Our report represents one of the first studies of the brain activation centers associated with the initiation of micturition in normal healthy females. To our knowledge this study included the largest number of subjects. Our group and network analyses revealed activation of a brain network consisting of interconnected regions of sensorimotor control, executive function and emotion processing as well as deeper brain structures during micturition. Future investigations are planned to create and validate a model of brain activity during normal voiding in women and expand our studies to those with dysfunctional and neuropathic voiding.

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Abbreviations and Acronyms

3D	3-dimensional
BOLD	blood oxygen level dependent
CNS	central nervous system
fMRI	functional magnetic resonance imaging

PAG	periaqueductal gray
PMC	pontine micturition center

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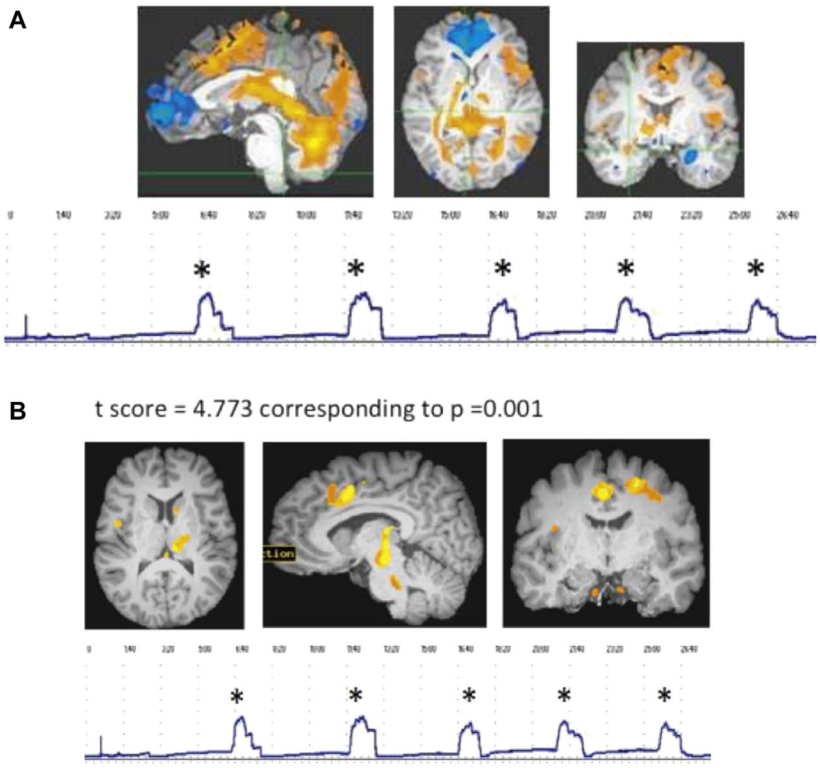

Figure 1.

A, average fMRI activation map shows activation in pons (micturition center), thalamus, cingulate gyrus, supplementary motor area and precentral gyrus. *B*, representative pressure time course from urology examination. Asterisks indicate start of voiding used in event related analysis of fMRI data (*A*).

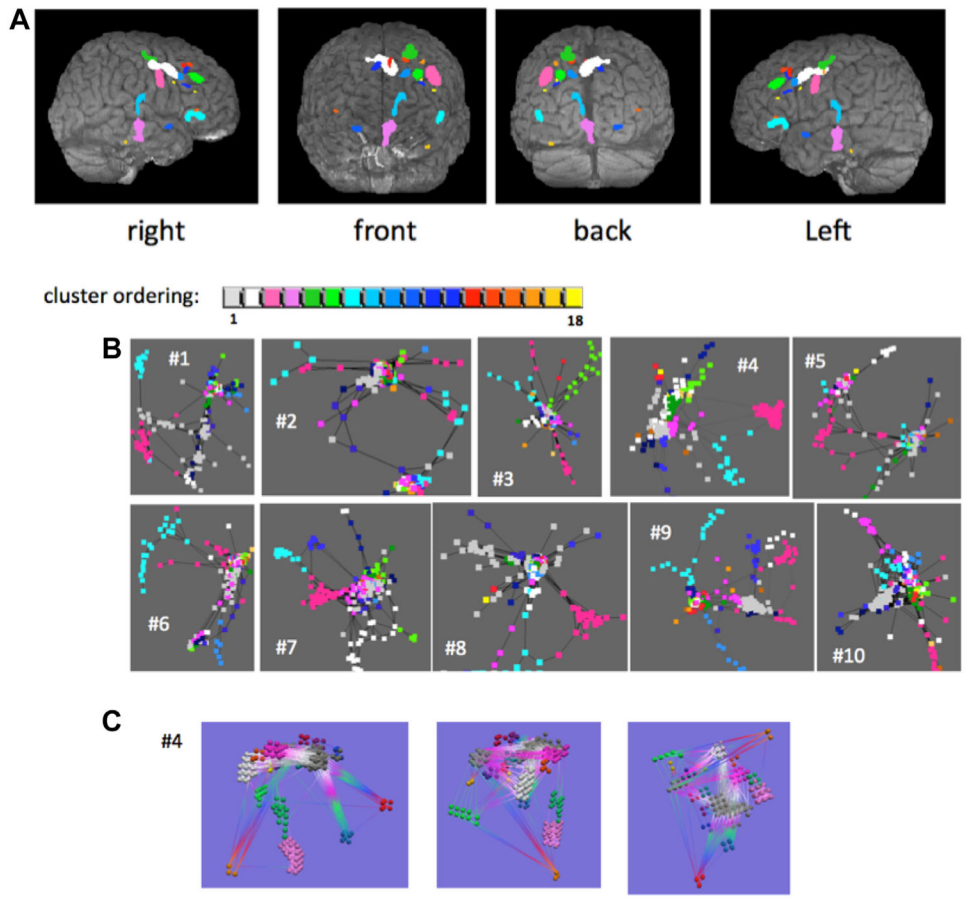

Figure 2.

A, clusters of highest fMRI activation derived from fMRI activation maps in see-through mode, allowing visualization of activation in entire brain. Note 18 clusters colored to serve as scale (*cluster ordering*). *B*, spring embedded network graphs of each subject show color coded clusters (*A*). Note small world behavior consisting of localized network node of high interaction in 1 cluster together with sparse long-range connectivity between clusters of most networks. *C*, 3D network display of subject 4 shows this small world behavior better than 2D graph networks.

Table 1

Clusters corresponding to location of largest fMRI activation (uncorrected p = 2.7e-4)

			MNI Coordinates		
Cluster No.	**AFNI Anatomical Site**	**Vol (mm^3)**	**Lt Rt**	**Anteroposterior**	**Inferior Superior**
1	Bilat cingulate gyrus	1,847	−7.1	13.6	38.8
2	Left precentral gyrus	905	−44.4	0.7	28.3
3	Pons + red nucleus	803	0.0	−16.3	−29.5
4	Lt middle frontal gyrus	544	−19.2	−8.7	51.8
5	Lt middle frontal gyrus	447	−28.3	36.5	35.7
6	Lt inferior frontal gyrus	434	−46.5	27.0	−4.4
7	Lt thalamus	333	−9.1	−21.7	−0.1
8	Lt cingulate gyrus	194	−16.2	16.8	36.8
9	Rt subcallosal gyrus	165	21.2	9.9	−13.7
10	Rt cingulate gyrus	122	8.1	21.7	43.6
11	Lt middle frontal gyrus	75	−33.3	26.5	29.7
12	Lt medial frontal gyrus	64	−5.1	20.5	46.8
13	Lt superior frontal gyrus	63	−18.2	27.5	51.5
14	Rt inferior frontal gyrus	45	40.4	34.8	6.2
15	Lt middle frontal gyrus	26	−32.3	−10.5	47.3
16	Lt culmen	23	−35.4	−31.7	−31.6
17	Lt middle frontal gyrus	12	−42.4	32.8	25.7
18	Lt middle frontal gyrus	7	−32.3	11.8	33.3