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Functional Magnetic Resonance Imaging with Concurrent Urodynamic Testing Identifies Brain Structures Involved in Micturition Cycle in Patients with Multiple Sclerosis

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Abstract

Purpose—Neurogenic lower urinary tract dysfunction, which is common in patients with multiple sclerosis, has a significant impact on quality of life. In this study we sought to determine brain activity processes during the micturition cycle in female patients with multiple sclerosis and neurogenic lower urinary tract dysfunction.

Materials and Methods—We report brain activity on functional magnetic resonance imaging and simultaneous urodynamic testing in 23 ambulatory female patients with multiple sclerosis. Individual functional magnetic resonance imaging activation maps at strong desire to void and at initiation of voiding were calculated and averaged at Montreal Neuroimaging Institute. Areas of significant activation were identified in these average maps. Subgroup analysis was performed in patients with elicitable neurogenic detrusor overactivity or detrusor-sphincter dyssynergia.

Results—Group analysis of all patients at strong desire to void yielded areas of activation in regions associated with executive function (frontal gyrus), emotional regulation (cingulate gyrus) and motor control (putamen, cerebellum and precuneus). Comparison of the average change in activation between previously reported healthy controls and patients with multiple sclerosis showed predominantly stronger, more focal activation in the former and lower, more diffused activation in the latter. Patients with multiple sclerosis who had demonstrable neurogenic detrusor overactivity and detrusor-sphincter dyssynergia showed a trend toward distinct brain activation at full urge and at initiation of voiding respectively.

Conclusions—We successfully studied brain activation during the entire micturition cycle in female patients with neurogenic lower urinary tract dysfunction and multiple sclerosis using a concurrent functional magnetic resonance imaging/urodynamic testing platform. Understanding

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the central neural processes involved in specific parts of micturition in patients with neurogenic lower urinary tract dysfunction may identify areas of interest for future intervention.

Keywords

urinary bladder; brain mapping; multiple sclerosis; urodynamics; magnetic resonance imaging

Normal lower urinary tract function is controlled by the peripheral and central nervous systems. In the last 2 decades with the evolution of neuroimaging technologies such as positron emission tomography and fMRI we have begun to gain more insight into higher neural control over the micturition cycle in healthy individuals.[1] Although many regions of the brain are involved in proper control of the micturition cycle in humans, it appears that in healthy individuals brain activation occurs mainly in the prefrontal cortex, the anterior and middle cingulate gyrus, and the supplementary motor area, previously known as the frontal micturition center.[2] Positron emission tomography and fMRI neuro-imaging have shown activation of the right dorsal pontine tegmentum, the right inferior frontal gyrus and other regions for motor control during voiding.[3–5] Following the identification of these circuits in healthy individuals, in recent years investigators have started to study patients with LUTS and urological chronic pelvic pain syndrome to better establish a phenotype and understand these complex urological syndromes.[6,7]

Despite extensive efforts to study patients with LUTS and urological chronic pelvic pain syndrome, neurogenic lower urinary tract dysfunction has hardly been studied. This is perhaps because of the heterogeneity of the disease and the inherent challenges in evaluating patients with mobility limitations and significant physical morbidities.[8]

LUTS are common in patients with MS and almost all patients report symptoms 10 years or more after the onset of MS.[9] Our pilot study was designed to enhance our understanding of CNS control of micturition in female patients with MS and NLUTD. To our knowledge this is the first reported study using a combined platform of fMRI/UDS in patients with MS and NLUTD.

We applied our previously established fMRI/UDS platform[5] to investigate the higher neural control involved during the complete micturition cycle (storage and voiding phase) in ambulatory female patients with MS and NLUTD. In addition, we explored whether patients with demonstrable NDO or DSD show a trend toward distinct supraspinal activation.

MATERIALS AND METHODS

Subjects

We screened ambulatory female patients with MS, a EDSS score[10] of 6.5 or less and bothersome LUTS who had previously undergone UDS. Subjects were asked to complete UDI-6 (Urogenital Distress Inventory), IIQ-7 (Incontinence Impact Questionnaire), HAM-A (Hamilton Anxiety Rating Scale), a demographic form and a MRI safety screening questionnaire. Subjects were excluded from analysis if they had a positive urine pregnancy test, a symptomatic urinary tract infection or contraindications to MRI. Control data were

provided by records from HC female subjects reported in our previous study.[5] Men were excluded from study to avoid confounding by prostate pathology.

Urodynamic Testing and Functional Magnetic Resonance Imaging Paradigm

Double lumen 7Fr MRI compatible bladder and rectal UDS catheters were inserted prior to fMRI and after the patient voided spontaneously. All MRI was performed at our institutional translational imaging MRI Core using an Ingenia 3.0 Tesla full body scanner (Philips, Eindhoven, The Netherlands) with a standard 12-channel head coil. Subjects were instructed to use right hand signals to indicate the times when they reached a strong desire to void, and initiated and completed voiding.

Functional MRI times were limited to 30 minutes. During this time the bladder was gradually filled at 75 ml per minute with room temperature sterile saline until subjects signaled to indicate a strong desire to urinate. At this point bladder filling ceased and subjects were asked to hold without voiding. After 30 seconds of holding, subjects were allowed to void spontaneously into absorbent pads on the scanner table. The patient signaled the initiation and completion of voiding. After voiding was completed the cycle was repeated up to 4 times.

Complete urodynamic data and final catheterized post-void residual volume were recorded. Functional scan times, hand movements, the fMRI/UDS platform, motion parameters and study exclusion criteria based on motion artifact were comparable in the MS and HC groups. Figure 1 indicates our protocol for concurrent UDS and fMRI.

Data Acquisition and Statistical Analysis

Supplementary Appendix 1 (http://jurology.com/) shows technical details. Briefly, functional and anatomical data were co-registered and motion correction was applied to functional data to remove drift and censor rapid movements. Subjects with detected rapid (no drift) motion greater than the 4 mm slice thickness were excluded from analysis and the remaining data sets were retained as viable.

Significant differentially activated voxels were identified at strong desire to void (3 volumes) and at the initiation of voiding (3 volumes) under the generalized linear model. Group level analysis was performed and significantly activated voxels were identified by the Student t-test. Comparisons were drawn between HCs and subjects with MS at the time of strong desire and at the initiation of voiding. In addition, subgroup analysis was done to compare patients who did and did not have demonstrable NDO on UDS. Another subgroup analysis was performed to compare subjects with and without DSD at initiation of voiding. Analysis was done in regard to NDO and DSD to determine a trend in the data as the study was not powered to obtain statistically significant results.

RESULTS

Patient Demographics and Urodynamics

A total of 40 ambulatory female patients with an EDSS score of 6.5 or less who were referred to our neurourology clinic by neurologists with a confirmed diagnosis of MS and

LUTS were screened and assessed for study eligibility. Of these patients 13 refused to participate and 3 did not meet inclusion criteria. Two of the latter patients had become significantly debilitated by MS exacerbation and 1 had been admitted to a psychiatric hospital.

Concurrent fMRI and UDS were performed in 23 patients. Our protocol was described in detail in our previously published HC series.[5] The table lists patient demographics. Mean age of female HCs was 32.4 years (range 25 to 45), which was less than the mean age of 46.8 years (range 33 to 57) in patients with MS.

Functional Magnetic Resonance Imaging Blood Oxygen Level Dependent Signal Analysis

Data acquisition and analysis, the fMRI/UDS platform and motion parameters were comparable in HCs and patients with MS. Seven subjects were excluded from analysis due to large translational motion (more than 4 mm). Supplementary Appendix 1 (http://jurology.com/) shows the maximum translational motion for each subject together with values in HCs for comparison. Mean functional neuroimaging time was 17.8 minutes in patients with MS and 25.36 minutes in HCs. Supplementary Appendix 2 (http://jurology.com/) shows prominent regions of activation and specific data on the regions.

At Strong Desire to Void—Patients with MS demonstrated significantly elevated activity in various regions ($p < 0.05$). This was notably associated with executive function (frontal gyrus), motor tone (lentiform nucleus), emotional recognition and attention (anterior and posterior cingulate, parietal lobules and precuneus), and anxiety/depression (subcallosal gyrus) (supplementary Appendix 2, http://jurology.com/). HCs showed less overall significant activity except for areas of the cerebellum, and the caudate and temporal gyrus (fig. 2). In addition, comparison of the average change in activations between HCs and patients revealed predominantly lower activation in patients (fig. 2). Subgroup analyses focused on the difference between 7 patients with MS and NDO at the time of the strong desire to void showed a trend toward different BOLD signal patterns (fig. 2). Patients with demonstrable NDO had a trend toward increased fMRI activity in regions associated with executive function (bilateral middle and right inferior frontal gyrus) and the brainstem.

At Initiation of Voiding—Patients with MS showed significant activity in regions of executive function (middle and medial frontal gyrus), motor control (supplementary motor area), motor tone (left lentiform nucleus), emotional recognition (cingulate gyrus and insula) and memory (parahippocampal gyrus), and areas associated with anxiety/depression (subcallosal gyrus) with further activity in the thalamus and throughout the cerebellum ($p < 0.05$, fig. 3). HCs displayed more widespread activation in the insula, the basal ganglia, including the caudate, lentiform nucleus and thalamus as well as in the frontal regions, and in motor control (the supplementary motor area, premotor and motor). Figure 3 shows the subtraction image between patients with MS and HCs at the initiation of voiding. There were predominantly negative differences, reflecting the higher, more widespread activation in the HC group. Supplementary Appendix 2 (http://jurology.com/) lists select regions of largest activations in patients with MS at the point of initiation of voiding. Analysis between patients with and without DSD showed that those with DSD expressed a trend toward

stronger activation in areas for executive function (right middle and medial frontal gyrus), emotional processing (right cingulate gyrus), movement (right caudate) and the brainstem ($p < 0.01$).

DISCUSSION

NLUTD symptoms experienced by patients with MS can include abnormalities in the storage and/or the voiding phase.[9,11] Due to the diffuse, multifocal involvement of the CNS in patients with MS symptom severity and impact on quality of life may vary from patient to patient. Urinary frequency, urgency or urgency incontinence are the most common storage symptoms, occurring in 37% to 99% of patients with MS with a negative impact on quality of life.[12,13] A recent meta-analysis showed that NDO was the most common urodynamic finding, noted in 25% to 100% of patients.[14] Voiding symptoms (hesitancy, incomplete bladder emptying and urinary retention) are also common in MS, occurring in 34% to 79% of patients.[12]

Various theories have been proposed as to what supraspinal circuit or circuits control bladder function in healthy individuals. There are 2 best established, most frequently cited circuits. 1) The medial prefrontal cortex, parahippocampal complex, and periaqueductal gray circuit is active at rest and deactivated when attention is required. 2) The second circuit, which is activated when the bladder fills, is responsible for sensations associated with urgency and desire to void, and includes the insula and cingulate cortex.[1]

However, our understanding of higher neural control continues to be rudimentary with regard to pathological states, such as those in patients with neurogenic bladder. Our results reveal regions of the brain that are activated at the time of strong urge to void and initiation of voiding, which are consistent with the circuits established in the literature and have been observed in other patients with overactive bladder, especially the second circuit.[6] Interestingly, our preliminary results showed predominantly lower BOLD signal activation of many regions of interest at the time of strong desire to void and of essentially all regions at initiation of voiding in patients with MS compared to female HCs. The cause of this finding must be further explored in larger trials.

Tadic et al evaluated urgency and urge urinary incontinence in older women, specifically distinguishing between patients with and without detrusor overactivity during filling.[15] They noted a distinct difference between these 2 groups. In women with overactive bladder brain activity in the supplementary motor area was greater in those with more easily elicited detrusor overactivity. In our study patients who demonstrated NDO tended to have more activation in the areas associated with executive function (bilateral middle and right inferior frontal gyrus) and the brainstem than the group without NDO. These regions of the frontal cortex have been associated with go/no-go tasks such as halting a task immediately, which ultimately measures a level of impulse control by inhibition of a prepotent response, in this case the risk of urinary incontinence that could follow NDO. Additionally, the right inferior frontal gyrus, which is implicated in risk aversion, is more activated in patients with NDO, which could be explained as an inhibition signal to accept a risky option of urinary incontinence.[16]

With regard to patients with DSD this small subgroup expressed a trend toward greater activation in areas of executive function, emotional processing, movement (right caudate) and the brainstem (each $p < 0.01$). Interestingly, the caudate nucleus, one of the structures in the basal ganglia that has been long associated with motor processes because of its role in Parkinson's disease, is also significantly activated in this group at the time of DSD. This reaction could possibly be explained by the learned behavior that these patients may require to initiate more abdominal straining and Valsalva maneuvers to begin to void due to higher bladder outlet resistance.

Study Limitations

Because MS and its urological manifestations are so heterogeneous, the population that we evaluated is only a subset of a larger and more complex group. In addition, selecting only female patients who were ambulatory (EDSS 6.5 or less) and mostly able to spontaneously void caused selection bias in our study with the intended benefit of having a more uniform study population.

Although patients with MS are generally accustomed to undergoing multiple UDS and MRI studies, the environment where combined testing was performed could have caused some anxiety or a nonphysiological state, which possibly could have affected cystometrogram or brain activation patterns. In addition, voiding while supine may pose a challenge to many individuals who can void spontaneously while seated, which may have affected brain activation patterns.

Despite various efforts trying to correlate the lesion burden in patients with MS to functional manifestations of the disease, the data are inconclusive. The literature suggests that the total white matter load or the number of focal lesions on MRI in patients with MS are poorly related to clinical disability.[16–18] We acknowledge that there is significant variability among patients with MS in regard to the underlying disease and the lesion burden, location and cortical reorganization. At this point we did not exclude or stratify patients in our study based on lesion specifics.

Due to significant motion in patients with MS we had to exclude 7 from our analysis. This is indicative of the challenges that exist when studying patients with muscle spasms and/or mobility limitations, and who use the abdominal muscles to void.

Despite the challenges, our attempt to study the entire micturition cycle, including the voiding phase, in patients with MS is a strength in our protocol compared to other neuroimaging studies in which voiding is not studied and the bladder is drained passively. This feasibility study presents invaluable information about regions of the brain involved in the entire micturition cycle of patients with MS and NLUTD. Further studies are undoubtedly needed in a larger population of patients with MS to further characterize CNS control centers in this complex disease.

CONCLUSIONS

Our group analyses demonstrated regions of brain activation at the time of strong desire to urinate and initiation of spontaneous voiding in female patients with NLUTD caused by MS. In addition, there was a trend in distinct areas of the brain that were significantly activated in patients with demonstrable NDO and DSD. Understanding the central neural processes involved in specific parts of micturition in patients with NLUTD may identify areas of interest for future intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

BOLD	blood oxygen level dependent
CNS	central nervous system
DSD	detrusor-sphincter dyssynergia
EDSS	Expanded Disability Status Scale
fMRI	functional MRI
HC	healthy control
LUTS	lower urinary tract symptoms
MRI	magnetic resonance imaging
MS	multiple sclerosis
NDO	neurogenic detrusor overactivity
NLUTD	neurogenic lower urinary tract dysfunction
UDS	urodynamic study

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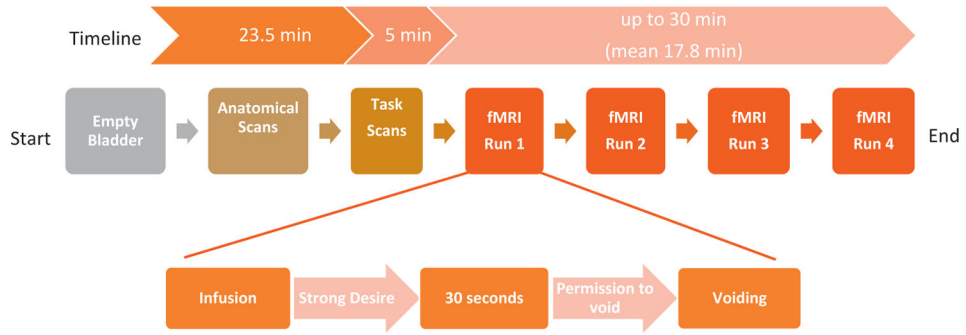

Figure 1.
Combined fMRI and UDS testing protocol

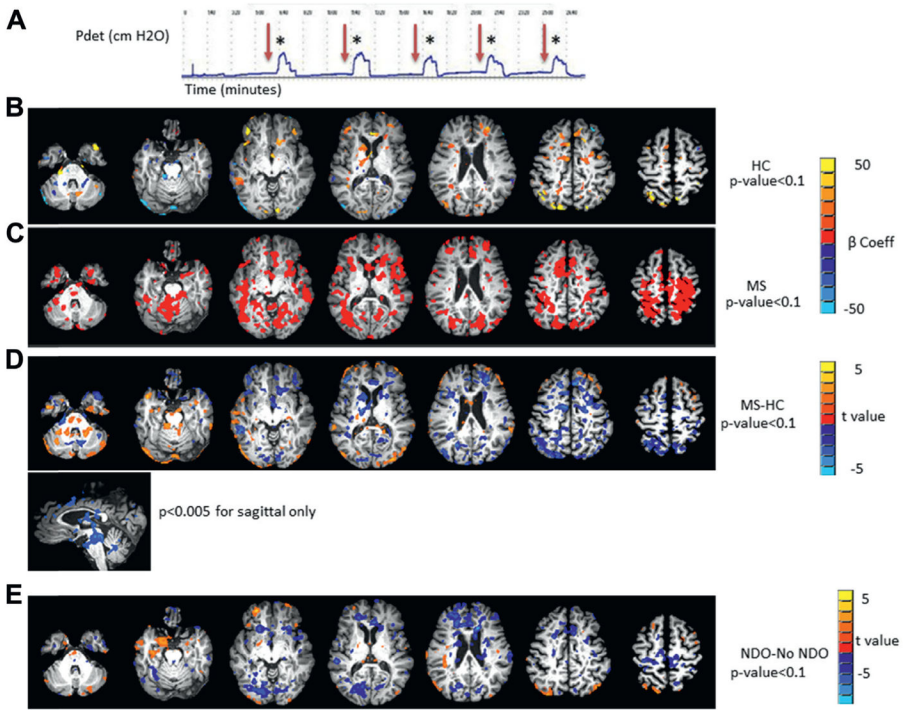

Figure 2.

BOLD activation signals at strong desire to void. *A*, UDS tracing of 5 cycles. *Pdet*, detrusor pressure. Arrows indicate voiding initiation. *B*, group analysis of HC. *C*, group analysis of patients with MS. *D,* subtraction between patients with MS and HCs demonstrates predominantly lower activation in patients at strong desire to void. *E,* trend in patients with MS with vs without demonstrable NDO. Warmer colors represent increased activation in patients with MS. Cooler colors represent decreased activation in HCs.

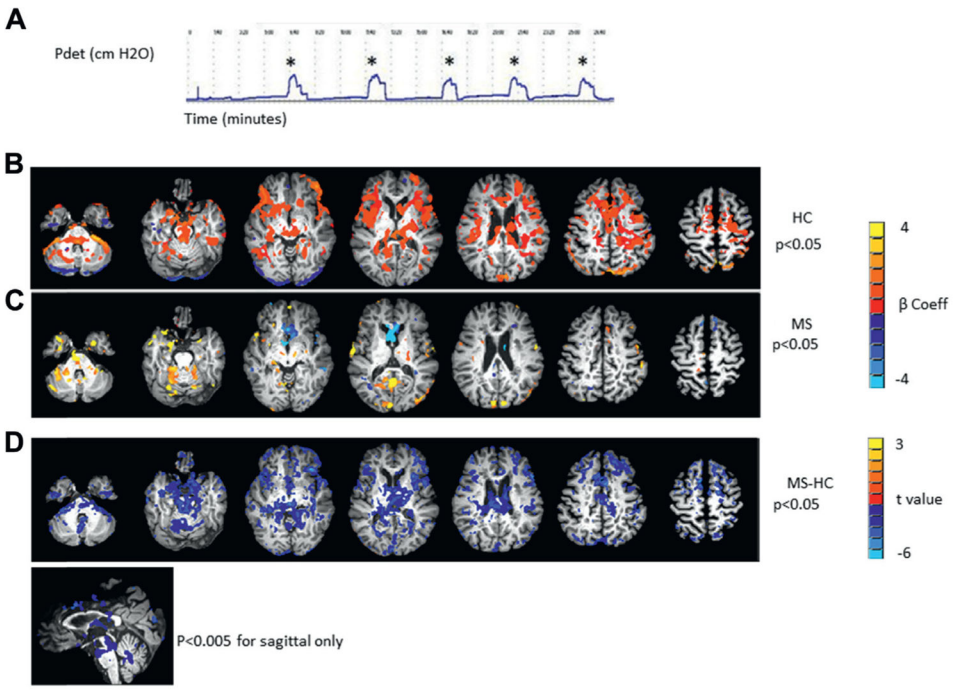

Figure 3.

BOLD activation signals at initiation of voiding. *A*, UDS tracing of 5 cycles. *Pdet*, detrusor pressure. Asterisks indicate voiding initiation. *B,* HC activation pattern. *C*, patients with MS showed greater activity and higher BOLD signal in regions with warmer colors. *D,* subtraction image between patients with MS and female HCs also reveals less activation in patients than in HCs.

Table 1

Baseline demographics of 17 patients with multiple sclerosis on overactive bladder medication at baseline

Mean age (range)	44.4	(33–57)
Mean kg/m^2 body mass index (range)	28.5	(21.30–40.4)
Mean yrs MS history (range)	11.1	(2–38)
No. spontaneous voiding (%)	16	(94.1)
No. self-catheterization (%)	5	(29.4) *
Mean UDI-6 (range)	11.1	(2–21)
Mean IIQ-7 (range)	8.5	(0–21)
No. previous genitourinary surgery (%):	2	(0.12)
Hysterectomy	1	(0.06)
Cesarean section	1	(0.06)
Urodynamics:		
Mean ml max cystometric capacity (range)	405.4	(194–680)
No. decreased compliance (%)	1	(0.06)
No. demonstrable neurogenic detrusor overactivity (%)	12	(70.6)
No. detrusor-sphincter dyssynergia (%)	3	(17.6)
Mean ml post-void residual vol (range)	132.6	(0–370)
No. fMRI (%):		
Demonstrable neurogenic detrusor overactivity	7	(31.8) †
Detrusor-sphincter dyssynergia	3	(13.6)
No. voiding during study (%)	7	(41.1)
No. baseline MRI (%):		
Cortical atrophy	3	(17.65)
Enhancing lesions	2	(11.8)
Cerebrum lesion	17	(100)
Cerebellum lesion	5	(29.4)
Brainstem lesion	7	(41.2)
Spinal cord lesion	10	(58.8)

* One patient depended completely on self-catheterization and 5 voided spontaneously with self-catheterization as needed.

† Seven of 12 patients with baseline neurogenic detrusor overactivity in clinic showed neurogenic detrusor overactivity during combined fMRI/urodynamics.