

Research paper

Higher neural contribution underlying persistent lower urinary tract symptoms in men with Benign Prostatic Hyperplasia undergoing bladder outlet procedures[☆]

Rose Khavari^{a,*}, Natalia Hernandez^a, Christof Karmonik^b, Zhaoyue Shi^b, Brian Miles^a, Ricardo R. Gonzalez^a

^a Department of Urology, Houston Methodist Research Institute, Houston, Texas, USA

^b Department of MRI Core, Houston Methodist Research Institute, Houston, Texas, USA



ARTICLE INFO

Keywords:

Functional MRI

Benign prostatic hyperplasia

LUTS

BOO

ABSTRACT

Introduction and Background: Benign Prostatic Hyperplasia (BPH) affects the micturition cycle. Lower urinary tract symptoms (LUTS) refers to storage symptoms such as urinary frequency, urgency, urge urinary incontinence and nocturia. Surgical options for bladder outlet obstruction (BOO) are currently offered for symptomatic improvement. However, 30% of patients report persistent LUTS after BOO procedures. Neuroplasticity induced by BPH and BOO can be contributory in these men, having different brain activation patterns during the micturition cycle. Our multimodal functional Magnetic Resonance Imaging (fMRI) study will identify for the first time, structural and functional brain contributions to LUTS in men with BPH and BOO at baseline and following BOO procedures. We hypothesize that men with symptomatic BPH with persistent LUTS following BOO procedures have a distinct brain activation pattern in regions of interest (ROIs) of the micturition cycle.

Methods: Male patients older than 45 years of age undergoing BOO procedures will be enrolled and categorized in two groups. Group 1: patients with BPH with significant improvement in storage symptoms after BOO procedures. Group 2: patients with BPH with persistent storage symptoms after BOO procedures. Our control group are male patients without LUTS undergoing radical prostatectomy. Patients will complete subjective questionnaires and post void residual at clinic visits. BOLD signals at full urge will be measured at baseline and following BOO procedures. All patients will undergo fMRI studies at baseline and at 6 months. Clinical data will be correlated to BOLD signal changes as well as to structural changes in white matter tracts.

Ethics and dissemination: After IRB approval, patients will be recruited and properly consented before enrolling to this study. Results of neural contribution to lower urinary tract symptoms will be presented at national and international meetings and will be published in scholarly journals.

1. Introduction

Benign prostatic hyperplasia (BPH) can affect the entire micturition cycle, including the storage (filling) phase and voiding phase. Storage phase symptoms, commonly referred to as Lower Urinary Tract In men with LUTS and BPH, the most bothersome symptoms are increased daytime frequency (21.3%) and nocturia (19.4%) [1,2]. Symptoms (LUTS), include urinary frequency, urgency, urge urinary incontinence and nocturia. Furthermore, this group of patients are also frequently bothered by voiding and bladder outlet obstruction (BOO) symptoms

such as decreased urinary flow and incomplete bladder emptying. In patients with symptomatic BPH, commonly the BOO is addressed first requiring bladder outlet procedures such as transurethral resection or ablation of the prostate. However, up to 33% of patients have persistent symptoms after surgical removal of the bladder outlet obstruction procedures [3].

It appears that the bladder as a whole, including smooth muscle, connective tissue and neural structure undergo remodeling with bladder outlet obstruction associated with BPH [3,4]. Animal models have shown that when outflow obstruction is reversed, a subset of animals

[☆] Funding support: U54DK112079 - O'Brien Pilot Funding for research in BPH.

* Corresponding author.

E-mail address: rkhavari@houstonmethodist.org (R. Khavari).

continue to have overactive bladder activity and behavior [5]. Rats with urethral ligation show increased neural activity from the bladder and increased levels of neurotrophic factors. About 20% of these rats showed persistent hyperactive voiding following reversal of urethral ligation. The investigators proposed that a functional BOO caused changes in the central nervous system (CNS) regions responsible for regulating micturition, such as the dorsal root ganglia and sensory receptive fields of the spinal cord [4,5].

Advances in neuroimaging, such as functional Magnetic Resonance Imaging (fMRI) provides a useful tool to elucidate the central nervous system contribution to various organs autoregulation. The use of this technology has been correlated with the evolution of neurourology research in the last decades, elucidating the mechanism of brain control over bladder function [6,7]. Using simultaneous urodynamic study (UDS) and fMRI, one of the first reports of brain activation centers associated with micturition in healthy females demonstrated activation of a brain network including areas of motor control (cerebellum thalamus, caudate, lentiform nucleus, red nucleus, supplementary motor area and post central gyrus), executive function (left superior frontal gyrus) and emotion processing (anterior and posterior cingulate gyrus and insula) [7]. This study, developed at our institution was the beginning of the establishment of a concurrent fMRI and UDS platform which subsequently was evaluated in Multiple Sclerosis patients [7–9]. We have evaluated the entire bladder cycle in real time in over fifty individuals, specifically when patients void or attempt to void in the fMRI scanner while UDS is being performed.

We propose a unique multimodal study that will identify, for the first time, structural and functional brain contributions of LUTS in men with BPH and BOO at baseline and following BOO procedures.

2. Materials and methods

2.1. Specific aims

We hypothesize that men with symptomatic BPH who have persistent LUTS following BOO procedures have a distinct brain activation pattern in regions of interest (ROIs) that regulate the micturition cycle.

2.1.1. Specific aim 1

To investigate whether men with BPH and LUTS have a distinct pattern in a priori grey matter ROIs that are different than men without BPH and BOO at baseline via our established fMRI/UDS platform by: analyzing fMRI Blood Oxygen Level Dependent (BOLD) signals in the ROIs at the time of full urge in our patient cohort (Groups 1 and 2) at

baseline, and then quantitatively comparing these findings to our controls.

2.1.2. Specific aim 2

To determine whether men with BPH and LUTS with improvement of LUTS following BOO procedures have different neuroimaging characteristics in the ROIs at baseline and following intervention, by: analyzing BOLD signals in the ROIs in our patient cohort (Groups 1 and 2) following BOO procedures and subsequently comparing these findings between groups 1 and 2 versus controls.

2.1.3. Specific aim 3

To evaluate whether white matter tracts in two specific tracts that are associated with lower urinary tract function are different in men with BPH and LUTS via:

Measuring and comparing fractional anisotropy and mean diffusivity using diffusion tensor imaging in Ref. [1]: Anterior thalamic radiation (ATR) and [2] Superior longitudinal fasciculus (SLF) in groups 1, 2 and controls.

2.2. Study design

This is a hypothesis driven prospective pilot clinical trial. The primary endpoint is BOLD signal in regions of interest at the point of “full urge” at baseline and following BOO procedures with groups 1, 2 and controls. Secondary endpoints include fractional anisotropy (FA) and mean diffusivity (MD) of ATR and SLF white matter tracts in groups 1, 2 and controls. Finally, clinical scores such as uroflow parameters, urinary symptom scores, and questionnaires will be assessed and correlated with neuroimaging data.

2.3. Study population

Men aged ≥ 45 years who have failed conservative therapy for BPH and are planning to undergo BOO procedures will be recruited (See Table 1). Patients with an International Prostate Symptom Score (IPSS) ≥ 12 and a maximum urinary flow rate (Qmax) ≤ 15 mL/s are the main selection criteria. For the control group, men aged ≥ 45 years with prostate cancer who will undergo robotic assisted laparoscopic prostatectomy, with a normal IPSS (≤ 7 and ≤ 1 for nocturia), prostate volume < 50 mL on imaging (transrectal ultrasound or MRI) and a postvoid residual lower than 100 mL will be recruited. Patients with history of neurogenic bladder, urethral stricture, previous bladder outlet obstruction procedures will be excluded. Additionally, patients with

Table 1
Inclusion and exclusion criteria.

Inclusion	Exclusion
Men > 45 years of age	Men with neurogenic bladder
Subjects who are to continue on oral medications (e.g. anticholinergics, beta-3 agonists, alpha-blockers) for detrusor overactivity during the study must be stable and on it for 30 days prior to screening without intolerable side effects	History of urinary retention with indwelling foley catheter or intermittent catheterization
Group 1:	Prior bladder outlet obstruction (BOO) procedures
Men with improved LUTS after 6 months of a BOO procedure	Urethral stricture
IPSS < 12	Additional exclusion criteria for Group 1 and Group 2
Improvement in IPSS in at least 3 points of storage symptoms	History of bladder cancer within 5 years
Nocturia ≤ 2 on a two day bladder diary	History of treatment for prostate cancer other than active surveillance
Group 2:	Intradetrusor injection of BTX-A within 9 months prior to screening for any urological condition
Men with persistent LUTS at six months post BOO procedure	
IPSS > 8	
Nocturia > 2	
Delta, change in IPSS score less than negative 3 points	
Controls:	
Men undergoing radical prostatectomy without LUTS	
IPSS < 12	
Nocturia ≤ 2 on two day bladder diary	

history of chronic urinary retention who are catheter dependent will be excluded in order to limit confounding factor related to bladder underactivity. Our institution (Houston Methodist Hospital) has four full-time fellowship trained Urologists in the field of functional Urology and voiding dysfunction who perform over 300 BOO procedures every year. Patients will be recruited from our clinics.

Patients will be divided into three different groups:

Group 1 (n = 18): Patients with BPH who underwent BOO procedures and demonstrated improved storage symptoms at six months follow up based on IPSS improvement, QoL improvement and nocturia ≤ 2 .

Group 2 (n = 9): Patients with BPH who present persistent storage symptoms after BOO procedures at 6 month follow up.

Controls (n = 9): Men without LUTS who are planning to undergo radical prostatectomy.

2.4. Power analysis

Desmond et al. presented a statistical approach for group analysis in fMRI while accounting for intra and inter subject variability, suggesting that about 12 subjects were required to achieve 80% power at a single voxel level for typical activations [10]. Previous neuroimaging studies in urology have used a study population between 8 and 12 subjects. Therefore, to estimate the power for this study, we are taking into account the 10% exclusions for movement and artifact and 20% drop out rates where patients may not return for their post BOO procedure fMRI scans and would estimate a total of 40 subjects, 13 controls, 18 in group 1 and 9 subjects on group 2.

2.5. Study procedures

2.5.1. Subject evaluations

Each patient will provide a detailed history and undergo a complete physical examination. Each patient will have the following assessments: IPSS, Incontinence Severity Index (ISI), Patient Global Impression of Severity (PGI-S) and Improvement (PGI-I), International Index of Erectile Function (IIEF-5), MRI Safety Screening Questionnaire, and screening for Obstructive Sleep Apnea. A two day bladder diary will also be obtained from each patient. A clinical UDS will be performed within a year prior to the neuroimaging scan (group 1 and 2) (See Table 2).

2.5.2. Follow up assessments

Uroflow and post void residual (PVR) assessment, 2 day bladder diary and all questionnaires will be repeated in all patients at one, three and six months.

2.5.3. BOO procedures

Patients undergoing any BOO procedure, such as transurethral resection/ablation of prostate of any modality and simple prostatectomy will be recruited.

2.5.4. Simultaneous functional brain MRI and urodynamic studies

Double lumen 7 Fr MRI –Compatible catheters will be placed in the

bladder and rectum. A Siemens Vida 3.0T full body MRI scanner with standard 20 channel head coil MRI will be used. Instructions to communicate using right hand signals representing “full urge” and “voiding or attempt of voiding” will be given. (See Fig. 1) Signs will be shown to the patient when filling of the bladder is begun and when filling is stopped. Furthermore, in order to keep our signal-to-noise ratio (SNR) high, all stimulators including any extra visual stimuli and the UDS machine will be removed from the MRI scanner room. The filling and voiding cycle will be repeated up to four times in each patient. Bladder will be aspirated after each voiding. This experimental protocol will be performed before and six months following BOO procedures.

2.6. Data collection and statistical analysis

Three dimensional structural images will be obtained from a T1-weighted sequence: (sagittal direction, 0.7 mm in-plane resolution). Functional images will be collected afterwards by means of simultaneous urodynamic analysis (axial echo-planar, TR = 1500 ms, 4.0 mm slice thickness, 3.38 mm in-plane resolution). Structural and functional images will be registered and motion-corrected. Patients with rapid motion (4.5 mm) will be excluded from analysis. Voxel activation will be identified at the time of “full urge” will be identified at this time point under the generalized linear model (GLM). Group level analysis will be performed by transforming data into Talairach space, and significantly activated voxels ($p < 0.05$) will be identified using a Student's T-test. Comparisons will be drawn between groups 1,2 and 3 (control group) comparing baseline scans to the post BOO procedures. AFNI software will be used for analysis. We will use SPSS (v10.0) to perform statistical analysis of the clinical data. Demographics, UDS, flow parameters and symptom scores will be correlated to BOLD signal changes as well as to structural markers (e.g., integrity of WMT) using regression analyses.

Diffusion Tensor Imaging (DTI) images will be acquired (32 directions, one B0 image) using the standard MRI pulse sequence available on the Siemens 3.0 T Vida scanner. The original DTI images as well as the fractional anisotropy (FA) and mean diffusivity (MD) calculated on the scanner will be transferred to an offline workstation for further processing. The software packages TackVis (version 0.6.0.1) and the Diffusion Toolkit (version 0.6.3, trackvis.org) will be used to calculate and extract selected white matter tracts of interest. This software also enables calculating FA and MD values for the segmented white matter tracts.

3. Discussion

Brain contribution to lower urinary tract symptoms in BPH and BOO remains unknown. To our knowledge, there are no studies that have evaluated brain involvement in LUTS in men with BPH. Abnormal pathways and dysfunctional neural components will be identified in this population and will elucidate the effects of neuroplasticity in voiding dysfunction. We acknowledge that one potential limitation is the inability to obtain flow data such as Abrams Griffith nomogram or bladder outlet obstruction index since patients are laying down in the MRI scanner during simultaneous UDS. However, brain activity during CMG and attempted voiding will provide adequate insight regarding

Table 2
Questionnaires.

Questionnaire	Description
Bladder diary	Instrument that allows the patient to record fluid intake, pattern of urinating, presence of incontinence or urgency.
International Index of Erectile Function (IIEF)	5 item instrument assessing male sexual function including erectile function, orgasmic function, sexual desire and intercourse satisfaction.
International Prostate Symptom Score (IPSS)	7 item question assessing urinary symptoms and 1 additional question assessing quality of life.
Incontinence Severity Index (ISI)	2 item instrument assessing the frequency and quantity of urinary leakage.
Patient Global Impression of Improvement (PGI-I) and Severity (PGI-S)	2 item instrument assessing the response of a condition to a therapy.

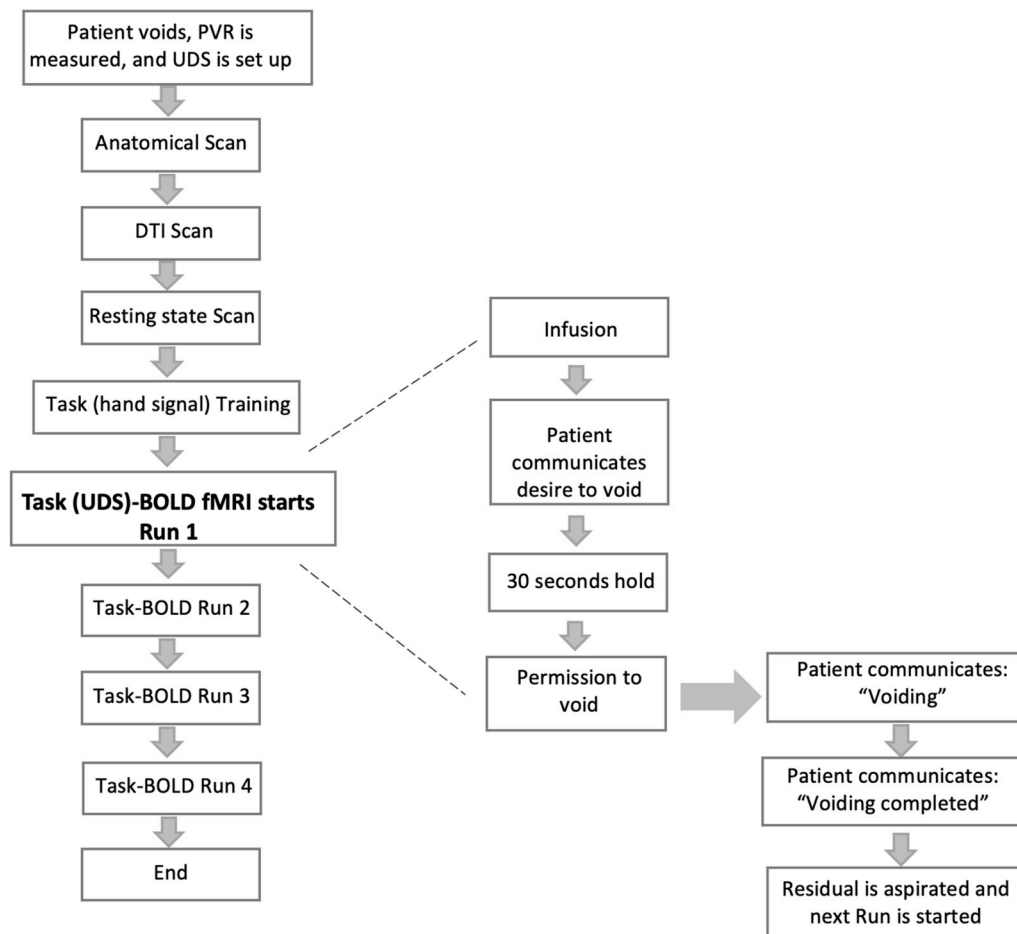


Fig. 1. Simultaneous functional brain MRI and Urodynamic studies protocol.

neuroplasticity in the voiding cycle of patients with BPH.

These findings could be used to examine the current working model of LUTS in men and illuminate on the neuroplasticity process that may follow BOO in these set of patients. Providing a new understanding of LUTS might shift clinical attention from the end organ centered (bladder and prostate centric) approach to a more cerebral centric focus, thus creating new avenues for intervention in LUTS in the setting of BOO secondary to BPH [11].

Our findings will provide the scientific rationale for subsequent multicenter, efficacy based clinical trials that could potentially transform LUTS management in men with BPH and BOO. This is a unique model that will lay the foundation to study brain control in LUTS to further phenotype and potentially stratify management for patients in this group. Additionally, these findings will be the starting point to the study of supraspinal control in underactive bladder (UAB) or detrusor underactivity in men with or without BPH, therefore creating new opportunities for translational clinical trials in neurourology.

References

- [1] K. Everaert, P. Anderson, R. Wood, F.L. Andersson, T. Holm-Larsen, Nocturia is more bothersome than daytime LUTS: results from an Observational, Real-life Practice Database including 8659 European and American LUTS patients, *Int. J. Clin. Pract.* 72 (6) (2018), e13091.
- [2] Y.S. Lee, H.N. Lee, J.Y. Han, M.S. Choo, K.S. Lee, Most bothersome symptom and symptom specific goal achievement in patients with benign prostatic obstruction: a prospective open label study, *J. Urol.* 185 (3) (2011) 1003–1009.
- [3] K.E. Andersson, Storage and voiding symptoms: pathophysiologic aspects, *Urology* 62 (5 Suppl 2) (2003) 3–10.
- [4] W.D. Steers, J. Ciambotti, B. Etzel, S. Erdman, W.C. de Groat, Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction, *J. Comp. Neurol.* 310 (3) (1991) 401–410.
- [5] T.C. Chai, H. Gemalmaz, K.E. Andersson, J.B. Tuttle, W.D. Steers, Persistently increased voiding frequency despite relief of bladder outlet obstruction, *J. Urol.* 161 (5) (1999) 1689–1693.
- [6] J. Krhut, J. Tintera, P. Holy, R. Zachoval, P. Zvara, A preliminary report on the use of functional magnetic resonance imaging with simultaneous urodynamics to record brain activity during micturition, *J. Urol.* 188 (2) (2012) 474–479.
- [7] M. Shy, S. Fung, T.B. Boone, C. Karmonik, S.G. Fletcher, R. Khavari, Functional magnetic resonance imaging during urodynamic testing identifies brain structures initiating micturition, *J. Urol.* 192 (4) (2014) 1149–1154.
- [8] R.A. Elizondo, C. Karmonik, T.B. Boone, R. Khavari, Protocol for a prospective observational study of cortical lower urinary tract control changes following intradetrusor injection of botulinum toxin-A in patients with multiple sclerosis, *BMJ Open* 7 (2) (2017), e013225.
- [9] R. Khavari, C. Karmonik, M. Shy, S. Fletcher, T. Boone, Functional magnetic resonance imaging with concurrent urodynamic testing identifies brain structures involved in micturition cycle in patients with multiple sclerosis, *J. Urol.* 197 (2) (2017) 438–444.
- [10] J.E. Desmond, G.H. Glover, Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses, *J. Neurosci. Methods* 118 (2) (2002) 115–128.
- [11] A.L. Green, E. Stone, H. Sitsapesan, B.W. Turney, J.H. Coote, T.Z. Aziz, et al., Switching off micturition using deep brain stimulation at midbrain sites, *Ann. Neurol.* 72 (1) (2012) 144–147.