



Original Article

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White Matter Integrity in Men With Benign Prostatic Hyperplasia and Bladder Outlet Obstruction and Its Contribution to Lower Urinary Tract Symptoms

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Purpose: Lower urinary tract symptoms (LUTS) associated with bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) can negatively impact quality of life. We evaluated the structural connectivity of the brain in men with BPH with chronic BOO using diffusion tensor imaging (DTI).


Methods: Ambulatory male patients aged ≥ 45 years with BPH and BOO were recruited. LUTS was defined as an International Prostate Symptom Score (IPSS) ≥ 12 and a maximum urinary flow rate ≤ 15 mL/sec. Upon recruitment, uroflowmetry and validated questionnaires regarding bladder status were collected. DTI images from each subject were aligned with the ICBM-DTI-81 atlas, defining 50 white matter tracts (WMTs). The mean values of DTI parameters — fractional anisotropy and mean diffusivity — for each WMT were extracted. These measures were then utilized to compute Pearson correlation coefficients with clinical parameters. Objective clinical parameters included uroflowmetry parameters, postvoid residual (PVR) volume, and bladder capacity. Subjective clinical parameters were assessed using validated questionnaires: the IPSS, Incontinence Symptom Index, and Sexual Health Inventory for Men.

Results: The correlation analysis revealed 15 WMTs that showed statistically significant associations ($P < 0.05$) with objective and subjective clinical parameters. Eight tracts were associated with uroflowmetry parameters: maximum flow rate (Qmax), mean flow rate (Qmean), and PVR. Among these tracts, the middle cerebellar peduncles and left medial lemniscus were associated with Qmax; the genu of the corpus callosum, left superior corona radiata, corticospinal tract, right medial lemniscus, posterior corona radiata with Qmean; and the left posterior corona radiata with PVR. Seven tracts also demonstrated significant associations with the IPSS.


Conclusions: Our results suggest correlations between the preserved white matter integrity of specific WMTs and the severity of LUTS based on objective and subjective clinical parameters, leading us to believe that a distinct pathology of the central nervous system might exist.

Keywords: Benign prostatic hyperplasia; Bladder outlet obstruction; Lower urinary tract symptoms; Diffusion tensor imaging; Neurourology

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INTRODUCTION

Lower urinary tract symptoms (LUTS) may significantly deteriorate quality of life. They can be categorized into storage, voiding, and post-micturition symptoms [1]. Bladder outlet obstruction (BOO) from benign prostatic hyperplasia (BPH) commonly leads to LUTS with both voiding and storage symptoms, such as daytime frequency (21.3%), nocturia (19.4%), urgency (5.6%), and incontinence (0.9%) [2]. Currently, most BOO interventions focus on treating the genitourinary system by performing various surgical procedures to relieve the obstruction. Despite BOO procedures, up to 33% of patients experience persistent LUTS even after surgical correction of the obstruction [3]. Similar findings were observed in animal models, with 20% of rats exhibiting persistent bladder hypercontractility after surgical relief [4]. These observations may suggest that there is a distinct pathophysiology of chronic BPH leading to functional BOO beyond its physically obstructive nature, such as changes in the central nervous system (CNS).

Advances in functional neuroimaging have allowed us to better understand the supraspinal (brain) contribution to the micturition cycle [5,6]. Despite its crucial role in micturition, no data have been reported in the literature on the integrity of white matter—structural connectivity—and its contribution to LUTS in BPH patients with BOO. A magnetic resonance imaging (MRI) technique called diffusion tensor imaging (DTI) is commonly used to study the axonal (white matter) organization of the brain. For the first time, we evaluated the effects of chronic BOO on the structural white matter integrity of the brain using DTI to study the contributions of white matter to LUTS in men with BPH. We hypothesized that there is a distinct pathophysiology of chronic BOO secondary to BPH affecting the white matter integrity associated with LUTS.

MATERIALS AND METHODS

1. Patient Population

Men aged ≥ 45 years in whom conservative management of BPH failed and who were scheduled for BOO procedures were recruited. An International Prostate Symptom Score (IPSS) ≥ 12 and a maximum urinary flow rate (Qmax) ≤ 15 mL/sec were the main selection criteria. The exclusion criteria were neurogenic bladder, a history of urinary retention with an indwelling Foley catheter or intermittent catheterization, or a prior BOO procedure [7]. Once included, detailed history and

physical examination, baseline characteristics, noninstrumented uroflow, postvoid residual (PVR), and validated questionnaires were obtained. The questionnaires included the IPSS, Incontinence Symptom Index (ISI), and Sexual Health Inventory for Men (SHIM). In addition to the total IPSS, storage symptom-specific IPSS questions were evaluated specifically for frequency (number 2), urgency (4), and frequency (7).

2. MRI Protocol

For each subject, DTI images were acquired as part of a concurrent functional MRI (fMRI)-urodynamic study (UDS) (MAGNETOM Vida, 3.0 Tesla, Siemens, Erlangen, Germany) using a standard 20-channel head coil (spatial resolution, 2 mm \times 2 mm; slice thickness, 2.5 mm; 64 directions; bipolar diffusion scheme; 2 b-values [0 s/mm², 5 averages, 1,000 s/mm², 1 average]).

3. DTI Analysis

The DTI images were then aligned on the ICBM-DTI-81 white matter atlas using affine registration tools provided by an open-source software called Analysis of Functional NeuroImages (AFNI, <https://afni.nimh.nih.gov>). The ICBM-DTI-81 is a population-averaged white matter atlas defining 50 distinct white matter tracts (WMTs) obtained from 81 normal subjects and is a standard tool used for WMT parcellation during analysis [8]. The mean values of the DTI parameters for these 50 tracts from each subject were then extracted using tools provided by AFNI [9-11]. DTI allows the calculation of the diffusion pattern of the water molecules using the diffusion tensor, a $[3 \times 3]$ matrix of each voxel within a WMT. Eigenvalues of the diffusion tensor represent the principal diffusivities, and eigenvectors correspond to its directions [12,13]. Fractional anisotropy (FA) is a measure of the fraction of magnitude of the diffusion tensor; FA values range from 0 (isotropic diffusion) and 1 (anisotropic diffusion along a single axis). Mean diffusivity (MD) is the average of the eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) of the diffusion tensor, and pathologic phenomena such as edema, inflammation, and chronic ischemia of lesions in the CNS have been reported to be associated with increased MD [12,14].

4. Correlation Analysis with Clinical Findings

Pearson correlation coefficients were computed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) to evaluate the association of each tract with the collected clinical parameters (both objective and subjective). Only the WMTs

Table 1. Baseline BPH patient demographics and uroflowmetry data (n = 7)

Variable	Value
Age (yr)	
Mean ± SD	62.6 ± 7.7
Range	48–71
Prostate volume (mL)	
Mean ± SD	46.6 ± 17.6
Range	29–69
Uroflowmetry	
Qmax (mL/sec)	8.9 ± 3.1
Qmean (mL/sec)	3.8 ± 1.3
Voiding time (sec)	36.8 ± 22.3
Time to peak flow (sec)	9.4 ± 9.3
Voided volume (mL)	175.8 ± 147.6
PVR (mL)	87.6 ± 67.6

Values are presented as mean ± standard deviation (SD) unless otherwise indicated.

BPH, benign prostatic hyperplasia; Qmax, maximum flow rate; Qmean, mean flow rate; PVR, postvoid residual.

with statistically significant ($P < 0.05$) and strong correlations ($|r| \geq 0.7$) between the DTI metrics and clinical parameters are reported.

RESULTS

Eleven men were recruited from June 2019 to March 2021 based on the inclusion criteria from the 149 screened patients. This DTI analysis was based on seven patients who completed the concurrent fMRI/UDS protocol. It is important to note that UDS is not necessary for DTI analysis and therefore was not included in our analysis. The baseline demographics and clinical uroflow parameters from this study are found in Table 1. DTI analysis revealed eight white matter tracts that were significantly correlated with uroflow parameters (Table 2). Two of these eight WMTs showed significant associations with Qmax (Fig. 1A). The FA of the middle cerebellar peduncles (MCP) was positively ($r = 0.930$) correlated, and the MD of the left medial lemniscus (ML) was negatively ($r = -0.909$) correlated with the Qmax. Five tracts exhibited associations with Qmean (Fig. 1B). The FA of the left superior corona radiata (SCR), the MD of the genu of the corpus callosum (CC), the right ML and posterior corona radiata (PCR) were positively correlated, and the FA of the left corticospinal tract (CST) was negatively correlated with

Table 2. Correlation between DTI parameters of white matter tracts and clinical parameters

Variable	r	P-value
Qmax		
Middle cerebellar peduncle, FA	0.930	0.022
Left medial lemniscus, MD	-0.909	0.033
Qmean		
Left superior corona radiata, FA	0.943	0.016
Left corticospinal tract, FA	-0.900	0.038
Genu of corpus callosum, MD	0.909	0.032
Right medial lemniscus, MD	0.954	0.012
Right posterior corona radiata, MD	0.918	0.028
PVR		
Left posterior corona radiata, FA	0.921	0.026
IPSS, total		
Right external capsule, FA	-0.817	0.025
IPSS, nocturia		
Left inferior fronto-occipital fasciculus, FA	-0.931	0.002
Left tapetum, FA	-0.870	0.011
Left tapetum, MD	0.909	0.005
Right tapetum, FA	-0.767	0.044
ISI, total		
Right external capsule, FA	-0.923	0.003
Fornix/stria terminalis, FA	0.767	0.044
SHIM, total		
Right inferior fronto-occipital fasciculus, FA	0.879	<0.05

DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; Qmax, maximum flow rate; Qmean, mean flow rate; PVR, postvoid residual; IPSS, International Prostate Symptom Score; ISI, Incontinence Symptom Index; SHIM, Sexual Health Inventory for Men.

the Qmean. Lastly, the left PCR, which was associated with PVR, showed a positive correlation with respect to its FA (Fig. 1C). A larger PVR indicates more severe LUTS, unlike Qmax and Qmean. This inverse relationship between PVR and preserved bladder function will be addressed in detail in the Discussion section. The correlation coefficient and P-value of each significant tract are shown in Table 2.

Seven WMTs were associated with scores on the IPSS, ISI, and SHIM questionnaires. Four tracts showed significant associations with the IPSS. The FA of the right external capsule (EC) was positively correlated with the total IPSS. The FA of the left inferior fronto-occipital fasciculus (IFO), the FA of the right tapetum, and the FA and MD of the left tapetum were positively

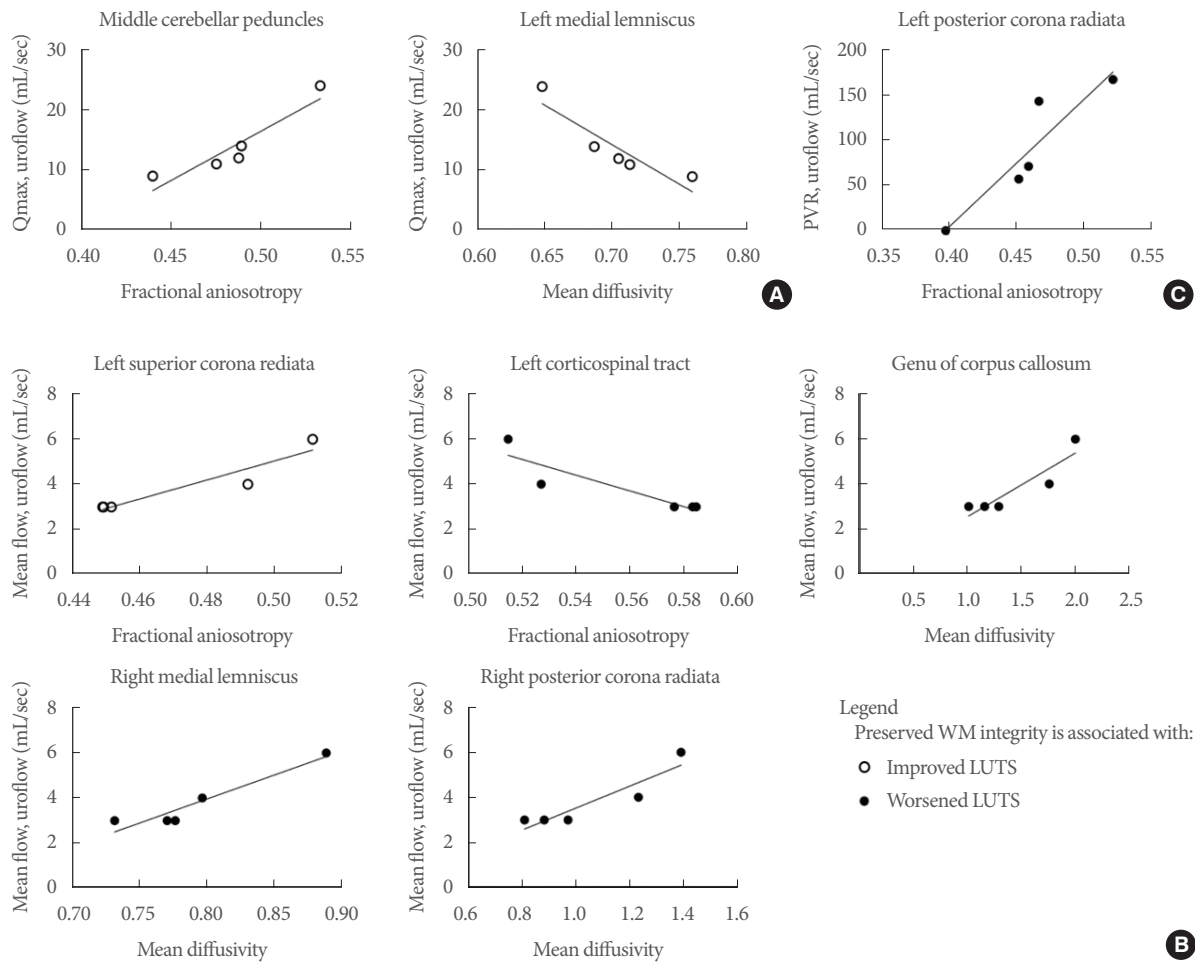


Fig. 1. White matter tracts with statistically significant correlations with uroflow parameters based on DTI analysis. Tracts associated with Qmax (A), Qmean (B), and PVR (C). Unfilled circles indicate that the preserved white matter integrity of the tract is associated with improved LUTS. Filled circles meaning an inverse relationship between preserved white matter integrity and improved LUTS. DTI, diffusion tensor imaging; Qmax, maximum flow rate; Qmean, mean flow rate; PVR, postvoid residual; LUTS, lower urinary tract symptoms.

correlated with nocturia on the IPSS questionnaire. However, the DTI parameters did not show any significant association with the frequency- or urgency-specific IPSS scores. Two tracts demonstrated associations with the total ISI score. The FA of the right EC was positively correlated, and the FA of the left fornix/stria terminalis was negatively correlated with the total ISI score. Lastly, one tract — the right IFO — was associated with the total SHIM score, with a positive correlation with its FA.

DISCUSSION

Chronic BOO leads to physical changes to the detrusor smooth muscle in humans and in rabbit models to overcome the in-

creased resistance during micturition [15-17]. However, it is not clear why a subset of men with BOO experience persistent LUTS after surgical intervention [3,4]. This suggests that there may be a distinct pathophysiology of chronic BOO affecting the CNS, leading to LUTS beyond the mechanical obstruction involved in BPH. Our study is the first attempt to explore the contribution of white matter to chronic BOO in men with BPH using DTI.

Supraspinal Contribution to the Micturition Cycle

Although the brain circuitry associated with lower urinary tract (LUT) control is complex and has yet to be deciphered, it is generally established that the pontine micturition center (PMC)

plays a major role [18,19]. It is proposed that sensations of bladder fullness from the LUT are sent to the periaqueductal gray (PAG), which has multiple connections directly or indirectly with other cortical areas of the brain. These cortical regions include the prefrontal cortex, insula, cingulate gyrus, and other higher brain centers possibly associated with emotion and urgency [20]. Integrated information at the PAG then allows one to switch on the PMC in an appropriate setting [20].

DTI Patterns in Neuropathology

In neuropathology, smaller FA and larger MD values generally indicate compromised or dispersed signal transduction [14,21]. It was suggested based on in vitro and in vivo studies that preserved axonal membrane plays the primary role in maintaining anisotropic diffusion and that myelination contributes to the degree of anisotropy [22]. In neurodegenerative and demyelinating diseases such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), respectively, smaller FA was reported from the affected lesions [23]. Lower FA values are consistently observed throughout a broad spectrum of neuropathologic conditions, and the trend is generally for MD to be larger [14]. Although BPH is neither considered a neurodegenerative nor demyelinating disease, we adopted this DTI pattern of generally established neuropathology. In this study of BPH, we considered preserved white matter integrity to be associated with larger FA and smaller MD values. That is, intact transmission of signals along its axons with less signal dispersion is associated with these DTI patterns. It is important to note that previous DTI studies on age-related decline of white matter integrity were characterized by decreased FA and increased MD [24]. This age-related change could have an impact on our results and should be addressed in future studies by the inclusion of age-matched controls.

Correlations of DTI Parameters With Objective Clinical Parameters

Among the eight WMTs associated with uroflow parameters, four tracts were associated with respect to FA as illustrated in Table 2. The FA of the MCP was positively correlated with Q_{max} . It should be noted that neither the FA acquired from each tract, nor the correlation coefficient, tell us whether the white matter integrity of the specific tract is preserved or impaired. Although we conceptually know what FA values indicate, there is no established normal range of FA in each tract. This correlation, however, still provides valuable information

that may be able to predict the contribution of white matter to LUTS. We can infer from the positive correlation that preserved integrity of the MCP may be associated with improved Q_{max} , while, conversely, impaired integrity may be associated with worsened Q_{max} . This information could be useful for tracking therapeutic responses. A study involving MS patients revealed increased FA in gadolinium-enhancing lesions over the course of natalizumab therapy [25]. In the same notion, the positive correlation observed in the FA of the left SCR with Q_{mean} suggests that preserved integrity of the left SCR may be associated with improved LUTS.

Unlike the positive correlations of FA with Q_{max} or Q_{mean} , the positive correlation between the FA of the left PCR and the PVR should be interpreted differently. Since a larger PVR indicates more severe LUTS, the positive correlation between the FA and PVR represents an inverse relationship. In other words, preserved integrity of the left PCR may indicate an association with worsening of the LUTS regarding PVR. There are several possible explanations. First, the left PCR could transmit inhibitory signals as part of its normal physiology. Secondly, this could indicate axonal regeneration taking place, allowing limited axial diffusivity (AD). Lastly, in MS patients, it has been found that in a chronic disease state, the sensitivity of increased AD changes is limited by changes such as gliosis and infiltration of inflammatory cells. Such patterns could also be observed in age-related degenerative processes [25]. To our knowledge, no such inverse relationships between the FA of the left PCR and symptom severity have been observed in other disease states. A similar pattern was seen in the right PCR, but with higher mean values of FA in men with lifelong premature ejaculation than in controls [26]. The negative correlation seen between the FA of the left CST and Q_{mean} may be explained in the same manner, where preserved integrity is associated with worsening of LUTS.

The MD values of the genu of the CC, right ML, and right PCR were positively correlated with Q_{mean} . Unlike FA, a lower MD value is typically associated with preserved white matter integrity [21]. This means that preserved integrity of the genu of the CC, right ML, and right PCR could be associated with worsening of Q_{mean} . Such relationships, again, may be due to possible inhibitory input to the micturition cycle, axonal regeneration, cellular response in a chronic CNS disease state, and the age-related degenerative process. The negative correlation reported for the MD of the left ML with Q_{max} implies a possible association between preserved integrity of the left ML and

Table 3. White matter tracts in the brainstem [8]

Name
Corticospinal tract (CST)
Medial lemniscus (ML)
Medial longitudinal fasciculus (MLF)
Inferior cerebellar peduncle (ICP)
Middle cerebellar peduncle (MCP)
Superior cerebellar peduncle (SCP)

improved Qmax. It should be noted that the suggested relationship is strictly an association and does not represent causation.

A Considerable Number of Tracts are Found in the Brainstem

In the ICBM-DTI-81 atlas used during segmentation, there is an additional group of WMTs classified as “tracts in the brainstem” (Table 3) in addition to projections, associations, and commissural fibers [8]. Among the eight tracts associated with Qmax, Qmean, or PVR, half of them were tracts found in the brainstem: the MCP, right and left ML, and CST. The MCP is known to relay information from the pons to the contralateral cerebellum as part of the cortico-ponto-cerebellar (CPC) pathways (Fig. 2) [27]. Interestingly, the prefrontal lobe — a cortical region thought to be directly involved in voiding initiation — communicates within the CPC pathway [27,28]. In addition, the proximity of these 4 tracts to the pons may further support the association of brain circuitry with the micturition cycle, especially the neural network associated with PMC at the brainstem.

Correlations of DTI Parameters With IPSS Questionnaire

Our analysis focused on the IPSS questionnaire, as it is the most relevant to the study of LUTS. Four tracts exhibited statistically significant associations. The FA of the right EC showed a negative correlation with the total IPSS score. Since the symptom severity decreases as the IPSS score becomes higher, preserved white matter integrity of the right EC suggests an association with improved overall subjective perceptions of LUTS. Nocturia-specific IPSS scores revealed negative correlations with the FA values of the left IFO and right tapetum. This could mean that nocturia is expected to improve with the preserved integrity of these WMTs. Lastly, the left tapetum is suggested to have an association with nocturia based on the negative correlation with its FA and positive correlation with MD. No significant as-

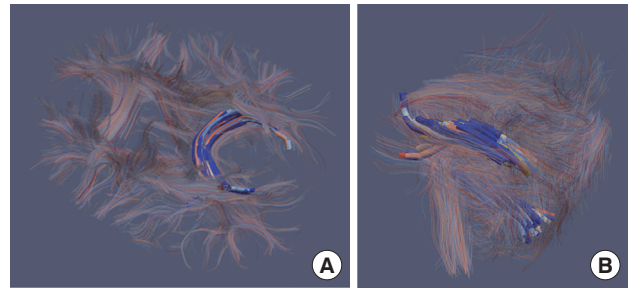


Fig. 2. Tractography of a significantly associated tract in the brainstem: Middle cerebellar peduncle (highlighted). Axial view at an oblique angle (A) and 3-dimensional view (B) including the brainstem and cerebellum only (the cerebrum is excluded for better visualization of the tract).

sociation was found in IPSS questions specific to frequency or urgency.

Limitations

Although our cohort was very homogeneous, with strict inclusion and exclusion criteria, it contained only seven subjects. Additionally, we intended to recruit age-matched men with minimal LUTS as controls; however, challenges from the ongoing coronavirus disease 2019 pandemic, as well as significant hesitation from this group and healthy controls to undergo catheterization during fMRI/UDS sessions ultimately hindered participation. If there had been controls, we could have established unique patterns of adversely affected neural networks due to chronic BOO resultant from BPH independent from age-related changes in white matter integrity. Such patterns would have also provided a stronger and more meaningful means of phenotyping LUTS due to distinct changes in neural networks from chronic obstruction. Furthermore, DTI parameters may be susceptible to variability depending on the location and chronicity of the lesion. Variability has been reported in neuropathologic phenomena such as edema, inflammation, and ischemia. One such example is the finding that acute ischemia of brain tissue was associated with decreased MD and chronic ischemia with increased MD [14]. Although axonal degeneration and demyelination in damaged tracts are the main proposed mechanisms that lead to decreased axial and increased radial diffusivity of water molecules, the cerebrospinal fluid (CSF) may influence DTI measurements. Anatomically thinner tracts, such as the body of the CC, may be more susceptible to the volume effect from CSF [29]. Local edema, inflammation, or scarring may also exhibit similar effects by

physically compressing the axonal tracts, leading to secondary changes in FA and MD [25]. Lastly, adopting the typical DTI change patterns of classic neuropathology such as ALS and MD in higher neural contributions in the setting of BPH may require further modification and adaptation.

This was a pilot assessment of the white matter, and this analysis was part of a larger study that included a gray matter analysis of the same cohort utilizing the concurrent fMRI/UDS platform. Here, we present the first study that explores the possible role of preserved white matter integrity in LUTS in patients with BPH and chronic BOO. Our results yielded statistically significant correlations suggestive of a possible link between preserved integrity of specific WMTs and LUTS based on uroflow parameters. While we are still in the early stages of understanding neural network changes associated with the micturition cycle, we hope that our study will serve as the first step toward the advancement of future neuroimaging studies of BPH and ultimately lead to novel prognostic and therapeutic tools.

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AUTHOR CONTRIBUTION STATEMENT

Conceptualization: RRG, CK, RK

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Formal analysis: YJ, KT, LH, DC, RRG, CK, ZS, RK

Funding acquisition: RK

Methodology: YJ, KT, LH, DC, RRG, CK, RK

Project administration: RRG, RK

Visualization: YJ, KT, LH, RRG, CK, RK

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