



Functional Brain Imaging in Voiding Dysfunction

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Abstract

Purpose of Review Voiding dysfunction (VD) is morbid, costly, and leads to urinary tract infections, stones, sepsis, and permanent renal failure. Evaluation and diagnosis of VD in non-obstructed patients can be challenging. Potential diagnostic and therapeutic options beyond the bladder, such as brain centers involved in voiding have been proposed as promising targets. This review focuses on current and future applications of functional neuroimaging in human in voiding and in patients with VD.

Recent Findings The current understanding of brain centers and their roles in initiating, maintaining, and/or modulating voiding is rudimentary in humans and in patients with VD. With the advent and advancement in functional neuroimaging, we are gaining more insight into specific brain regions involved in the voiding phase of micturition. In healthy individuals, right dorsomedial pontine tegmentum, periaqueductal gray, hypothalamus, and the inferior, medial, and superior frontal gyrus have been identified as regions of interest in voiding.

Summary Functional neuroimaging could suggest new diagnostic methods and provides crucial steps towards therapeutic options for the morbid and intractable VD condition, in patients with neurogenic (e.g., MS or strokes) or non-neurogenic VD (e.g., underactive bladder or Fowler's syndrome).

Keywords Voiding · fMRI · Neuroimaging · Bladder dysfunction · Micturition

Introduction

The human lower urinary tract has two functions: storage and voiding. This review will concentrate on supraspinal (brain) areas controlling the delicate and complex neural circuitry (the “switch”) from storage of urine to voiding. Voiding dysfunction (VD) is a morbid and costly urological condition characterized by intermittent, fluctuating, or absent flow of urine [1]. VD leads to incomplete bladder emptying and/or urinary retention, urinary tract infections, sepsis, stones, or permanent renal failure. VD can be present in patients with or without neurologic disorders (multiple sclerosis or stroke

versus idiopathic underactive bladder) [2]. VD occurs if the detrusor muscle cannot maintain effective contractions (e.g., detrusor underactivity), if the urethra fails to relax and lower urethral resistance, or if there is failure in synchronizing these actions leading to detrusor sphincter dyssynergia (DSD) in subset of neuropathic patients [3, 4].

- Currently, the only available therapies for VD include indwelling bladder catheters, intermittent self-catheterization, and sacral neuromodulation only in certain and small group of patients.

Catheterization is a burden, in general, and even more so in neuropathic patients, in whom lower extremity spasms, compromised hand dexterity, or visual disturbances may be present. The cost and morbid side effects (hematuria, pain, trauma, strictures, and infections), associated with catheterizations, drive us to look into alternate etiologies and therapeutic targets for VD, possibly beyond the bladder, such as the brain where bladder and urethral control centers are located. This is where functional neuroimaging has been providing promising opportunities over the past decade.

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Functional neuroimaging studies thus far suggest that normal voluntary voiding is meticulously orchestrated by suprapontine centers in the brain, allowing the pontine micturition center to trigger (switch on) the voiding reflex. Animal models have conventionally been used to study neural control of the bladder. However, when investigating the voiding phase of micturition, we need to realize that animals differ from humans in numerous ways (e.g., social behavior). Critical distinctions exist between voluntary voiding (humans) and more instinctive bladder emptying (animals), when all the social, emotional, and mechanical criteria for voiding are considered. The conscious and complex human intention to void, or not to void, highlights the need for human research in functional neuroimaging, rather than exclusive reliance on animal data given these differences in brain control over voiding.

Functional Neuroimaging and Voiding

With the evolution of neuroimaging tools and resources, such as functional magnetic resonance imaging (fMRI), we have begun to gain additional insight into brain control over bladder function in healthy individuals and patients with overactive bladder [5]. Yet, our understanding of supraspinal centers and their role in *initiating*, *maintaining*, or *modulating* voiding continues to be rudimentary in healthy and in patients with neurogenic (e.g., multiple sclerosis [MS] or stroke) or nonneurogenic voiding dysfunction (e.g., underactive bladder or Fowler's syndrome).

Investigation of brain control over the bladder in healthy individuals through the use of functional neuroimaging shows that the initial afferent sensory input comes from the bladder distention during “bladder fullness or the strong desire to void”. Next, the forebrain determines the person's social circumstances and whether to proceed with voiding or not. Once it is socially acceptable to void, centers in the brain and spinal cord coordinate and initiate urethral sphincter/pelvic floor relaxation, followed by a sustained detrusor contraction [6]. Specifically, the pontine micturition center (PMC) signals the bladder to begin the voiding phase when the sensations from the bladder are transmitted to the periaqueductal gray (PAG) and higher brain centers [6–8]. Previous positron emission topography (PET) studies in healthy individuals have demonstrated activation of the right dorsomedial pontine tegmentum, periaqueductal gray (PAG), hypothalamus, and the right inferior frontal gyrus at the time of voiding [9, 10]. Functional neuroimaging may augment the diagnosis of VD and aid in identifying therapeutic targets for certain types of VD [11–13, 14, 15].

Challenges and Gaps in Knowledge of Functional Neuroimaging During the Voiding Phase

Evaluating the voiding phase of the micturition cycle during brain neuroimaging requires the individual to urinate while lying down in the magnetic resonance imaging (MRI) or PET scanner which is difficult for all adults (men more than women). This is even more challenging during brain MRI scans where the head is secured to helmet-like head coil and the individual is requested to initiate and complete the task of voiding while trying to be as still as possible. Since motion artifact [16] (even up to 4 mm in any direction) interferes with the quality of the data acquired.

Therefore, majority of the functional neuroimaging studies, especially the ones using MRI over the past 20 years, have focused on the storage phase. Despite the challenges, our research team and few others have developed a fMRI and urodynamic study (UDS) platform that evaluates the entire bladder cycle, including the voiding phase (or attempt of voiding in patients with VD).

Another challenge is obtaining appropriate image and data that could be used to evaluate voiding. fMRI studies localize brain areas that are activated or deactivated in real time in regions that are relevant to the specific task performed by the individual such as finger tapping or speech. These regions of interests are assessed by blood oxygen level dependent (BOLD) signals. Noise in the BOLD signals obtained during a task requires averaging the signals to extract more reliable functional information. This requires the task to be repeated many times [17]. While repletion of most tasks such as finger tapping or speech can be easily achieved, voiding or attempt of voiding multiple times may not be feasible unless the individual is catheterized. Additionally, combining UDS with fMRI is technically challenging, but necessary, in order to elucidate simultaneous brain-bladder activities during voiding or attempting to void by being able to drain and refill the bladder as many times as needed. Our team and a few other groups have established and refined simultaneous platform of fMRI/UDS in healthy [18–20] individuals and neuropathic [14] patients during voiding [21].

Alternatively, fMRI techniques such as arterial spin labeling (ASL) which allows for measurement of absolute cerebral perfusion can be used without the need to repeat the task (thus avoiding catheterization). ASL has been used to quantify regional cerebral blood flow in patients with overactive bladder following consumption of fluid in both states of low urgency and high urgency [22]. However, thus far cerebral perfusion changes associated with the voiding phase of micturition cycle have not been performed.

Functional connectivity is another neuroimaging method that investigates the spatial connectivity between

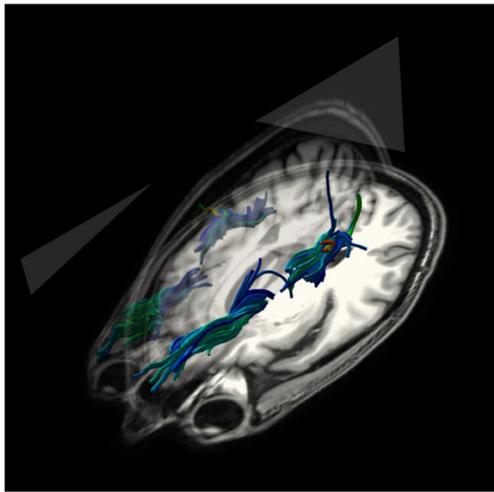


Fig. 1 Anterior thalamic radiation (ATR) and the Superior longitudinal fasciculus (SLF) are the main two white matter tracts in the brain involved in proper lower urinary tract function. (Unpublished data of the authors)

regions of the brain that are remote, however, become activated/deactivated during a certain task such as voiding. This analysis may be more meaningful in LUT control and specifically voiding since multiple regions of the brain are involved during initiation and maintenance of voiding [23]. Few groups have overcome this challenge by evaluating the resting state functional connectivity (rsFC) where the task (bladder distention) may only be performed once and passively by accelerated hydration [24], such as evaluating the brain at the beginning of the

study with an empty bladder and at the time of bladder fullness following consumption of water.

Connecting pathways between brain regions involved in voiding (white matter tracts) are also of significance when evaluating brain control over voiding. White matter abnormalities such as hyperintensities are becoming increasingly more known to be associated with LUTS especially in elderly [25, 26]. Two white matter tracts (WMT)s are particularly important in proper function of the bladder: the anterior thalamic radiation (ATR) and superior longitudinal fasciculus (SLF) [27, 28]. WMT integrity can be evaluated using diffusion tensor imaging and assessing the fractional anisotropy and mean diffusivity of each tract to provide additional meaningful data in evaluation of voiding dysfunction Fig. 1.

Regions of interest (ROI) in Voiding in Humans from Current Literature Earlier neuroimaging studies have identified brain regions directly involved in initiating or continuing voiding in healthy individuals. These regions include precentral gyrus, supplementary motor area, dorsolateral prefrontal lobe, inferior frontal gyrus (IFG), cingulate gyrus, insula, hypothalamus, PAG, and pons (PMC) [9•, 10•, 18, 29]. Table 1 summarizes the currently available *cortical* brain regions involved in *voiding* as potential ROI's in healthy, MS, and non-neurogenic VD.

In a small group of women with urinary retention, due to urethral sphincter dysfunction, peripheral nerve neuromodulation modified the activity of the right postcentral gyrus, precentral/temporal, and inferior temporal regions [11, 32]. fMRI studies report that medial prefrontal cortex and supplementary motor areas are the main cortical regions

Table 1 MNI, Montreal Neurological Institute coordinates; BA, Brodmann areas; HA, hemisphere; PF, pelvic floor

MNI	BA	HA	Area	Scan	Task	Reference
Healthy						
52, 24, 12	45/44	Right	IFG	PET	Voiding	Blok 1998 [9•]
63, 18, 18	44/45	Right	IFG	fMRI	Initiation of voiding	Mehnert 2015 [20]
40, 35, 6	46	Right	IFG	fMRI	Initiation of voiding	Khavari 2014 [18]
8, -8, 62	6	Right	Medial frontal gyrus	fMRI	PF contraction	Zhang 2005 [30]
6, -18, 57	6	Right	Medial frontal gyrus	PET	PF contraction	Kuhtz-buschbeck 2005 [8]
3, -18, 57						
2, 2, 62	6	Right	Superior frontal gyrus	fMRI	PF contraction	Kuhtz-buschbeck 2011 [31]
48, 4, 10	6	Right	IFG	PET	Voiding (urethral)	Nour 2000 [29]
-44, 1, 28	6	Left	Precentral gyrus	fMRI	Initiation of voiding	Khavari 2014 [18]
2, -32, 66	4	Right	Superiomedial precentral	PET	Voiding	Blok/Holstege 1997 [9•, 10•]
-6, -26, 74	4	Left	Superiomedial precentral	PET	Voiding	Blok/Holstege 1997 [9•, 10•]
Non-neurogenic voiding dysfunction						
54, -4, 6	6	Right	Precentral	fMRI	Urethra	Fowler 2010 [32]
Neurogenic voiding dysfunction (MS)						
-39, 34, 5	45	Left	IFG	fMRI	Initiation of voiding	Khavari 2017 [14••]
38, 33, 6	45	Right	IFG	fMRI	Voiding	Khavari 2017 [14••]

involved in pelvic floor contraction [8, 31, 33], and could be used to phenotype responders versus non-responders to biofeedback assisted pelvic floor physical therapy in overactive bladder patients [34••].

Potential Therapeutic Options

It is becoming more prudent to move beyond the exploratory phase of identifying supraspinal areas involved in VD using functional neuroimaging and advance targeted modulation of these regions.

Currently, the only neuromodulation modalities available for the bladder target the peripheral nerves, including the Sacral Neuromodulator, the Posterior Tibial Nerve Stimulator, and the intradetrusor injection of neurotoxin OnabotulinumtoxinA. Additionally, these therapies, mainly modulate the storage phase (urinary urgency and incontinence) of micturition. We have used functional neuroimaging to investigate brain correlates in MS patients with Neurogenic OAB following OnabotulinumtoxinA [15] while others have evaluated the brain changes following sacral neuromodulator use for overactive bladder patients [35, 36]. To date, there has been no central (brain) neuromodulation for bladder control, specifically for the voiding phase. It is rational to use the data provided by the functional neuroimaging literature and look beyond the bladder in managing VD. Brain regions identified by fMRI evaluation may offer promise for potential therapeutic targets.

Proposed options for neuromodulation at the level of brain (including stimulation and/or inhibition) have been expanding over the past 10 years specifically within neurology and psychiatry specialties. The most promising neuromodulation modalities thus far include deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS).

Deep Brain Stimulation Deep brain stimulation has been shown to improve motor and non-motor symptoms and quality of life of patients with movement disorder such as Parkinson's disease (PD). DBS can be implanted in various deep locations of the brain such as the subthalamic nucleus [37], pedunculopontine nucleus (STN) [38], or globus pallidus pars interna (GPi). The Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) study evaluated functional improvements following GPi versus STN DBS implantation in PD patients and showed only slight preference of STN in regard to off-drug phase and some motor examination scores [39]. A post-hoc analysis of the 128 patients in this cohort showed that urinary incontinence and frequency improved with both GPi and STN DBS implantation. However, this was only significant for STN DBS group in both men and women. Interestingly, nocturia and nighttime urinary incontinence did not improve in either groups. [40]

One male patient in this cohort used a catheter initially and was catheter free at 12 months. There is additional data that DBS implantation, even in moderate LUTS, may improve quality of life especially deploying the STN target [41]. There seems to be increasing data to support DBS implantation in other neurological disorders such as MS with modest improvement in LUTS [42, 43].

fMRI-identified deep brain targets in VD may be potential regions for further investigation. Improvements in LUTS have been secondary outcome evaluations in all human DBS studies thus far. However, this is laying the foundation to explore DBS targets especially for urinary symptoms and possibly voiding dysfunction. Animal studies are beginning to investigate the feasibility of modulating deep brain targets involved in regulating bladder function. Deep brain targets such as PAG, locus coeruleus, rostral pontine reticular nucleus, and pedunculopontine tegmental nucleus (PPTg) have been investigated [44, 45]. PPTg appears to provide a promising target as a neuromodulatory target specifically for LUTS [44].

Transcranial Magnetic Stimulation Although the PAG and PMC are the more apparent regions involved in initiation of voiding and could serve as potential targets, they are deep and inaccessible with our current technological ability in humans. Besides, these regions are responsible for other core vital functions such as regulating circulation and breathing wherein modulation may not be safe with our current technologies.

Therefore, TMS may be an exciting and safer alternative to investigate in VD. TMS is a non-invasive centrally acting electromagnetic neuromodulator that is held over the scalp and delivers a rapidly pulsed magnetic field to the cortex to activate neurons, within a limited area, without requiring anesthesia or causing any significant side effects. TMS and repetitive TMS (rTMS) are substantially safe and are widely used for brain mapping and/or to modulate cortical excitability [46, 47]. Two small studies have demonstrated the feasibility and efficacy of rTMS in patients with MS ($n = 10$), and Parkinson's disease ($n = 8$) with bladder symptoms. Their findings suggest that TMS improves both the storage and voiding phase and reduces postvoid residuals of the urine, while appropriately increasing the detrusor pressure at the time of voiding [48, 49]. Interestingly, in three MS patients with DSD, following rTMS, the abnormally high detrusor pressures at the time of voiding were decreased to a more appropriate level, possibly implying the restoration of synergistic voiding with coordinated relaxation of urethral sphincter and the pelvic floor. [48] In a more recent study, 58 children (ages from 6 to 14) with nocturnal enuresis were randomly assigned to receive anticholinergic medication (oxybutynin), TMS, or placebo TMS. Authors reported improvements in bladder capacity, voiding scores, and enuresis events, 7 months following TMS use [50].

Other neuromodulation techniques such as brain-computer interface, hypnosis, hippocampal exercises, and neurorehabilitation are also being explored to modulate the brain in order to improve LUTS. A recent trial is planning to randomize women with overactive bladder to hypnotherapy (brain-centered therapy) versus pharmacotherapy and use fMRI assessment to show changes in the brain following both treatment modalities [51].

Future Directions

The etiology of voiding dysfunction (neurogenic and non-neurogenic) remains unknown in most patient scenarios. Future and more robust functional neuroimaging studies are needed to do the following:

- Investigate patients with non-neurogenic voiding dysfunction, such as patients with Fowler's syndrome, where the data concerning the etiology and effective treatments are scarce [52]. Concerning etiology, some investigators believe this is a result of learned behavior in response to pain or injury, such as UTI or trauma. Others theorize that the dyssynergic sphincter exists, and is due to habitual contraction of the pelvic floor (external sphincter) that results in reflexive abnormal muscle contractions. Recent DTI evaluation of the lumbosacral plexus in nonneurogenic neurogenic patients suggests abnormal DTI parameters as seen in patient with peripheral nerve injury [53].
- Investigate patients with Underactive Bladder (UAB) or detrusor underactivity. The National Institute on Aging and the National Institute of Diabetes and Digestive and Kidney Diseases have placed investigation of the etiology, diagnosis, evaluation, and treatment at their high priority. Authors believe more robust fMRI studies in this field could lay the foundation in brain control in UAB, and potentially create avenues for translational clinical trials.
- Investigate patients with neurogenic voiding dysfunction. Most evaluations thus far using fMRI have focused on healthy subjects and patients with OAB. With further improvements in our protocols and expansion on the foundation of our knowledge on the brain control over bladder, we need to extend these trials and evaluation to patients with neurogenic voiding dysfunction such as patients with multiple sclerosis or stroke. A few groups internationally have started to investigate specific subgroups of neurogenic bladder patients such as spinal cord injury [54, 55] or spina bifida [56] with functional neuroimaging technologies. Evidence of extraspinal sensory pathways that relay bladder sensation to the brain possibly via vagal nerve in SCI patients may open possibilities for neuromodulation (centrally or peripherally) in the early or later phase of SCI [57, 58].

Compliance with Ethical Standards

Conflict of Interest Dr. Khavari reports that she is partially supported by K23DK118209, by National Institute of Health, NIDDK.

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