

*Review article* ■

## **CNS and Bladder (short review for clinicians)**

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### **SUMMARY**

**Symptoms of bladder dysfunction are significant public health problem due to their prevalence, morbidity and treatment costs. Most stem from bladder control problem which is governed by the brain, yet we know little about CNS and bladder. Advances in brain imaging technology have brought new insight in how brain works in different bladder diseases and opened new possibilities to study lower urinary tract. Thus, it is important for urologists and clinicians alike to get informed about basic concepts of brain-bladder control. The aim of this article is to review basic neuroanatomy of central continence control based on the results of recent brain imaging studies in patients with symptoms of impaired bladder control.**

**Key words:** brain, bladder, brain imaging, urinary incontinence

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## INTRODUCTION

Lower urinary tracts symptoms (LUTS) are significant from public health perspective as they are prevalent, morbid and costly (1, 2). Most of LUTS are the sign of voiding dysfunction which stems from various bladder disorders that may have idiopathic or known (neurogenic) etiology. They all have in common a degree of impaired bladder control which may be influenced not only by lower urinary tract pathology but the brain function as well.

Until recently, little was known about the brain's role in bladder control and the organization of cortical centers in regulation of the micturition cycle (both storage and voiding). A major breakthrough has been made in the last two decades with the advancement of imaging technology and functional brain imaging techniques that measure and map regional cerebral metabolism or blood flow that (indirectly) represents local neuronal activity (3). Such methods include single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). More recently, other functional brain imaging modalities have become available, for example, near infrared spectroscopy (NIRS). As these functional brain imaging techniques improve, so does our ability to investigate the brain-bladder connection. With an increased knowledge on CNS correlates of LUTS, there is a need for clinicians, urologists and complementary disciplines, to learn and understand brain and bladder connection and utilize current information as to advance their thinking on patient presenting with urinary symptoms.

Therefore, the aim of this review is to inform targeted audience on basic neuroanatomy of central continence control, and provide results of brain imaging studies in patients with and without symptoms of impaired bladder control.

## CNS CONTROL OF BLADDER FUNCTION

Urinary incontinence is often considered a disorder of the lower urinary tract (LUT) clinically characterized by patient-reported episodes of urine leakage, with or without urgency, suggesting a failure of bladder control. Control of the bladder is a learned skill which starts and finishes in childhood, and the brain's role is critical. The major role of such a skill is to accommodate the social environment and provide the ability to void or postpone voiding willingly, regardless of strength of bladder sensation. In adult life, such control may be lost in the case of a pathogenic factor affecting the brain, with brain injury and stroke as examples. Rarely, it may be a purely mechanical problem, as it is in the case of stress urinary incontinence.

The micturition cycle encompasses two phases: *storage* - when bladder is gradually filled with urine and *voiding* when bladder is emptied. Central control of the micturition cycle can be divided into two main domains: the

*voiding reflex*-a spinal reflex responsible for automatic emptying of the bladder as occurs in babies and spinally injured patients; and *executive control* of the bladder - the higher brain function which allows voluntary control of the voiding reflex, and provides the ability to remain continent. The specific brain areas involved in these processes are described in this section, along with the current working model of central bladder control (4).

### The voiding reflex

Experimental work in animals confirms that micturition is mediated by a *spinobulbospinal* reflex pathway which responds to the increase in bladder volume by activating centers in the brain stem, periaqueductal gray (PAG) and pontine micturition center (PMC). As bladder volume increases during the storage phase, afferent signals from the bladder and urethra ascend through the spinal cord to synapse in the midbrain and PAG, and at some volume threshold neurons descending from the PAG excite the PMC. PMC excitation activates descending motor efferents (including parasympathetic fibers), causing coordinated urethral sphincter relaxation and detrusor contraction - the commencement of the voiding phase (Figure 1).

Such neuronal function is not automatic and, in continent individuals, the firing of the voiding reflex is under strict voluntary control, which enables voiding to occur at a socially acceptable place and time and in concert with one's emotional state. Such a mode of operation implies that, normally, the reflex is inhibited and that afferent signals do not trigger it directly, but are relayed to the forebrain where, gradually (with bladder filling), they produce a series of increasingly strong sensations (from first sensation of filling to strong desire to void). These sensations are mostly ignored, but ultimately cause the individual to attend to the stimulus from the bladder and voluntarily decide to void. Failure of this control system leads to an automatic triggering of the reflex and involuntary voiding (incontinence).

### Functional neuroanatomy (brain imaging studies to date)

The bladder is controlled by a complex neural network that consists of many functionally specialized areas and regions within all segments of nervous system (central, autonomic and peripheral). In this section we describe, in brief, the role of each region within the brain and how these areas mediate between the voiding reflex and the executive control of continence.

#### Brain stem

##### *Periaqueductal Gray (PAG)*

The PAG has a crucial role in voluntary control of the bladder due to its involvement in registration of bladder filling sensations and timing and manipulation of the

firing of the voiding reflex. It receives and forwards ascending bladder signals (sacral afferents) to higher brain centers and receives projections from many higher brain centers (e.g. orbital and pre-frontal cortex, amygdala, and pre-optic hypothalamus), while controlling the primary input to the PMC. In this way, the PAG allows suppression of the excitatory signals to the PMC from higher brain centers (e.g. prefrontal cortex - PFC) during bladder filling and thus prevents voiding or incontinence.

Brain imaging studies have shown activation of the PAG during bladder filling and confirmed its postulated role in receiving bladder afferents and relaying them via the thalamus to the insula, where normal visceral sensations such as desire to void are thought to be mapped (4-7).

#### *Pontine micturition center (PMC)*

Sometimes referred to as Barrington's nucleus or the M-region (M for medial), the PMC (see Figure 3B) is located in the dorsal portion of the caudal pontine tegmentum, close to the locus ceruleus. Together with the PAG, the PMC plays a critical role in coordinated contraction of the bladder detrusor muscle and relaxation of the external urethral sphincter during micturition. Bladder afferents excite the PMC indirectly via the ventrolateral PAG, and then the PMC sends descending glutamatergic projections to the sacral spinal cord via the lateral funiculus and activates the sacral preganglionic neurons. At the same time it inhibits, via local interneurons, both the thoracolumbar sympathetic neurons and Onuf's nucleus motor neurons innervating the external urethral sphincter.

Activation of the PMC revealed by PET studies during the voiding phase (5-8) has confirmed that the long-loop voiding reflex is excited during normal voiding. In addition, fMRI studies have shown that the PMC responds to bladder filling during the storage phase as well (both in normal subjects and in urge incontinent subjects prior to onset of detrusor overactivity, DO) (8-10). Thus imaging studies indicate that PMC responses during the storage phase represent inhibition of the PMC and the voiding reflex. PMC activation and cerebellar activity occur simultaneously, suggesting the PMC may be controlled by the cerebellum to provide inhibition during urine storage, concurring with previous beliefs that the cerebellum modulates the threshold of many pontine reflexes.

#### *Pontine L-Region*

A pontine region located ventrolateral to the PMC, referred to as the L-region (L for lateral) or pontine incontinence center, sends a direct excitatory projection to Onuf's nucleus, promoting contraction of the pelvic floor, thus maintaining continence.

Imaging studies have been inconsistent in showing this region during the storage phase (shown on PET studies but failed to be detected on fMRI studies) (10).

## **Cortical and sub-cortical structures**

### *Right Anterior Insula*

The insular cortex, especially the right anterior insula, is involved in mapping of visceral signals and making them accessible to higher cortical regions for further processing, which results in the subject's awareness of bladder sensations ("conscious or interoceptive awareness") (11). This is possibly due to connecting pathways with the PFC since conscious desire to void or urgency is lost after extensive lesions in that area.

Brain imaging studies have confirmed the role of the insula in mapping bladder sensations by showing activation during bladder filling in subjects with both normal bladder function and urge incontinence. Such activation appears to be significantly stronger in incontinent subjects during reported urgency albeit decreasing with advanced age (9, 12).

### *Anterior cingulate gyrus (ACG)*

The ACG (dorsal and ventral part) is a frontal part of the cingulate cortex situated around the corpus callosum (see Figure 3A). The role of the ACG is complex and related to autonomic control (e.g. heart rate) and various cognitive functions, including emotion, empathy and decision making. Its role in bladder control was inferred based on association of continence problems and lesions in this area (4, 10).

Functional brain imaging studies showed an abnormally pronounced response of the dorsal ACG to bladder filling in patients with urgency incontinence, even in the absence of DO (8). Connectivity studies suggested involvement of the ACG in both the recruitment of accessory pathways (to help avoid loss of control of the bladder) and in the sensation of urgency that accompanies this situation (10). It is also active during voiding and simulated voiding, although this role is less clear (13, 14).

### *Frontal cortex*

The role of the frontal cortex has been established clinically by the classic description of strong association between symptoms of impaired continence and anatomical findings of frontal lobe pathology done by Andrew and Nathan (15). Its role is in activation and/or suppression of the voiding reflex, since neuroanatomical observations indicate direct connection from the medial PFC to the PAG. Centers involved in higher cognitive processing, without direct connections with the brain stem, are also involved (e.g. dorsolateral prefrontal cortex - dlPFC).

Imaging studies have indicated the role of several frontal regions involved with regulation of the micturition cycle. For example, during voiding the activation of the right inferior frontal gyrus (adjacent to the dlPFC) and the medial PFC (adjacent/near to the anterior cingulate

gyrus) has been identified (6,7,13,16). Studies during filling of an already well-filled bladder and reported urgency also show significant activation in the dlPFC and deactivation in the ventromedial and medial part of PFC (17).

### Hypothalamus

Imaging studies during bladder filling show activation in the caudal hypothalamus, which confirms the previous discovery of synaptic connections between the anterior and caudal part of hypothalamus and the PAG and PMC. Parts of the hypothalamus (around the preoptic area) are weakly activated in subjects with urinary incontinence when the bladder is full, which may suggest an inhibition due to a perception that voiding is unsafe (10).

### Amygdala

The amygdala plays an important role in the generation of emotions (e.g. fear) and mediates between unconscious and conscious reactions to emotive events. Although there are no specific reports of amygdala activity in most major studies of bladder control, its role is highly suggested since urgency is associated with an emotion (e.g. fear of urine leakage). More recent studies from the University of Pittsburgh show amygdala activation during bladder filling in both normal and incontinent subjects suggesting involvement in the normal response to filling to suppress an unpleasant (or stressful) sensation provoked by increasing bladder volume (10).

### Other Regions

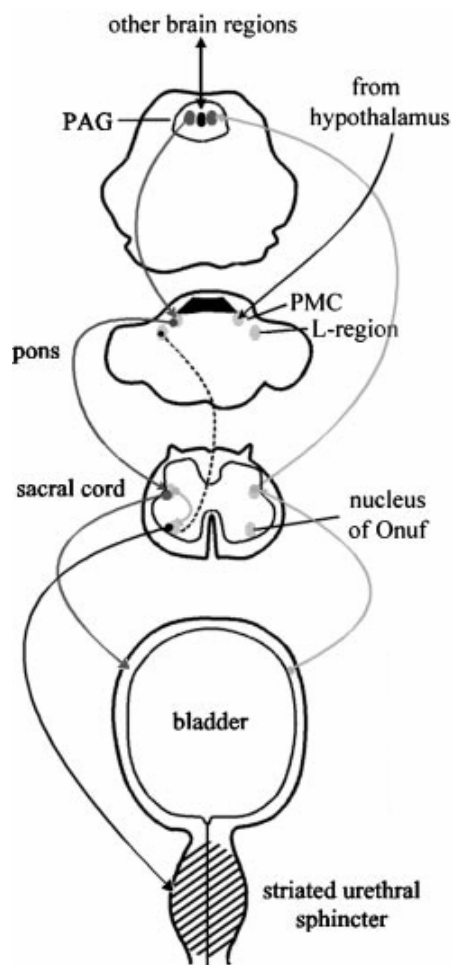
In addition to the regions described, there have been a host of regions activated during bladder filling in normal and urge-incontinent subjects, including the cerebellum, cuneus and precuneus, parts of the parietal and temporal lobes, fusiform gyrus and posterior ACG. These regions have been reported in previous studies using a bladder filling protocol but have not been systematically discussed (10).

### A working model of brain-bladder control

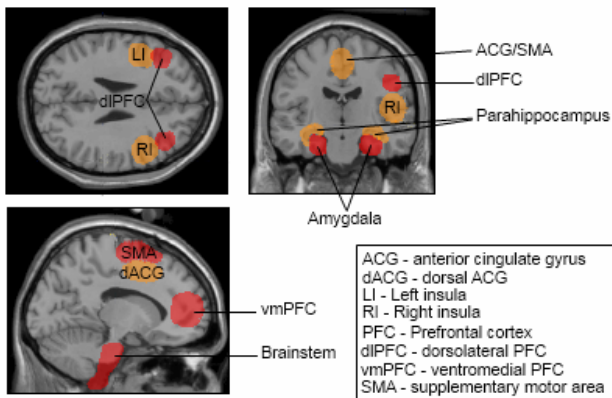
Multiple brain regions are activated during bladder filling and voiding forming a neural circuit - the brain-bladder control network - involved in regulation of micturition cycle. Most likely, afferent signals relay in the PAG and are mapped in the RI (interoceptive awareness). Most of the time, signal processing is automated and is tonically inhibited by centers in the ventromedial PFC. After a certain threshold, the signal is forwarded to higher cognitive centers (e.g. dlPFC). If decision to void is made, voluntary disinhibition of PAG/PMC occurs, which allows triggering of the micturition reflex and voiding in socially acceptable circumstances. In subjects with urgency and incontinence, appraisal and inhibition of affe-

rent signals is impaired. Thus, an autonomic/motor and emotional response is also activated, as suggested by abnormally strong activation of the dorsal ACG (e.g. emotional arousal) and supplementary motor area, which controls pelvic floor muscles and, perhaps, the urethral sphincter. Such a shift in functional connectivity from the RI and ACG in urgency incontinent subjects is different compared to normal subjects (18).

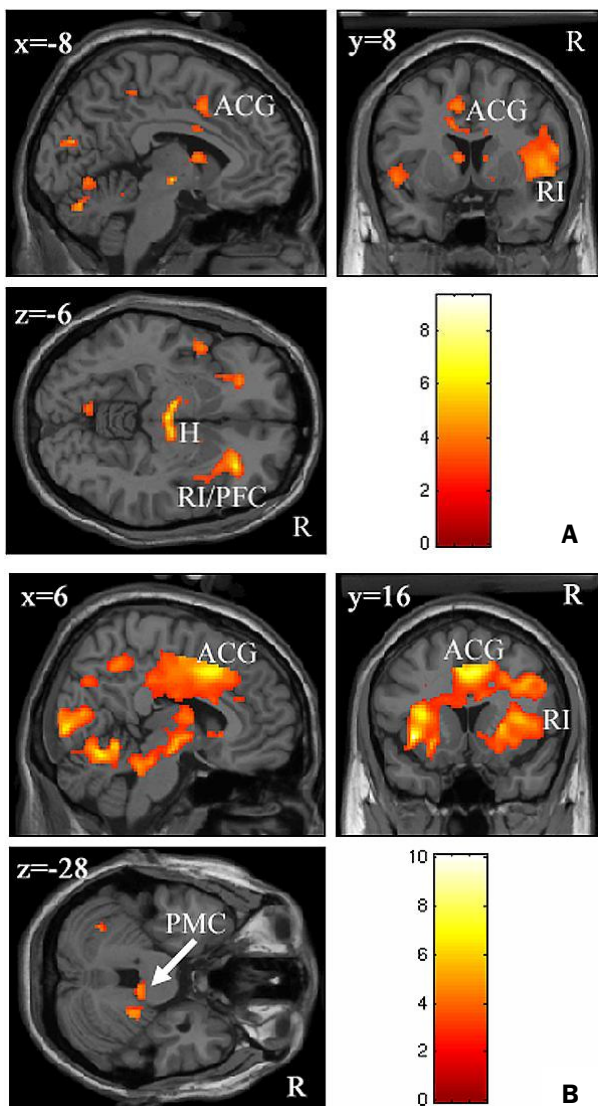
Some of the imaging studies also suggest involvement of the parahippocampus and hypothalamus suggesting that a neural circuit related to safety is also involved (see Figure 4) (19).



**Figure 1.** The long-loop voiding reflex. Afferent signals from the bladder (light gray) synapse in the sacral cord. Ascending secondary afferents bypass the pontine micturition center (PMC) and synapse in the periaqueductal grey (PAG). If the reflex is triggered, PAG efferents excite the PMC (dark gray pathways). Efferents descend to the sacral cord where they excite a pathway to the bladder that leads to detrusor contraction and an indirect pathway to the nucleus of Onuf, leading to sphincter relaxation and voiding. In normal adults, reflex is controlled by higher brain regions. The PMC also receives direct innervation from the hypothalamus. (with permission: Continence Research Unit at University of Pittsburgh)

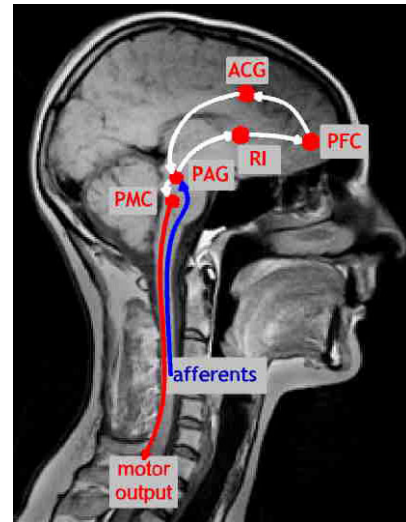


**Figure 2.** Brain areas related to continence control (shown projected on sagittal, transverse and coronal MRI planes). (with permission: Continence Research Unit at University of Pittsburgh)

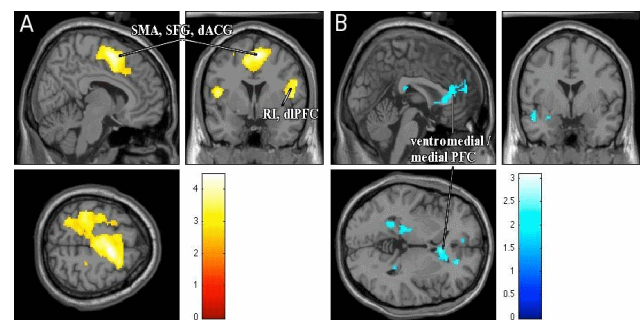


**Figure 3.** Regional brain activity with full bladder. **A.** Responses to bladder infusion in normal controls at large bladder volumes. **B.** Responses to bladder infusion in subjects with urge incontinence at large bladder volumes.

RI=right insula; ACG=anterior cingulate gyrus; H=hypothalamus; RI/PFC=right anterior insula and/or lateral prefrontal cortex. PMC=pontine micturition center. R=right side. Color bar shows scale of student's t values. (with permission: Continence Research Unit at University of Pittsburgh)



**Figure 4.** Brain-bladder control network - simplified model. Bladder afferents synapse in PAG and are relayed to insula (RI), forming the substrate for sensation. ACG is responsible for monitoring arousal and efferent output to the PAG and PMC. Prefrontal cortex (PFC) is involved in voluntary decision about voiding and generates efferent signals to control ACG and ultimately PMC. PMC provides motor output to cause voiding. (with permission: Continence Research Unit at University of Pittsburgh)



**Figure 5.** Regional brain activity during urgency. **A.** Regions with significant activations during bladder filling. **B.** Regions with significant deactivations during bladder filling of a well filled bladder. SMA=supplemental motor area; SFG=superior frontal gyrus; dACG=dorsal anterior cingulate gyrus; RI=right insula; dIPFC=dorso-lateral prefrontal cortex; PFC=prefrontal cortex. Color bar shows scale of student's t values. (with permission: Continence Research Unit at University of Pittsburgh)

## **BRAIN IMAGING STUDIES ON BRAIN BLADDER CONTROL - CLINICAL CORRELATES (short review)**

Urinary incontinence is defined clinically as an involuntary leakage of urine, and may be accompanied by a feeling of urgency (urge urinary incontinence), or as a result of laugh, cough or exertion (stress urinary incontinence) (20, 21). An urge incontinence episode is caused by an involuntary, uninhibited contraction of bladder detrusor muscle - known as DO. In most cases the etiology of detrusor overactivity is unknown (idiopathic). Detrusor overactivity that occurs with suprapontine lesions (e.g. in stroke) affecting forebrain modulation of the PAG and PMC, or following spinal cord injury, is defined as neurogenic. In this section, we will review findings of brain imaging studies in subjects with urge urinary incontinence ('*idiopathic*' DO) and urinary incontinence related to neurodegenerative diseases, including spinal cord injury ('*neurogenic*' DO).

### **Imaging methods**

With advancement of imaging technology it is possible to assess brain activity during various phases of the micturition cycle. Paradigms during scanning include voiding, bladder filling, pelvic floor muscle contractions and comparing activity during an empty and full bladder. Participants in initial studies were mostly younger healthy volunteers. Initial studies utilized PET and were followed by series of fMRI studies. In the last 15 years, cumulative knowledge on brain activity during the micturition cycle has evolved from a simplistic description of brain regions to emergence of more complex models conceptualizing regional brain activity to a functional network of specialized regions (e.g. the brain-bladder control network) (3).

There are several methods in use for brain bladder studies. Each method has its advantages and disadvantages. Table 1 summarizes essential information on brain imaging methodology in use or with potential application to brain-bladder studies.

### **Normal bladder - the micturition cycle**

Most of the findings on normal bladder function originate from the first imaging studies on healthy volunteers of both genders. Blok, using PET, was first to report brain activity during voiding in healthy male volunteers, confirming previous anatomical findings that suggested the PFC as a seat of executive control of voiding (6, 7). Most notable areas active during voiding are the medial PFC and inferior frontal gyrus. Similar areas are active in normal female volunteers. In healthy subjects, areas activated during the storage phase (various bladder filling paradigms) are the RI and dACG adjacent to the SMA (8, 10, 22). There are other areas described

during bladder filling but the significance was not explored in detail.

Functional MRI studies confirmed initial PET studies and also suggested some activity in the brain stem during the bladder filling/storage phase (10). One study also showed that insular activity may be decreased with older age suggesting impaired processing of afferent signals (12). fMRI studies during contraction of pelvic floor muscles showed involvement of the SMA (14).

### **Bladder symptoms of idiopathic and non-neurogenic etiology**

Symptoms of impaired bladder control may be labeled as *overactive bladder* (OAB), which is manifested as urinary frequency, urgency and nocturia; with or without urine leakage (urgency incontinence). Urgency is a cornerstone symptom, defined as 'sudden compelling desire to void, which is difficult to defer'. On urodynamic testing, patients with urgency may exhibit DO - an involuntary contraction of the detrusor muscle, spontaneous or provoked (21).

A group from the University of Pittsburgh (Geriatric Continence Research Unit) has published several studies on older women with urgency incontinence describing regional brain activity during *urgency* (8, 9, 17, 23). Such activity encompasses abnormally strong activations in the SMA, dACG, insula and dIPFC, together with deactivations in the ventromedial cortex and parahippocampus (see Figure 5). This is believed to represent an emotional reaction and autonomic/motor arousal related to fear of leakage, and an attempt to resolve such conflict by contracting pelvic floor muscles to prevent relaxation of the urethral sphincter (activation in the SMA). Deactivations in the ventromedial cortex may represent an effort to suppress strong afferent signals from a full bladder or onset of the micturition reflex. In subjects who lost control of their bladder during bladder filling in the scanner, such activity amplifies (19). Regional brain activity during reported urgency in the scanner also correlates with reports of urgency incontinence on the bladder diary (17). One of the possible causes of such increased activity during urgency in older women with urinary incontinence may be due to the damage of white matter pathways that connect these centers in the brain. This idea is further supported by a study that showed strong association between functional brain activity (Blood oxygen level dependent - BOLD) and white matter damage (white matter hyperintensities - WMH on FLAIR images) (23), and epidemiological studies in community dwelling older adults that linked urgency with the extent of white matter damage (WMH) (24, 25).

Studies on OAB were lacking until recently (26). Brain activity during reported urgency upon bladder filling in women who complained of urgency but were continent showed similar activations in the right (and left) insula and dACG to previous reports in older women with urgency incontinence (17).

**Table 1.** *Imaging methods and tools for investigation of brain control of the micturition*

	<b>SPECT (single-photon emission computed tomography)</b>	<b>PET (positron emission tomography)</b>	<b>fMRI (functional magnetic resonance imaging)</b>	<b>NIRS (near-infrared spectroscopy)</b>
<i>How it works</i>	A photon-emitting radioisotope is attached to a ligand which is taken up by brain tissue (often $^{99m}\text{Tc}$ -HMPAO), proportionally to blood flow. Tomographic reconstruction of multiple planar images gives a 3D representation of the distribution of uptake of radiopharmaceutical in the brain at the time of tracer injection.	A positron emitting radioisotope is attached to a ligand which can be metabolized by brain tissue. Positrons annihilate with electrons within 1-2mm to give two gamma rays travelling in opposite directions. Coincident detection of these photons by a circular detector allows reconstruction of a 3D map of blood flow in the brain. Dynamic data may be acquired up to every 30 seconds.	Oxy- and deoxy-Hb in blood have different magnetic properties. Multiple, fast (1-2s), low-resolution MRI scans (usually T1 or T2-weighted, which can detect Hb) allow measurement of the change in concentration of oxy- and deoxy-Hb. This 'blood oxygenation level dependent' (BOLD) signal allows visualization of regional brain activation. Structural MRI images can be made during the same session to allow accurate localization of these areas.	Sources and detectors of at least two wavelengths of near infrared light are positioned around the areas of interest on the head. The intensity of detected light is dependent on the absorptive properties of the tissue between each source-detector pair. The differing properties of oxy- and deoxy-Hb allow monitoring of change in blood flow in that area. Accurate recording of optode position allows mapping of regional activity onto a standard MRI image.
<i>What it measures</i>	Blood flow within the brain	Blood flow within the brain ( $\text{H}_2^{15}\text{O}$ ) or metabolism of glucose ( $^{18}\text{F}$ -FDG)	Blood flow within the brain	Change in oxy- and deoxy-Hb concentration - blood flow
<i>Spatial resolution</i>	Approximately 1cm	Approximately 3-5mm	About 2-3mm	Poor - Approximately equal to source-detector separation
<i>Temporal resolution</i>	Snapshot of brain activity 30-60s after injection	Tens of seconds	Limited by hemodynamic response of ~5 seconds	Good temporal resolution, limited by delay of hemodynamic response
<i>Advantages</i>	Cheap and easily available; can image after the task	Good spatial resolution and localization when used with CT or MRI	Good spatial and temporal resolution; non-invasive, no ionizing radiation	Non-invasive, not physically restrictive, cheap
<i>Disadvantages</i>	Time consuming for a single static scan; radiation dose; physically restrictive; not a dynamic imaging technique	High radiation dose (especially PET/CT); Low temporal resolution; expensive; requires short half-life radioisotopes; physically restrictive	Must repeat stimulus to obtain good signal to noise ratio; physically restrictive	Poor depth penetration (up to 1cm into cortex), poor spatial resolution
<i>Summary</i>	<i>SPECT is readily available and can be used to give a snapshot of brain activity at a particular time, but does not give dynamic information. Due to the static nature of the radiotracer uptake, imaging can be performed after the task – scanner environment does not restrict tasks.</i>	<i>PET provides good localization of regional cerebral blood flow, and can be used to image dynamically during tasks, but has a radiation dose associated with it which is much increased with concurrent CT for localization. Tasks are restricted due to the scanner environment.</i>	<i>fMRI is non-invasive and has no associated radiation dose. Areas of activation are easily registered on structural MRIs taken at the same time. Spatial and temporal resolution are good, but tests must be repeated to get adequate signal to noise ratio, and tasks are restricted by the scanner environment.</i>	<i>NIRS provides an imaging method which is not physically restrictive, improving the number of task that can be performed, at the expense of lower spatial resolution and limited penetration depth. The technique is non-invasive and has no associated ionizing radiation dose.</i>

### **Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy utilizes the differing nuclear magnetic resonance properties of compounds to analytically assess the composition of a sample. This technique can be used *in vivo* to, for instance, assess the metabolites present in a certain brain area during an MRI scan if the correct protocols are available. This is a spectroscopic technique which, in combination with an MRI image, can give more information about the composition of selected voxels.

### **Diffusion Tensor Imaging**

Diffusion tensor imaging uses diffusion-weighted magnetic resonance scans to track the diffusion of water molecules. This allows identification and imaging of neural tracts in the brain. Fractional anisotropy is a measure of the anisotropy of water diffusion within the tissue. This fraction is calculated from the DTI MRI protocol in order to gauge the size, number and direction of tracts within the tissue, and can be used as a measure of white matter myelination.

### **Flair**

Fluid Attenuation Inversion Recovery (FLAIR) MRI sequences can be used to visualize white matter hyperintensities (WMH). WMH are representative of white matter damage due to, for example, demyelination of white matter, increase with age, and are often correlated with the presence of neurological disorders.

### **Bladder symptoms of neurological etiology - neurodegenerative diseases associated with LUTS and DO**

#### **Parkinsonism**

Urinary symptoms occur in up to 70% of patients with Parkinson's disease (PD), mostly nocturia, urgency and frequency. The most common urodynamic abnormality in PD is DO. The precise mechanism of neurogenic bladder dysfunction in PD is poorly understood but may involve dopamine metabolism since acute L-dopa challenge worsens, whereas chronic L-dopa treatment improves, LUTS and DO. Two single-photon emission computerized tomography (SPECT) studies demonstrated that degeneration of nigrostriatal dopaminergic neurons was associated with the presence of LUTS in Parkinson's disease (27, 28). Functional neuroimaging using positron emission tomography (PET) during bladder filing (until DO is provoked) revealed distinct differences in supraspinal activation of PD patients compared to healthy subjects, especially in the pons, ACG, SMA and cerebellum (29).

In addition, subthalamic nucleus deep brain stimulation (STN-DBS) improved bladder dysfunction in patients with PD by delaying the first desire to void and in-

creasing bladder capacity. This was associated with increased regional cerebral blood flow in the ACG and lateral PFC and enhanced modulation of activity in the posterior thalamus and insular cortex by the PAG activity (30, 31).

#### **Frontal lobe lesions**

Imaging studies showed involvement of the PFC in conditions and disease associated with urgency and incontinence, such as stroke, neoplasms, hydrocephalus, subdural hematoma, and frontotemporal lobe degeneration. Urodynamic studies confirm clinical findings by showing detrusor hyperreflexia with lesions in the frontal lobe and basal ganglia, involuntary sphincter relaxation with frontal lobe lesions and DSD in lesions involving the basal ganglia (32). No functional imaging studies specifically addressing brain activity during bladder filling in stroke patients are currently available. There is a PET study in patients with frontotemporal lobar dementia showing that patients with urinary incontinence had hypometabolism in the right premotor/anterior cingulate cortex and the putamen/caudate/insular regions compared to those without urinary symptoms (33).

#### **Spinal cord lesions**

The two most common spinal causes of neurogenic bladder dysfunction are traumatic spinal cord injury and multiple sclerosis. Spinal cord lesions above the lumbosacral levels eliminate voluntary and supraspinal reflex control of voiding, which progresses from an areflexic bladder at first, to development of automatic micturition, DO and DSD.

#### **Spinal cord injury (SCI)**

SCI frequently causes profound alterations of LUT function due to the interruption of efferent and afferent connections with supraspinal neuronal structures. Complete suprasacral SCI results in DO and DSD because the LUT is functioning on the level of sacral reflexes without the regulatory input from the pontine micturition center, which is responsible for synergic micturition. Although there are animal models of spinal cord injury, functional imaging brain studies are rare. One study in patients with incomplete SCI showed diminished brain responses in processing of LUT sensations, which partially improved after a 2-week period of pudendal nerve stimulation (34).

#### **Multiple sclerosis (MS)**

This disease is characterized by focal demyelination of axons and the replacement of the myelin sheaths by scar tissue, forming plaques (lesions) in the white matter of the brain and spinal cord. The prevalence of storage symptoms is up to 80% and may increase with disease progression, together with cognitive involvement.



Lesions in the pons are usually manifested with detrusor hyporeflexia, while cervical lesions correlate with DSD.

Although there are no major functional neuroimaging study regarding MS and LUT function to date, there are some structural imaging studies showing impaired white matter in these patients (35).

### Stress incontinence

Only one brain imaging study is available on stress incontinence today. Functional MRI performed during repetitive contraction of pelvic floor muscles was used to examine the effect of pelvic floor exercises in treating stress incontinence. With successful treatment, responses in the primary motor and somatosensory areas became more focused, while activation in supplementary motor and premotor areas disappeared. Authors suggested that the observed changes were consistent with more skillful performance of the pelvic-floor contraction task and reduced emotional involvement in bladder behavior after successful treatment (e.g. reduced activity in dACG, RI and putamen (36).

## SUMMARY AND RECOMMENDATIONS

CNS role remains important as to better understand the bladder symptoms and pathology. Brain imaging studies in past two decades have advanced our knowledge by providing the neural correlates relevant to bladder control and LUTS. Nevertheless, to bridge the gap with mainstream clinical practice, we must use available and novel methods and create new paradigms to *translate* current knowledge on brain and bladder connecti-

on. For example, we need to apply non-invasive measures of brain activity in clinical settings or during urodynamic exams. Or, for elderly, we need to assess structural brain changes in white (and in grey) matter and further investigate how they could contribute to voiding dysfunction (37).

We also need to attempt standardizing or following certain criteria when doing brain imaging studies in order to generate valid scientific data which would lead to plausible inferences and further improve knowledge on brain activity involved in bladder control. There are several general recommendations (38) made by the imaging community for conducting imaging studies and reporting imaging data which will increase the validity of acquired data: a) defining the study population (uniformly applying strict inclusion and exclusion criteria to ensure homogeneity of the study population and increase statistical power); b) defining the scanning protocol (e.g. design to optimize and not compromise the physiological signal of interest and apply the protocol consistently); c) ensure subjects are well informed of their role (e.g. explain the scanning protocol and check their understanding of tasks they must perform); d) specifying regions of interest in the hypotheses (e.g. wherever possible, analysis should be hypothesis driven or if defined differently, this needs to be explained); and, e) attempt to consistently use an internationally recognized topographic system, such as Talairach or MNI coordinates (Montreal Neurological Institute), to describe regional brain activity. In addition, the data interpretation should be supported by appropriate statistics, paying particular attention to corrections for multiple comparisons.

### List of Abbreviations

ACG	Anterior cingulate gyrus
dACG	Dorsal anterior cingulate gyrus
BOLD	Blood oxygen level dependent
CNS	Central nervous system
dIPFC	Dorsolateral prefrontal cortex
DO	Detrusor overactivity
FLAIR	Fluid attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
LUT	Lower urinary tract
MS	Multiple Sclerosis
OAB	Overactive bladder
PAG	Periaqueductal grey
PD	Parkinson's disease
PET	Positron emission tomography
PFC	Prefrontal cortex
PMC	Pontine micturition center
SCI	Spinal cord injury
SMA	Supplementary motor area
WMH	White matter hyperintensities

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## **CENTRALNI NERVNI SISTEM I MOKRAĆNA BEŠIKA (kratki pregledni članak za kliničare)**

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### **Sažetak**

**Simptomi poremećaja mokraćne bešike značajan su problem sa stanovišta javnog zdravlja zbog njihove učestalosti, morbiditeta i troškova lečenja. Malo se zna o tome da su ovi poremećaji u suštini u vezi sa moždanom kontrolom mokrenja. Napretkom tehnologije moždanog skeniranja i imidžinga, stečena su nova znanja o tome kako mozak funkcioniše u bolestima mokrenja, što je otvorilo nove mogućnosti za razvoj studija problema vezanih za donji urinarni trakt. Zato je neophodno da se i kliničari koji se bave problemima mokrenja informišu o osnovnim principima moždane kontrole mokrenja. Ovaj rad ima za cilj da objedini osnovne činjenice iz neuroanatomije moždane kontrole mokraćne bešike proistekle na osnovu imidžing studija kod bolesnika sa problemima mokrenja.**

***Ključne reči:* mozak, bešika, mokraćna inkontinencija, moždani imidžing**