



**Brain and Bladder  
Workshop 29  
Tuesday 24 August 2010, 09:00 – 12:00**

Time	Time	Topic	Speaker
9:00	9:05	Introduction	Stasa Tadic
9:05	9:30	Lecture 1: CURRENT KNOWLEDGE ABOUT BRAIN-BLADDER NETWORKS BASED ON BRAIN IMAGING STUDIES	Clare Fowler
9:30	9:35	Questions	
9:35	10:00	Lecture 2: BRAIN REGIONS ACTIVATED DURING STORAGE, URGENCY AND DETRUSOR OVERACTIVITY: METHOD AND RESULTS	Derek Griffiths
10:00	10:05	Questions	
10:05	10:30	Lecture 3: NEUROLOGICAL DISORDERS/NEURODEGENERATIVE DISEASES CAUSING LOWER URINARY TRACT DYSFUNCTION AND THEIR IMPACT ON SPINAL AND SUPRASPINAL NEURONAL CONTROL OF THE LOWER URINARY TRACT	Ulrich Mehnert
10:30	10:35	Questions	
10:35	11:05	Break	
11:05	11:25	Lecture 4: ROLE OF THE BRAIN IN GERIATRIC URINARY INCONTINENCE	Stasa Tadic
11:25	11:30	Questions	
11:30	11:55	Lecture 5: ASSESSING CLINICAL IMPROVEMENT AFTER BEHAVIORAL TREATMENT: IS NEUROIMAGING THE MISSING LINK?	Alida Di Gangi-Herms
11:55	12:00	Questions	
		End of workshop	

**Aims and Objectives:**

**Aims:**

1. To review current knowledge about brain-bladder network involved in continence control based on brain imaging studies to date.
2. Provide basic information about use of imaging methods (fMRI and PET), analytical approaches and paradigms (infusion/withdrawal protocol) to study bladder control.
3. Address specific topics:
  - Role of different brain structures in control of continence
  - Brain activity in urgency incontinence
  - Brain aging and bladder control
  - Review of other neurodegenerative diseases manifested with incontinence
  - Value of imaging studies to assess behavioural treatment of incontinence.



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**Objectives:**

1. Interactive discussion of presented material with audience and debating possible strategies for future research or translation/integration of brain imaging research into clinical practice.

**Educational Value:**

The workshop will cover a field of enquiry that is of critical importance for understanding bladder function but is unknown to most health care professionals because it has only recently become accessible to experimentation and observation. This field is the control of bladder and urethra by the brain. Failure of control can result in functional abnormalities of voiding and storage, such as OAB symptoms or urinary retention. The workshop will provide an introduction suitable for those with very little prior knowledge, and will progress to description of recent research findings and their clinical implications.

It is anticipated that following the presentations, in addition to basic information provided about neuroanatomy and methodology, there will be a lively debate about current state of knowledge in the field, future technologies and possible clinical applications.

## CURRENT KNOWLEDGE ABOUT BRAIN-BLADDER NETWORKS BASED ON BRAIN IMAGING STUDIES

Clare J. Fowler

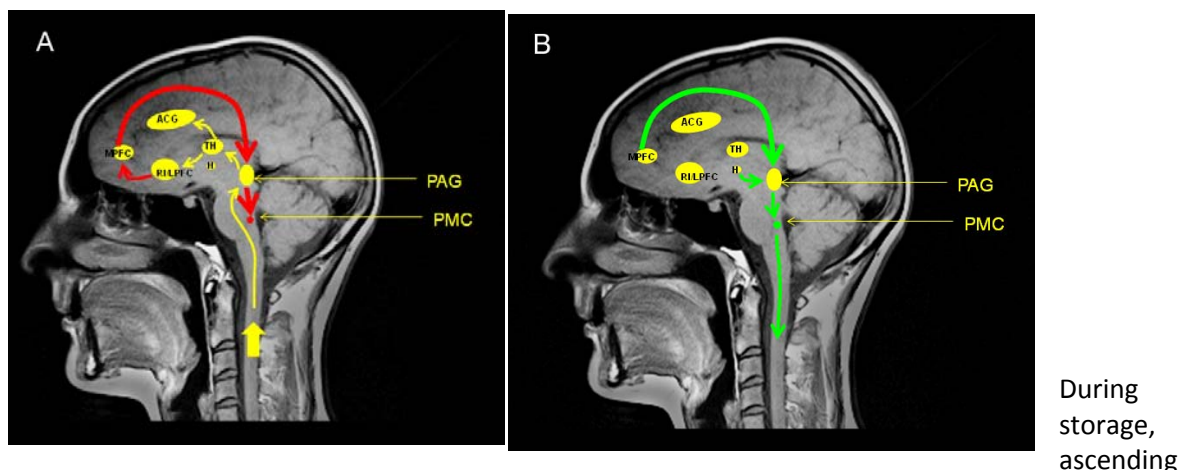
### TOPIC

In recent years, functional brain imaging has emerged as the most powerful technique for studying human brain function. Despite a vast literature which includes studies on many and varied aspects of human behaviour the number of papers reporting original new data relating to brain control of bladder function are quite limited. However those few have transformed our thinking and current theories appear to be converging on the model described below.

### SUMMARY

The earliest functional brain imaging discoveries were made using positron emission tomography (PET) (Blok, Willemsen et al. 1997) which required injection of a radioactive substance that was concentrated in a metabolically active brain region, emitting positrons when it decayed. In due course PET was complemented by functional MRI, which is completely non-invasive but the signal to noise ratio of the technique is low so that repeated captures of the event related data are necessary. For studies of bladder function using fMRI during phases of storage, subjects have been required to do repeated pelvic floor contractions with either full or empty bladder (Zhang, Reitz et al. 2005) (Kultz-Buschbeck, van der Horst et al. 2005) (Seseke, Baudewig et al. 2006), or had alternating bladder infusions and fluid removal via a catheter (Griffiths, Derbyshire et al. 2005). Voiding studies were performed with PET (Blok, Willemsen et al. 1997), but it has not been possible to study voiding with fMRI.

The figures below show a preliminary working model of brain control of the lower urinary tract during storage (A) and voiding (B).



afferents (yellow) synapse on the midbrain periaqueductal grey (PAG) and are relayed via the hypothalamus (H) and thalamus (TH) to the dorsal anterior cingulate cortex (ACC) and to the right insula (RI) and to the lateral prefrontal cortex (LPFC); in the storage phase they pass to the medial prefrontal cortex (MPFC, red arrow) where the decision to void or not maybe made. In this phase the decision is not to void, and this situation is maintained by chronic inhibition of the PAG via a long pathway (red arrows) from the MPFC. Tonically maintained inhibition of the pontine micturition centre (PMC) suppresses voiding during the storage phase.

B: When the decision to void is made, the MPFC relaxes its inhibition of the PAG (green arrow) and also the hypothalamus (H) provides a 'safe' signal. Consequently the PAG excites the PMC which in turn sends descending motor output (green arrow) to the sacral spinal cord that ultimately relaxes the urethral sphincter and contracts the detrusor, so that voiding occurs. Voiding is continued to completion by continuing afferent input, probably to the PAG. (Figure from (Fowler and Griffiths 2010))

The crucial role of the frontal regions in the control of the bladder is apparent from this model and further data relevant to that concept continues to emerge. Recent functional imaging studies in the elderly which examined white matter abnormalities in the tracts connecting these regions to other bladder controlling circuits have produced very interesting results (Tadic, Griffiths et al. 2010) and the possibility of visualising frontal activity on bladder filling through Near Infrared Spectroscopy holds considerable potential (Matsumoto, Ishikawa et al. 2009).

A technique for functional brain imaging in response to bladder filling in an animal model has very important experimental possibilities (Tai, Wang et al. 2009).

## CONCLUSIONS

Although there is now some general agreement about the proposed model for brain-bladder control, the ideas behind it will undoubtedly undergo changes and refinements in the future as new data emerges. Exciting studies of pathophysiological conditions based on current understanding are now beginning to appear. The techniques for functional brain imaging are likely to lead to an avalanche of new information about lower urinary tract function and dysfunction, new methods of assessment and treatment.

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## **BRAIN REGIONS ACTIVATED DURING STORAGE, URGENCY AND DETRUSOR OVERACTIVITY: METHOD AND RESULTS**

Derek Griffiths

**TOPIC:** To describe our method for studying brain/bladder control, our main findings, and the model – similar to Dr Fowler’s – that they suggest.

**INTRODUCTION:** In Pittsburgh we have studied the storage phase in normal and urge- or urgency-incontinent women, using fMRI. Images like Fig. 2 below usually show results from a small group of subjects, in which the variations from person to person are averaged out. Because the shape of individual brains varies, it has to be normalized to a standard shape. This standard brain also forms the anatomical background in pictures like Fig 2, while the colored blobs indicate where in the brain the fMRI signal is significantly different (from zero, or from some other situation). The size of the blobs, and even whether you see them at all, depend on the significance level (P-value) chosen, so the spatial resolution is not as good as the pictures suggest.

**PITTSBURGH METHODS:** To mimic urine storage (bladder filling) we use repetitive infusion and withdrawal of liquid in and out of bladder. The response to infusion (= filling) is taken to be the difference in fMRI signal corresponding to infusion minus withdrawal. The sequence pause-infuse-pause-withdraw is repeated 4 times and this whole sequence is itself repeated (see Figure 1). Because more liquid is infused than is withdrawn (and because of urine production) the mean volume in the bladder gradually increases, avoiding accommodation to the stimulus.

To avoid the strong magnetic field near the scanner the urodynamic equipment stands in an adjoining room. Two 10-m long stiff-walled tubes pass through the wall into the scanner room, one for filling/infusion/withdrawal and the other for bladder pressure measurement. This tubing (filled with water) can transmit a cough without noticeable smoothing or delay. The pause-infuse-pause-withdraw cycle is produced by a pump controlled by the scanner. From the variations in the pressure at the pump the periods of infusion and withdrawal can be identified on the urodynamic traces and synchronized with the scanner. The subject has a pushbutton to signal strong desire to void or urgency.

**FINDINGS:** We have investigated brain responses in many different situations and types of subject: normal women, older women, women with urge incontinence (with or without detrusor overactivity), relation to white matter damage in the brain, relation to daily life (bladder diaries, symptoms), effect of successful incontinence treatment, women in retention (with Dr Fowler’s group) and effect of neuromodulation.

The normal response to bladder infusion is the pattern of activations and deactivations shown in Fig. 2. In urge-incontinent subjects the responses are rather similar but exaggerated. A similar pattern is observed with other organ systems (cardiovascular, gut). In the light of the measurements, theoretical insights, and discussions, we have refined successive models of how brain/bladder control works. The current version (Fig. 3) consists of several neural circuits that answer different questions about the desirability of voiding and respond with appropriate motor output and sensation: Is the bladder full enough for voiding (brainstem)? Is voiding safe (limbic)? Is voiding socially appropriate (cortical)? The brainstem/midbrain circuit is part of the voiding reflex: when the reflex is triggered, voiding occurs. The limbic and cortical circuits suppress the voiding reflex unless voiding is safe and acceptable: during the storage phase, when fluid is infused into the bladder, they are activated so as to prevent triggering of the reflex.

In women with urge incontinence these suppressive circuits are abnormally strongly activated, suggesting that they represent a coping reaction to the threat of imminent leakage but are not the cause of the problem. In incontinent women with white-matter damage, increasing damage leads to increasing suppressive reaction, suggesting that white-matter damage is one possible cause of urge incontinence. Damage to the white-matter tract that carries cortical circuit 3P appears particularly likely to cause incontinence.

If detrusor overactivity occurs (i.e. control of the bladder is lost) it appears that these control mechanisms are switched off and many of the activations and deactivations characteristic of storage disappear. We are currently examining this situation and hope to report further in the workshop.

The cortical circuits 3P and 3S appear to be the origins of 2 different pathways that ultimately form the parasympathetic and sympathetic efferent innervation of the lower urinary tract. This postulate links brain imaging with the well-known peripheral innervation.

**CONCLUSIONS:** This simple infusion-withdrawal protocol combined with fMRI leads to understanding of how the brain maintains control during the storage phase, what happens when control is lost (detrusor overactivity), and even a possible cause of urge incontinence.

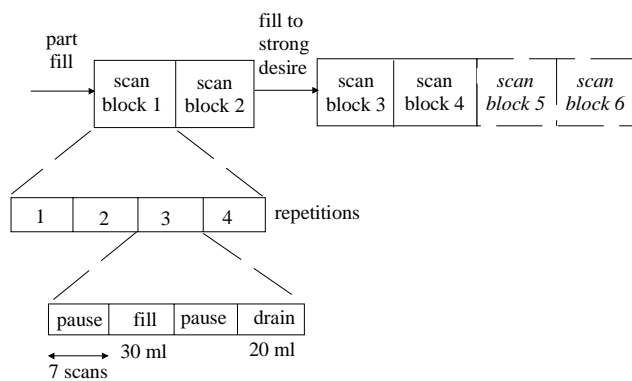


Fig. 1. Protocol for fMRI observations of brain/bladder control. Whole-brain scans were made at one per 1.5 s, so 7 scans occupy 10.5 s. More recently each pause, fill (= infusion) and drain period was lengthened to 12 s (6 scans at one per 2 s) and the fill (infusion) volume was reduced to 22 ml.

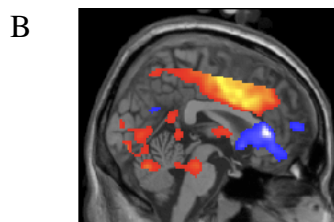
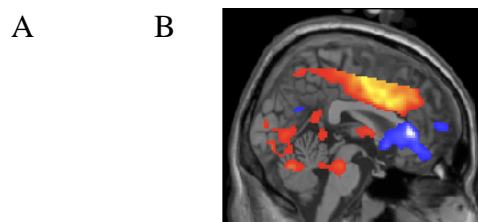
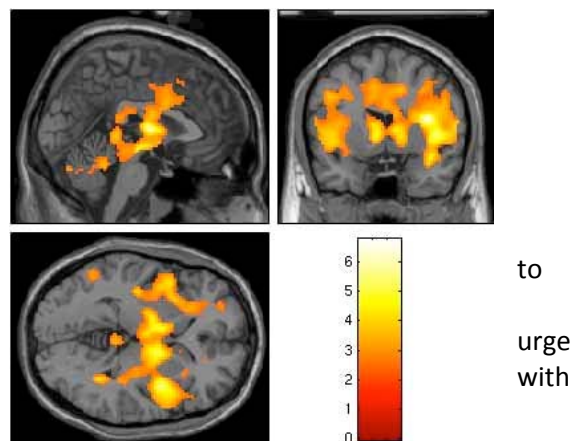


Fig. 2. A. Normal pattern of responses (activations) infusion causing strong sensation, shown in sagittal, coronal and axial sections. B. Responses in incontinence, with strong sensation (urgency?) but no detrusor overactivity: activation in orange, deactivation in blue; shown in sagittal section.



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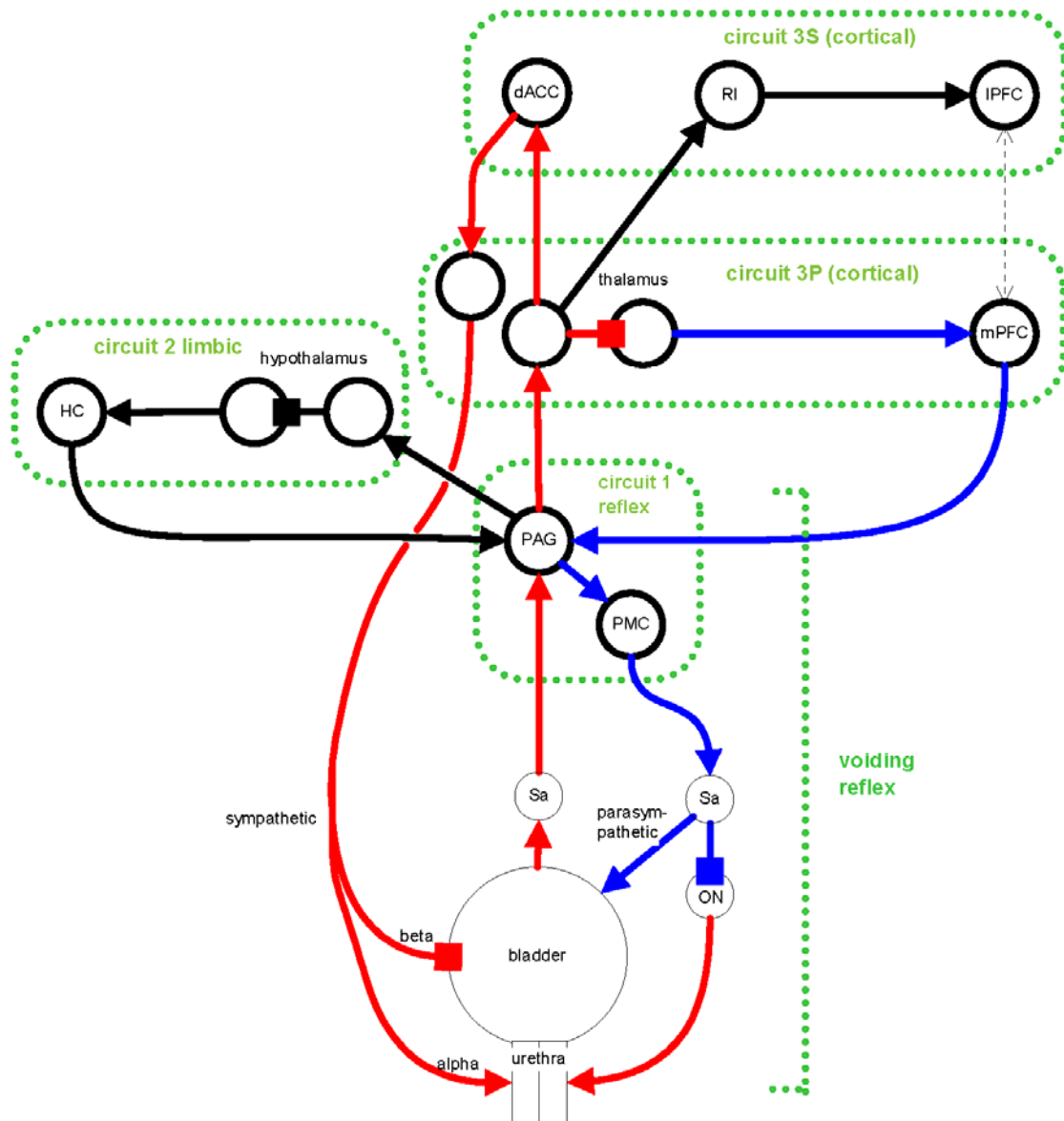


Fig. 3. Model of bladder control system showing voiding reflex and postulated neural circuits 1 (brainstem, reflex), 2 (limbic, emotional) and 3P and 3S (cortical, social). Bladder filling excites afferents that activate the midbrain (PAG). A signal to the thalamus (red) activates insula (RI), representing sensation. A signal to dACC (red) generates urgency and a motor output that inhibits bladder via its sympathetic innervation. Inhibitory interneurons in thalamus (red square) deactivate medial prefrontal cortex (blue) and suppress voiding reflex at PAG. (This blue pathway appears especially susceptible to white-matter damage in old age.) A similar negative feedback loop operates via circuit 2.

# NEUROLOGICAL DISORDERS / NEURODEGENERATIVE DISEASES CAUSING LOWER URINARY TRACT DYSFUNCTION AND THEIR IMPACT ON SPINAL AND SUPRASPINAL NEURONAL CONTROL OF THE LOWER URINARY TRACT.

Ulrich Mehnert

## INTRODUCTION

The human lower urinary tract (LUT) has two functions: 1) low pressure continent storage of urine and 2) periodically, self determined and more or less complete release of the stored urine.

For a proper execution of those functions, the LUT structures (bladder, bladder neck, urethra and urethral sphincter) rely on an intact neuronal innervation that is under control of a complex supraspinal network. The dependence of the LUT functions on the complex central neuronal circuits makes it unique in comparison to other visceral functions (e.g. gastrointestinal tract, cardiovascular system) but also more vulnerable to neurological disorders.

This talk will summarize the characteristics, possible pathomechanisms and the impact on supraspinal LUT control of four neurological disorders frequently associated with LUT dysfunction.

### 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 usually results in detrusor overactivity (DO) and detrusor-sphincter-dyssynergia (DSD) because the LUT is solely functioning on the level of sacral reflexes without the regulatory input from the pontine micturition center, responsible for a synergic micturition. Depending on lesion level and completeness of the SCI, different forms of bladder and sphincter dysfunctions can result.

SCI has been a pathophysiological role model for understanding and explaining the neuronal LUT control. One functional neuroimaging study is available investigating LUT function in incomplete SCI patients, demonstrating diminished and altered supraspinal processing of LUT sensations that partially improves and normalizes after a 2-week period of pudendal nerve stimulation [1].

### Stroke / Cerebrovascular accident

The prevalence of LUT symptoms (LUTS) and incontinence in stroke patients is high: ~ 94% and 38-60% respectively [2,3].

Storage symptoms like nocturia, urgency and frequency are common [3] as well as DO on urodynamic study [4], but detrusor underactivity can also be observed. DSD is much less common than in SCI since pontine micturition center and its spinal connections usually remain intact. However, lesions of the basal ganglia in stroke patients have been associated with DSD [5].

The reason of LUT dysfunction in stroke patients is, most likely, the loss of suprapontine inhibition. Lesions of the frontal and frontoparietal lobes, in particular, have been associated with LUT dysfunction after stroke [6]. Nevertheless, a significant correlation between the site of lesion and type of LUT dysfunction could not be established [2,7,8]. Stroke size seems to be more important than stroke site, with the exception of the occipital lobe, which seems to be unrelated to LUT dysfunction [6]. Urinary incontinence is a prognostic marker for stroke severity due to its association with death and disability [6]. However, age, pre-stroke LUTS, mobility and communication can be confounding factors when relating urinary incontinence to the stroke itself.

No functional neuroimaging study in stroke patients investigating the supraspinal correlates of LUT dysfunction in these patients is currently available.



### Parkinson's disease (PD)

The prevalence of LUTS in patients with PD ranges from 27-64% [9]. Like in stroke, storage symptoms are most prevalent (60% nocturia, 33-54% urgency, 16-36% frequency). However, it often remains very difficult to distinguish how much PD contributed to LUTS in addition to age, stress incontinence and prostate related symptoms.

Urodynamically, the most common finding is DO (45-93%) combined with involuntary sphincter relaxation (33%). DSD is rare but impaired contractile detrusor function during voiding (despite DO) might resemble obstruction [10].

LUT dysfunction seems to correlate with neurological disability and stage of PD, suggesting a relationship between dopaminergic degeneration and LUT dysfunction [11,12]. Two single-photon emission computerized tomography (SPECT) studies demonstrated that degeneration of nigrostriatal dopaminergic neurons was associated with the presence of LUTS [13,14].

Primary function of the basal ganglia on the supraspinal network controlling LUT is inhibitory and it is maintained by the direct dopamine D1-GABAergic pathway, which is usually activated by neuronal activity of nigrostriatal dopaminergic fibers and subsequent striatal dopamine release. The D1-GABAergic pathway inhibits basal ganglia output nuclei (e.g. internal globus pallidus) and, probably, PMC. Thus, a reduced inhibition of basal ganglia output nuclei and PMC due to a lack of dopaminergic neurons in the substantia nigra and subsequently a diminished D1-GABAergic pathway, might explain the origin of urgency and DO in PD [15]. This is supported by the fact that subcutaneous administration of a dopamine D1, but not D2 agonist, inhibited the micturition reflex in monkeys [16]. Nevertheless, the exact mechanism inducing DO in PD remains only partly understood.

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 pons, anterior cingulate gyrus, supplementary motor area and cerebellum [17].

Two other PET studies investigated the effect of subthalamic nucleus deep brain stimulation (STN-DBS) on supraspinal LUT control, demonstrating an amelioration of LUT sensory processing with normalization of activation in the lateral frontal cortex and anterior cingulate gyrus [18]. In addition, STN-DBS seems to improve sensory gating and discrimination of different body states (e.g. gradual bladder filling) in terms of activation in periaqueductal gray, thalamus and insula with STN-DBS "on" compared to no activation with STN-DBS "off" [19]. These neuroimaging findings correspond well with the reports of urodynamical studies, showing the beneficial effect of STN-DBS on LUT function in patients with PD [20,21].

### Multiple sclerosis (MS)

Prevalence of storage symptoms in MS patients ranges between 37-99% and 34-79% for micturition symptoms with a high rate of mixed symptom presentation (55%) [22]. Clinical symptoms are highly variable due to different extents in severity and localization of lesions, cognitive involvement, and state of disease progression. In general, there is little correlation between clinical symptoms and urodynamic findings. The clinical presentation of LUT dysfunction is variable over time but there seems to be a correlation between duration of MS and presence and severity of LUT dysfunction [22].

The underlying cause for LUT dysfunction in MS – as for any other neurological symptom in MS – is the 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.

Pontine lesions seem to be significantly correlated with detrusor hyporeflexia and cervical lesions are significantly correlated with DSD [23]. However, no correlation between site of lesion and urodynamic parameters could be observed.

No functional neuroimaging study regarding MS and LUT function is currently available.

## CONCLUSION

Neurological disorders easily disturb the central neuronal circuits responsible for LUT function and, thus, frequently cause LUT dysfunction manifested as urinary incontinence, retention, DSD and DO. Functional neuroimaging studies are useful tool for further investigation of LUT dysfunction and may reveal details about the underlying neurological mechanism. Yet there are only few functional neuroimaging studies available in patients with neurological diseases. Further studies utilizing functional neuroimaging are needed as to help improve our understanding of the role of the different supraspinal areas involved in LUT control in neurological disorders.

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## ROLE OF THE BRAIN IN GERIATRIC URINARY INCONTINENCE

Stasa D. Tadic

### TOPIC

Prevalence of urinary incontinence increases with age and becomes morbid and costly public problem.

Epidemiologic and cross-sectional studies link age-related structural changes in the brain's white matter (current synonyms: white matter hyperintensities – WMH or age-related white matter changes – ARWMC) with urgency and urinary incontinence.<sup>1,2</sup>

More information how white matter damage (WMH) affects brain-bladder control network is lacking.

Using novel methods to assess the extent of WMH coupled with functional magnetic resonance imaging (fMRI) may reveal potential mechanism of the role of WMH in geriatric urinary incontinence.

### SUMMARY

**Methods:** To study relation between age-related white matter changes and brain-bladder control we combine 2 methods: **a)** *Fully automated method for quantifying and localizing white matter hyperintensities* on MR images<sup>3</sup> and, **b)** *functional MRI with simultaneous urodynamic study*<sup>4</sup> to monitor brain response to bladder filling during self-reported urgency in the scanner. We use correlation/regression analyses in *Statistical Parametric Mapping program* (SPM5) to ascertain how the increase in WMH affects functional brain activity during urgency.

**a)** *Fully automated method for quantifying and localizing white matter hyperintensities* on MR images<sup>3</sup> uses fast-FLAIR images (fast **FL**uid-**A**ttenuated **I**nversion **R**ecovery) obtained on a 3 T scanner to apply a 'fuzzy-connected algorithm' to segment the WMH, and the 'Automated Labeling Pathway (ALP) to localize the WMH into the anatomical space. The method features an advanced WMH segmentation by allowing different threshold for each WMH cluster; objective automatic identification of WMH seeds and fully deformable registration combined with the piecewise linear registration for coarse alignment with Demons algorithm for accurate WMH localization on the white matter atlas. Additionally, the method allows for assessment of WMH burden region-wise.

**b)** Our experimental *paradigm*<sup>4</sup> utilizes fMRI block-design to measure brain activity during cycles of bladder filling and emptying during self-reported urgency in order to study voiding *storage* function and changes in brain-bladder control network.

**Results:** We conducted a study<sup>5</sup> of 25 women aged > 65 years (avg 71.5 years) with moderate to severe urge predominant urinary incontinence (avg 2.5 urge incontinence episodes/daytime). For each subject we recorded functional brain responses to bladder filling during self-reported urgency and obtained the readings of the extent of WMH globally and in each of 10 white matter pathways, on both sides of the brain (20 pathways total). In addition, we did a factor analysis of the WMH distribution that showed 2 distinct patterns: pathways with high WMH burden (anterior thalamic radiation-ATR, left and right) and those with low burden (entire superior longitudinal fasciculus and its branch to the temporal lobe (SLFB/SLFT, on the right side). Using SPM, we, then, correlated the increase in WMH burden in these different pathways with functional brain responses to bladder filling during self-reported urgency.

## Major findings:<sup>5</sup>

1. The global increase in WMH burden correlated significantly with brain activity during self-reported urgency:
  - a. Positively, in regions of dorsal anterior cingulate gyrus (ACG), supplemental motor area (SMA), brain stem (pontine micturition center-PMC and periaqueductal gray-PAG) and parts of cerebellum (**Figure 1.A**).
  - b. Negatively, in regions of pregenual ACG adjacent to orbitofrontal cortex, precuneus, caudate and lingual gyrus (**Figure 1.A**).
2. Relation between pathways with high and low WMH burden and functional brain responses differs:
  - a. Increase in WMH in anterior thalamic radiation (ATR) had relation to functional brain responses similar to global WMH burden.
  - b. Increase in WMH in superior longitudinal fasciculus (SLF) pathway correlated negatively with activity in ACG, medial frontal gyrus, parietal lobe and inferior frontal gyrus.

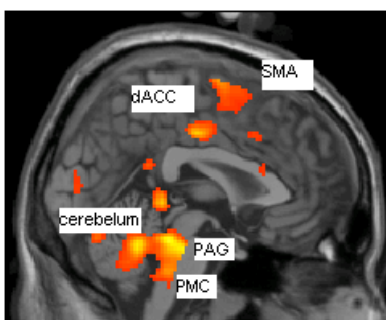


Figure 1.A

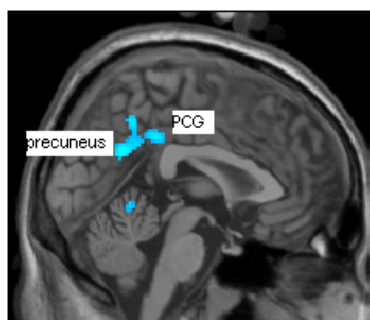


Figure 1.B

## CONCLUSIONS

Increase in age-related white matter changes, either globally or in specific pathways correlates significantly brain activity during bladder filling and self-reported urgency.

Brain regions associated with changes in WMH burden are part of the network involved in regulating bladder storage function and continence control.

The mechanism of how WMH (e.g. global white matter burden) affect functional brain activity that regulates continence is unknown but likely involves the effect of structural changes in specific white matter pathways (e.g. ATR) on functional connections between key centers involved in continence control (**Figure 2**).

Multi-modal approach combining brain structural changes and functional brain responses during experimental paradigms that mimic bladder function may offer the mechanism to explain the role of structural brain changes as a contributing factor to impaired continence control in elderly.

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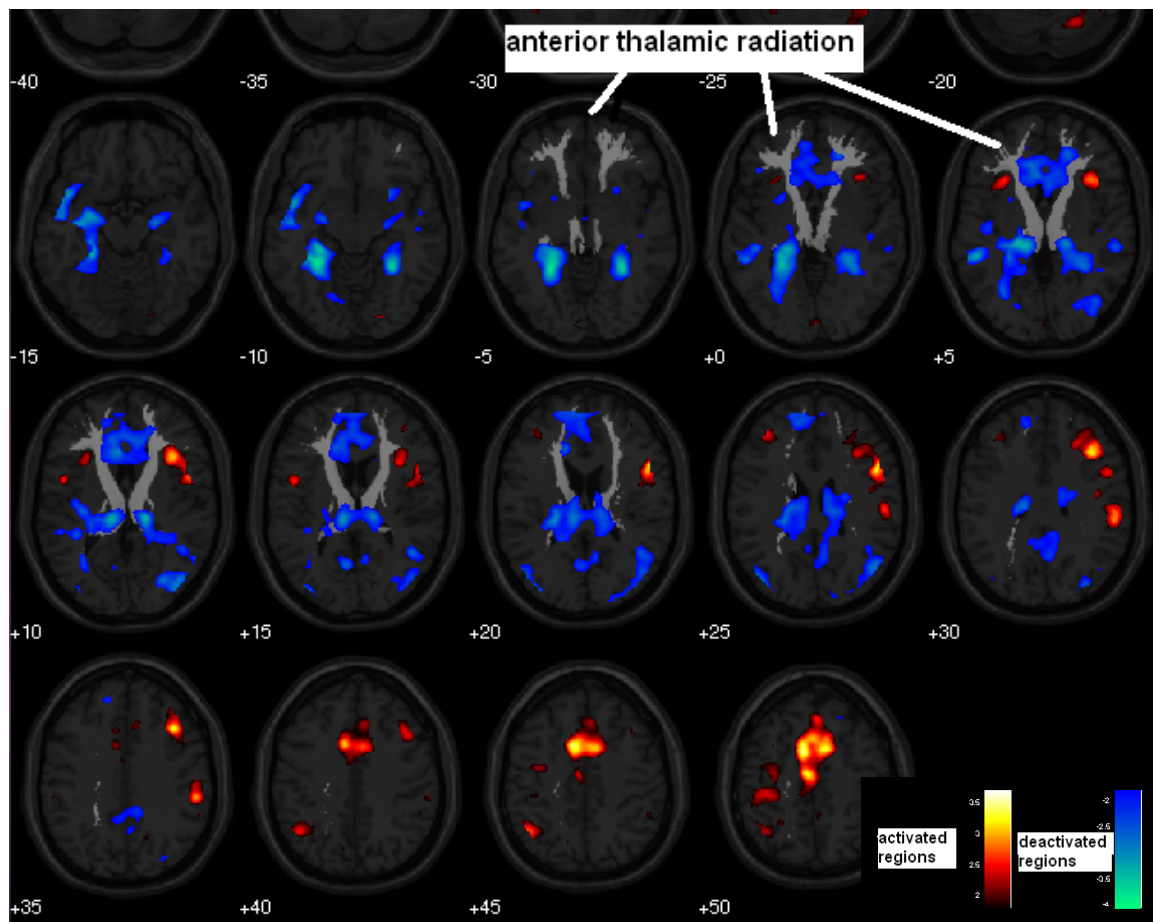


Figure 2. Anatomic projections of ATR on functional brain activity (also see reference 5).

## **ASSESSING CLINICAL IMPROVEMENT AFTER BEHAVIORAL TREATMENT: IS NEUROIMAGING THE MISSING LINK?**

Alida M.R. Di Gangi Herms

### **INTRODUCTION**

Behavioral treatment aims at improving bladder control by changing the incontinent patient's behavior, especially their voiding habits, and by teaching skills for preventing urine loss<sup>1</sup>. It has indeed limitations: despite significant reduction in the frequency of incontinent episodes, most patients are not completely dry and its effectiveness greatly relies on the cooperation and active participation of an involved and motivated patient while onset of clinical improvement depends on adherence to a consistent daily regimen. Moreover only limited data are available that adequately assess the outcomes of these treatments<sup>2</sup>. Comparison of these data is difficult because there is no consistency in the selection and reporting of outcome measures. For example, for pelvic floor muscle training (PFMT) there seems to be no consistency in programmes used in clinical practice<sup>2</sup>.

### **MAJOR QUESTIONS IN BEHAVIORAL TREATMENT OF URINARY INCONTINENCE**

The therapeutic change produced by behavioral treatment can be hypothetically attributed to two different processes<sup>1</sup>:

1. The training enhances bladder or pelvic floor function. In this perspective, clinical improvement means "restoring" those mechanisms observed in healthy subjects.
2. The training leads to acquisition of behavioral skills, which the patient actively utilizes in order to avoid incontinence episodes. In this perspective clinical improvement means in a wider sense "rearranging" the mechanisms involved in continence.

Regardless the type of incontinence they address, behavioral training protocols share the acquisition of some general skills:

1. Patients learn to pay more attention to visceral sensation, in order to intervene earlier with specific strategies;
2. Patients learn to voluntary control their pelvic floor muscle in order to suppress urge or to avoid leaking urine;
3. Patients learn to modulate their emotional response to leaking, eventually suppressing the fear of leaking urine.

The acquisition of skills mentioned above could probably imply a modification in the activity of the network of suprapontine structures involved in continence control, especially the function of frontal lobes.

### **URGE INCONTINENCE (UI): BEHAVIORAL TREATMENT AND ITS POSSIBLE EFFECTS ON SUPRAPONTINE CONTROL**

The most important behavioral approaches for the treatment of urge incontinence are bladder drill and bladder training. The therapeutic change produced by this approaches can be explained in terms of restoring bladder function or rearranging it. From a "restoring" perspective, patients are instructed to gradually increase the time interval between voids, basing on the premise that frequent urination is a precipitant of detrusor instability. On the other hand, behavioral training of UI can also be seen as a skill acquisition therapy: from this perspective patients acquire new skills helping them to reach a better control of urgency episodes e.g. contracting pelvic floor muscles to suppress urge.

In general, successful behavioral training probably helps patients to pay attention more frequently to visceral sensation and to differentiate it from genuine urge, probably enhancing frontal activity which could finally lead to a modulation of the exaggerated overall activity of the network controlling continence. Basing on the "bladder control matrix"<sup>3</sup> cited elsewhere we can hence

postulate that successful behavioral training for UI may improve the inhibiting function of the medial prefrontal cortex (MPFC) on the periaqueductal gray (PAG) consequently suppressing the pontine micturition center (PMC) and preventing voiding.

### ***STRESS INCONTINENCE (SI): BEHAVIORAL TREATMENT AND ITS POSSIBLE EFFECTS ON SUPRAPONTINE CONTROL***

Behavioral treatment of SI principally consists of pelvic floor muscle training (PFMT) utilizing biofeedback to help patients identify the pelvic floor muscles and exercise them properly. Similarly to UI, the mechanism leading to clinical improvement can be seen as restoring the pelvic floor support function or alternatively as skill acquisition. In particular patients learn in the first place a new motor skill i.e. learning to strain the pelvic floor muscle (PFM) in specific situations.

This aspects are reflected in changes in brain activation patterns<sup>4</sup>. A more focused (and therefore more „economic“) activation in the primary motor and somatosensory areas can be observed after behavioral treatment, probably representing more effective voluntary control of the pelvic floor muscle. A smaller Insula activation after training may indicate a clearer dissociation of holding from voiding and therefore the fact that patients learn to contract the PFM only in particular situations. Finally the activation of rostral ACC during pelvic floor contraction may suggest the involvement of affective components, while a reduction of the emotional response to incontinence episodes may be reflected in a reduction of ACC activation after treatment.

### ***CAN NEUROIMAGING BE A TOOL TO EVALUATE CLINICAL IMPROVEMENT AFTER BEHAVIORAL TREATMENT OF URINARY INCONTINENCE?***

Basing on the experimental evidence a possible paradigm to evaluate clinical improvement after behavioral treatment via neuroimaging should not necessarily focus on number of incontinence episodes or patient's satisfaction but rather on the skills acquired after training and how and to which extent these skills influence or are reflected by brain dynamics:

1. Is the patient able to pay more attention to visceral sensation and to differentiate urge from other feelings? We expect that successful training should lead to an enhancement of frontal function and a reduction of Insula activation.
2. Has the patient's ability to voluntary control the PFM in order either to prevent leakage or to suppress urge improved? A more focused activity of MI and SMA should be evident after successful behavioral training.
3. Is the patient capable to better modulate his or her emotive response to urge and fear of leakage? A successful training in this respect should be reflected by a decrease in ACC activation.

On the other hand the fact that urinary incontinence may occur in ageing patients, patients who already suffer from other degenerative diseases or patients with chronicized forms of urinary incontinence, complicates the imaging results which could be expected. Therefore a major question to be considered would be to which extent brain plasticity processes have been occurring, probably interfering with the activity of those suprapontine structures responsible for clinical improvement. This leads to some important parameters which have to be evaluated:

1. How old is the patient?
2. How long has he or she been suffering from urinary incontinence?
3. Has been the onset abrupt (i.e. through a trauma) or insidious?
4. Has the patient developed naïve strategies to cope with incontinence episodes?
5. Does the patient suffer from other cerebral degenerative conditions such as Parkinson's disease, Alzheimer's disease or Multiple Sclerosis?

### ***PERSPECTIVES***

Over the last decade neuroimaging techniques have been used in order to gather data about brain responses related to different aspects of urinary function; most notably the question about the



emerging of bladder sensation and urge has been successfully addressed with the data being arranged in a working model. The future challenges in this respect will be at least two:

1. To further develop the working model into a theory describing the central control of continence and the emergence of pathologies;
2. To adapt neuroimaging techniques in order to make them suitable to better quantify clinical improvement especially after conservative (behavioral) treatment of incontinence. In this respect the parameters defining clinical improvement should shift from the idea that treatment implies “restoring” functions to the idea that successful treatment means the acquisition and the successful utilization of new skills. As a consequence, the measurement of clinical improvement should include not only subjective and objective measures but also changes in patterns of brain activation.

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