Brain and Bladder

W4, 29 August 2011 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:05	Introduction	• Stasa Tadic
09:05	09:30	CURRENT KNOWLEDGE ABOUT BRAIN- BLADDER NETWORKS BASED ON BRAIN IMAGING STUDIES	• Stasa Tadic
09:30	09:35	Questions	All
09:35	10:00	BRAIN REGIONS ACTIVATED DURING STORAGE, URGENCY AND DETRUSOR OVERACTIVITY: METHOD AND RESULTS	• Derek Griffiths
10:00	10:05	Questions	All
10:05	10:25	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
10:25	10:30	Questions	All
10:30	11:00	Break	None
11:00	11:25	ROLE OF THE BRAIN IN GERIATRIC URINARY INCONTINENCE	• Stasa Tadic
11:25	11:30	Questions	All
11:30	11:55	ASSESSING CLINICAL IMPROVEMENT AFTER BEHAVIORAL TREATMENT: IS NEUROIMAGING THE MISSING LINK?	• Alida DiGangi-Herms
11:55	12:00	Questions	All
12:00	12:00	End of workshop	None

Aims of course/workshop

AIMS

1. To review current knowledge about brain-bladder control network 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 during urgency and role of aging in bladder control
- Neurodegenerative diseases and incontinence
- Brain imaging and behavioral treatment of incontinence.

OBJECTIVES

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

Educational Objectives

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.

BRAIN CONTROL OF THE BLADDER DURING STORAGE: FUNCTIONAL ANATOMY AND PHYSIOLOGY AND METHODOLOGICAL APPROACH: POSSIBILITY OF TRANSLATION INTO CLINICAL PRACTICE

Derek Griffiths

TOPIC: To describe our method for studying brain/bladder control, our main findings, and the model that they suggest; and to discuss potential clinical utility

INTRODUCTION:

The earliest functional brain imaging discoveries related to the bladder were made using positron emission tomography (PET) [Blok et al 1997], which requires injection of a radioactive substance that is concentrated in metabolically active regions. More recently it has been complemented by functional MRI (fMRI), which is non-invasive but has a low signal to noise ratio so that multiple captures and averaging of event-related data are necessary. Subjects have therefore been required to perform (during scanning) repeated pelvic floor contractions or have had alternating bladder infusions and fluid withdrawal via a catheter. It has not yet been possible to study actual voiding with fMRI, although imagined voiding has been investigated [Kuhtz-Buschbeck et al 2005], and Blok et al performed voiding studies with PET. These observations (supplemented by studies of neuroanatomy and other organ systems) have led to a functional model of the bladder control system, which we will update in this workshop. A good model may suggest potential clinically useful interventions.

In Pittsburgh we have studied the storage phase in normal and urgency-incontinent women, using fMRI [Griffiths & Tadic 2008]. Images like Fig. 1 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, each one has to be normalized to a standard shape. This standard brain also forms the anatomical background in pictures like Fig. 1, 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 position of the blobs is not as definite as the pictures suggest.

PITTSBURGH METHODS: To mimic urine storage (bladder filling) we use repetitive infusion and withdrawal of liquid in and out of the bladder. The response to 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 several times. Thus when we speak of 'activation' we mean the brain response to infusion minus withdrawal, averaged over multiple repetitions and over a small number (10 to 20) of subjects.

To avoid the strong magnetic field of the scanner the urodynamic equipment stands in an adjoining room, connected by 2 long, stiff-walled, water-filled tubes to catheters in the subject's bladder, one for filling/infusion/withdrawal and the other for bladder pressure measurement. 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 (which usually occurs during or just after infusion), and voice communication is possible outside scanning periods.

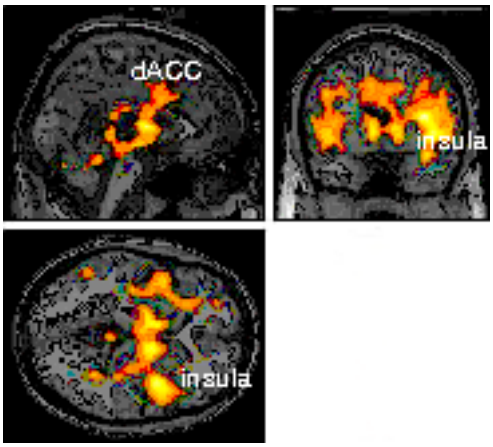

Fig. 1. Normal subjects. Activated regions (left) and deactivations (in blue, right).
dACC = dorsal anterior cingulate cortex (barely activated in normals).

FINDINGS: We have investigated brain responses in many different situations and types of subject, but in this talk I want to concentrate on normal, mostly older, women, with occasional reference to findings in urge incontinence.

The normal response to bladder infusion is the pattern of activations and deactivations shown in Fig. 1. One clearly activated region is near the insula, bilaterally though slightly stronger on the right side. In urgency-incontinent subjects the responses are rather similar but stronger, especially in a complex that includes the dorsal anterior cingulate cortex (dACC) and the supplementary motor area (SMA). There is also **deactivation** of some areas (ventromedial prefrontal cortex and some subcortical structures, see Fig. 1 right).

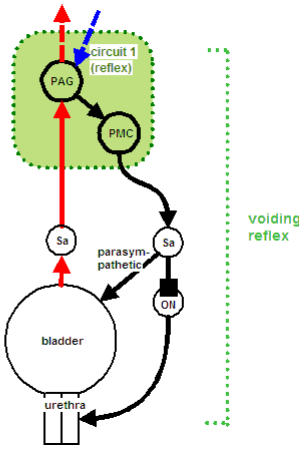

Fig. 2. Voiding reflex, midbrain output to higher regions (dashed red arrow), and return signal suppressing voiding (dashed blue arrow).
PAG = periaqueductal gray, PMC = pontine micturition center, Sa = sacral cord, ON= Onuf's nucleus.

To understand the meaning of these observations we need a model that goes beyond a simple summary of activated regions and shows how they are interconnected, what their function is, and how voiding (an activity essential for homeostasis) is controlled. According to current ideas (Fig.2) [Fowler et al 2008], the bladder and sphincter are governed primarily by the voiding reflex, which ensures that, if the afferent signals arriving in the midbrain from the bladder (continuous red arrows) reach a certain trigger level, the urethra relaxes, the detrusor contracts, and voiding occurs (black arrows). Of course, if this reflex operated in isolation homeostasis would certainly be maintained – the bladder would be emptied reflexly, without sensation, whenever it became full – but this would be a situation of total incontinence. In reality, the control system has to ensure that the bladder is emptied regularly, yet only when appropriate. To this end a midbrain region (the periaqueductal gray (PAG, the cranial terminus of the voiding reflex) passes afferent signals to higher parts of the brain (dashed red arrow), where they give rise to the familiar bladder sensations of desire to void and urgency that motivate us to go to

the bathroom or toilet. These sensations are accompanied by corresponding motor output that maintains continence by allowing the reflex to be triggered only if voiding is consciously judged appropriate. Thus the net effect of the motor output from higher brain regions (dashed blue arrow) is to tonically suppress the voiding reflex (probably via the PAG) except for those brief periods when we wish it to occur. When voiding is desired and appropriate the PAG is activated and excites the pontine micturition center (PMC), triggering the voiding reflex.

How does the control system assess whether voiding is appropriate? The decision to void or not depends on the answers to questions concerning voiding and homeostasis, such as:
(1) Is voiding mechanically appropriate? I.e. is the bladder full enough? This is answered by the voiding reflex itself, which can be triggered only if bladder afferents (i.e. bladder volume) are adequate. Midbrain (PAG) and brainstem (PMC) regions are involved.
(2) Is voiding safe? Basic emotions such as fear hinder voiding, and so this question should be answered by parts of the emotional nervous system. Hippocampal and posterior parts of the brain are involved.
(3) Is voiding socially appropriate? Social assessments and voluntary decisions involve the frontal cortex. Lateral and medial prefrontal regions are involved.

If voiding is safe and mechanically and socially appropriate, motor output to cause it to occur is put into effect and suppression of the voiding reflex is lifted. Otherwise continence is maintained.

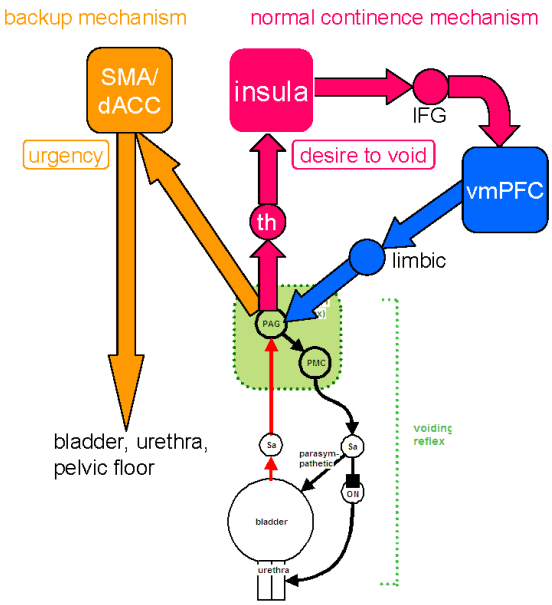

Fig. 3. Schematic diagram of neural circuits maintaining continence.
th = thalamus, IFG = inferior frontal gyrus, vmPF = ventromedial prefrontal cortex, SMA = supplementary motor area.

As a simplification, the regions, inter-connections and functions that we have described can be grouped into a few neural circuits (Fig. 3). In normal subjects the insula is the primary target of afferents originating in the bladder (Fig. 1 and red arrows in Fig. 3). Insular activation represents visceral sensation [Craig 2003] - in this case normal desire to void. In turn, the insula activates a lateral part of the prefrontal cortex, the inferior frontal gyrus (IFG), where executive decisions such as whether to void are made. If voiding is desired the medial prefrontal cortex is deactivated (shown in blue), and the deactivation signal is passed back to limbic (emotional) regions near the base of the brain. This signal acts in the midbrain to suppress the voiding reflex (presumably by raising the trigger threshold). We postulate that this is the normal continence mechanism.

In urgency-incontinent subjects the normal mechanism fails or threatens to fail. In this case a backup mechanism comes into play (orange arrows in Fig. 3). The dACC is activated (Fig. 1), generating the sensation of urgency and also motor output to bladder and urethra, designed to

reinforce the sphincter mechanism and suppress detrusor activity. This pathway may operate independently of the voiding reflex, bypassing the PAG and PMC. Whether to activate the backup mechanism or not is presumably computed in the PAG however, which has the information and the processing power to assess whether loss of bladder control – involuntary triggering of the voiding reflex – is imminent.

Clinical utility: Since dACC/SMA activation apparently represents the sensation of urgency, it may be a marker of this elusive sensation that can be used to assess severity of disease or response to therapy. Similarly, insular activation (and perhaps IFG activation) may provide information about desire to void. Use of an MR scanner to determine such markers of sensation is not clinically attractive, but dACC/SMA and IFG are near the brain surface and may be accessible to more easily performed measurements of brain activity such as near-infrared spectroscopy (NIRS) [Matsumoto et al 2011].

Urgency incontinence or OAB may be precipitated by damage to the normal continence mechanism. Fig. 3 suggests that the integrity of the connecting pathways may be as important as that of the regions they connect. The long pathway from the medial frontal cortex to the limbic system (blue arrow) seems particularly susceptible to damage (see Dr Tadic's talk). Prevention, treatment or compensation for pathway damage may offer new therapeutic possibilities.

SUMMARY: fMRI observations suggest that two cortical mechanisms maintain continence. The normal mechanism is associated with activation of the insula and desire to void. It involves cortical and subcortical regions and acts by suppressing the voiding reflex. A backup mechanism, used when the primary mechanism threatens to fail, is associated with activation of the dACC and adjacent SMA and with urgency. Activation of some of these regions may provide markers of disease severity or therapeutic success. Damage to neuronal pathways maintaining continence may contribute to disease and offer new targets for therapy.

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BRAIN ACTIVITY RELATED TO CLINICAL SYNDROMES/PHENOTYPES OF IMPAIRED BLADDER CONTROL: OAB, URGENCY, DO AND OLDER AGE

Stasa Tadic

TOPIC:

Using brain imaging to investigate symptoms and clinical syndromes related to impaired continence control.

INTRODUCTION:

Clinical symptoms/syndromes and definitions: Impaired continence control is suggested by several symptoms reported by patients. Urgency is a corner stone of lower urinary tract symptoms (LUTS) related to impaired continence control and it is defined as sudden onset of compelling desire to void which is difficult to defer.[1] Patient reported symptoms and complaints are grouped and defined as syndrome of overactive bladder (OAB). If accompanied by episodes of urine leakage, OAB is then manifested as urgency urinary incontinence.
Urinary incontinence is associated with detrusor overactivity (DO), defined as involuntary detrusor contraction observed during urodynamic examination and either spontaneous or provoked.[1] Contrary to subjective patients' reports, observed DO is the only objective patophysiological sign of impaired continence control.
Its involuntary character implies, at least in part, an abnormality in CNS function, since the CNS is essential for the regulation of voluntary micturition and continence.

Brain imaging studies on impaired continence control: *Functional* brain-imaging studies have identified a group of brain regions believed to be a part of a network that regulates all phases of the micturition cycle (the 'brain-bladder control network').[2]
Furthermore, studies on brain activity during *patient-reported* 'urgency,' (provoked in the scanner by further filling of a well-filled bladder) suggest a specific pattern of regional *activations* and *deactivations* most likely related to effort to suppress urgency.[3,4]
Large epidemiological studies reported increased prevalence of urgency and urgency incontinence in older functional community dwelling subjects and linked them with increased (age-related) *structural* changes in the brain's white matter (e.g. white matter hyperintensities –WMH).[5,6]

METHODS:

To study CNS regulation during storage phase, bladder filling and patient reported symptoms, we combine functional and structural brain imaging methods: **a)** *functional MRI with simultaneous urodynamic* study to monitor brain response to bladder filling during self-reported urgency in the scanner, and **b)** *Fully automated method for quantifying and localizing white mater hyperintensities* on MR images. We use correlation/regression analyses in *Statistical Parametric Mapping program* (SPM5) to ascertain how the increase in WMH affects functional brain activity during urgency.

Functional brain imaging (fMRI): Our experimental *paradigm* utilizes fMRI/block design to measure brain activity during cycles of bladder filling and emptying during self-reported

urgency in order to study *storage* function and changes in brain-bladder control network.[7]

Structural brain imaging: for assessment of white matter changes - white matter hyperintensities (WMH) we use *Fully automated method for quantifying and localizing white mater hyperintensities* on MR images3 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.[8] 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.

FINDINGS:

Study in women with OAB manifested as urgency incontinence (age > 60 years).
Regional brain activity during urgency.[4] As in previous studies, in a group as a whole, during filling of well filled bladder that provoked sensations of strong urgency as reported by subjects, we observed brain *activations* in supplemental motor area/SMA - adjacent to dorsal anterior cingulate gyrus/dACG and superior frontal gyrus/SFG; and in right insula and dorsolateral prefrontal cortex/dlPFC) together with *deactivations* in the ventromedial and medial prefrontal cortex (vmPFC/mPFC) and in parahippocampal or paralimbic areas. Such display of regions/network represent results of activity of several circuits involved in processing of afferent sensation, from initial registration (e.g. right insula – interoceptive awareness), to cognitive and emotional appraisal (regions in PFC and limbic system). Strong *activation*s in cingulate cortex represent an overall arousal with sensation from full bladder that creates feeling of urgency and it is coupled with activation in motor cortex, such as SMA and primary motor cortex (post central gyrus), which are, most likely aimed to control the urgency by activation of pelvic floor muscles and urethral sphincter. *Deactivations* in vm/mPFC are believed to be aimed at suppression of urgency, since there regions are involved in voluntary control of voiding and control of emotional response to various triggers.[4] What is more evident in recent years is the deactivation in parahippocampal area believed to be involved in memory retrieval and 'contextual' processing.

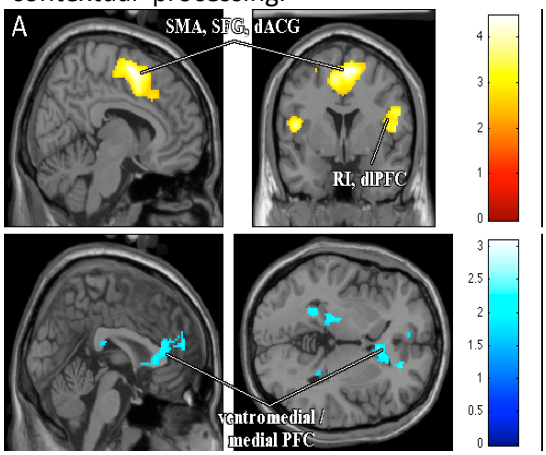

Figure 1. Study results in women with OAB/UI aged over 60. Significant regional brain activity (statistical maps) during urgency provoked and reported in the brain scanner is displayed. Activations: red/yellow; deactivation: blue.

Regional brain activity in patients with phenotypic/functional differences (e.g. DO elicitability): During bladder filling experiments in the brain scanner, we observed DO and loss of bladder control (urine leakage) in 1/3 of all subjects. To test if this difference in DO elicitability reflects functional/phenotypic difference between these subjects we conducted a secondary analyses. We found that the group of subjects that exhibited DO in the scanner, also exhibited DO during standard urodynamic exam. These subjects were older, with more severe incontinence and burden of the disease and had more changes in brain's white matter, which are linked to urinary incontinence. This suggested that OAB is a heterogeneous syndrome and that older age may represent a phenotype with more advanced OAB/UI due to age-related structural changes in the brain's white matter.
Furthermore, there were significant differences between the groups in brain activity during urgency (without DO). More activations in SMA/motor cortex were observed in the group with subsequent DO compare to 'no DO' subjects and such differences were also apparent when the bladder was nearly empty and without strong sensations.

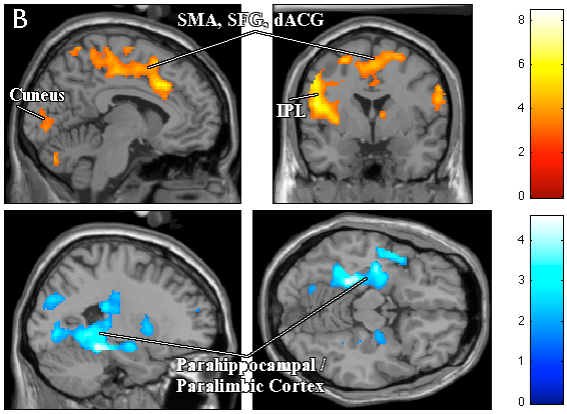

Figure 2. Regional brain activity during urgency in subjects who lost control in the scanner and subjects who remained continent. **Upper** part: significant activations in motor areas (e.g. SMA) in 'DO group'. **Lower** part: significant deactivations in 'no DO' group in parahippocampal area.

Regional brain activity during urgency in relation to age-related structural changes in white matter (e.g. white matter hyperintensities)
Based on epidemiological studies and our data, older age is associated with more advanced impairment of continence control, which may be caused, at least in part, by the damage of brain's white matter, known as the white matter hyperintensities. In our recent study, we have found that the extent of white matter changes relates to functional brain activity during urgency. Activations in posterior cortex and cerebellum are increased in those subjects with more intense white matter changes, while activity in dorsal ACG, part of SMA and SFG is decreased. Deactivations in vm/mPFC are less pronounced, since activity in these regions increased with the increase of WMH. Such findings suggest that structural changes in white matter affect the regional brain activity involved in continence control, possibly making efforts to regulate less effective. Structural damage of individual white matter *pathways* connecting these functionally important regions is most likely mechanism of white matter effects on continence control. Our data also confirm this hypothesis, showing that damage in one of pathways, anterior thalamic radiation (ATR), accounted for most of the effects.[4]

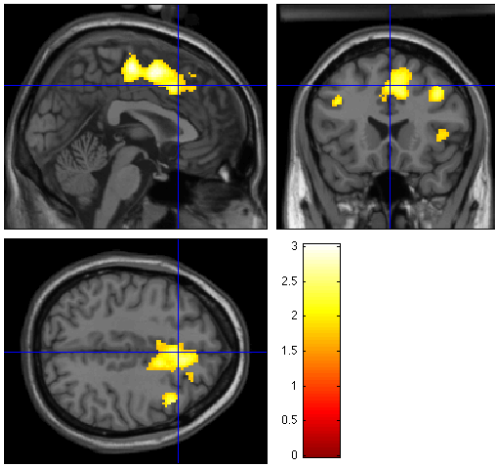

Figure 3. Regional brain activity significantly related to structural changes in white matter (e.g. ATR).

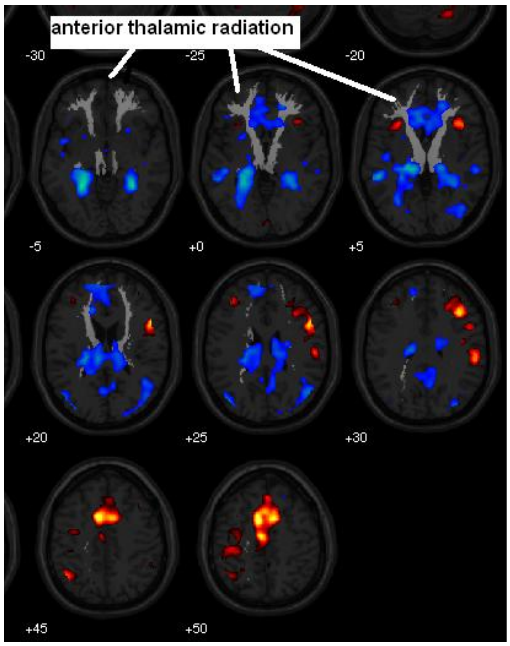

Figure 4. Projections of white matter connective pathways (e.g. ATR) and regional brain activity during bladder filling and reported urgency in the scanner.

CONCLUSIONS:

1. Brain activity during patient reported symptoms in subjects with OAB/UI is different from normal and reflects activity in neural circuits involved in continence control and storage phase. Processing of bladder signals in the brain is a complex activity and encompasses activity in several circuits involved in sensory registration and emotional/cognitive appraisal that creates motor/sympathetic output activity with the aim to control the urgency.
2. Regional brain activity differs in subjects with different functional and phenotypic characteristics such are, for example, advanced age and extent of structural changes in the brain. Such regions of difference may serve as potential markers for functional characterization of continence impairment.
3. Imaging methods that assess functional brain activity and structural changes, when coupled with urodynamic studies in the scanner, may give an insight on neural correlates of impaired continence control in clinical syndromes related to impaired continence control.

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IMPAIRED CNS BLADDER CONTROL RELATED TO CNS INJURY AND NEURODEGENERATIVE DISEASES

Ulrich Mehnert

TOPIC:

Neurological disorders / Neurodegenerative diseases causing lower urinary tract dysfunction and their impact on spinal and supraspinal neuronal control of the lower urinary tract.

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 cingulated 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 cingulated 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 seems 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.

SUMMARY:

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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EFFECT OF BEHAVIORAL TREATMENT AND PSYCHOLOGICAL FACTORS ON BRAIN-BLADDER CONTROL

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INTRODUCTION

Continence is acquired throughout childhood and results from the interaction of maturation of neural pathways and training. In healthy subjects voluntary control of micturition can therefore be massively influenced by learning processes. Conversely patients suffering from urinary incontinence can regain control of continence via behavioral training which greatly consists of learning strategies.

The goals of this presentation are:
1. To briefly describe some aspects of learning involved in acquisition of continence as well as in behavioral training for continence and brain areas involved;
2. To concisely reflect about the association empirically observed between continence and some mood disorders with respect to brain networks controlling them and;
3. To describe to which extent the knowledge gained through brain imaging research could help to better evaluate clinical outcome after behavioral training of urinary incontinence.

MAJOR QUESTIONS IN BEHAVIORAL TREATMENT OF URINARY INCONTINENCE

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.[1] It has 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.[2] 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 programs used in clinical practice.[2]
The therapeutic change produced by behavioral treatment can be hypothetically attributed to two different processes:
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.

CONTINENCE AND LEARNING

In healthy subjects micturition in itself can be seen as a goal-oriented-behavior[3] while the acquisition of continence can be seen as resulting from reinforcement learning, which studies the way that natural and artificial systems can learn to predict the consequences of and optimize their behavior in environments in which actions lead them from one state or situation to the next, and can also lead to rewards and punishments.[4] Optimization can be performed by reinforcement learning via two different broad classes of methods namely model-based and model-free. Model-based reinforcement learning uses experience to construct an internal model of the transitions and immediate outcomes in the environment. Appropriate actions are then chosen by searching or planning in this world model.[4] The flexibility of model-based reinforcement learning makes it suitable for supporting goal-directed actions. Studies on human brain imaging and animal models have suggested the involvement of the following structures: the dorsomedial striatum (or its primate homologue, the caudate nucleus), prelimbic prefrontal cortex, the orbitofrontal cortex, the medial prefrontal cortex, and parts of the amygdala.[4]
On the other hand model-free reinforcement learning uses experience to learn directly one or both of two simpler quantities (state/action values or policies) which can achieve the same optimal behavior but without estimation or use of a world model. In model-free methods information from the environment is combined with previous, and possibly erroneous, estimates or beliefs about state values, rather than being used directly. Given that these methods are statistically less efficient and less adaptable model-free reinforcement learning has been suggested as a model of habitual actions, in which areas such as the dorsolateral striatum and the amygdala are believed to play a key role.[4]
Micturition in healthy subjects can involve model-based reinforcement learning (e.g. deciding whether it would be appropriate to urinate in a particular situation) as well as model-free reinforcement learning (e.g. habitually emptying the bladder before leaving home).
As said above, behavioral treatment of incontinence doesn't not only involve learning new skills but also suppressing the fear of leaking. In this respect an important aspect is extinction of conditioned responses. The term "conditioning" refers to the process of learning the association between two previous unrelated stimuli.[5] Extinction occurs through the repeated exposure of the originally neutral stimulus without presenting the aversive stimulus, which in turn eliminates the fear reaction, which in this case is the fear of leaking. A systematic review of studies on extinction[5] has highlighted major activation foci in the amygdala, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula, prefrontal cortex (PFC) and ventromedial prefrontal cortex[5](VMPFC). On the other hand, recent studies on the acquisition of conditioned fear[6] have pointed to the role of the medial prefrontal cortex (MPFC) as an important part of the neural circuit for fear extinction: prefrontal activation seems to be essential for extinction learning.[6]

PSYCHOLOGICAL AND COGNITIVE FACTORS IN URINARY INCONTINENCE

There is considerable evidence that a variety of psychological factors such as low self-esteem, depression, anger, and stress often occur in subjects with urinary incontinence.[7] Recent study identified a high prevalence of psychiatric comorbidity and sexual trauma in women referred for the evaluation of LUTS.[8] In children, attention-deficit-hyperactivity disorder (ADHD) has been identified as a risk factor for persistent nocturnal enuresis[9] and voiding dysfunction.[10,11]
Although these associations, the literature on predictors of outcomes of behavioral and drug treatment for urinary incontinence is inconsistent and does not provide guidelines for treatment selection[12] and it has not been determined whether psychological symptoms contribute to urinary incontinence or are a consequence of it.
Decline of cognitive function and hypoperfusion of the frontal lobe has also been associated to

urinary incontinence. Stroke for example can lead to urinary incontinence in several ways:[7]
1. Neurological pathways controlling micturition can be disrupted, leading to bladder hyperreflexia and urge urinary incontinence;
2. Cognitive and language disruption may occur in persons with normal bladder function; consequently the inability to communicate one's needs would contribute to the incidence of urinary incontinence, particularly if the individual has limited mobility, as is often the case in assisted-living institutions;
3. Concurrent neuropathy or medication use may cause bladder hyporeflexia and overflow Incontinence.
Regardless the fact that a clear causative link between control of continence and mood and attention disorders has not been yet ascertained it is important to note that bearing in mind evidence coming from brain imaging studies, it can be gathered that brain areas involved in depression, PTSD or attention disorders –eminently PFC, ACC and insula- play also a pivotal role in the voluntary control of continence. A question that should be addressed in the next years is whether mood or attention disorders are associated to incontinence because they impair the subject's ability to plan and to control his or her behavior or rather because mood and attention disorders share to some extent the same brain networks and a dysfunction on one side necessarily influences or disrupts the other one.

BEHAVIORAL TREATMENT AND ITS POSSIBLE EFFECTS ON SUPRAPONTINE CONTROL

Treatment of incontinence defined as the acquisition of skills listed 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) 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 episode 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" [13] cited elsewhere we can hence postulate that successful behavioral training for UI may improve the inhibiting function of the MPFC on the periaqueductal gray (PAG) consequently suppressing the pontine micturition center (PMC) and preventing voiding.

Stress incontinence (SI) 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. These aspects are reflected in changes in brain activation patterns**.**[14] 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 chronic 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:
1. To further develop the working model into a theory describing the central control of continence and the emergence of pathologies;
2. To investigate whether and to which extent the brain networks controlling mood and attention interact with those controlling continence;
3. 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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