Brain and Bladder

W7, 15 October 2012 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:05	Introduction	• Stasa Tadic
09:05	09:45	Functional brain activity during voiding in humans	• Bertil Blok
09:45	10:15	Brain activity during bladder storage and reported urgency; effect of age-related structural brain changes	• Stasa Tadic
10:15	10:25	Brain activity during urgency and anticholinergics - effects of fesoterodine in women with OAB	• Marusa Strgulc
10:25	10:30	Discussion	All
10:30	11:00	Break	None
11:00	11:30	Brain activity related to LUTS in brain diseases (MSA, NPH and others)	• Sakakibara Ryuji
11:30	11:55	Acute and short term neuromodulatory effects on supraspinal LUT control in healthy, SCI and Fowler's Syndrome	• Ulrich Mehnert
11:55	12:00	Discussion	All

Aims of course/workshop

AIMS: 1. To provide an overview of brain imaging techniques (PET, fMRI, SPECT and fNIRS) and methodological approaches (e.g. bladder filling using infusion/withdrawal protocol) to study brain-bladder control. 2. Review functional brain anatomy (e.g. regions/centres) of normal and impaired bladder control and effect of clinical interventions: - micturition and storage - urgency and detrusor overactivity - advanced age, neurodegenerative diseases, spinal cord injury - imaging studies on biofeedback, anticholinergics, neuromodulation OBJECTIVES: 1. To advance understanding of brain's role and imaging methods in continence research. 2. Discuss with audience about translation of brain-imaging research into clinical practice.

Educational Objectives

The workshop brings comprehensive information on brain activity involved in bladder control, which is based on brain imaging studies published in past 15 years. Such knowledge is unknown to most health care professionals involved in urinary continence but is critical to understanding bladder function, reported-symptoms of impaired continence control and effects of clinical interventions to improve it. In addition, multidisciplinary speakers (2 urologists, neurologist, geriatrician and urogynecologist) will present their own brain-bladder studies findings using different designs and imaging techniques in various patient populations. Didactically, the workshop will provide more basic information on functional brain anatomy of micturition cycle and major brain imaging techniques suitable for those with very little prior knowledge and, then, progress to recent brain imaging studies before/after therapeutic interventions. It is anticipated that such a combination of didactic and advanced information will motivate the audience for a lively debate about current state of knowledge in the field, future technologies and possible clinical applications.

Start	End	Topic	Speakers
09:00	**09:05**	**INTRODUCTION**	**Chair**
09:05	**09:40**	FUNCTIONAL BRAIN ACTIVITY DURING VOIDING IN HUMANS	• Bertil Blok, Netherlands
09:40	**09:45**	**QUESTIONS**	
09:45	**10:10**	BRAIN ACTIVITY DURING BLADDER STORAGE AND REPORTED URGENCY; EFFECT OF AGE-RELATED STRUCTURAL BRAIN CHANGES	• Stasa Tadic, United States
10:10	**10:15**	QUESTIONS	
10:15	**10:25**	IMPACT OF FESOTERODINE TREATMENT OF OVERACTIVE BLADDER ON BRAIN ACTIVATION	• Marusa Strgulc, Slovenia
10:25	**10:30**	QUESTIONS	
10:30	**11:00**	BREAK	
11:00	**11:30**	BRAIN IMAGING RELATED TO LUT IN NORMAL AND BRAIN DISEASES: A DYNAMIC ASPECT	• Ryuji Sakakibara, Japan
11:30	**11:35**	QUESTIONS	
11:35	**11:55**	ACUTE AND SHORT TERM NEUROMODULATORY EFFECTS ON SUPRASPINAL LOWER URINARY TRACT CONTROL IN HEALTHY SUBJECTS AND PATIENTS WITH LOWER URINARY TRACT DYSFUNCTIONS	• Ulrich Mehnert, Germany
11:55	**12:00**	QUESTIONS	

TARGET AUDIENCE: physicians, nurses, physical therapists, researchers, students and trainees.

AIMS:

1. To review current knowledge about brain-bladder control network based on brain imaging studies to date.
2. To provide basic information about use of imaging methods (especially fMRI), analytical approaches and paradigms (infusion/withdrawal protocol) to study bladder control.
3. To 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
4. To provoke a discussion about strategies for translating brain-imaging research into clinical practice.

OBJECTIVES:

1. Interactive discussion of presented material with audience; debating strategies for translation/integration of brain imaging research into clinical practice.
2. To understand how functional brain scanning can be combined with urodynamics to show the relation between brain and bladder events.

3. To know the names and approximate locations of at least 2 brain regions involved in bladder control.

4. To be able to describe one brain-imaging signature of urgency in OAB patients.

5. To participate in a debate among presenters and audience about strategies for translation of brain-imaging research findings into clinical practice.

6. To know at least one probable cerebral cause or causal factor of urgency incontinence, common in the elderly.

7. To understand the role of neurodegenerative diseases in incontinence.

FUNCTIONAL BRAIN ACTIVITY DURING VOIDING IN HUMANS

Bertil Blok

Normal micturition and continence are under control of the periferal and central nervous system. The specific brain areas involved have been investigated and described with the use of animal experiments and dynamic imaging in healthy volunteers. This presentation provides an thorough overview of the relevant brain areas. It is important to distinguise areas which are part of the micturition reflex (i.e. pontine micturition center, bladder motoneurons) and those which maintain urinary continence (i.e. pontine continence center, sphincter motoneurons). Furthermore, pathways of the voluntary control of the pelvic floor musculature (i.e. corticospinal tract) are separate anatomically and functionally from those responsible for the (involuntary) control of micturition and urinary continence (brainstem-spinal tracts).

At present, it is not clear whether dynamic imaging can play an important future role in clinical urology. This presentation provides criteria which are necessary to make this exciting field as successful as molecular biology in clinical urology. Moreover, we will discus several potential symptoms and diseases which have been or can be investigated with dynamic imaging. Examples are overactive bladder, stress urinary incontinence, bladder pain syndrome and their treatments. Functional MRI may play a role in treatment selection and treatment evaluation provided that it can give significant individual information specifically related to a functional dysfunction.

BRAIN ACTIVITY DURING BLADDER STORAGE AND REPORTED URGENCY; EFFECT OF AGE-RELATED STRUCTURAL BRAIN CHANGES

Stasa Tadic

TOPIC:

Using brain imaging to investigate symptoms related to impaired continence control in older women and effect of age-related structural changes in brain's white matter.

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 pathophysiological 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 Labelling 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.

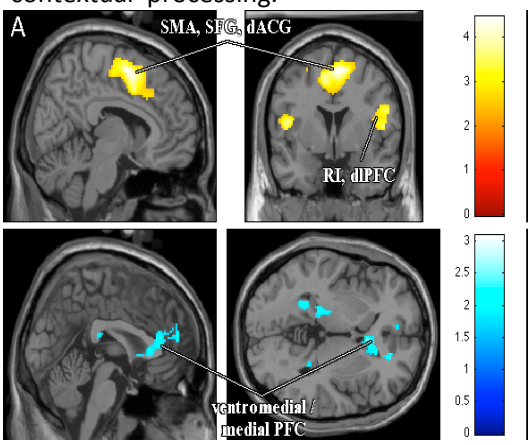

Figure 1. Study results in women with OAB/UI aged over 60. Significant regional brain activity (statistical maps) during urgency provoked and reported in the brain scanner is displayed. Activations: red/yellow; deactivation: blue.

Regional brain activity 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]

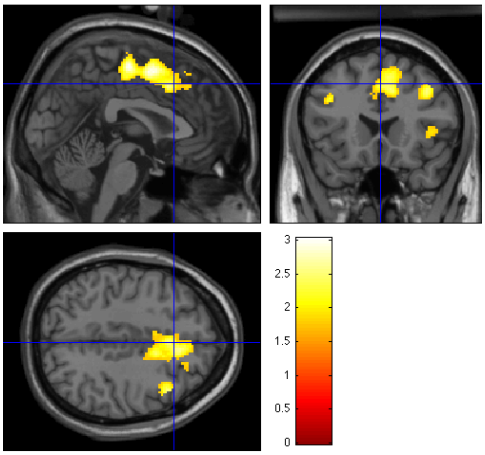

Figure 2. Regional brain activity significantly related to structural changes in white matter (e.g. ATR).

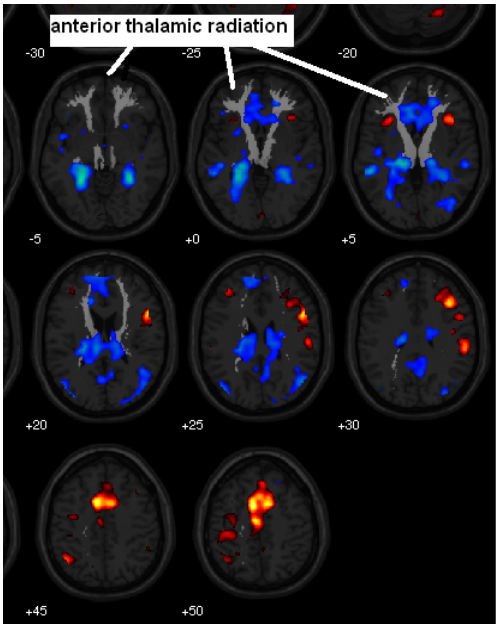

Figure 3. Projections of white matter connective pathways (e.g. ATR) and regional brain activity during bladder filling and reported urgency in the scanner.

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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IMPACT OF FESOTERODINE TREATMENT OF OVERACTIVE BLADDER ON BRAIN ACTIVATION

Maruša Strgulc

INTRODUCTION

Overactive bladder is defined as 'urinary urgency', usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other pathology (1). In epidemiological studies, the overall prevalence in adult women is reported to be between 11.8% and 16.9% (2). F esoteridine is derivate of 3,3 diphenylpropylamine and one of the pharmacological options for OAB treatment. It is a non-selective antimuscarinic agent that has recently been developed for management of OAB. It blocks muscarinic receptors in detrusor muscle and prevent its contractions(2).

In previous functional magnetic resonance imaging (fMRI) studies of patients with OAB, a diferent pattern of brain activation was shown compared to healthy subjects. In urge-incontinent subjects, brain responses to bladder flling differed from normal. Weak response or deactivation was observed in the prefrontal cortex or the limbic system, exaggerated response was observed in anterior cingulate gyrus (3,4,5). The aim of our study was to identify changes of brain activation in patients with OAB using fMRI before and aftertreatment with antimuscarinic drug fesoterodine.

METHODS

fMRI was used to measure brain activation related to bladder flling in 10 women with OAB. Before imaging, the bladder was flled with saline to a volume of 100 ml (low volume condition) and 400 ml (high volume condition). During scanning, 50 ml of saline were rapidly infused and withdrawn in 12 s intervals. Scanning was performed at baseline and after 3 months of fesoteridine therapy. Statistical analysis was performed using SPM8. We calculated the difference of the brain activation between high and low volume conditions as well as the diference before and after therapy.

RESULTS

At low bladder volume, there were no signifcant brain activations neither before nor after therapy. At high volume signifcant activations were found in anterior cingualte cortex, dorsolateral prefrontal cortex and anterior insula bilaterally. After therapy brain activity was significantly decreased in anterior cingulate cortex and insula.

CONCLUSION

Treatment of OAB with fesoterodine was related to decreased activation in anterior cingulate cortex. This region is associated with motivation and emotions. In many other studies the activation in this region was found to be related to stimuli with largely an emotional content. We conclude that because of successful treatment (less urgency, better QoL score) with an

antimuscarinic drug patients experienced less emotional arousal. They were more confident in their bladder control. This results are also promising because the pattern of activation is similar to the pattern seen in healthy volunteers studies.

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BRAIN IMAGING RELATED TO LUT IN NORMAL AND BRAIN DISEASES: A DYNAMIC ASPECT

Ryuji Sakakibara

TOPIC: To review a dynamic aspect of brain imaging data related to lower urinary tract (LUT) in normal individuals using real-time near-infrared spectroscopy (NIRS)-urodynamics; and those related to LUT symptom (LUTS) in brain diseases including Parkinson's disease before/after deep brain stimulation turned on (cited from Herzog), normal pressure hydrocephalus (NPH) before/after shunt surgery; elderly Parkinson's disease patients before/after anticholinergic medication, with particular reference to frontal role of bladder control.

INTRODUCTION: The frontal cortex has been regarded as the higher center for micturition because lesions in the frontal cortex, e.g., the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex and supplemental motor area produce marked lower urinary tract dysfunction in humans [1]. Detrusor overactivity is the most common urodynamic finding in the above brain areas, whereas lesions in the basal ganglia may produce unrelaxing sphincter on voiding [2,3]. During the initial phase of illness, areas where detrusor overactivity appears afterwards might produce transient acontractile detrusor [3]. Functional neuroimaging in normal volunteers using single-photon emission computed tomography (SPECT), positron-emission tomography (PET), and functional magnetic resonance imaging (fMRI) is able to show brain activation in response to bladder fullness and urination [4]; and the activated areas strikingly overlap the lesions described in clinical studies [2]. However, a dynamic aspect of brain imaging data related to lower urinary tract (LUT) in normal individuals, and those related to LUT symptom (LUTS) in brain diseases are not well known. In this talk we highlight such a dynamic aspect of brain imaging related to LUT/LUTS.

METHODOLOGY: To see dynamic changes of brain function during urodynamics, we chose real-time near-infrared spectroscopy (NIRS) measurement since it is subjects-friendly; e.g., the head gear with the probe array for NIRS is small and light (hundreds of grams). We can perform the test with the subject sitting in an urodynamic tilting chair. It is equipped with 16 light emitting and 17 detector probes and 52 channels can be measured simultaneously. NIRS measures oxy-haemoglobin concentration (oxy-Hb) and deoxy-hemoglobin concentration (deoxy-Hb) several cm beneath the surface through the bone. Concentration changes in oxy-Hb and deoxy-Hb were calculated based on a modified Beer-Lambert approach. According to a standardized brain atlas, the probe array covers the areas 8, 10, 44, 46 and the more anterior parts of the frontal cortex.

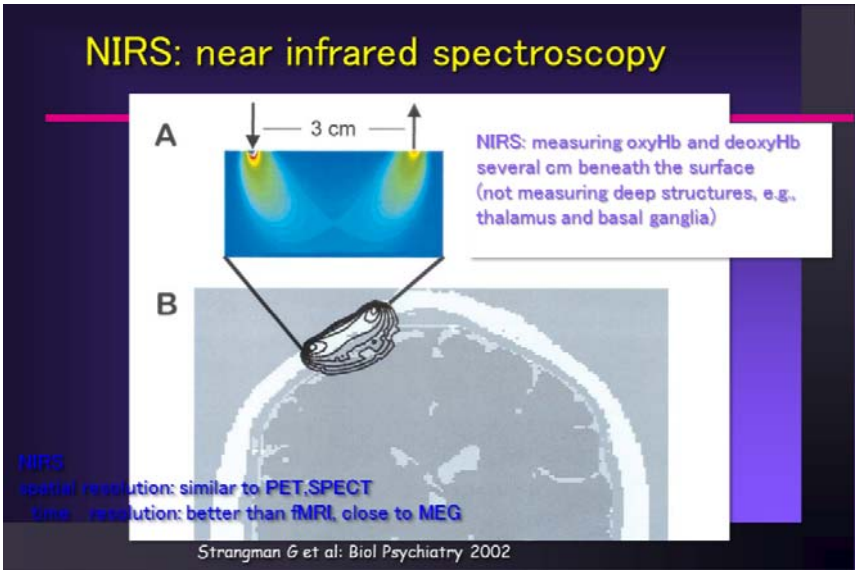

Fig. 1. Method of NIRS (cited from Strangman 2002).

To see dynamic changes of brain function before and after various intervention for LUTS in brain diseases, storage phase brain activation by PET, NIRS (Parkinson's disease) and resting phase brain circulation by SPECT (normal pressure hydrocephalus) have been used.

FINDINGS:

NIRS study:

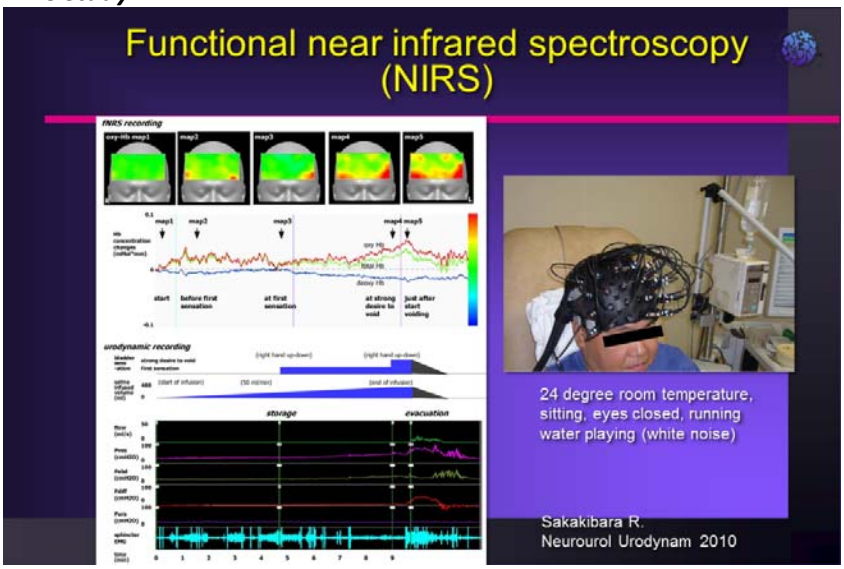

Fig. 2. Slow brain activation during a slow bladder filling in a normal subject.

In the control group, 1) a slight increase of oxy-Hb before first sensation occurred, 2) there was a continuous increase of oxy-Hb during bladder filling to the point just after voiding began, 3) there was a continuous decrease of oxy-Hb after voiding, and 4) the area activated was the bilateral lateral prefrontal area, particularly Brodmann's areas 8, 10 and 46. In the detrusor overactivity group, 5) an increase of oxy-Hb before first sensation was rare and frontal cortical activation was weak, but otherwise the results were almost the same as those in the control group [5].

Parkinson's disease before/after deep brain stimulation turned on (cited from Herzog):
Parkinson's disease is a common neurodegenerative disease that affects not only motor but also bladder. Overactive bladder is the most common, due probably to basal ganglia dysfunction that normally suppresses the micturition reflex. According to Herzog (2006) [6], in Parkinson's disease, prefrontal cortex is deactivated that is normally activated during bladder filling. Deep brain stimulation suppresses the subthalamic nucleus (a key nucleus in the indirect basal ganglia pathway, hyperactive in disease state) that leads to both motor and bladder amelioration. When deep brain stimulation is turned on, right prefrontal area is also (re)activated.

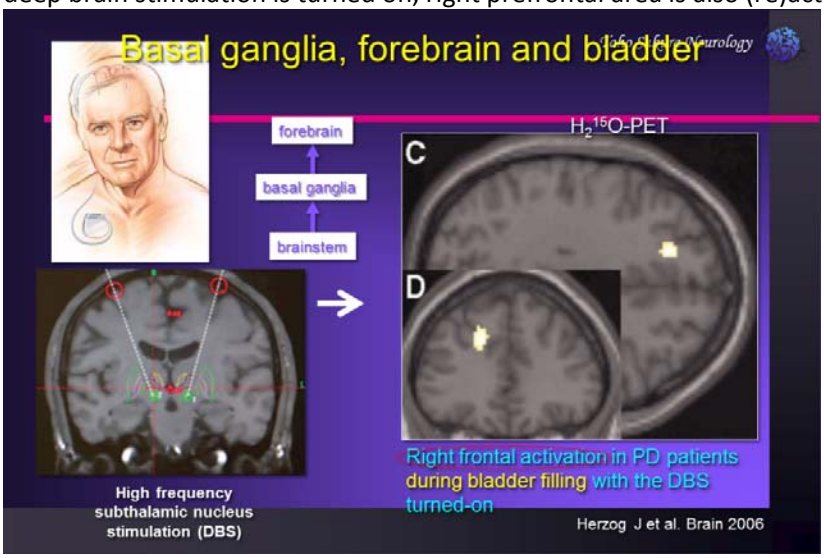

Fig. 3. In Parkinson's disease, right prefrontal area is activated when deep brain stimulation is turned on.

Normal pressure hydrocephalus (NPH) before/after shunt surgery:
NPH is a common elderly disease of unknown etiology, characterized by easy fall, dementia, and urinary incontinence. In NPH urinary incontinence is often preceded by overactive bladder (OAB). Shunt surgery (lumboperitoneal shunt etc.) can ameliorate above clinical features. Before shunt surgery, urinary dysfunction is closely correlated with frontal hypoperfusion [7].

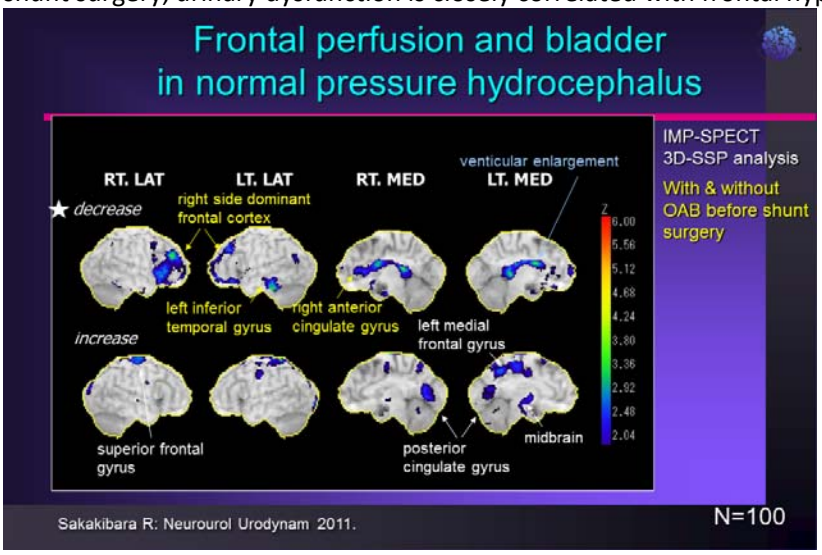

Fig. 4. In normal pressure hydrocephalus (NPH), urinary dysfunction is closely correlated with frontal hypoperfusion.

After shunt surgery, amelioration of urinary dysfunction is closely correlated with regaining of frontal perfusion.

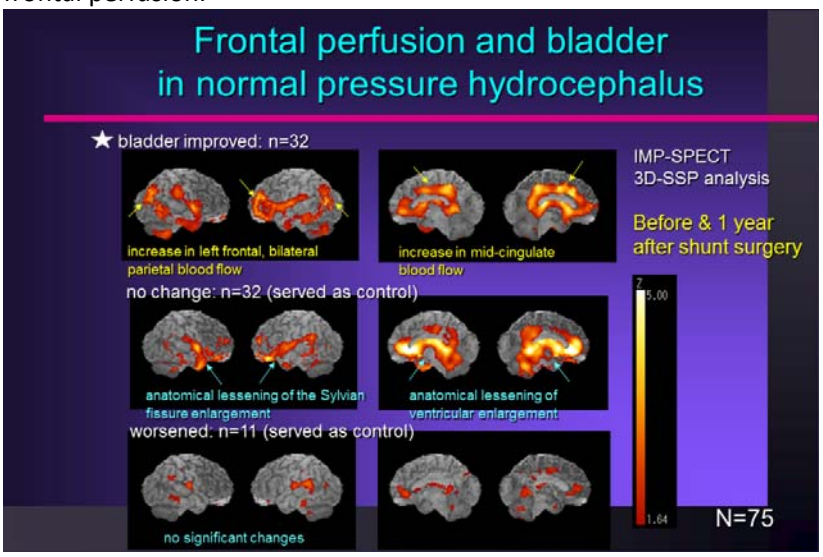

Fig. 5. In NPH, after shunt surgery, amelioration of urinary dysfunction is closely correlated with regaining of frontal perfusion.

Elderly Parkinson's disease patients before/after anticholinergic medication:
In 8 elderly Parkinson's disease patients and 3 white matter disease patients (7 men, one woman), we compared brain NIRS activation before and after 3 months, 0.2 mg/day imidafenacin, an anticholinergic agent. After imidafenacin, first sensation volume (114 ml to 137 ml) and bladder capacity (149 ml to 207 ml) increased. During this period, three cognitive measures (MMSE, FAB, ADAScog) did not change/worsen significantly. Subtraction of oxy-Hb between start filling and first sensation increased in the bilateral prefrontal area, particularly in Brodmann's area 8, 10 of the upper prefrontal cortex.

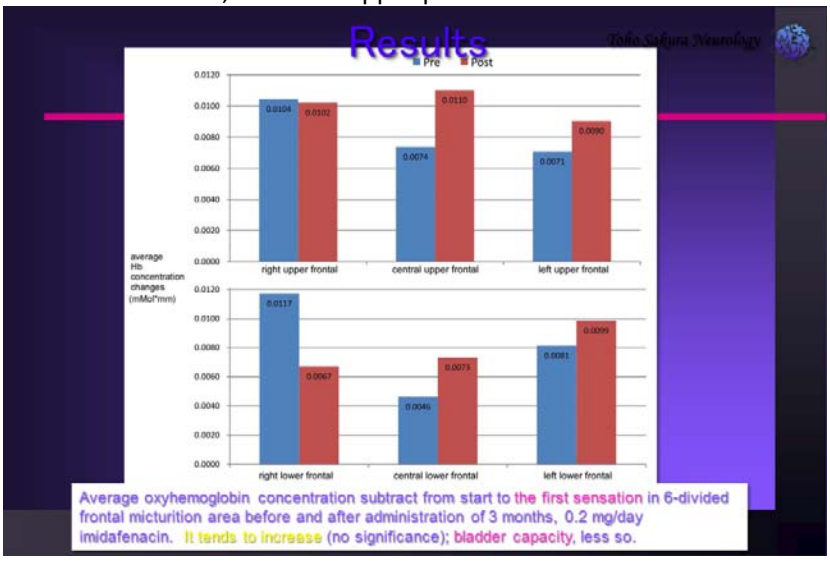

Fig. 6. In elderly subjects with Parkinson's disease/white matter change, oxy-Hb between start filling and first sensation increased in the bilateral prefrontal area.

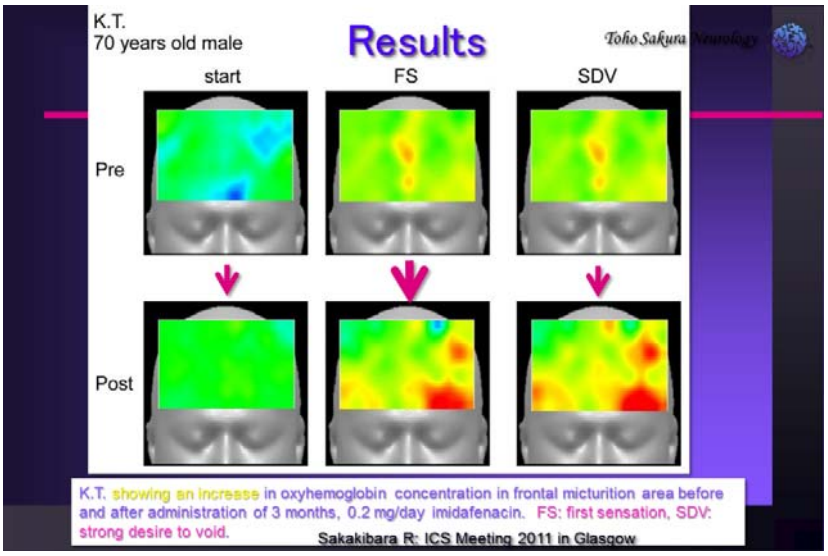

Fig. 7. An example, Mr KT.

SUMMARY:

NIRS, PET and SPECT observations suggest that there is a dynamic change in brain activation in between start and end of bladder filling; and before and after various interventions on OAB/LUTS in neurologic diseases. Generally, after intervention, the prefrontal cortex regains activation together with amelioration of OAB/LUTS. A recent study also showed that frontal transcranial magnetic stimulation ameliorated LUTS in Parkinson's disease. The role of prefrontal cortex on higher control of micturition might become important in neurologic as well as urologic clinical practice.

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ACUTE AND SHORT TERM NEUROMODULATORY EFFECTS ON SUPRASPINAL LOWER URINARY TRACT CONTROL IN HEALTHY SUBJECTS AND PATIENTS WITH LOWER URINARY TRACT DYSFUNCTIONS

Ulrich Mehnert

Topic: Investigation of central effects of peripheral neuromodulation on neuronal lower urinary tract (LUT) control using neuroimaging of the supraspinal central nervous system.

Introduction: A frequently used treatment of LUT dysfunction (i.e. urinary frequency, urinary urgency, urinary urgency incontinence, non-obstructive urinary retention), refractory to conservative, non-invasive, therapies (i.e. behavioral modifications, pelvic floor rehabilitation, pharmacological therapy), is electrical neuromodulation [1]. Commonly used sites to apply such neuromodulation are the sacral foramina S3 or S4 (sacral neuromodulation, SNM), the pudendal nerve, the posterior tibial nerve and anogenitally. Next to favorable success rates (pooled success rate of 92% for permanent SNM) [2] neuromodulation offers the benefit of being non- or minimally invasive, reversible and non-ablative. Several external devices for neurostimulation are commercially available and implantation of electrodes and stimulator for SNM is an FDA approved treatment for previously mentioned LUT dysfunctions since more than a decade [1].
However, the mechanism of action of neuromodulation for LUT dysfunction remains largely unknown, but appears to be associated with the modulation of afferent nerve activity, reorganization of spinal reflexes, and regulation of supraspinal signal processing [3, 4]. Functional Neuroimaging studies that can visualize supraspinal activity in response to LUT afferent signals can therefore contribute to a better understanding of how neuromodulation influences LUT control and improves LUT dysfunctions.

Methodology: Using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), changes in supraspinal regional cerebral blood flow (rCBF) were investigated in response to bladder filling and different modes of neuromodulation (i.e. dorsal genital nerve (DGN) stimulation, SNM) in healthy female subjects [5], female patients with urgency incontinence [6], female patients with Fowler's syndrome [7, 8], and spinal cord injury (SCI) patients [9]. In all studies, bladder filling was performed via a transurethral catheter.

Findings: Pneumatic stimulation of the dorsal genital nerve (DGN) in healthy female subjects as a form of peripheral pudendal nerve stimulation during bladder filling has been demonstrated to reduce the activity of areas that are normally activated during bladder filling (inferior frontal gyrus (IFG), right anterior cingulated cortex (ACC) and putamen). Considering that the IFG and the ACC are involved in functions as thinking of future consequences, controlling social behavior (e.g. the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes) and focusing attention on emotionally significant events, anticipation of events and tasks, respectively, it is not surprising that activity increases in both areas with increasing desire to void. Several neuroimaging studies reported increased IFG activation during the storage phase [10-12] and increased ACC activation in healthy subjects during bladder filling [10, 13]. The latter was even exaggerated when strong desire to void (SDV) was reported. This observation can be justified in light of an increasing inhibitory influence of the ACC on the PMC in an attempt to avoid micturition [13].
With DCN stimulation such activity could be significantly reduced in healthy females. The influence of somatic afferent fibers on bladder function can be explained by the gate-control-theory in pain, described by Melzack and Wall [14]. The underlying theory is, that bladder

afferents travelling through the lateral dorsal horn of the sacral spinal cord can be inhibited by interneurons, which are activated by afferent sensory fibers of the pudendal nerve [15].
In line with that, Blok et al showed that chronic SNM in female patients with urgency urinary incontinence decreased activity in the cerebellum, midbrain and adjacent midline thalamus and limbic cortical areas, i.e. the cingulate cortex, ventromedial orbitofrontal cortex and prefrontal cortex, areas previously implicated in the control of micturition and urinary storage [6]. Those changes observed with chronic SNM might indicate a restoration of supraspinal activity in frontal areas and ACC to normal levels that are necessary for appropriate bladder control and timing of micturition [6]. Interestingly, acute SNM predominantly caused activity in areas related to sensory and motor learning (i.e. the right premotor cortex and the lateral and intermediate cerebellum) whereas chronic SNM showed mainly changes in bladder control areas, implicating plasticity related changes in the CNS due to chronic SNM [6]. This corresponds well with the observation that prolonged intravaginal stimulation of the pudendal nerve resulted in a lasting inhibitory effect on detrusor overactivity, although stimulation was stopped [16].
However, it has to be considered that part of the observed supraspinal changes following SNM (especially in the acute phase) might be related to effects at the lumbosacral level influencing afferent activity and consequently alter brain activation, which might be unrelated to the beneficial effects of long-term SNM [6].
DasGupta et al. demonstrated effects on supraspinal activation following chronic SNM in patients with urinary retention (Fowler's syndrome) [8]. In healthy controls, bladder fullness was associated with enhanced activity in brainstem (midbrain and pons), and anterior and posterior cingulate cortices. In contrast, women with Fowler's syndrome showed absence of this "normal" pattern of midbrain activation, instead an increased activity of anterior and posterior cingulate cortices was observed [8]. With SNM "on" however, fullness related brainstem (midbrain) activity returned to even higher levels than observed in healthy controls whereas cingulate activity was markedly attenuated [8]. In consistence with previous studies, cingulate cortex activity seems to be of inhibitory nature towards the pontine micturition center and subsequently towards micturition. In patients with urinary retention cingulate cortex activity might be exaggerated and thus resulting in the inability to sufficiently initiate micturition. The findings presented by DasGupta et al. suggest that sensory gating in patients with Fowlers syndrome is improved by SNM and that an exaggerated inhibitory input from the cingulate cortex is reduced, enabling successful micturition. This is supported by the observation that only with SNM "on" patient's reported desire to void correlating with the bladder volume and that micturition was possible [8].
Although, posterior cingulate cortex (PCC) activation equated ACC activation in the study by DasGupta et al., it has to be considered that PCC and ACC may have complementary functions in regard to LUT control [8]. The ACC has been suggested to be of predominantly executive function whereas the PCC has been described as evaluative [17].
According to the findings of DasGupta et al., Kavia et al. demonstrated in a similar group of patients with Fowler's syndrome using fMRI that these patients have abnormal supraspinal responses to bladder filling in means of pronounced deactivations that were reversed by SNM [7]. This finding has been attributed to overactive urethral afferents that generate abnormally strong inhibitory signals, effectively blocking bladder afferent activity at the sacral level and subsequently deactivating the periaqueductal grey and higher centers, with consequent loss of bladder sensation and ability to void [7]. Hence, SNM seems to act at the sacral level, by blocking the inhibition of overactive urethral afferents [7].
In incomplete SCI patients, Zempleni et al. demonstrated supraspinal activations towards bladder filling that were generally of much lower intensity than in the healthy subjects and with

an emphasis on the left hemisphere (especially for the prefrontal areas) [9]. The acute effect of neuromodulation by DGN stimulation resulted in several alterations of cerebral activation, mainly decreasing of the BOLD (blood oxygen dependency level) signal similar to the effect observed in healthy subjects. The effect of a 2 weeks stimulation treatment resulted in a signal increase of regions implicated in the normal cortical substrate of bladder control (i.e. right insula, right orbito-frontal, middle and superior frontal gyrus, right cerebellum, right ACC). Thus, DGN stimulation during bladder filling in SCI patients seems to induce a significant neuromodulation, with an effect even in the acute stimulation phase, which was similar to the acute effect observed in healthy subjects [9]. A "normalization" of the supraspinal activation pattern was observed after the 2 weeks stimulation treatment. Correlations with the patients' urodynamical status indicate that the neuromodulatory effect of DGN stimulation observed with fMRI may reflect the clinical improvement noticeable in incomplete SCI patients following stimulation treatment.

Summary: Using functional neuroimaging studies it seems to be possible to distinguish between healthy ("normal") supraspinal activity of LUT control and sensory processing and LUT dysfunctions that are reflected by abnormal supraspinal activation. In addition, the effects of neuromodulation on supraspinal activation can be evaluated whereas acute effects of neuromodulation differ from short term and chronic effects. With the current neuroimaging studies it could be demonstrated that neuromodulation of the LUT has supraspinal effects next to the presumed effects on the sacral level. However, in the acute phase of neuromodulation, supraspinal effects might be more a subsequent cause of the sacral effects rather than a direct supraspinal effect. With chronic or long term stimulation, plasticity related changes in CNS and thus sustaining changes in supraspinal LUT control can be observed with functional neuroimaging. In general, LUT neuromodulation results in a "normalization" of supraspinal activity in areas known to be of relevance in LUT control and thus facilitating LUT function. The supraspinal "normalization" of activation often correlates with the clinical improvements. Further studies in larger patient populations are necessary to confirm the previous findings.

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Notes

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