

## A BETTER UNDERSTANDING OF THE PERCEPTUAL PSYCHOPHYSICS OF BRAIN RESPONSES IN FMRI STUDIES OF URINARY URGENCY IN HEALTHY OLDER SUBJECTS

### Hypothesis / aims of study

Functional MRI (fMRI) is a non-invasive imaging method that allows brain regions engaged by a specific task or stimulus to be detected and localized. The MRI contrast mechanism used is based on changes in blood oxygenation caused by localized increases in blood flow and oxygen delivery which are believed to support increased synaptic activity. Depending on the size of brain response produced, robust activation maps can be obtained at either the individual or group levels. Group activation maps are generated by spatially normalizing individual brains to account for differences in gross brain anatomy, then computing a spatial average of responses over all subjects.

The use of fMRI to study the organization of neural systems mediating the perception of urinary urgency is a relatively new application with unique challenges (1). There is little data regarding the perceptual psychophysics of bladder fullness, let alone the degree and extent of responses anticipated in the brain. The goal of this study was to better understand the perceptual psychophysics of bladder fullness in healthy subjects, and the consistency of these responses over time.

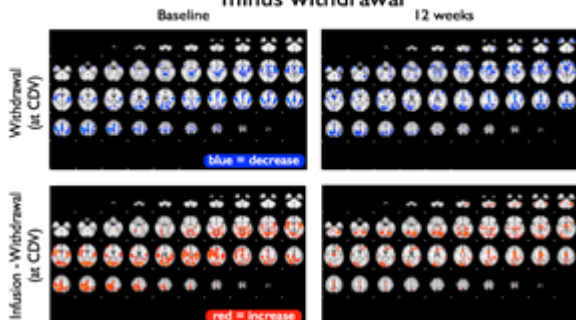
### Study design, materials and methods

Six healthy control subjects without urinary tract symptoms aged 60 to 88 were imaged, each at two time points separated by twelve weeks. A block design with 2 bladder conditions was used for fMRI scanning: the first bladder condition consisted of a bladder volume pre-determined to produce no perceptible feeling of fullness (100 ml). The second bladder condition consisted of a bladder volume threshold determined to produce feelings of a compelling desire to void (CDV), ranging from 300-620 ml, tailored to each patient prior to scanning. Bladder volumes were achieved by infusing slightly warmed saline into the participant's bladder through a 14 Fr two-way valve latex-free 100% silicone Foley catheter (Kendall®) using sterile technique. As in previous protocols, each condition was scanned twice, while 20 cc of fluid was repeatedly infused and withdrawn from the bladder over a 10 second period, with a 10 second pause in between (2). Data was acquired from a 3 Tesla Siemens TIM Trio system using a T2\*-weighted EPI sequence with TR/TE/alpha = 2s/30ms/90deg, on a 64x64 matrix with 4 mm in-plane resolution, in 33 slices of 4 mm thickness with no gap, acquired in ascending order. A T1-weighted anatomic scan was also acquired, using the MPRAGE sequence for assignment of anatomic context to the activation patterns seen in individuals and for spatial normalization prior to group analysis.

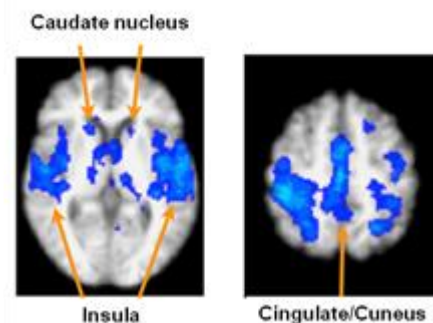
fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRI's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Image series were motion corrected by serial alignment, and then spatially smoothed using a 6 mm 3D Gaussian kernel. Following these preprocessing steps, linear modelling fits were performed at the run level to estimate response amplitudes and associated standard errors. Each subject's MRI data was then spatially normalized in FSL to a stereotaxic standardized space (MNI 152 brain) and then entered into a group level analysis to compute an average response map over all subjects. The identical analysis procedure was repeated at time points one and two to produce a z score map at each time point. The maps were compared by visual inspection of thresholded group average maps for infusion contrasts, withdrawal contrasts and infusion-withdrawal contrasts across time points.

### Results

**Fig. 1 Test-retest images of withdrawal and infusion minus withdrawal**



**Fig. 2 Reduction of activity in brain structures associated with aversive stimuli**



At the higher-volume (CDV) bladder threshold, the activation map for fluid withdrawal revealed a predominant pattern of decreasing activity in brain regions previously associated with noxious stimulation including insular, cingulated/cuneus, and caudate nucleus (Fig 1 and 2) (3). Interestingly, there was no significant change in MR signal associated with the infusion condition at this bladder volume. This suggests that previous reports of activation for an infusion minus withdrawal contrast (2) may in fact reflect signal decreases in response to withdrawal rather than increases during infusion.

At the lower-volume bladder baseline, responses tended to be of marginal significance, consistent with the lack of perceptible feeling in this condition.

While the pattern of withdrawal response at the higher-volume CDV threshold included a number of structures associated with

aversive stimuli, there was some variability in the response pattern between the first and second time points (Fig 1). This may be attributable to differences in psychological factors such as anxiety, anticipation, and familiarity with the MRI environment and the bladder filling protocol. It may also reflect limitations in statistical power given the small sample size.

#### Interpretation of results

Our results suggest that, at the higher-volume CDV condition, infusion of additional saline elicits minimal increases in synaptic activity. This would be consistent with a perceptual saturation effect, in which afferent bladder input has already reached a maximal level. The observation of significant and widespread decreases in activity upon withdrawal of fluid suggests that withdrawal activates different neural pathways than bladder filling. One explanation for these findings is that the changes observed reflect relief from an aversive stimulus. In addition to pain studies, the regions found to undergo signal decrease in our study have been found to activate in response to other uncomfortable physiological sensations such as air hunger and itch.

#### Concluding message

Further studies are needed to enlarge the databank of healthy control subjects in order to better establish "normal" networks subserving urinary urgency and relief as well as demonstrate test-retest reliability of the perceptual psychophysical responses to urinary urgency over time. This will lay the foundation for clinical studies of behavioural and pharmacological interventions in patients with overactive bladder.

#### References

1. Drake et al. N & U 2010; 29:629-33
2. Tadic et al. J Urol 2010;183:221-228)
3. Piché et al. Pain 2010;149:453-62

<b><i>Specify source of funding or grant</i></b>	<b>Canadian Institutes of Health Research #IAP CFCA-108262</b>
<b><i>Is this a clinical trial?</i></b>	<b>No</b>
<b><i>What were the subjects in the study?</i></b>	<b>HUMAN</b>
<b><i>Was this study approved by an ethics committee?</i></b>	<b>Yes</b>
<b><i>Specify Name of Ethics Committee</i></b>	<b>Comité d'éthique de l'Institut universitaire de gériatrie de Montréal</b>
<b><i>Was the Declaration of Helsinki followed?</i></b>	<b>Yes</b>
<b><i>Was informed consent obtained from the patients?</i></b>	<b>Yes</b>