

## THE EFFECT OF BLADDER COLD SENSATION ON SUPRASPINAL ACTIVATION – AN FMRI STUDY IN HEALTHY FEMALES

### Hypothesis / aims of study

In the last years a defined network of brain regions involved in voiding control and filling sensations could be established using PET and fMRI. However, still little is known about the cerebral regions involved in cold perception of the bladder. Specific cold receptors (TRPM8) have been found on the urothelium and on bladder afferent fibers that may play a role in the symptomatology and pathophysiology of overactive bladder (OAB) and painful bladders [1]. As distension and cooling are different sensations and supposed to be transmitted via different fiber types, it was the aim of this study to investigate the cortical response pattern to bladder cooling.

### Study design, materials and methods

After approval of the local ethics committee, 14 healthy female subjects (mean age 24.8 ±3.4 years) gave their written informed consent and were included. The study was performed using a 3 Tesla Scanner (Philips Achieva) and a voxel size of 3 mm<sup>3</sup>. Subjects were catheterized using a 14 Fr Foley catheter. The fMRI protocol was adapted to the mean time of bladder cooling sensation, which was determined in a test run prior to scanning. The scanning consisted of 10 repetitive cycles and each cycle consisted of 5 conditions: REST, FILLING, SENSATION, DRAIN1, and DRAIN2 (Fig. 1)

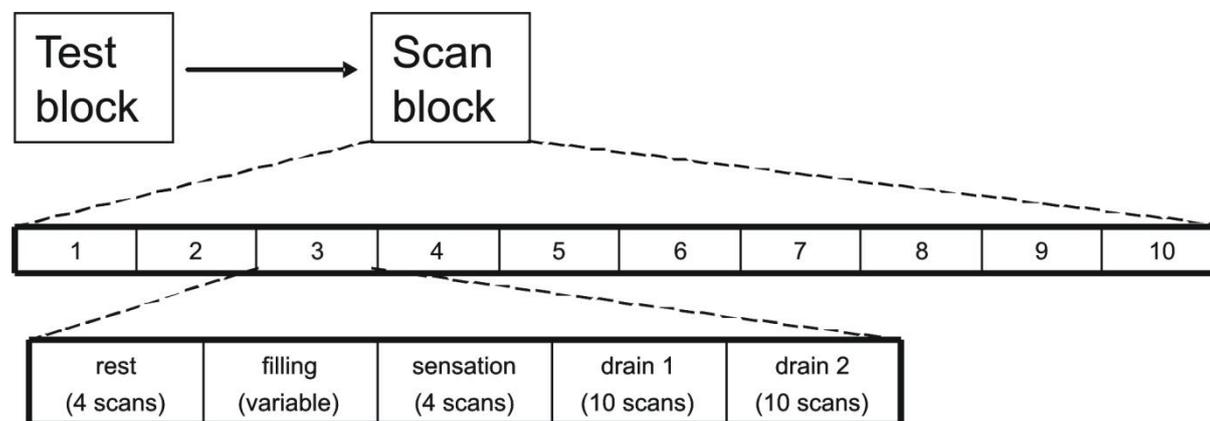


Fig. 1: Scanning paradigm used in this study

Cold saline was passively infused at 4-8°C during scanning. Filling was stopped at the end of the SENSATION condition. Not more than 100 ml of saline were infused. Analysis was performed with BrainVoyager 1.8 using spatial smoothing of 4 mm, a high pass linear trend removal, temporal filtering (3 cycles in time course), and a cluster size > 75 voxel. All activations were evaluated on random effects level with  $t = 3.5$  ( $p = 0.005$ ).

### Results

All subjects tolerated the measurements well and completed the study. However, the datasets of 2 subjects had to be excluded due to artefacts caused by strong head movements.

Cooling of the bladder was perceived on average after 9.8 ±1.9s. The INFUSION condition showed no activation.

The SENSATION condition showed activation in the right inferior parietal lobe (BA 40) and right middle frontal gyrus.

The DRAIN1 condition showed activation in the inferior parietal lobe (BA 40), the insula (BA 13), the putamen, the cerebellum, the precuneus (BA 7, 31), the middle and inferior temporal gyrus (BA 20,21) the right frontal gyrus (BA 9, 46), right fusiform gyrus (BA 37), the right pons, the right parahippocampal gyrus (BA 35), the right thalamus, and the right postcentral gyrus (BA 3, OP1/SII and SI).

The DRAIN2 condition showed activation in the right posterior insula (BA 13), the post- and precentral gyrus (BA 3,4), right middle temporal gyrus (BA 20), right fusiform gyrus (BA 37), and right cerebellum.

There was a clear right predominance in all bilateral activations. The PAG could not be found in any condition, even at insignificant levels.

### Interpretation of results

That cold sensation can be perceived in the urinary bladder and distinguished from distention is known since Blinn and Bors introduced ice water testing into urodynamic investigations and specific cold receptors have been discovered in the urothelium [1].

Up to date only one single PET study exist investigating cerebral response to thermal stimulation (i.e. bladder cooling) of the bladder [2].

In this study by Matsuura et al., the investigators found during bladder distention with strong desire to void, the same areas previously and there after described by others in PET or fMRI studies, namely ACG, Insula, Thalamus, PAG, Pons (ventral & dorsal), and Cerebellum [2, 3]. The PET scans in the ice water group in contrast showed activations in the ACG, inferior and middle frontal gyrus, inferior parietal lobe, Hippocampus, and crus cerebri.

Despite methodological differences, our results are quite similar to those from Matsuura et al. who found a different cortical network of activation during cold stimulation compared to bladder filling, with strong activation in the inferior parietal lobe (BA 40), which was not activated in the bladder filling group.

Parts of the inferior parietal lobe are known to be involved in interoception and especially the parietal operculum has been found to be involved in the sensation of cold. Regarding the cerebellar activation, which was also quite prominent in our findings, it has been suggested that the cerebellar projections to the posterior parietal cortex may provide signals that contribute to the sensory recalibration that occurs during adaptive processes (e.g. during bladder cooling). The activations of the postcentral gyrus might represent the somatosensory representation of the urethra during the passage of cold water.

The mechanism and the urodynamical effects of bladder cold stimulation have been extensively investigated by Geirsson and Fall. They postulated that a detrusor contraction following bladder cooling (bladder cooling reflex) is a pathological reflex, originating from cold receptors in the bladder and urethra and mediated by unmyelinated C-fiber afferents. The reflex is supposed to be positive in neurologically normal infants and young children. During normal development it becomes suppressed by descending signals from higher centers and it is typically negative in older children and adults with intact bladder control. However, it may be unmasked by pathological processes that disturb the normal neuronal control of voiding.

Changes in C-fibre activity have been suggested to play a role in OAB symptoms caused by neurogenic conditions like SCI and MS, but also from non-neurogenic origin.

Therefore investigation of c-fibre activation and the cortical substrate to c-fibre activation can be of relevant interest for the understanding of LUT function and regulation.

This study reveals new findings in bladder perception and central processing of bladder sensations. The specific experimental setup might offer new opportunities to investigate patients with OAB and painful bladder syndrome. As the c-fibre activity and the expression of several receptors is supposed to be modified in those pathological conditions, it might show differences in brain activations as well.

#### Concluding message

Cold sensation in the bladder activates a different network compared to bladder distension. The findings would support our hypothesis that cold sensation is processed differently from bladder distension.

#### References

1. Mukerji et al. (2006) BMC Urology, 6:6
2. Matsuura et al. (2002) J Urol, 168:2035-2039
3. Griffiths and Tadic (2008) Neurourol Urodyn, 27:466–474

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<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>Kantonale Ethikkommission Zürich</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>