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TRIAL OF A NEW BLADDER STIMULATION METHOD TO INCREASE BRAIN RESPONSE SIGNAL IN FMRI

Hypothesis / aims of study

Urgency urinary incontinence (UUI) imposes a significant burden on quality of life for sufferers and is associated with substantial costs and morbidities. The search for a cause has moved beyond the bladder to a central origin; the brain has become the newest target for LUT research. Studies over the last 10 years have used functional MRI to begin to understand the complex brain mechanism involved in continence control. The elucidation of the relevant brain activity in no trivial matter—attempting to single out one continuous signal from myriad other brain processes requires a carefully designed stimulus protocol. To date, the most consistently used protocol has been carefully regulated and repeated infusion of fluid into a full bladder to simulate urinary urgency, coupled with matched withdrawal to standardize bladder volume, sensation and reduce risk of spontaneous events such as detrusor overactivity and leakage. Associated brain activity from such a repeated stimulus can be summed to increase signal to noise ratio and the contrast between fluid infusion and withdrawal is assumed to approximate to the brain mechanism involved in urinary urgency, which can be used as a stepping stone to investigate mediators of pathology, reaction to treatment and compensatory mechanisms. While somewhat successful, these studies require large (~20) groups to obtain statistically useful information due to low signal to noise ratio. In order to reduce the number of participants in each group and allow analysis of groups with greater homogeneity, it would be beneficial to increase this signal to noise ratio, specifically by improving the bladder filling stimulus.

The aim of this study was to test an improved bladder infusion protocol and compare it to the standard infusion protocol that has been used to stimulate brain response to bladder filling in many previous studies.

Study design, materials and methods

We recruited 5 women aged over 60 that had previously had our concurrent fMRI imaging with bladder filling protocol. All had UUI with leakage episodes reported >5 times per week. Participants attended for two visits, the first for clinical history and evaluation of incontinence and the second for the functional MRI scan with improved protocol.

On the second visit, women were catheterized and positioned in a Siemens Trio 3T MRI scanner, with multiband acquisition scheme (32-channel head coil). An MPRAGE structural image was obtained, then blood oxygenation level dependent (BOLD) image using echo planar imaging (EPI), with repetition rate (TR) = 1.5 s, echo time (TE) = 30ms, flip angle = 850, with 54 slices in a 220mm field of view with voxel size of 2.3mm^3. The new protocol (fig 1 right) was then implemented as follows: the participant's bladder is filled, via catheter until she signals strong desire to void via button. Blood oxygenation level dependent (BOLD) images are obtained while sterile water is infused and withdrawn from the bladder. The protocol starts with a 7-scan pause, followed by infusion (57ml; 10 scans; 15s), pause (7 scans; 10.5s), and withdrawal (53ml; 26 scans; 39s), repeated 8 times (see figure 1). The contrasts obtained are the sum of activity calculated in infusion images minus the sum of withdrawal images. Activity was then analysed in regions of interest known to be important in the continence mechanism: the dorsal anterior cingulate cortex/supplementary motor area (dACC/SMA – motor control, MNI coordinates [4 14 42]), the medial prefrontal cortex (mPFC – executive control [4 50 14]) and the right insula (visceral sensation, [38 16 6]). Regional activity was compared between blocks and the intraclass correlation coefficient calculated to assess reliability of repeated measurements. Regional activity and ICC was also calculated for each participant's historical fMRI scan (fig 1, left, between 3-8 years previously) to assess whether the new protocol was more repeatable.

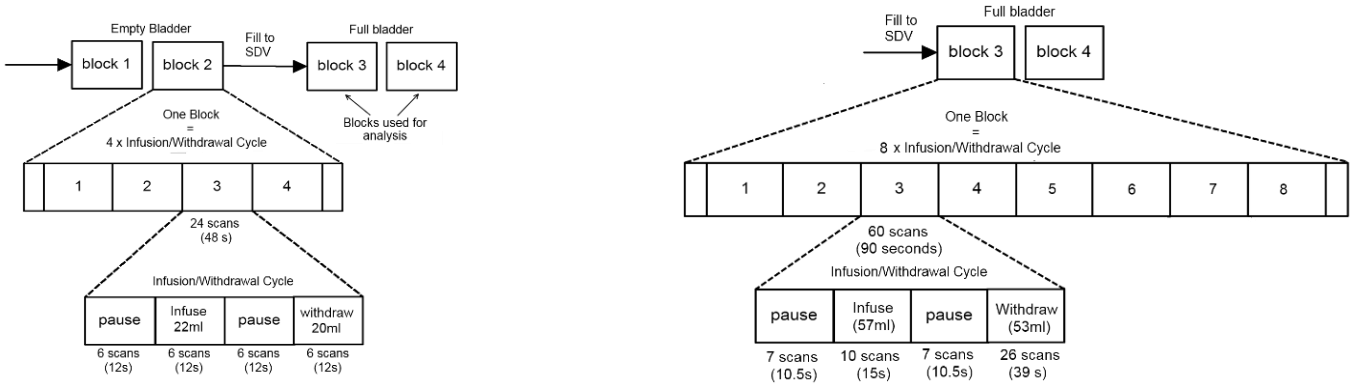

Figure 1, left 'original' protocol; right 'improved' protocol

Results

In the initial 5 test subjects (more to come), the reproducibility of the protocol for two measurements made minutes apart was markedly improved: the intraclass correlation coefficient (ICC) was 0.53 vs 0.31, calculated over three important ROIs (dACC, mPFC, R Insula). The magnitude of the signal in each ROI increased by 38% in the dACC and 35% in the R Insula, with the standard deviations decreasing by 29% in the dACC and as much as 50% in the right insula. There was no significant difference between the magnitude of activation in the two blocks (old or new protocol) in any region of interest at $P<0.05$.

Interpretation of results

The increase in signal magnitude suggests that the new protocol does indeed provoke a stronger brain response. The improvement of ICC suggests that the stronger stimulus provokes less variability in brain response, making measurements more repeatable using the new technique suggesting a higher signal to noise ratio and stronger response to stimulus. The lack of difference between activity in the subsequent blocks suggests neither technique promotes habituation nor increased sensitivity to stimulus.

Concluding message

These preliminary results suggest that strengthening the stimulus to the bladder by increasing the rate and volume of infused fluid, plus the number of repeats might improve the repeatability and size of this fMRI BOLD signal. Increasing signal size will allow investigation of smaller numbers of subjects per group and consequently, tighter grouping of phenotypes with similar symptoms. This will allow better investigation of disease phenotypes.

Disclosures

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