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ASSESSMENT OF REPEATABILITY OF FUNCTIONAL MRI PROTOCOL TO ASSESS BRAIN ACTIVITY DURING URGENCY

Hypothesis / aims of study

Urgency urinary incontinence (UUI) is a prevalent, morbid and costly problem in older adults. Explanations and treatments that focus on the bladder alone are inadequate as it is increasingly recognized that part of the cause of overactive bladder symptoms is linked to central cerebral control. Numerous brain imaging techniques have been employed to understand the brain's role in the continence mechanism, in particular functional methods to assess brain activation caused by bladder stimulation. Our group, among others, has measured such activation by implementing a functional MRI protocol consisting of blood oxygenation level dependent (BOLD) signal measurement in the brain during repeated infusion and withdrawal of fluid to and from the bladder as a standardised method of stimulating urinary urgency. Until now the reliability of this technique has not been evaluated.

The aim of this study was to evaluate, in a large group, the test-retest repeatability of BOLD brain response to the infusion-withdrawal protocol in consecutively repeated measures.

Study design, materials and methods

We evaluated scans from women >60 years of age with UUI attending for fMRI evaluation in our continence research centre. All gave informed consent and the studies were approved by the University of Pittsburgh Institutional Review Board.

fMRI protocol proceeded thusly: women were catheterized and positioned in a Siemens Trio 3T MRI scanner. Structural MPRAGE scans were initially obtained, followed by fMRI BOLD sequences during the simultaneous stimulus protocol on an empty (blocks not used for this analysis) then full (measurement blocks) bladder. This stimulus consisted of four repeats of a cycle of infusion and withdrawal of sterile water into the bladder via 8Fr catheter: one cycle consisted of 22ml infused over 12 seconds with subsequent 20ml withdrawn over 12s – four of this cycle constituted a measurement 'block'. fMRI scans from women who had two 'blocks' performed consecutively (<5 mins apart), accompanied by signals of 'strong urge to void' (button press) with less than 50ml infused fluid between blocks and no urodynamic sign of detrusor overactivity or leak were included in this analysis.

fMRI scans are first evaluated by calculating the 'contrast' - the difference in brain activation (BOLD signal) between the sum of all four infusion (high sensation) and the sum of all four withdrawal (low sensation) segments, which represents brain response to a strong urge to void from rapid bladder distension. We evaluated the activation in brain regions of interest (RoIs) selected from previous studies and current working knowledge of brain-bladder control mechanisms: 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]). We calculated intraclass correlation of mean brain activity (evaluated using REX MatLAB package) in each region of interest ($18mm^2$) between the two consecutive scan 'blocks' selected for each individual. We also performed paired t-tests to assess the presence of systematic difference between the two blocks, for both the regions of interest and the whole brain.

Results

In total, 59 women, mean (SD) age 70 (7.5), median 69, range 60-90, reporting more than five UUI episodes per week, had pairs of blocks that were eligible for inclusion. The mean (SD) volume infused between blocks was 9.6 (14) ml. Comparing blocks in each RoI, there were no significant differences in magnitude of activation (paired t-test), but variance was significantly larger in block B in the right insula (F-test) (see Table 1). Bland-Altman analysis showed no systematic difference in activity in the repeated blocks A and B. Intraclass correlation coefficient (ICC) was 0.19 for the right insula, 0.32 for the dACC/SMA and 0.44 for the mPFC. A t-test for systematic differences between blocks in the whole brain suggested less activation in the second block (B) in the medial frontal and post central gyri and posterior cingulate cortex (P<0.001 at cluster level, thresholded at P<0.05, corrected for multiple comparisons).

	Mean (SD)		**p-value**	
Brain region	Block A	Block B	Paired t-test	F-test
Right Insula	0.157 (0.312)	0.010 (0.492)	0.406	**0.0004**
dACC/SMA	0.162 (0.349)	0.094 (0.366)	0.212	0.360
mPFC	-0.108 (0.441)	-0.119 (0.535	0.876	0.073

Table 1. Mean (SD) of activation in regions of interest, and results of paired T-tests for the difference between blocks, and F-tests for the ratio of their variances

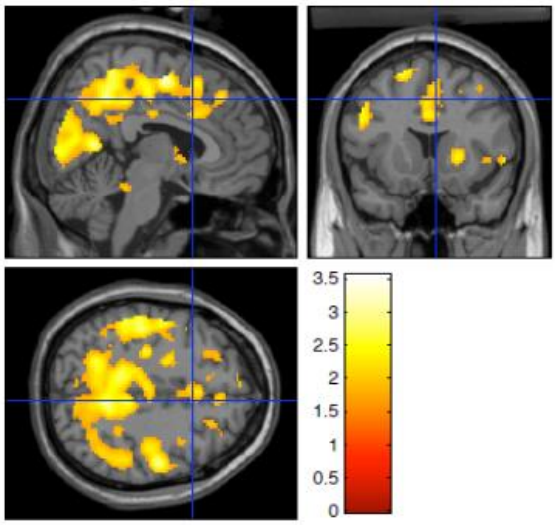

Figure 3. Whole-brain paired t-test for the difference between block A and block B. Activation is significantly less in block B than Block A in a region of the post central and medial frontal gyri and posterior cingulate (significant P<0.001 at cluster level, corrected for multiple comparisons). The cross-hairs indicate the centre of the dACC/SMA region of interest.

Interpretation of results

Brain activation is not increased by bladder filling/time between blocks (possible increased sensation), nor does it decrease which might indicate habituation to stimulus. Significantly increased variance in the right insula, might reflect general variation in the response to increasing stimulus. Brain areas other than the RoIs may reflect habituation including parts of the occipital lobe and the posterior- and mid-cingulate cortex, but these are less important in the brain-bladder mechanism. Despite the lack of systematic change between blocks, the ICC suggests considerable variability ranging from poor to fair. Although these values are low they fall within the range reported for other similar fMRI studies (1) and will serve as a benchmark for assessing other protocols. The fact that the ICC is low suggests considerable opportunity for strengthening bladder stimulation methods to provoke brain activity. Alternatively, variation may be attributable to physiological variation. This analysis was limited by its secondary nature, and data for long-term repeatability is still unavailable, however, this is the first attempt to assess the reliability of brain imaging using this type of bladder stimulus protocol.

Concluding message

Short-term repeatability of brain activation using this protocol is low. In the 3 predetermined bladder-control RoIs, habituation is not significant and repeatability appears to be limited by random variation in the patterns of brain activation. Repeatability could be improved by improving the bladder stimulation protocol so as to magnify brain responses, however, if this variation reflects physiological changes, improving the protocol would have little effect.

This study shows the limitations of designing robust studies to assess brain control of bladder function – an intrinsically unreproducible system which is difficult to standardise. We can see that use of fMRI to assess bladder control in **individuals** is inappropriate. This is, however, the best method that we have to unravel the complexity of brain-bladder control, and much progress has been made. Examination of **group-level** fMRI has yielded important insights into brain control of the bladder; this technique is highly useful in this domain. An approach mindful of the limits of technology and natural variability will ensure the future of this field.

References

1. Ann N Y Acad Sci. 2010;1191:133-55

Disclosures

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