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Tadic S[1], Schaefer W[1], Griffiths D[1], Resnick N[1]
1. University of Pittsburgh

ABNORMAL SUPRASPINAL CONTROL PATHWAYS IN URGE INCONTINENCE

Hypothesis / aims of study

Functional imaging has revealed regional brain responses to bladder filling that reflect the operation of the supraspinal bladder control system. The response patterns depend on bladder fullness and on whether bladder control is good or poor. However, these patterns are created by underlying neural interconnections that cannot be visualized by standard analytical techniques. To reveal such connections we have analyzed functional MRI (fMRI) data using a statistical method new to this field. The hypothesis is that the effective connections between regions differ in subjects with and without good bladder control.

Study design, materials and methods

Subjects were 17 female volunteers aged 30-85 y, without overt neurological abnormality. Nine had good bladder control (no OAB symptoms and no detrusor overactivity [DO] on urodynamics) and 8 had poor control (urge incontinence and DO on previous urodynamics, but not during scanning). These numbers provide adequate power to detect significant effects at a group level. Each subject underwent fMRI of the brain (3 T magnet, repetition time = 1.5 s) while a small amount of fluid was repeatedly infused into and withdrawn from the bladder. This was done initially with a small volume of liquid in the bladder, and then repeated after filling the bladder to strong desire to void. Intravesical pressure was monitored to rule out DO during scanning.

The fMRI signal was processed to show regional differences in brain activity between infusion and withdrawal, representing responses to bladder filling. Results in individuals were combined to obtain patterns of response for the groups with and without good bladder control.

Connectivity analyses were performed using the physio-physiological interaction (PPI) method. Starting from a pair of regions with prominent responses, PPI generates a map of new regions where activities in this chosen pair interact to reinforce or to reduce the response, indicating underlying connections. Connectivity can be positive or negative, implying either reinforcement or reduction. Based on prior knowledge and prominence of response, we selected a pair of regions for initial PPI analysis. We performed further PPI analyses iteratively to sequentially identify relevant connections.

Results

Normal subjects (good bladder control). With a small volume in the bladder, the main response to bladder filling was bilateral and near the posterior insula (Fig. 1), with slight activity in the anterior cingulate (ACG), frontal cortex, and a few posterior parts of the brain. When bladder volume was increased to elicit strong desire to void, there were only small changes: the insular response shifted anteriorly (consistent with more unpleasant sensation) and ACG activity became more prominent.

PPI analysis revealed connections from right insula and ACG to prefrontal cortex and also to a specific midline posterior region of the cortex (the precuneus, see Fig. 2 for location). Subsequent PPI analysis, based on right insula and prefrontal cortex, again suggested connections to the precuneus. In every case the connectivity was negative.

Urge incontinence (poor bladder control). With a small volume in the bladder, responses were weaker than those seen in normals. When bladder volume was increased to elicit strong desire to void, responses became markedly greater, especially in the insula, ACG, and precuneus.

PPI analysis revealed positive connections from right insula and ACG to the precuneus, although not to the frontal cortex. This connectivity pattern was significantly different from normal in precuneus and prefrontal cortex (Fig. 2). Further PPI analysis based on right insula and prefrontal cortex suggested a connection to the precuneus, also with positive connectivity.

Interpretation of results

We have identified interconnections of 4 regions of the bladder control network: the insula (mapping of afferents), the prefrontal cortex (voluntary control), the ACG (autonomic/ emotional motor control), and the precuneus (function not known). Normally the effect of activation of one region tends to be cancelled by activation elsewhere (negative connectivity), perhaps maintaining stability. Thus the normal response to bladder filling (Fig. 1) changes only slightly as sensation increases. In subjects with poor bladder control however the connectivity is positive, so that the effect of activity in one region is reinforced by activity in another. Accordingly, in subjects with poor bladder control the precuneus responds abnormally strongly as the bladder fills. Thus, in subjects with poor bladder control, responses tend to be stronger in posterior than in prefrontal regions.

Concluding message

In women with poor bladder control the cerebral control pathways function abnormally. A newly recognized pathway involving the posterior cortex (the precuneus) becomes prominent, while prefrontal control may be reduced. These observations suggest that urge incontinence and idiopathic detrusor overactivity may involve abnormal function of the supraspinal control system, and not just a bladder abnormality as is often supposed. Potential targets of therapy therefore include the brain.

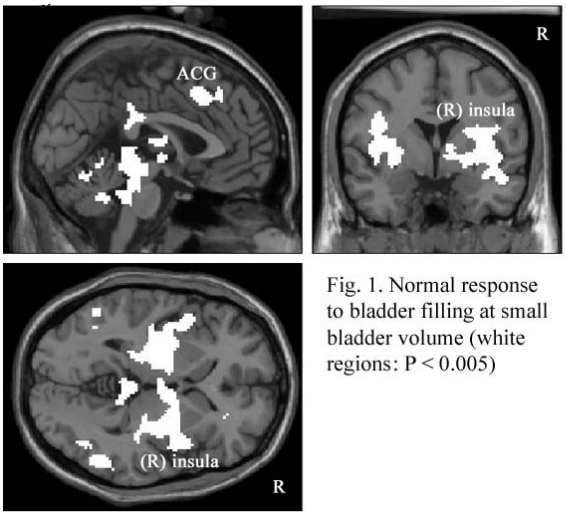

Fig. 1. Normal response to bladder filling at small bladder volume (white regions: $P < 0.005$)

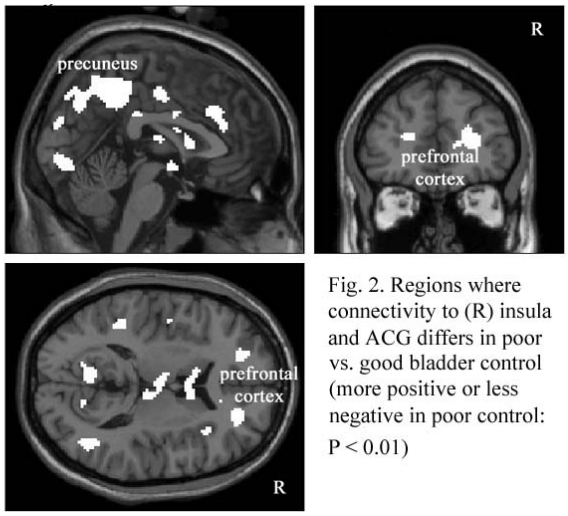

Fig. 2. Regions where connectivity to (R) insula and ACG differs in poor vs. good bladder control (more positive or less negative in poor control: $P < 0.01$)

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