197

Resnick N[1], Tadic S[1], Clarkson B[1], Murrin A[1], Griffiths D[2]
***1.** University of Pittsburgh, **2.** University of Pittsburgh (ret)*

BRAIN MECHANISMS UNDERLYING BEHAVIORAL THERAPY FOR URGENCY INCONTINENCE IN OLDER WOMEN

Hypothesis / aims of study

Urgency incontinence (UI) is common and troublesome in older people, yet despite recent advances it is still difficult to treat effectively. One reason is that the mechanisms underlying disease and therapy are poorly understood. Symptoms such as "latchkey incontinence" and the effects of cortical lesions indicate that UI is at least partly a disorder of cerebral control, but this possibility has until recently been little explored. We employed behavioral therapy (biofeedback-assisted pelvic floor exercises, BFB, intended to strengthen bladder control) as a probe to identify such mechanisms. Using functional magnetic resonance imaging (fMRI) we examined neural activity in 3 cerebral regions of interest (ROIs) defined *a priori*: the midline dorsal anterior cingulate cortex (dACC) with the adjacent supplementary motor area (SMA); the medial pre-frontal cortex (mPFC); and the right insula. Together these 3 ROIs form a sensorimotor network that is involved in many aspects of homeostasis, presumably including bladder control.

If these brain regions truly are involved in the mechanism of UI improvement, their activity should change after BFB in concert with the improvement. Accordingly, we hypothesized (1) that dACC/SMA activity would decrease in responders to treatment (but not in non-responders), indicating a reaction to UI improvement, and (2) that abnormally weak activation of mPFC in UI subjects would be reversed after successful BFB, reflecting a strengthening of the bladder control mechanism with consequent reduction in UI severity. We expected the insula to be activated but made no hypothesis regarding change after BFB.

Study design, materials and methods

To test these hypotheses we performed a pre/post trial of the effect of BFB on regional brain activity. Participants were independently mobile, community-dwelling, cognitively intact women with moderate to severe UI symptoms and detrusor overactivity (DO) on urodynamics, aged 60+ y (mean 72 y), without clinically evident neurological disease Before and after therapy, they underwent clinical evaluation, comprehensive urodynamics, and a 3-day bladder diary, followed by fMRI evaluation of brain responses to rapid bladder filling. Incontinence severity was measured at baseline and post-BFB by the number of UI episodes on the 3-day bladder diary. At baseline all had at least one such episode. BFB consisted of 4 biweekly visits (for EMG biofeedback, teaching and advice), with intervening home practice and bladder diaries. Since previous work suggested that susceptibility or refractoriness to treatment might be an important variable, we operationally defined subjects with >50% reduction in UI episodes after BFB as responders to treatment, expecting that about half would qualify. The total number of subjects (60) provided sufficient statistical power to examine regional activations in subgroups as small as 20 subjects. A small group of near-age-matched continent subjects ("normals") underwent baseline testing only, for comparison.

For fMRI, with the subject supine in the 3T MR scanner prior to scanning, the bladder was filled until the subject signalled strong desire to void, but without DO. With the scanner recording a whole brain scan every 2 s, a small amount of liquid was repeatedly infused into and withdrawn from the bladder. Using the program SPM5, after standard fMRI pre-processing, the difference between the signals during infusion and withdrawal (adjusted for hemodynamic delay) was used to represent the activation associated with bladder filling, a procedure well established in the literature. For every voxel in the brain, the probability of activation was calculated, expressed as a t-value and mapped to form a 3-dimensional contrast image for each subject. Single-subject images were entered into appropriate second-level group analyses – e.g. one-sample or paired-sample t-tests. The resulting group maps were thresholded at $P<0.05$ to determine the number of activated voxels in the predetermined ROIs (as shown in the table) and to identify clusters of activity. (P-values in table represent the probability that the largest observed cluster could have arisen by chance, either corrected or uncorrected for multiple comparisons, see table legend.)

Results

Subjects: (n=60); mean age was 72.3 y: 70.1 in responders and 73.8 in non-responders (P=0.14). Normals (n=18); mean age was 65 y.

BFB: With BFB the median frequency of UI episodes decreased from 3.3 to 1.7/24 h ($P < 0.0001$). 24/60 (40%) were responders. Median UI frequency decreased from 3.0 to 0.3 episodes/24 h in responders and from 3.4 to 2.7/24 h in non-responders. 9/60 subjects (15%) became dry. Baseline UI frequency did not differ between responders and non-responders (P=0.5).

fMRI: *dACC/SMA* was strongly activated at baseline in responders and the activation tended to decrease after BFB, supporting hypothesis (1). See table.

mPFC was strongly deactivated at baseline, but only in non-responders, and it did not change significantly after treatment. Thus the hypothesized region was involved but its behavior was not as expected: mPFC deactivation predicted but did not mediate failure of UI to improve.

Insula was activated in responders at baseline and was unchanged after BFB. Activation was much less pronounced in non-responders. Insula activation thus tended to predict success of BFB but not to mediate it.

fMRI results in responders did not differ significantly from normal ($P>0.7$ in every case). The mPFC deactivation seen in non-responders however was absent in normals.

	dACC/SMA			mPFC			insula		
	Responders	Non-resp	Resp minus nonresp	Responders	Non-resp	Resp minus nonresp	Responders	Non-resp	Resp minus nonresp
Pre	**2091****	90	755	0	**–2125 ***	**1730 ***	**1369 ***	-27	47
Post	1066	233		-94	**–2272 ****		**1356 ***	96	
Pre minus post	239	0		123	0		44	0	
Normal minus UI	3	0		6	**2304 ***		79	0	

Numbers of activated or deactivated (-) voxels in 3 predetermined ROIs, pre- and post-BFB and stratified by response to BFB.
For bolded entries, ** = significant P<0.05 at corrected cluster level; * = trend to significance at P<0.1 corrected or P<0.05 uncorrected cluster level.
Note: differences between pre and post or between responders and nonresponders (pre-BFB) are the result of separate t-tests, not simple subtraction of post from pre values or nonresponder from responder values.
Normal comparisons are all with the same group of 18 normal scans, regardless of whether pre- or post-BFB.

Interpretation of results

These results support hypothesis (1) and, since SMA activation is known to cause pelvic floor/sphincter contraction, they imply that, when dACC/SMA activation diminishes after treatment, it is a reaction to improvement in UI, not a cause. Hypothesis (2), regarding mPFC, is not supported: there is no evidence that changes in mPFC activation among responders are a cause of UI improvement. Intriguingly however, at baseline non-responders show a completely different activation pattern than responders or normals: mPFC deactivation takes the place of dACC and insula activation, suggesting that it represents an alternative continence or coping mechanism, perhaps an attempt to *consciously* control the bladder. This mechanism is unaffected by BFB. Thus this work brings into focus the existence of 2 different UI phenotypes with different treatment requirements and different brain responses to bladder filling. How the brain decides which of these responses to express is a new and exciting direction of research.

Concluding message

In older community-dwelling women with UI, behavioral treatment such as BFB has modest efficacy but, when successful, it leads to measurable changes in brain function. These changes are a consequence rather than a cause of UI improvement.
Subjects refractory to treatment show an entirely different pattern of brain activity, even before treatment, suggesting that they represent a different phenotype. Identification of the neural substrate of this phenotype is the next step toward novel, more effective interventions that will offer relief to many millions of patients.

Disclosures

Funding: US Public Health Service - NIH **Clinical Trial:** Yes **Registration Number:** clinicaltrials.gov (NCT00177541) **RCT:** No **Subjects:** HUMAN **Ethics Committee:** University of Pittsburgh Institutional Review Board **Helsinki:** Yes **Informed Consent:** Yes