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CHANGES IN BRAIN ACTIVITY DURING REPORTED URGENCY AFTER 8 WEEK TRIAL OF FESOTERODINE IN OLDER WOMEN WITH REFRACTORY URINARY INCONTINENCE

Hypothesis / aims of study
Specific regional brain activity is seen during reported urinary urgency in patients undergoing artificial bladder filling with simultaneous functional MRI. This regional activity is thought to reflect the suppression of urgency and an attempt to maintain continence. The sensation of urgency elicited in the scanner mimics the compelling need to void that patients experience in their daily life. In clinical practice, these symptoms are reduced by treatment with anticholinergic drugs. While the effect of anticholinergics on the brain-bladder control network are not known, it is plausible to hypothesize that symptomatic relief will be mirrored by changes in the brain's response to bladder filling. As such, our aim was to use an anticholinergic drug (fesoterodine fumarate,Toviaz®) as a biological probe to explore such changes. We hypothesized that after an 8-week course of drug therapy, regional responses to bladder filling would be reduced in intensity.

Study design, materials and methods
We enrolled a sample of 8 functionally independent, community-dwelling women aged 61-83 (mean 70) with moderate to severe urgency urinary incontinence. All women had previously undergone biofeedback therapy and failed to improve (improvement defined as a reduction of incontinence episodes by more than 50%). We excluded women with significant cognitive impairment (Mini-Mental State Examination score ≤27/30), secondary causes for severe urinary incontinence (e.g. history of bladder cancer, spinal cord lesions, multiple sclerosis, pelvic radiation, interstitial cystitis, or sphincter implant), characteristics that would preclude performing functional MRI (e.g. claustrophobia, presence of implanted metal or electromagnetic devices and medical instability), as well as subjects with allergies and/or contraindications to anticholinergic drugs (e.g. open angle glaucoma).
Prior to intervention, we assessed severity of urinary incontinence, defined as a number of urge incontinent episodes per 24 hours (assessed by 3-day bladder diary) and perception of urgency, measured by the Urgency Perception Scale (UPS). Regional brain activity prior to drug trial was assessed using an established protocol combining functional brain imaging (fMRI) with simultaneous urodynamic monitoring during bladder filling. All measures were repeated after 2 months of drug therapy (pre-post study design). After baseline evaluations, each subject was started on fesoterodine 4mg dose and monitored for adverse events and adherence by phone. There was an interim assessment of therapeutic efficacy after 4 weeks of therapy with an option for dose adjustment and increase to 8mg if necessary. Primary outcome of the study was the change in brain activity, defined as blood oxygen level dependent [BOLD] signal change measured by fMRI during bladder filling and patient-reported urgency. Change in brain activity (pre-post) was mapped and analyzed using SPM (Statistical Parametric Mapping) program and paired t-tests. Secondary outcomes measured change in incontinence severity.

Results
All subjects tolerated the medication well, with an expected complaint of dry mouth which was mild. There were no reported CNS adverse effects. At interim assessment, two subjects required an increase in dose of fesoterodine to 8 mg daily. After treatment, the number of episodes of urgency with leakage per 24 hours decreased significantly from mean 5.42 to 3.20 ($p<0.01$). Perception of urgency also improved, from mean of 1.75 to 2.00 but was not significant ($p=0.63$).
At baseline (before drug therapy), significant activations during bladder filling were seen in the sensory motor cortex and frontal lobe, bilateral insula, pre- and post- central gyrus, supplemental motor area (SMA) and brain stem, including periaqueductal gray (PAG) and pontine micturition center (PMC) as shown in Figure 1. Compare to baseline, activity in some of these key regions decreased after the course of drug therapy – bilateral insula and regions in frontal lobe adjacent to SMA (Figure 2). Activity in superior temporal gyrus also significantly decreased after drug trial (Figure 2).

Interpretation of results
As expected, an 8 weeks course of fesoterodine has improved symptoms in older women with moderate to severe, refractory urgency urinary incontinence as noted by reduction of the number of episodes of urgency with urine leakage. Their baseline brain activity showed significant activation of the regions involved in response to bladder filling, and fesoterodine therapy has alleviated this response in some areas. Since there was a significant improvement in severity of symptoms and reduction in perceived symptoms, we believe that the changes seen in the brain are indirect and a consequence of improved lower urinary tract symptoms. Observed changes in key regions of insula and frontal lobe further support this. For example, reduced activation in the bilateral insula may indicate a lessened perception of full bladder or urgency after drug therapy, while a decrease in frontal lobe/SMA activation may indicate a reduced need for compensatory CNS effort to maintain continence.

Figure 1. Regional brain activity in urge-incontinent women during urgency - before therapy (see 'Results' section).

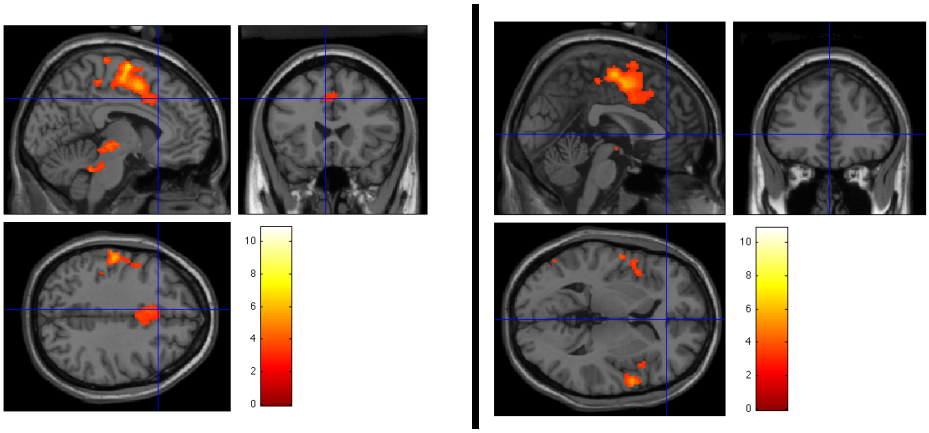
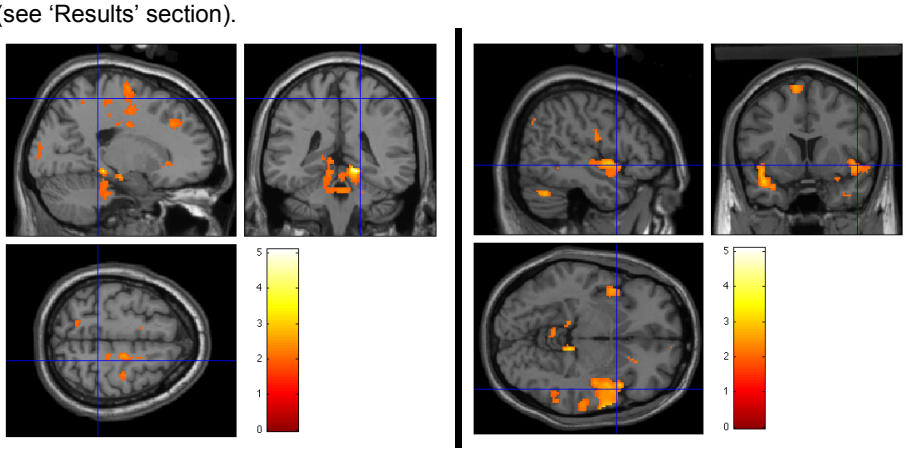


Figure 2. Regional brain activity during urgency (activity decreased) - after therapy with fesoterodine (see 'Results' section).



Concluding message

Fesoterodine therapy improved symptoms of urgency urinary incontinence in older women with refractory disease. In addition, brain activity during urgency provoked by bladder filling was alleviated after a course of fesoterine, suggesting an improvement of symptoms and reduced need for compensatory activation due to an effect of the drug at the level of lower urinary tract.

Disclosures

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