PRIZE AWARD: Best Clinical Abstract (Joint Prize)

214

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BRAIN ACTIVITY MEASURED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) IS RELATED TO PATIENT REPORTS AND CLINICAL SEVERITY OF URGE URINARY INCONTINENCE

Hypothesis / aims of study

Urge urinary incontinence (UI) is diagnosed clinically using bladder diary and pads which also help grade its severity and further guide and assess the therapy outcomes. Unfortunately, the effectiveness of treatment has not greatly improved, partly due to our lack of understanding of the pathobiology of the disease. Our group has adapted functional brain imaging to study UI by adding urodynamics to fMRI. This enables simultaneous monitoring of brain and bladder activity during bladder filling so that bladder storage and continence control can be studied under experimental conditions.[1,2] Studies using this methodology in older women have shown significantly increased activity of brain regions involved in mapping body sensations (right insula/somatosensory cortex), emotional processing (anterior cingulated cortex – ACC, limbic cortex) and decision-making (various parts of frontal cortex), implying their potential role in continence control. [3]These responses are most pronounced when subjects report strong bladder sensation – probably 'urgency' – while in the scanner, further implying that such brain activity might represent a neural correlate of this symptom. Despite these findings, it is not yet known whether these experimental observations reflect patients' everyday experience, as registered by standard clinical tests such as a bladder diary or a pad test. A significant association between observed brain responses and clinical data would imply that activity recorded under artificial conditions in the scanning session reflects the clinical severity of the condition in daily life. Thus, our **primary hypothesis** was that the brain responses to bladder filling observed in the scanner during reported sensations of 'urgency' would be correlated with the number of episodes of urge UI recorded in the bladder diary and with the severity of leakage measured by pads. **Secondary analysis** included correlation of brain responses with patients' reports of the burden of disease using the Urge Impact Scale (URIS-24).

Study design, materials and methods

We conducted a cross-sectional study of older women with urge UI. All had been previously undergone detailed clinical and video urodynamic testing followed by fMRI and simultaneous simple urodynamics. All were functionally independent, community-dwelling women aged 60 and older with at least two urge UI episodes per week for at least 3 months despite correction of potentially reversible causes. According to history and voiding diary, incontinence had to be pure or predominantly urge in nature. All subjects had to be able to complete a voiding diary accurately and to perform a 24-hour pad test.

Scanning session: we used an originally developed method that allows simultaneous monitoring of brain and bladder function by combining fMRI and simple urodynamics. This allows us to examine brain responses to bladder filling. The bladder was filled quickly until subjects signalled strong urge. We then repeated 1 or 2 cycles of filling/emptying. After image acquisition, pre-processing and all further analyses, were done using Statistical Parametric Mapping (SPM2) (http://www.fil.ion.ucl.ac.uk/spm/spm2.html).[1,2]

Results

The average age of our 14 subjects was 76 years, range 64-88. Average UI episodes/day of 2.3 (range 0.7-4.7). Seven subjects had demonstratable detrusor overactivity during their detailed urodynamics testing and seven did not.

Among these patients, a group analysis based on the measurements made with full bladder (evoking a strong bladder sensation believed to be equivalent to urgency but not evoking DO) showed that bladder filling provoked brain activity in many regions, including dorsal anterior cingulate (dACC, BA 32), insula (BA13), frontal cortex (superior, middle and medial frontal gyrus; BA 6/9), precentral gyrus (BA44), fusiform gyrus (BA19) and cerebellum. In contrast, bladder filling led to deactivation in some frontal locations: pregenual and ACC (BA 24/32), orbitofrontal cortex, and medial and superior frontal gyrus (BA 10).

Some of the brain responses during bladder filling (as illustrated on **Figure 1A**) were significantly correlated with daytime incontinence frequency (urge UI episodes per day), measured with a 3-day bladder diary. The correlation was positive in ACC (BA 24/32) (**Figure 1B**), insula (BA13), inferior frontal gyrus (BA47), orbitofrontal cortex (BA10), and posterior cingulate gyrus (BA31). There were no regions where response correlated negatively with daytime incontinence frequency. Brain responses were also significantly and positively correlated with weight of urine loss in 24 h, measured by a pad test, in similar regions, as shown in Figure 1A. There were no regions with significant negative correlation.

The planned secondary analysis showed that the psychological burden of urge UI, represented by Urge Impact Scale (URIS-24), was also significantly and positively correlated with brain activity in the scanner, but in different regions: precuneus (BA47), superior temporal gyrus (BA39/13), supramarginal and transverse gyrus (BA41) and posterior cingulate gurys (BA31). There were again no significant negative correlations.

Interpretation of results

Regional brain activity provoked by bladder filling (in the presence of self-reported urgency but in the absence of DO) was significantly correlated with the severity of UI in daily life. The regions involved are similar, whether the objective severity of incontinence is represented by the number of daytime incontinence episodes on a 3-day bladder diary or by the weight of urine lost in one day, measured with a pad test. These findings confirm our primary hypothesis. Interestingly, the brain regions where activation is significantly related to the subjective burden of the UI are different, confirming that subjective and objective measures of incontinence represent fundamentally different dimensions of this disease. Taken together, the data from this study demonstrate a cross-sectional relation between the clinically assessed severity of urge incontinence and changes in brain activity during bladder filling, measured under experimental conditions.

Concluding message

The activation of brain regions involved in control of continence is related to commonly used patient-derived clinical measures of urge-incontinence severity. Thus observations made under artificial conditions in the scanner reflect patients' real-life experience.

The cross-sectional approach used in this study has revealed potential neural correlates of symptoms and different aspects of the urge UI and has suggested targets for future investigations to improve the understanding of its pathophysiology, therapy and treatment outcomes.

Figure 1A

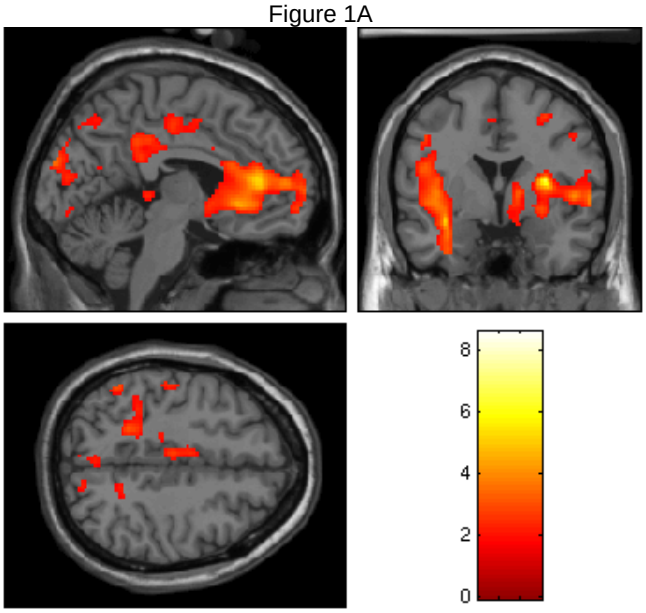
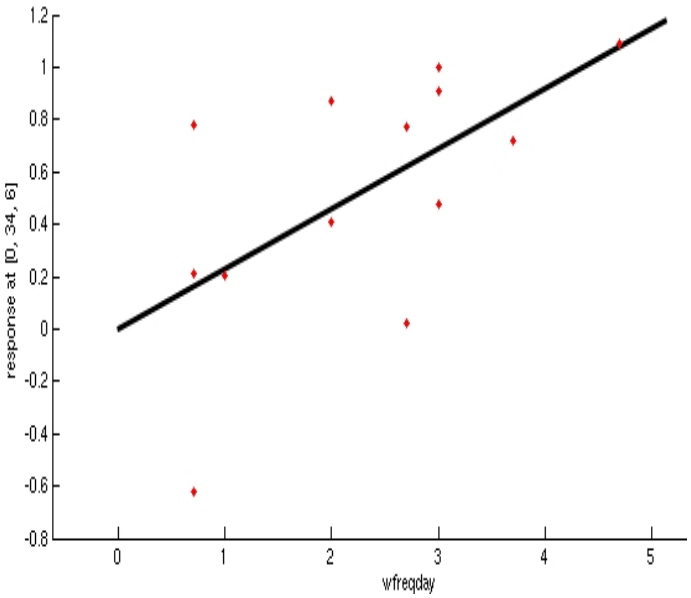


Figure1B



Legend: Brain activity correlates positively with UI severity on bladder diary (display of the regions – left; response in ACC – plot on the right)

References

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Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**University of Pittsburgh Institutional Review Board**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**