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BRAIN ACTIVITY MEASURED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) DURING SIMULATED EPISODES OF URGENCY DIFFERS FOR THOSE WITH A HISTORY OF DEPRESSION

Hypothesis / aims of study

Depression is prevalent in older women with urgency incontinence (UI) since approximately one third has either history or current symptoms. Epidemiological studies have shown an association between UI (severity or burden) and depression (symptoms or history), but the mechanism by which depression might affect continence control is unknown. More importantly, the presence of depressive symptoms at baseline significantly impairs response to therapy (e.g., biofeedback with urge suppression strategies) [1].

Women with UI have altered brain responses to bladder filling [2], and such findings may represent a neural correlate of their symptoms (e.g., urgency) and reveal part of the mechanism underlying impaired continence control. Since depression affects neural circuits involved in mood, affect, and cognitive control, depression may alter these brain responses and thus contribute to UI.

We therefore aimed 1) to determine whether regional brain activity during simulated episodes of urgency differs for subjects with and without a history of depression and 2) to determine whether the differences might be related to the severity of current depressive symptoms.

We postulated that 1) regional brain activity during self-reported urgency would differ for subjects with and without a history of depression, particularly in regions involved in bladder control and related to emotional and cognitive function and 2) the degree of activation of these or other regions would be negatively affected by the severity of current depressive symptoms.

Study design, materials and methods

We conducted a secondary analysis of an ongoing, cross-sectional brain-bladder fMRI study, which involved 38 functionally-independent, community-dwelling women aged ≥60 years with moderate-severe UI. We excluded women with significant cognitive impairment (Mini Mental State Exam total score ≤ 24), secondary causes of incontinence, and characteristics that would preclude fMRI (e.g., claustrophobia and implanted metal devices). All subjects underwent a detailed clinical assessment (physical exam, 3-day bladder diary, 24-hour pad test, and quality-of-life assessment with URIS-24) and urodynamic testing. Brain activity during self-reported urgency was assessed using a method that combines fMRI with simultaneous urodynamic monitoring during repetitive bladder filling/emptying cycles. We used statistical parametric mapping (SPM5) to obtain maps of regional brain activity during bladder filling and urgency, and we stratified data by previous depression history so as to investigate differences between these two groups. We used regression/correlation analyses to study the relation between regional brain activity and depressive symptom score on CES-D10 (Center for Epidemiologic Studies Short Depression Scale), which measures current depressive symptoms; a CES-D10 score ≥ 10 suggests clinical depression.

Results

Regional brain activity in the 2 groups: During self-reported urgency, regional patterns of brain activation/deactivation differ for those without and with a history of depression. In subjects **without** history of depression, the regions of activation include bilateral insula, supplemental motor area (SMA), and adjacent dorsal anterior cingulate gyrus (dACG), middle frontal gyrus, and right inferior parietal lobe; while deactivations were noted in the paralimbic system (parahippocampal cortex and hippocampus) bilaterally. In subjects **with** a history of depression, the regions of activation again include the SMA and right insula, and in addition the cerebellum, parahippocampal cortex (BA 28/35), superior temporal gyrus, inferior frontal gyrus, precentral gyrus, and pons. Regions with deactivation include ventromedial orbitofrontal cortex (OFC), parahippocampal cortex (BA 37), precuneus, and superior temporal gyrus **(**some of these regions are presented in **Figure 1)**. Analysis of between-group differences showed significantly different activations in the paralimbic system (parahippocampal cortex and hippocampus); deactivations in ventromedial OFC also differed significantly ($p<0.01$).

Regression correlation analyses: activity in an occipito-parietal region correlated positively with an increase in CES-D10 score, while activity in dACG correlated negatively **(Figure 2)**.

Post-hoc analyses also showed that women with a history of depression had significantly higher CES-D10 scores ($p<0.05$) and increased psychological burden of incontinence (lower URIS-24 score; $p=0.08$). Although women with a history of depression also had more incontinent episodes per week, the difference was not significant.

Interpretation of results

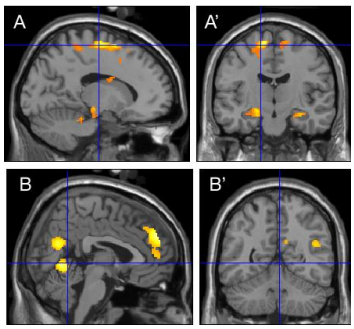
As postulated, during self-reported urgency brain activation/deactivation differs between those with or without a history of depression, particularly in regions known to be involved in bladder control. There are significant differences in responses in the (para)limbic system (increased activations in parahippocampal cortex and hippocampus, as well as SMA) and in the executive cortex (greater deactivation in medial prefrontal cortex). In confirmation of postulate (2), the activation of dACG (adjacent to SMA) becomes weaker with increasing severity of current depressive symptoms.

All these regions are known also to be involved in emotional regulation and the response to psychological stress in healthy volunteers. Their differing activity in women with a history of depression, in particular the reduced activation in SMA/dACG, may be consistent with decreased motivation and sympathetic arousal. At the same time, increased responses in the paralimbic system together with increased deactivation in medial prefrontal cortex suggest increased emotional involvement

as well as difficulty in coping or controlling the disease. Overall, this pattern of increased and decreased (de)activations may represent a neural correlate of the psychological burden of UI and of the poorer response to therapy.

Concluding message

1. Women with urgency incontinence and a history of depression have different brain activity, measured as response to bladder filling during simulated urgency in the scanner, than their peers who also suffer from urgency incontinence but do not have this mental health problem. The brain regions showing different responses are known to be involved in bladder control but also suggest an overactive emotional response together with decreased motivation and sympathetic arousal.
2. These differences in regional brain activity may offer a neural biomarker that can be used as a target in future studies aiming to improve therapeutic outcomes in women who suffer from urgency incontinence and depression.



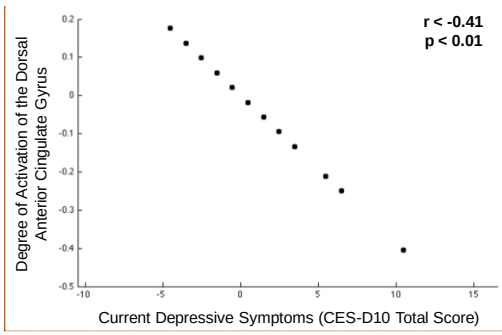


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Figure 1 (left). During self-reported urgency, there is significantly more **activation** in SMA and paralimbic (parahippocampal) cortex (images A and A') and significantly more **deactivation** in medial prefrontal cortex and posterior brain (images B and B'), for those with a history of depression versus those with no history of depression.

Figure 2 (right). Graph depicting the correlation between current depressive symptoms and activity in limbic system (dACG, dorsal anterior cingulate gyrus) during self-reported urgency in the scanner.

References

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**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**