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Tadic S[1], Aizenstein H[2], Nable M[2], Griffiths D[1], Schaefer W[1], Resnick N[1]
1. *University of Pittsburgh, Department of Medicine, Division of Geriatrics,* ***2.*** *University of Pittsburgh, Department of Psychiatry*

AGE-ASSOCIATED BRAIN CHANGES IN REGULATION OF BLADDER FUNCTION AMONG OLDER URGE-INCONTINENT WOMEN: ROLE OF WHITE MATTER HYPERINTENSITIES.

Hypothesis / aims of study

Background: Urge urinary incontinence (UI) is a significant public health problem in elderly characterized clinically by loss of voluntary bladder control, with repetitive episodes of abrupt urine leakage, generally preceded by urgency and frequently associated with detrusor overactivity, suggesting a failure of cerebral control of bladder storage function due to an inadequate brain response to increased bladder volume. White matter hyperintensities (WMH) are structural brain changes (verified by magnetic resonance imaging - MRI) specific to *aging* and are associated with functional decline and major geriatric syndromes (cognition, mobility, mood and incontinence). The clinical and urodynamic association of WMH with urge incontinence and detrusor overactivity has been reported.[1] Previously, we have identified, by using functional magnetic resonance imaging (fMRI), abnormalities in brain responses in bladder filling in urge incontinent older women.[2,3] Since both functional and structural abnormalities in cortical pathways (white matter hyperintensities, WMH) are common in the elderly we have used a multimodal approach to

Investigate possible structural basis for the previously-identified functional abnormalities of the brain-bladder control mechanism observed in urge-incontinent older women. We **hypothesized** that increase in WMH severity will have a negative impact on functional responses in brain regions related to or part of brain-bladder control network. Specific aims of this study were to: 1) investigate the difference in WMH intensity (global and in specific pathways) between urge-incontinence subjects and age-matched normal control; and 2) investigate relationships between WMH (both global and in specific pathways) and functional brain responses during bladder filling in urge-incontinent subjects.

Study design, materials and methods

WMH assessed in 8 women (> 60 years) with urge UI and 8 age- and cognition-matched continent controls. In the UI group, functional MRI was also performed to map regional brain responses to bladder filling at low and high volume (with strong urge). We used an originally developed method that allows simultaneous monitoring of brain and bladder function by combining the fMRI and simple urodynamics. Paradigm for imaging study was to examine brain responses to bladder filling with gradual increase of bladder volume at various bladder volumes in order to mimic bladder storage function. Furthermore, we combined fMRi analysis with a newly developed WMH assessment method (fully automated method for quantifying and localizing white matter hyperintensities on MRI), developed by one of the co-investigators. This method uses a fuzzy-connected algorithm to segment the WMH, and the Automated Labeling Pathway (ALP) to localize the WMH into the anatomical space. The histograms of the FLAIR (fast **FL**uid-**A**ttenuated **I**nversion **R**ecovery) images are used to automatically generate the WMH seeds, and then the fuzzy-connected algorithm uses specific parameters to form a WMH cluster (containing the respective seed). The method automatically identifies WMH seeds and generates WMH segmentation, which is objective and does not require any manual interaction. Additionally, the method allows for assessment of WMH burden region-wise. The method has been validated by high correlation with accepted 'gold standard' method (manual rating of WMH).

Results

1. Women with urge UI did not have a significant excess of WMH, either globally or in any of 19 cortical pathways compare to normal control.
2. At large bladder volumes, increased WMH correlated with decreased activity in the posterior associative cortex, cerebellum, and parahippocampal gyrus (all $r < -0.63$) (Figure 1. A-left), while it correlated with increased activity in the amygdala, PAG, and executive cortex (all $r > 0.63$) (Figure 1. B-right).
3. At low bladder volumes, increased WMH correlated with decreased activity in the parahippocampal gyrus ($P < 0.05$, all $r < -0.63$), and with increased activity in the sensory, limbic and executive cortices (right insula, anterior cingulate and medial frontal gyrus; all $r > 0.63$).

Interpretation of results

As postulated, the relationships between structural (WMH) abnormalities and functional brain responses involve the same regions that we have previously found to be abnormal in older women with urge UI. The brain regions (regions of interest – ROI) reported in this study, whose activity correlates with the increase of WMH, are also described as parts of various pathways involved in perception and registering of the afferent signals arising from peripheral organs such are, for example, bladder, colon or heart. Furthermore, same pathways connect to executive, memory and emotional control network, which, in turn, may better explain the role of brain function in control of the bladder.

Concluding message

1. WMH, as structural abnormalities associated with age, relate to the same regions previously found to be abnormal in older women with urge UI.
2. Multimodal approach combining structural and functional brain imaging during bladder study may further contribute to the study of bladder control and incontinence by adding a new information about a regulatory brain network that governs a bladder control and factors that contribute to increased vulnerability to impaired bladder control in older subjects.

References

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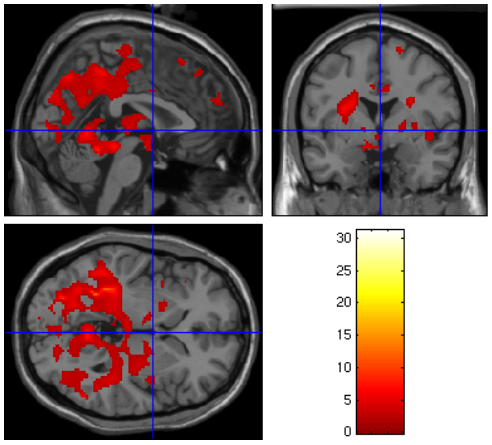
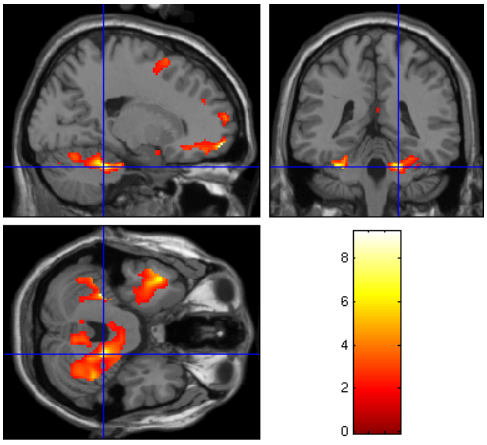
3. NeuroImage (2008) 39; 1647-53.

Figure 1. A (left) and B (right).





Specify source of funding or grant	**NIH (RO3AG25166, RO1AG020629, 5T32AG021885-04); University of Pittsburgh Competitive Medical Research Fund; Institute of Clinical Research and Education, University of Pittsburgh – NIH KI2 award.**
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	**Institutional Review Board, University of Pittsburgh**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**