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

STRUCTURAL DAMAGE OF BRAIN'S WHITE MATTER AFFECTS BRAIN-BLADDER CONTROL IN OLDER WOMEN WITH URGENCY INCONTINENCE

Hypothesis / aims of study

Prevalence of urgency and other lower urinary tract (LUTS) symptoms increases with age leading to incontinence which affects health and quality of life in otherwise functional elderly. Recent epidemiological studies in this group link subtle structural changes in their brain's white matter, shown on magnetic resonance imaging (MRI) as **white matter hyperintensities** (WMH), with incontinence symptoms. The studies consistently show that the prevalence of urgency increases with the global extent of white mater damage (WMH '**burden**') which reflects the damage in **white matter pathways**.

Nevertheless, the mechanism how WMH might lead to incontinence remains elusive, since information about how these structural changes relate to functional brain activity and the neural circuits involved in continence control is lacking. Our group has adapted urodynamics to the fMRI environment to allow simultaneous monitoring of bladder pressure and brain activity in the scanner during bladder filling. This method has shown an altered brain activity during bladder filling and self-reported urgency in older women with urgency incontinence (UI) and has helped outline key centers in the brain's neural circuits involved in regulation of the bladder storage phase ('brain-bladder control network').

The aim of this study was to investigate the potential role of WMH in altered brain activity in older women with urgency incontinence during self-reported urgency in the scanner. We postulated that increase in global WMH burden would be associated with changes in brain responses to bladder filling. As a secondary hypothesis, we proposed that such apparent effects of global WMH burden might in fact be specifically related to the burden in a few critical white matter pathways.

Study design, materials and methods

We conducted a cross-sectional study of 25 functional community-dwelling older women (>60 yrs) with moderate to severe urgency incontinence and quantified the extent of WMH, globally ('global WMH burden') and in specific white matter tracts. We used brain imaging software (SPM5) to correlate WMH severity with regional brain activity measured by fMRI during bladder filling and reported 'urgency' in the scanner.

The comprehensive examination and the recruitment criteria were employed to ensure a population of functionally independent, community-dwelling older women with urgency incontinence but without significant comorbidities that could contribute to UI (e.g. cognitive, mobility or mood impairment). In addition to functional brain imaging, we used a fully automated method for quantifying and localizing white matter hyperintensities on MR images with use of fast-FLAIR images (fast FLuid-Attenuated Inversion Recovery). The amount of white matter changes (hyperintensities) is registered and then converted to a volume (cm^3). In addition to analysis related to global WMH burden, we investigated 2 white matter pathways (**anterior thalamic radiation** – ATR and superior longitudinal fasciculus - SLF) that showed distinguished underlying pattern of the distribution of WMH burden on factor analysis.

Results

In average, the study population represented functional, community-dwelling, older women (71.5 years) with moderate to severe UI (2.5 urgency incontinence episodes during daytime), few chronic conditions (2.3), good cognitive function (MMSE 29.2/30) and moderate WMH burden (3.3 cm^3). 14 subjects (56%) had detrusor overactivity present during urodynamic evaluation. Severity of incontinence was significantly correlated with global white matter burden ($r = 0.5$; $P < 0.01$).

Global WMH burden: Brain activity (in response to bladder filling during self-reported urgency in the scanner) was positively correlated ($r = > + 0.46$ at significance threshold level of $P < 0.01$) with global WMH burden in several regions shown to be activated during urgency, for example: a cluster of superior frontal regions in supplemental motor area (SMA) adjacent to dorsal anterior cingulate gyrus (ACG) (Figure 1). The activity in cerebellum and brainstem at the level of the pontine micturition center (PMC) strongly positively correlated as well. The activity in pre-/subgenualACG and precuneus (PCun), regions that show consistent pattern of deactivations during urgency, showed negative association ($r = > -0.46$ at significance threshold level of $P < 0.01$) with increased global WMH burden, together with activity in caudate and lingual gyrus.

WMH burden in specific pathways: Brain activity during urgency was correlated with WMH burden in ATR in a regional pattern similar to that for global WMH burden. For SLF, however, there was a negative correlation with WMH burden in dorsal ACG (BA24/32) and right inferior frontal gyrus adjacent to insula, as well as other regions ($r = > -0.34$ at significance threshold level of $P < 0.05$). Post hoc analyses showed that ATR caries ~ 55% of global WMH burden and its anatomical projections appeared to connect several regions that were deactivated by bladder filling during self-reported urgency (Figure 2).

Interpretation of results

Correlation analyses show that most of the regional brain activations and deactivations during bladder filling that provoked urgency in the scanner are augmented with increased WMH burden. If this activity represents an effort to suppress urgency and pending loss of continence, this relation would suggest that WMH affect continence control by requiring more extensive activity to maintain it. In elderly that would suggest a compensatory process.

Further analyses also showed that such structure-function relation reflects damage in specific white matter tracts that connect regions involved in continence control, as shown for ATR. This particular tract seems to carry bladder signals to the regions that are deactivated, perhaps in an effort to further inhibit PMC and voiding. If the signal is distorted, the inhibition of voiding reflex or urge suppression may be inadequate and create symptoms. Indeed, the activity in PMC was increased with WMH burden suggesting at least 2 possibilities: 1) the inhibitory activity in the PMC became stronger with increasing WMH in order to maintain continence or 2) that PMC excitation became stronger as inhibition began to fail, threatening incontinence. This

suggest, overall, that structural damage of white matter may have multiple implications for continence control in elderly: firstly, by affecting critical cerebral pathways it may lead directly to poor bladder control and contribute to the presence of urge symptoms or
DO; secondly, it may also exacerbate incontinence by affecting potential compensatory factors such as the ability to suppress urgency and DO, or the ability to reach a bathroom in time to prevent leakage.

Concluding message

This is the first study to demonstrate a link between structural changes in cerebral white matter and brain activity during bladder filling and storage phase and, thus, provides intriguing clues to the possible role of white-matter damage in the genesis of urgency incontinence in functional elderly. Apparent effect of global WMH burden might be attributable to the presence of WMH in specific white matter pathways that connect cortical regions involved in processing bladder signals and thus impair continence.

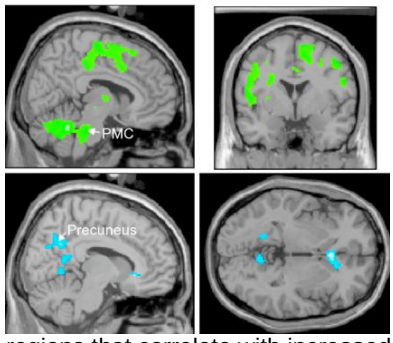

Figure 1. Brain regions that correlate with increased in white matter structural damage – WMH burden; green: positive correlation; blue: negative correlation).

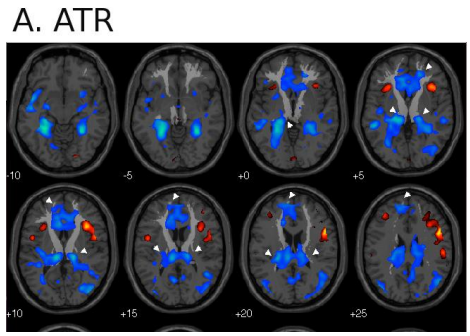

Figure 2. (right) Projections of ATR (in grey) - white matter pathway with significant WMH burden – to brain regions deactivated during bladder filling and self-reported urgency (in blue).

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What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**