URGENCY INCONTINENCE IN OLDER WOMEN IS ASSOCIATED WITH ABNORMALITIES OF BRAIN STRUCTURE

Hypothesis / aims of study
The past decade has seen sustained effort, using functional brain imaging (PET and fMRI), to study brain activation in subjects with and without urgency urinary incontinence (UUI). This work has shed light on the brain control of the bladder and how it can go wrong [1]. So far however it has not revealed a cause of UUI. Structural MRI on the other hand has suggested that increased burden of white-matter hyperintensities (WMH) is associated with UUI and may cause it [2], although the association is not robust. This work has not yet clearly identified critical sites where WMH leads to UUI, but WMH is increased in UUI in two large white-matter tracts – the right anterior thalamic radiation (ATR) and the right superior longitudinal fasciculus (SLF) – and so they may contain such critical sites.

WMH reflect overt white-matter structural damage. Other methods of structural imaging may be able to pinpoint more subtle abnormalities in white matter (e.g. by diffusion tensor imaging, DTI) or in gray matter (by voxel-based morphometry, VBM). DTI assesses fractional anisotropy (FA), a measure of structural integrity, with lower values suggesting impaired integrity of white matter fiber bundles; VBM measures local deviations in gray-matter volume (atrophy or hypertrophy).

This study was a secondary analysis of subjects and data gathered for a larger study [3]. We aimed to confirm increased WMH in the whole brain of UUI subjects, and also in the ATR and SLF. We aimed further to use DTI and VBM measurements to locate critical regions where white- and gray-matter abnormalities were associated with presence of UUI, supporting a causal relationship. We expected that these abnormalities would be located in critical regions where they could interfere with cerebral control.

Study design, materials and methods
We recruited 62 community-dwelling women aged ≥60 years, reporting urgency-predominant incontinence (≥5x/week) confirmed by at least 1 episode on 3-day bladder diary, and with detrusor overactivity (DO) on urodynamics. Eleven continent controls aged ≥60 years were also recruited, showing no DO on urodynamics (or in the scanner) and no UUI or overactive bladder symptoms by diary or self-report. Thus we selected 2 groups: one with ‘pure UUI’ and one of ‘strictly normal’ subjects, in order to accentuate any intergroup difference.

Each subject underwent several structural MRI scans with pulse sequences designed to measure and compare the integrity of brain structure in UUI subjects and normal, using:
(1) white-matter hyperintensities both globally and in 21 white-matter tracts included in the computer software, including the two mentioned a priori (see above);
(2) diffusion tensor imaging, to assess local white-matter integrity (FA); and
(3) voxel-based morphometry, to identify local gray-matter atrophy or hypertrophy.

Results
(1) The global burden of white-matter hyperintensities was greater in UUI than in normals with similar ages, but the difference did not quite attain significance (p = 0.07). The difference was significant in one of the white-matter tracts suggested a priori (right ATR) but not in the other (right SLF) (see Table). Post hoc inspection showed that only two other white-matter tracts differed significantly in WMH burden – right inferior fronto-occipital (IFO) and right uncinate (UNC). These two are included in the Table.
(2) Diffusion tensor imaging suggested that mean FA was smaller in UUI subjects than in normal controls, specifically in the body and crura of the fornix (p < 0.05 at uncorrected cluster level, see Fig. 1).
(3) Voxel-based morphometry showed that, in the right parahippocampal complex, the volume of gray matter (GM) was locally smaller in UUI than in controls (P < 0.01 at cluster level, corrected for multiple comparisons and adjusted for age, see Fig. 2).

Table: Burden of white-matter hyperintensities, normalized by dividing by total brain volume. * = a priori region.

<table>
<thead>
<tr>
<th></th>
<th>Subjects with UUI (n=60)</th>
<th>Normal controls (n=10)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global WMH burden</td>
<td>0.00240</td>
<td>0.00065</td>
<td>p = 0.07</td>
</tr>
<tr>
<td>WMH burden in right ATR*</td>
<td>0.00068</td>
<td>0.00029</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>WMH burden in right SLF*</td>
<td>0.00016</td>
<td>0.000002</td>
<td>p = 0.32</td>
</tr>
<tr>
<td>WMH burden in right IFO</td>
<td>0.00060</td>
<td>0.00014</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>WMH burden in right UNC</td>
<td>0.00016</td>
<td>0.000006</td>
<td>p = 0.03</td>
</tr>
</tbody>
</table>
Interpretation of results
In older women with UUI, the observation that 3 different methods identify brain structural abnormalities that may be related to each other and to UUI suggests that the abnormalities are involved in incontinence. In UUI: there is increased WMH in right-sided ATR and uncinate and inferior fronto-occipital fasciculi; there is atrophy of the parahippocampal complex (which includes the hippocampus); and there is loss of white-matter integrity in the fornix. The fornix is part of the limbic system and is the main connecting pathway between hippocampus and hypothalamus. The uncinate and inferior fronto-occipital fasciculi both send fibres to the parahippocampal area; in addition the parahippocampal complex is believed to take part in subcortical bladder control. Together these findings suggest that an anomaly in bladder control circuitry, centered on the hippocampus, is associated with UUI. Association does not prove causation, but the findings fit with what is currently understood about the roles of and relationships between these structures. Regardless, a prospective study is required to confirm these findings.

Concluding message
Structural abnormalities that appear to contribute to UUI are located in the subcortical parts of the brain, where they are relatively inaccessible to intervention. Nonetheless, if confirmed in subsequent studies, they may add to our understanding of the pathophysiology of UUI. Furthermore, despite their location, they may be amenable to conservative treatment such as exercise to increase hippocampal size, or to invasive treatment such as deep brain stimulation.

References
1. de Groat, W.C., Griffiths, D. & Yoshimura, N. in Comprehensive Physiology (Wiley/American Physiological Society, Published online (comprehensivephysiology.com) DOI: 10.1002/cphy.c130056, 2015).

Disclosures