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## BRAIN ACTIVITY DURING BLADDER FILLING IS RELATED TO WHITE MATTER STRUCTURAL CHANGES IN OLDER WOMEN WITH URINARY INCONTINENCE

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### Abstract

Evidence from longitudinal studies in community-dwelling elderly links complaints of urgency and urinary incontinence with structural white matter changes known as white matter hyperintensities (WMH). How WMH might lead to incontinence remains unknown, since information about how they relate to neural circuits involved in continence control is lacking. The aim of this study was to investigate the role of WMH in altered brain activity in older women with urgency incontinence. In a cross-sectional study, we measured WMH, globally and in specific white matter tracts, and correlated them with regional brain activity measured by fMRI (combined with simultaneous urodynamic monitoring) during bladder filling and reported 'urgency'. We postulated that increase in global WMH burden would be associated with changes (either attenuation or reinforcement) in responses to bladder filling in brain regions involved in bladder control. Secondly, we proposed that such apparent effects of global WMH burden might be specifically related to the burden in a few critical white matter pathways. The results showed that regional activations (e.g. medial/superior frontal gyrus adjacent to dorsal ACG) and deactivations (e.g. perigenual ACG adjacent to ventromedial prefrontal cortex) became more prominent with increased global WMH burden, suggesting that activity aimed at suppressing urgency was augmented. Secondary analyses confirmed that the apparent effect of global WMH burden might reflect the presence of WMH in specific pathways (anterior thalamic radiation and superior longitudinal fasciculus), thus affecting connections between key regions and suggesting possible mechanisms involved in continence control.

### Introduction

The most prevalent and morbid form of *urinary incontinence* (UI) in the elderly (Resnick et al., 2007; Norton and Brubaker, 2006) is *urgency incontinence*: urine leakage associated with the sensation of *urgency*. It is conventionally thought to be caused by involuntary bladder contractions called *detrusor overactivity* (DO). Such contractions are observed on urodynamic testing in some (but not all) subjects with urgency incontinence and are a physiological indicator of loss of bladder control. The clinical hallmark of urgency incontinence, the urgency

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itself, is an abnormal sensation, defined as a sudden, compelling desire to void (Abrams et al., 2002), typically with fear of leakage (Abrams et al., 1988) and, therefore, preceding actual urine leakage).

Patients with the syndrome of geriatric urinary incontinence are usually pictured as functionally disabled, although without overt brain pathology such as stroke or dementia (Resnick et al., 2007). However, recent evidence links this syndrome with rather subtle structural changes in the brain's white matter, known from their MRI appearance as *white matter hyperintensities* (WMH; synonyms: leucoaraiosis or age-related white matter changes/ARWMC). Contrary to the conventional view WMH affect many functional community-dwelling elderly (Kuo and Lipsitz 2004; Pantoni, et al., 2006; Inzitari et al., 2007; Pogessi et al., 2008). The white matter hyperintensity burden (the volume affected) progresses with age and is linked to increased prevalence of *urgency* (Pogessi et al., 2008). In addition, the accumulation of WMH in specific pathways is associated with the symptom of urgency UI and its severity (Kuchel et al., 2009). Elderly individuals with greater white matter hyperintensity burden also show increased prevalence of detrusor overactivity and difficulty maintaining continence on urodynamic studies (Sakakibara et al., 1999). Yet the mechanism whereby 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.

With the use of functional brain imaging (PET and fMRI) in the past decade, the principal brain regions involved in continence control have been identified (Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths et al., 2005; Kavia et al., 2005; Griffiths and Tadic., 2008). Our own group has adapted urodynamic methods to the fMRI environment so as to monitor bladder pressure and brain activity in the scanner simultaneously, during bladder filling (Griffiths et al., 2005). We have used this experimental paradigm to study the neural circuits involved in regulation of the bladder storage phase (Griffiths et al., 2005; Griffiths et al., 2007; Tadic et al., 2008; Griffiths and Tadic., 2008; Griffiths et al., 2009; Tadic et al., 2009). In particular we have studied this network in older women who suffer from urgency incontinence. These patients signal a compelling need to void – mimicking the *urgency* that they describe in real life – when the bladder is full but there is no detrusor overactivity. Under these circumstances their brain activity is markedly different from that in age-matched controls (Griffiths et al., 2007). It displays a pattern of activations and deactivations (in response to bladder filling) in regions of the limbic system (e.g. anterior cingulate gyrus – ACG), insular cortex (e.g. right insula, involved in interoceptive awareness) and executive cortex (e.g. inferior, medial and dorsolateral parts of orbitofrontal cortex) (Griffiths et al., 2007; Griffiths and Tadic, 2008; Griffiths et al., 2009; Tadic et al., 2009). In addition, the effective connectivity between these regions differs in location and intensity, compared to subjects with normal bladder function (Tadic et al., 2008). Altogether, the abnormal brain activity in such patients seems to be aimed at suppressing urgency and maintaining continence and thus reflects clinical symptoms related to difficulty controlling the bladder (Griffiths and Tadic, 2008). Indeed, a recent analysis confirmed the association between the objective severity of incontinence and abnormal activity in similar brain regions (Tadic et al., 2010). Nevertheless, the causal link between altered activity in the gray matter of the brain and changes in the white-matter pathways that connect them is unknown.

Gray matter regions involved in continence control can only function as a control system because of white matter pathways containing the neuronal axons that connect them. Pathways occupy a large part of the interior of the brain and are organized as relatively broad tracts containing fibres that proceed in generally similar directions to make contact with various gray matter regions (Schmahmann et al., 2008). The tracts have been mapped by imaging and neuroanatomical methods and displayed in atlases (e.g. Wakana et al., 2004). The effects of possible damage to these tracts (WMH) are studied in this paper. Two white matter tracts that

prove to be particularly important are (1) the anterior thalamic radiation (ATR) that runs bilaterally, primarily between the thalamus (an important relay and interaction station) and the frontal and prefrontal parts of the brain; and (2) the superior longitudinal fasciculus (SLF) that interconnects lateral and some more medial parts of the cortex on each side of the superior brain (see Figure 3).

The aim of this study was to investigate the potential role of WMH in altered brain activity in older women with urgency incontinence. In a cross-sectional study, we obtained measurements of WMH, globally and in specific white matter tracts, and correlated them with regional brain activity measured by fMRI during bladder filling and reported 'urgency', in the absence of detrusor overactivity. We postulated that increase in global WMH burden would be associated with changes in brain responses to bladder filling. We reasoned that, as for other bodily functions (Nordahl, et al., 2006), damage to white matter pathways might attenuate responses in regions involved in bladder control, thus exacerbating or causing incontinence; or alternatively that, by endangering continence, it might evoke stronger compensatory (coping) reactions and thus more prominent brain responses. We examined each possibility separately. 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.

## Materials and methods

### Study subjects

Regional brain responses to bladder filling and white matter hyperintensities were examined in female volunteers aged > 60 years, recruited by advertising or from our other studies that used the same recruitment methods and criteria. All underwent comprehensive clinical evaluation, including detailed history, physical examination (including neurological testing and a pelvic exam), a test of cognitive status (Mini-Mental State Examination - MMSE) and comprehensive urodynamic evaluation (Tadic et al., 2007; Griffiths et al., 2007; Tadic et al., 2009). This comprehensive examination and the recruitment criteria listed below were employed to ensure a population of functionally independent, community-dwelling older women with urgency UI but without significant comorbidities that could contribute to UI (e.g. cognitive, mobility or mood impairment). All subjects had urgency incontinence, either pure or with a minor component of stress-related leakage, as determined clinically and by voiding diary and pads. Only those who had more than 2 urgency incontinence episodes in a 3-day bladder diary were recruited for further study, thus ensuring recruitment only of subjects with either moderate (between 5 and 10 episodes per week) or severe (> 10 episodes per week) incontinence as defined by Burgio et al., 1998. According to our previous experience, women with moderate to severe incontinence are clinically and phenotypically a more homogenous group than those with mild disease

Women with significant cognitive impairment (MMSE score  $\leq 24/30$ ), secondary causes of urinary incontinence (e.g. bladder cancer, spinal cord lesions, multiple sclerosis, pelvic radiation, interstitial cystitis), sphincter implant or significant neurological and vascular disease (history of strokes, neurodegenerative diseases and complicated diabetes mellitus) were excluded. We also excluded subjects with claustrophobia and the presence of implanted metal or electromagnetic devices that would preclude performing MRI. The study was approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent.

### Bladder filling protocol

All subjects underwent a brain scanning protocol that includes fMRI and simultaneous urodynamic monitoring. Details of our fMRI methods have been described previously

(Griffiths et al., 2007; Tadic et al., 2008). Briefly, two 8 F urethral catheters were introduced to allow for bladder filling/emptying and bladder pressure measurement to detect detrusor overactivity (DO). Structural MRI was performed. A small volume of sterile water (10–20 ml) was introduced into the empty bladder, followed by functional MRI while fluid was repeatedly infused into and withdrawn from the bladder using an automated pump system (acquisition details: 3 T magnet; one brain scan per 2 s;  $3 \times 3 \times 3$  mm resolution, field of view 21 cm covering brainstem to near top of anterior cingulate gyrus). Each infusion/withdrawal cycle comprised: pause (12 s); infusion (22 ml in 12 s); pause (12 s); withdrawal (20 ml in 12 s). Four cycles formed one measurement block. After 2 measurement blocks, the bladder was filled quickly, without scanning, until the subject signalled compelling desire to void. With the subject's permission, 1 to 2 further measurement blocks were performed with scanning until subjects stopped the study to void, or developed involuntary bladder muscle contraction (detrusor overactivity/DO) and urine leakage. The BOLD signal acquired in the final measurement block (or the last block before DO onset) was used for analysis. This measurement block was comparable in different subjects because it was always performed in the same situation: with full bladder and just tolerable sensation but before onset of any involuntary bladder contraction (detrusor overactivity). We refer to this situation as 'urgency' because it mimics most aspects of its definition (compelling desire to void, difficult to defer and associated with fear of leakage) (Abrams et al., 2002; Abrams et al., 1988).

### Assessment of white matter hyperintensities

We used a fully automated method for quantifying and localizing white matter hyperintensities on MR images (Wu et al., 2006) which uses fast-FLAIR images (fast FLuid-Attenuated Inversion Recovery) and a 'fuzzy-connected algorithm' to identify WMH clusters in the anatomical space for each subject. The amount of white matter changes (hyperintensities) is registered in voxels and then converted to a volume (1 voxel =  $4.2 \text{ mm}^3$ ). For regression analyses, to account for individual differences in brain size, we normalized the global WMH burden by dividing each individual's total WMH volume by her total brain volume. Regional WMH burdens were calculated as follows: the 20 white-matter tracts identified by the Johns Hopkins white matter atlas [Wakana et al, 2004] were warped into the anatomical space and the normalized WMH burden was calculated for each tract by dividing the volume of WMH in the tract by the whole-brain volume.

### Selection of white matter tracts for regression analysis

The distribution of WHM burden over the 25 subjects was similar for many of the tracts. Consequently, the correlations between brain activity and regional WMH burden in these tracts were also similar and could not be used to distinguish between them. A factor analysis (see Appendix) revealed only two distinct underlying patterns (factors) in the distribution of WMH burden over subjects. We therefore examined correlations between brain responses and regional WMH burden for the tract showing pattern 2 (SLF, superior longitudinal fasciculus) and the four tracts showing pattern 1 (anterior thalamic radiation, ATR; uncinat fasciculus, UNC; inferior fronto-occipital fasciculus, IFO; and inferior longitudinal fasciculus, ILF). We paid particular attention to ATR and SLF (see Appendix).

### fMRI analyses

After image acquisition, pre-processing and further analyses were done using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, 2003, <http://www.fil.ion.ucl.ac.uk/spm/spm2.html>). As previously, first-level analysis was performed in each subject to determine regional brain responses to bladder filling by comparing the fMRI signal during fluid infusion with the baseline during fluid withdrawal (see Griffiths et al., 2007; Tadic et al., 2008; Griffiths et al., 2009 and Griffiths et al., 2005 at

www.learncontinence.com/griffiths\_suppl\_material). To determine the main effects of bladder filling we combined the single-subject results for the selected measurement block in a standard second-level (random-effects) analysis and thresholded statistical maps at  $P < 0.01$  (uncorrected for multiple comparisons). For second-level correlation analyses, the first-level image for this measurement block was selected for each individual, together with the covariate of interest (normalized white matter burden: global, or in ATR or SLF). A voxel-by-voxel correlation between the images and the covariate was then performed. The statistical maps showing voxels with a significant correlation with each of the covariates were thresholded at  $P < 0.01$  (uncorrected for multiple comparisons) which corresponds to correlation coefficient  $r \geq 0.6$ .

## Results

### Study participants

As outlined in Table 1, the study population represented functional, community-dwelling, older women with moderate to severe urgency urinary incontinence (Burgio et al., 1998). 14 subjects (56%) had detrusor overactivity present during urodynamic evaluation. Severity of incontinence (number of daytime urgency incontinence episodes on bladder diary) was significantly correlated with global white matter burden ( $r = 0.5$ ;  $P < 0.01$ ).

### Functional brain activity: main effect of bladder filling

Brain response to bladder filling during self-reported 'urgency' showed significant activations in a cluster of frontal regions, including medial and superior frontal gyrus (BA 6 and BA 9), adjacent to dorsal anterior cingulate gyrus (dACG) (BA24/32) (see Fig. 1(a)); as well as right inferior frontal gyrus (BA 44 and BA45) adjacent to right insula (BA 13); dorsolateral prefrontal cortex (BA 9) and cerebellum (Fig. 1(a) and Table 2). Activations were significant in the parahippocampal complex (PHC) and pre/subgenual ACG (BA24/32) as shown in Fig. 1(b), as well as other regions listed in Table 2.

### Functional brain activity: association with global white matter burden

Brain activity (in response to bladder filling) was positively correlated with global WMH burden in cerebellum and brainstem at the level of the pontine micturition center (PMC), as shown in Fig. 2A(a), and a cluster of frontal regions adjacent to dorsal ACG as listed in Table 3. Thus not only did brain activity change in concert with WMH burden, but it changed in regions specifically concerned with bladder control (medial/superior frontal gyrus adjacent to dorsal ACG and PMC). Frontal cortex adjacent to dorsal ACG in particular was activated in response to bladder filling (Fig. 1(a)) and this response became more pronounced with increasing WMH burden (Fig. 2A(a), picture and graph). Note that one subject with WMH burden greater than the rest (but still only moderate) also showed more prominent brain (de)activation, thus confirming the trend indicated by the subjects with smaller burden (see Fig. 2).

In pre-/subgenual ACG, precuneus (PCun), caudate and lingual gyrus, brain response was negatively associated with global WMH burden (Fig. 2A(b) and Table 3). In perigenual ACG and precuneus in particular there was deactivation in response to bladder filling (Fig. 1(b)) and this deactivation became more pronounced with increasing WMH burden (Fig. 2A(b), picture and graph). Thus increasingly prominent deactivation in brain regions specifically involved in bladder control was associated with increasing WMH burden.



## WMH burden in specific pathways

The factor analysis described in the Appendix showed that, in each of 4 white matter tracts (ATR, UNC, IFO, ILF), the distribution of WMH burden over the 25 subjects was similar to the global distribution. The distribution was entirely different in one other tract (SLF). Consistent with this finding, for each of the first 4 tracts, brain activity was positively correlated with WMH burden in a regional pattern similar to that for global WMH burden (data shown for ATR in Fig. 2B(a); compare with Fig. 2A(a)). Negative correlation with ATR burden at threshold level of  $P < 0.01$  was scarce, but there was evidence for it in the ventromedial prefrontal cortex similar to global burden analyses (data not shown). 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 shown in Fig. 2B(b) and Table 3.

In order to locate the brain responses with respect to the tracts containing WMH, the main-effects activations and deactivations were superimposed on diagrams showing ATR and SLF in standard MNI space (Figs. 3A and B). The anatomical projections of ATR appeared to connect several regions that were deactivated by bladder filling (Fig. 1(b)). In contrast, projections of SLF appeared to connect mainly to regions that were activated by bladder filling (Fig. 1(a)).

## Discussion

### Regional brain activity and global white matter hyperintensity burden

The results confirmed our initial postulate that, in older women with urgency incontinence, responses to bladder filling in many brain regions correlated significantly with global WMH burden. The correlation was positive in some of the regions that were activated during bladder filling (e.g. medial/superior frontal gyrus adjacent to dorsal ACG) (Figs. 1(a) and 2A (a)), implying increasing activity with increasing white matter burden. As indicated in the Introduction, this behaviour suggests that the activity is a reaction to a threat to continence engendered by the white matter burden. Negative correlations were observed also, and some of them occurred in regions that were deactivated during bladder filling (e.g. perigenual ACG adjacent to ventromedial prefrontal cortex) (Figs. 1(b) and 2A (b)), implying that brain deactivations became more pronounced with increasing WMH burden. Again this suggests that the deactivation is a reaction to threatened incontinence, aimed at suppressing it. These effects of WMH on the function of the cerebral control system have clinical consequences: incontinence, as assessed by the number of daytime urgency incontinent episodes on bladder diary was more severe in those with greater WMH burden.

Although this is the first study of the effect of WMH on brain responses to bladder filling, other studies have confirmed that the area of the subgenual ACG and ventromedial prefrontal cortex is less active during withholding of urine than during micturition (Blok et al., 1997; Athwal et al., 2001; Nour et al., 2000; Griffiths and Tadic, 2008; Tadic et al., 2009), consistent with the deactivation during bladder filling reported here. Similarly, regions activated during scanning experiments that required urine withholding or control of voiding (Blok et al., 1997; Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Yin et al., 2006; Kuitz-Buschbeck et al., 2005; Seseke et al., 2006; Zhang et al., 2005) include the anterior insula/lateral prefrontal cortex and the area adjacent to dorsal ACG, as reported in this study, further confirming their role in executive control of continence.

The responses to bladder filling observed in the brainstem at the level of the pontine micturition center (PMC) and adjacent cerebellum were puzzling. They were not clearly seen in main-effects analyses but showed strong positive correlations with global WMH burden. One possibility is that inhibitory activity in the PMC became stronger with increasing WMH in

order to maintain continence. Another is that PMC excitation became stronger as inhibition began to fail, threatening incontinence.

Some areas in the posterior cortex (e.g. precuneus) became less active with increasing WMH burden. In our recent study (Tadic et al., 2009) activity in these regions was negatively correlated with the reported severity of incontinence-related psychological burden. Thus the present findings may suggest that brain activity related to coping with incontinence psychologically is also affected by increased WMH burden.

### Regional brain activity and WMH burden in white matter tracts

According to our secondary hypothesis the apparent effect of global WMH burden might in fact be attributable to the presence of WMH in specific white matter pathways critical to continence. The white-matter changes in the four tracts with WMH distribution similar to that of the global burden were more ubiquitous and more severe than those in other white matter pathways. For these four tracts (ATR, UNC, IFO and ILF) the correlations of brain activity with WMH burden showed a regional pattern similar to that of global burden (e.g. compare Figs. 2A(a) and 2B (a)). This is mathematically inevitable, but suggests that, *if* there are a few critical pathways whose integrity is critical for continence, at least one of these four is among them. The anterior thalamic radiation (ATR) is a likely candidate, firstly because it accounts for about 55% of global WMH, secondly because its anterior terminus in the medial prefrontal cortex is in the area identified by stroke and trauma studies as critical to long-term continence (Andrew and Nathan, 1964; Fowler and Griffiths., 2009; Fowler et al., 2008), and thirdly because, as shown in Fig. 3A, its anatomical projections appear to connect several regions that are deactivated by bladder filling (Kahle and Frotscher, 2002; Schmahmann, et al., 2008). Thus the ATR seems to carry a signal to or from all these regions that is associated with their deactivation and presumably maintains continence by inhibiting the PAG or PMC. The pathway through which this occurs is still unclear however.

The other white matter tract for which there is information, the SLF, appears on the contrary to connect regions that are activated by bladder filling (Fig. 3B), including those adjoining dorsal ACG. The SLF carries only 8% of the global burden and shows changes in 40% of subjects. Nevertheless, increased WMH burden in SLF caused some of the activations that it carried to become less prominent (e.g. dorsal ACG and right inferior frontal gyrus adjacent to insula). One might speculate that WMH in this pathway interfere directly with afferent and efferent signals to and from the regions it serves, including insula/inferior frontal gyrus and dorsal ACG that are critical to bladder control (Griffiths and Tadic, 2008). In contrast, increased WMH burden in ATR caused activations apparently carried by SLF to become stronger (e.g. near dorsal ACG). Perhaps ATR damage leads to compensatory strengthening of the SLF pathway, so maintaining continence. Thus there may be two continence mechanisms, one involving the SLF and the dorsal ACG and the other involving the ATR and the medial frontal cortex and perigenual ACG. Additional areas apparently deactivated by the ATR mechanism include hippocampus and parahippocampal complex, suggesting reaction to an emotionally unpleasant event (e.g. retrieval of the memory of an incontinence episode).

Our findings related to ATR and SLF corroborate those of Kuchel et al. (2009), who showed that accumulation of WMH in similar locations (the corona radiata and the frontal-occipital zone) predicted urgency incontinence and was associated with its severity. It is important to note that the burden of white matter disease was only moderate in our group of 'functional' community-dwelling older women (Wu et al., 2006; Vannorsdall et al., 2009; Schmidt et al., 2007; Chen et al., 2006). There was no significant impairment of cognition, mobility or mood, all of which might contribute to worsening of continence control (Resnick et al., 2007). Hajjar et al. (2009) have suggested that damage to frontal white-matter pathways might lead to poor executive function, slow gait speed, and depressive symptoms in older non-demented

individuals, but they did not report continence status. Possibly, the effects of WMH on brain activity related to continence control in our group may represent an early stage (or variant) of this phenotype, the changes in brain activity that we observe being compensatory to a relatively small increase in the burden of WMH in critical pathways. Such behaviour would be consistent with a general principle governing functional impairment in the elderly, that increased effort is required to maintain homeostasis (Kuchel, 2009).

### **Clinical implications**

Unlike in younger subjects, urgency UI is multifactorial in the elderly (Resnick and Yalla, 2007) and white matter damage might have multiple implications for continence control. 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. Clinically therefore there are compelling reasons to believe that prevention or perhaps treatment of white matter damage at an early stage would avert incontinence in some older adults.

### **Significance and conclusion**

Overall, this study is the first to demonstrate a link between structural changes in cerebral white matter and brain activity in neural circuits involved in bladder control and, thus, provides intriguing clues to the possible role of white-matter damage in the genesis of urgency incontinence and furthermore to the cerebral mechanisms of bladder control in older women. Although it remains possible that global white-matter changes are responsible for the development of urgency incontinence, it seems plausible that two specific white-matter pathways are involved, probably the anterior thalamic radiation and the superior longitudinal fasciculus. Damage in either of these pathways appears to affect connections between the cortical regions involved in processing bladder signals, consistent with the observed connectivity differences between urgency-incontinent women and normal controls (Tadic et al., 2008). Thus, the findings of this study underline the importance of white-matter tracts as targets for further investigations to reveal the mechanism of impaired control of continence in the elderly. This new area of research, coupled with other promising methods of assessing white-matter damage (e.g. diffusion tensor imaging) will improve our understanding of the syndrome of geriatric urinary incontinence and may change our clinical approach to incontinence in the elderly.

### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

### **Acknowledgments**

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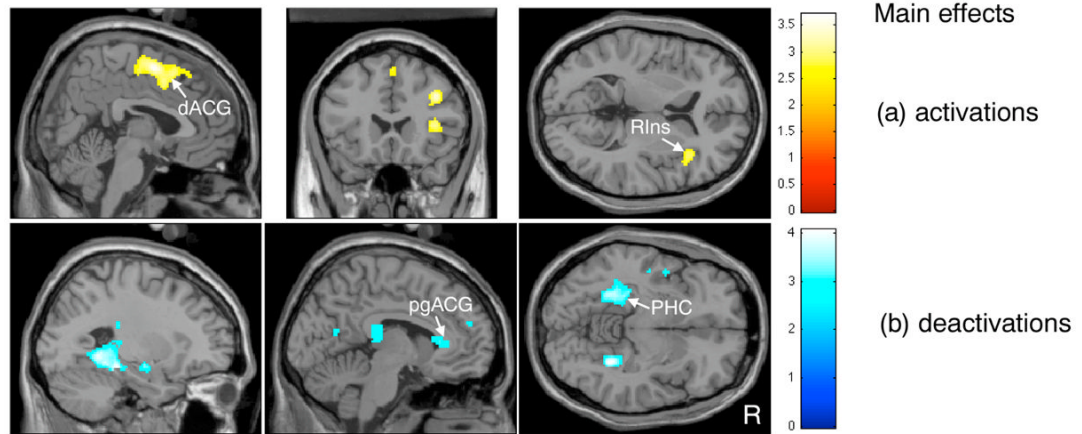
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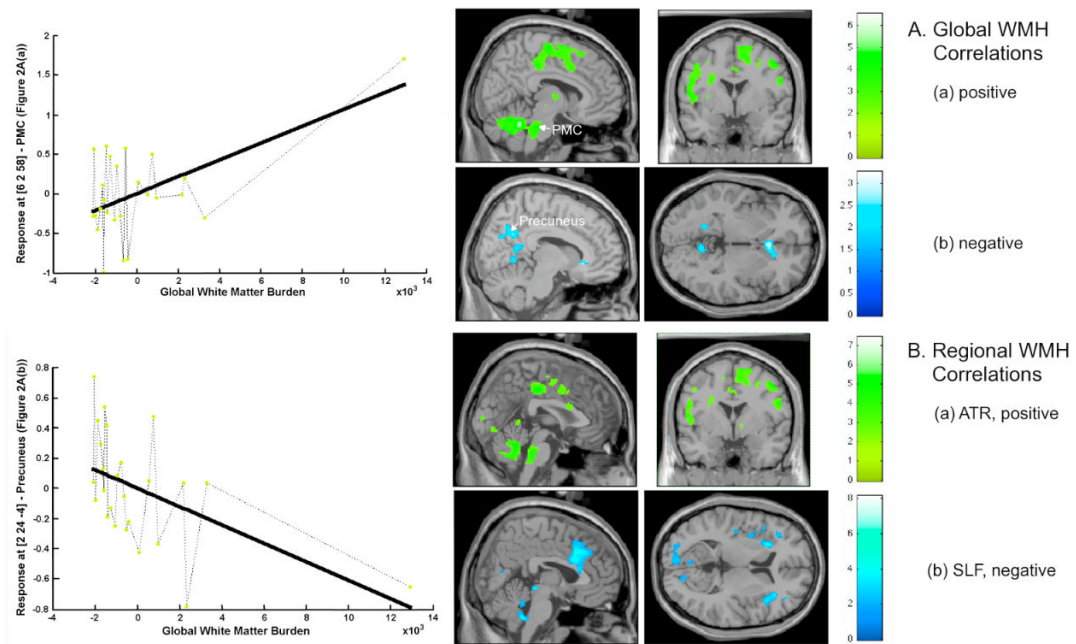
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**Fig 1.**

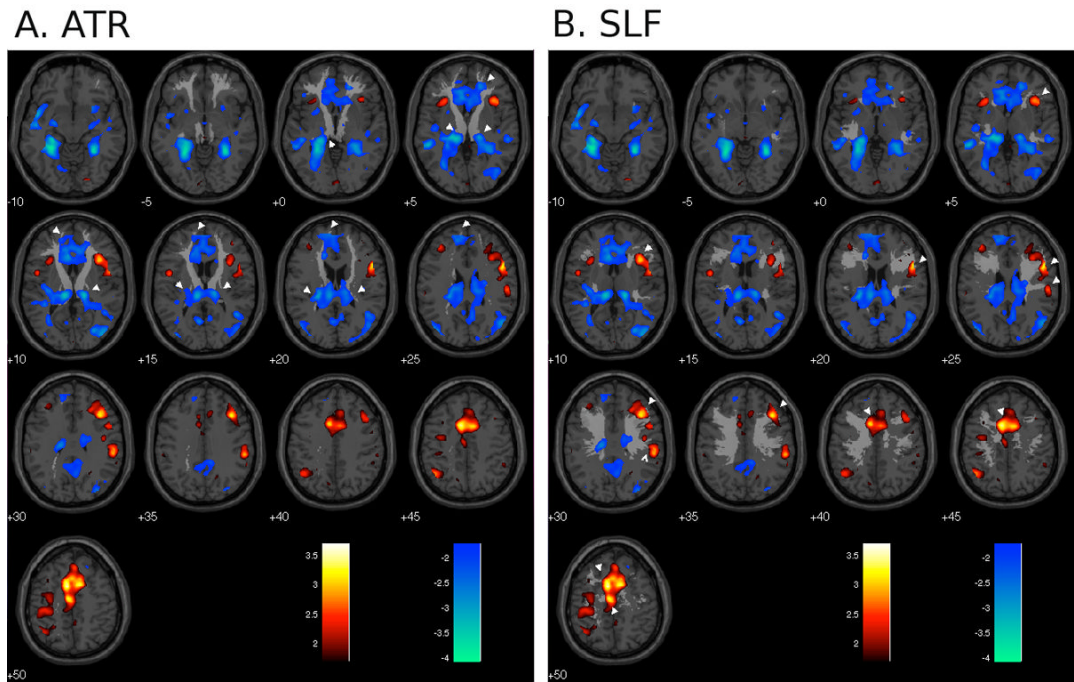
Images related to main effects (regions activated or deactivated on bladder filling): **(a)** activations ( $P < 0.01$  uncorrected); **(b)** deactivations ( $P < 0.01$  uncorrected). dACG = dorsal anterior cingulate gyrus; RIns = right anterior insula; pgACG = perigenual anterior cingulate gyrus; PHC = parahippocampal complex.



**Figure 2. Images related to correlations**

**A.** Correlations between regional brain activity on fMRI and global WMH burden: **(a)** positive correlations ( $P < 0.01$ , uncorrected;  $r \geq 0.46$ ); upper left graph: correlations in PMC; **(b)** negative correlations ( $P < 0.05^*$  uncorrected;  $r \geq 0.34$ ); lower left graph: correlations in Precuneus.

**B.** Correlations between regional brain activity on fMRI and WMH burden in selected white-matter tracts: **(a)** positive correlations with ATR burden ( $P < 0.01$  uncorrected;  $r \geq 0.46$ ); **(b)** negative correlations with SLF burden ( $P < 0.05^*$  uncorrected;  $r \geq 0.34$ ). \*threshold chosen for image display only.



**Fig. 3.** Regional brain responses to bladder filling (main effects) superimposed on selected white-matter tracts; red/yellow = activation, blue = deactivation ( $P < 0.01$  uncorrected); numbers show z-coordinates in mm. White pointers show some of the regions where the tract appears to project to activated or deactivated areas. A. anterior thalamic radiation (ATR); B. superior longitudinal fasciculus (SLF).



**Table 1**

Characteristics of study participants (n=25).

<b>Variable</b>	<b>Mean (SD)</b>
Age (years)	71.5 (7.5)
Chronic conditions	2.3 (1.3)
Depression history (n and %)	8 (32)
MMSE (0–30)	29.2 (1.04)
Urge Incontinence Episodes/Day	2.5 (1.3)
Urine Leakage/Day (mL)	29.2 (44.3)
White Matter Hyperintensities (cm <sup>3</sup> )	3.3 (4.5)

Table 2

Regional brain activity in response to bladder filling (main effects) (n=25, threshold  $P < 0.01$  uncorrected). Coordinates are given in MNI space.

Region	Coordinates			Z-Value	Voxel Level Significance (uncorrected)
	x	y	z		
<b>Activations</b>					
<b>Cluster 1: SMA, superior/medial frontal gyrus adjacent to dorsal ACG; <math>P &lt; 0.01</math> (corrected)</b>					
Medial Frontal Gyrus (BA 6)	2, -8	0, -8	58,56	3.27,3.21	
Superior Frontal Gyrus (BA 8)	-2,2	16,30	52,52	2.86,2.48	
Anterior Cingulate Gyrus (BA 24/32)	-10, -10	4,8	50,48	3.17,3.15	
<b>Other regions:</b>					
Right Middle Frontal Gyrus (BA 9)	36	22	34	3.07	0.001
Right Insula (BA 13)	34	24	4	2.79	0.003
Right Inferior Frontal Gyrus (BA 45)	44	18	6	2.53	0.006
Right Inferior Frontal Gyrus (BA 44)	50	12	22	2.99	0.001
Inferior Parietal Lobule (BA 40)	-44,54	-58, -32	44,34	2.59,2.75	0.005
Postcentral Gyrus (BA 2/3)	54, -36	-22, -34	28,60	2.59,2.79	0.005
Left cerebellum (posterior lobe)	-38	-52	-34	2.69	0.004
<b>Deactivations</b>					
<b>Cluster 1: parahippocampus, hippocampus, thalamic nuclei; <math>P &lt; 0.04</math> (corrected)</b>					
Parahippocampal Gyrus (BA 19)	-26,28	-44, -48	-2, -8	3.41,3.51	
Left Parahippocampal Gyrus (BA 36)	-28	-32	-14	3.43	
Left Hippocampus	-24	-38	-2	3.18	
Thalamus	-22,14	-28, -28	2,10	3.17,3.09	
Caudate	-18,14	-18, -22	30,24	2.55,2.53	
<b>Other regions:</b>					
Left Anterior Cingulate Gyrus (BA 24)	-8, -10	26,34	8,6	2.80,2.61	0.003
Anterior Cingulate Gyrus (BA 32)	-16,16	26,42	20,2	2.47,2.5	0.007
Left Medial/Superior Frontal Gyrus (BA 9)	-8, -14	52,48	22,26	2.46,2.39	0.007
Left Middle/Superior Temporal Gyrus (BA 22)	-54, -48 -38, -32		4,2	3.01,2.92	0.001
Right Middle Occipital Gyrus (BA 19)	38	-82	10	2.70	0.004
Right Cuneus (BA 30)	28	-78	10	2.61	0.005

Table 3

Regions where brain activity correlated with white matter hyperintensities (WMH):

A. correlations with global WMH burden (n=25, threshold P<0.01 uncorrected); B. correlations with WMH burden in superior longitudinal fasciculus (SLF) (n=10, threshold P < 0.01 uncorrected). Coordinates are given in MNI space.

Region	Coordinates			Z-Value	Voxel Level Significance (uncorrected)
	x	y	z		
<b>A. Global WMH burden</b>					
<b>Positive Correlations:</b>					
<b>Cluster 1: Cerebellum and Brainstem; P&lt;0.000 (corrected)</b>					
Cerebellum, Anterior Lobe	-6,12	-50,-46	-24,-26	4,86,4,84*	
Cerebellum, Anterior Lobe	-24	-44	-26	3,25	
Cerebellum, Posterior Lobe	24,38	-40,-60	-32,-30	4,27,4,25	
Cerebellum, Posterior Lobe	10	-60	-38	4,02	
Pons (PMC)	8,0	-28,-30	-30,-32	3,58,3,48	
Left Pons	-16	-34	-28	3,70	
Midbrain (PAG)	-2	-28	-18	2,44	
<b>Cluster 2: SMA, Superior/Medial Frontal Gyrus adjacent to Dorsal ACG; P&lt;0.000 (corrected)</b>					
Postcentral Gyrus (BA3)	-56,-24	-14,-32	22,64	4,08,3,60	
Precentral Gyrus (BA 4)	-16,-32	-20,-16	60,54	3,96,3,20	
Precentral Gyrus (BA 6)	-48	-6	22	3,19	
Precentral Gyrus	48,54	2,0	46,26	3,84,3,30	
Medial Frontal Gyrus (BA 6)	14,-10	-20,-14	54,48	3,68,3,64	
Medial Frontal Gyrus (BA 32)	12	14	44	3,48	
Superior Frontal Gyrus (BA 6)	8,8	2,24	66,58	3,53,3,09	
Anterior Cingulate Gyrus (BA24)	-20	-12	44	3,77	
Inferior Frontal Gyrus (BA 9)	-54	4	28	3,37	
Left Insula (BA13)	-38	-8	6	3,12	
Paracentral Lobule (BA31)	0	-22	42	3,59	
Superior Temporal Gyrus (BA 22)	-50	-2	6	3,57	
<b>Other Regions:</b>					
Middle frontal gyrus (BA 8)	30	20	42	2,83	0,002
Thalamus (ventral posterior lateral nucleus)	18	-20	6	2,99	0,001

Region	Coordinates			Z-Value	Voxel Level Significance (uncorrected)
	x	y	z		
Midbrain, Red nucleus	8	-18	-4	2.84	0.002
Hippocampus/parahippocampus	28	-20	-14	3.12	0.001
Cuneus (BA18)	-2	-94	10	3.15	0.001
<b>Negative Correlations:</b>					
Anterior Cingulate Gyrus (BA 24)	4	24	-4	2.93	0.002
Caudate	12	26	-4	2.72	0.002
Precuneus (BA 7)	4	-62	32	2.66	0.004
<b>B. Superior Longitudinal Fasciculus (Entire Pathway)</b>					
<b>Negative Correlations:</b>					
<b>Cluster 1: Dorsal ACG/Medial Frontal Gyrus; P &lt; 0.006 (uncorrected)</b>					
Anterior Cingulate Gyrus (BA24/32)	6, -4	22,24	24,36	3.53,3.44	
Medial Frontal Gyrus (BA 9/8)	10,4	38,26	28,38	3.15,3.06	
ACG/BA 32	-2,2	20,20	28,28	3.12,3.12	
<b>Other Regions:</b>					
Left Parietal Lobe (Angular Gyrus/BA 39)	-42	-58	36	4.21	0.000
Inferior Frontal Gyrus/BA13	40	20	8	2.80	0.003

\* Significant after corrections for multiple comparisons (FWE, P < 0.05)