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Cerebral control of the bladder in normal and urge-incontinent women

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Abstract

Aim: To identify age-related changes in the normal brain/bladder control system, and differences between urge incontinence in younger and older women, as shown by brain responses to bladder filling; and to use age, bladder volume, urge incontinence and detrusor overactivity (DO) as probes to reveal control-system function. Functional MRI was used to examine regional brain responses to bladder infusion in 21 females (26 – 85 years): 11 “cases” with urge incontinence and DO (proven previously) and 10 normal “controls”. Responses and their age dependence were determined at small and large bladder volumes, in whole brain and in regions of interest representing right insula and anterior cingulate (ACG). In “controls”, increasing bladder volume/sensation led to increasing insular responses; with increasing age, insular responses became weaker. In younger “cases”, ACG responded abnormally strongly at large bladder volumes/strong sensation. Elderly “cases” showed strong ACG responses even at small bladder volume, but more moderate responses at larger volumes; if DO occurred, pontine micturition center (PMC) activation did not increase.

Conclusion: Among normal “controls”, increasing age leads to decreased responses in brain regions involved in bladder control, including right insula, consistent with its role in mapping normal bladder sensations. Strong ACG activation occurs in urge-incontinent “cases” and may be a sign of urgency, indicating recruitment of alternative pathways when loss of bladder control is feared. Easier ACG provocation in older “cases” reflects lack of physiological reserve or different etiology. ACG responses seem associated with PMC inhibition: reduced ACG activity accompanies failure of inhibition (DO).

Keywords

functional magnetic resonance imaging; aging; urge incontinence; detrusor overactivity; urgency; overactive bladder; insula; anterior cingulate

Introduction

Loss of bladder control – urge incontinence or urgency incontinence – is a common and troublesome problem, especially in older women (Hu et al., 2004; Hunskaar et al., 2002). Typically it is associated with detrusor overactivity (DO), which frequently is idiopathic (Abrams et al., 2002; Fowler, 2006). Bladder control is exercised by the brain via a long-loop spinobulbospinal reflex pathway that includes the midbrain periaqueductal gray (PAG) and

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the pontine micturition center (PMC), which in turn are controlled by a supratentorial network. The main network landmarks are known from animal and clinical observations, and from functional imaging by positron emission tomography (PET) (Athwal et al., 2001; Blok et al., 1997b; Kitta et al., 2006; Matsuura et al., 2002; Nour et al., 2000) or functional magnetic resonance imaging (fMRI) (Di Gangi Herms et al., 2006; Griffiths et al., 2005; Kuhtz-Buschbeck et al., 2005; Seseke et al., 2006; Zhang et al., 2005).

Prominent features include insula (Griffiths et al., 2005) and anterior cingulate gyrus (ACG) (Athwal et al., 2001; Griffiths et al., 2005). Control tends to be lateralized on the right (Blok et al., 1997b). Knowledge of the normal function of the network remains superficial (Kavia et al., 2005) and little is known about loss of bladder control. Generally however the insula is concerned with mapping visceral sensation (Craig, 2002; Craig, 2003; Derbyshire, 2003) and the ACG is involved in autonomic emotional and motor arousal and in monitoring (Botvinick et al., 2004; Critchley et al., 2003). The PMC is specific to motor control of the lower urinary tract (Holstege et al., 1986) and is expected to be active when the long-loop voiding reflex is engaged.

Normal patient-reported sensations of bladder filling and desire to void (Abrams et al., 2002) encode sensory (afferent) feedback from the bladder that enables the brain to exert effective control. Urgency, an abnormal sensation, signifies impending or actual loss of control (Abrams et al., 2002) and carries an emotional charge (fear of leakage) (Abrams et al., 1988). Reduced sensation is also significant: among frail elderly, urge incontinence with reduced sensation is particularly severe (Griffiths et al., 1992) and may have different etiology (Fall et al., 1995).

The goal of this work was first to determine the effect of increasing age on normal brain/bladder control – presumably reflecting normal aging – and secondly to determine whether there are differences between urge incontinence in young and old, as shown by differing brain responses to bladder events. Thirdly we aimed to use age, bladder volume, history of urge incontinence and actual DO as probes to reveal the function and dysfunction of the brain/bladder control system, paying particular attention to right insula, ACG, and PMC. To this end we performed fMRI of brain responses to bladder filling, in adults with and without urge incontinence and with a wide range of ages. To avoid possible confounding by prostatic obstruction we used only female subjects.

Materials and methods

Regional brain responses to bladder filling were examined in female volunteers, with or without urge incontinence, aged at least 20 y with no upper limit, and with no overt neurological disease. Exclusion criteria included dementia; spinal cord disease resulting in gross neurological defect; pelvic irradiation or bladder cancer; mobility or mentation problems precluding scanning; claustrophobia; implanted ferromagnetic or electronic device; positive pregnancy test; or current urinary tract infection. Subjects were recruited by advertising or from another study and signed written informed consent. Results from some subjects were included in a previous smaller study (Griffiths et al., 2005). All procedures were approved by the University of Pittsburgh IRB.

Normal “controls” had no overactive bladder symptoms (urge incontinence, urgency, or increased frequency not accounted for by fluid intake) on history or bladder diary and no DO on urodynamics prior to scanning. Urge-incontinent “cases” had symptomatic urge incontinence on history and diary and DO on urodynamics prior to scanning. Potential subjects not classifiable as cases or controls were excluded.

Full details of the methods have been described previously (Griffiths, 2005; Griffiths et al., 2005). Urodynamic methods, definitions and units conform to the standards recommended by

the International Continence Society (Abrams et al., 2002). The standard term “urge incontinence”, used here, may in the future be replaced by the more descriptive term “urgency incontinence”. Brain responses to bladder filling were determined as follows. Two 8 F urethral catheters were introduced, for bladder pressure measurement and bladder filling/emptying. A structural brain MRI was recorded. The bladder filling and scanning protocol is shown in Figure 1. A small volume of saline solution (50-100 ml) was introduced into the empty bladder. Saline solution was then repeatedly infused into and withdrawn from the bladder while functional brain imaging (fMRI) was performed (reverse spiral imaging; 3 T magnet; one whole brain scan per 1.5 s; 3×3×3 mm resolution). The infusion/withdrawal cycle (42 s duration) was performed 8 times, in 2 blocks of 4 cycles, more liquid being infused (22 ml/cycle) than was withdrawn (15 ml/cycle). The bladder was then filled further, without scanning, until the subject signaled strong bladder sensation. Infusion/withdrawal cycles were performed again (2 to 4 blocks), with scanning, until sensation became uncomfortable. Intravesical pressure was monitored to show DO; it occurred during scanning in only a few cases and only in the last 2 blocks.

After preprocessing, using Statistical Parametric Mapping (SPM2) (Wellcome Department of Imaging Neuroscience, 2003), regional brain responses were determined by comparing the fMRI BOLD (blood oxygen level dependent) signal during infusion with the baseline signal during withdrawal (Griffiths et al., 2005). Functional images were smoothed with an 8 mm Gaussian filter. The fMRI signal does not indicate whether activation is excitatory or inhibitory; this must be determined from the context.

In older subjects, possible difficulties include excessive head movement, abnormal brain morphology, and abnormal hemodynamic responses. We eliminated subjects with sudden head movements exceeding 3 mm; we used the program INRIAlign (INRIAlign, 2000) to allow for head movement without overcorrection; for older subjects we used the segmented gray-matter image for coregistration with functional and canonical images. Individual results were combined in groups for random-effects analyses (Holmes et al., 1998), using t-tests or correlation as appropriate. Results were thresholded at an uncorrected P-value of 0.01 and statistical significance was assessed after correction for multiple comparisons at cluster level (corrected $P < 0.05$). Clusters of less than 16 voxels were ignored. Some responses that met only the uncorrected level of significance have been reported as trends. Fixed-effects analyses were used for a few comparisons involving small numbers of subjects. Locations of brain areas are given in Montreal Neurological Institute (MNI) coordinates.

To quantify responses in right insula and ACG, a small volume correction was used to examine empirically defined spherical regions of interest at (38, 16, -6; radius 12 mm) and (2, 12, 42; radius 18 mm) respectively. For illustrative purposes the level of response in each region was expressed as the percentage of suprathreshold ($P < 0.01$) voxels (see Tables 2-4). The significance of differences between subgroups in each of the regions of interest, shown in the footnotes to the tables, was assessed by pairwise comparisons, using t-tests. However, correlation with age (using random-effects analysis) was the primary method of assessing age-associated changes, since it makes use of larger numbers and has greater statistical power.

Results

24 subjects entered the scanner. Two could not tolerate scanning and one was eliminated because of large head movements (> 3 mm). Of the remainder, 10 were normal controls and 11 were cases with urge incontinence and DO on prior urodynamics. Basic data are shown in Table 1. The volume in the bladder at the end of scanning usually exceeded cystometric capacity and maximum voided volume on bladder-diary (which was already large among those with urge incontinence), thus confirming strong bladder sensation during the last measurement

blocks. 3 cases reported strong sensation even during the first 2 measurement blocks and one declined further scanning and has been omitted from this analysis. DO did not occur during scanning except in 3 elderly cases at large bladder volume; they are discussed separately. Tables 2-4 summarize responses to bladder filling in the brain as a whole and in the regions of interest. Results at small and large bladder volumes were obtained from first 2 and last 2 measurement blocks respectively.

Supplementary Tables 5-8 provide summaries of the brain regions responding to bladder filling.

(a) Normal responses and effect of increasing age

In normal controls, particularly younger individuals, right insular response to bladder filling increased from low levels at small bladder volumes to higher levels when bladder volume was large and sensation strong (see Table 3 and Figure 2; see also Supplementary Figures 5 and 6). Anterior cingulate responses remained weak at all volumes (Table 4).

At small bladder volumes the PAG and some frontal, parietal and temporal regions showed a trend to activation (Supplementary Table 5 and Supplementary Figures 5 and 6). At large volumes a hypothalamic region became prominent (Figure 2 and Supplementary Table 6). Activation of the PAG was detected only at a very low level of significance ($P < 0.05$ uncorrected).

In normal controls, random-effects correlation analysis showed that responses decreased significantly with age, especially near the posterior insula at small bladder volumes (see Figure 4 left panel). This area is part of a bilateral cluster that falls just outside the insular ROI used to generate the results in Table 3. At large volumes responses decreased with age in an anterior insula/caudate/frontal location (corrected $P = 0.005$ and 0.15 on left and right respectively). There was no evidence for increasing response with age in any brain region. Indeed all responses – insular, ACG and whole-brain – were weak in elderly controls (Tables 2-4).

(b) Responses in cases with urge incontinence and effect of increasing age

Among cases with urge incontinence, age had a marked effect. At small bladder volumes many responses, including those in right posterior insula, *increased* significantly with increasing age (Figure 4, right panel), in contrast to the decrease seen in normal controls (left panel). At large bladder volumes no correlations with age were significant at cluster level. Stratification into younger and older cases (Tables 2-4) helped to understand these unexpected results, even though subgroup numbers were small, as follows.

Younger cases—In younger cases, whole-brain responses (Table 2) tended to be weaker than normal at small volumes (significant in the left posterior insula/putamen; corrected $P < 0.0005$) but apparently stronger than normal at large volumes. Similarly, ACG response was weak at small bladder volumes but strong at large volumes (Table 4). Insular response showed similar but less marked behavior (Table 3).

Older cases—In older cases the strongest insular, ACG and whole-brain responses all occurred at *small* bladder volumes (Tables 2-4). They were stronger than in controls, stronger than in younger cases, and – surprisingly – stronger even than the more moderate responses at large volumes.

Comparison of Tables 2 and 4 showed that, overall, whole-brain responses were elevated whenever the ACG was strongly activated, indicating co-activation of other brain regions with ACG (see for example Figure 3).

(c) Pontine micturition center and effect of DO

A region at the expected location of the PMC (8, -34, -28) (Blok et al., 1997b) showed a trend to response in the 10 cases with urge incontinence at both small and large volumes (Figure 3 and Supplementary Tables 7 and 8). Response was still present at large volumes after excluding the 3 elderly cases with DO during scanning (see footnote to Supplementary Table 8). A fixed-effects analysis of results obtained during the DO episodes in these 3 cases failed to demonstrate a significant PMC response ($P > 0.01$ uncorrected), although it showed significant responses elsewhere.

(d) Other observations

In a previous study of mainly younger cases, using fixed-effects analysis, an orbitofrontal chain of regions was abnormally underactive at large bladder volumes (Griffiths, 2005; Griffiths et al., 2005). This was true in the present study also, while a similar analysis of older cases at small bladder volumes showed a trend to abnormal underactivity ($P < 0.05$ vs normal controls) in an almost identical orbitofrontal chain, in direct contrast to the pronounced activity in many other parts of the brain. A more stringent random-effects analysis, although not attaining significance ($P < 0.1$), supported this finding. The orbitofrontal chain was centered at (0, 48, -10) and extended approximately from $x = -40$ to $x = +40$,

We failed to convincingly identify the pontine L-region, postulated to act as a continence center and located near (12, -20, -32) (Blok, 2002).

Discussion

Normal responses and effect of aging

In normal controls some of the brain regions responding to bladder filling (PAG, insula, frontal cortex, Supplementary Tables 5 and 6 and Supplementary Figures 5 and 6) are well known from other studies (Di Gangi Herms et al., 2006; Kavia et al., 2005; Kuhtz-Buschbeck et al., 2005; Seseke et al., 2006; Zhang et al., 2005). Other regions have received less attention. For example, the parietal region shown in Supplementary Table 5 and Supplementary Figure 6 is close to a similar region activated by increasing bladder volume in a PET study (Athwal et al., 2001). The hypothalamic region in Supplementary Table 6 and Figure 3 is identical to one responding to decreased urge to void in the same study; it appears to be the perifornical area of the hypothalamus, which in the cat has direct monosynaptic access to the PMC (Holstege, 2005). Strong activation at large bladder volumes in subjects with normal bladder control suggests an inhibitory influence on the PMC. The responses in the PAG were relatively weak, especially at large bladder volumes.

The effect of increasing age is a general decrease of these responses, consistent with either a decrease in afferents or an overall decrease in brain responsiveness, probably reflecting normal aging. Decreasing afferents would imply reduced sensory feedback, making bladder control more difficult and perhaps predisposing to the development of urge incontinence in older people (Andersson, 2004).

Urge incontinence in younger and older individuals

The generally positive correlation of brain responses with age in urge incontinence (Figure 4, right panel) indicates that urge incontinence has different characteristics in older and younger people. Younger individuals show reduced responses at smaller bladder volumes, as if they are neglecting bladder information, but exaggerated responses at large volumes when they are experiencing strong sensation. Older urge-incontinent individuals show abnormally strong responses even at small bladder volumes, and paradoxically somewhat more moderate responses at large volumes. Possible explanations will be discussed below (see Motor control).

Sensation

Among normal controls, increased right-insular response at large bladder volumes (when there is strong desire to void) and diminished response in old age are consistent with the postulated role of the right insula in mapping normal bladder sensations, as for other visceral afferent (sensory) signals (Craig, 2002; Craig, 2003; Derbyshire, 2003)

For urge-incontinent subjects, however, the common belief that sensations and afferent signals are abnormally strong is questionable, at least in younger individuals, because at small bladder volumes their responses are weaker than normal. Even when sensation is strong it may be different from normal strong desire to void. Tables 2-4 show that the distinguishing characteristic of cases with urge incontinence is strong ACG activation (Figure 3). Since the ACG belongs to the limbic (emotional) nervous system, its activation suggests the involvement of emotion, as expected for the abnormal sensation of urgency that clinically is characteristic of these subjects. Thus strong ACG response to bladder filling may be the fMRI sign of urgency. It is unlikely however to be the *cause* of urgency, because simultaneous responses elsewhere in the brain (e.g. left parietal cortex, Supplementary Table 8) suggest that ACG activation is part of the recruitment of alternative pathways when loss of bladder control is feared.

Motor control

The ACG is a large region with several presumed functions (Botvinick et al., 2004; Bush et al., 2000; Critchley et al., 2003). The part activated in response to bladder filling (see Figure 3) is also concerned with regulation of heart rate in response to emotional stimuli (Critchley et al., 2003). Plausibly, in response to urgency, it may exert similar motor regulation of bladder behavior via brainstem nuclei. The pathway must be indirect since the ACG has no monosynaptic connection to the PMC (Kuipers et al., 2006). ACG activation seems to be a response to threatened loss of bladder control; therefore one might expect that its action on the PMC should be inhibitory.

The evidence supports this expectation. In older cases, ACG activation is strongest at small bladder volumes; there is no DO, implying adequate inhibition of the PMC. At large volumes, however, inhibition may fail (DO actually occurred in 3/6 cases) and if so the ACG response becomes correspondingly somewhat weaker. This reasoning is confirmed by fixed-effects analyses. The 3 cases who showed DO during scanning were responsible for the paradoxical behavior referred to above: they showed very strong responses at low bladder volumes (when successfully inhibiting DO) and a decrease at larger volumes when DO developed (implying failure of inhibition); the other 3 cases did not show DO nor this behavior. An alternative hypothesis concerning the paradoxical behavior in the elderly might be that age-related changes in afferent signals may provoke strong brain responses even at small bladder volumes.

Interestingly, the PMC response itself was evident when there was no DO (see Figure 3), but could not be demonstrated when DO developed (see pontine micturition center and effect of DO, above), suggesting that it too represents inhibitory activity. In Parkinson's disease, perhaps for similar reasons, the PMC is apparently not active during DO (Kitta et al., 2006).

An underlying cerebral cause of detrusor overactivity?

Detrusor overactivity and urge incontinence are clearly multifactorial (Mostwin, 2002; Resnick et al., 1989). Among potential causes, as argued above, neither increased bladder afferents nor ACG activation are plausible (although changed bladder afferents, specific to urgency, remain a possible causal factor). Lack or neglect of bladder afferents, leading to inadequate sensory feedback, is a possible contributory factor, but may not be causal. There is no clear evidence in this study for involvement of the postulated pontine continence center (L-region). There is however weak evidence that an orbitofrontal chain of brain regions is underactive in cases with

urge incontinence; because this part of the brain is concerned with executive control, its dysfunction is a plausible cause of DO and urge incontinence. This possibility merits further research.

Limitations

Although 20 subjects provided adequate statistical power for basic analyses (Murphy et al., 2004), stratified subgroups were small. We minimized this difficulty by assessing correlations with age as a continuous variable. Very few subjects showed DO during scanning; further measurements during DO are required. Our cases were a little older than the normal controls, although the youngest subject had urge incontinence. We examined only women; future studies should include men.

A limitation is the repeated and rapid infusion minus withdrawal used to elicit brain responses which, although unphysiological, mimicked bladder filling more closely than other fMRI paradigms (Kuhnz-Buschbeck et al., 2005; Seseke et al., 2006; Zhang et al., 2005). The imaged field of view was restricted axially to 90 mm; to ensure coverage of the PMC and L-region, the paracentral lobule, important in pelvic floor control (Blok et al., 1997a; Kuhnz-Buschbeck et al., 2005; Zhang et al., 2005), was omitted in some subjects.

PET studies have revealed brain regions that become less active with increasing volume or desire to void, suggesting inhibition (Athwal et al., 2001; Blok et al., 1997b) but this fMRI study demonstrated only increased (possibly inhibitory) responses. Such apparent discrepancies show that PET and fMRI provide complementary insights that require further study.

Conclusions

Among normal subjects, brain responses to bladder filling decline with increasing age, in particular in the right insula (where normal bladder sensations are mapped). In subjects with urge incontinence, brain responses to bladder filling differ greatly between young and old, and in both age groups they are different from normal even when no DO is present. Strong activation of the anterior cingulate gyrus is characteristic of all these urge-incontinent subjects. It is probably a sign of the abnormal sensation of urgency, may indicate recruitment of alternative pathways in the face of fear of leakage, and seems to have an inhibitory effect on the pontine micturition center. An underlying cerebral cause of urge incontinence and DO remains uncertain but may be related to dysfunction of the prefrontal (orbitofrontal) cortex.

Functional brain scanning has been criticized as “phrenology,” providing little evidence about function (Kavira et al., 2005). This study has shown that it is possible to go beyond identification of brain regions and begin to understand how the brain control network functions in health and disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic diagram of bladder filling and scanning protocol. 4 blocks of measurements were made in all subjects. Blocks 5 and/or 6 were performed only if subjects agreed. Each block included 4 repetitions of a basic pattern of infusion and withdrawal. Reproduced from (Griffiths et al., 2005) by permission of the publisher, Elsevier.

Figure 2.

Responses to bladder infusion in normal controls at large bladder volumes. Insular response is greater on the right. RI = right insula; ACG = anterior cingulate gyrus; H = hypothalamus; RI/PFC = right anterior insula and/or lateral prefrontal cortex. R = right side. Color bar shows scale of student's t values.

Figure 3.

Responses to bladder infusion in subjects with urge incontinence at large bladder volumes. RI = right insula; ACG = anterior cingulate gyrus; PMC = pontine micturition center.

Figure 4.

Correlation with age of response to bladder infusion at small bladder volumes. Left panel: in normal controls, areas of *negative* correlation with age (thresholded at $P < 0.01$). Right panel: in subjects with urge incontinence, areas of *positive* correlation with age (thresholded at $P < 0.05$ for display). Right posterior insula (white arrows) shows negative correlation with age in normal controls (in bilateral cluster, $P < 0.0005$, corrected) but positive correlation in urge-incontinent subjects ($P < 0.01$, uncorrected).

Table 1
Demographic and urodynamic data for the subjects in the study

	controls n = 10 median	range	cases n = 11 median	range	P-value of difference
age, y	56.5	30-79	71	26-85	0.35
parity	2	0-5	3	0-5	0.93
minimal state exam /30	30	28-30	29	27-30	0.01
maximum voided volume	525 *	200-800	500	300-700	0.96
on bladder diary, ml					
strong desire to void	320 *	220-556	201	91-490	0.01
on urodynamics, ml					
maximum cystometric	599	475-980	369	246-961	0.02
capacity, ml					
post-fMRI bladder	675	270-1100	600	300-842	0.14
volume, ml					

* variables positively correlated with age in normal subjects, implying decreasing sensation with increasing age; r = 0.47 and 0.29 respectively (n.s.)

Table 2
Percentage of activated voxels ($P < 0.01$) in the scanned region of the whole brain. Results of random-effects analyses.

	all ages controls n = 10	cases n = 10	young (< 60 y) controls n = 5	cases n = 4	elderly (≥ 60 y) controls n = 5	cases n = 6
small volume, mild sensation	3	8	4	1	0	10 ^{##}
large volume, strong sensation	3	10	3	7	1	3

^{*} significantly greater than corresponding value in controls ($P < 0.001$ after correction for multiple comparisons)

[#] significantly greater than corresponding value in young cases ($P < 0.001$ after correction)

Table 3

Percentage of activated voxels in a region of interest surrounding the right insula (12 mm radius sphere at 38, 16, -6). Results of random-effects analyses at small and large bladder volumes, in controls and cases.

	all ages controls n = 10	cases n = 10	young (< 60 y) controls n = 5	cases n = 4	elderly (≥ 60 y) controls n = 5	cases n = 6
small volume, mild sensation	1	29	1	2	0	29 [#]
large volume, strong sensation	32[unk]	35	18 ^{*§¶}	6	2	5

^{*} significantly greater than corresponding value at small volume (P < 0.05 after correction)

[#] significantly greater than corresponding value in young cases (P < 0.05 after correction for multiple comparisons)

[§] significantly greater than corresponding value in cases (P < 0.05 after correction)

[¶] trend to significant increase over corresponding value in elderly controls (P < 0.01 uncorrected)

[unk] trend to significant increase over value at small volume (P < 0.01 uncorrected)

Percentage of activated voxels in a region of interest surrounding the anterior cingulate gyrus (18 mm sphere at 2, 12, 42). Results of random-effects analyses at small and large bladder volumes, in controls and cases.

	all ages controls n = 10	cases n = 10	young (< 60 y) controls n = 5	cases n = 4	elderly (≥ 60 y) controls n = 5	cases n = 6
small volume, mild sensation	0	42	0	0	0	44#§
large volume, strong sensation	7	49	0	32	1	18

significantly greater than corresponding value in young cases ($P < 0.0005$ after correction)

§ significantly greater than corresponding normal value in elderly controls ($P < 0.0005$, after correction)