Physiology & pathophysiology of the ageing bladder

The outflow tract - smooth muscle[1]

Contraction

sympathetic: contraction mediated by $\alpha_{1A/L}$ agonists

parasympathetic: muscarinic receptors - no significant effect

Relaxation

mediated predominantly by NO

- NO defective in diabetes, BOO, bladder inflammation

β_3-receptors may mediate relaxation - less than in detrusor

Effect of estrogens

lack of estrogen contributes to lack of urethral tone

however estrogen supplementation reduces urethral closure pressure due to reduction of collagen content

Spontaneous activity

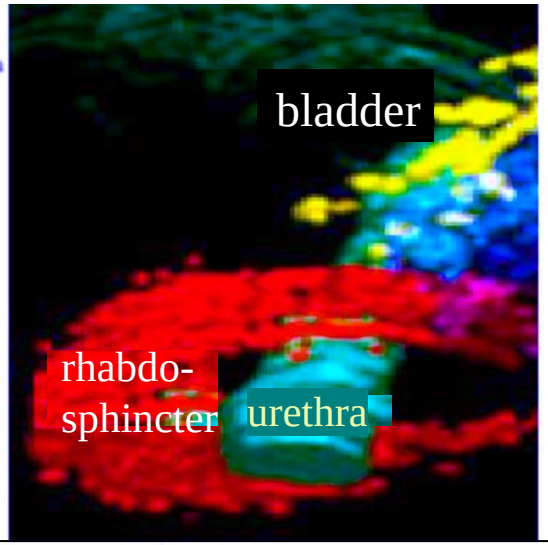
arises from smooth muscle cells

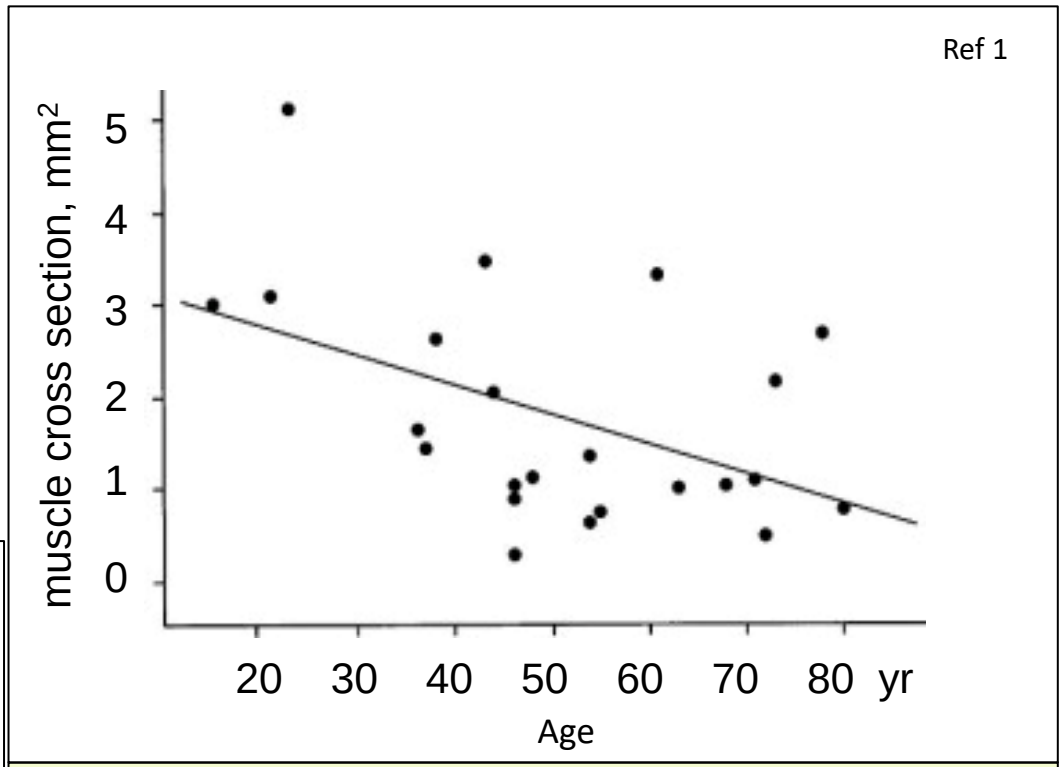
modulated by interstitial cells

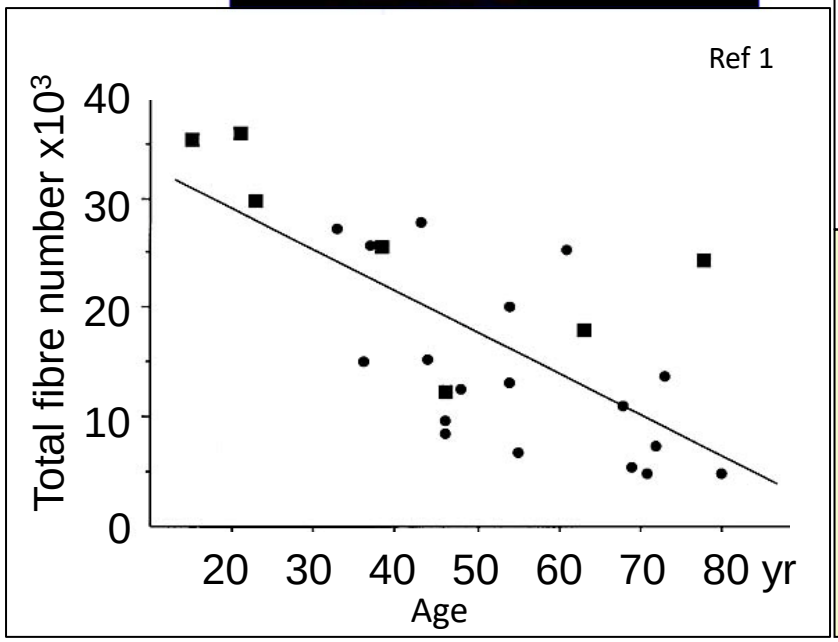
1. Fry CH, *et al. Auton Neurosci*. 2010; 154:3-13.

BOO: bladder outlet obstruction

Urethral skeletal muscle - rhabdosphincter





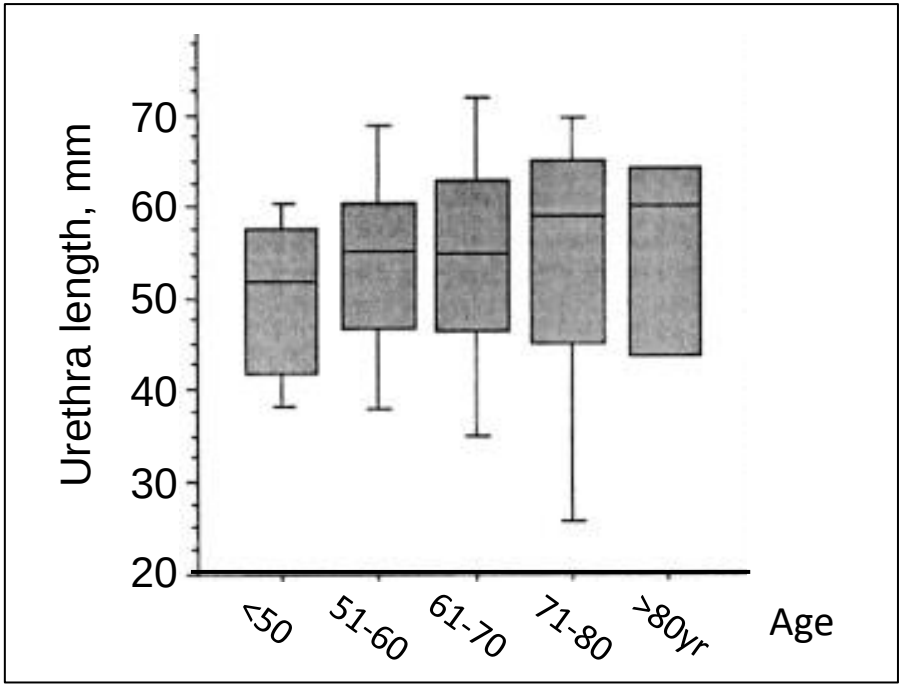


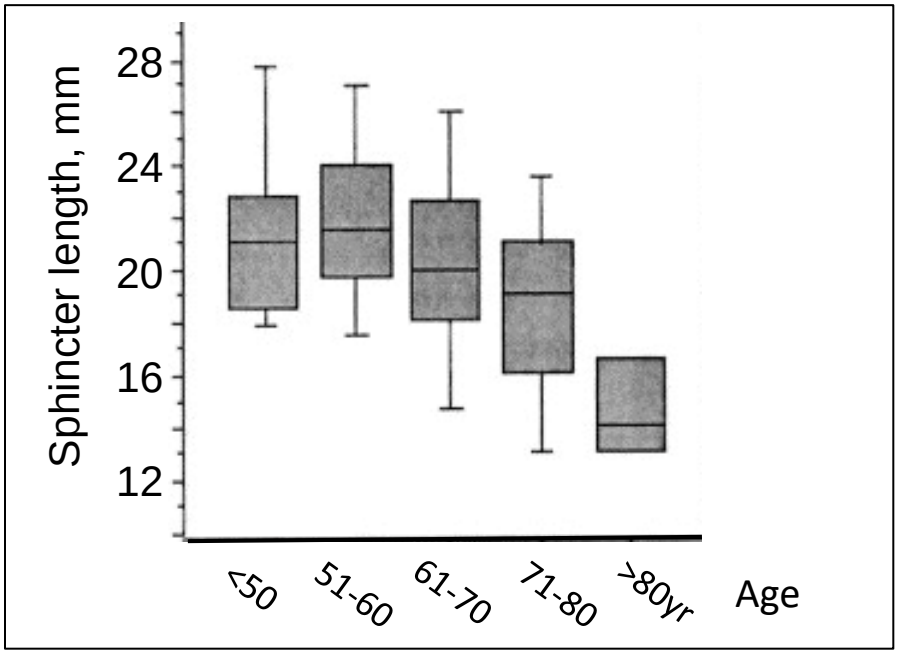
Strategies to increase sphincter function

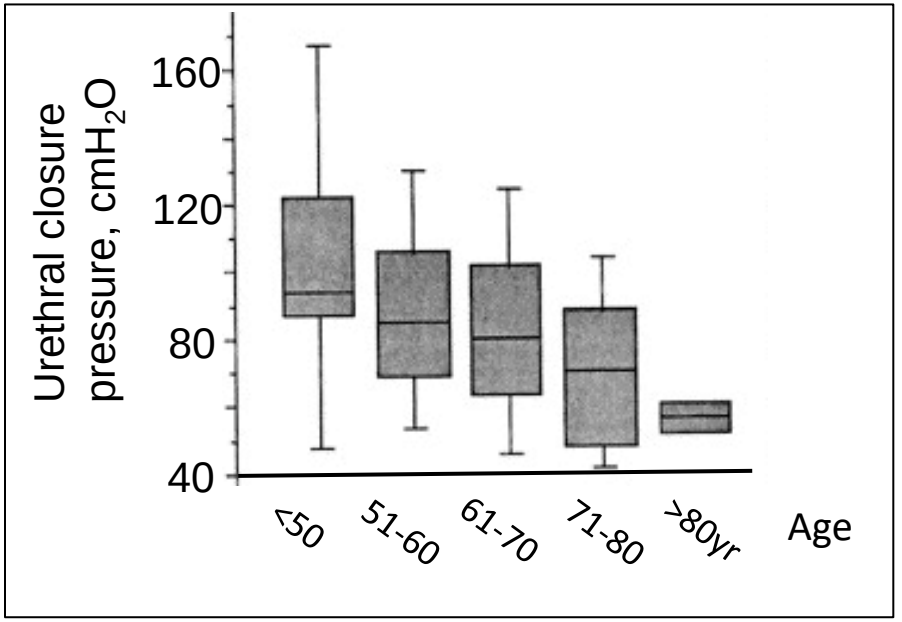
- myoblast implants to increase muscle bulk[2]
- Selective inhibitors of serotonin and noradrenaline - transmitters in Onuf's nucleus[3]

1. Perucchini D, *et al. Am J Obstet Gynae*. 2002; 186:351-355. 2. Fry CH, *et al. Auton Neurosci*. 2010; 154:3-13.
3. Nitti VW. *Rev Urol*. 2004; 6:S48-55.

External sphincter geometry[1]







1. Hammerer P, *et al. J Urol.* 1996; 156:1741-1743.

Conclusions:
Abnormalities of the outflow tract

Less quantitative work

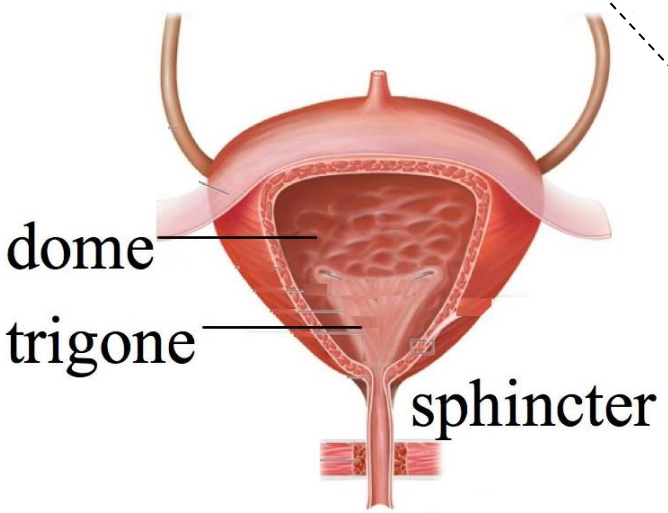
But

External sphincter geometry altered

Rhabdosphincter integrity reduced

Scope of research into age-related changes to urethral smooth muscle function and innervation

Storage and emptying



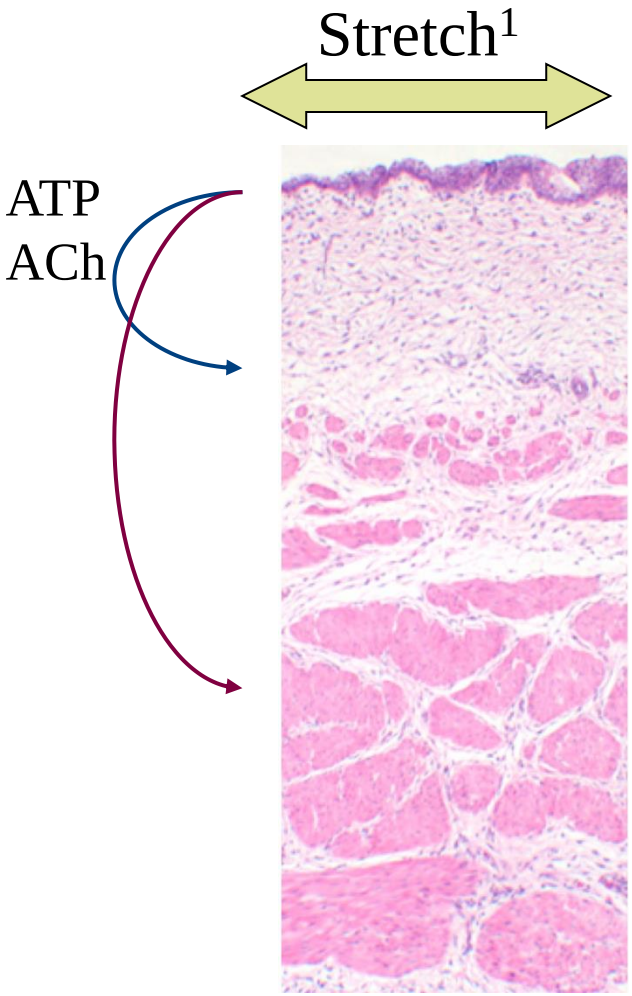
The urinary tract has a dual function:

To store urine

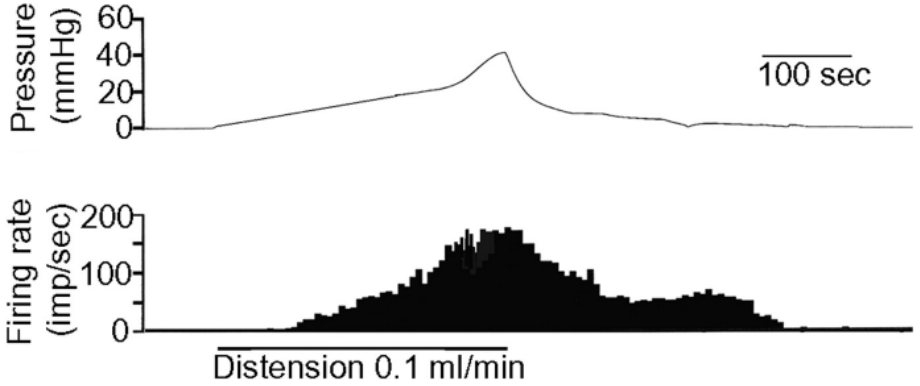
the bladder is relaxed

the sphincter closed

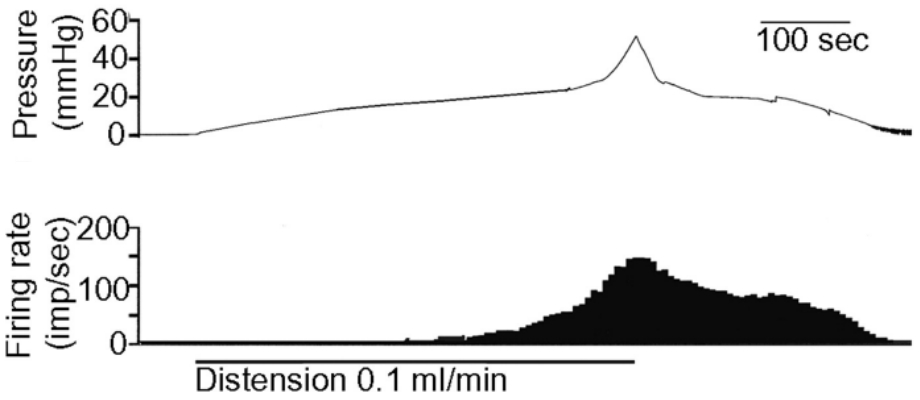
Abnormalities of storage
The urothelium: stretch and release of transmitters



wild-type mice[2]



ATP receptor ($P2X_3$) knock-out mice[2]



1. Adapted from Young JS, *et al. BJU Int*. 2012; 110:E397-401.
2. Vlaskovska M, *et al. J Neurosci.* 2001; 21:5670-5677.

Abnormalities of storage
ATP release for urothelium and its relevance to pathology

Stretch of isolated urothelium increases ATP release.

ATP release is **increased** in:

- cultured urothelium cells from patients with interstitial cystitis[1]
- urothelium cells taken from overactive bladders[1]

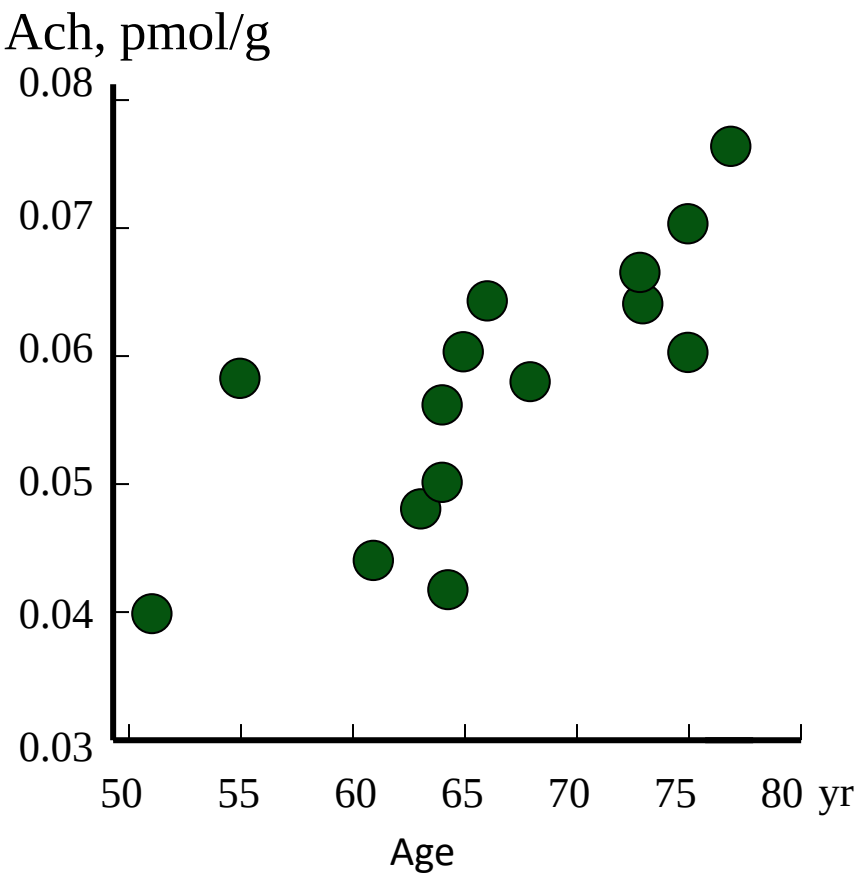
ATP release is **decreased** in:

- urothelium patients treated with botulinum toxin[1]

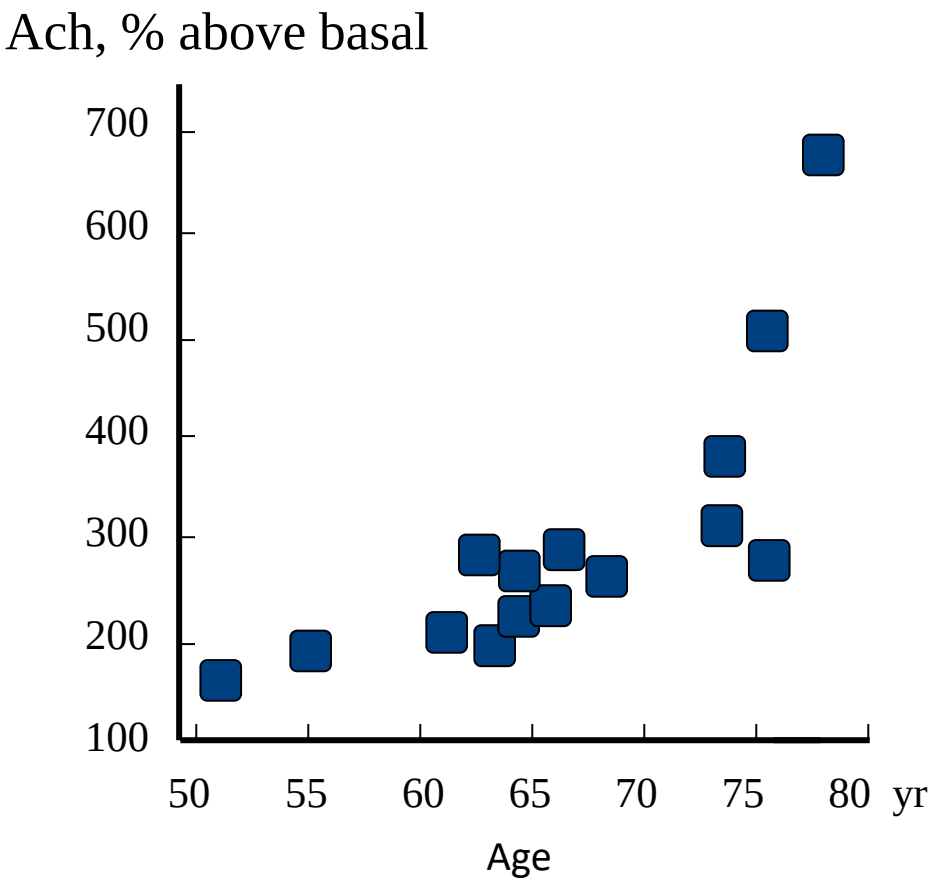
1. Fry CH, *et al. Basic Clin Pharmacol Toxicol*. 2016; 119:57-62.

Abnormalities of storage
Acetylcholine release for urothelium - ageing

Non-neuronal stimulated release[1]



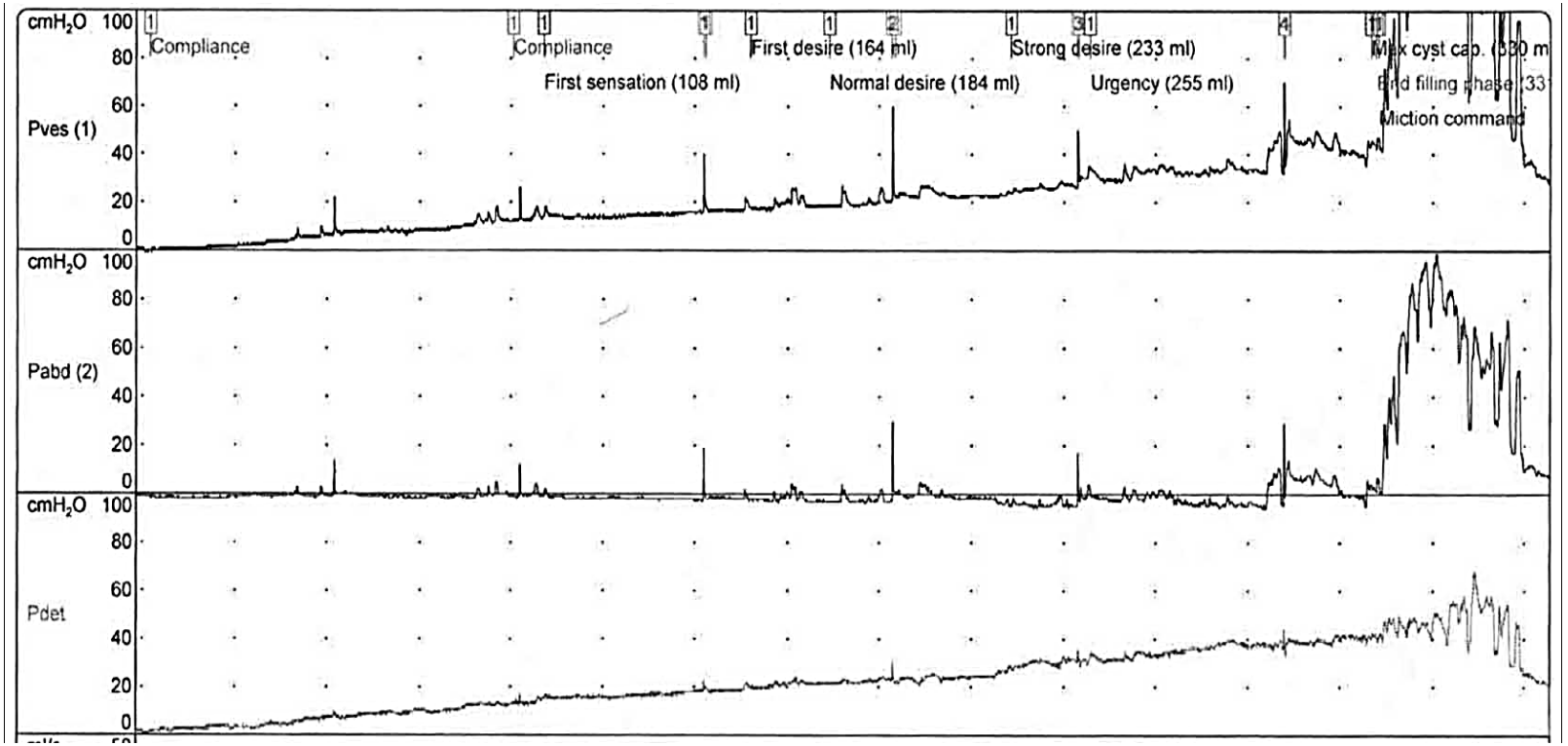
Stretch-induced release[1]



1. Yoshida M, et al. *Urology*. 2006; 67:425-430.

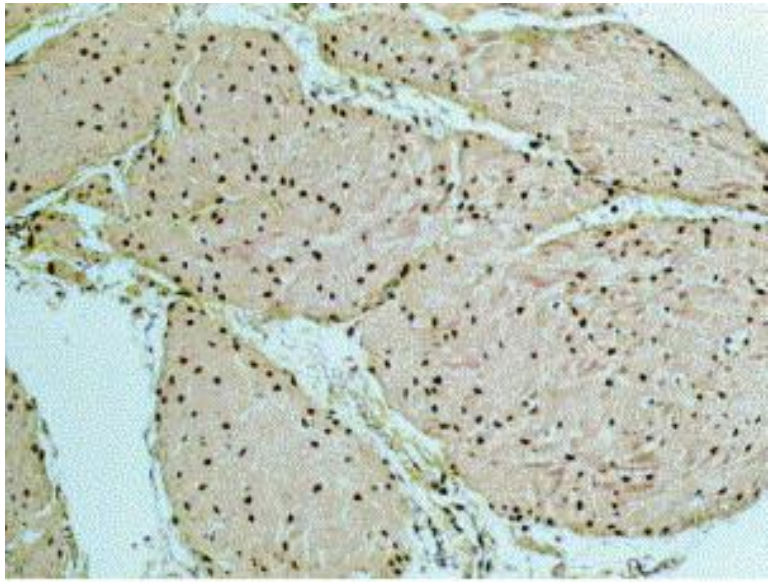
Abnormalities of storage
Compliance and extracellular matrix

An increase of extracellular matrix is associated with a decrease of bladder filling compliance

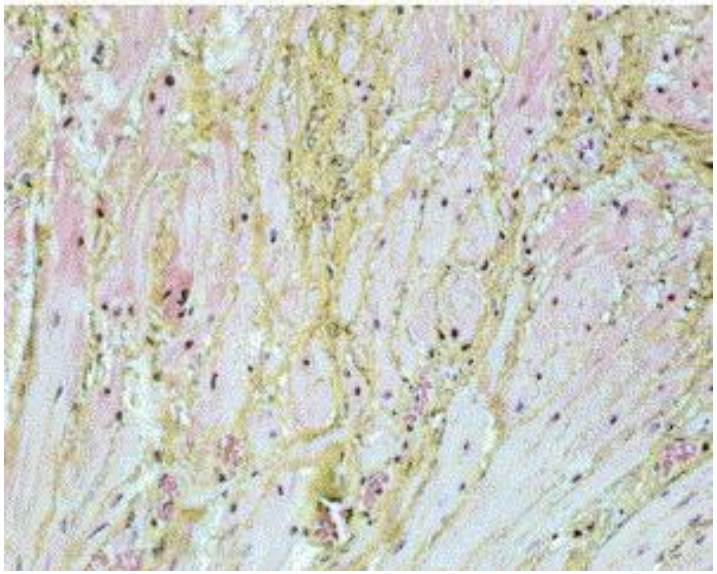


Abnormalities of storage
Compliance and extracellular matrix

Stable (non-overactive) bladder[1]



Obstructed, overactive bladder[1]



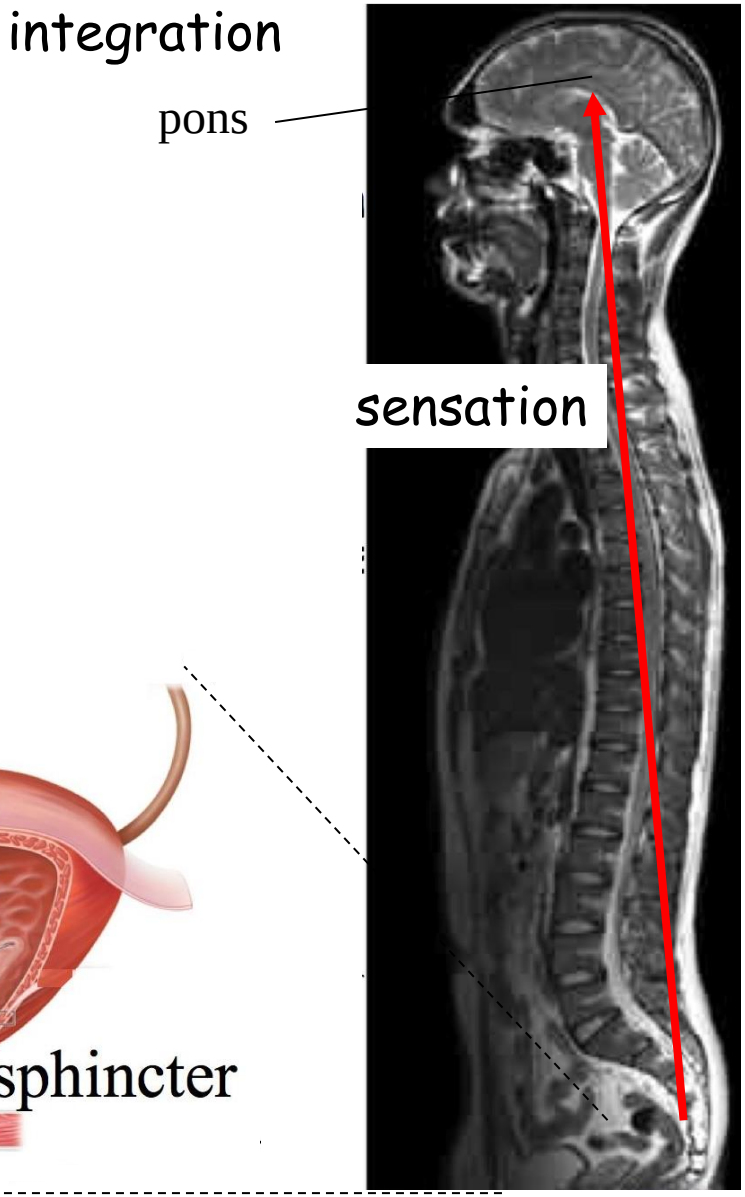
Noted changes in MMP expression between non-obstructed and obstructed states

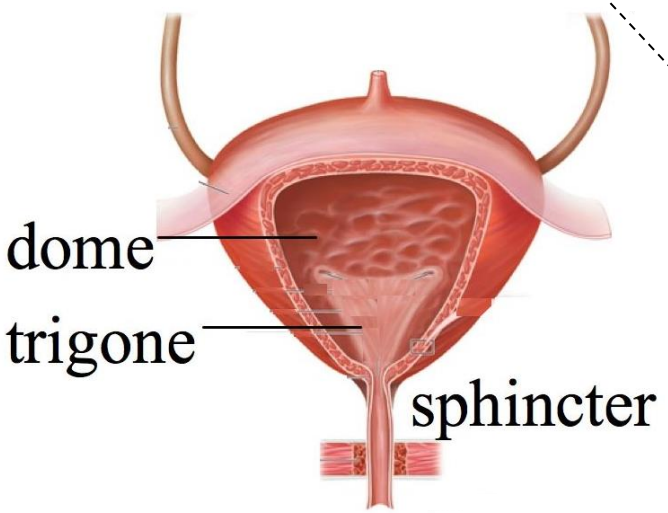
1. Nordling J. *Exp Geront*. 2002; 37:991–999.
2. Yang L, et al. BJU Int. 2013; 112:e391-397.

Conclusions: Abnormalities of storage

Aspects of filling sensation	Aspects of bladder compliance
Bladder filling associated with neuromodulator release from urothelium	Reduced compliance leads to threshold pressure for micturition at lower volumes
ATP release increased in the ageing bladder	No change to compliance associated with age
Acetylcholine release increased in the ageing bladder	Obstruction, DO associated with decreased compliance and increased extracellular matrix

Abnormalities of integration





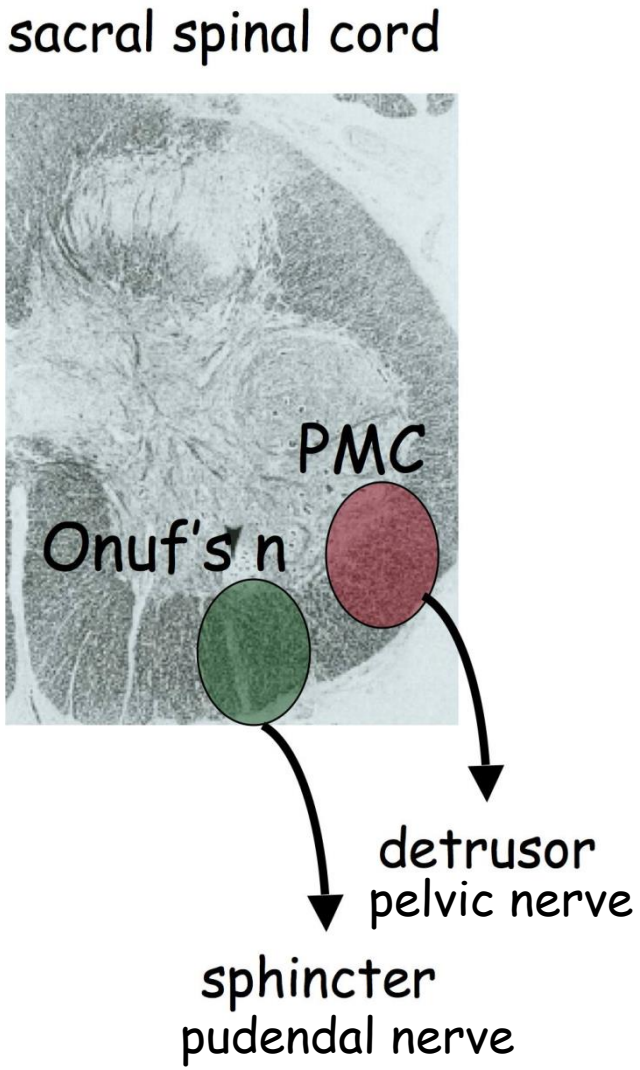
The urinary tract has a dual function:

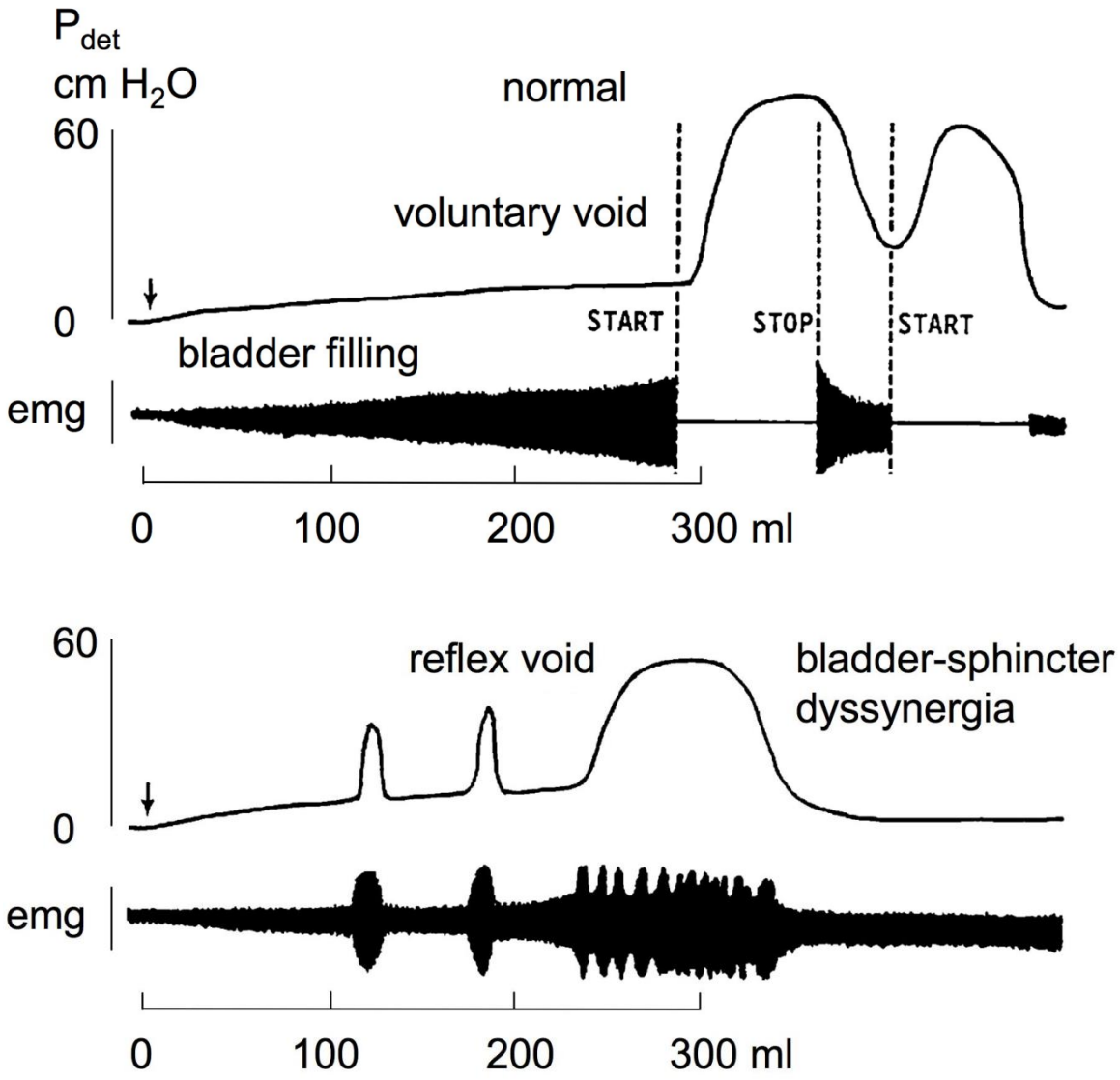
To store urine

the bladder is relaxed

the sphincter closed

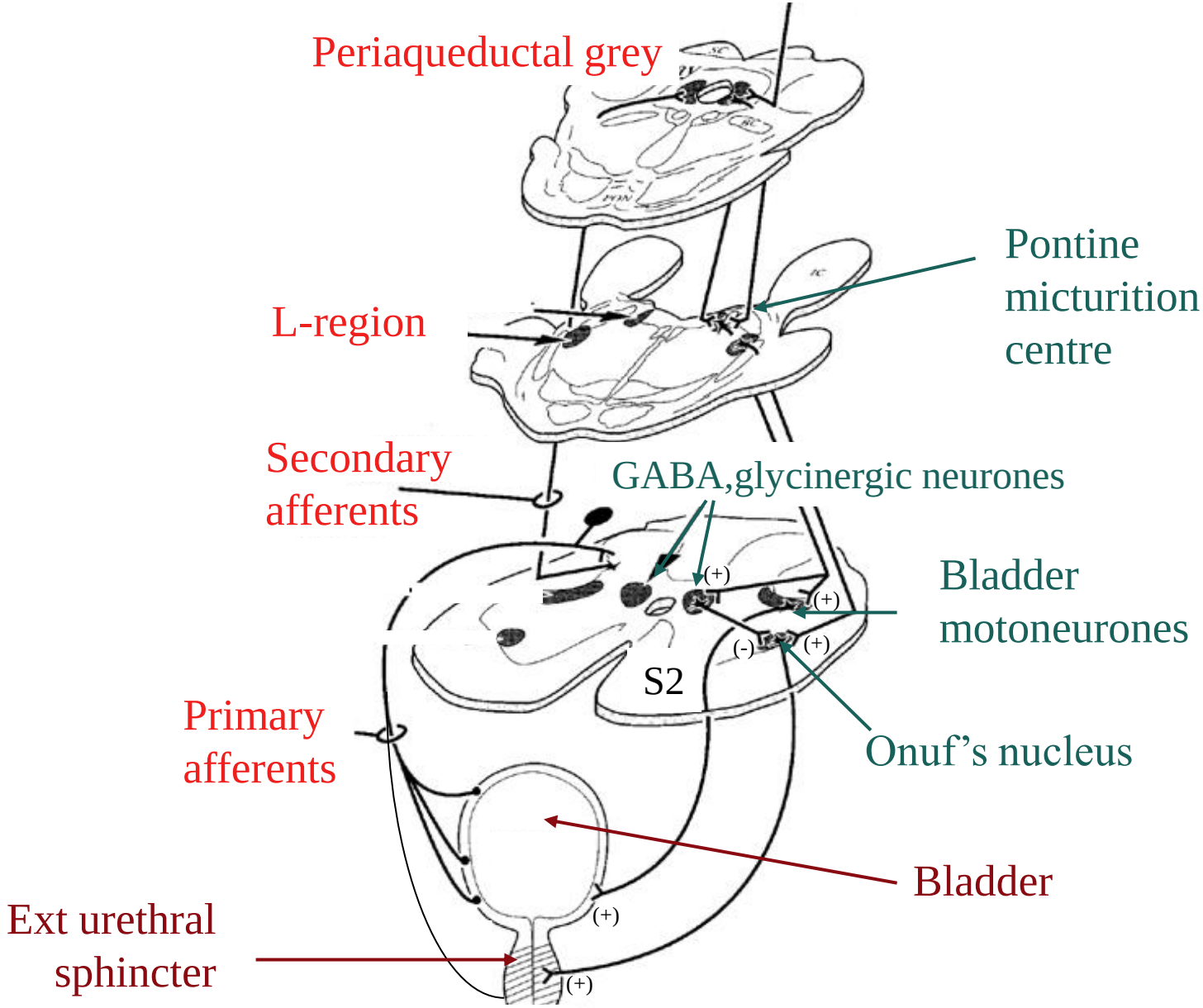
Integration in the spinal cord[1]





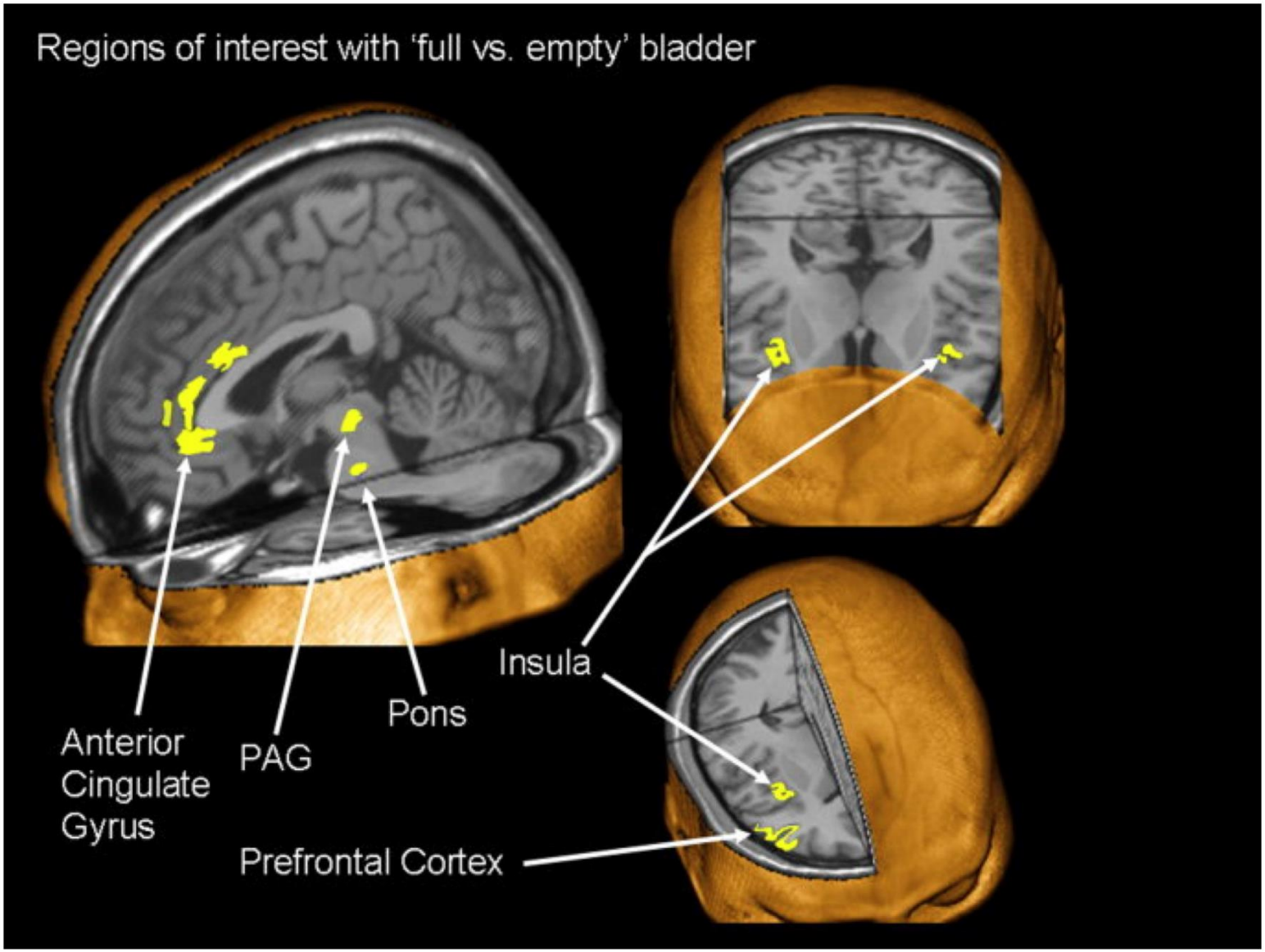
1. De Groat WC, *et al. Br J Pharmacol.* 2006; 147:S25-40.

Central connections of the lower urinary tract



Adapted from Tadic SD, *et al. F1000 Med Rep* 4:20-6. 2012.

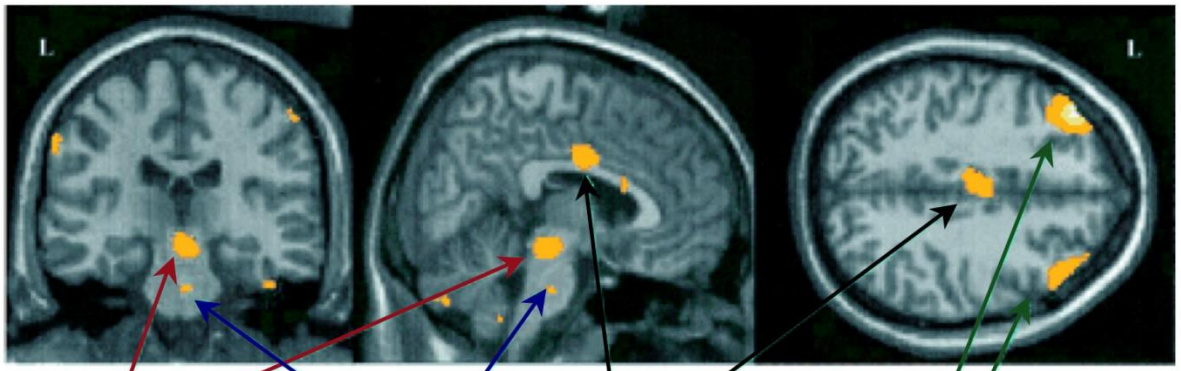
Identification of higher control pathways[1]



1. Kavia RB, *et al. J Comp Neurol*. 2005; 493:27-32.

Abnormalities of integration

Athwal et al[1]



PET

peri-aqueductal grey

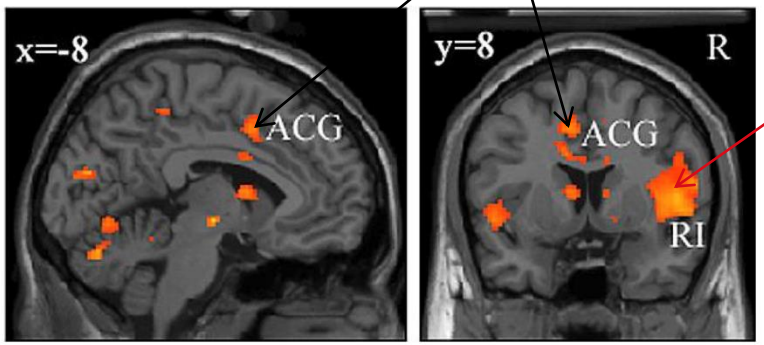
pons

cingulate

frontal lobe

insula

Griffiths et al[2]



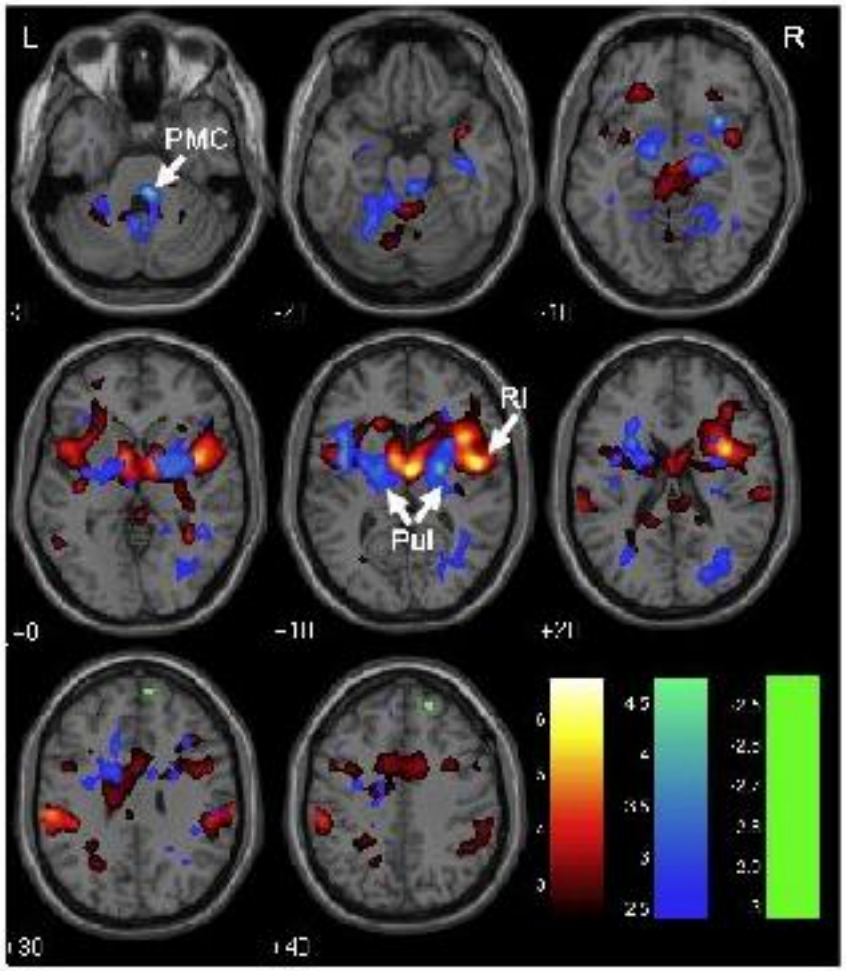
fMRI

Tadic et al[3]

Control

1. Athwal *BS, et al*. Brain. 2001; 124:369-377.
2. Griffiths D, *et al. Neuroimage*. 2007; 37:1-7.
3. Tadic SD, *et al. Neurourol Urodyn*. 2013; 32:435-440.

Abnormalities of integration
The normal situation[1]



Bladder filling:

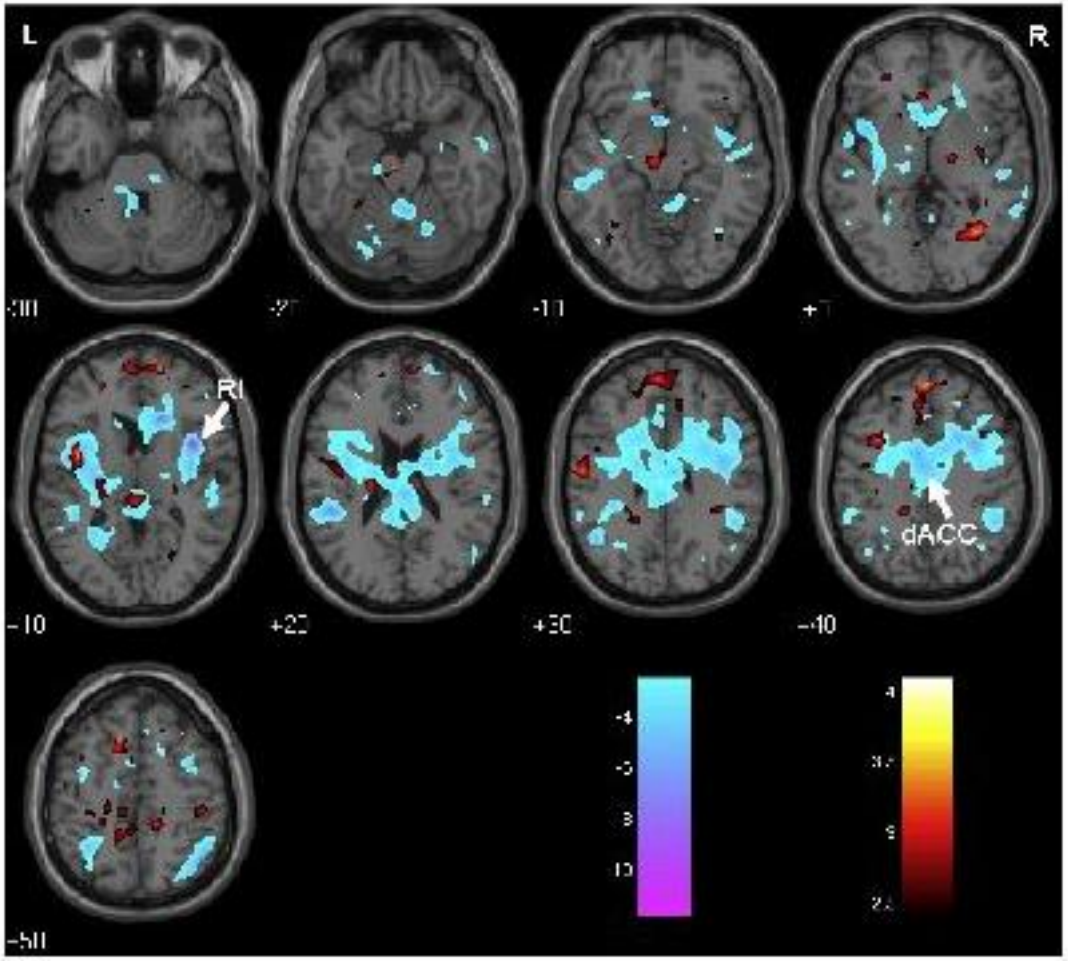
Red/Yellow - activation

Green - deactivation

Blue - connectivity with Right Insula and Anterior Cingulate Gyrus

1. Griffiths DJ, *et al. NeuroImage*. 2009; 47:981-986.

Abnormalities of integration
Effect of age[1]



Bladder filling:

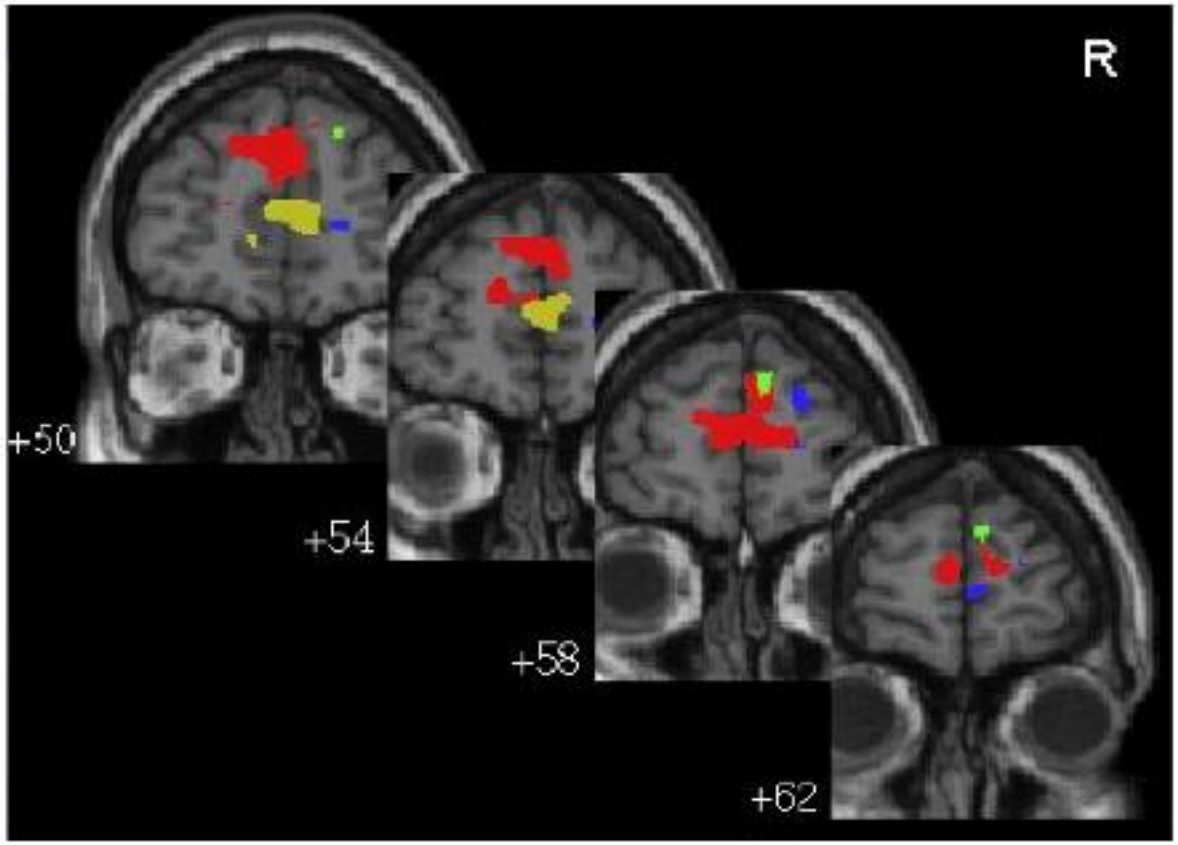
Blue - regions where response to filling decreased with age

Red/Yellow - regions where connectivity increase with age

RI - right insula
dACC - dorsal anterior cingulate cortex

1. Griffiths DJ, *et al. NeuroImage*. 2009; 47:981-986.

Abnormalities of integration
Effect of age[1]



Medial prefrontal cortex
Bladder filling:

Blue - negative response to filling

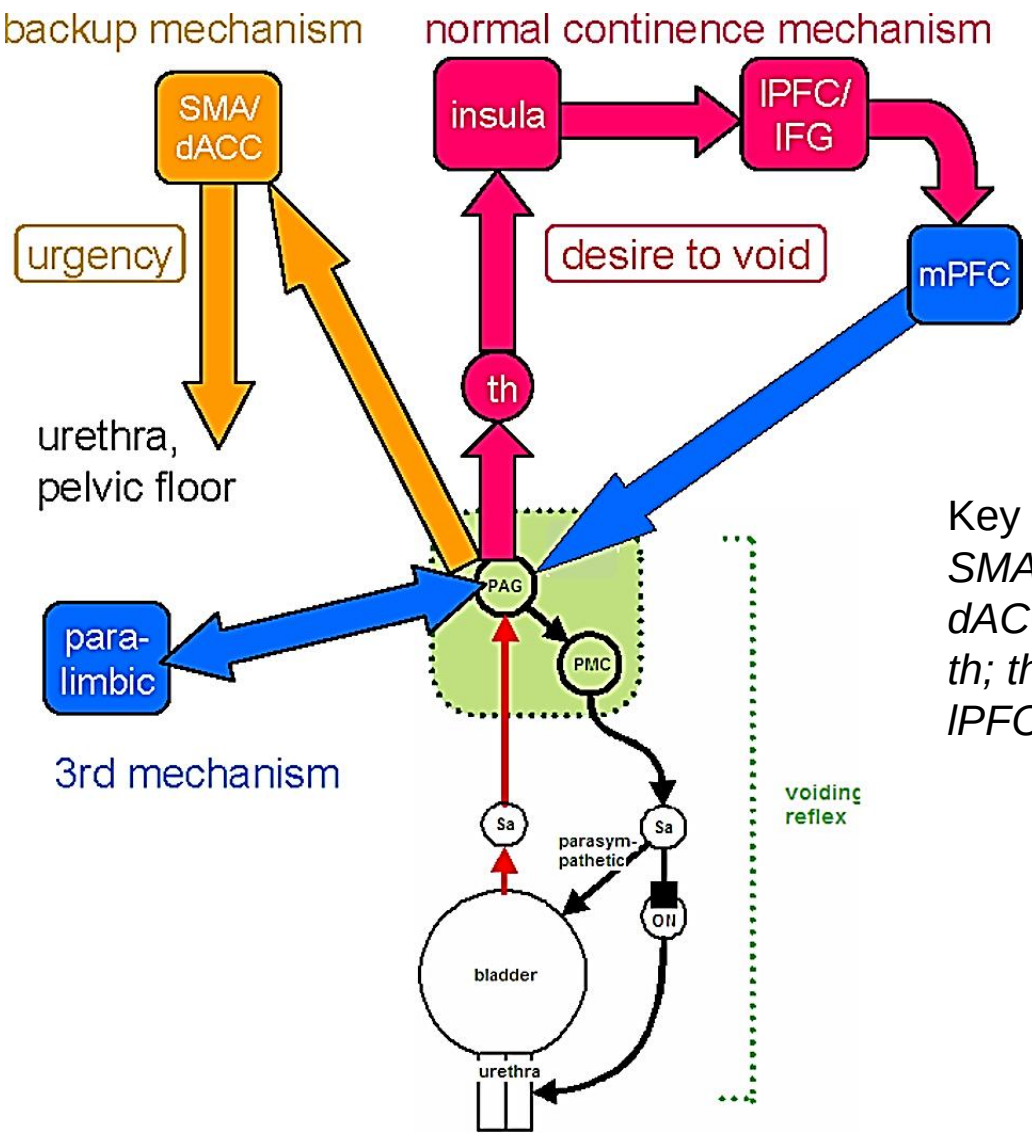
Green - response negatively correlated with age

Red - response positively correlated with age

Yellow - connectivity negatively correlated with bladder volume

1. Griffiths DJ, *et al. NeuroImage*. 2009; 47:981-986.

Control of lower urinary tract function[1]



Key

SMA; supplementary motor area

dACC; dorsal anterior cingulate gyrus

th; thalamus

lPFC; lateral prefrontal cortex

1. Tadic SD, *et al. Neurourol Urodyn*. 2012; 31:652-658.

Conclusions:
Age and lower urinary tract function
What do we know?

Detrusor function

Denervation

Atropine resistance

Spontaneous activity

Bladder outflow

Urethral geometry

Rhabdosphincter activity

Urethral smooth muscle

Bladder filling

Urothelial neuromodulator release increases

Factors affecting bladder compliance

Central integration

Sacral integration

Mid- and forebrain function

Physiology of the LUT

Warning

- Normal ageing changes are difficult to study because longitudinal data including large numbers of individuals spanning many years are necessary to definitively separate "normal LUT ageing" from confounding factors and comorbidity

- Cross-sectional studies are subject to confounding by comorbidity and time-dependent cohort effects, such as change in labour and delivery practices. Thus, to date many studies actually describe "age-related" associations, as opposed to normal ageing

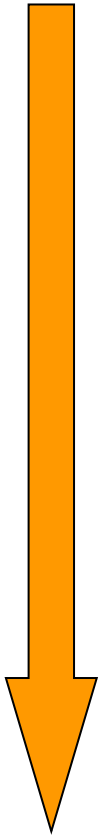
- Even the definition of "normal" can be difficult: is it continence, absence of LUTS, lack of comorbid disease, or normal physiological testing?

Ageing and the lower urinary tract – what's normal?[1]

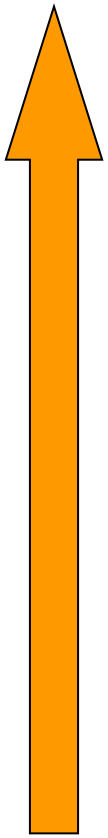
- 56 "elderly" (> 65 y) subjects (26 men) comprehensive urodynamic assessment and CT/MRI
- "Normal" urodynamic studies in 18% (Post Void Residual volume up to 250mL included as normal)
- Detrusor Overactivity commonest diagnosis
- Detrusor Overactivity seen as commonly in unobstructed as obstructed men
- Obstruction with and without symptoms equally common in the men

1. Resnick N, *et al. Neurourol Urodyn* 1995;14:577–578.

Physiology

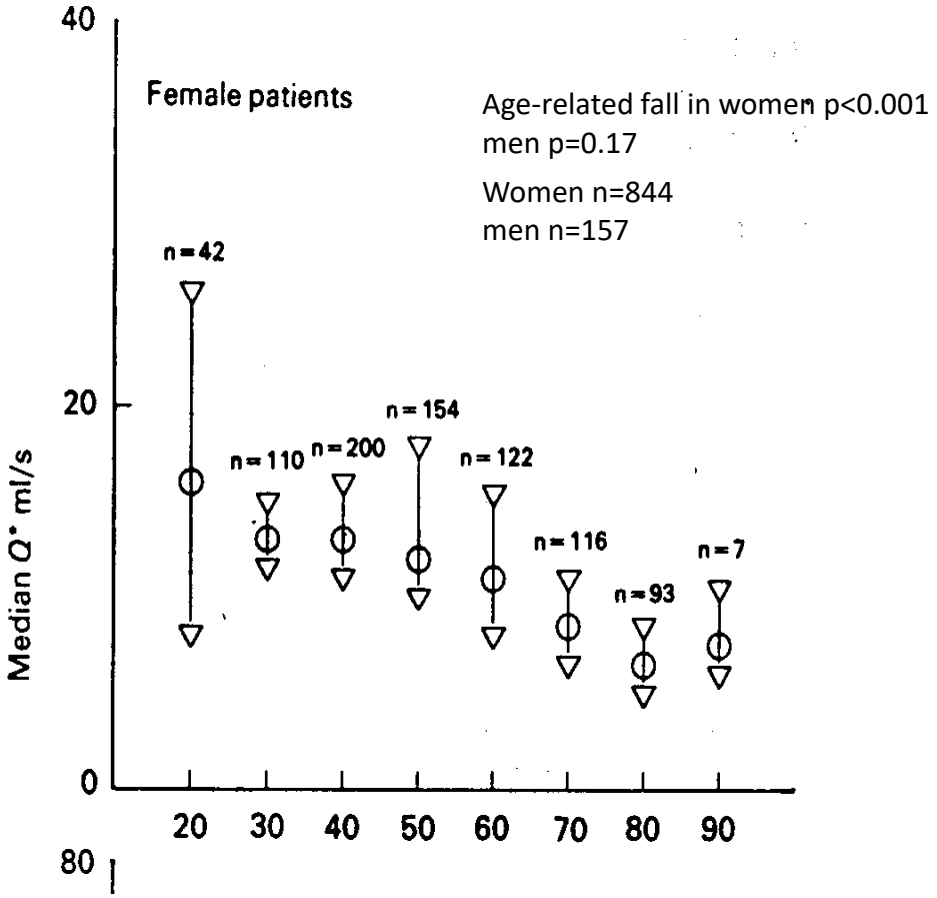


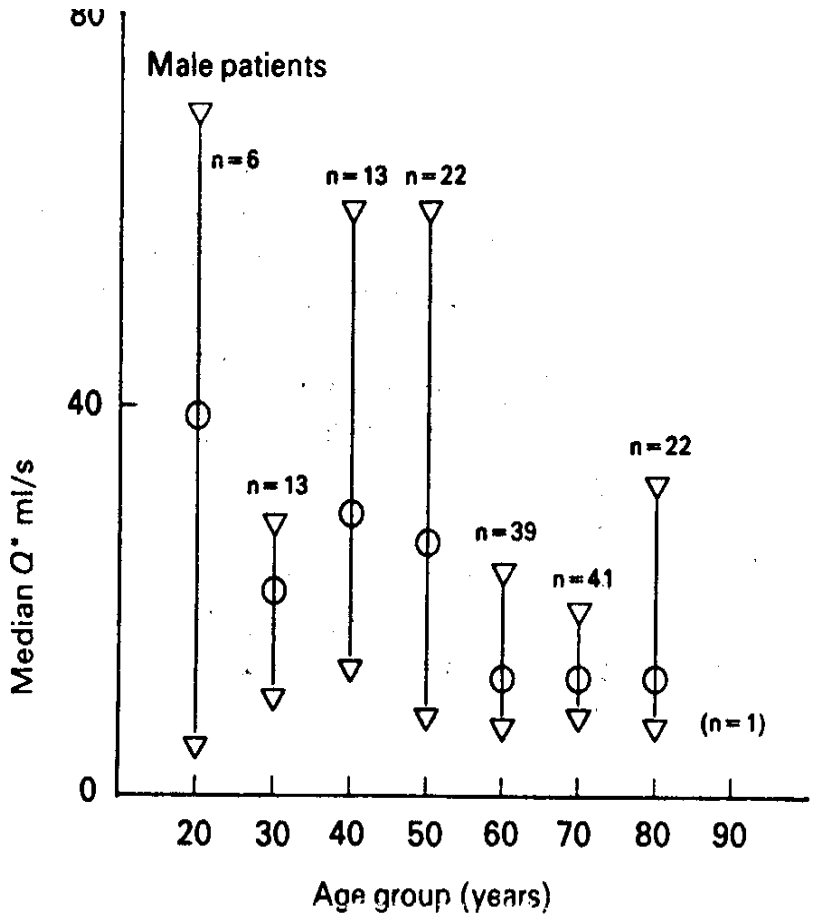
- Bladder capacity
- Sensation of filling
- Speed of contraction of detrusor
- Pelvic floor muscle tone (?bulk)
- Sphincteric “resistance”
- Urinary flow rate



- Urinary frequency
- Prevalence of post void residual volumes
- Outflow tract obstruction (♂)

Detrusor contractile function as measured by Q*
(index of smooth muscle shortening speed in association with age)[1]

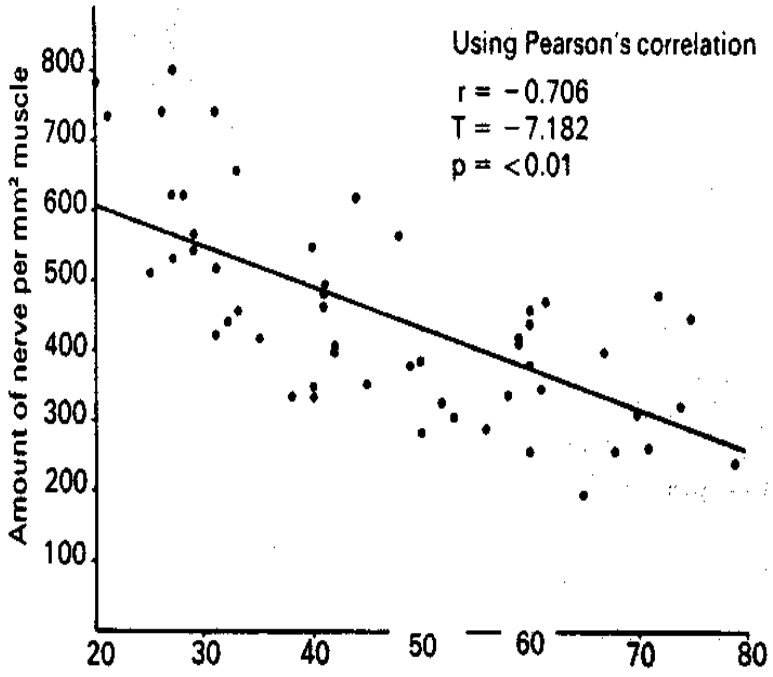




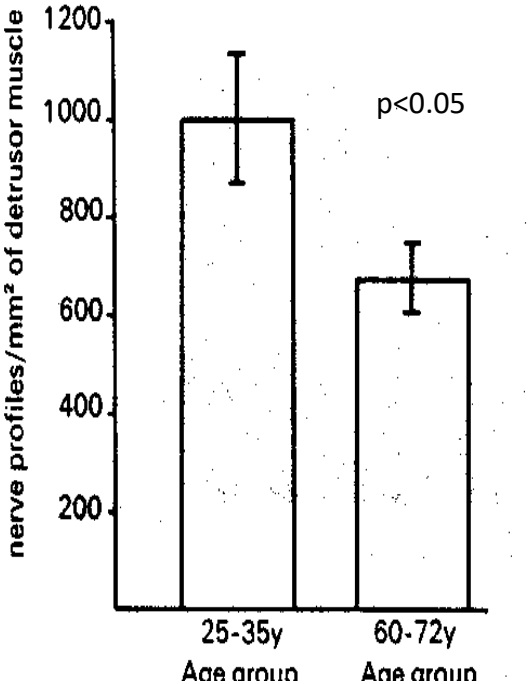
1. Malone-Lee J, Wahedna I. *Br J Urol* 1993;72:873–80.

Changes in innervation[1]

Linear loss of acetylcholinesterase containing nerves in association with greater age



Mean nerve/mm² muscle measured by light microscopy related to subject age



Mean nerve profiles/mm² of detrusor measured by e.m

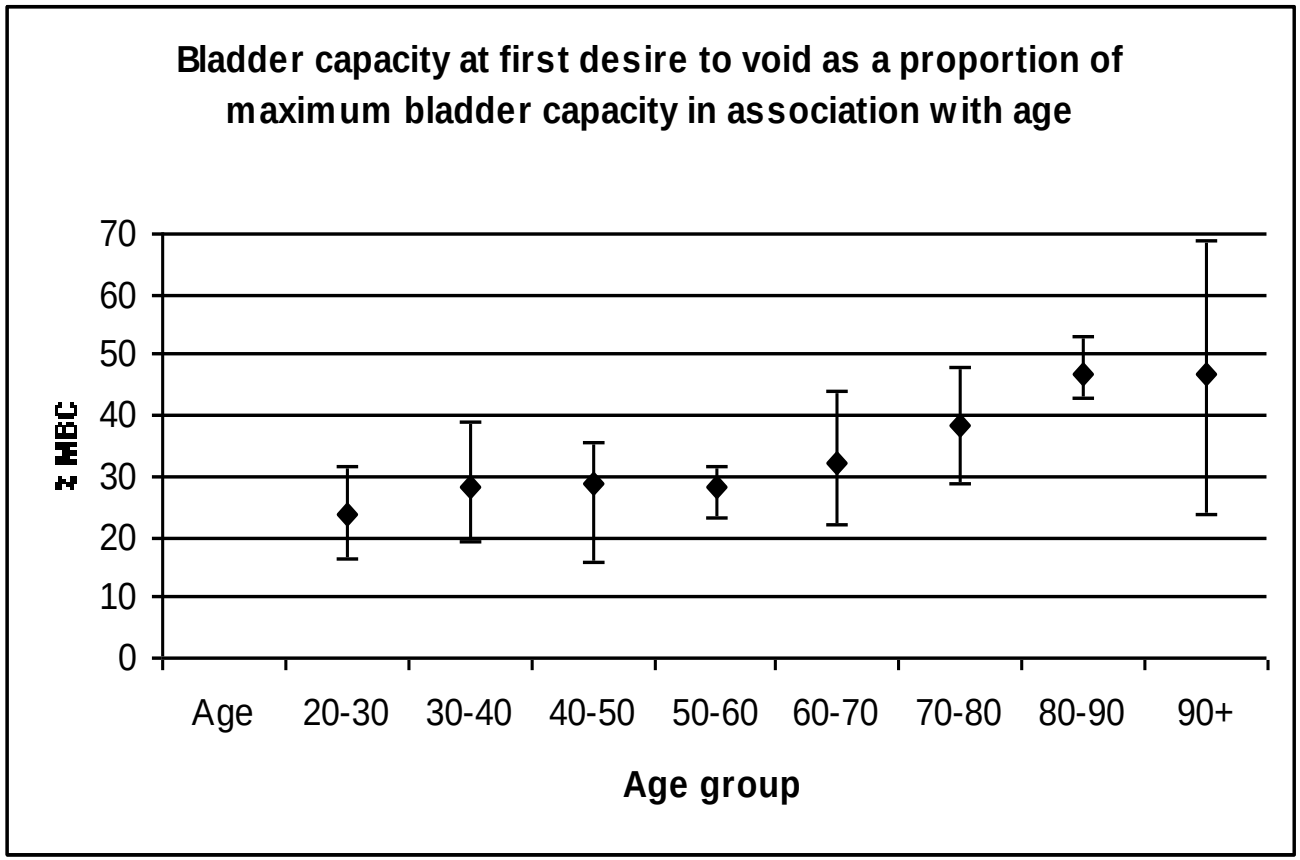
1. Gosling JA, *et al. J Urol* 1986;136:501–3.

Changes in matrix[1]

- Increase in collagen in association with greater age
- **Collagen**: muscle >53% and infiltration of the smooth muscle bundles
- **Decrease smooth muscle**: connective tissue ration in older bladders
- Similar increase in response to ischaemia
- Hypertrophy in detrusor smooth muscle in response to outflow obstruction
- Increased fibrosis and elastin (30%) deposition in elderly, non-obstructed bladders - identical to that found in obstructed bladders

1. Lepor H, *et al. J Urol* 1992;148(2 Pt 1):414–7.

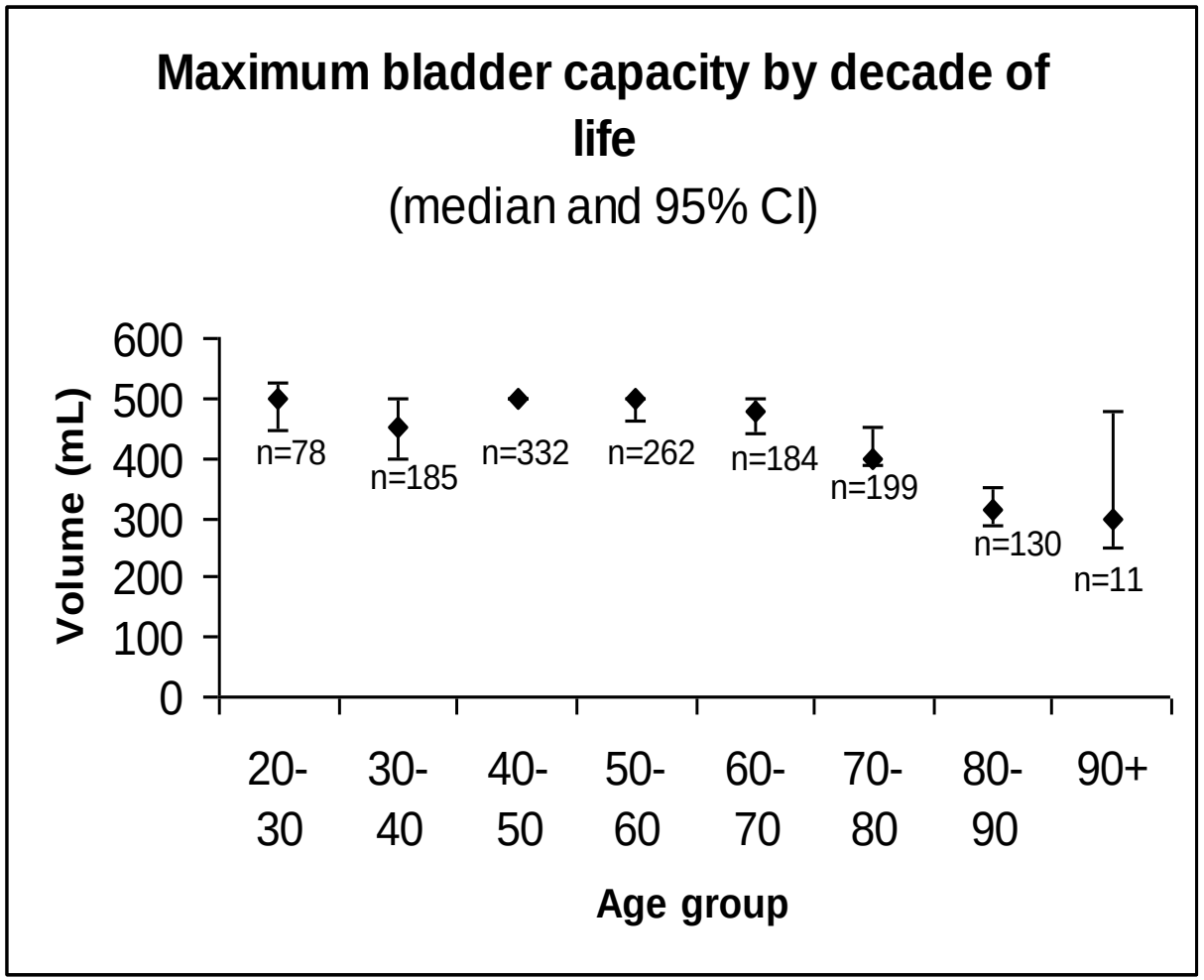
Bladder sensation



Adapted from Malone-Lee JG. *Br J Urol* 1993; 72: 873–880.

Bladder capacity falls[1]

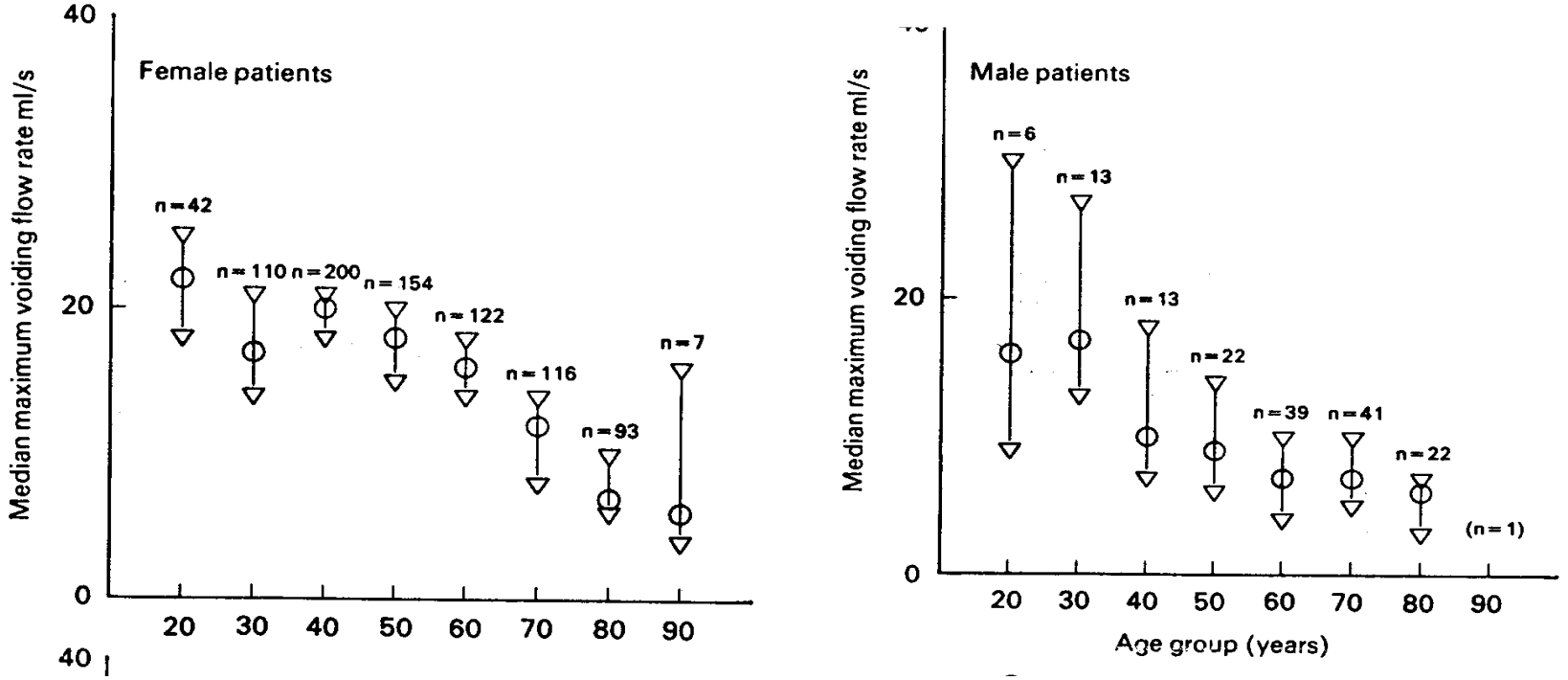
? Confounded by increased prevalence of DO - Perhaps no true fall



DO, detrusor overactivity

1. Collas DM. *Int Urogynecol J Pelvic Floor Dysfunct* 1996;7:24–29.

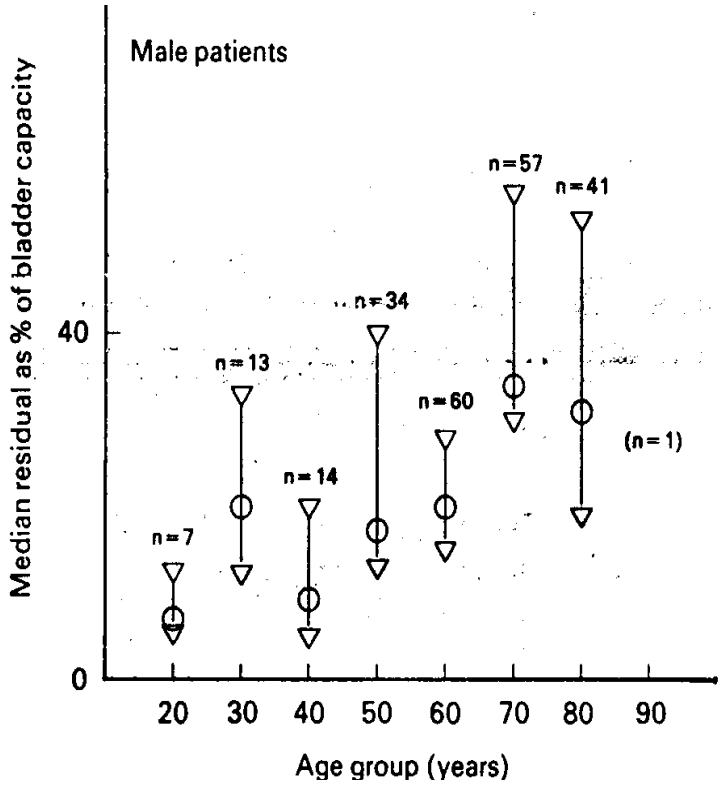
Median (95% CI) maximum flow rate for men and women in relation to greater age[1]

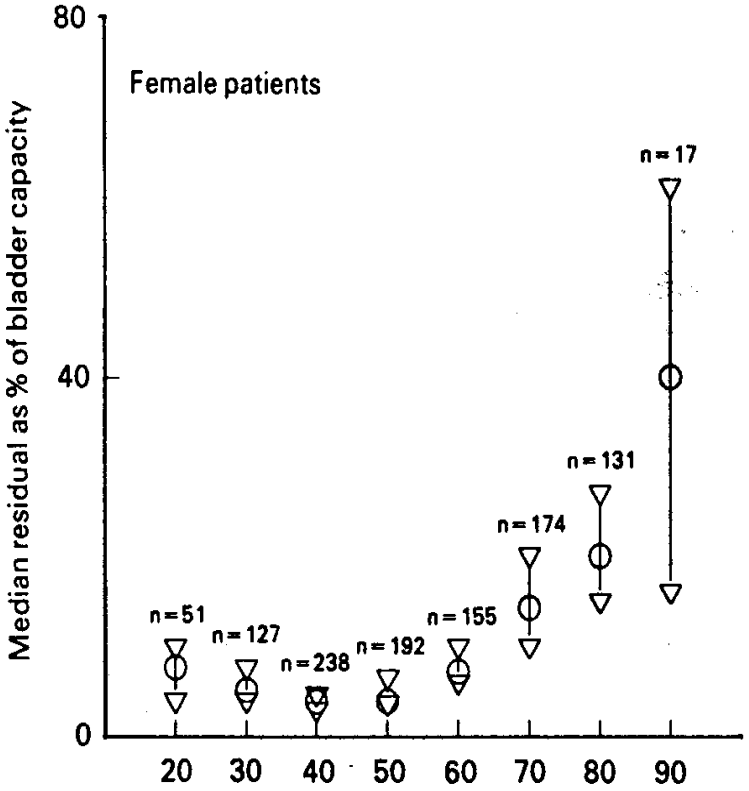


Women and men, p<0.001

1. Malone-Lee JG. *Br J Urol* 1993;72:873–80.

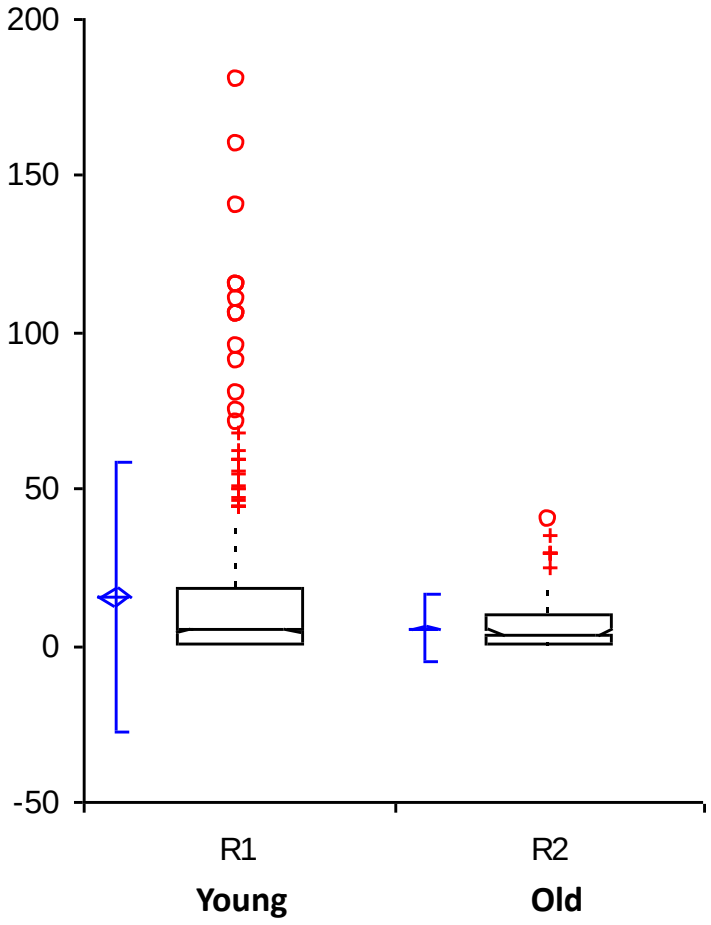
Residual volumes[1]





1. Malone-Lee JG. *Br J Urol* 1993; 72: 873–880.

Holding time in older men[1]



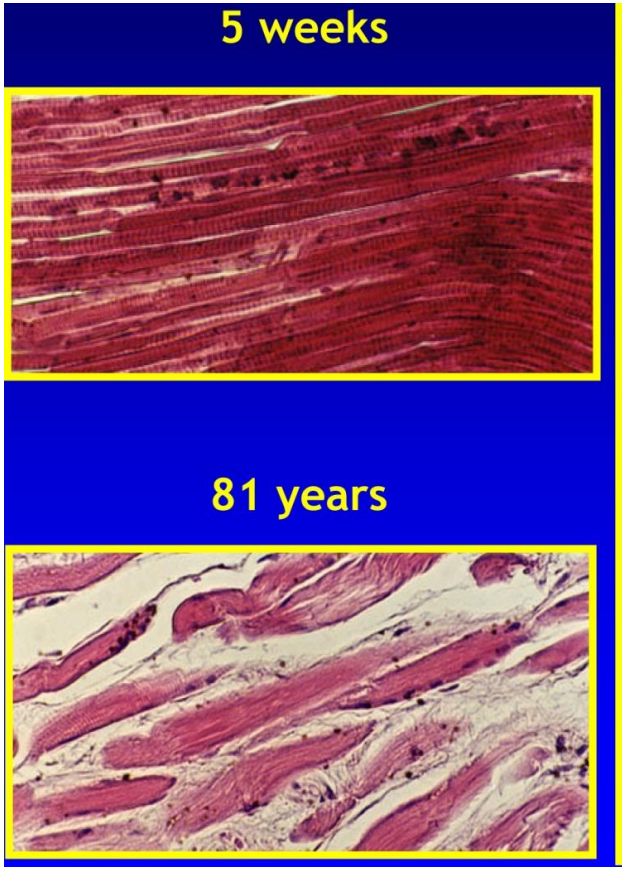
The interval was (median and 95% CI) **5** (4–5) minutes in younger men and **3** (3–5) minutes in older men.

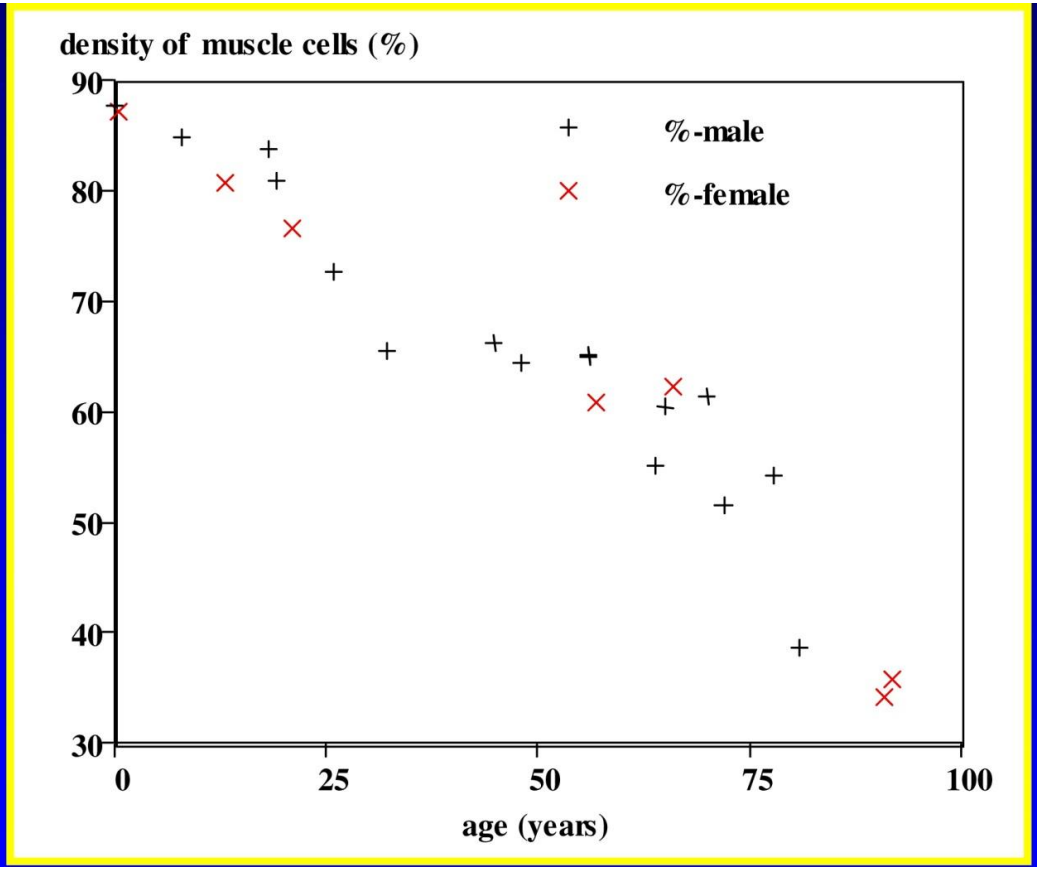
The intervals were statistically significantly different (W=31294.5, p<0.0001)

1. Woo WW, Wagg A. Urge time in younger vs. older asymptomatic men: normal characteristics. Abstract number 176 presented at ICS 2005. Available at: https://www.ics.org/2005/abstract/176. Date accessed: February 2017

Urethral Function[1]

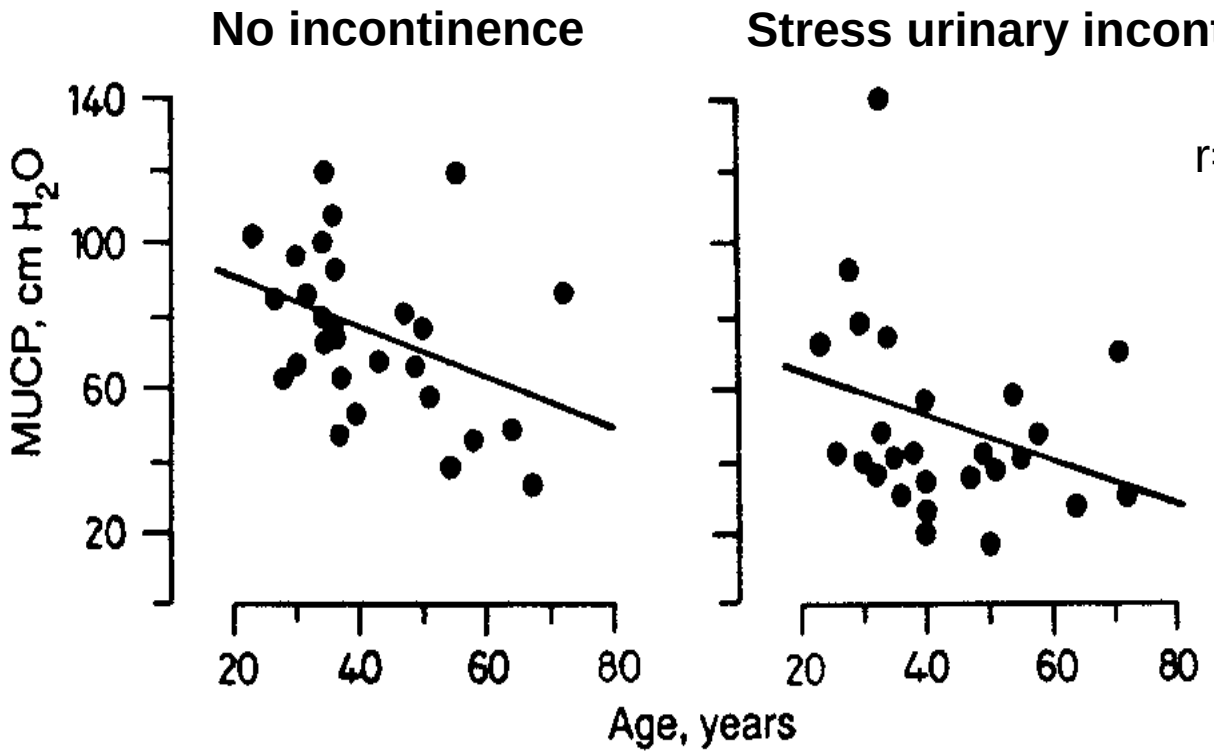
Loss of striated muscle cells in association with greater age





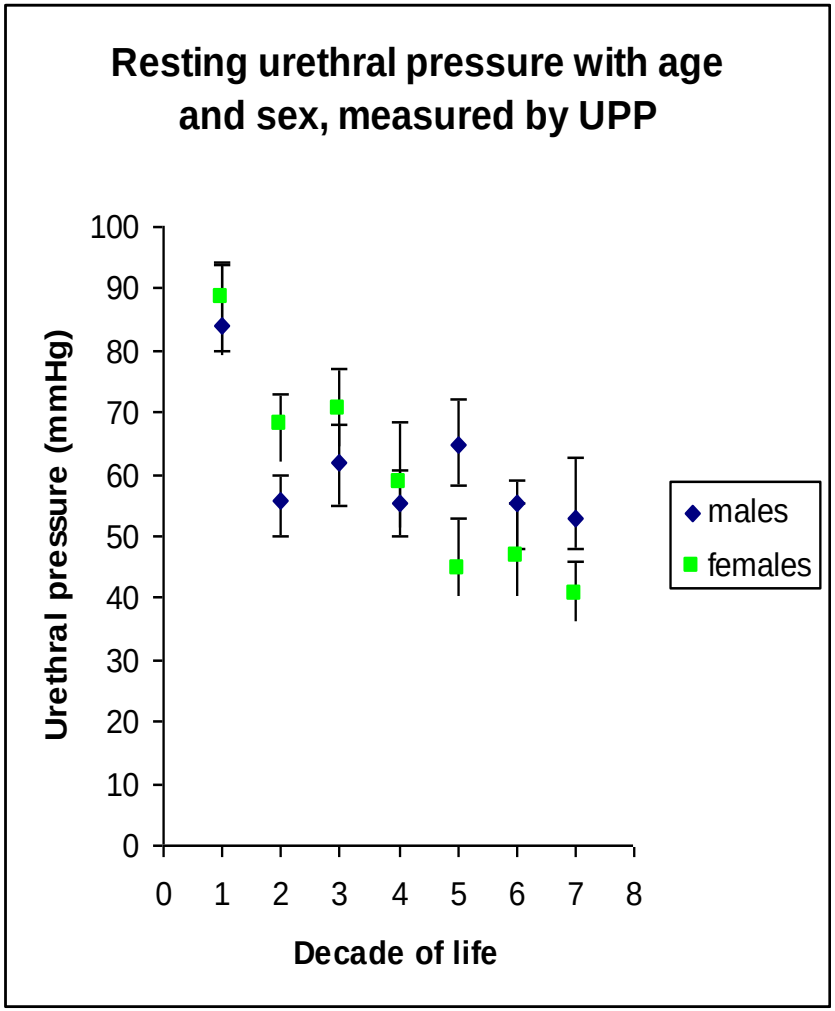
1. Strasser H, *et al. Lancet* 1999;354:918–9.

Maximum urethral closure pressure is lower in association with greater age[1]



1. Rud T. *Acta Obstet Gynecol Scand* 1980;59:331–5.

Urethral pressure & age in men and women[1]



1. Haubensak K. *Urol Int* 1975;30(1):29–32.

Pelvic floor

- In women, the effect of age on pelvic floor structure and function is difficult to differentiate from the effects of hormonal status and parity[1]

- A number of studies are cross sectional rather than longitudinal, and focus on symptomatic women[1]

- A random sample of 343 Austrian women aged 18-79 years, impaired pelvic muscle contraction (graded by the Modified Oxford Scale) was weakly associated with parity and body mass index but not age[2]

1. Tinelli, A., et al. Menopause, 2010. **17**(1): p. 204-12.
2. Talasz H, et al. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008 Jan;19:131-5.

Pelvic floor[1-5]

- In contrast, age identified as a weak but statistically significant predictor of pelvic muscle weakness and levator ani muscle morphometry even after controlling confounders

- Evidence of denervation and changes in pelvic striated muscle fibre number, type, and diameter have been found in asymptomatic and nulliparous women

- Constipation may independently contribute to pelvic floor dysfunction in older women.

1. Tinelli A, *et al. Menopause* 2010;17(1):204-12.
2. Lawrence JM, *et al. Obstet Gynecol* 2008;111(3):678-85.
3. Weemhoff M, Shek KL, Dietz HP. *Int Urogynecol J* 2010;21(9):1137-42.
4. Jundt K, *et al. Neurourol Urodyn* 2005;24(1):44-50.
5. Spence-Jones C, *et al. Br J Obstet Gynaecol* 1994;101(2):147-52.

Prostate

- Histological benign prostate hyperplasia (BPH) is strongly age-related and may lead to prostate enlargement and outlet obstruction[1]
- BPH results from the development of an oestrogen-predominant hormonal milieu in the prostate[2]
- Histological BPH occurs is nearly 80% of men by age 80[3]
- Mean prostate volume increases with age but is very variable; its strongest predictor is prostate specific antigen level of >1.4-2 ng/mL[4]
- LUTS in men increase linearly over time, with the fastest increase during the seventh decade, such that by age 80 approximately one-third of men have received treatment for moderate to severe LUTS[5]

BPH, benign prostate hyperplasia

1. Lepor, H. *Rev Urol*. 2005; 7(Suppl 4): S3–S12.
2. Shibata Y, *et al. Prostate* 2000;42(1):45-55.
3. Roehrborn, CG. *Rev Urol.* 2005; 7(Suppl 9): S3–S14.
4. Roehrborn CG, *et al. Urology* 1999;54(4):662-9.
5. Jacobsen SJ, *et al. J Urol* 1999;162(4):1301-6.