Wie *corticotropin releasing factor signaling* die Harnblase und den Dickdarm steuern kann

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EBDS – a multi-center controlled trial of standard treatment, placebo, oxybutynin, bladder training, and pelvic floor training, in children with functional incontinence

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European Bladder Dysfunction Study
EU BMH1-CT94-1006

Clinical classification in urge syndrome and dysfunctional voiding

In each branch, randomized interventions plus standard treatment

Before and after treatment:

- urodynamic studies
- Achenbach's CBCL, fecal soiling questionnaire

Outcome: urinary continence with/without urinary tract infection

Comorbidity *versus* treatment outcome

After treatment, fecal incontinence dropped from 32% to 21% ($p<0.02$). Fecal incontinence did not influence treatment outcome.

Bael, A. M., Benninga, M. A., Lax, H., Bachmann, H., Janhsen, E., De Jong, T. P., Vijverberg, M., van Gool, J. D.: Functional urinary and fecal incontinence in neurologically normal children: symptoms of one 'functional elimination disorder'? *BJU Int*, 99:409, 2007

After treatment, abnormal total behavior problem scores (18%) decreased to the level of the normative population.

These scores did not correlate with treatment outcome.

Bael, A. M., Lax, H., Hirche, H., Gäbel, E., Winkler, P., Vijverberg, M., van Zon, R., Van Hoecke, E., van Gool, J. D.: Behavior profiles in children with functional urinary incontinence before and after incontinence treatment. *Pediatrics*, 121:1652, 2008

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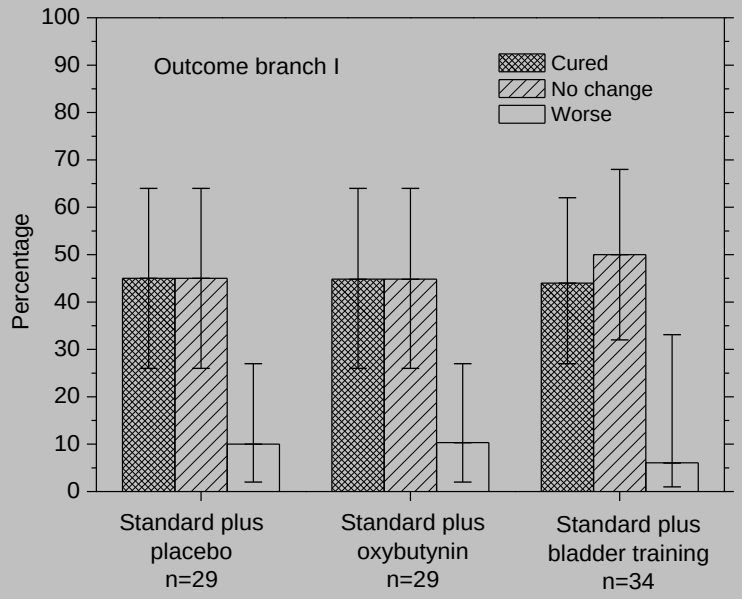
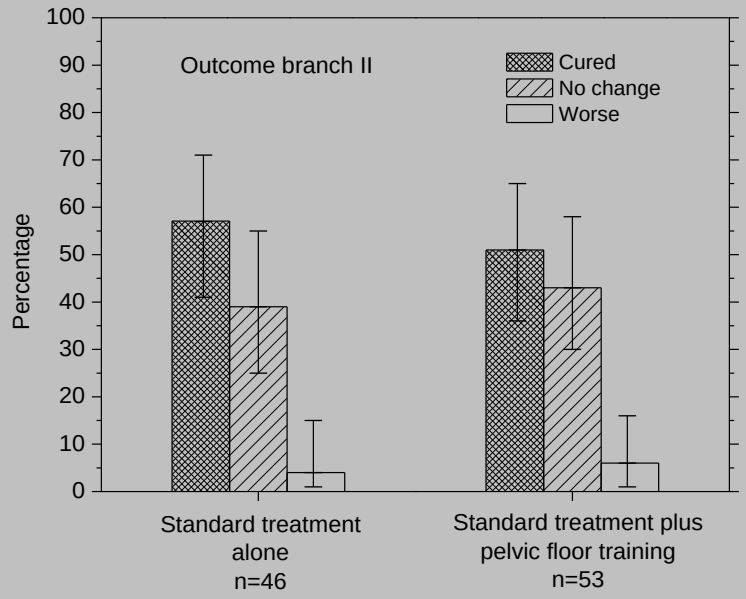
EBDS cure rates after 12 months follow up





No significant difference in cure rates between interventions (5%-95% CI).

van Gool, J.D., Tom P.V.M. de Jong, Pauline Winkler-Seinstra, Tytti Tamminen-Möbius, Hildegard Lax, Herbert Hirche, Rien M. Nijman, Kelm Hjälmås†, Ulf Jodal, Hannsjörg Bachmann, Piet Hoebeke, Johan Vande Walle, Joachim Misselwitz, Ulrike John, An Bael (on behalf of the European Bladder Dysfunction Study, EU BHM1-CT94-1006). A randomized controlled trial of pharmacotherapy, bladder/pelvic floor training, and standard therapy, in children with non-neuropathic bladder-sphincter dysfunction. *J Urol*, 2011 [submitted]

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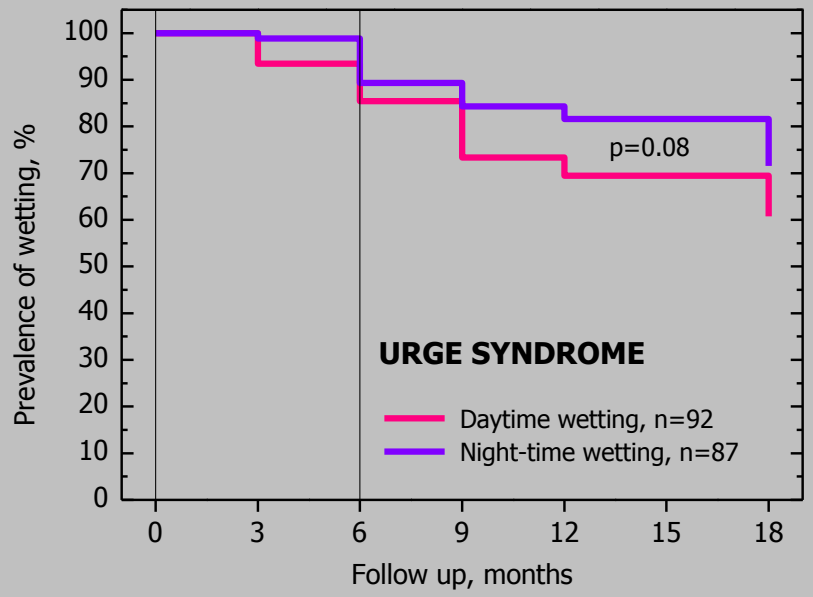
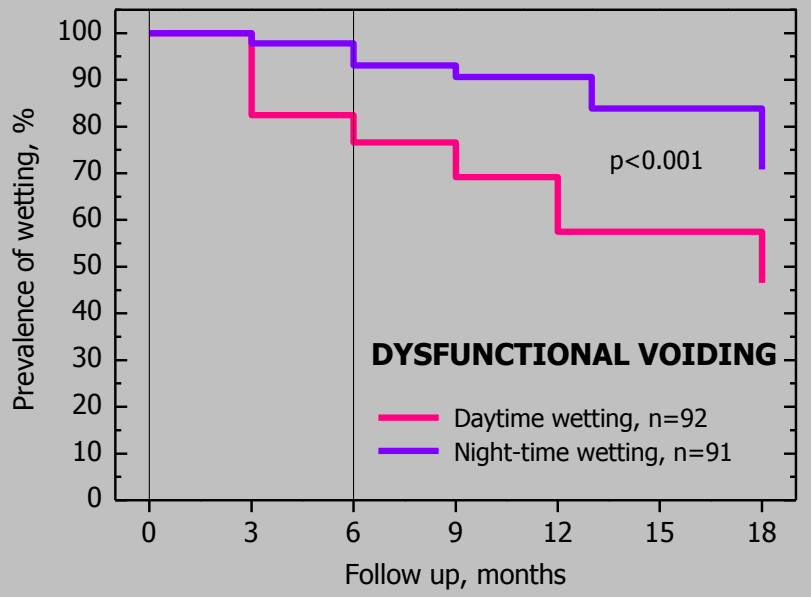
Incontinence during treatment and follow up
Kaplan-Meier survival estimates





Slow and steady resolution of incontinence during treatment and follow up.

van Gool, J.D., Tom P.V.M. de Jong, Pauline Winkler-Seinstra, Tytti Tamminen-Möbius, Hildegard Lax, Herbert Hirche, Rien M. Nijman, Kelm Hjälmås†, Ulf Jodal, Hannsjörg Bachmann, Piet Hoebeke, Johan Vande Walle, Joachim Misselwitz, Ulrike John, An Bael (on behalf of the European Bladder Dysfunction Study, EU BHM1-CT94-1006). A randomized controlled trial of pharmacotherapy, bladder/pelvic floor training, and standard therapy, in children with non-neuropathic bladder-sphincter dysfunction. *Neurourol Urodyn* 2011 [submitted]

EBDS

Abnormal urodynamic patterns before and after treatment

	Urge syndrome (n=97) Detrusor overactivity	Dysf. voiding (n=105) Pelvic floor overactivity
Before	33%	67%
After	27%	56%

No significant change in pattern prevalence after treatment.
After treatment, the abnormal patterns occurred *de novo* in >50%.

Bael, A.M., Hildegard Lax, Tom P.V.M. de Jong, Piet Hoebeke, Rien M. Nijman, Rune Sixt, J. Verhulst, Herbert Hirche, Jan D. van Gool (on behalf of the European Bladder Dysfunction Study EU BMH1-CT94-1006). The relevance of urodynamic studies in urge syndrome and dysfunctional voiding: a multi-center controlled trial in children. *J Urol* 180 (2008) pp1486-1495

EBDS results: conclusions

Clinical diagnosis is a poor predictor for abnormal urodynamic patterns, and abnormal patterns occur *de novo* after treatment. It follows that cure was not linked to the interventions, aimed at abnormal urodynamics, but to standard treatment.

Standard treatment – explanation and remedial teaching – is a form of cognitive-behavioral therapy.

The gradual resolution of incontinence – a learning curve – is typical for response to cognitive-behavioral therapy.

Bachmann, H. and Steuber, C.: Kontinenzschulung im Kindes- und Jugendalter: Grundlagenmanual. Lengerich: Pabst Science Publishers; 2010. <http://dnb.ddb.de>

EBDS: unexplained characteristics

Gender specificity (girls/boys ratio 3.7)

Variations of urodynamic patterns over time

Co-existence of urinary and fecal incontinence

Response to cognitive-behavioral therapy

van Gool, J.D., Tom P.V.M. de Jong, Pauline Winkler-Seinstra, Tytti Tamminen-Möbius, Hildegard Lax, Herbert Hirche, Rien M. Nijman, Kelm Hjälmås†, Ulf Jodal, Hannsjörg Bachmann, Piet Hoebeke, Johan Vande Walle, Joachim Misselwitz, Ulrike John, An Bael (on behalf of the European Bladder Dysfunction Study, EU BHM1-CT94-1006). A randomized controlled trial of pharmacotherapy, bladder/pelvic floor training, and standard therapy, in children with non-neuropathic bladder-sphincter dysfunction. *Neurourol Urodyn* 2011 [submitted]

EBDS: unexplained characteristics

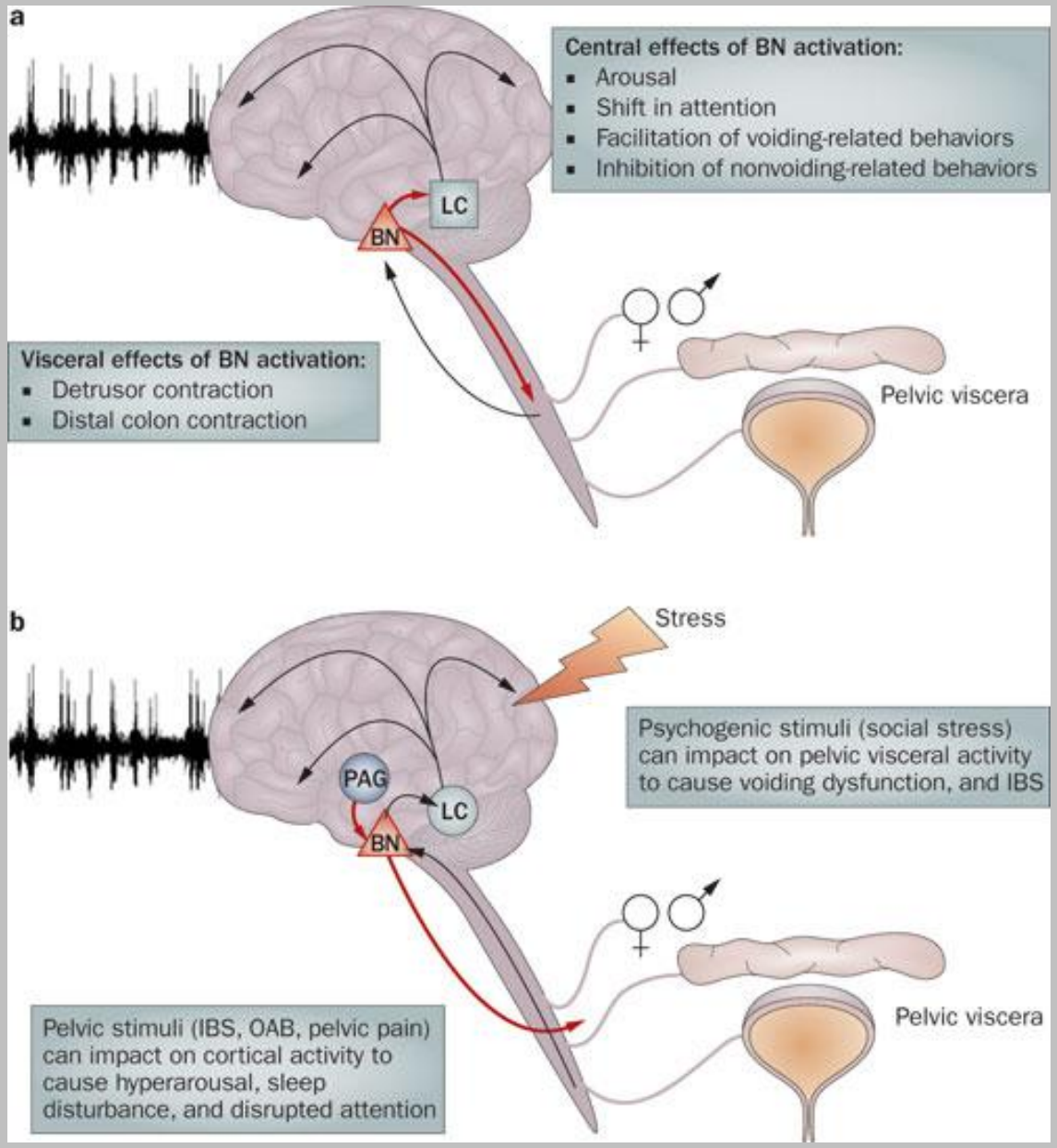
Gender specificity (girls/boys ratio 3.70)
Variations of urodynamic patterns over time
Co-existence of urinary and fecal incontinence
Response to cognitive-behavioral therapy

In rodents, these characteristics are all hallmarks of the response to social stress, mediated by the corticotropin (CRF) signaling pathway:

models for functional incontinence in children?

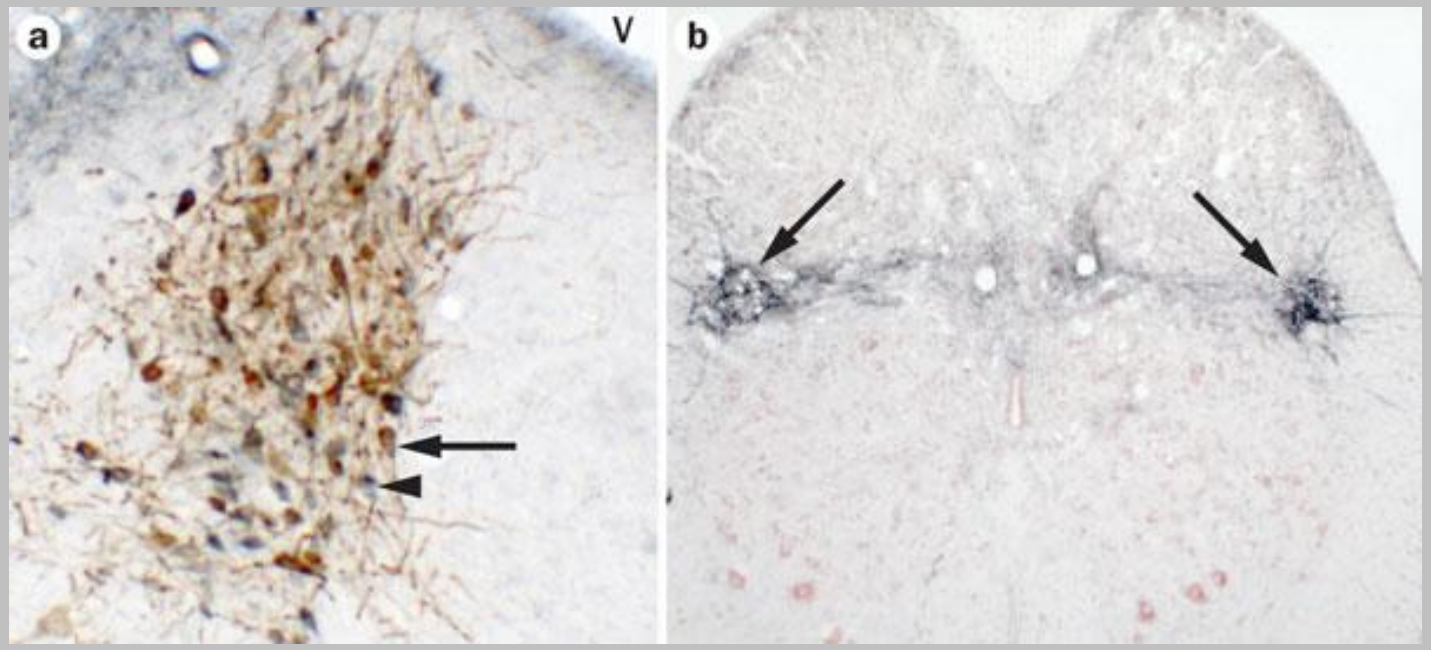
Topography of corticotropin releasing factor (CRF) signalling pathways

BN: Barrington's nucleus
LC: Locus coeruleus
PAG: para-aquaductal gray matter



Valentino, R. J. *et al.* (2010) The bladder–brain connection: putative role of corticotropin-releasing factor. *Nat Rev Urol* doi:10.1038/nrurol.2010.203

CRF: a major neurotransmitter in Barrington's nucleus



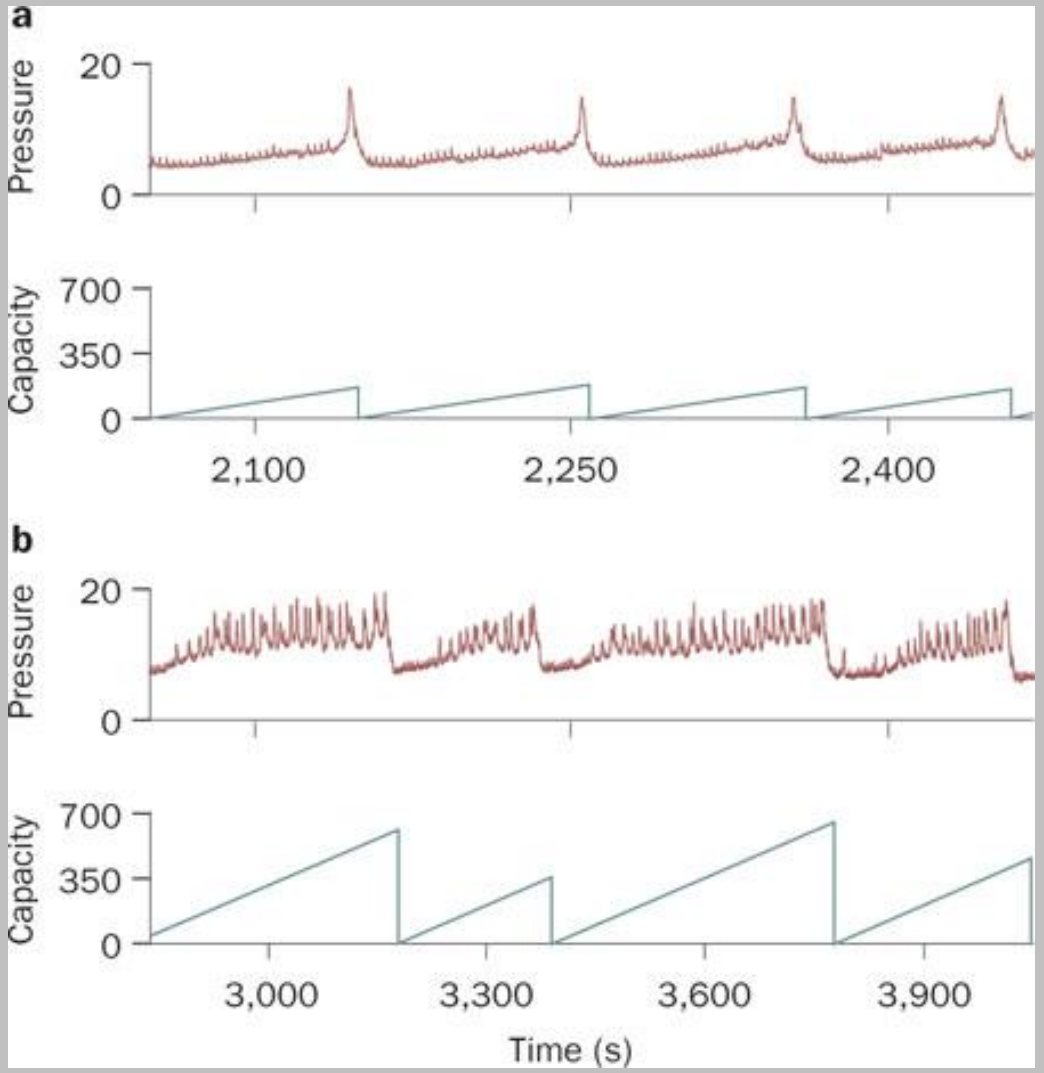
[a] Rat brain section at level of Barrington's nucleus showing CRF-immunorecative neurons (blue) and neurons labeled retrogradely from the lumbosacral spinal cord (brown).
[b] Lumbosacral spinal cord section with dense CRF-immunoreactive terminal fields (blue) within the parasympathetic motor neuron regions.

Valentino, R. J. *et al.* (2010) The bladder–brain connection: putative role of corticotropin-releasing factor. *Nat Rev Urol* doi:10.1038/nrurol.2010.203

Social stress alters bladder urodynamics

[a] Control rat cystometry

[b] Cystometry in rat exposed to resident-intruder stress, with numerous non-voiding contractions, prolonged intermicturition intervals, and greater bladder capacity



Wood SK, Baez MA, Bhatnagar S, Valentino RJ. Social stress-induced bladder dysfunction: potential role of corticotropin-releasing factor. Am J Physiol Regul Integr Comp Physiol 2009; 296(5)

Social stress in rodents: response of bladder/colon

STUDY CONTROLS	SEX	RODENT	STRESS	NUMBER BLOTS	BLOT SIZE	NUMBER PELLETS	COLONIC TRANSIT
*Wood 2009	M	rat	Social defeat	decrease	increase	–	–
Kiddoo 2006	M	rat	CRF agonist	decrease	increase	–	–
*Larauche 2009	M	rat	CRF agonist	–	–	increase[1]	decrease[1]
*Larauche 2009	M	mouse	CRF agonist	–	–	increase[1]	decrease[1]
Klausner 2005	F	rat	CRF	increase[2]	decrease[2]	_	_

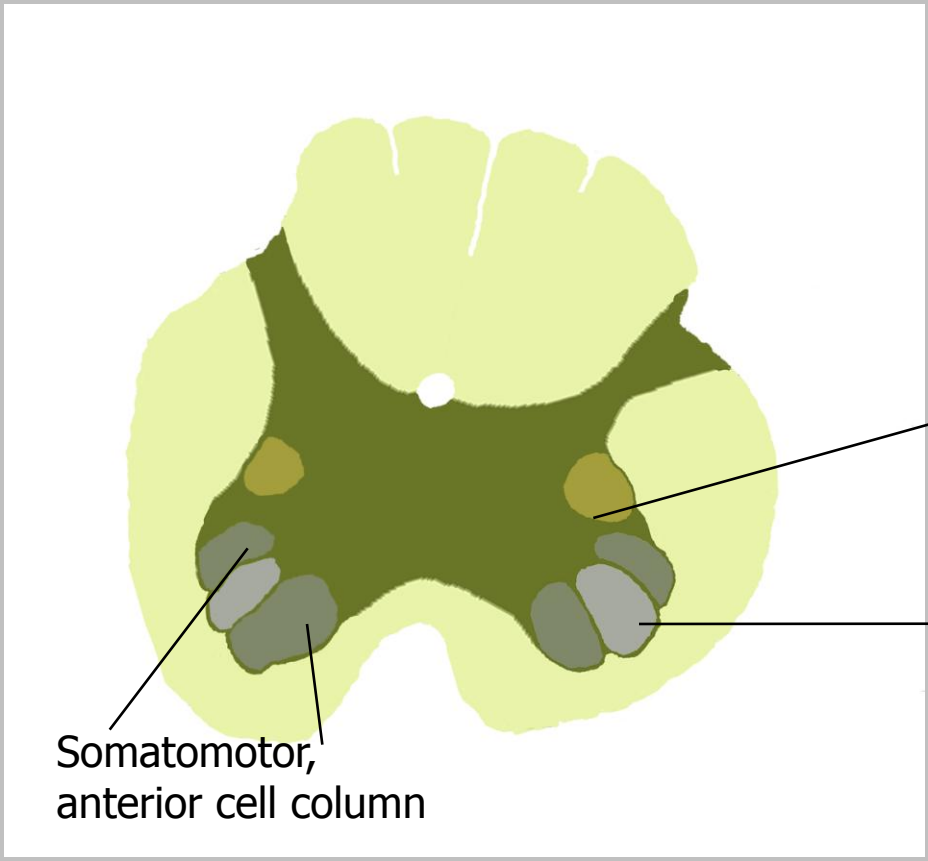
[*] mRNA expression and immunoreactivity in Barrington's nucleus
[1] dose-dependent effects
[2] reversible with CRF antagonist (astressin 1)

Models for responses of bladder (and colon) to social stress, mediated by the CRF signaling pathway

Gender specificity (girls/boys ratio 3.70)
Variations of urodynamic patterns over time
Co-existence of urinary and fecal incontinence
(Response to cognitive-behavioral therapy)

In rodents, stress-provoked responses of bladder (and colon) are gender-specific, and mediated by the CRF signaling pathway: homologous models are available, for urge syndrome in girls, and Hinman's syndrome in boys.

Segmental topography S1-S2 for motor innervation of detrusor and urethral sphincter/pelvic floor



Heldoorn M. Qualitative and quantitative study of the ultrastructure of Onuf's nucleus in human an cat. In: Heldoorn M, editor. Modelling Onuf's nucleus: single cell and network simulations. Leiden: Leiden University; 2003

Kontinenzschulung im Kindes- und Jugendalter[KgKS e.V.]

Protocoll zur Evaluation der Kurzschulung

Find indicators for social stress

Document wetting not for just 3 days, but continuously

Find the link for wetting and stress

European Bladder Dysfunction Study, branch II

Clinically diagnosed dysfunctional voiding (n=105)

	standard treatment			pelvic floor training		
Mnths	T0	T6	T18	T0	T6	T18
Girls	42	40	30	47	45	40
Boys	8	6	5	8	8	8
Total	50	46	35	55	53	48

Girls/boys ratio 3.7

European Bladder Dysfunction Study branch I

Clinically diagnosed urge syndrome, branch I (n=97)

	standard plus placebo			standard plus oxybutynin			standard plus training		
Mnths	T0	T6	T18	T0	T6	T18	T0	T6	T18
Girls	20	17	12	22	21	18	28	28	27
Boys	13	12	11	8	8	7	6	6	4
Total	33	29	24	30	29	25	34	34	31

Girls/boys ratio 3.7

Functional incontinence: two-tiered approach

EBDS results suggest that 50% of children with functional incontinence can be cured with explanation and 'remedial teaching' – the main components of standard treatment.

Bachmann, H. en Steuber, C.: Kontinenzschulung im Kindes- und Jugendalter: Grundlagenmanual. Lengerich: Pabst Science Publishers; 2010. http://dnb.ddb.de

When this approach fails, a more continuous assessment of incontinence is indicated, as well as a full assessment of psychiatric co-morbidity.