Underactive Bladder & Detrusor Underactivity

Yuan-Hong Jiang, M.D.
Department of Urology, Hualien Tzu Chi Hospital,
Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien Taiwan

Definitions of DU and UAB

- **Detrusor underactivity (DU)**
  - Contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/ or failure to achieve complete bladder emptying within a normal time span

    (UDS diagnosis)

    Neurourol Urodyn. 2002;21(2):167

- **Underactive bladder (UAB)**
  - A slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying, sometimes with storage symptoms

    (Symptom diagnosis)

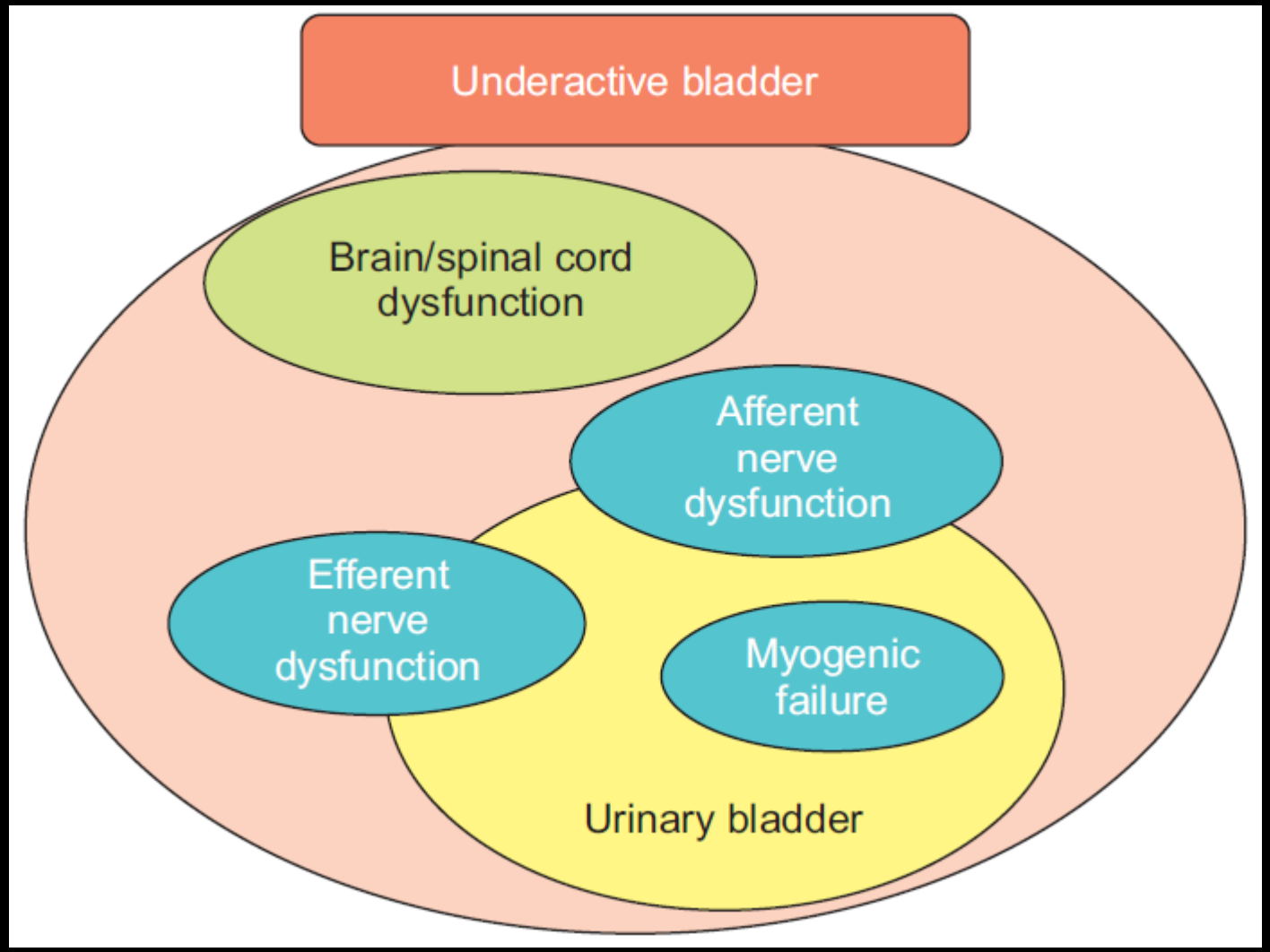
    Eur Urol. 2015 Sep;68(3):351

- **Consistence**

  between **the clinical presentation of DU patients** & **UAB working definition**

  Eur Urol. 2016 Feb;69(2):361

Mechanisms Involved in DU/ UAB



- **Myogenic failure:**
  loss of intrinsic contractility
- **Efferent nerve dysfunction:**
  impaired activation of detrusor
- **Afferent nerve dysfunction:**
  failure / early terminate of voiding reflex
- **Brain/ spinal cord dysfunction:**
  failure of integration processing

Nat Rev Urol. 2014 Nov;11(11):639
Investig Clin Urol. 2017 Dec;58(Suppl 2):S82

Etiologies of Detrusor Underactivity

Idiopathic

Normal ageing

Unknown factors in younger people

Neurogenic injury and/or disease

Vascular

- Stroke (early phase)

Degenerative

- Parkinson disease
- Multisystem atrophy

Demyelinating neuropathies

- Multiple sclerosis

Peripheral neuropathies

- Guillain–Barré syndrome
- Neurosyphilis (tabes dorsalis)
- Herpes zoster and herpes simplex
- Diabetes mellitus
- AIDS

Spinal cord and cauda equina

- Intravertebral disc prolapse
- Cauda equina lesions
- Spinal cord tumours
- Spinal canal stenosis
- Spinal cord injury
- Sacral fracture

Pelvic fracture

Pudendal nerve injury (bilateral)

Myogenic

Bladder outlet obstruction

Diabetes

Iatrogenic

Radical pelvic surgery

- Radical prostatectomy
- Radical hysterectomy
- Anterior resection, abdomino-perineal resection

Radiation therapy

Functional

- Fowler's syndrome
- Dysfunctional voiding

Pharmacotherapy

Drugs with anticholinergic effects

- Antimuscarinics
- Antihistamines
- Antipsychotics
- Antiparkinson medications
- Antispasmodics
- Tricyclic antidepressants

Opioids

Nat Rev Urol. 2014 Nov;11(11):639

Aging-related changes in DU

Altered bladder/ detrusor morphology and function

- ↑ collagen deposition
- ↓ ratio of muscle to connective tissue, ↑ fibrosis
- Altered detrusor contractility (rats)
- “a dense band pattern”
- weaker contractile responses to carbachol and electrical field stimulation related to decreased cholinergic mediated contraction, lower muscarinic M3 receptor mRNA expression (rats)

Neurologic changes

- ↓ axon density of the human detrusor muscle
- ↓ autonomic bladder innervation

Decline in sensory function

- ↑threshold of bladder capacity
- ↓bladder response to filling

Nat Rev Urol. 2014 Nov;11(11):639; Low Urin Tract Symptoms. 2019 May;11(3):92

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Neurologic changes

- ↓ axon density of the human detrusor muscle
- ↓ autonomic b

Decline in sensory function

- ↑threshold of bladder capacity
- lling

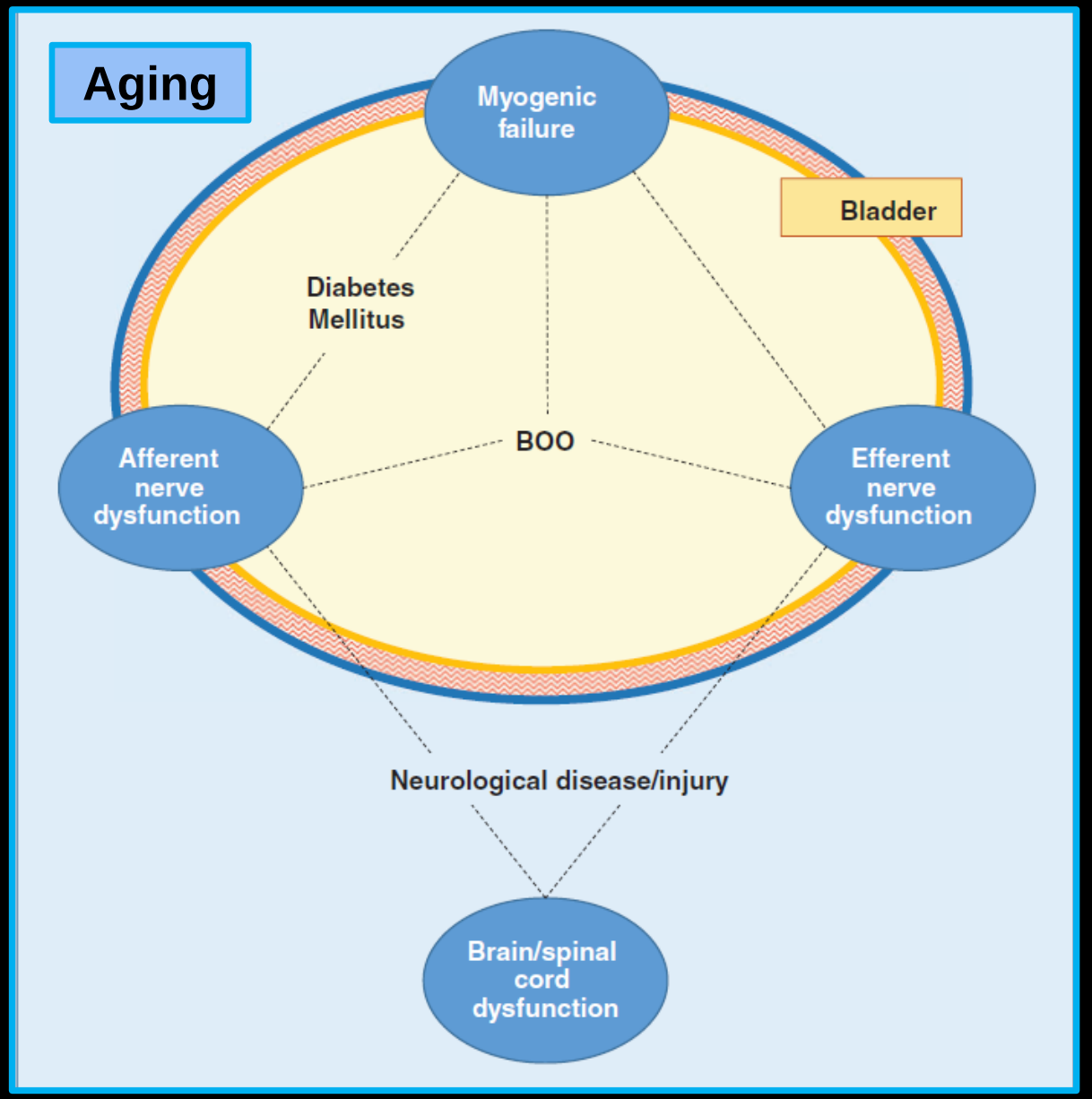
However,

- some contradictory results

- not strong evidence support

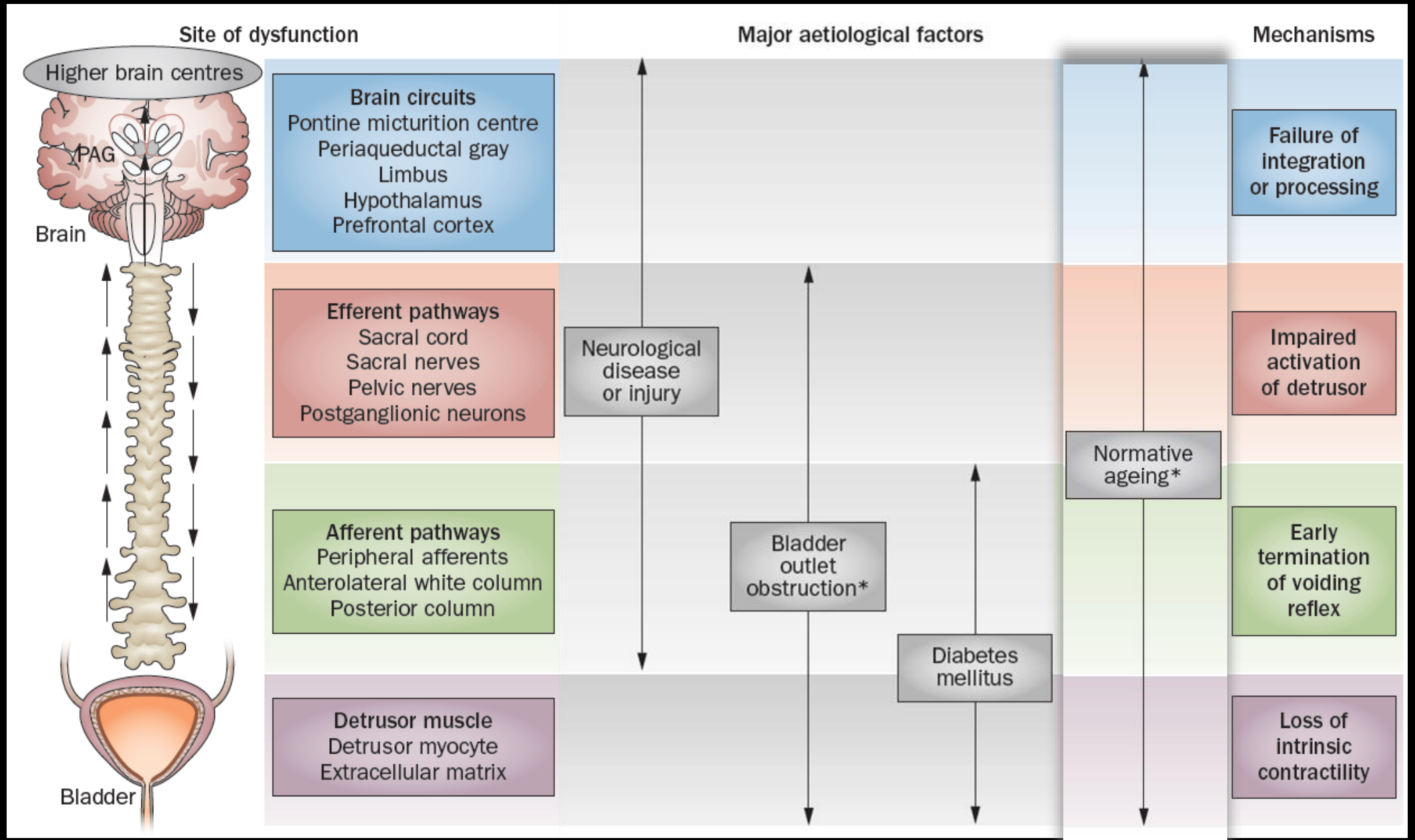
Nat Rev Urol. 2014 Nov;11(11):639; Low Urin Tract Symptoms. 2019 May;11(3):92

Unclear “exact” role of aging in DU



Low Urin Tract Symptoms. 2019 May;11(3):92

Major etiologies, sites of dysfunction and pathogenic mechanisms in DU



Nat Rev Urol. 2014 Nov;11(11):639

Pathophysiology of DBD (Diabetic bladder dysfunction)

Polyuria/ Diuresis

→ **Bladder hypertrophy** (physical adaptation)

→ also **↑oxidative stress**

(Chronic) Hyperglycemia

→ **excess oxidative stress & ROS**

→ ↑cellular damage, accumulation of toxic metabolites

Detrusor, neuronal, urothelial, and microvascular alternations/ damages

- **Detrusor myocyte:** abnormalities in intracellular connections & excitability, intracellular signaling, receptor density and distribution
- **Nerve:** destruction of nerve fibers, ↓nerve density
- **Urothelium:** altered receptor & neurotransmitters released
- **Microvascular damage:** damaging urothelium, muscle, and nerve

1: J Urol. 2009 Dec;182(6 Suppl):S18; 2: Neurourol Urodyn. 2012 Mar;31(3):359;
3: J Urol. 2013 Mar;189(3):1130; 4: Urology. 2019 Jan;123

DBD Temporal Theory

(time dependent changes of diabetic uropathy)

	Early Phase →	Late Phase
	Compensated Function	Decompensated Function
	Time Course/Risk factors ??	
Clinical:	**Storage problems**	**Voiding Problems**
Urodynamics:	**Overactive Bladder**	**Atonic Bladder**
In-vitro:	**Hypercontractile Detrusor**	**Hypocontractile Detrusor**

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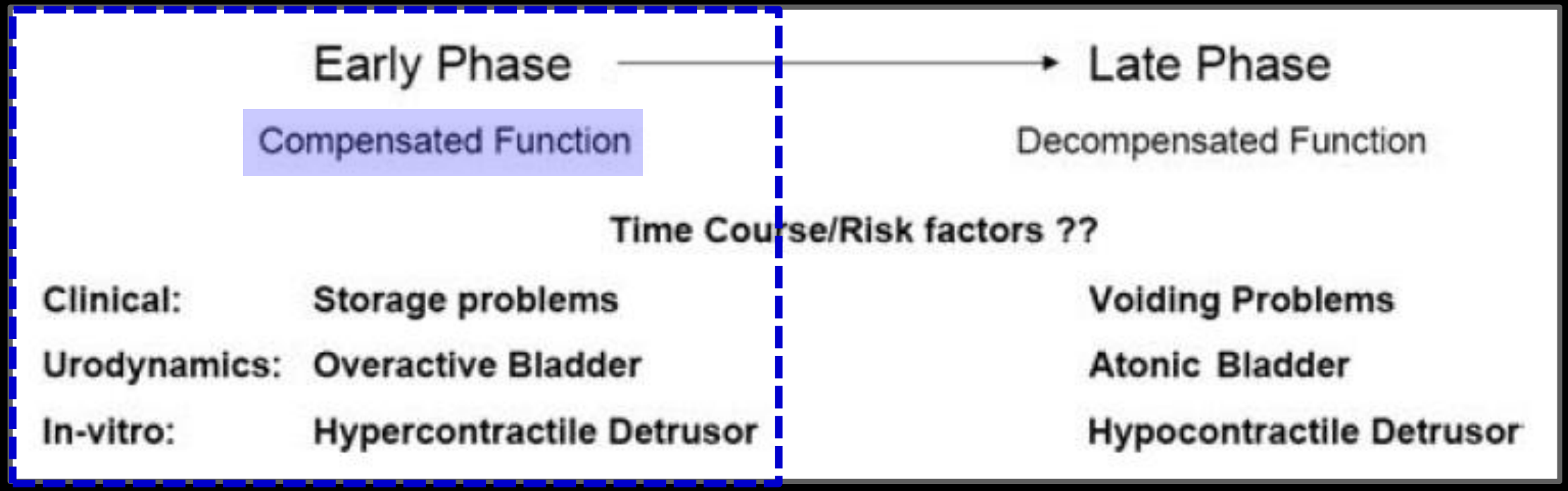

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Decompensated DBD (triad)

- ↓ bladder sensation
- ↑bladder capacity
- **↓ detrusor contractility → UAB/DU**

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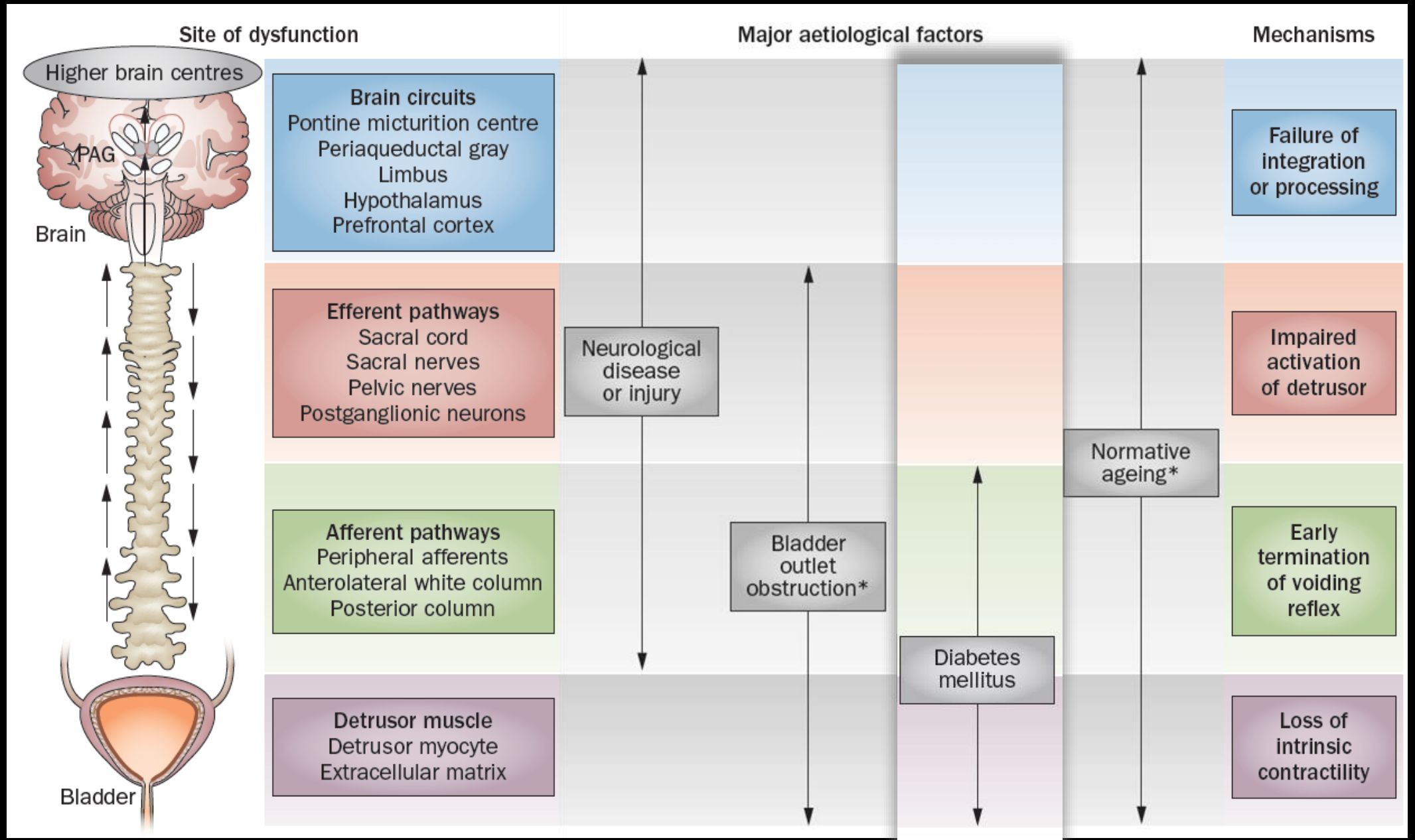
Major etiologies, sites of dysfunction and pathogenic mechanisms in DU



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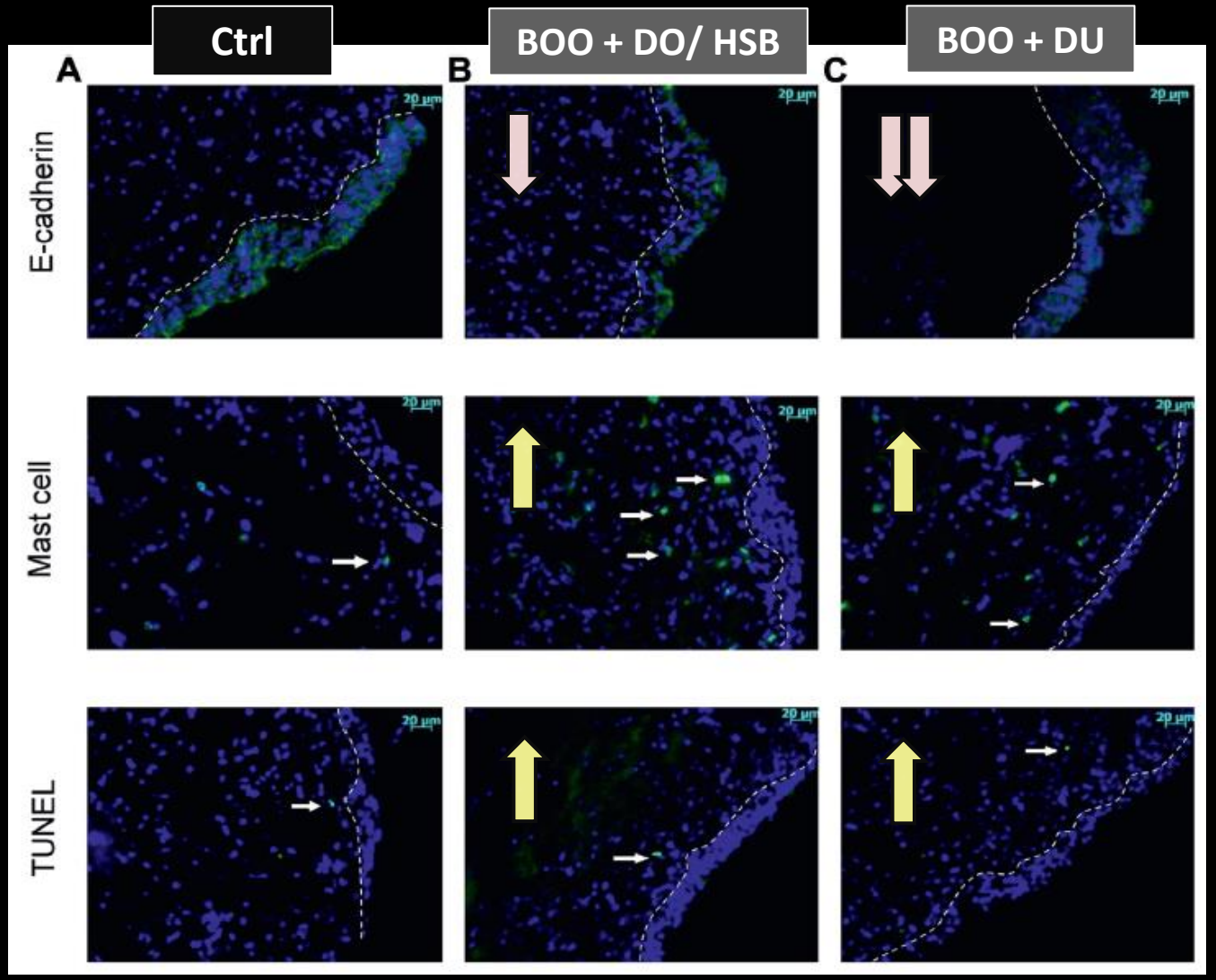
BOO with bladder dysfunction:

Urothelial dysfunction, suburothelial inflammation, cellular apoptosis



J Urol. 2016 Sep;196(3):831

BOO with bladder dysfunction:

Altered sensory protein expression in the bladder mucosa

		BOO			p Value	
	Control	Overall	DO/HSB	DU	Control vs BOO	DO/HSB vs DU
No. pts	10	33	23	10	—	—
Mean ± SD age	64.6 ± 11.45	68.5 ± 11.1	69.0 ± 11.6	67.5 ± 10.5	0.258	0.764
Mean ± SD immunofluorescence:						
E-cadherin	27.70 ± 10.42	15.93 ± 13.20	18.85 ± 13.60	9.21 ± 9.57*	0.015	0.038
Tryptase	4.16 ± 2.68	15.12 ± 7.89	16.11 ± 6.16*	12.84 ± 10.96	0.000	0.652
TUNEL	0.85 ± 1.31	2.64 ± 2.57	2.47 ± 2.41*	3.03 ± 3.01	0.028	0.844
Mean ± SD Western blot:						
ZO-1	6.90 ± 1.82	7.83 ± 3.98	7.29 ± 2.58	9.08 ± 6.14	0.358	0.570
TRPV 1	0.131 ± 0.070	0.139 ± 0.096	0.137 ± 0.102	0.145 ± 0.084	0.840	0.695
TRPV 4	0.188 ± 0.286	0.155 ± 0.243	0.152 ± 0.249	0.164 ± 0.241	0.565	0.570
iNOS	0.258 ± 0.325	0.171 ± 0.332	0.219 ± 0.389	0.062 ± 0.039*	0.128	0.147
eNOS	0.094 ± 0.088	0.104 ± 0.096	0.119 ± 0.107	0.071 ± 0.058	0.885	0.254
P2X3	0.097 ± 0.109	0.257 ± 0.206	0.247 ± 0.145*	0.278 ± 0.315*	0.001 ↑	0.456
β3	0.878 ± 0.584	1.012 ± 0.415	0.864 ± 0.269	1.35 ± 0.499*	0.289	0.009 ↑
M2	0.405 ± 0.303	0.912 ± 1.043	1.073 ± 1.184*	0.558 ± 0.490	0.041 ↑	0.108
M3	1.593 ± 0.708	0.797 ± 0.342	0.703 ± 0.308*	1.013 ± 0.330*	0.000 ↓	0.024 ↑
M2/M3	0.313 ± 0.280	1.371 ± 1.610	1.691 ± 1.796*	0.634 ± 0.685	0.001 ↑	0.012 ↓

- **BOO + DU** vs BOO + DO/ HSB:

  ↑ β3 receptor, ↑ M3 receptor,↓ M2/M3 ratio

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Impaired signaling and sensory transduction pathways appear to reflect the pathophysiology of DU in patients with BOO.

- **BOO + DU** vs BOO + DO/ HSB:

  ↑ β3 receptor, ↑ M3 receptor,↓ M2/M3 ratio

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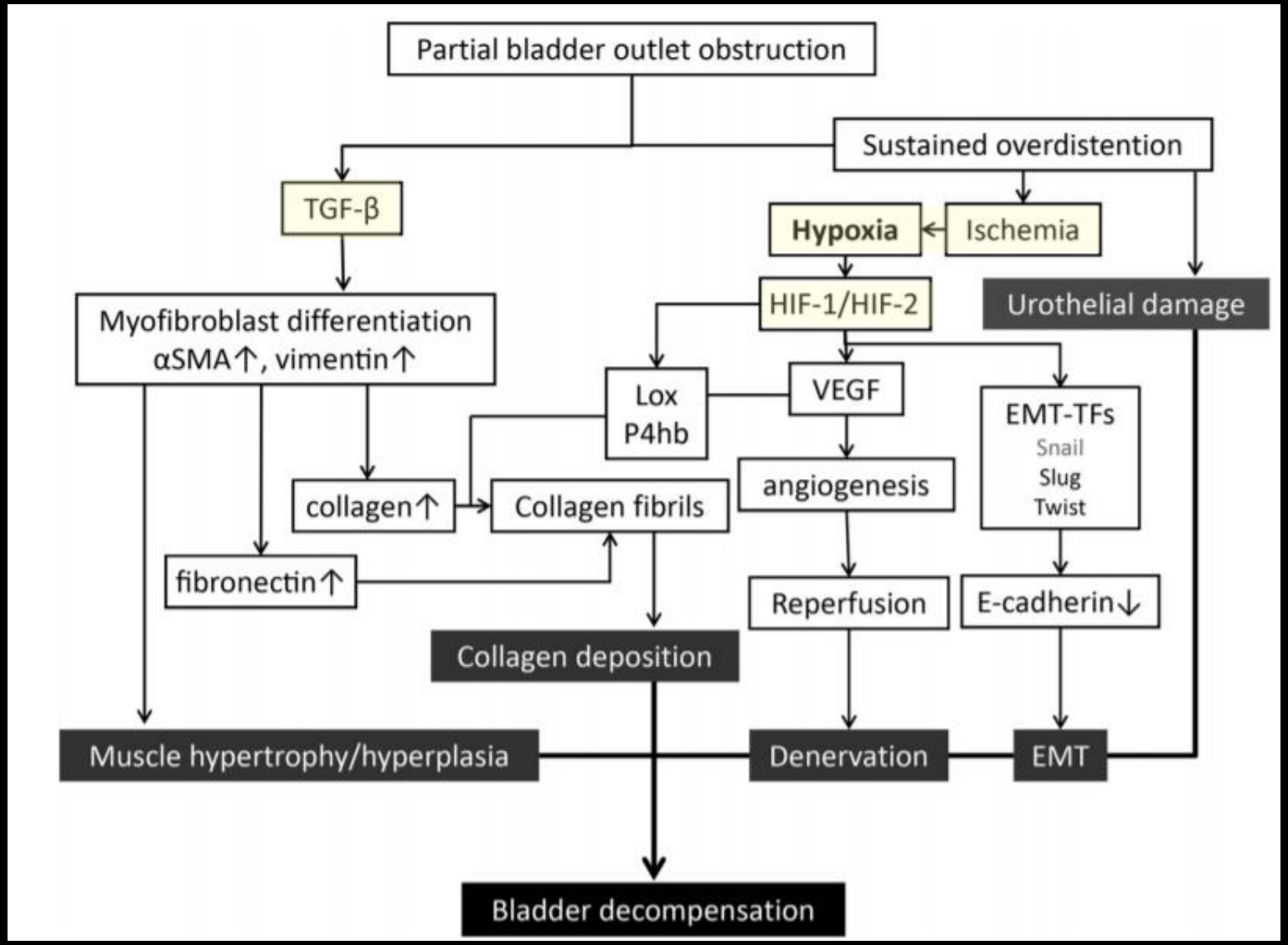
Roles of activation of
TGF-β and hypoxia-inducible factors pathway in BOO



J Urol. 2014 Sep;192(3):964

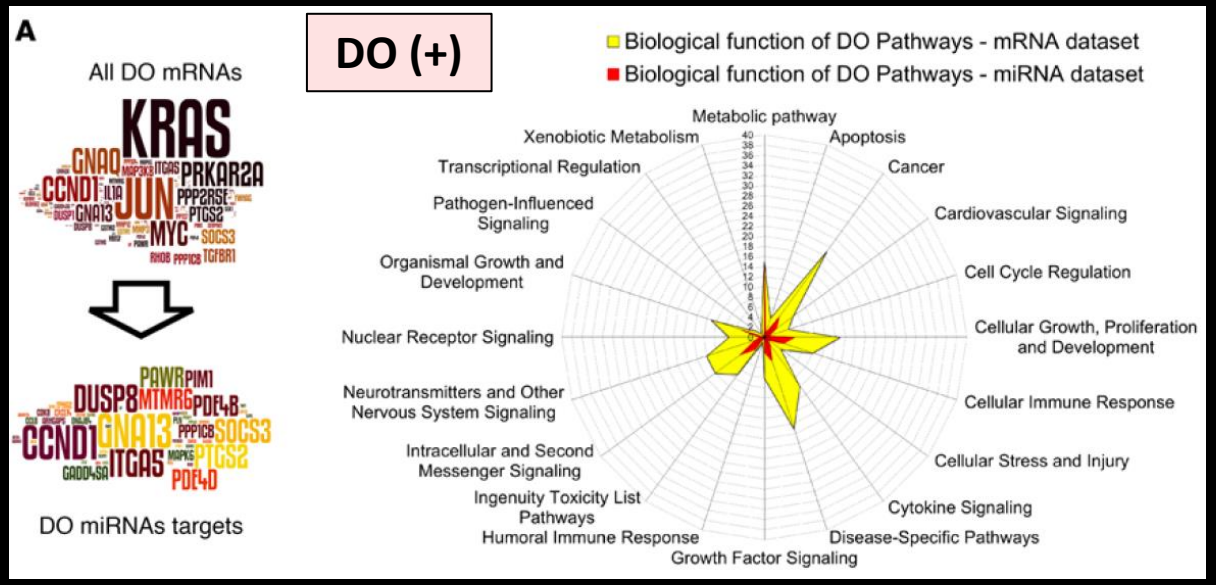
Key signaling pathways defining bladder remodeling in BOO

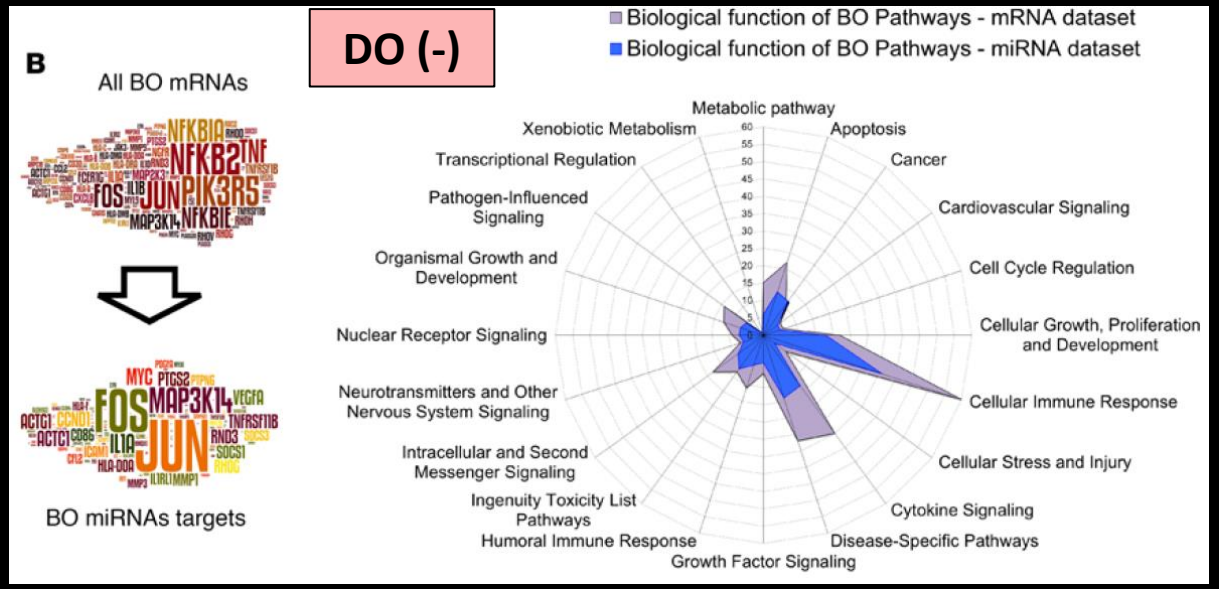
Pathways	DO		BO		UA		BOO vs. C	
	-log(*P* value)	*Z* score	-log(*P* value)	*Z* score	-log(*P* value)	*Z* score	-log(*P* value)	*Z* score
ERK5 signaling	6.88	2.828	2.22	2.449	7.66	2.887	3.19	2.449
PI3K/AKT signaling[A]	4.43	1.89	2.11	-0.632	4.21	3	2.34	1.414
Protein kinase A signaling	3.7	0.775	1.93	0.229	3.39	1.59	1.29	0
Colorectal cancer metastasis signaling[A]	3.51	2.111	3.93	3.674	9.16	4.111	5.41	3.411
Cholecystokinin/gastrin-mediated signaling[A]	3.42	2.646	3.33	3.051	4.89	4.644	3.57	3.317
TGF-β signaling	2.99	2.449	2.33	0.632	2.64	1.877	2.86	1.414
IGF-1 signaling	2.75	1	1.58	0.447	4.85	2.268	1.53	0
HGF signaling[A]	2.57	2.236	1.39	1.89	3.55	4.382	2.3	2.121
STAT3 pathway	2.56	1.342	1.39	0.378	2.39	0.408	2.16	-0.378
Pancreatic adenocarcinoma signaling	2.55	2	2.63	2.309	5.94	4.004	3.39	3
HMGB1 signaling[A]	2.29	2.236	7.96	3.71	6.22	4.523	8.37	3.771
IL-1 signaling	2.15	2.236	2.19	1.897	5.01	4.131	1.66	2.449
Acute phase response signaling[A]	2.14	1.89	5.85	1.789	7.91	4.18	6.59	3.153
Endothelin-1 signaling[A]	2.1	2.646	3.24	2	3.99	2.828	1.77	3.162
IL-8 signaling[A]	1.95	2.646	6.29	4.2	9.32	5.253	3.75	3.357
Chemokine signaling	1.84	1	1.91	2.828	2.31	2.858	2.22	2.646
JAK/STAT signaling[A]	1.82	1	2.94	0	5.63	2.335	3.47	1
Prolactin signaling	1.8	1	1.84	1.134	4.57	3.157	2.76	1.134
IL-6 signaling[A]	1.73	1.342	11.3	3.4	10.9	5.357	7.04	3.153
Production of nitric oxide and reactive oxygen species in macrophages	1.49	0	8.9	2.117	7.88	6.155	3.35	3.357
PPAR signaling[A]	1.45	-2	6.21	-2.668	5.01	-3.55	2.63	-3
ILK signaling[A]	1.43	1.342	7.35	1	2.19	3.355	2.31	3.162

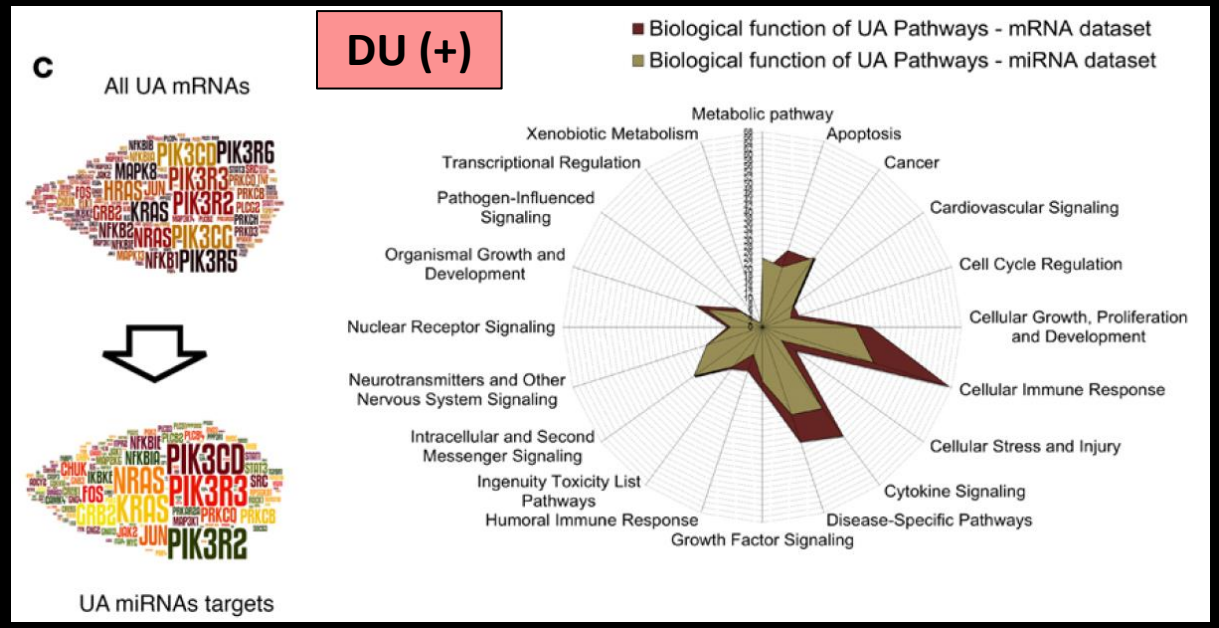
[A]These pathways contain at least 3 of 4 of the most representative signaling molecules: JUN, NRAS, PTGS2, and NFKB2. BOO, all bladder outlet obstruction patients (n = 18 patients); DO, BOO patients with urodynamically determined detrusor overactivity; BO, BOO patients without detrusor overactivity; UA, underactive bladder; C, controls (n = 6 patients per group). LUTD, lower urinary tract dysfunction.

JCI Insight. 2017 Jan 26;2(2):e89560

Roles of miRNA
in different states of BOO-induced bladder dysfunctions







- **miRNA** and **mRNA** expression profiles in BOO patients:

  DO (+) < DO (-) < **DU (+)**

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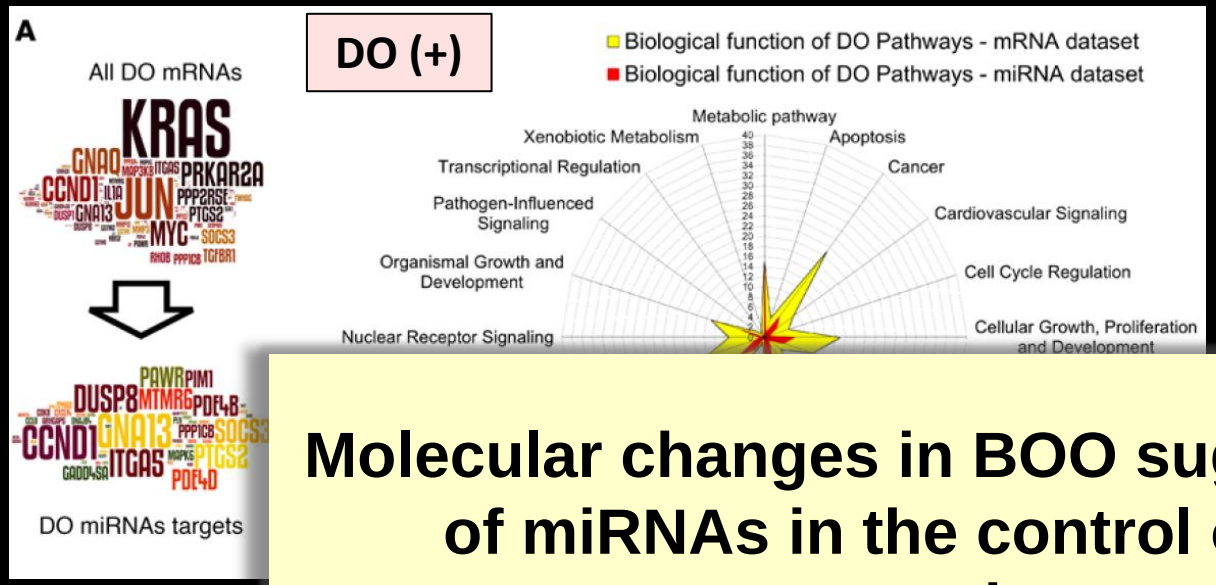
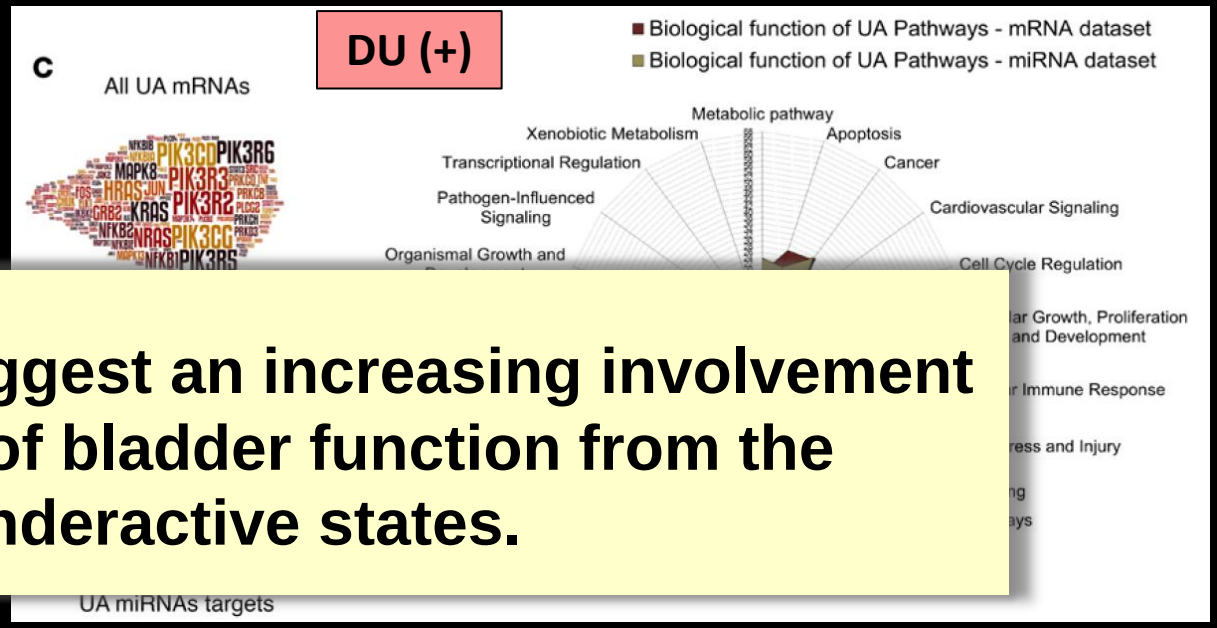
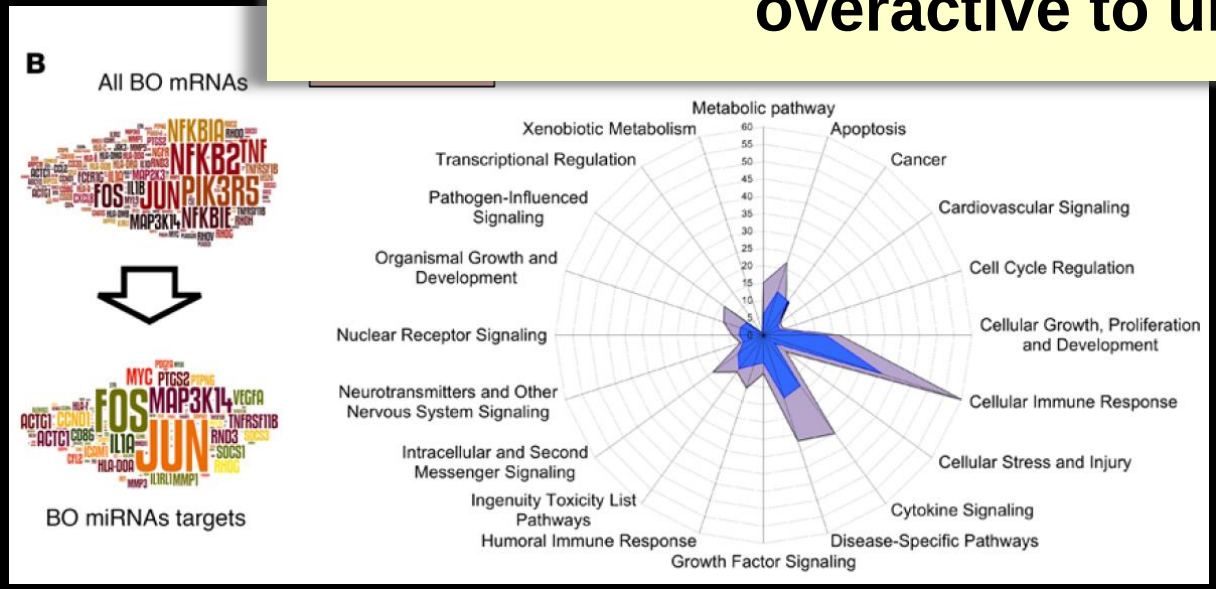




Molecular changes in BOO suggest an increasing involvement of miRNAs in the control of bladder function from the overactive to underactive states.



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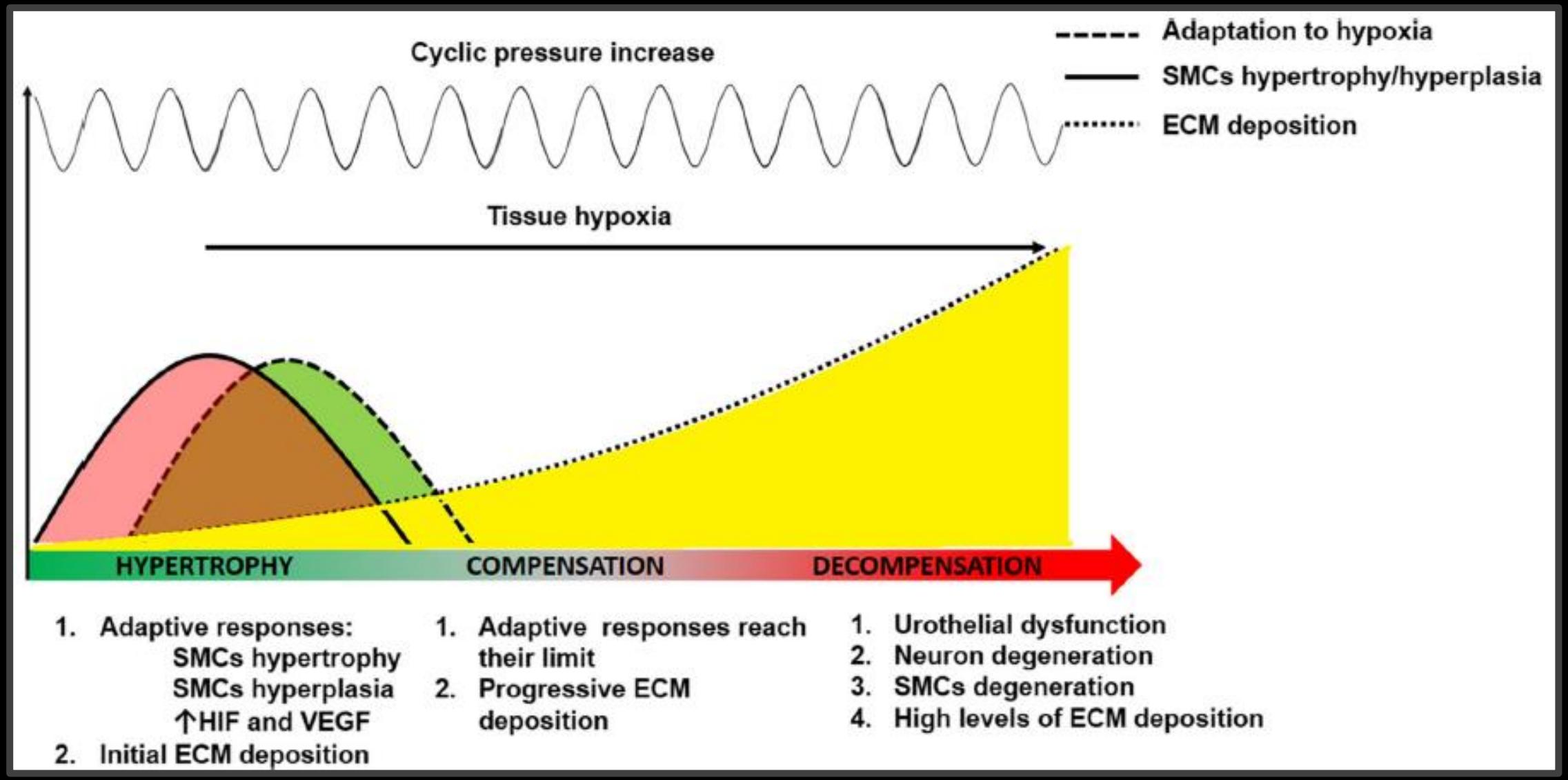
Proposed 3-stage model for BOO-induced bladder remodeling



BMC Urol. 2018 Mar 9;18(1):15

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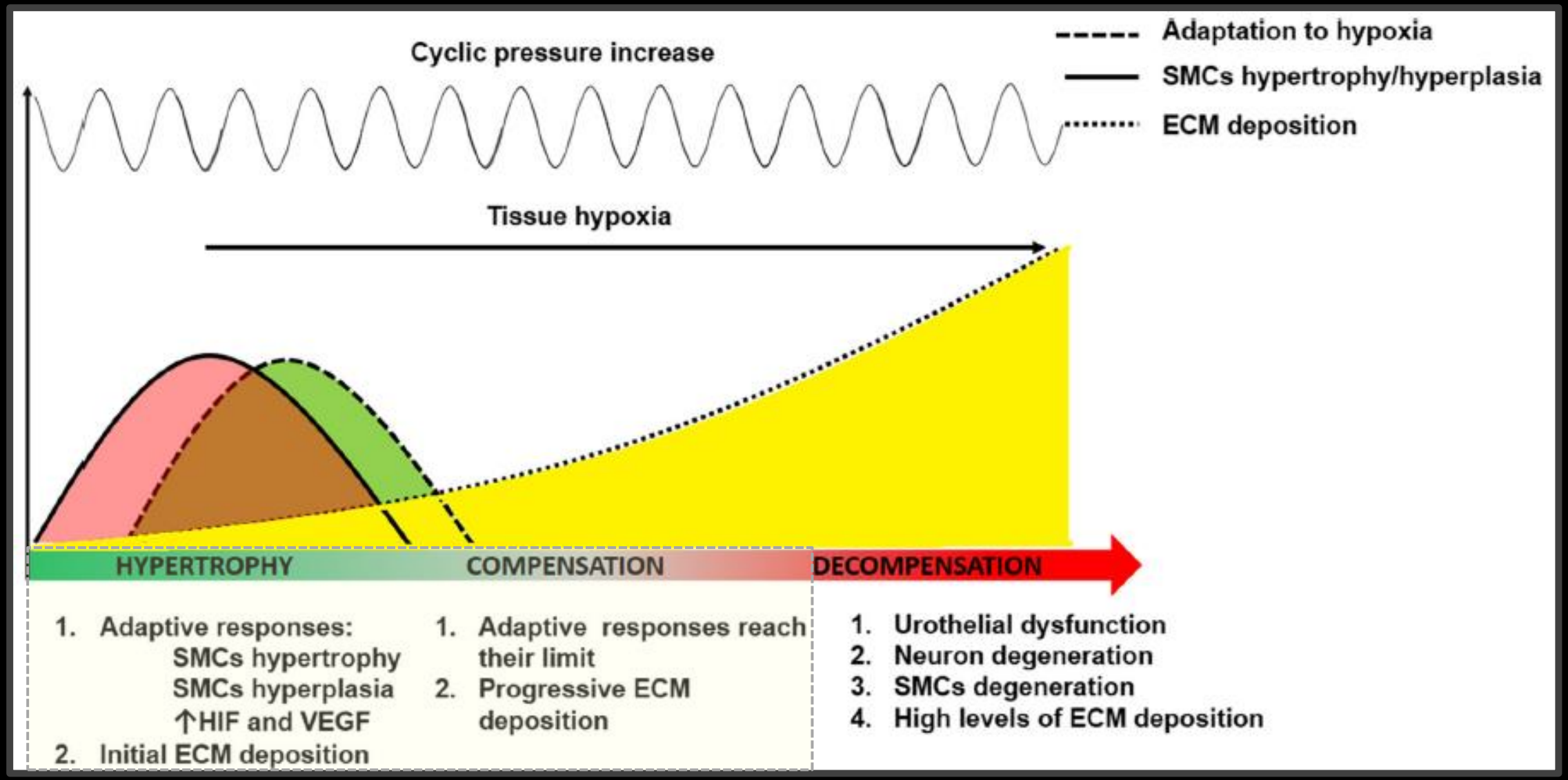

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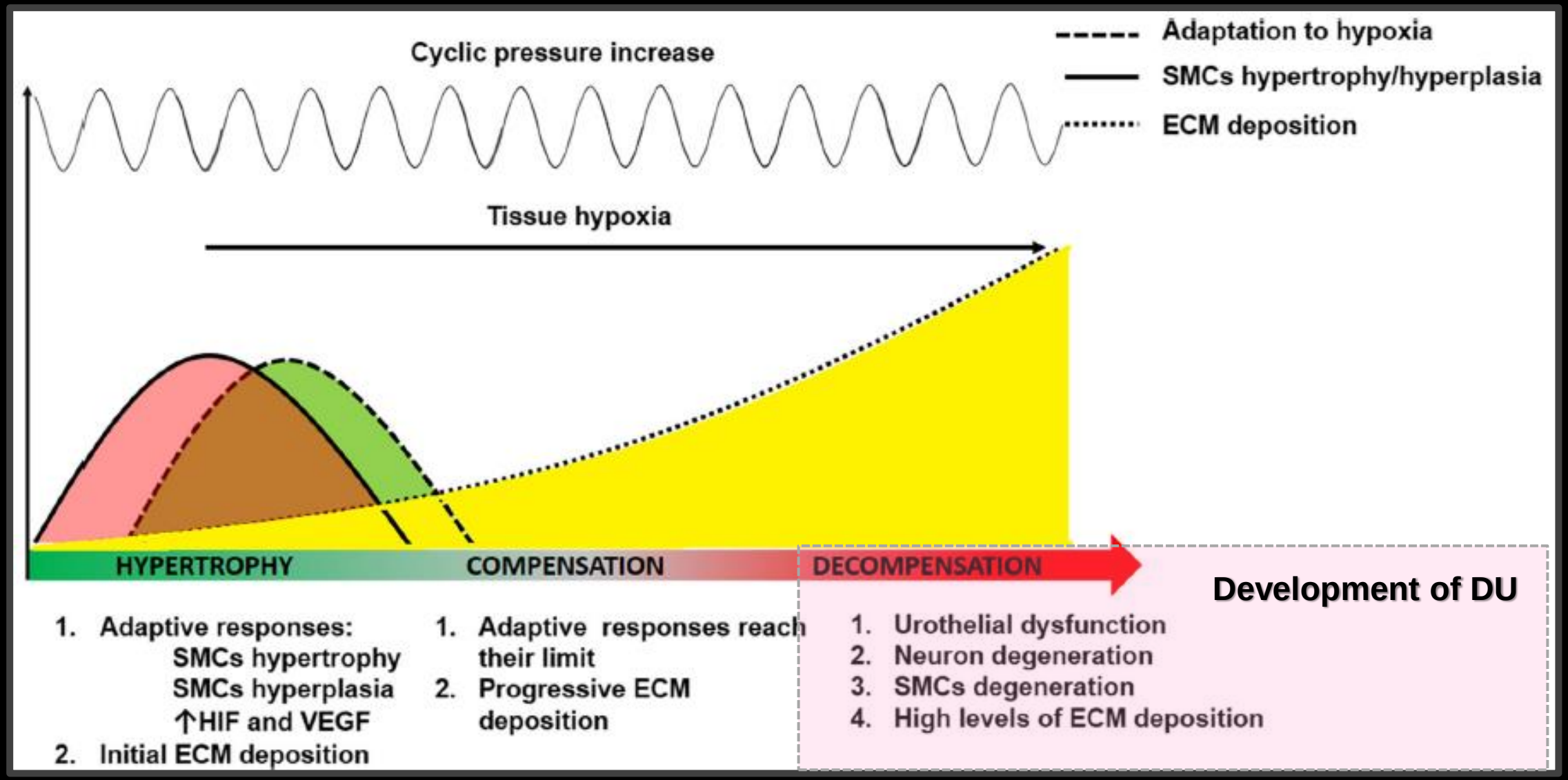

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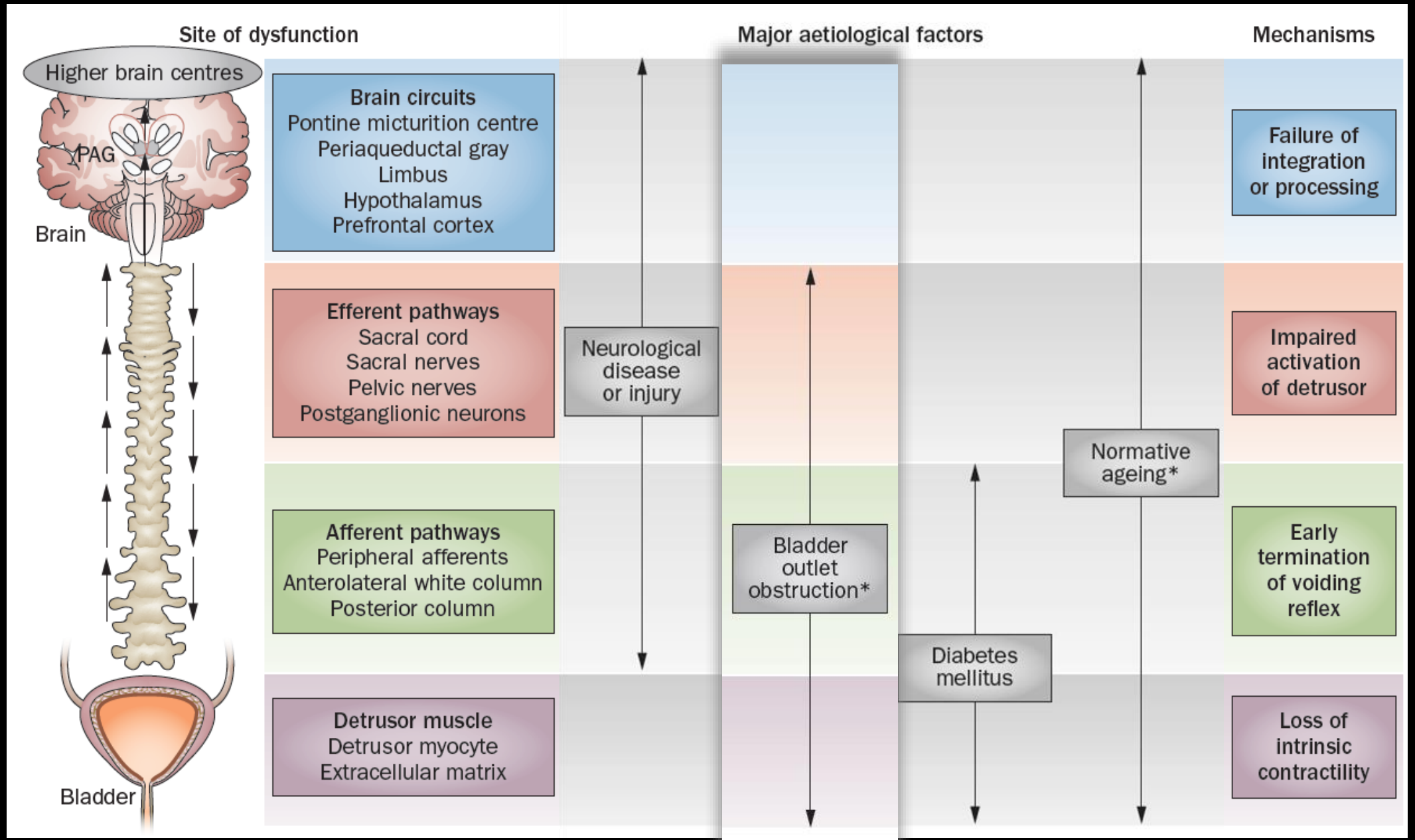
Major etiologies, sites of dysfunction and pathogenic mechanisms in DU



Nat Rev Urol. 2014 Nov;11(11):639

Neurological disease/ injury leading to DU

- **CVA (stroke):**
  - **50%** urinary retention in acute setting (75%: acontractility) (cerebral shock)
  - DO: most common long term bladder dysfunction
- **Parkinson disease: < 20%** DU
- **Multisystem atrophy: 52-95%** DU (atrophy of efferent nerve system)
- **Multiple sclerosis: 20%** DU (plaque in LS cord)
- **LS cord trauma/ HIVD**
- **Radical urological, gynecological, or rectal surgery** (pelvic plexus injury)
- **Infectious disease of nervous system**

(Guillain–Barré syndrome or herpes zoster, neurosyphilis [tabes dorsalis]).

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A multitude of nervous system disease/ injury can lead to DU.

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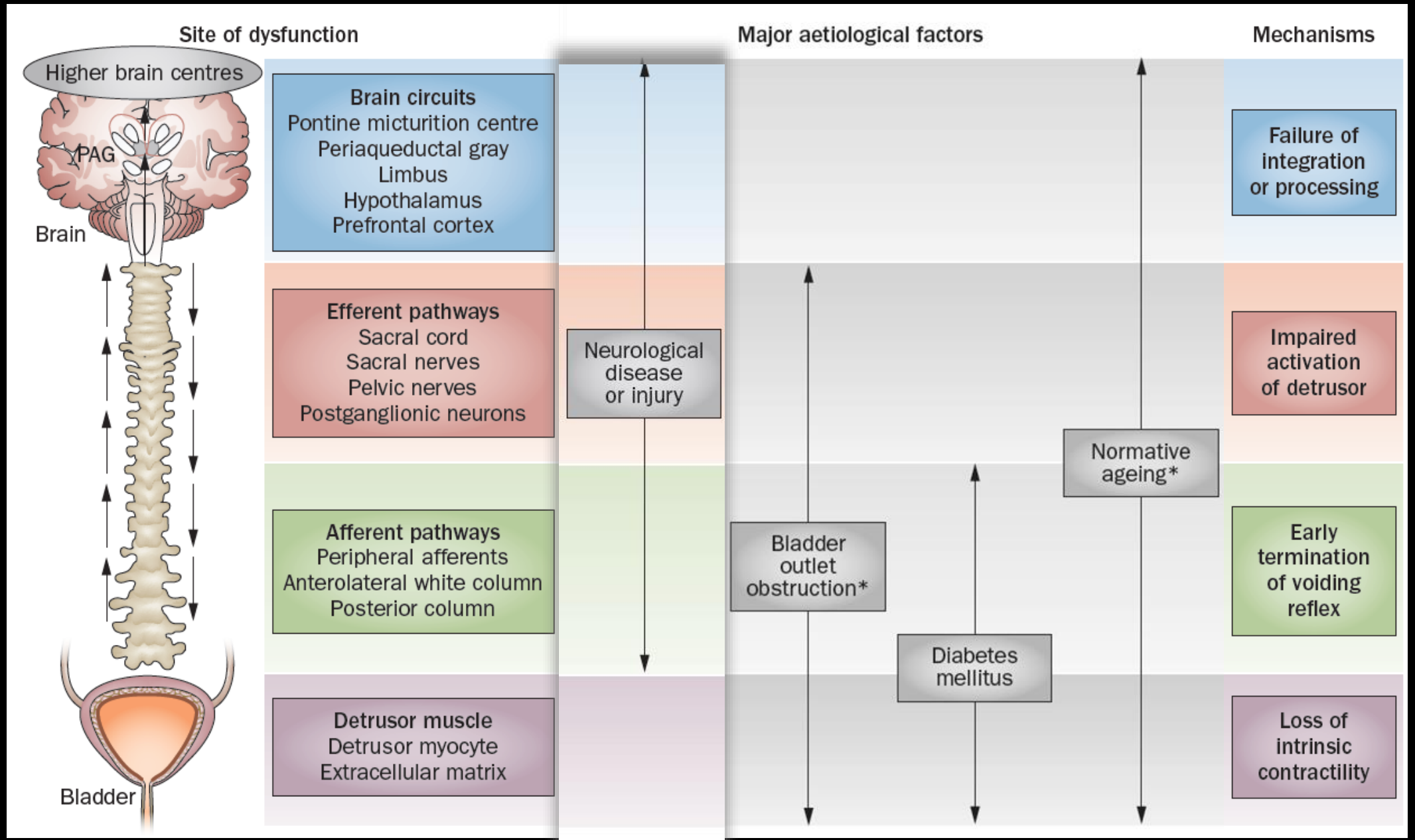

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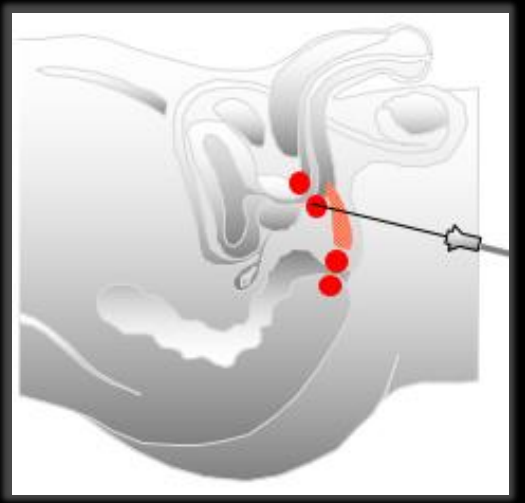
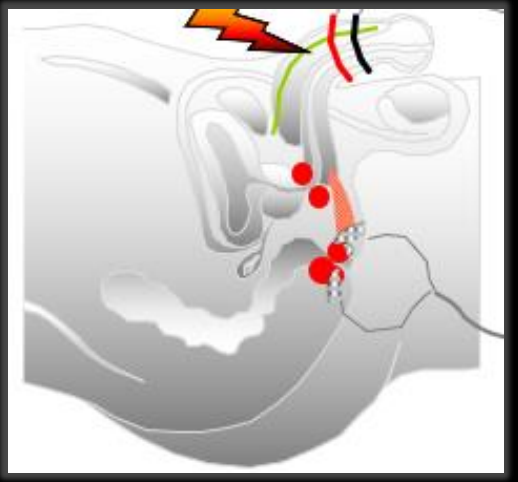
High percentage of LUT neurologic deficits in DU patients

	Etiology subgroups of DU					
	CVA	Postlumbar spine surgery	Postradical hysterectomy	Idiopathic	Overall DU	*p* value
Patient no.	10	35	5	10	60	
Age	63.7 ± 12.1	56.5 ± 18.1	66.8 ± 7.8	67.7 ± 18.1	60.4 ± 17.0	0.191
Sex	7 M, 3 F	17 M, 18 F	0 M, 5 F	4 M, 6 F	28 M, 32 F	0.079
DM	70% (7)	28.6% (10)	0%	20.0% (2)	31.7% (19)	0.020
Sacral neuropathy in NE	0%	54.3% (19)	0%	0%	31.7% (19)	<0.001
BCR (+)	60.0% (6)	31.4% (11)	20.0% (1)	70.0% (7)	41.7% (25)	0.067
EMG of EUS						
DeN	0%	31.4% (11)	0%	20.0% (2)	21.7% (13)	0.095
ReIN	90.0% (9)	68.6% (24)	100.0% (5)	50.0% (5)	71.7% (43)	0.108
Recruitment						
Preserved	0%	8.6% (3)	20.0% (1)	30.0% (3)	11.7% (7)	0.437
Decreased	80.0% (8)	62.9% (22)	60.0% (3)	60.0% (6)	65.0% (39)	
Absent	20.0% (2)	28.6% (10)	20.0% (1)	10.0% (1)	23.3% (14)	
NCV						
Decreased amplitude	50.0% (5)	82.9% (29)	80.0% (4)	60.0% (6)	73.3% (44)	0.143





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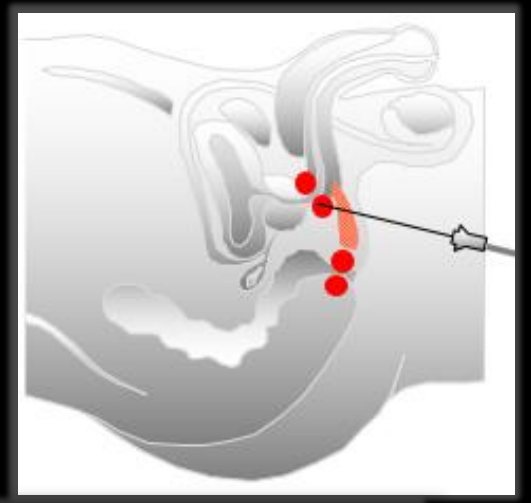
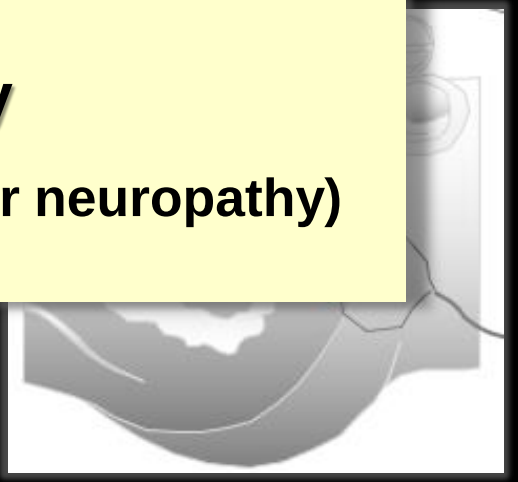
High percentage of LUT neurologic deficits in DU patients

	Etiology subgroups of DU					
	CVA	Postlumbar spine surgery	Postradical hysterectomy	Idiopathic	Overall DU	*p* value
Patient no.	10	35	5	10	60	
Age	63.7 ± 12.1	56.5 ± 18.1	66.8 ± 7.8	67.7 ± 18.1	60.4 ± 17.0	0.191
Sex	7 M, 3 F	17 M, 18 F	0 M, 5 F	4 M, 6 F	28 M, 32 F	0.079
DM	70% (7)	28.6% (10)	0%	20.0% (2)	31.7% (19)	0.020
Sacral neuropathy in NE	0%	54.3% (19)	0%	0%	31.7% (19)	<0.001
BCR (+)	60.0% (6)	31.4% (11)	20.0% (1)	70.0% (7)	41.7% (25)	0.067
EMG of EUS						
DeN						
ReIN						
Recruitme						
Preserved						
Decreased						
Absent	20.0% (2)	28.6% (10)	20.0% (1)	10.0% (1)	23.3% (14)	
NCV						
Decreased amplitude	50.0% (5)	82.9% (29)	80.0% (4)	60.0% (6)	73.3% (44)	0.143





Urodynamic DU with occult LUT neuropathy

(BCR dysfunction, pudendal neuropathy, and the urethral sphincter neuropathy)

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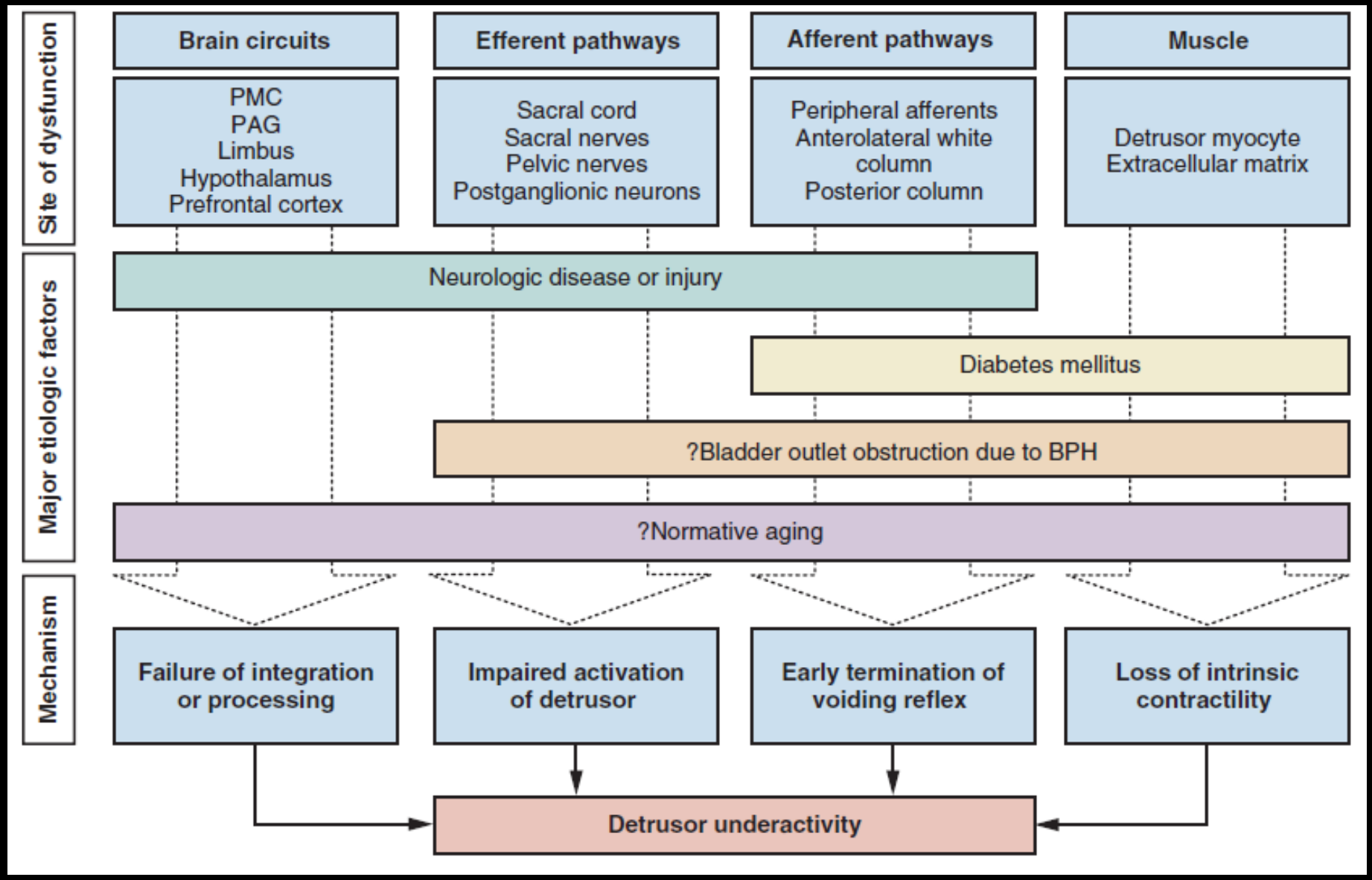
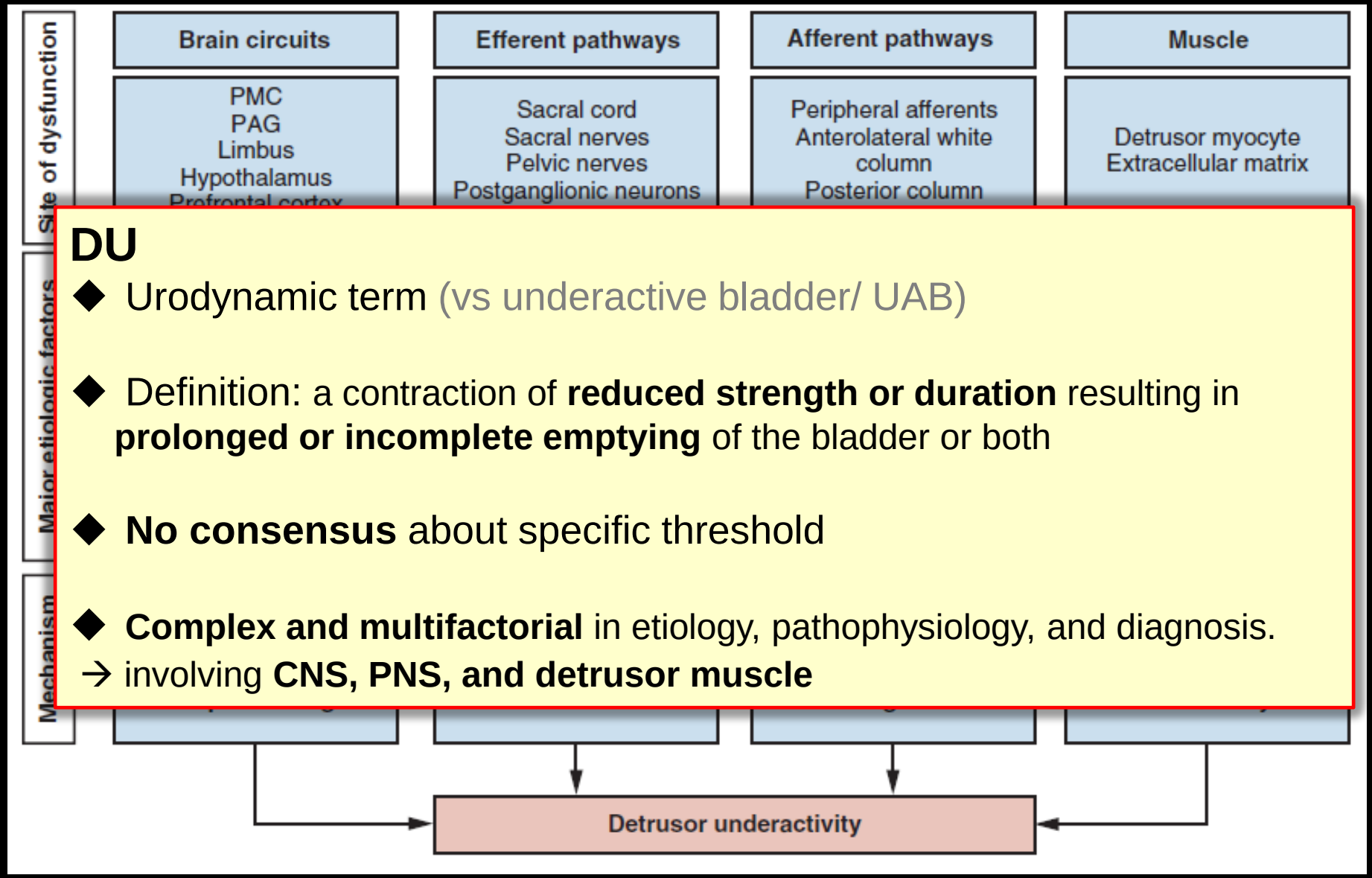
Etiopathogenesis of DU



Etiopathogenesis of DU

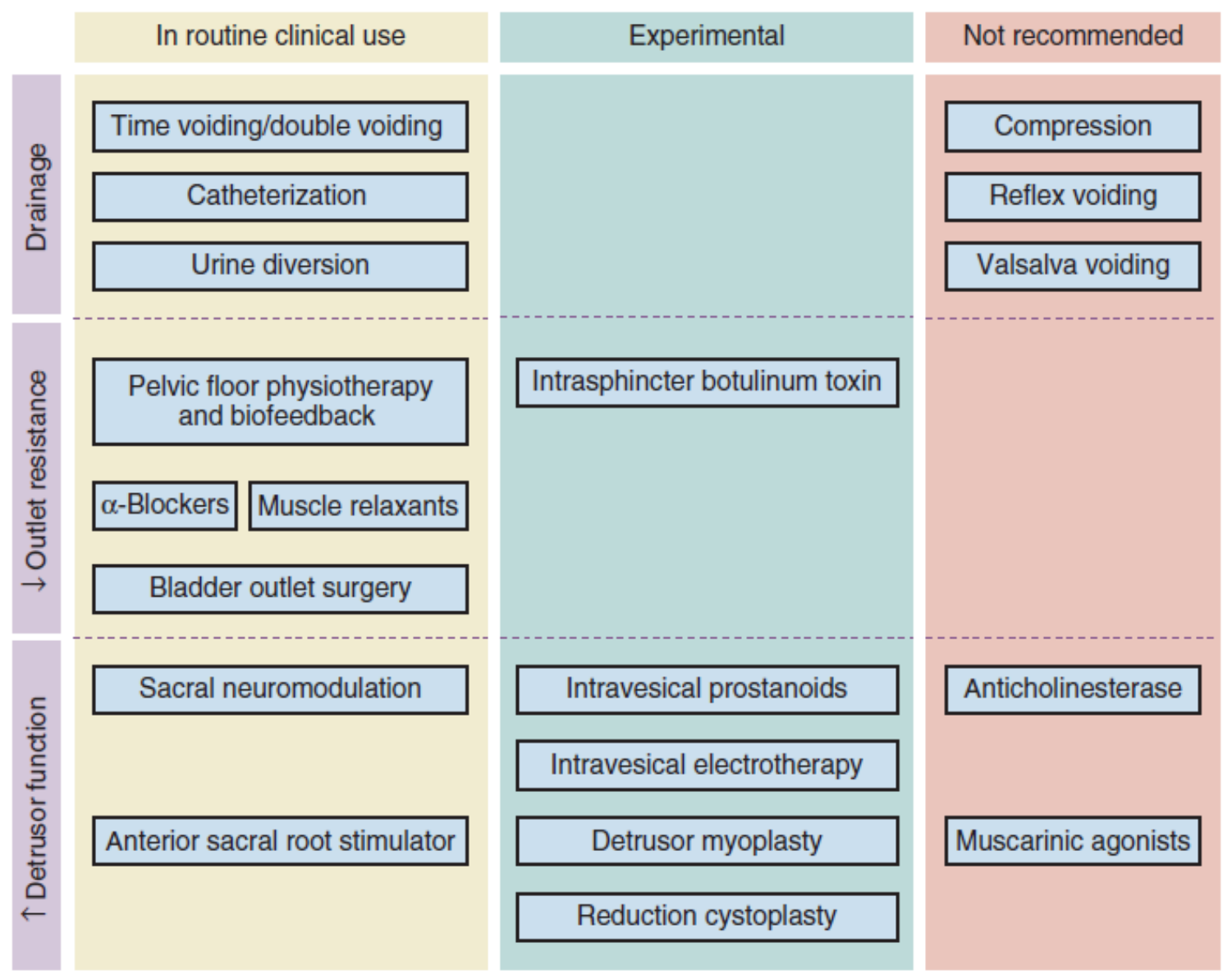


DU

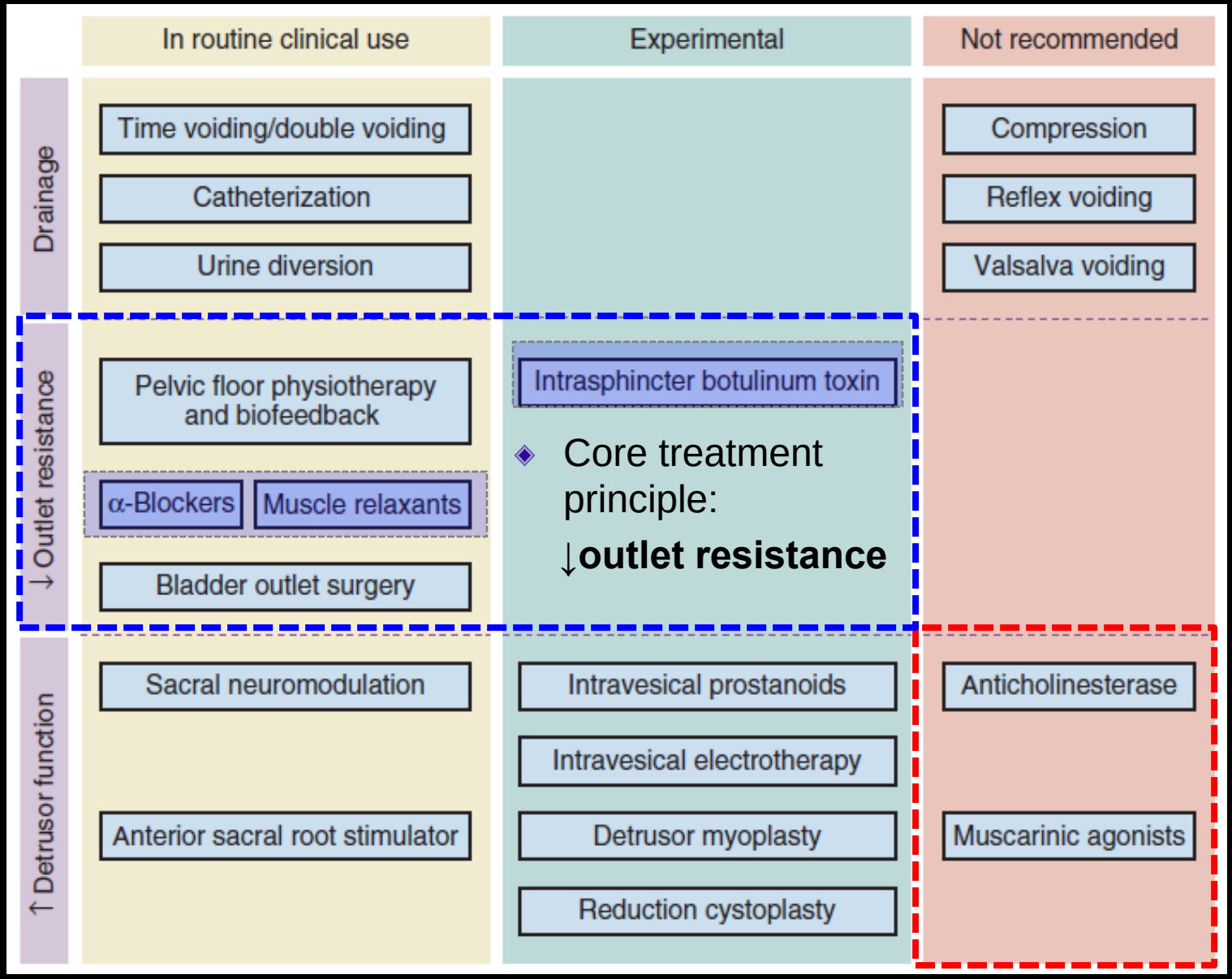
- Urodynamic term (vs underactive bladder/ UAB)
- Definition: a contraction of **reduced strength or duration** resulting in **prolonged or incomplete emptying** of the bladder or both
- **No consensus** about specific threshold
- **Complex and multifactorial** in etiology, pathophysiology, and diagnosis.

→ involving **CNS, PNS, and detrusor muscle**

Management Options in Detrusor Underactivity



Management Options in Detrusor Underactivity



- ↑muscle tonicity ≠ active contraction

Summary

- **Incompletely understood etiology and pathogenesis** of DU/ UAB
  - a diverse range of factors and mechanisms

- Confirmed etiologic factors: **neurologic injury/ disease, DM**

  Probable factors: **aging, BOO**

- Pathophysiologic mechanisms
  - **Myogenic**
  - **Neurogenic:** brain/ spinal cord dysfunction, efferent nerve dysfunction, afferent nerve dysfunction