Neural Control of Lower Urinary Tract Function

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Disclosures

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- Conflicts of interest: None

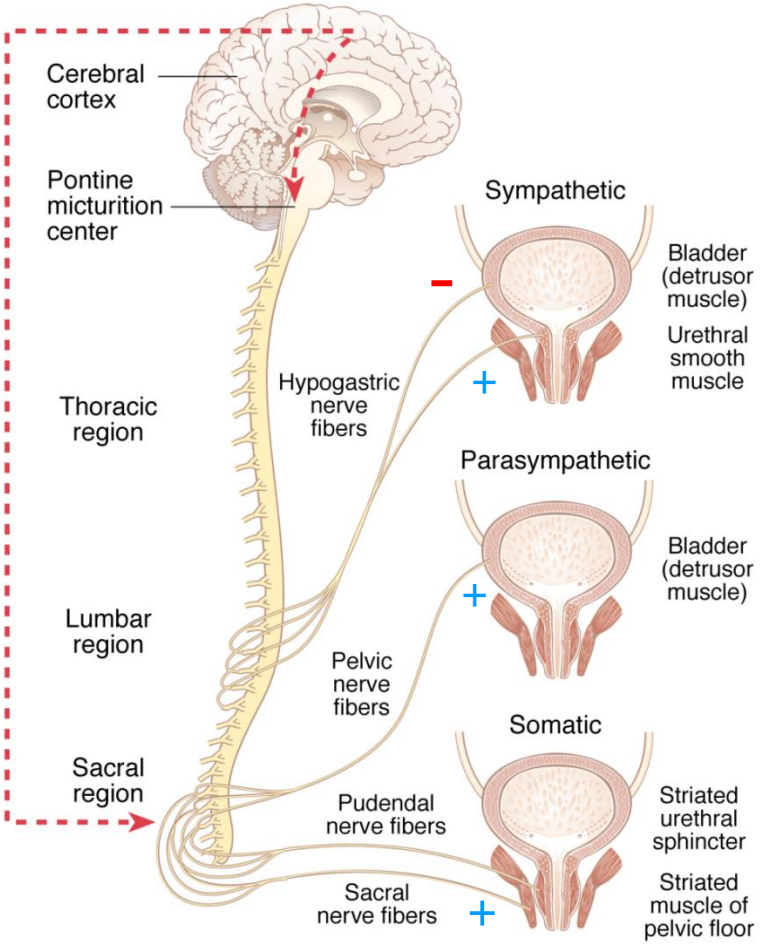
Topics

- Lower urinary tract: functions, anatomy and innervation.
- Properties of bladder afferent nerves
- Central neural control of voiding
- Mechanisms underlying urine storage and voiding dysfunction

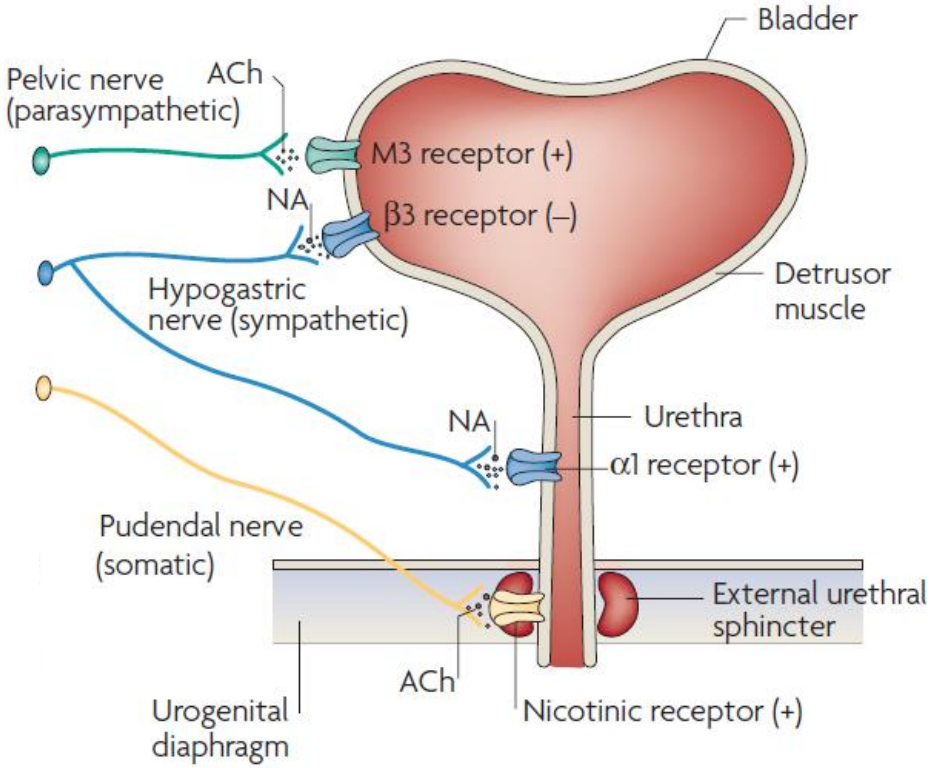
Functions of the Lower Urinary Tract

- Urine storage in a reservoir (bladder)
- Urine release through an outlet (urethra)
- Both functions controlled by circuitry in the central nervous system.
- Neural circuitry acts like a switch to turn micturition off and on.
- Micturition requires the coordination of smooth and striated muscle.

Lower Urinary Tract Innervation

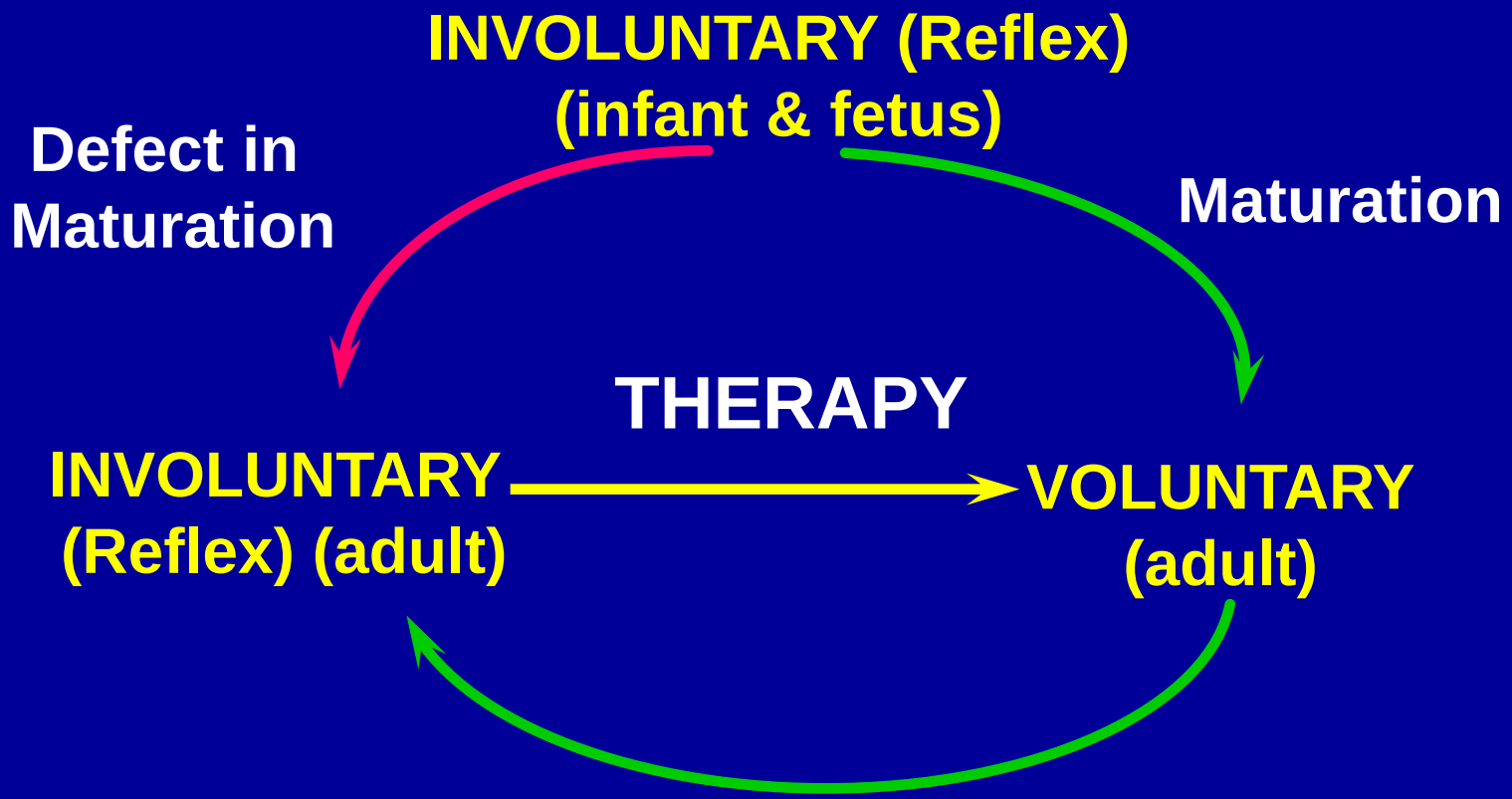


Reservoir

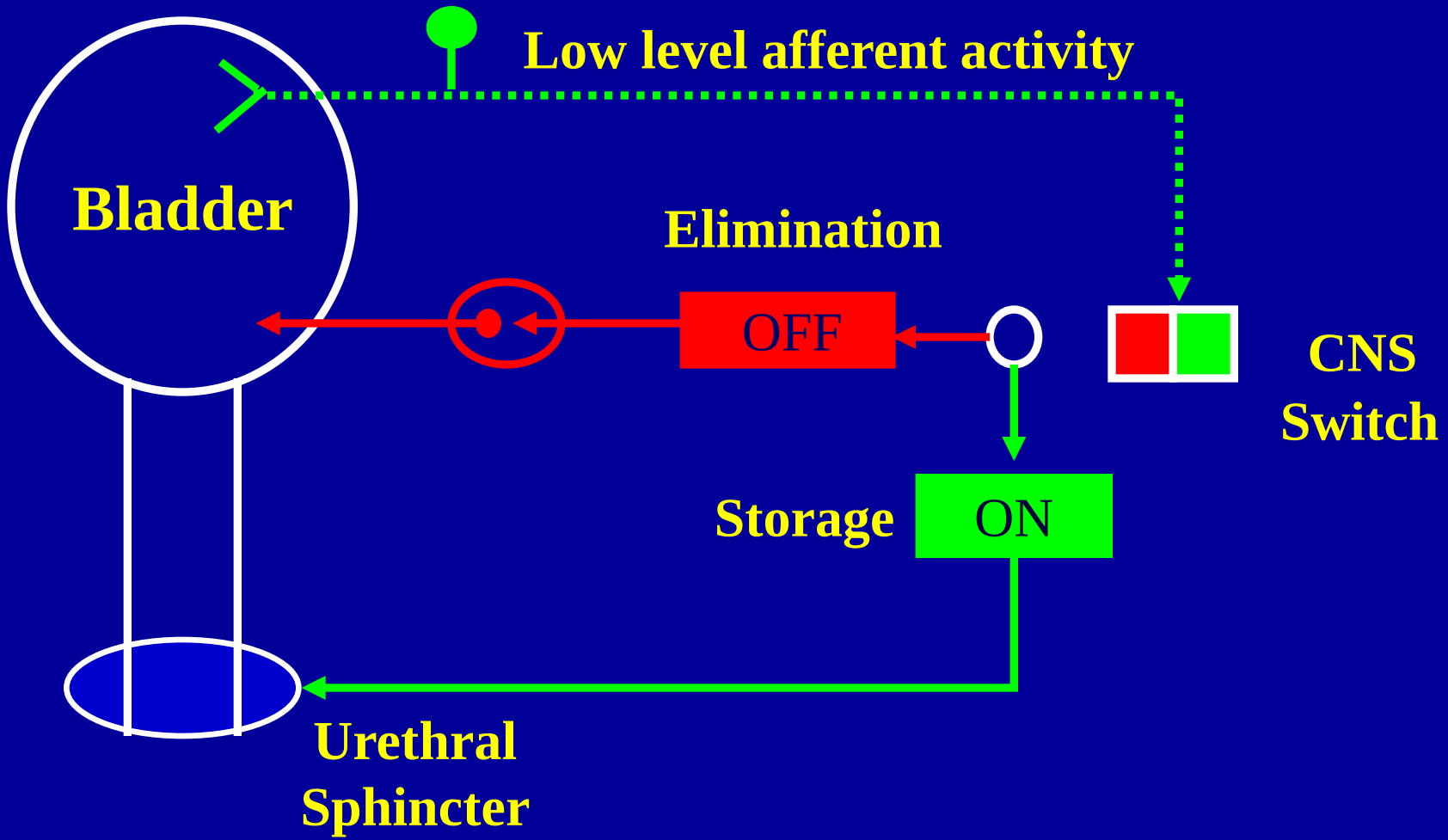


Urethral Outlet

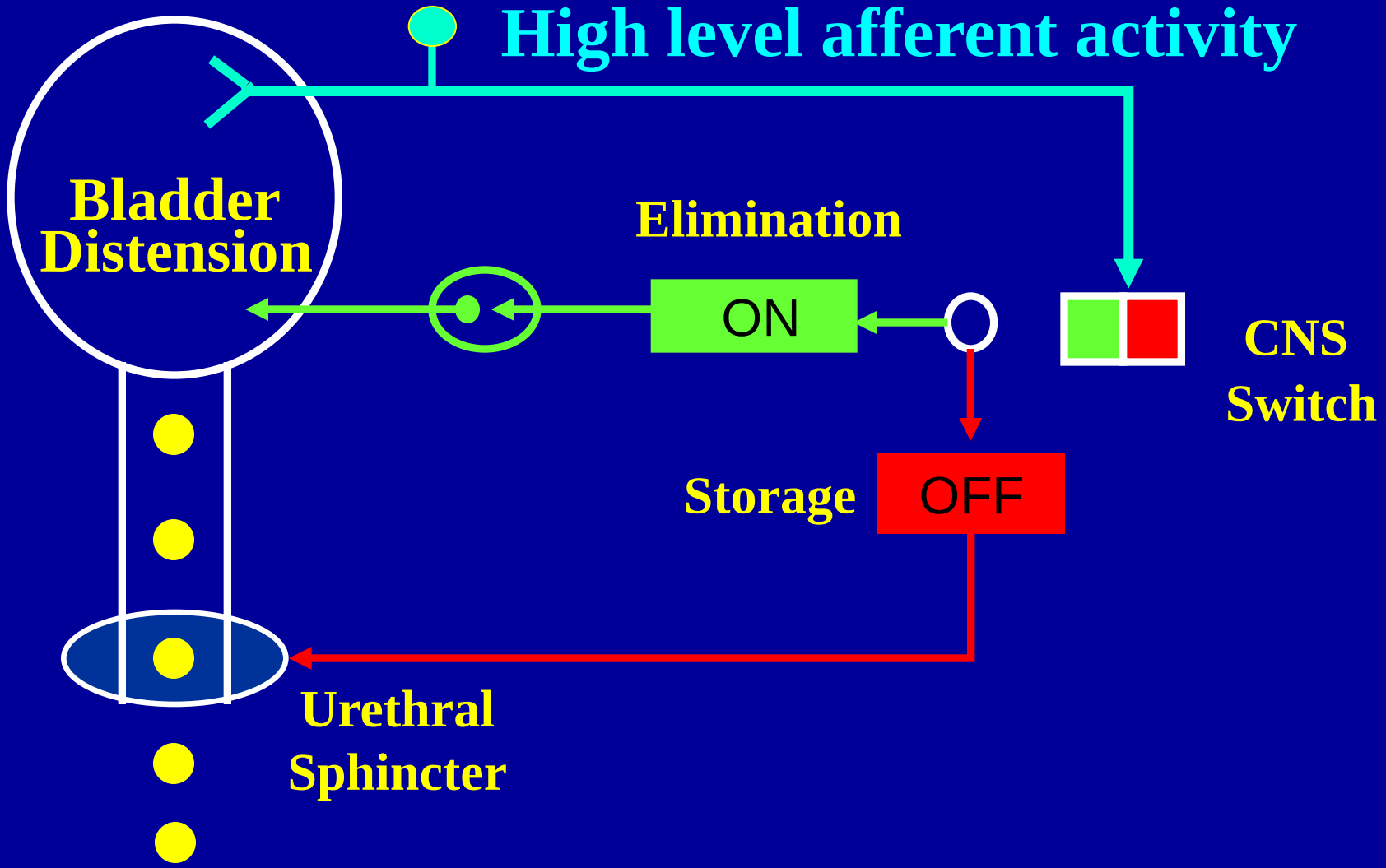
TYPES OF VOIDING



Micturition Switching Circuit



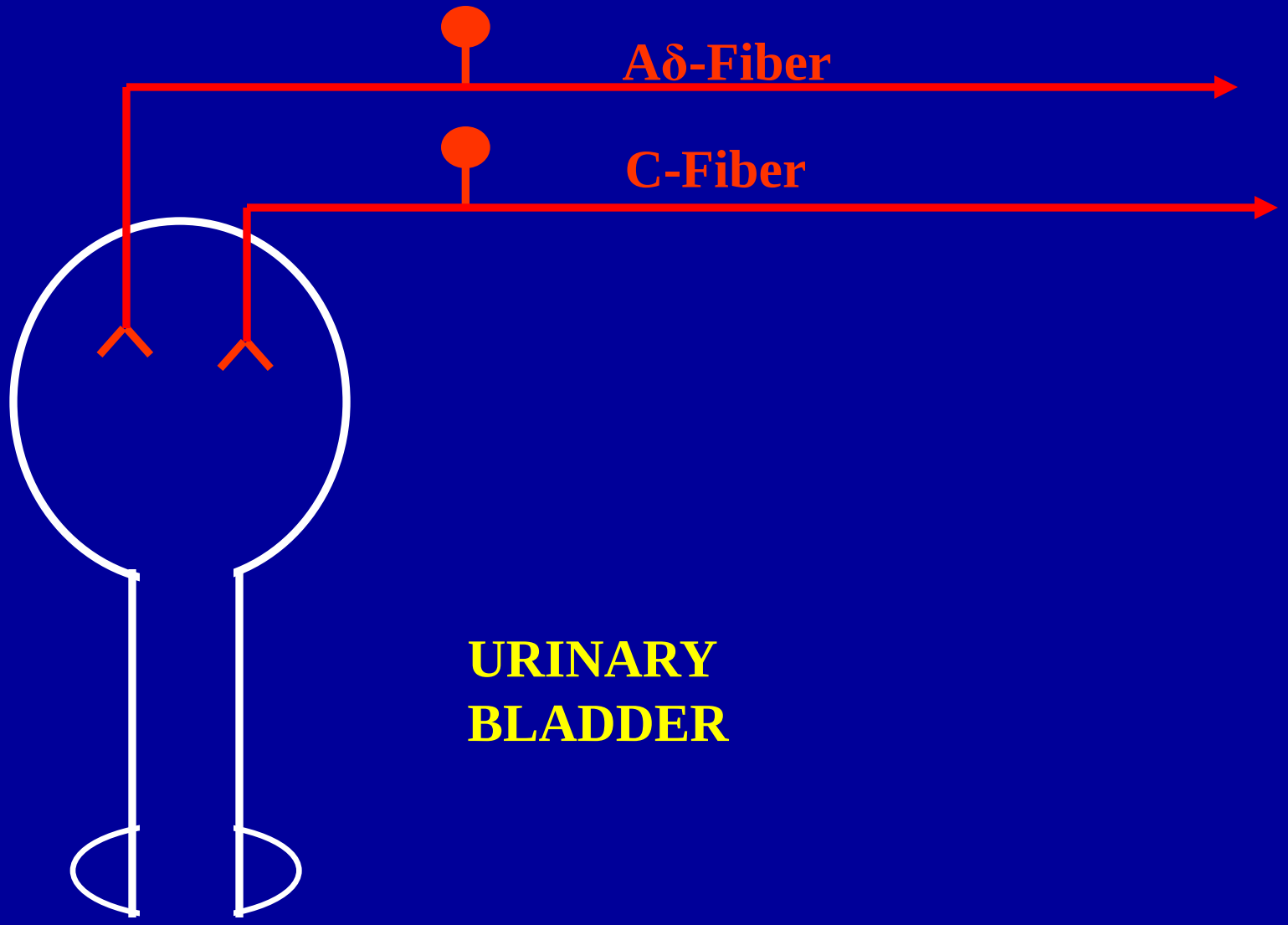
Micturition Switching Circuit



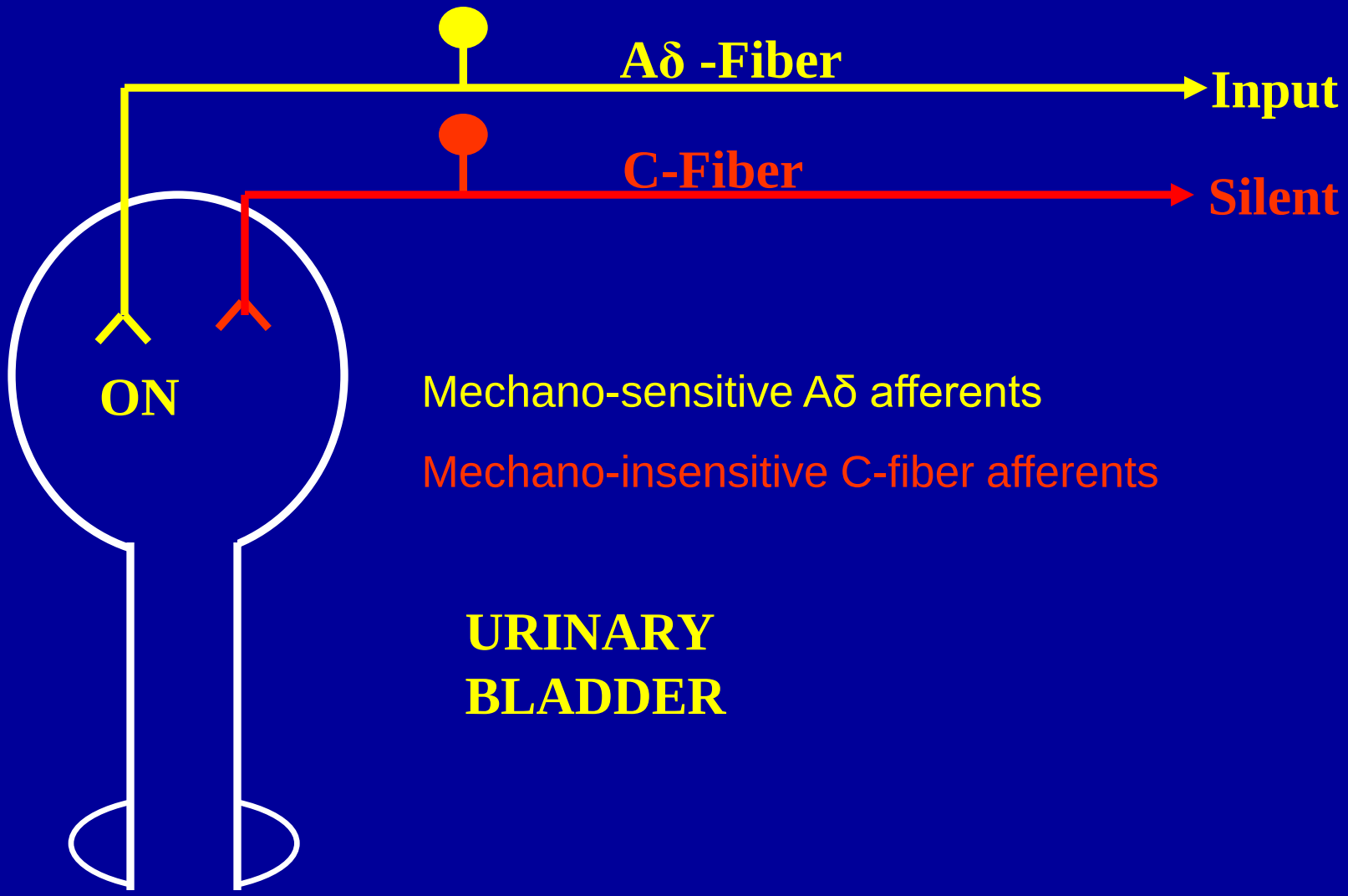
Two Types of Bladder Afferents

- *A-fiber type:* small myelinated axons that respond to bladder distension and trigger sensation of bladder fullness and desire to void.
- *C-fiber type:* unmyelinated axons that do not respond to bladder distension but do respond to noxious stimuli. These afferents trigger painful sensations and may be responsible for urgency and urge incontinence.

Healthy: Empty Bladder



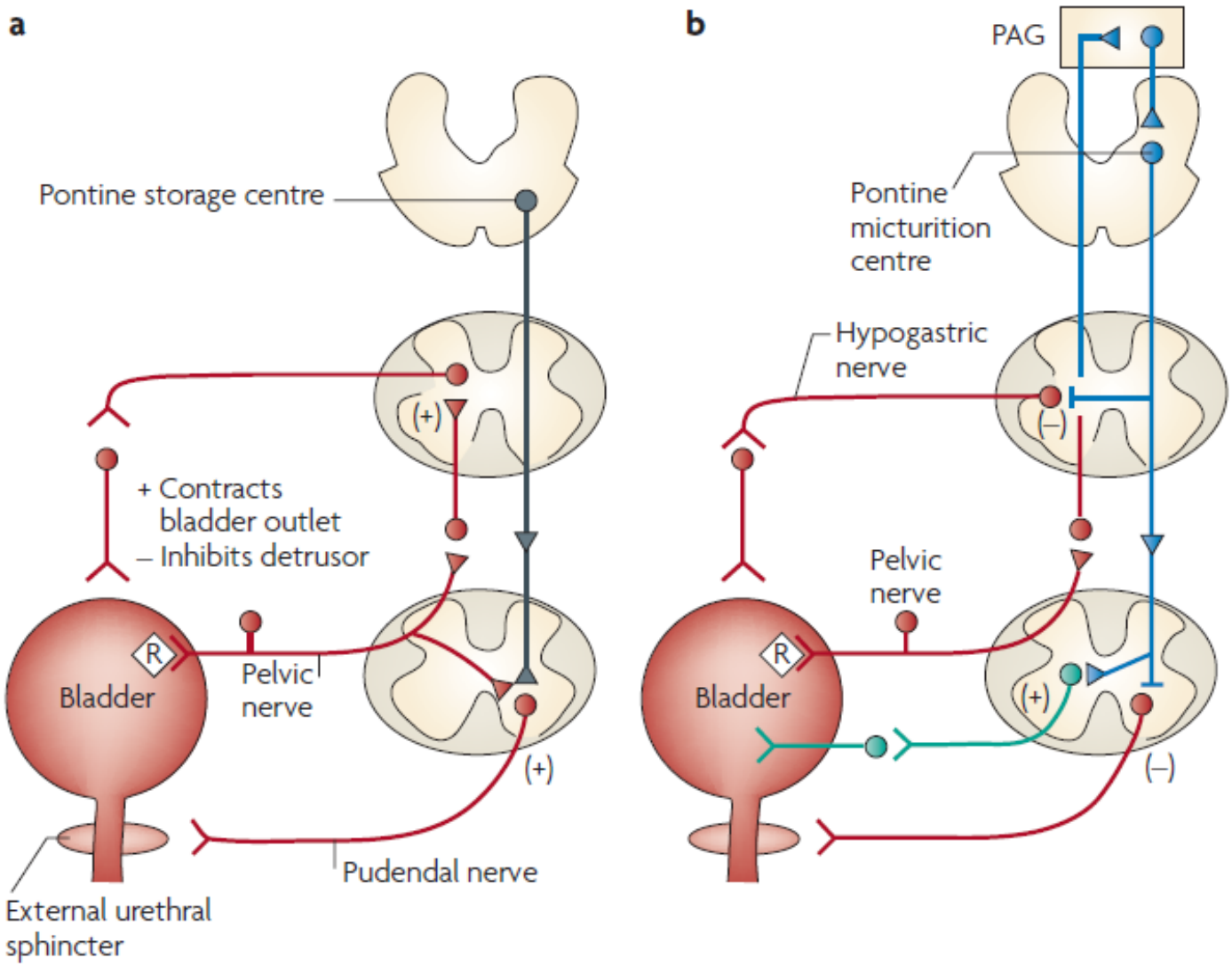
Healthy: Bladder Distension



Reflexes Evoked by Aδ Afferents in the Pelvic Nerve

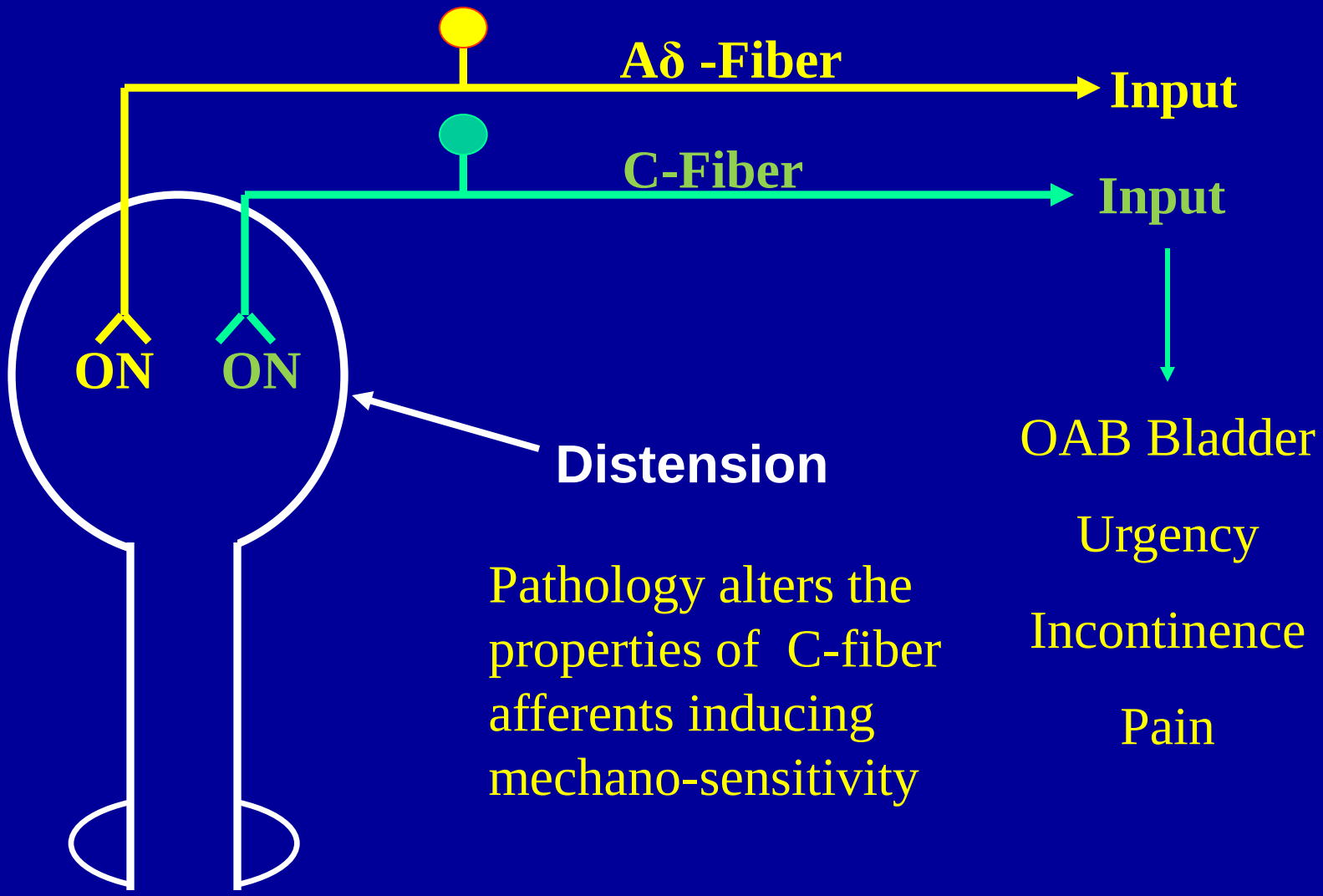
Spinal Storage Reflexes

Supraspinal Voiding Reflexes



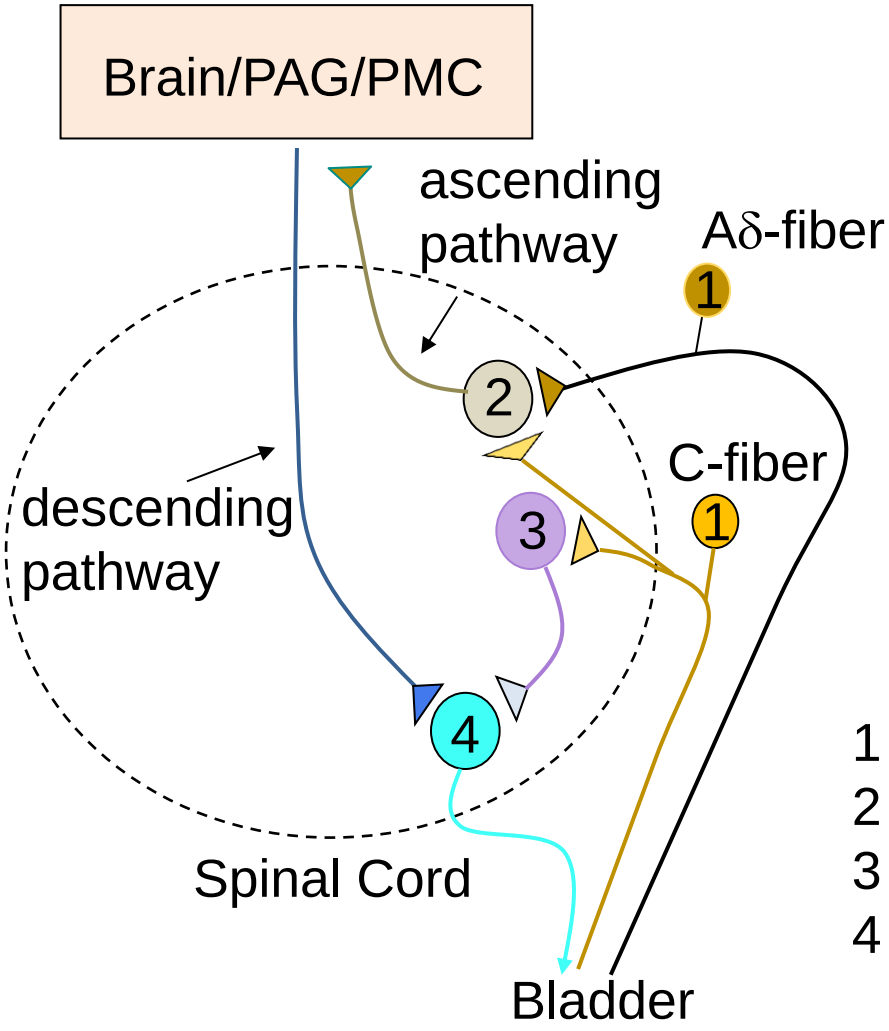
Fowler, Griffiths & de Groat, Nature Rev Neurosci., 9: 453, 2008

Pathology: Bladder Distension



Pathology alters the properties of C-fiber afferents inducing mechano-sensitivity

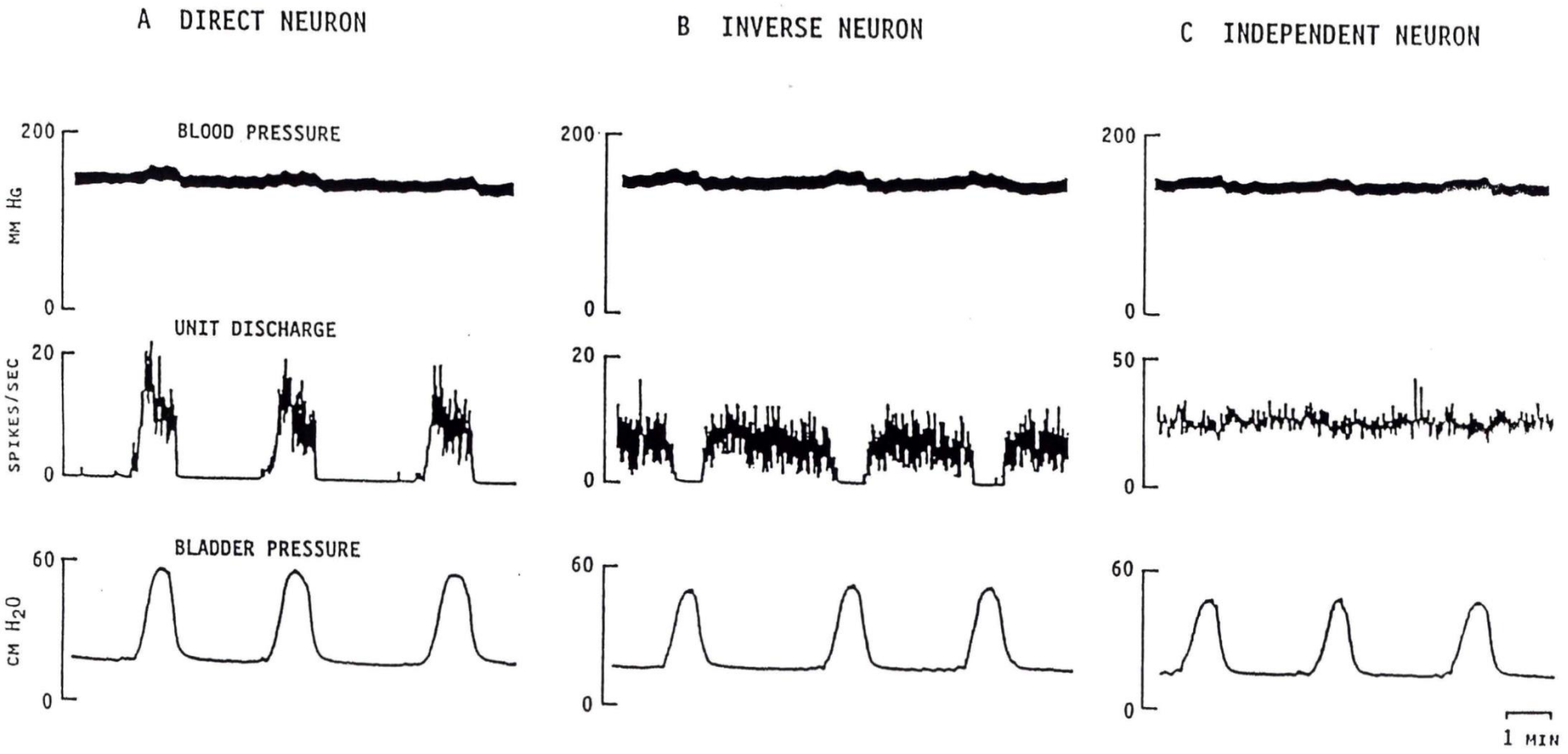
Central Pathways Activated by C-Fiber Afferents



PMC = Pontine micturition center
PAG = Periaqueductal grey

1 = Primary afferent neuron
2 = Spinal tract neuron
3 = Excitatory interneuron
4 = Parasympathetic preganglionic Neuron

Neuronal subtypes in the pontine micturition center of the cat



Similar subtypes are present in the PAG

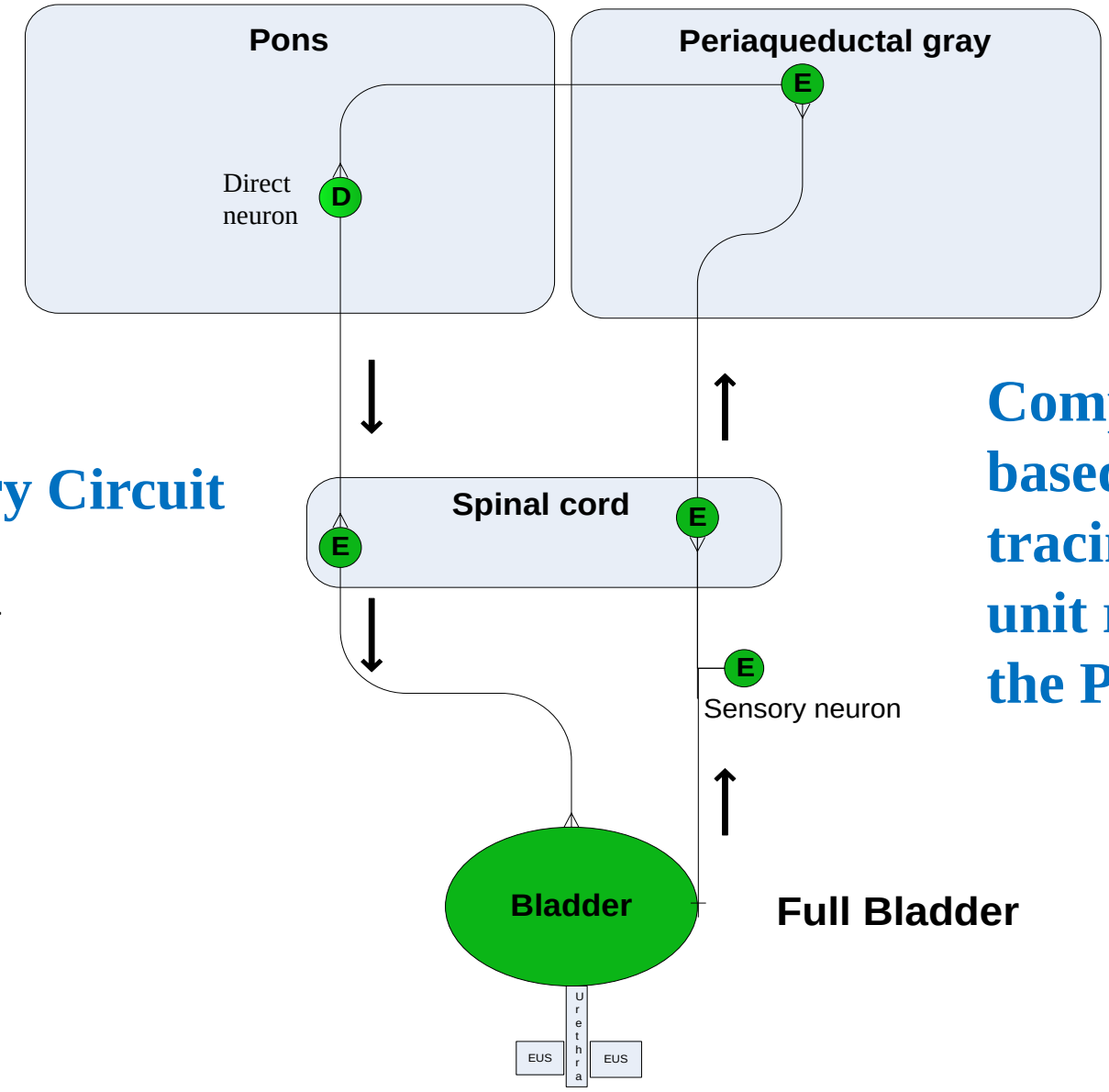
Contractions recorded in a distended bladder under isovolumetric conditions

Distribution of Different Types of Bladder Neurons in the Rostral Pons

Type of Neuron	Count	Percent
Direct Neurons	35	20.7
Inverse Neurons	86	50.9
On-Off Neurons	6	3.6
Independent Neurons	42	24.9*
Total	169	100.0

de Groat, W., et. al., Behav Brain Res, 1998;

Sasaki, M. J Physiol, 2004; Br Res 2005, J Comp Neurol, 2005



Excitatory Circuit

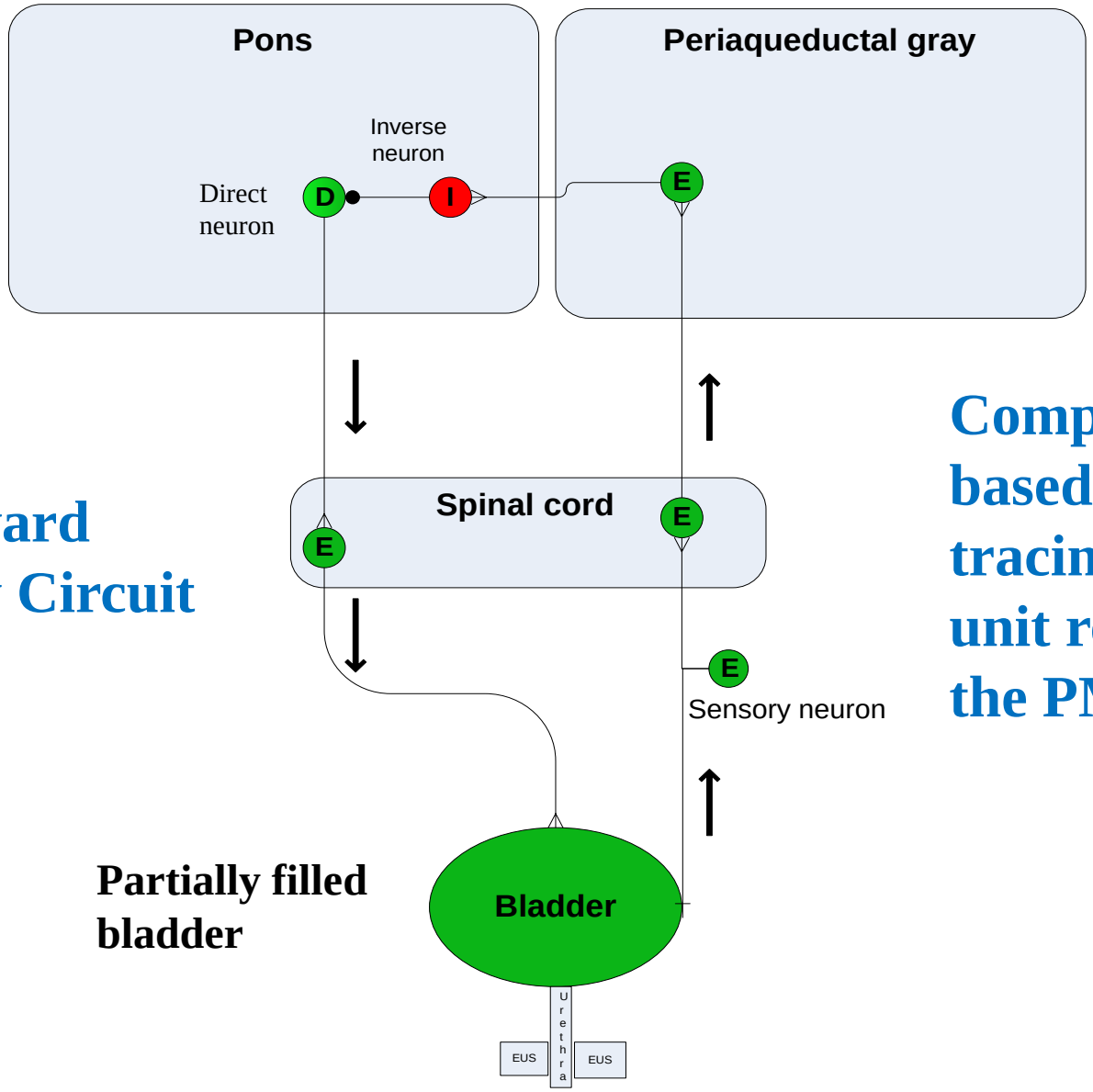
Circuit #1

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

de Groat & Wickens, 2013

Feed-forward Inhibitory Circuit

Circuit #2



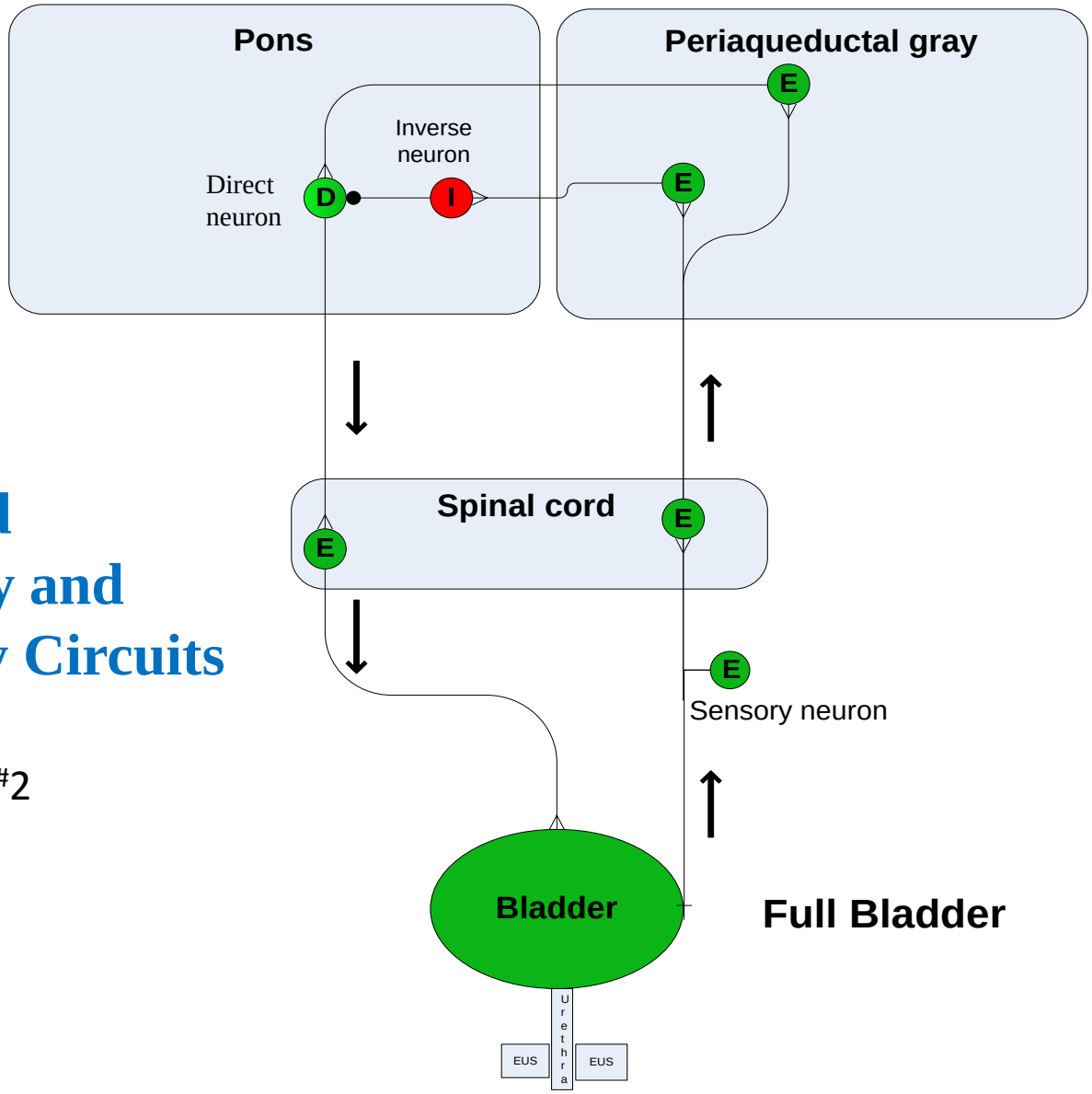
Partially filled bladder

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

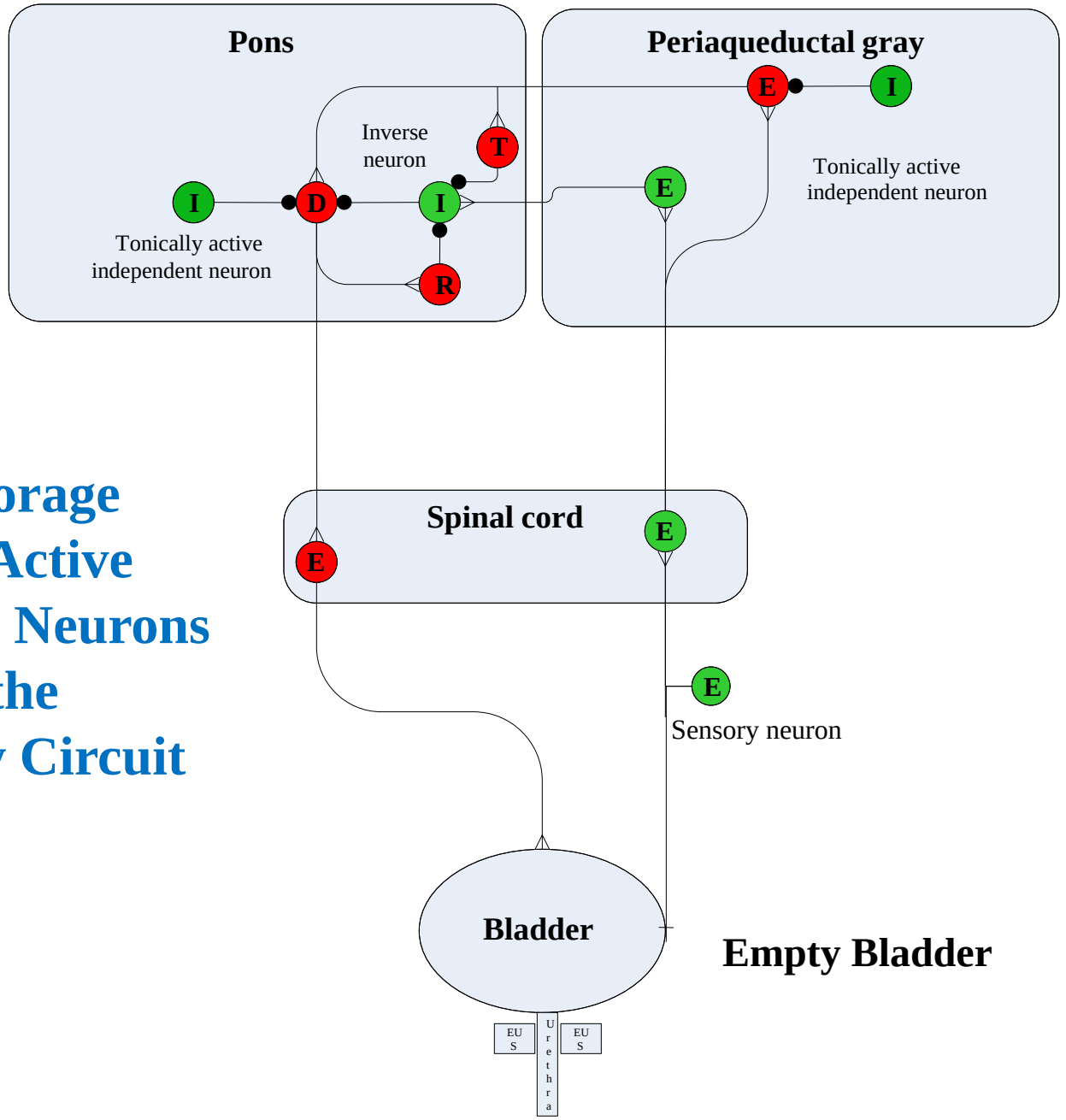
de Groat & Wickens, 2013

Combined Excitatory and Inhibitory Circuits

Circuits #1 & #2



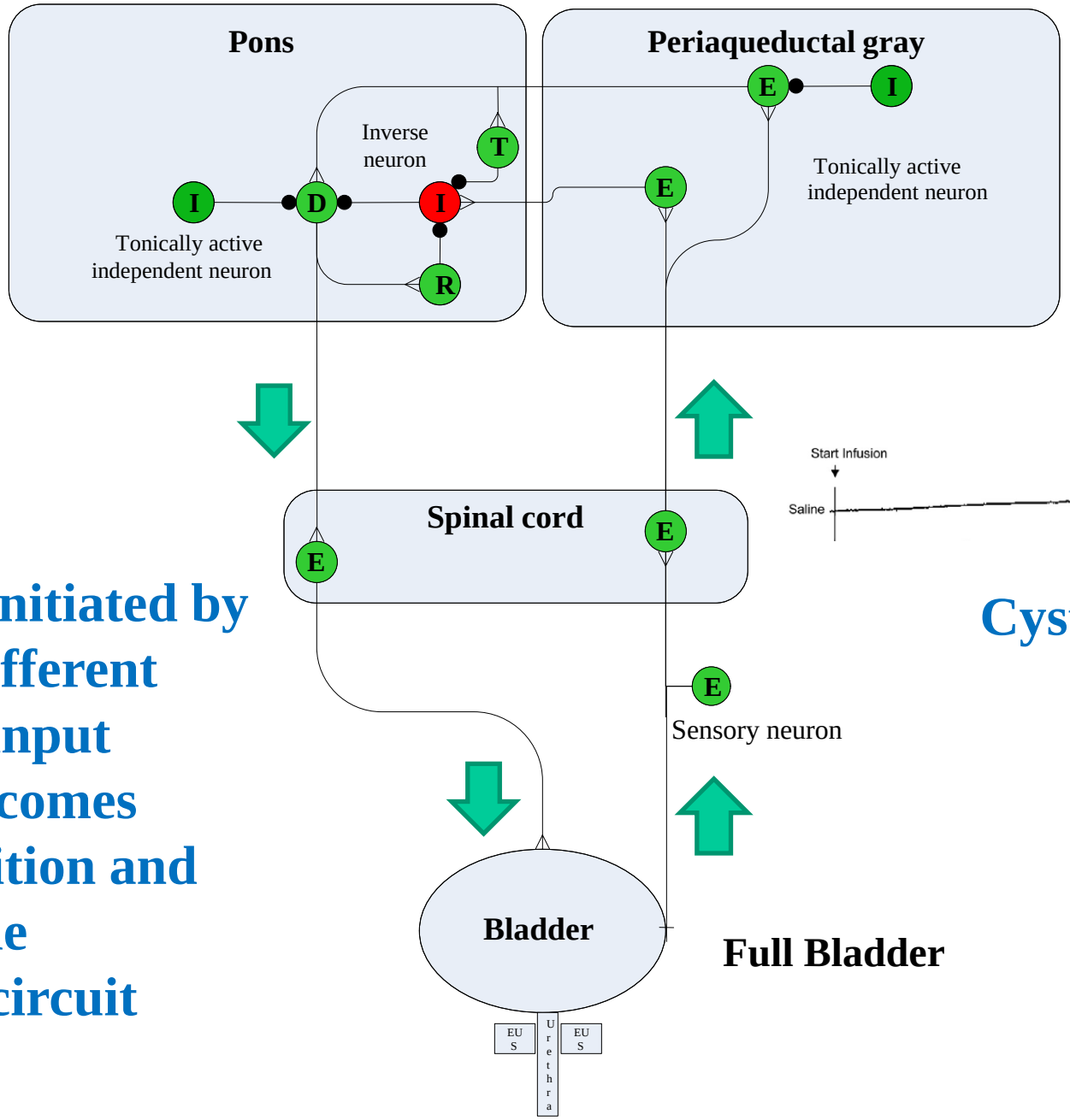
Storage



During Storage Tonically Active Inhibitory Neurons Suppress the Excitatory Circuit

Empty Bladder

Voiding

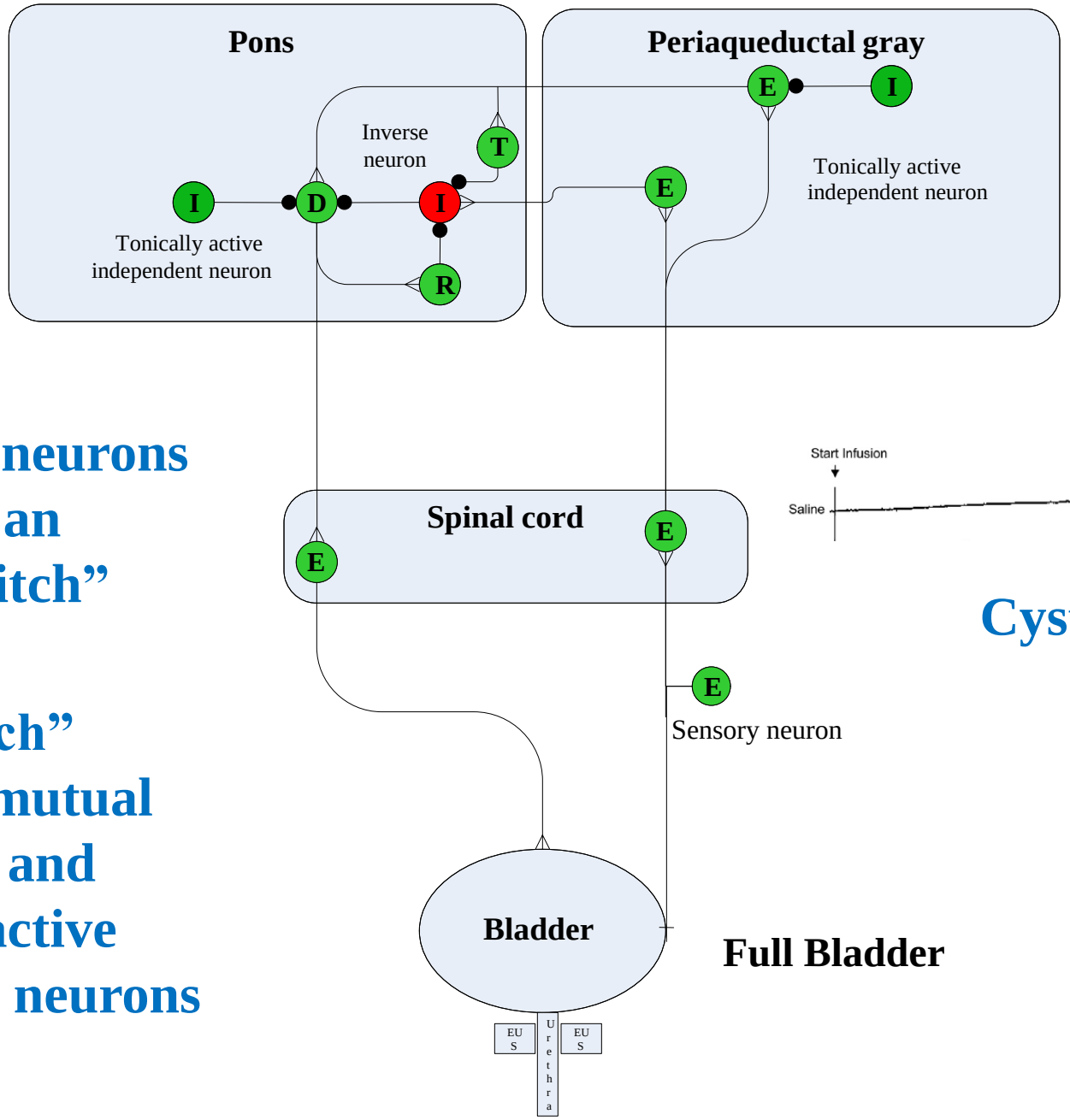


Cystometry

Full Bladder

Voiding is initiated by increased afferent excitatory input which overcomes tonic inhibition and turns off the inhibitory circuit

Voiding



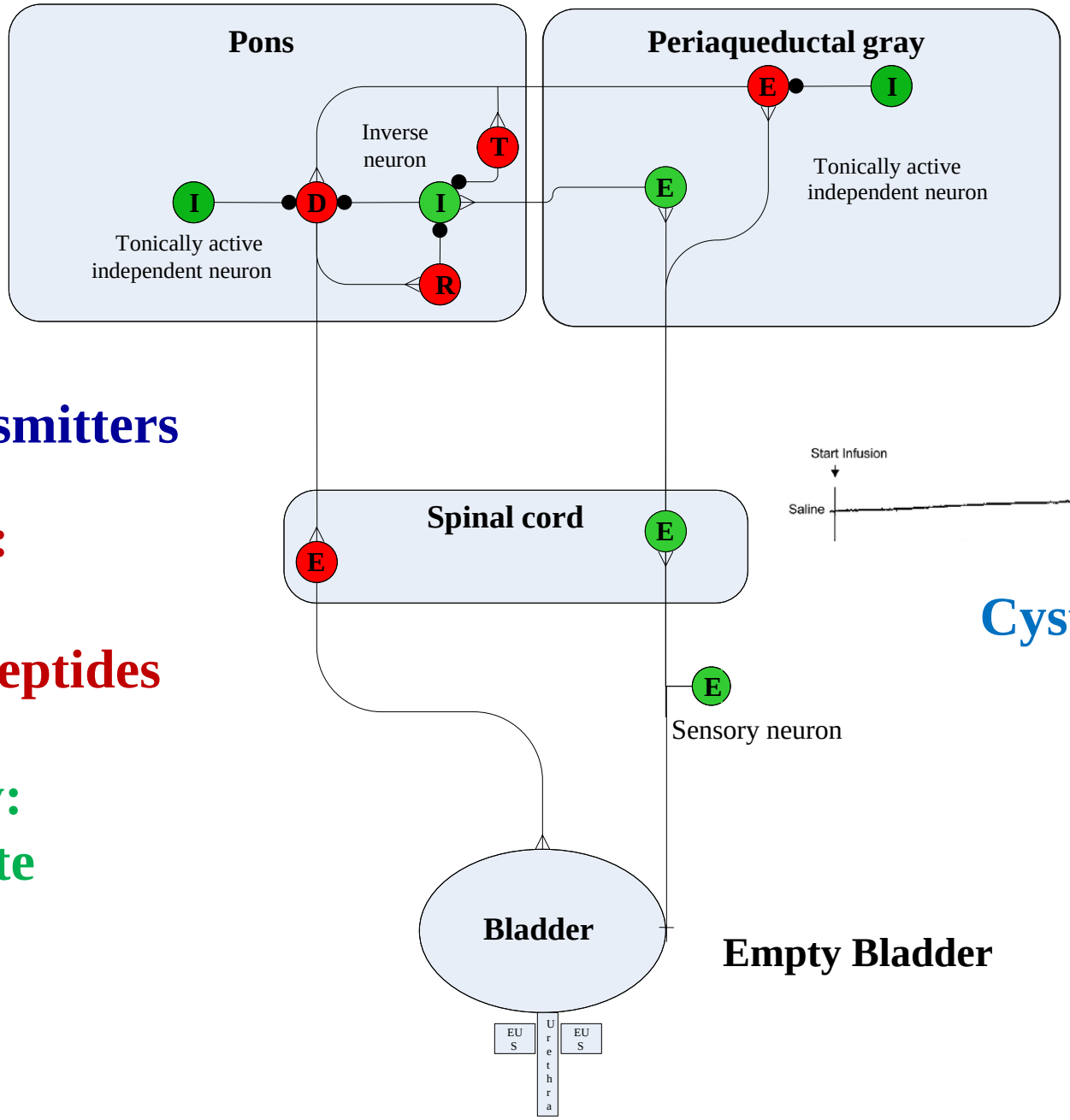
8 Types of neurons can create an "on-off switch"

Cystometry

The "switch" requires mutual inhibition and tonically active inhibitory neurons

Full Bladder

Storage



Neurotransmitters

Inhibitory:

- GABA
- Opioid peptides

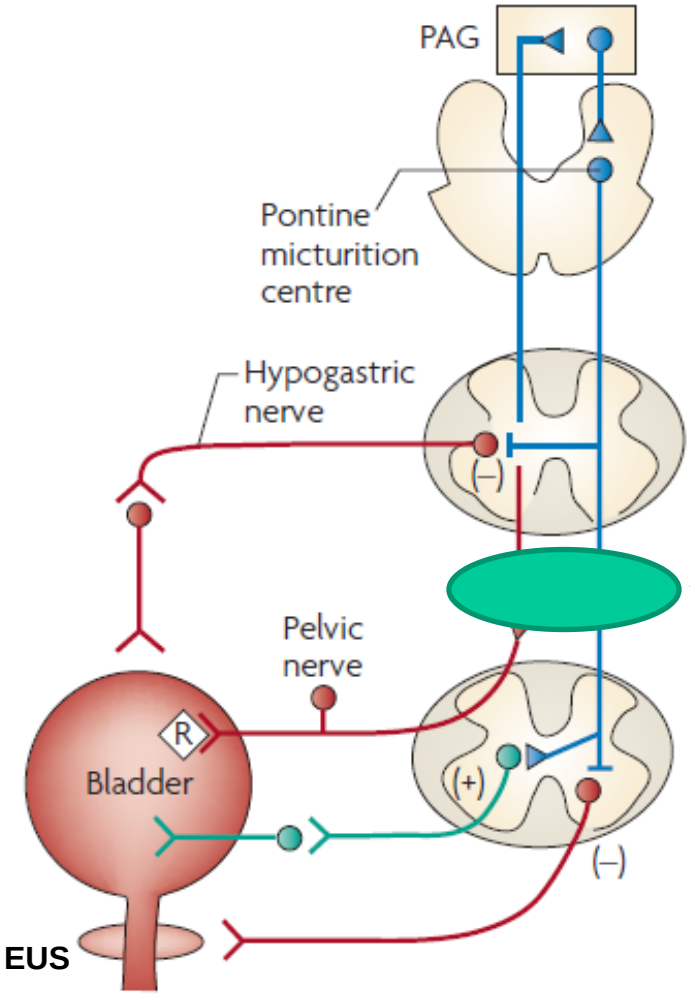
Excitatory:

- Glutamate

Cystometry

Empty Bladder

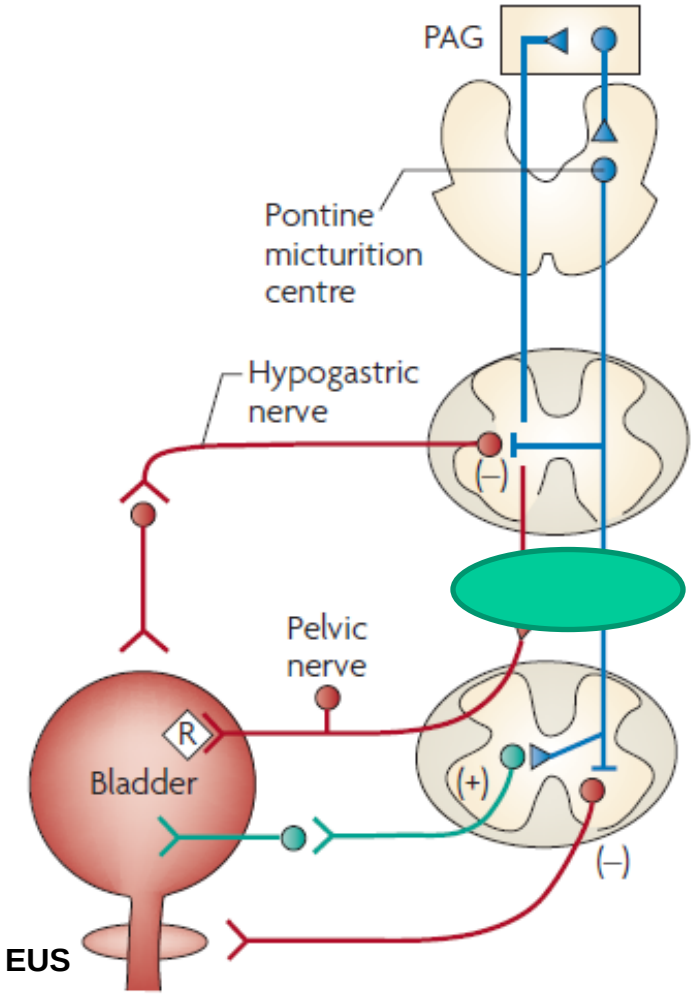
L3-L4 spinal cord is also involved in bladder and sphincter function



This region of the spinal cord has been ignored until recently because it does not contain autonomic neurons that innervate the bladder or motoneurons that innervate the uretharal sphincter

L3-L4 lumbar spinal cord

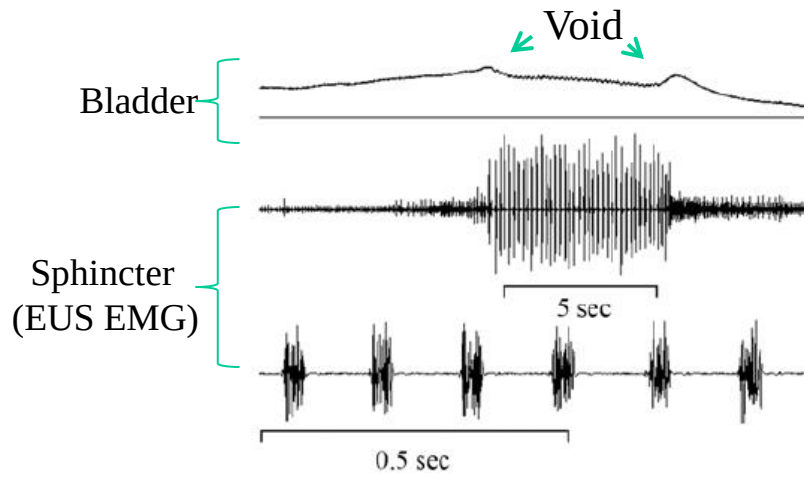
L3-L4 spinal cord contains a lumbar spinal coordinating center (LSCC)



Electrical stimulation in these segments induces phasic sphincter activity in rats

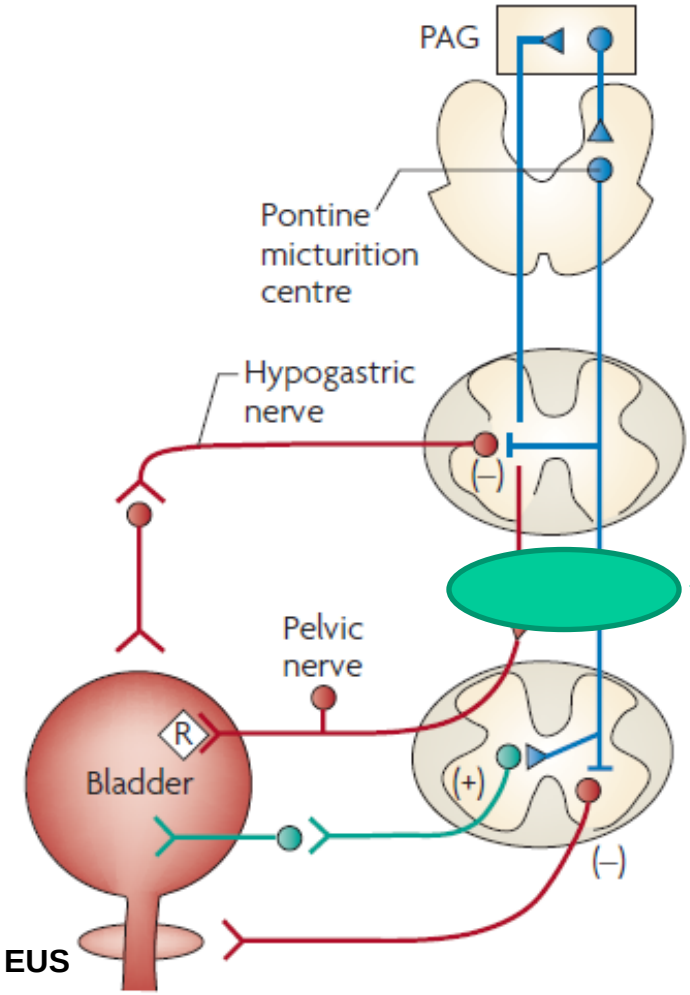
After spinal injury in rats L3-L4 lumbar spinal mechanisms are essential for coordinating bladder and sphincter activity.

LSCC



Chang, H. et al., AJP Renal 2007

L3-L4 spinal cord contains a lumbar spinal coordinating center (LSCC)



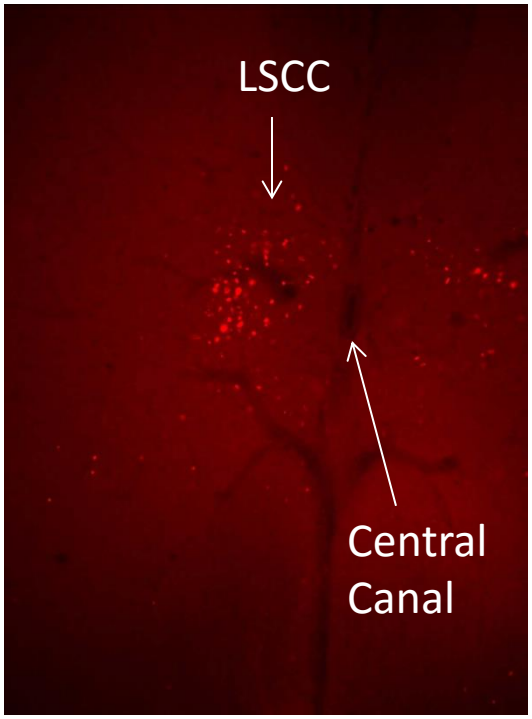
These segments of the cord also contain the central pattern generator for locomotion. Thus electrical epidural stimulation was applied in this region to improve motor function in spinal cord injured patients.

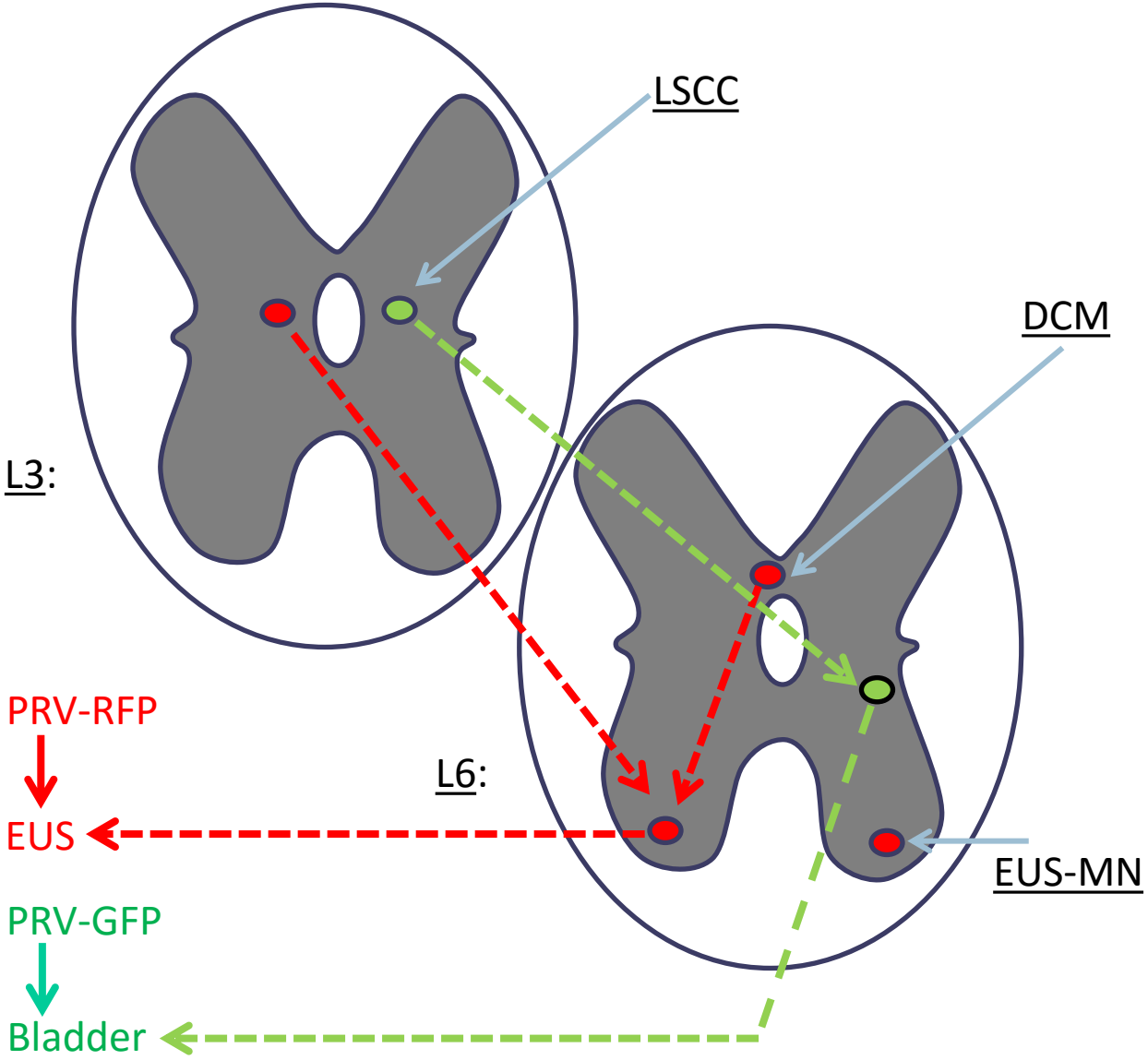
LSCC

Unexpectedly bladder function including voluntary voiding and bladder sensation also improved.

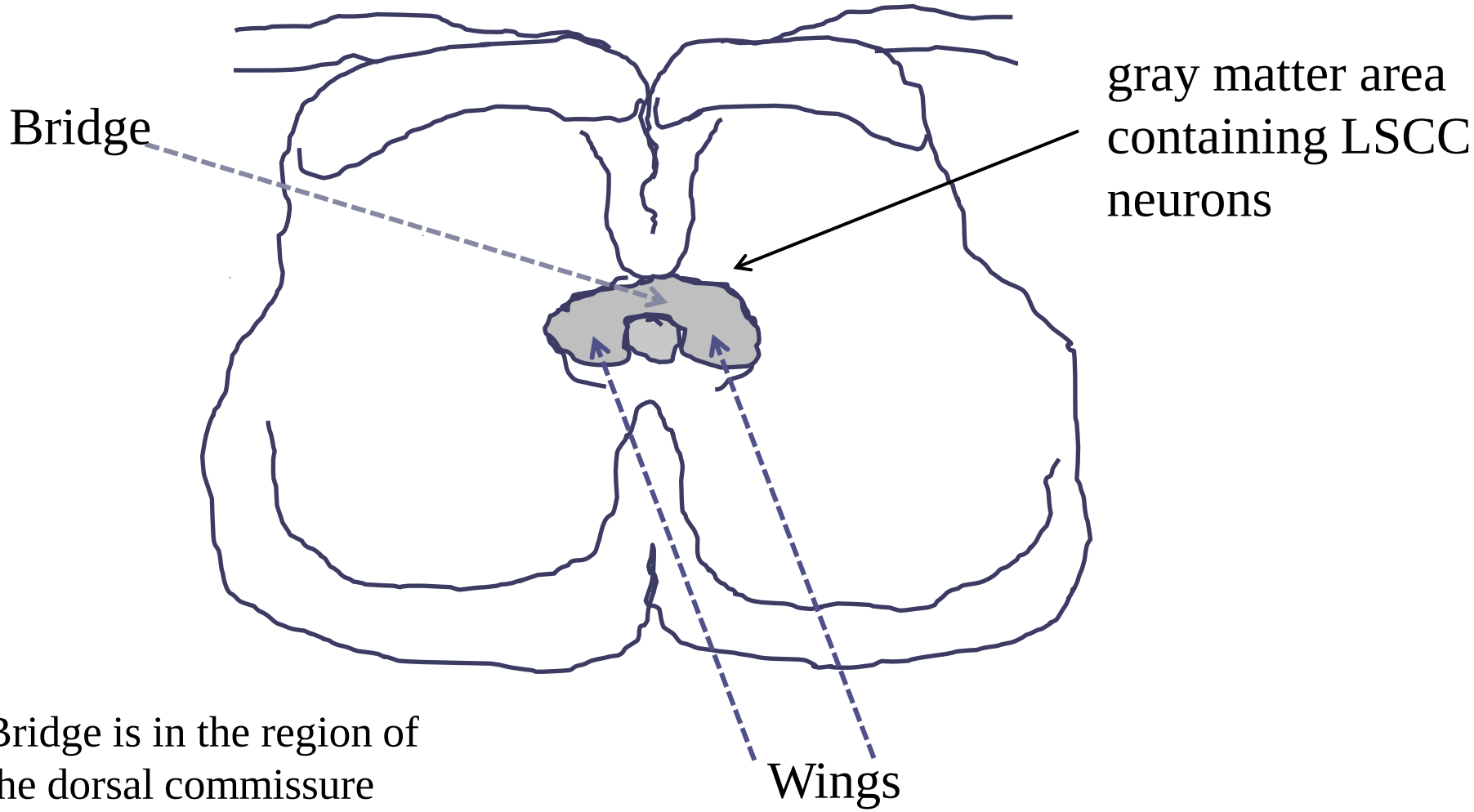
(Harkema et al., 2015)

Pseudorabies Virus (PRV) Transneuronal Tracing

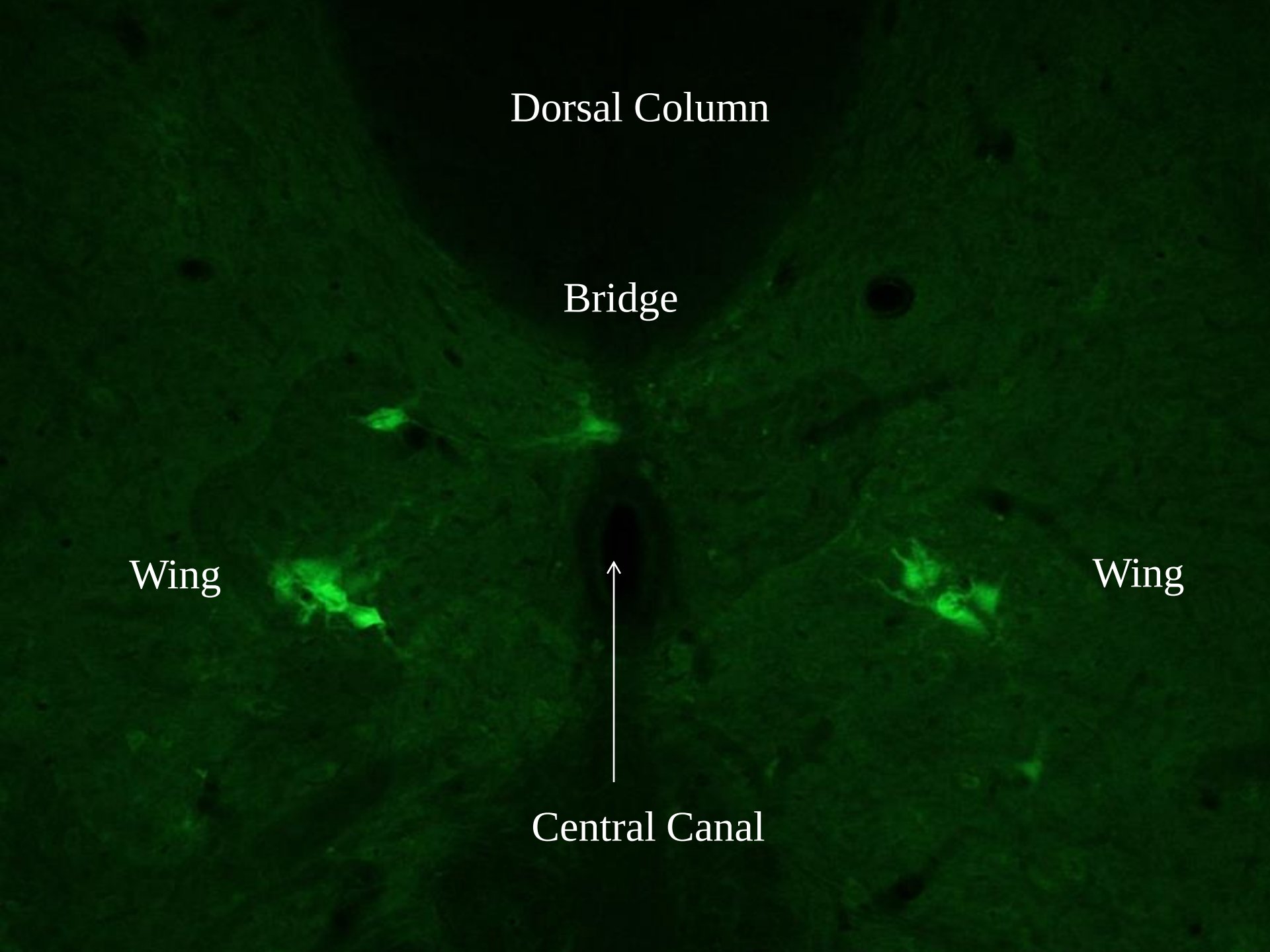




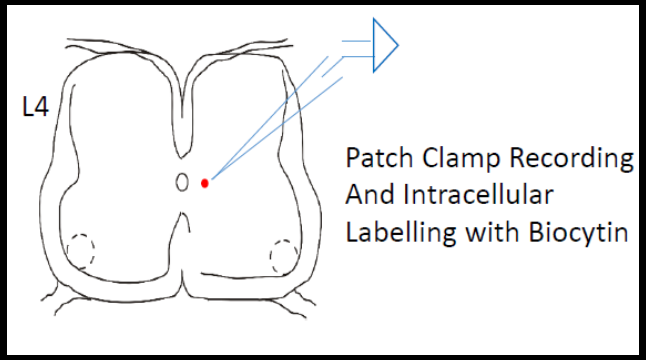
RFP: Red Fluorescent Protein
GFP: Green Fluorescent Protein

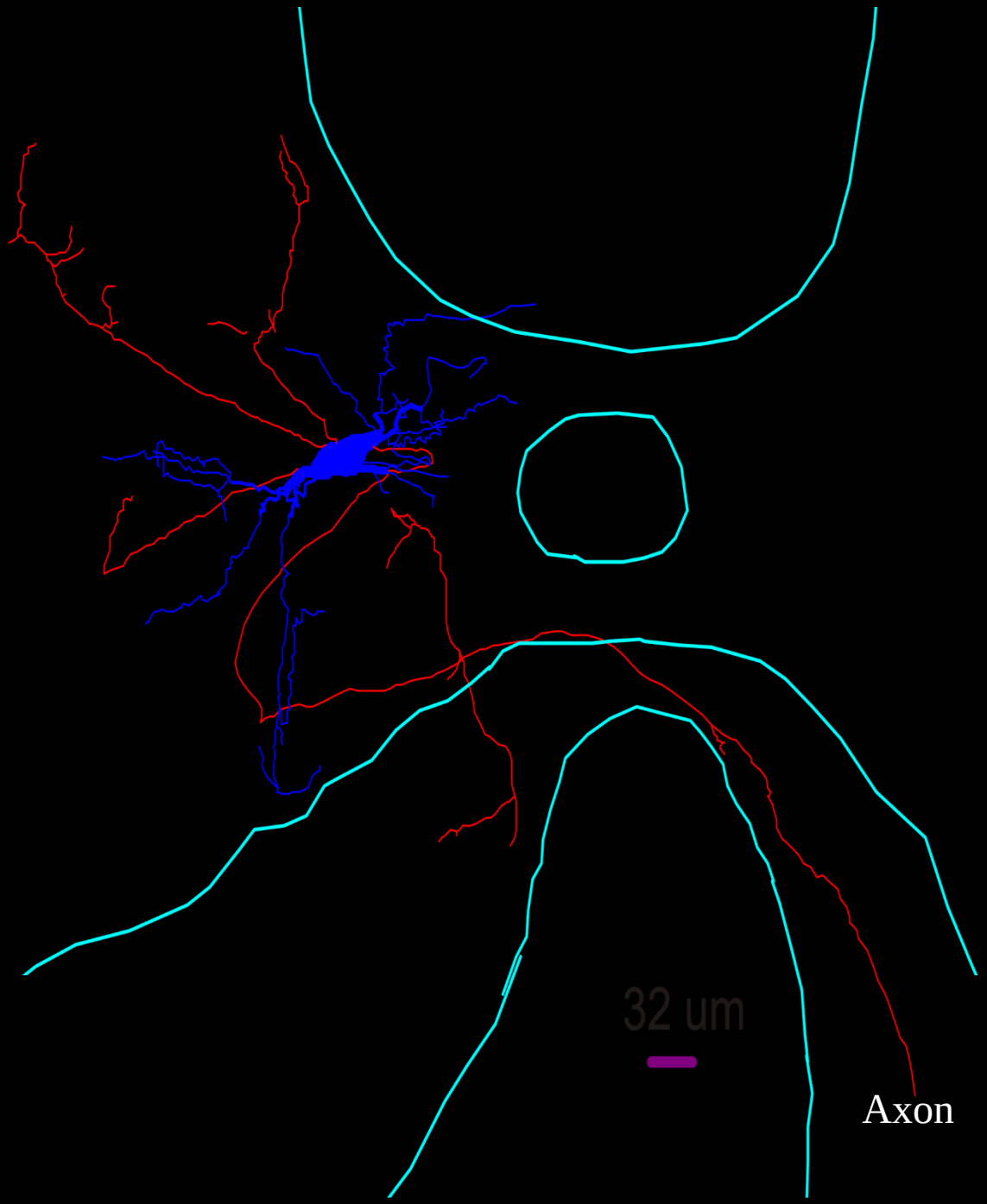


Transverse slice of the spinal cord
(P20-P24)

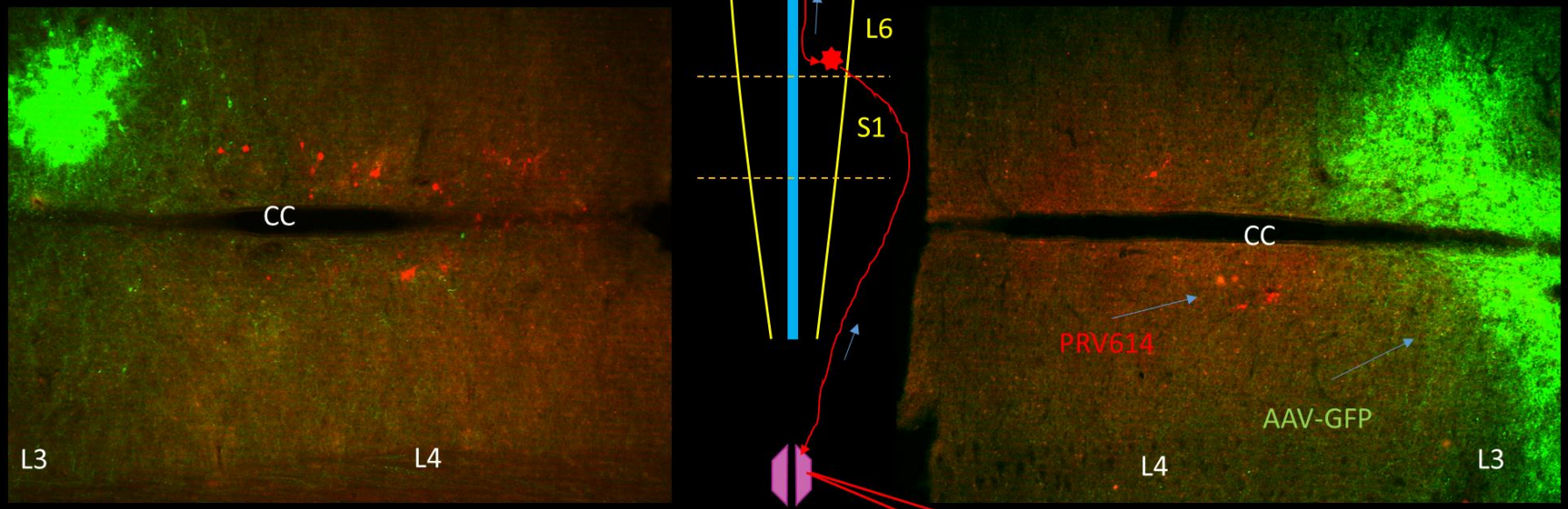

Dorsal Column
Bridge
Wing
Wing
Central Canal


32 um

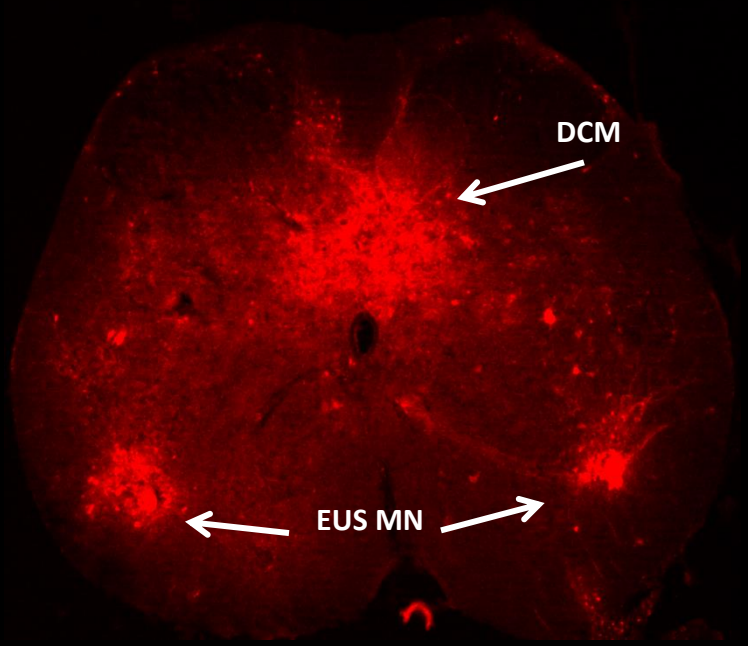

L4
Patch Clamp Recording
And Intracellular
Labelling with Biocytin

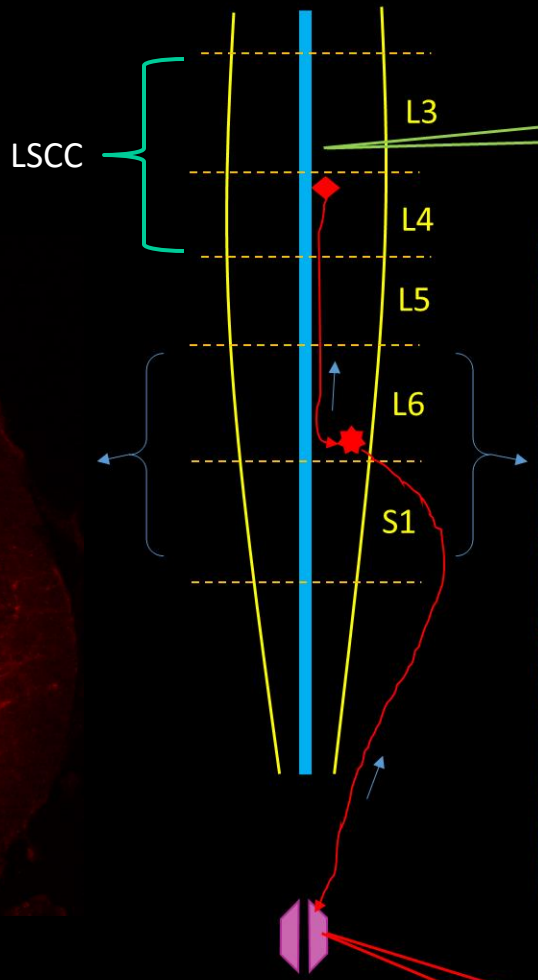

32 um
Axon

Horizontal L4-L3 sections at CC level
in two different rats (both P65)
with clouds of viral infection

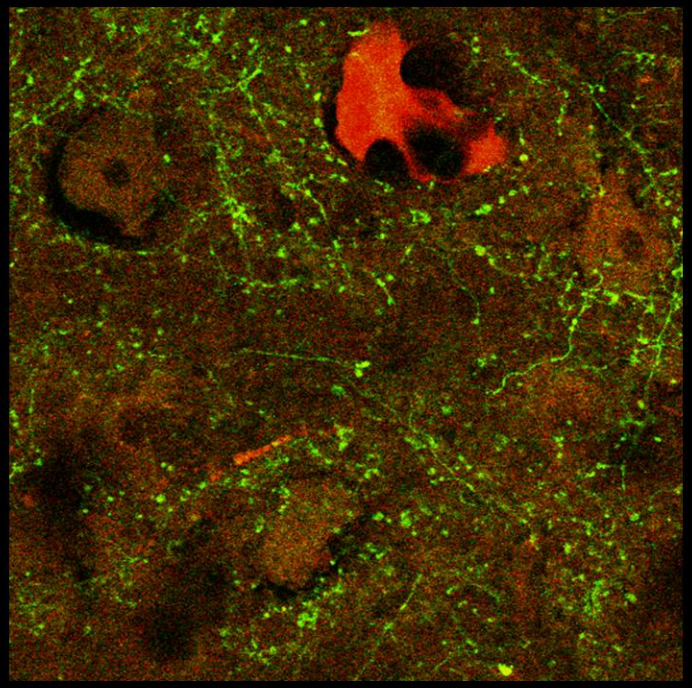


PRV-RFP Labelling in L6 spinal cord

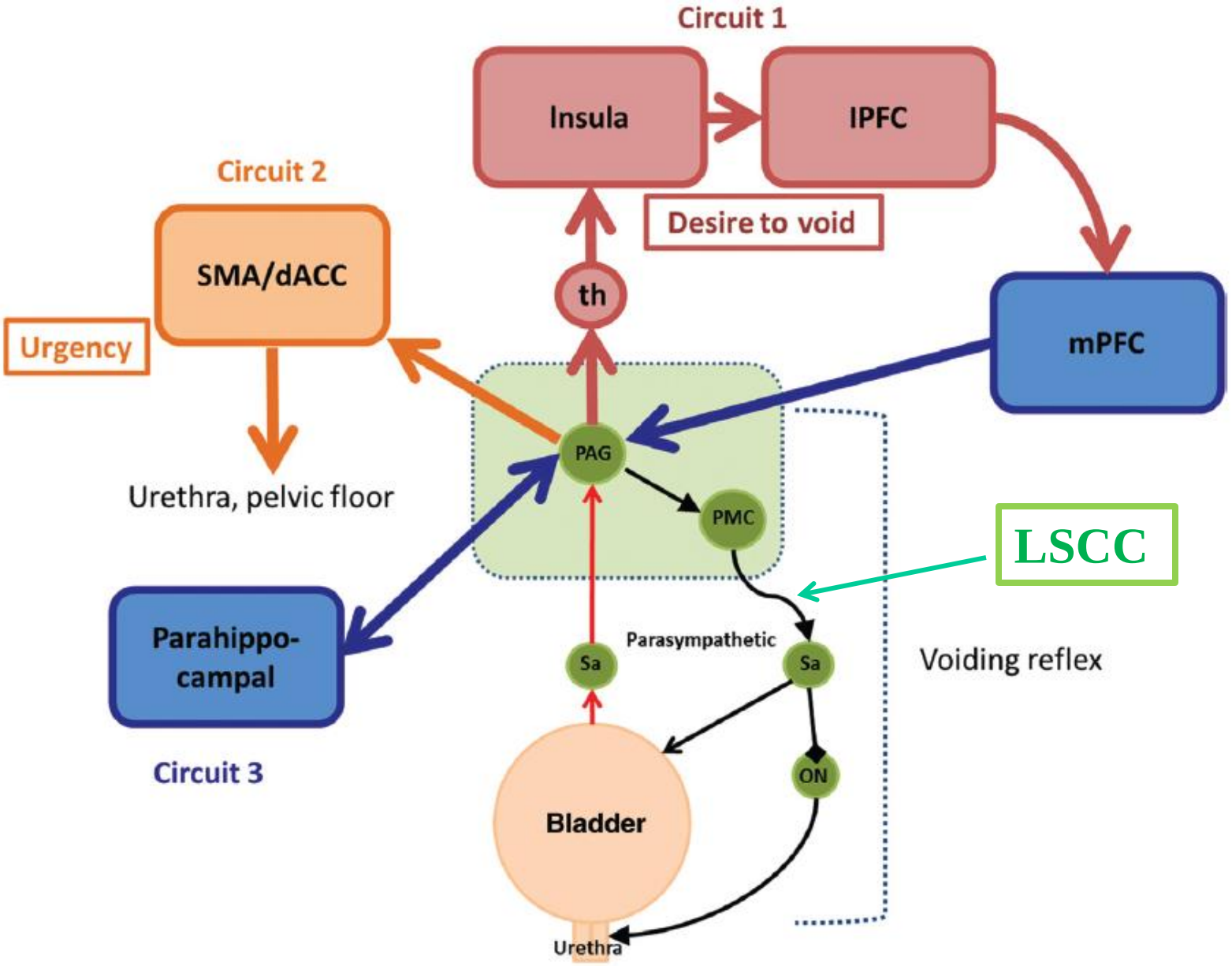




Neurons infected with AAV-GFP in L3-L4 project their axons down into L6-S1. Dense axonal ramification within Onuf's nucleus suggests synaptic contacts with motoneurons.



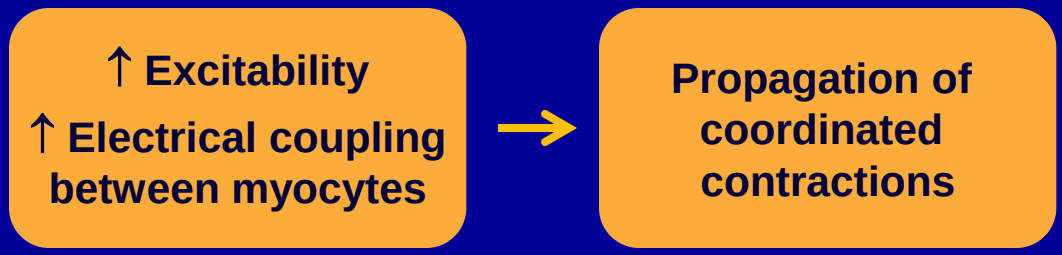
PRV614-RFP in EUS reveals EUS-related propriospinal neurons in L3-L4



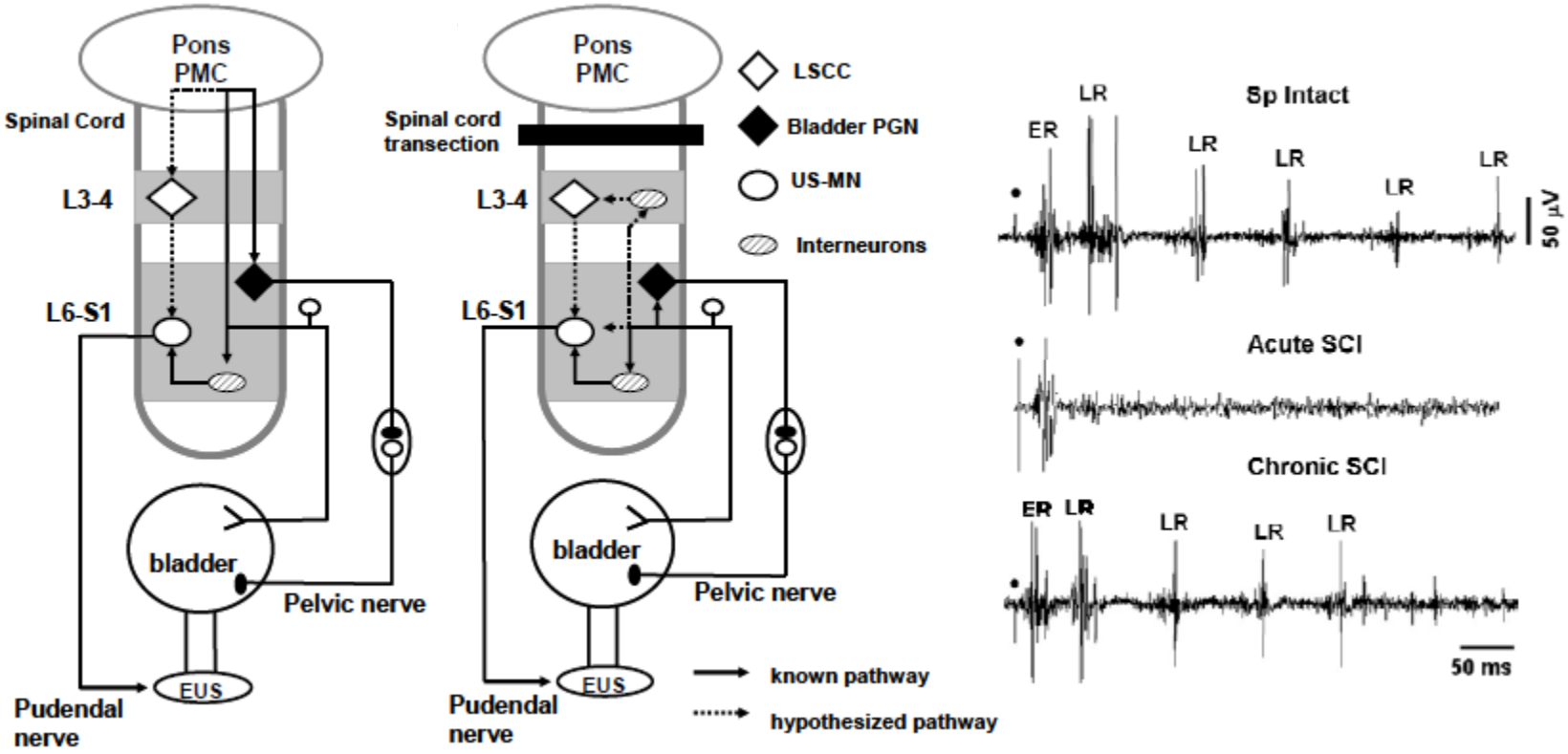
de Groat, Griffiths & Yoshimura, 2015

Conclusions

- The etiology of OAB is uncertain but may be neurogenic, myogenic, or both
- Neurogenic theory
  - —Reduced pontine or suprapontine inhibition
  - —Damaged axonal paths in the spinal cord and/or brain
  - —Increased primary afferent input
  - —Loss of peripheral or spinal inhibition
  - —Enhanced excitatory neurotransmission in the micturition reflex pathway
- Myogenic theory

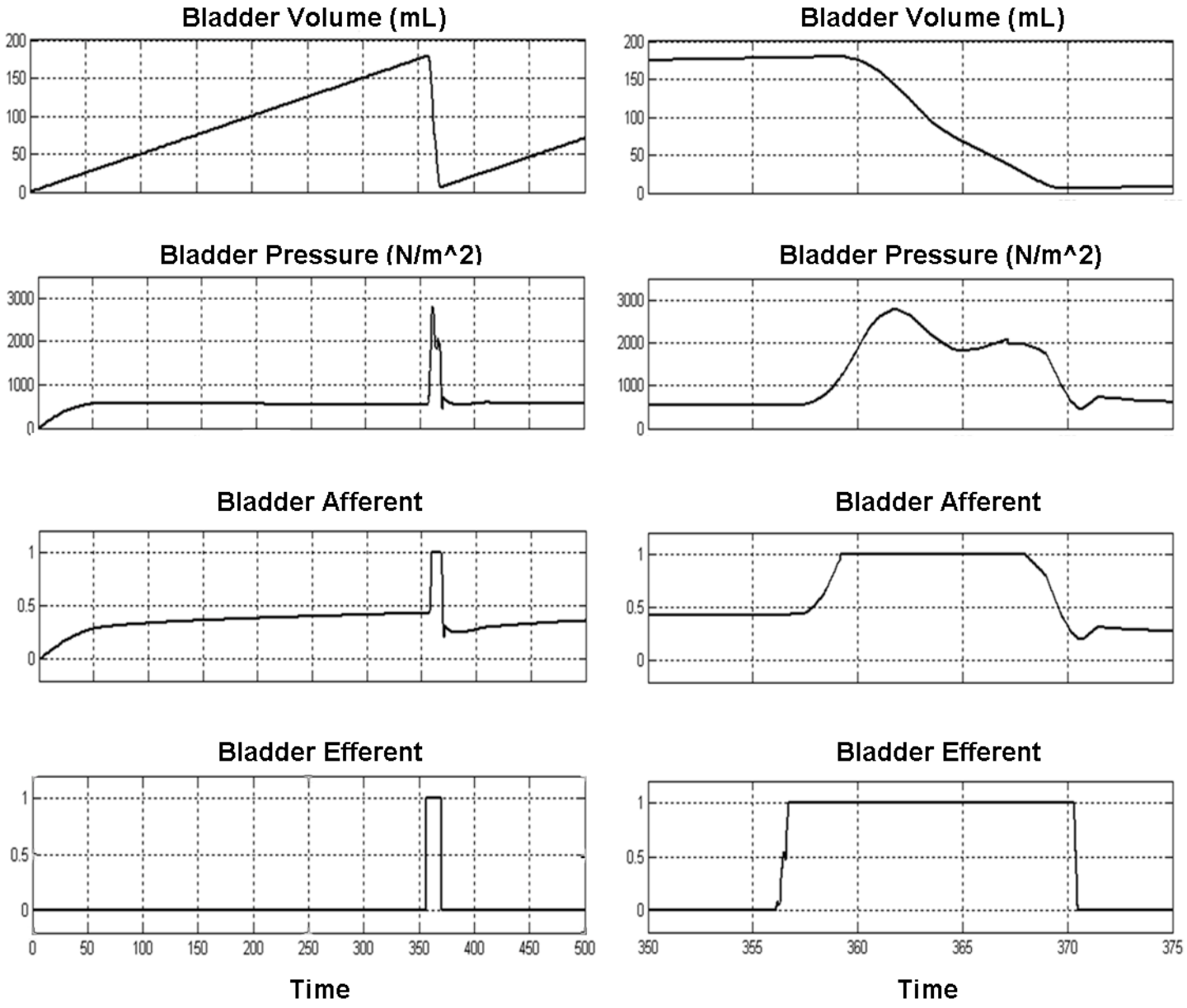


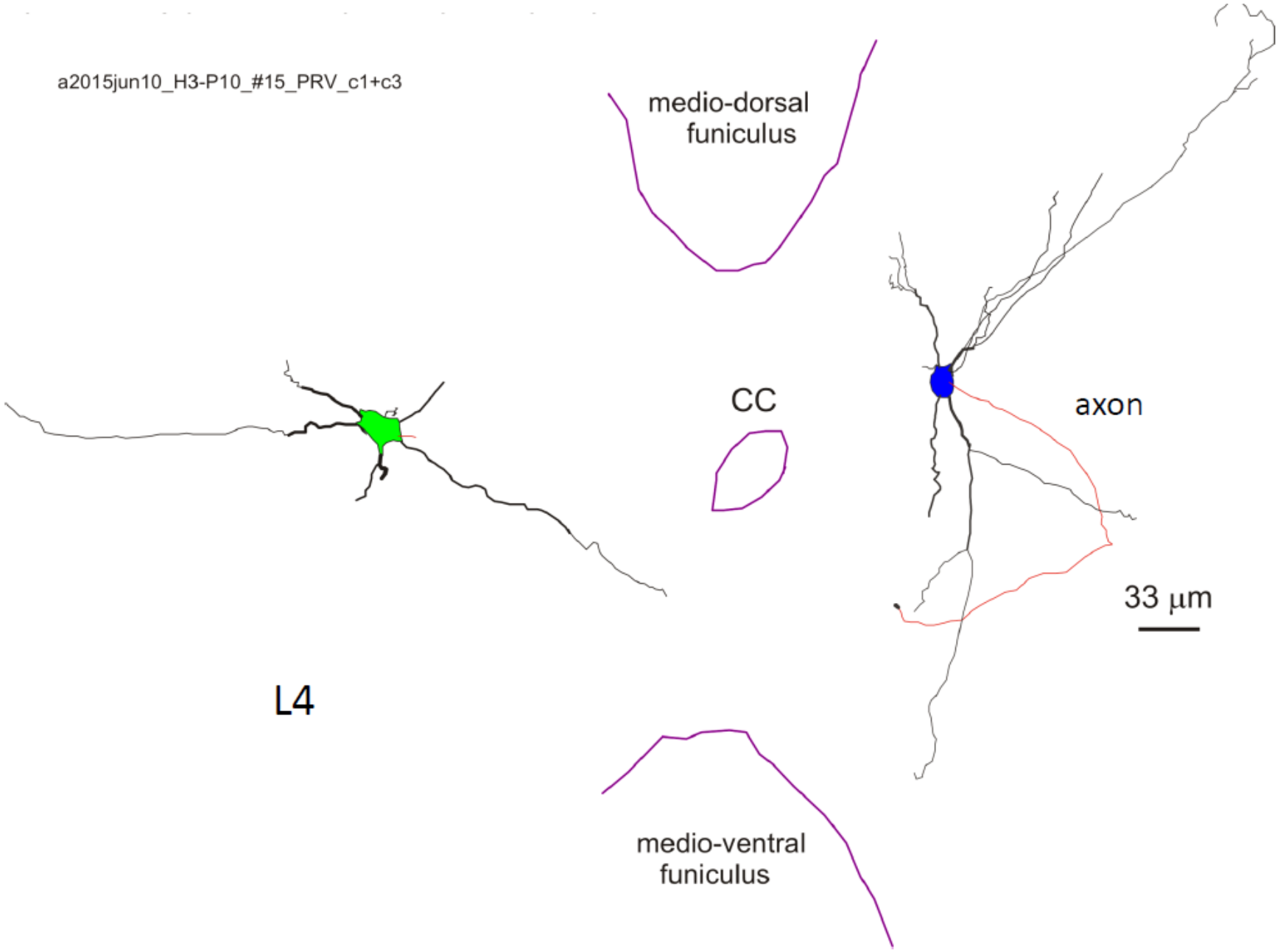
Spinal And Supraspinal EUS Reflex Mechanisms

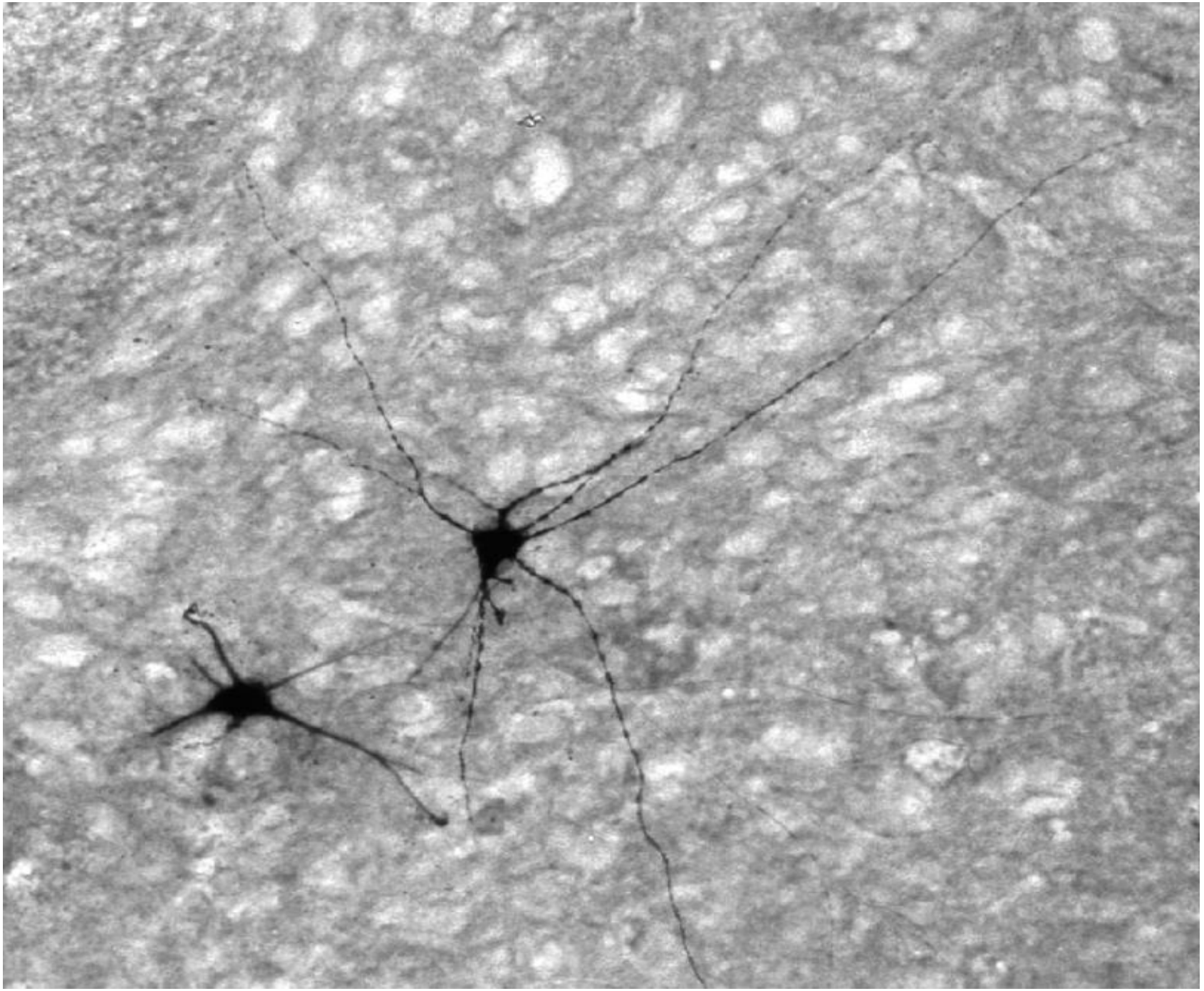


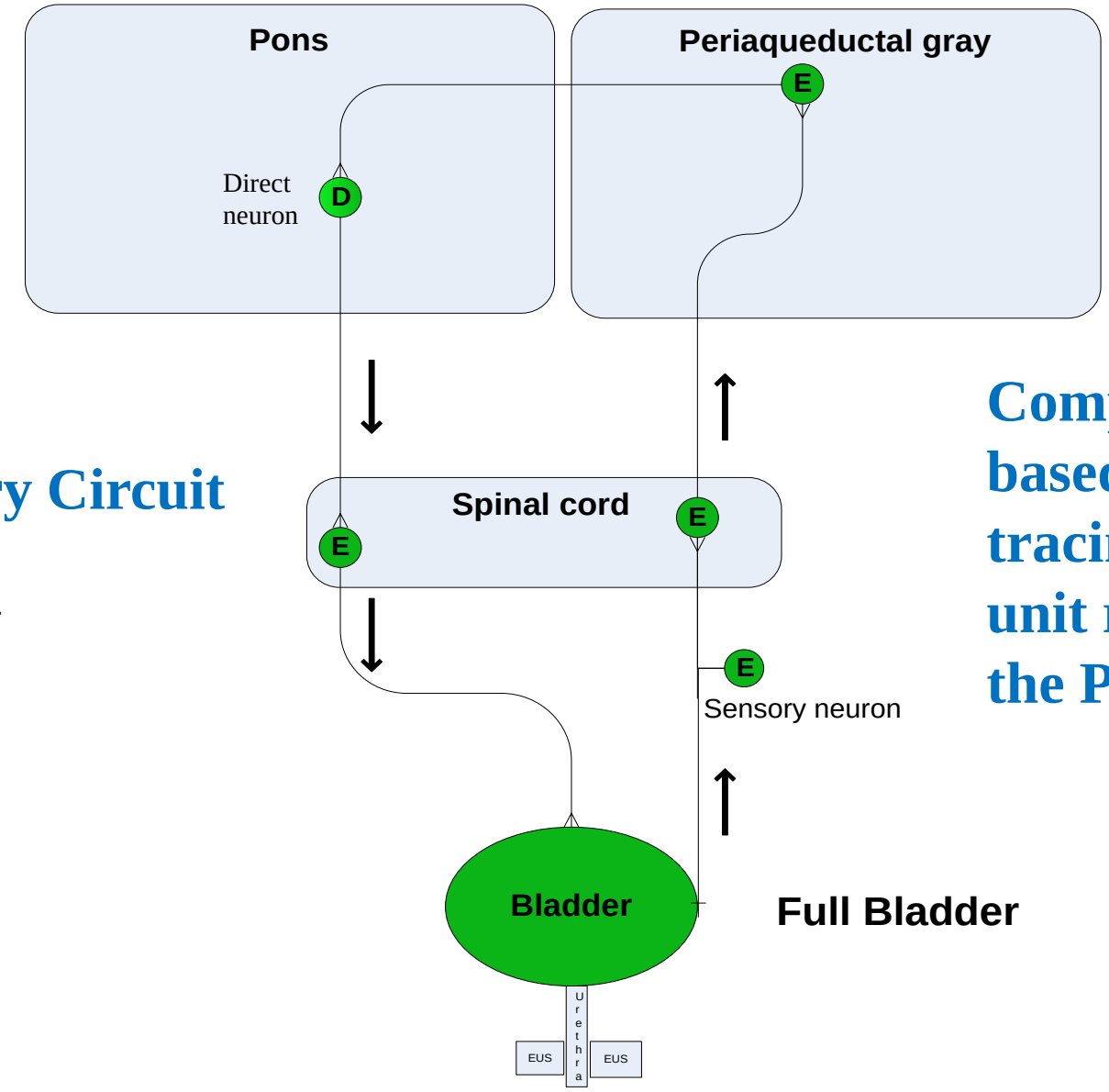
Spinal Bursting Mechanism in the L3-L4 Spinal Cord

Chang, H., et al., AJP Renal 2007


Bladder Volume (mL)
200
150
100
50
0
Bladder Volume (mL)
200
150
100
50
0
Bladder Pressure (N/m^2)
3000
2000
1000
0
Bladder Pressure (N/m^2)
3000
2000
1000
0
Bladder Afferent
1
0.5
0
Bladder Afferent
1
0.5
0
Bladder Efferent
1
0.5
0
0
50
100
150
200
250
300
350
400
450
500
Time
Bladder Efferent
1
0.5
0
350
355
360
365
370
375
Time


a2015jun10_H3-P10_#15_PRV_c1+c3
medio-dorsal
funiculus
CC
axon
33 µm
L4
medio-ventral
funiculus





Excitatory Circuit

Circuit #2

Computer model based on axonal tracing and single unit recordings in the PMC and PAG

de Groat & Wickens, 2013