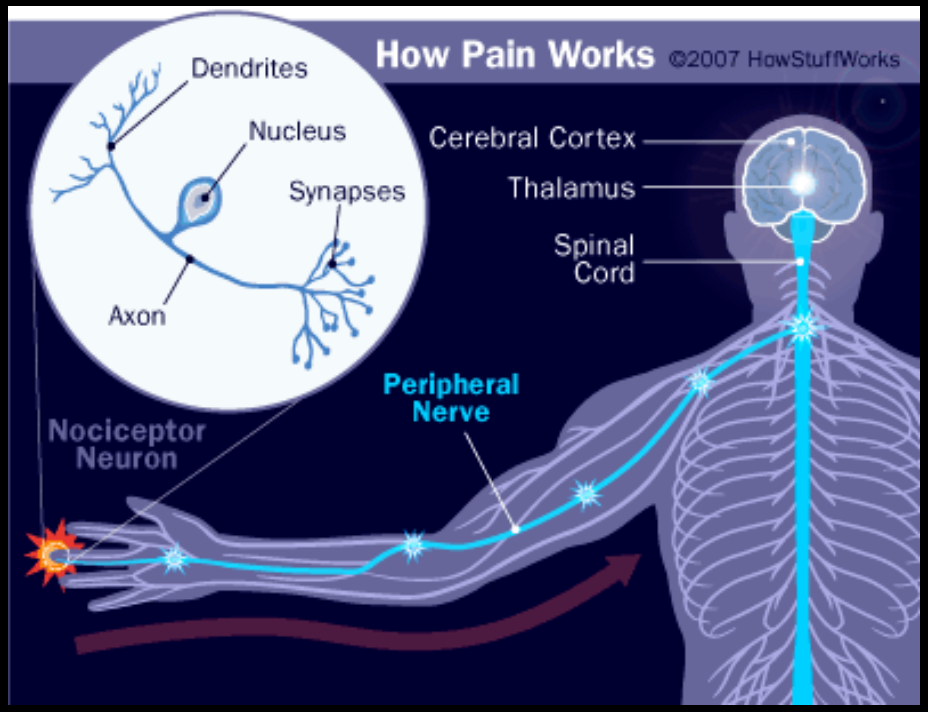
Study of nociceptive processing in the isolated spinal cord and brainstem

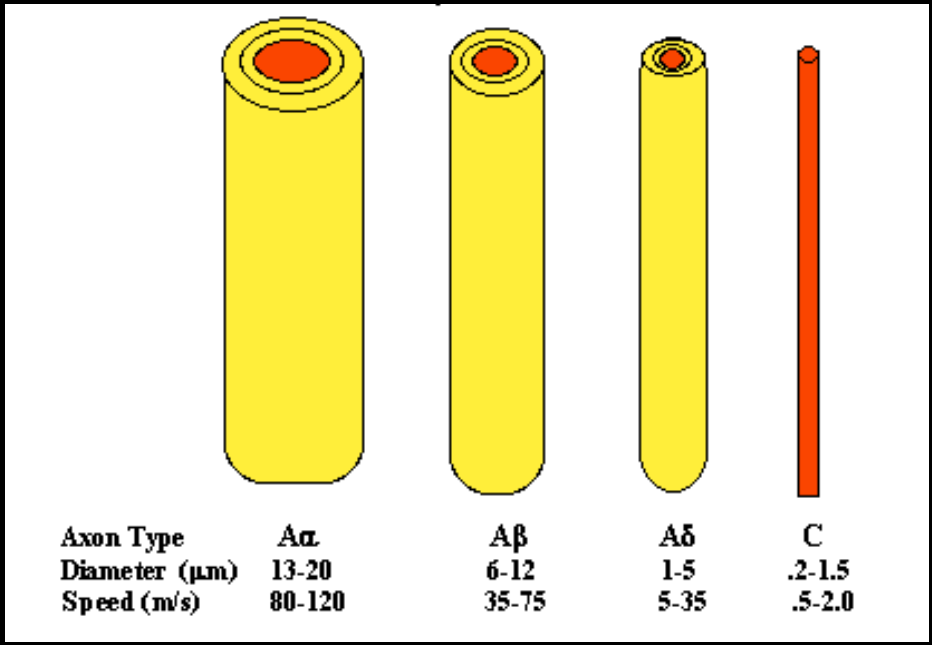
Boris Safronov

Instituto de Biologia Molecular e Celular,
Porto, Portugal

Pain processing pathways

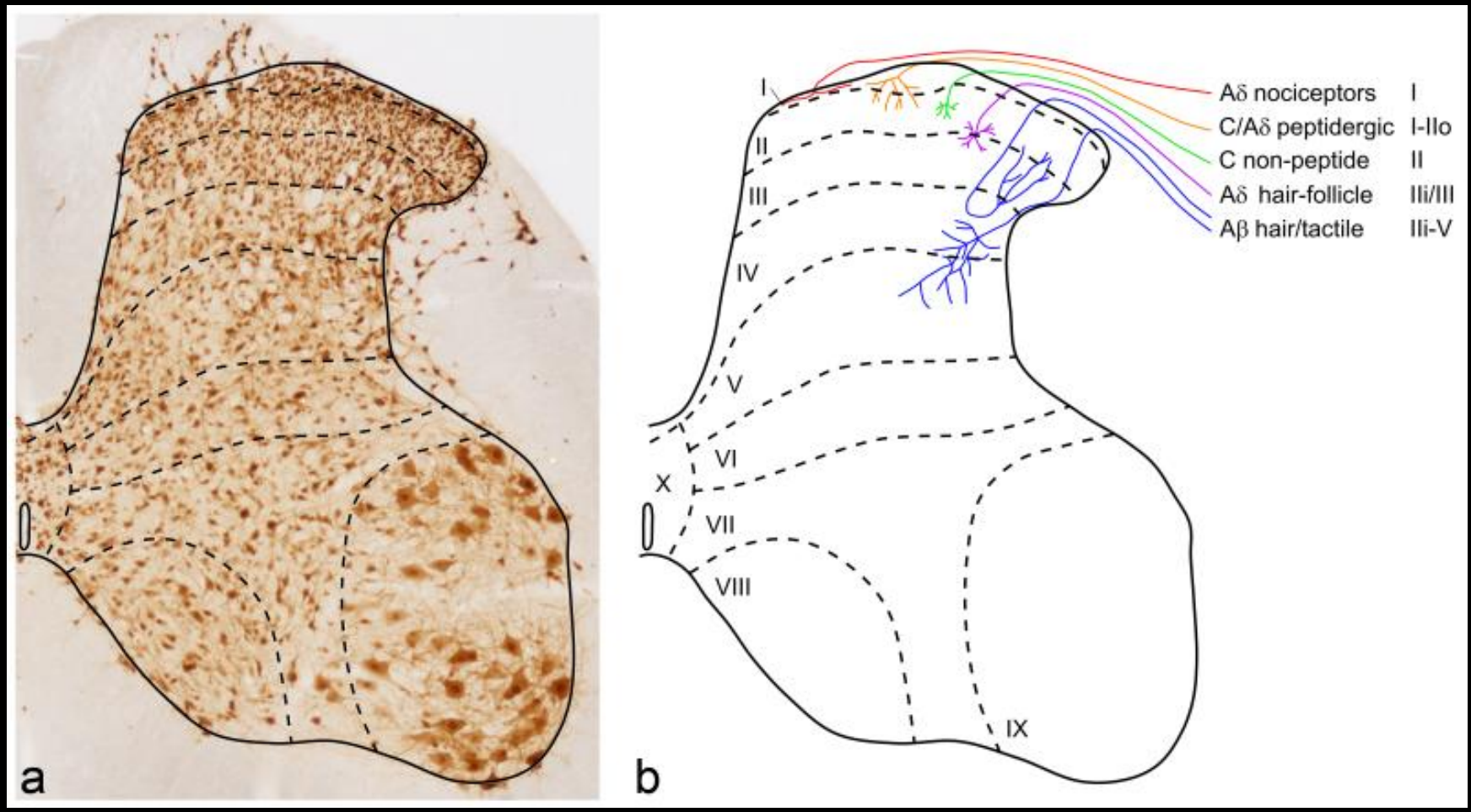


Primary afferent fibers

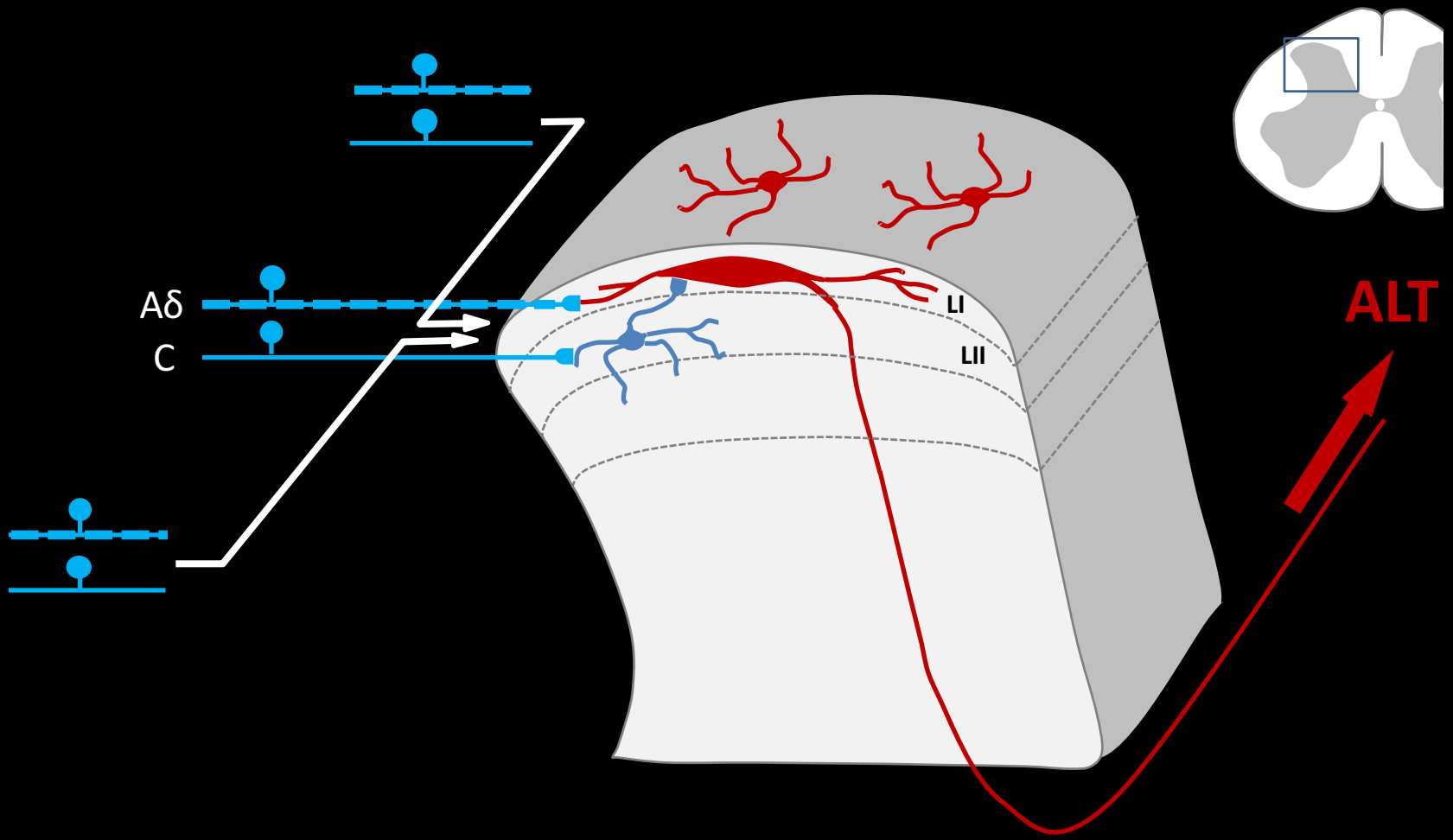


Axon Type	Aα	Aβ	Aδ	C
Diameter (μm)	13-20	6-12	1-5	.2-1.5
Speed (m/s)	80-120	35-75	5-35	.5-2.0

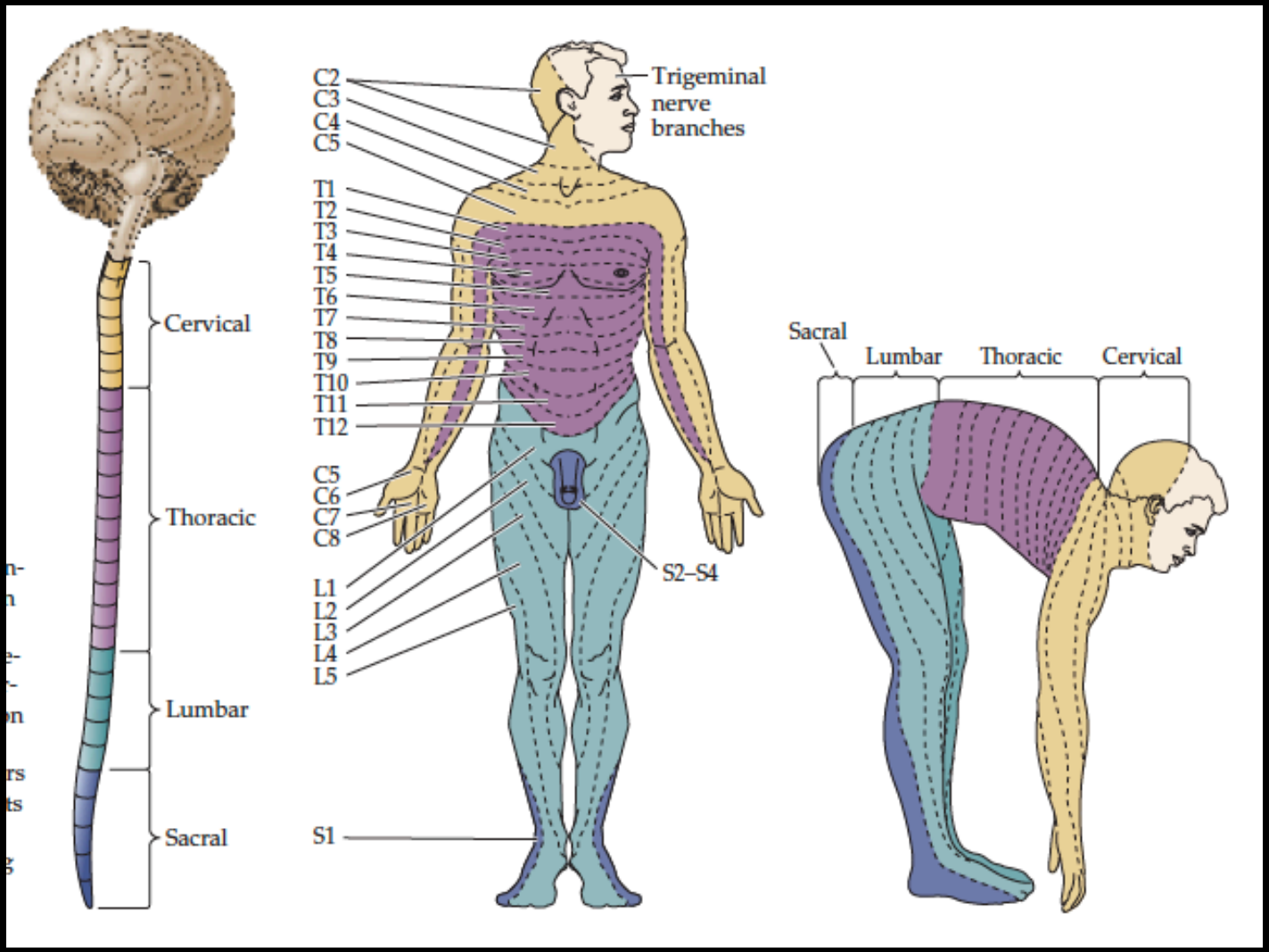
Nociceptors project to laminae I-II



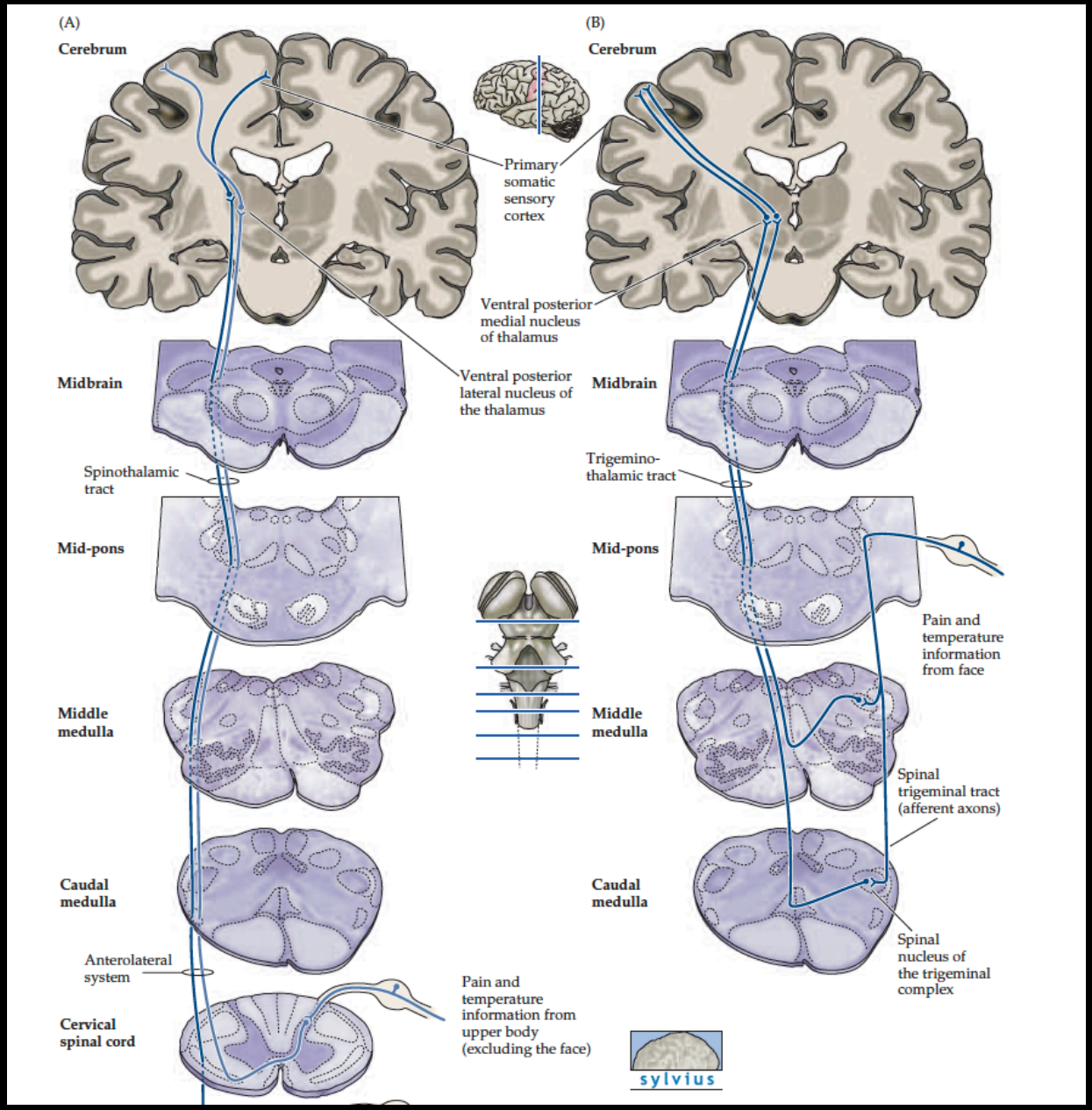
The superficial dorsal horn (laminae I-II)



Innervation areas of dorsal roots and trigeminal nerve



Spinal and trigeminal pain-processing pathways

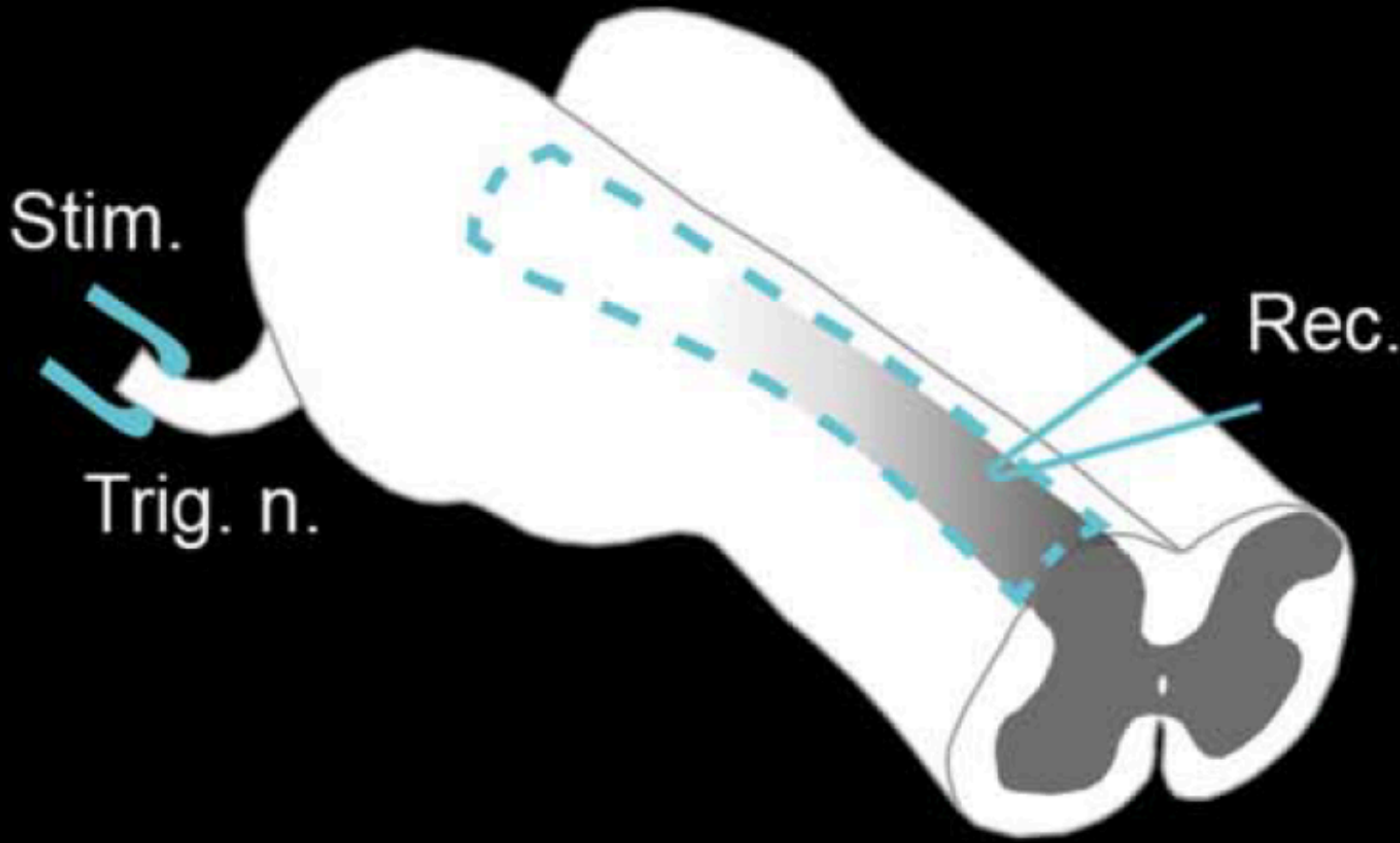


Segmental
L5 ➡ L5

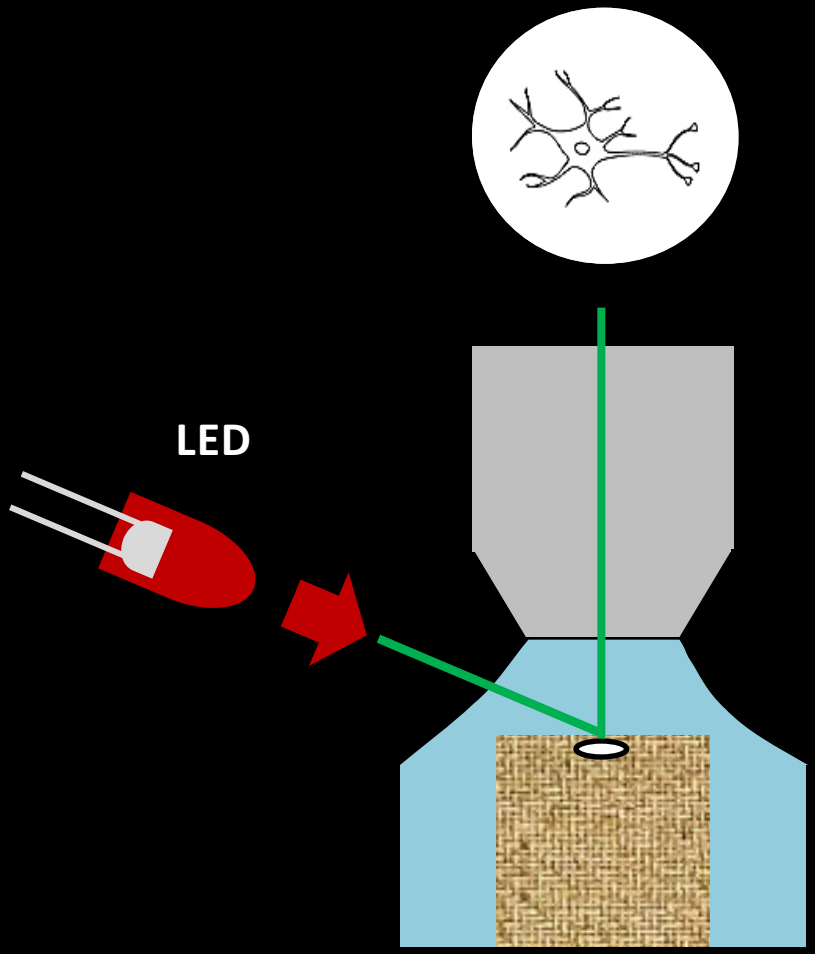
TN

TNC
C1-C2

The preparation should be ….



Cell imaging in thick tissues: The basic idea

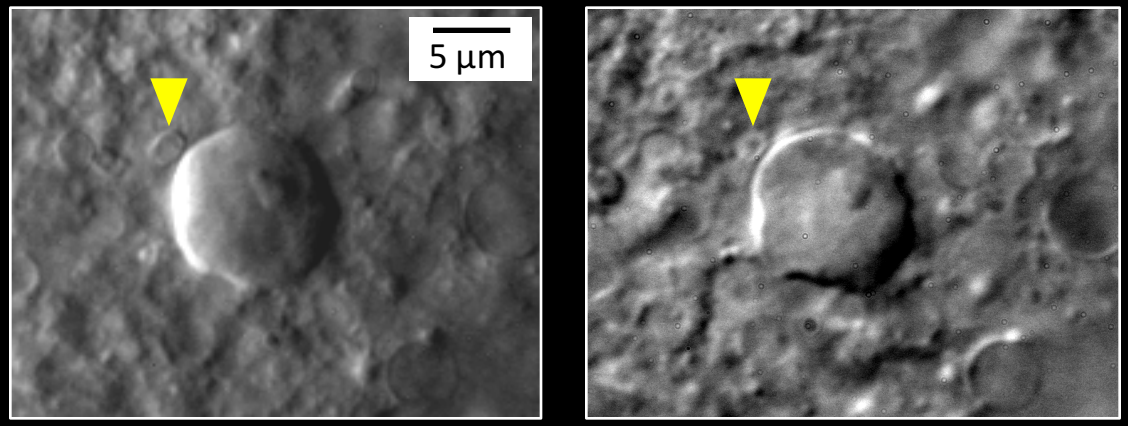


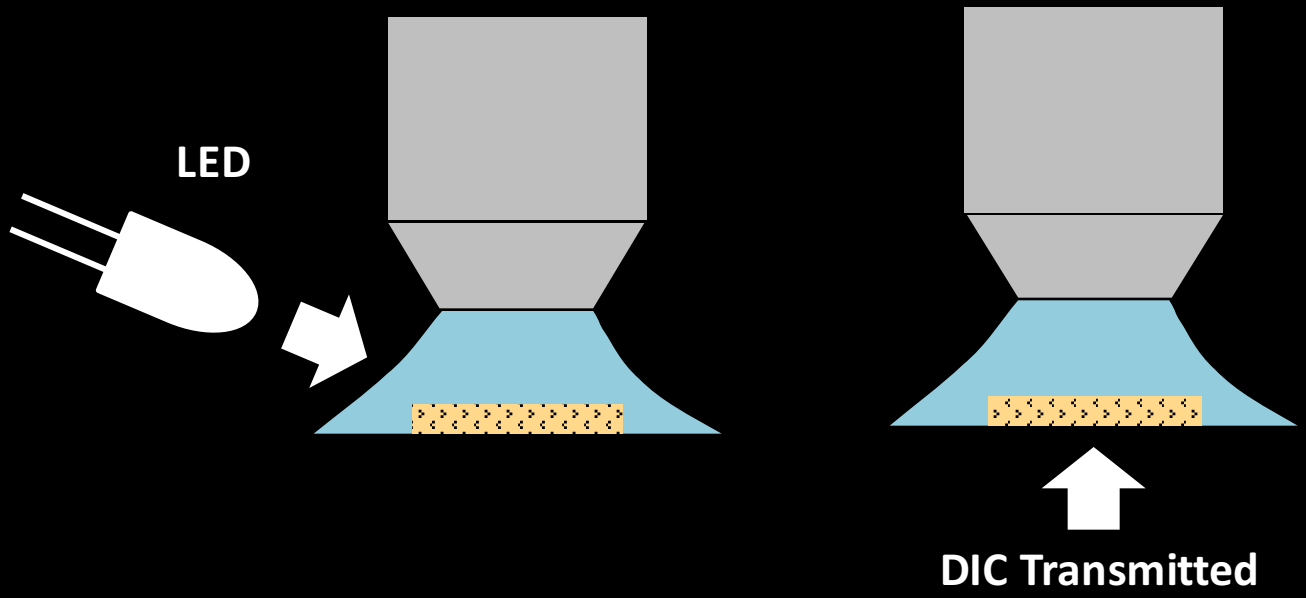
The Fresnel equation

Refractive indices n_1=1.33 n_2=1.35

Angle

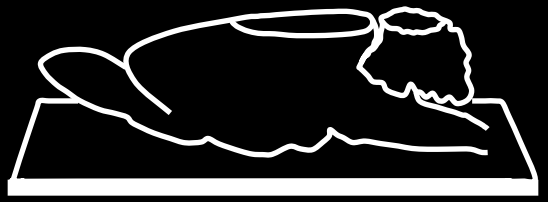
LED *versus* DIC in a 200-µm slice





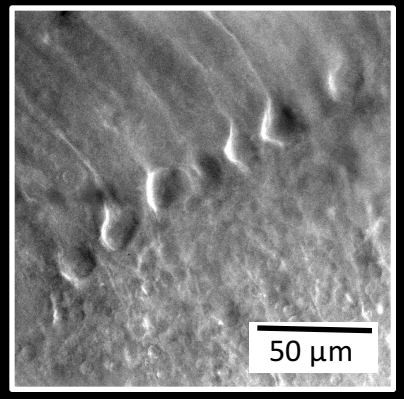
Oblique LED illumination

Whole brain

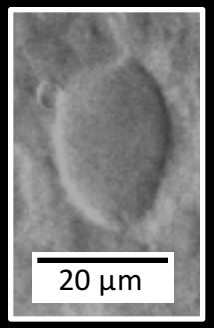


metal plate

cerebellar cortex

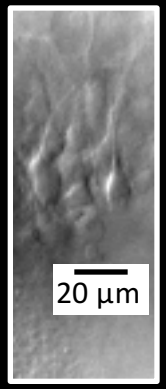


Purkinje cell layer



soma

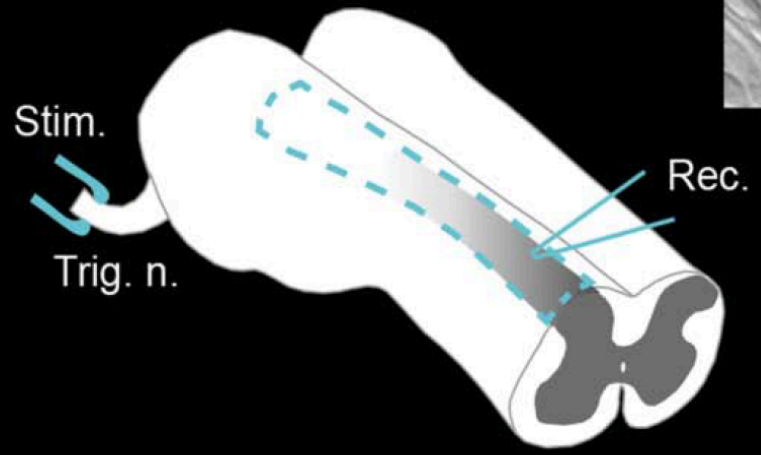
cerebral cortex

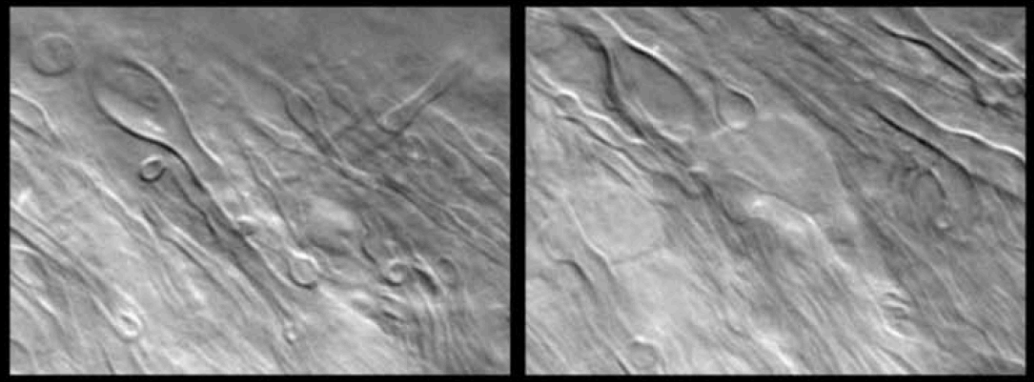


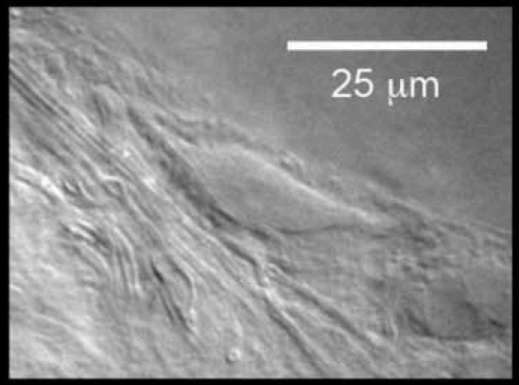
cell layer

soma

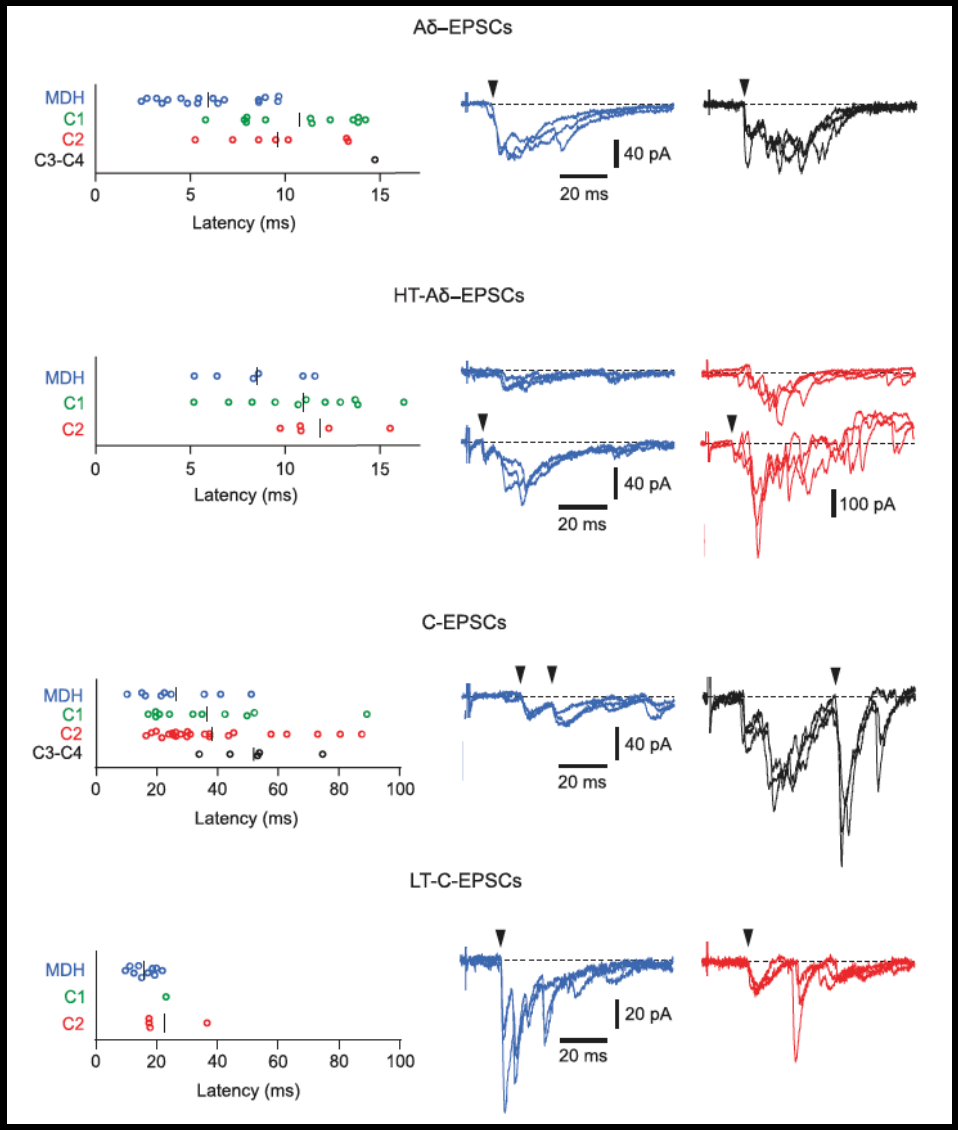
The trigeminocervical complex



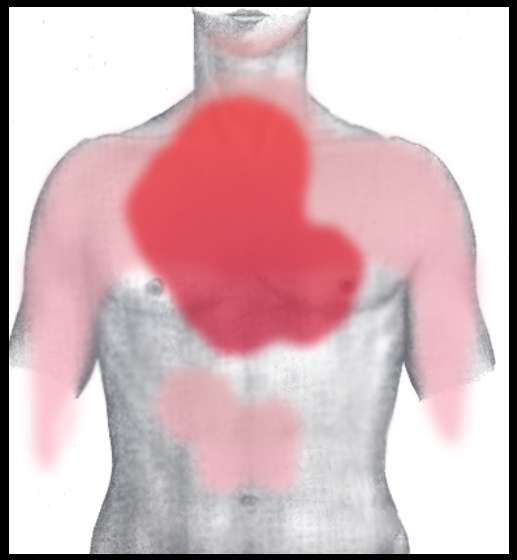


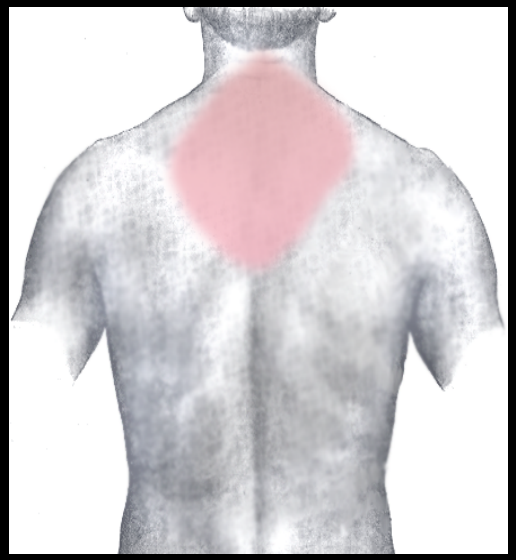


4 types of trigeminal Aδ- and C-fiber inputs to trigeminocervical lamina I neurons

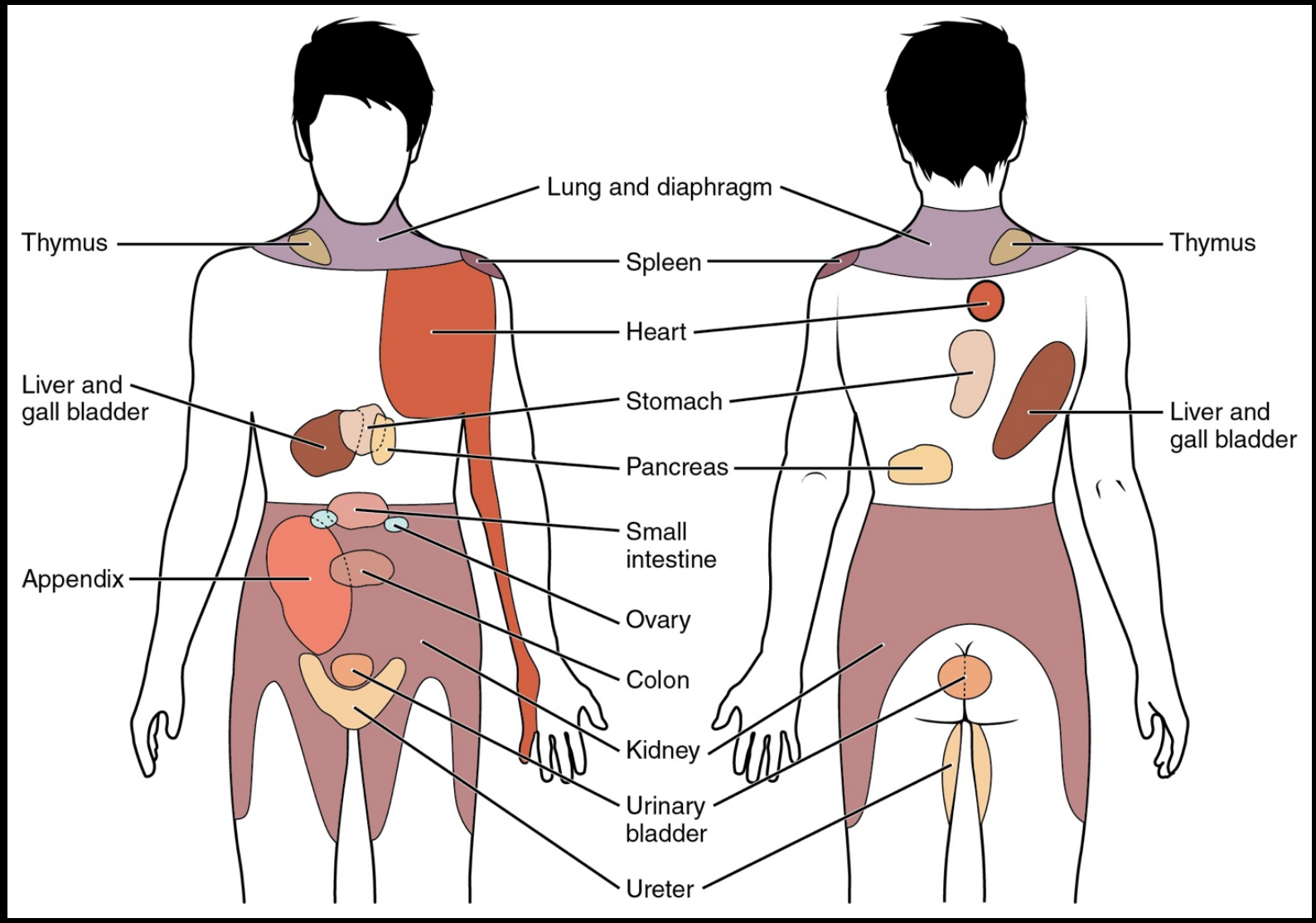


Referred pain is perceived at a location other than the site of the painful stimulus origin.

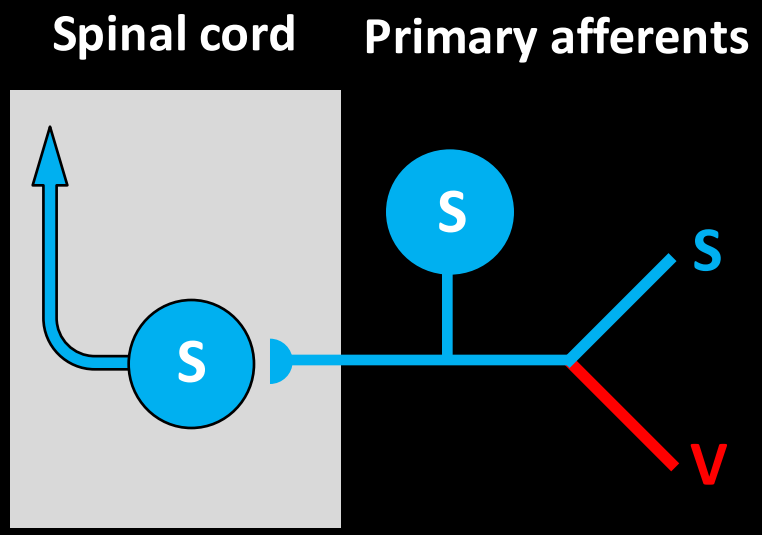




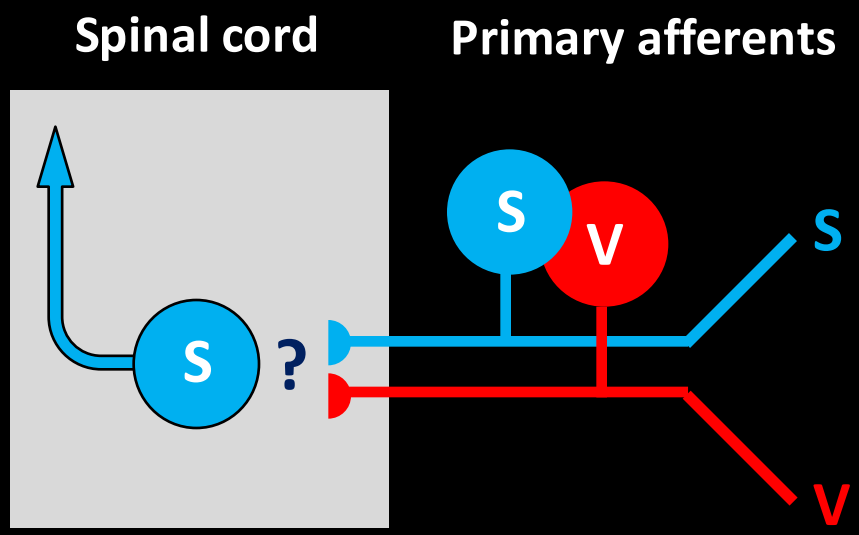
Somatic projections of visceral pain



Theories of referred pain origin

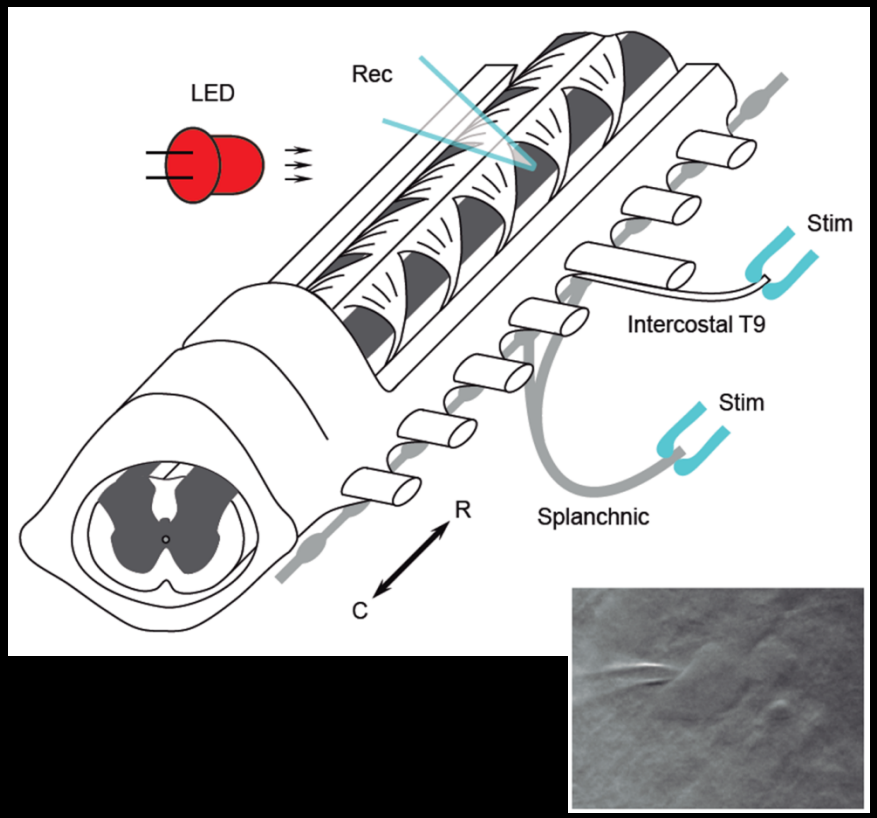


Dichotomizing axons
(are rare)



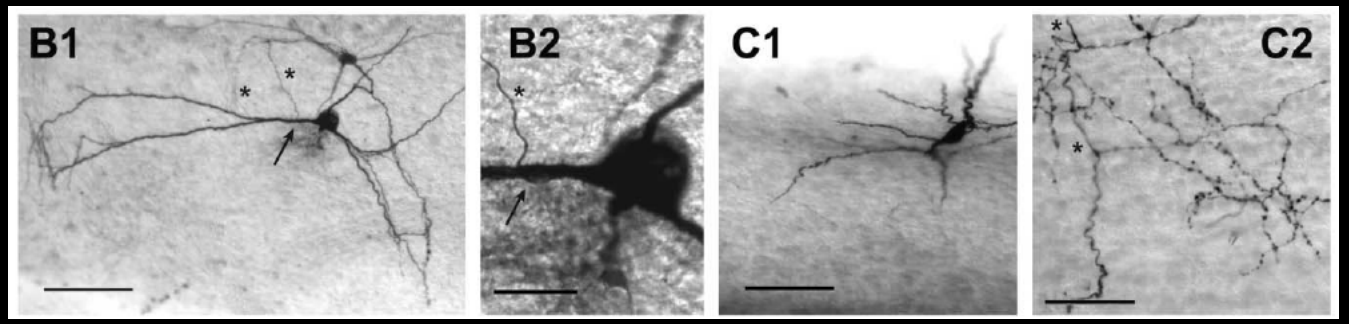
Spinal cord integration
(how?)

Study of somatovisceral convergence

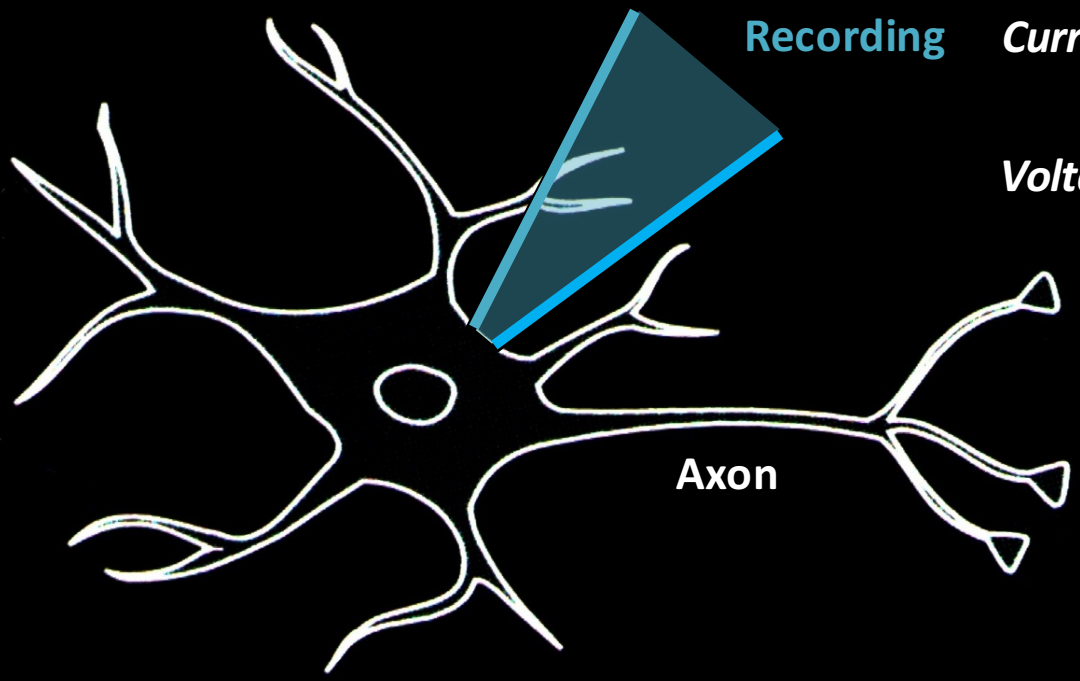


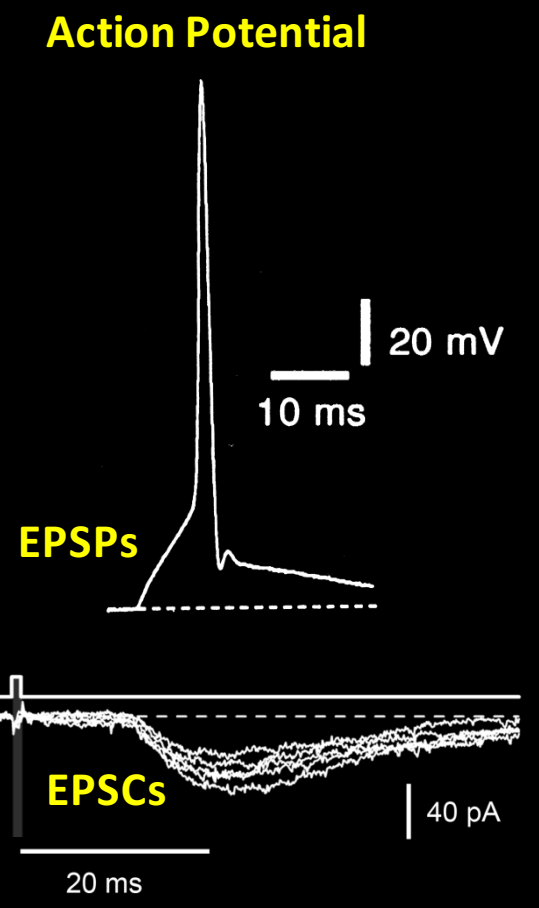
Somatic: Intercostal nerve

Visceral: Splanchnic nerve

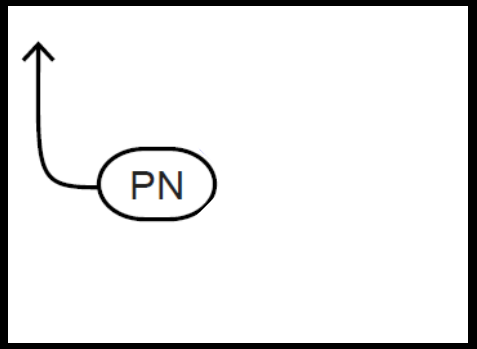


Patch-clamp recording from spinal neurons

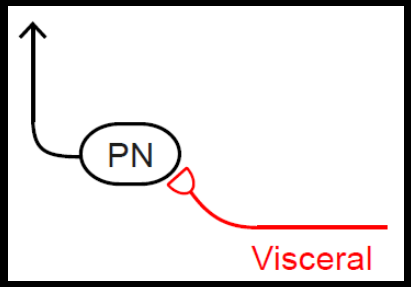


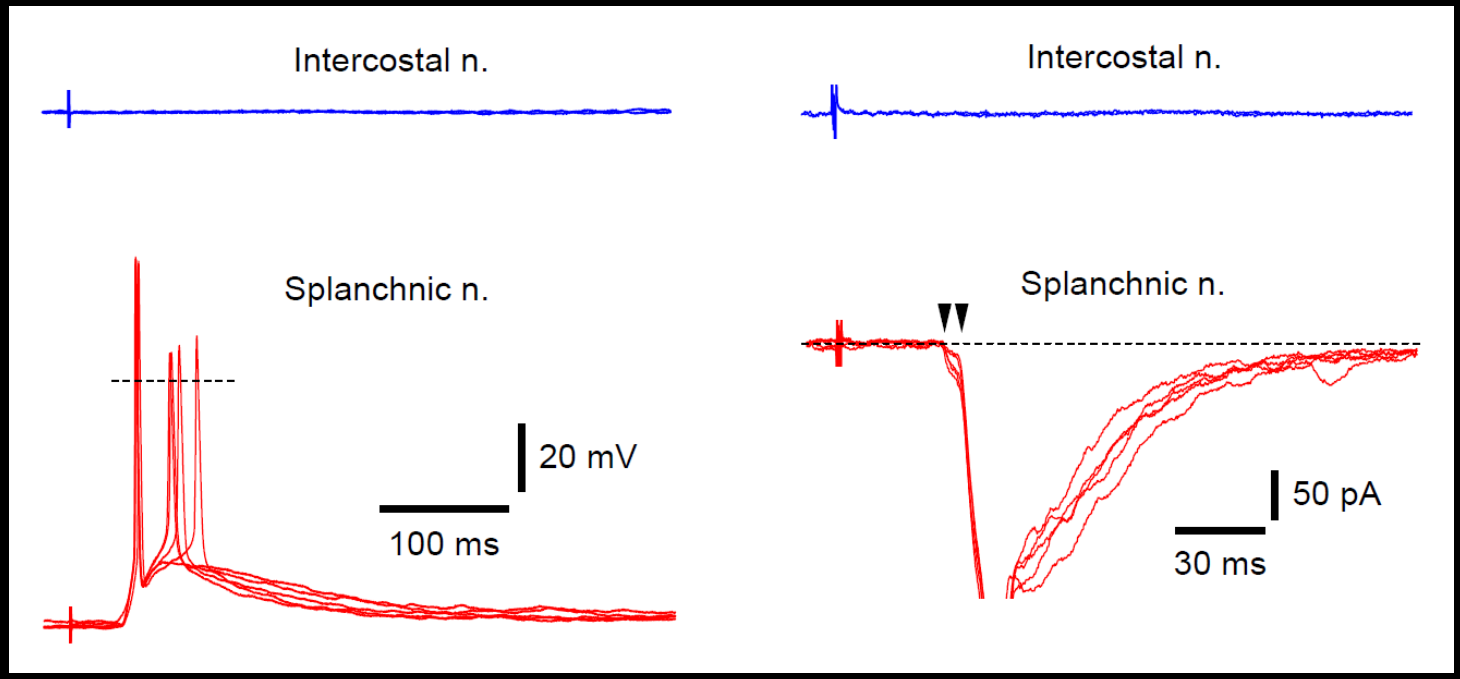


Somatovisceral lamina I neuron

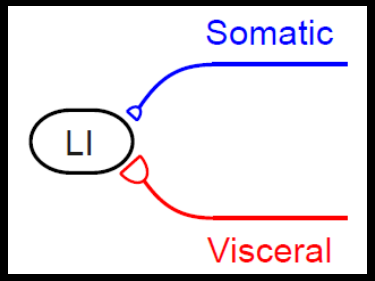


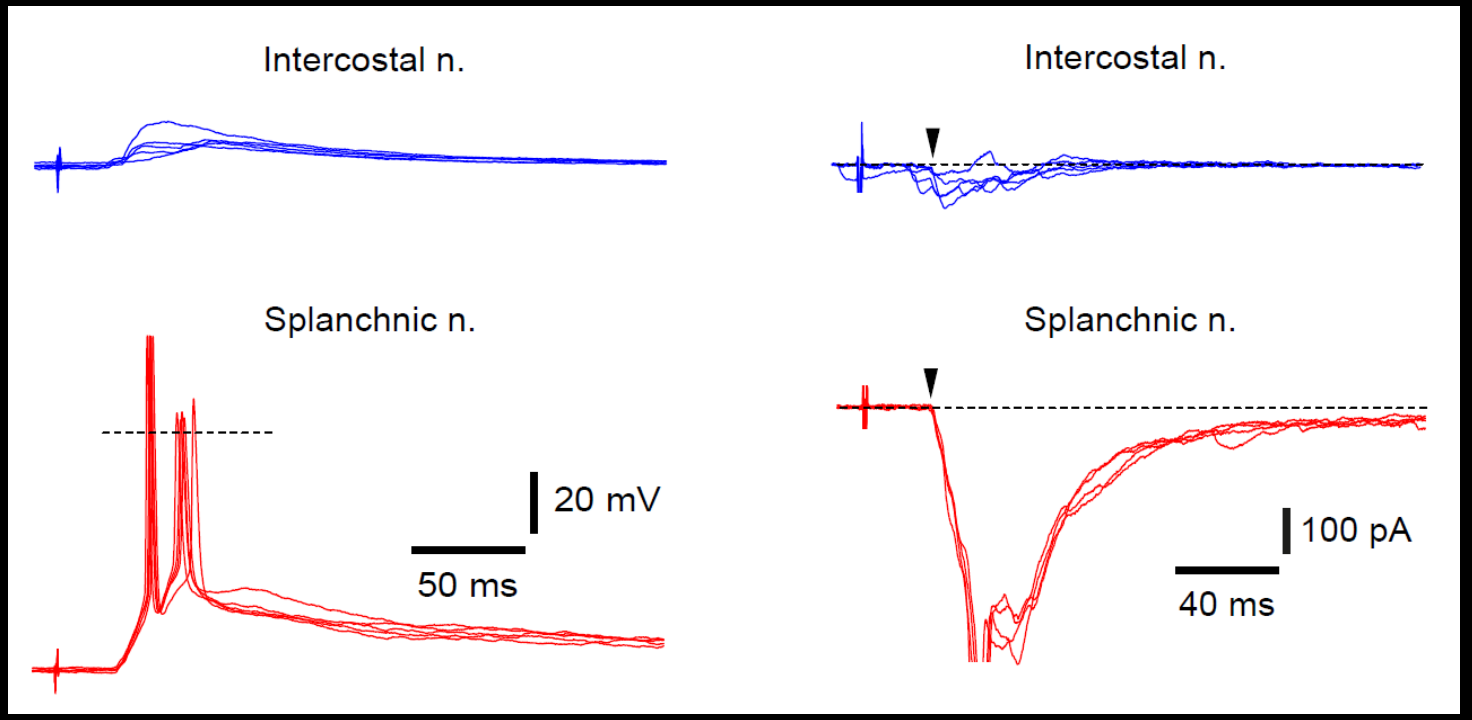
Visceral-specific neuron: Type 1



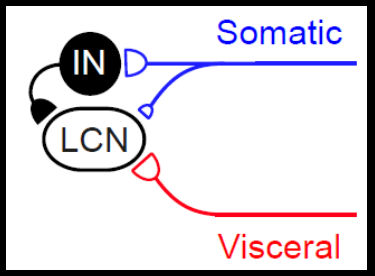


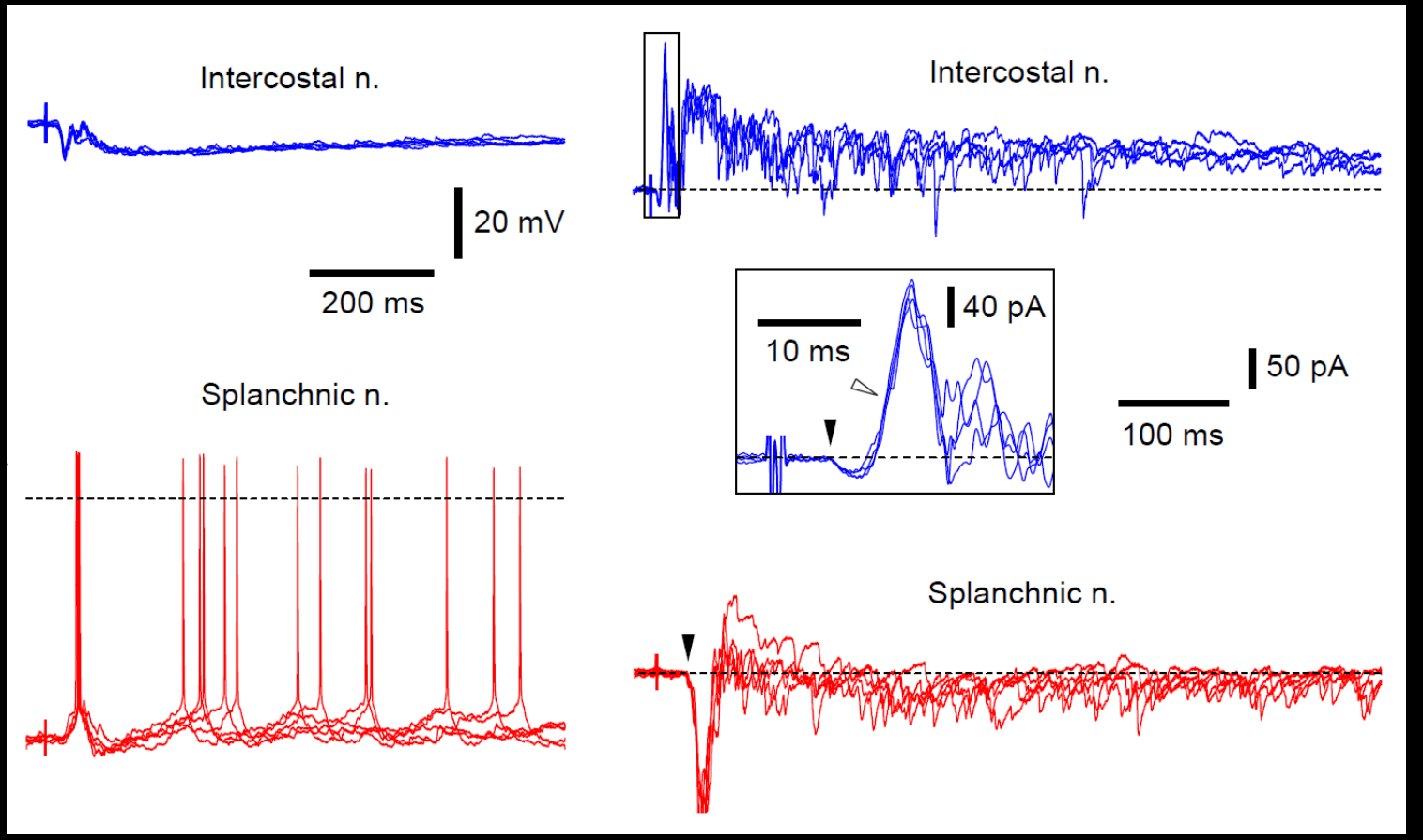
Visceral-specific neuron: Type 2



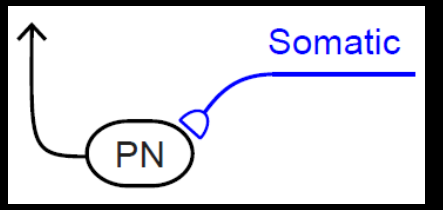


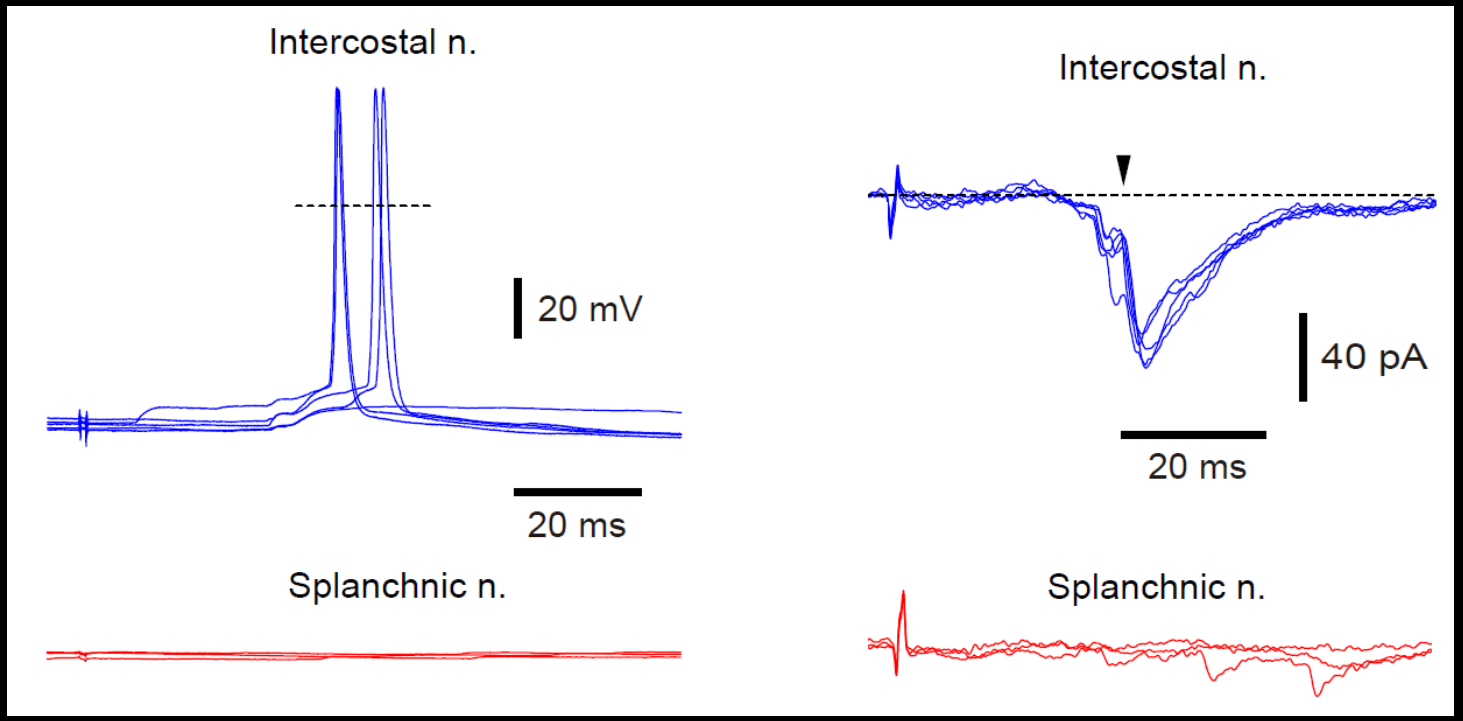
Visceral-specific neuron: Type 3



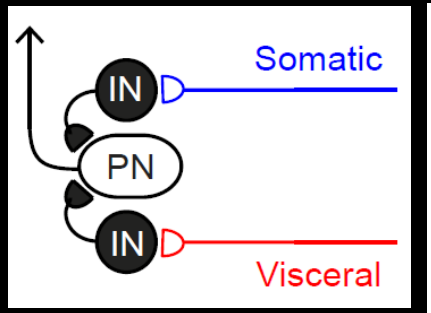


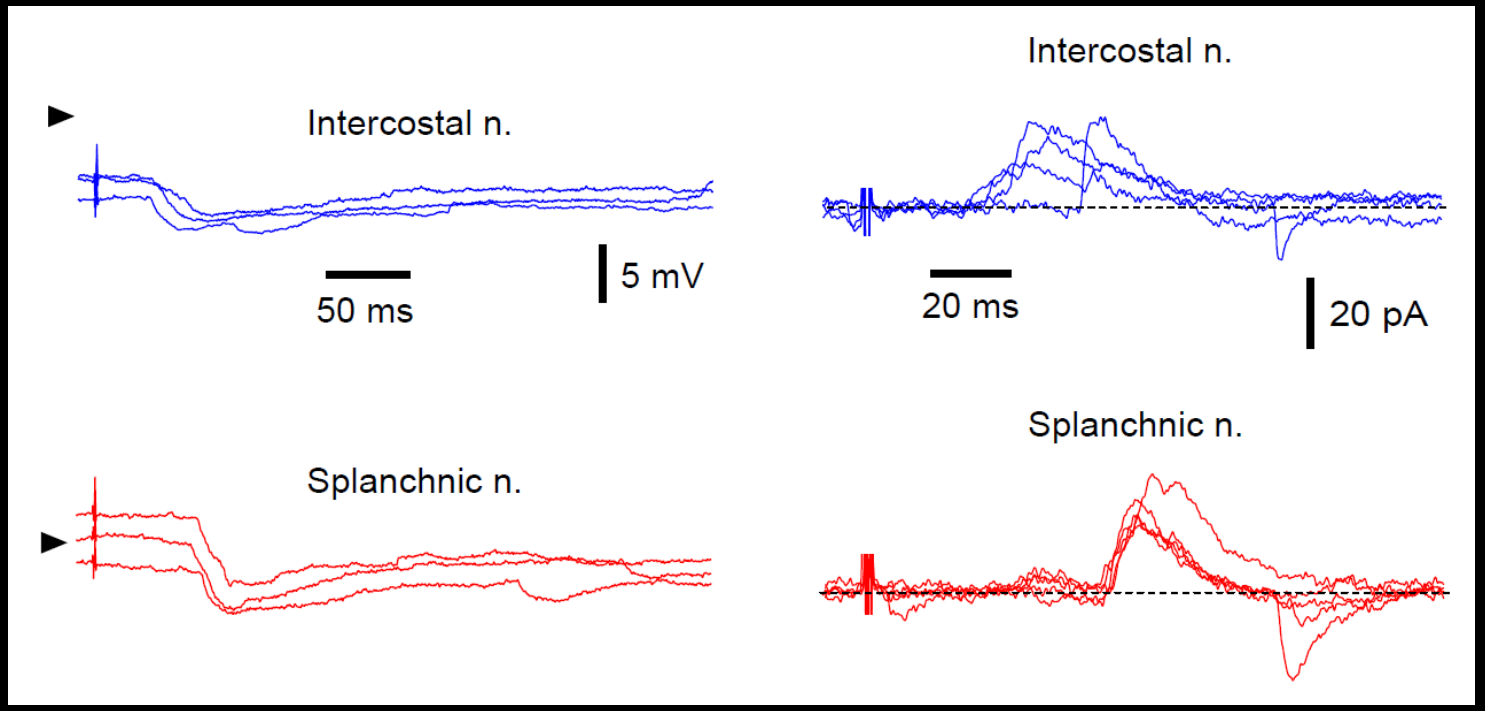
Somatic-specific neuron



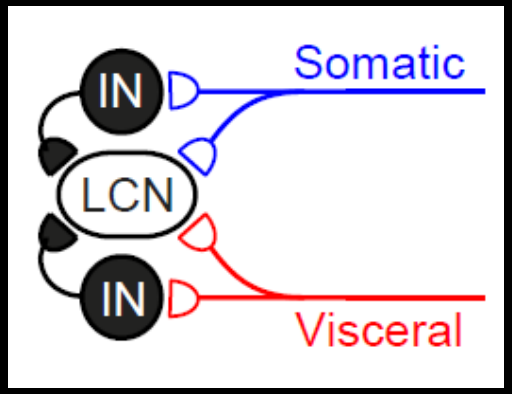


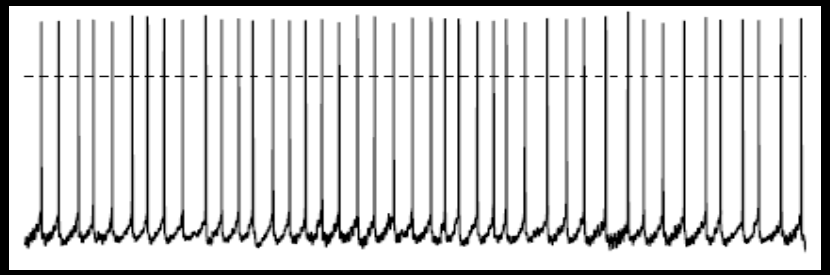
‘Inhibited’ neuron: Type 1

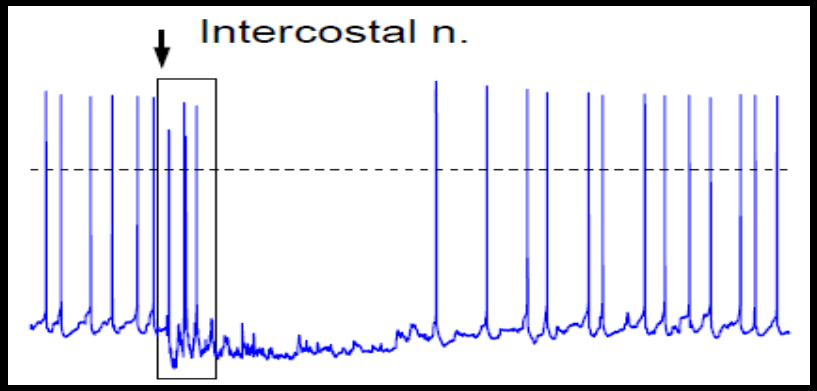


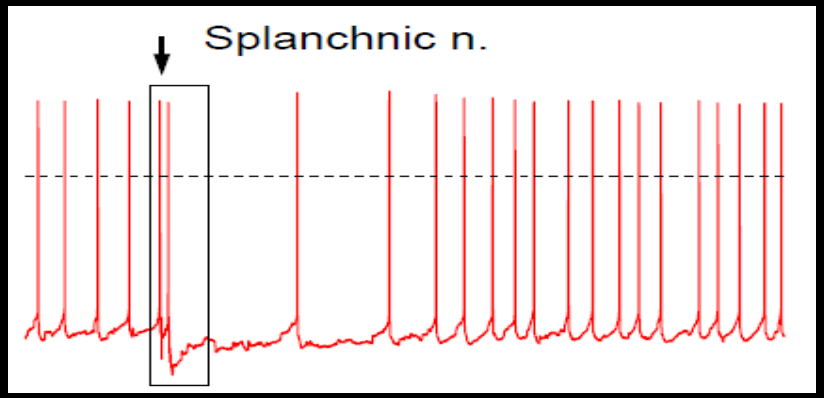


‘Inhibited’ neuron: Type 2

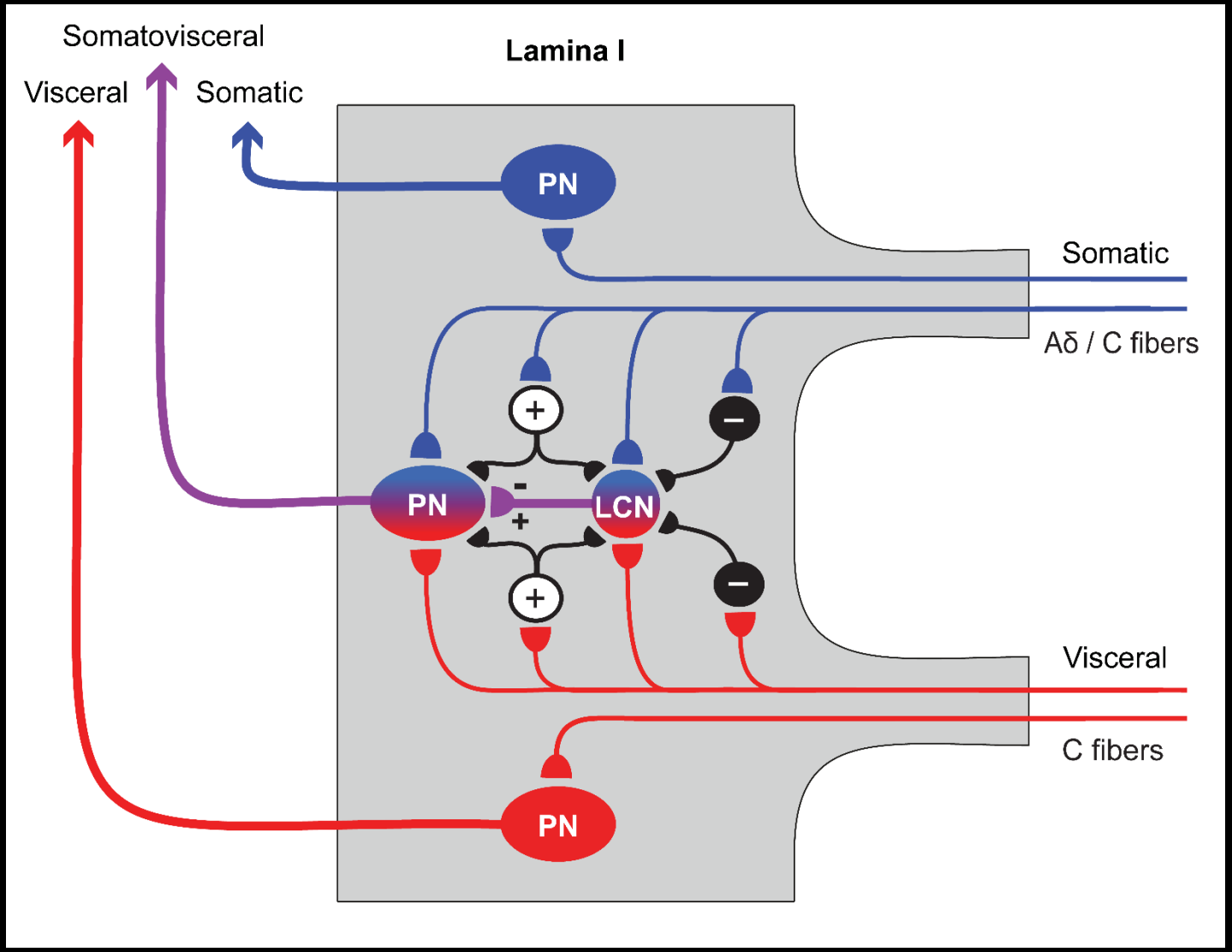








Somatovisceral integration in lamina I

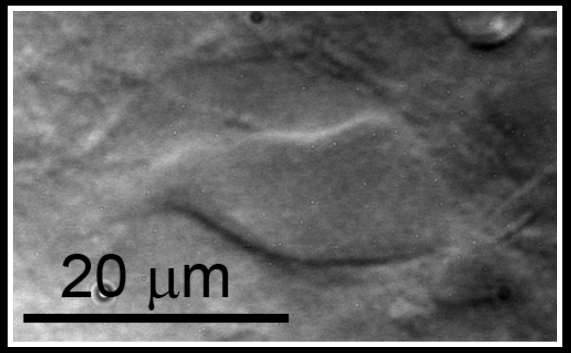


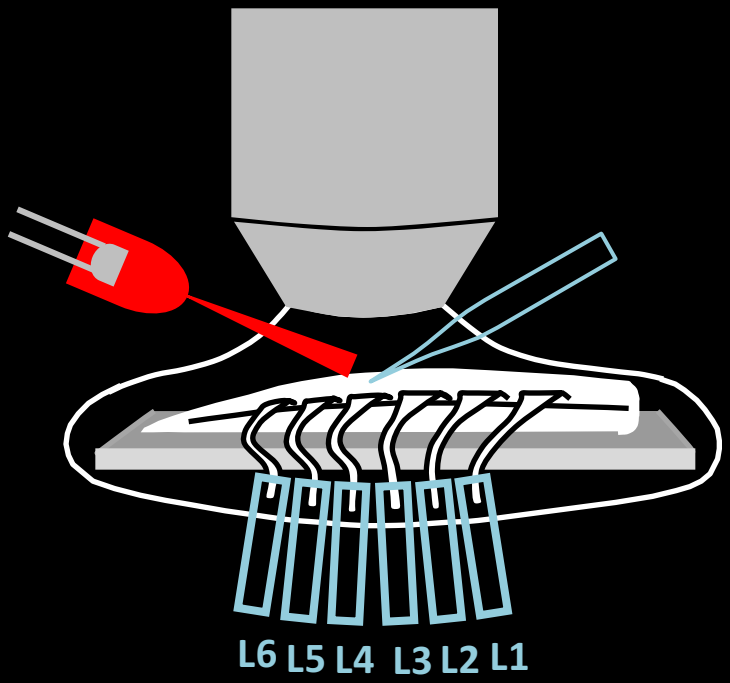
Conclusions:

There is a monosynaptic somatovisceral afferent convergence on lamina I neurons, which

Can underlie complex neurological phenomenon of Referred Pain

Multi-segmental input to lamina I neurons

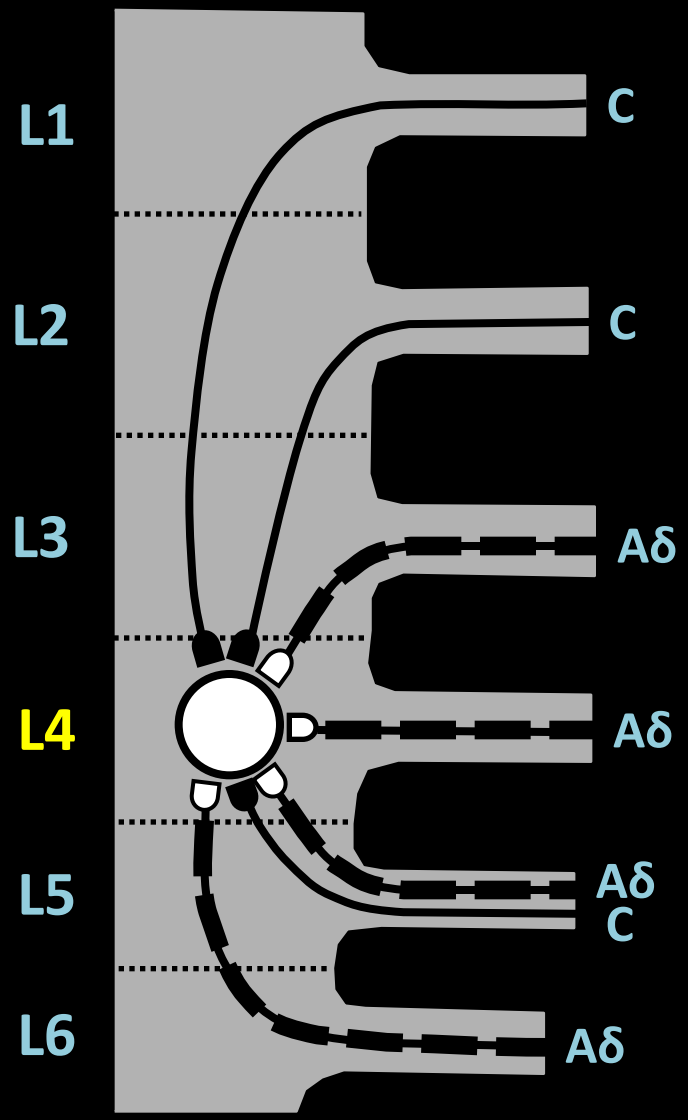




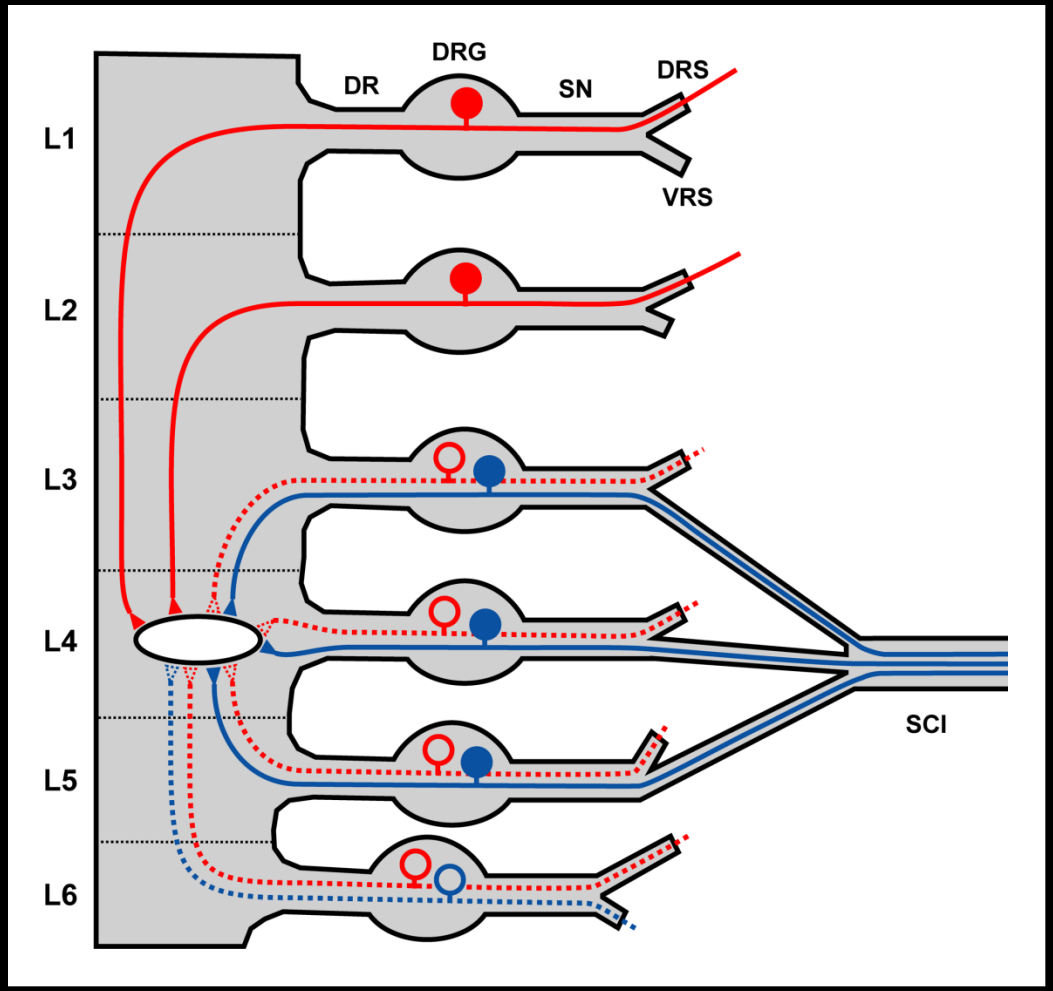
Broad monosynaptic inputs to lamina I neurons

Aδ + C

Aδ



Somatovisceral convergence on lamina I neurons?

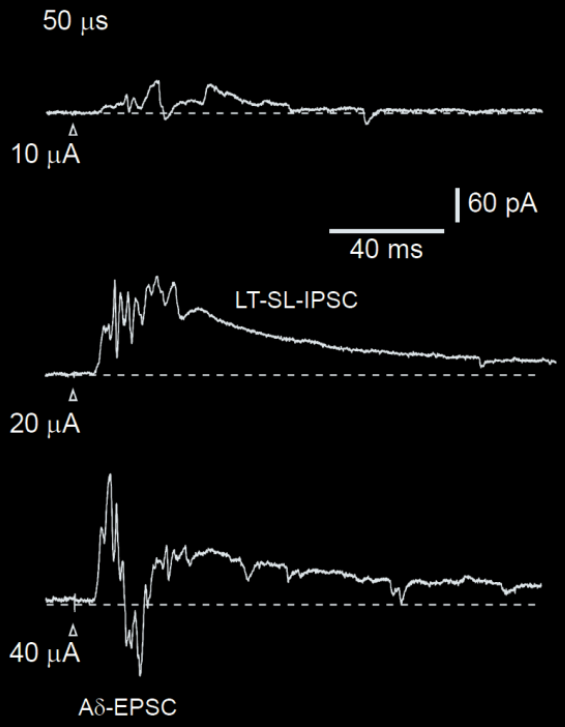


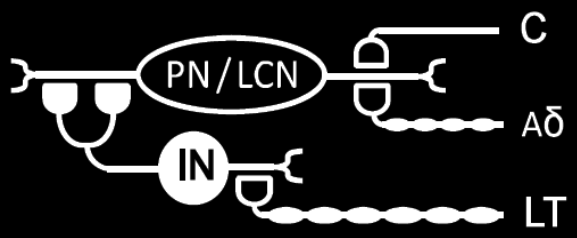
Preliminary conclusions:

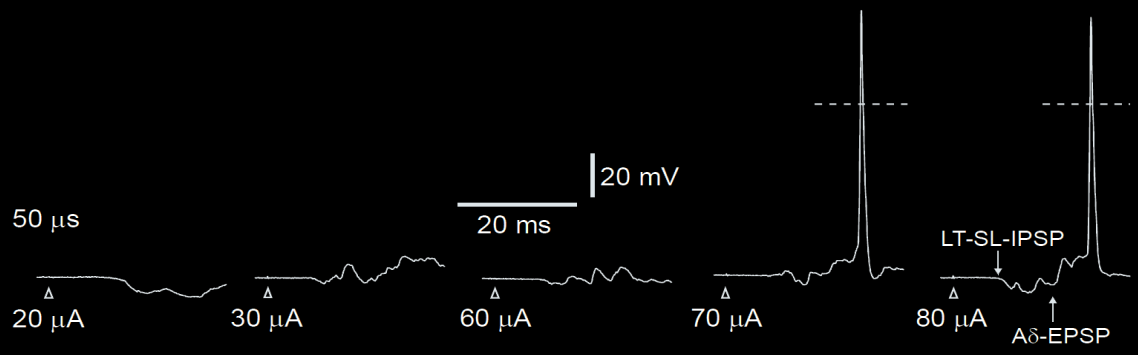
Aδ- and C-fibers from six roots can directly converge onto one lamina I neuron, which functions as an intersegmental integrator of primary afferent inputs

- Can lamina I neurons integrate somatovisceral inputs and serve as neuronal substrates of referred pain?

Low-threshold afferent-driven inhibition of lamina I neurons: a ‘postsynaptic gate’





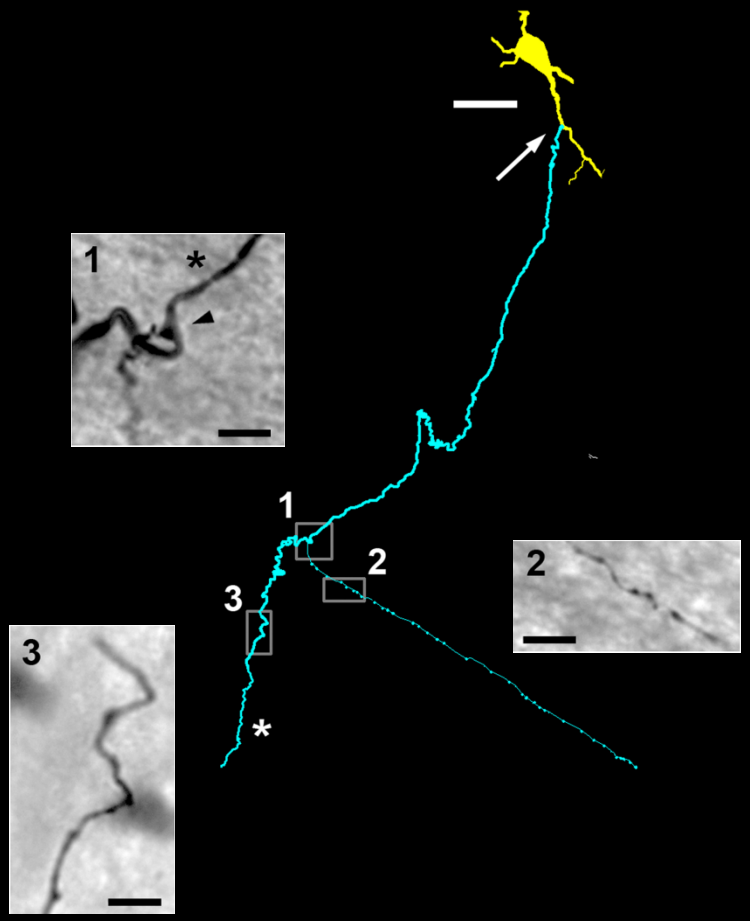


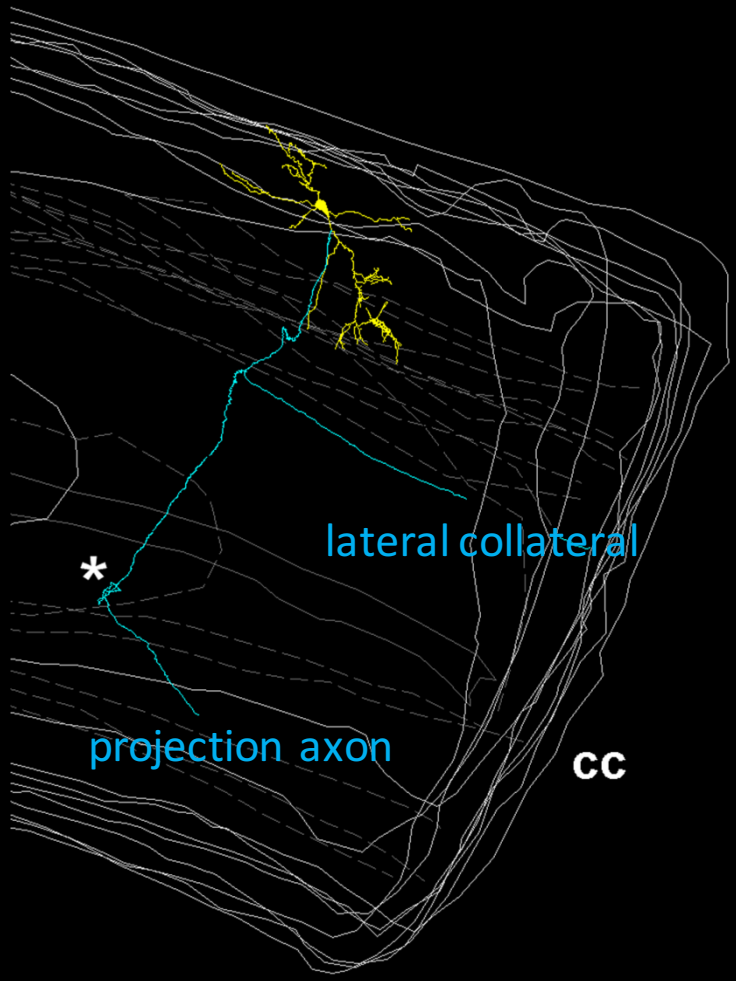
Conclusions:

Lamina I **local-circuit** and **projection neurons** receive low-threshold afferent-driven inhibition, which, in many cases, is disynaptic and temporally precedes classical high-threshold excitatory inputs

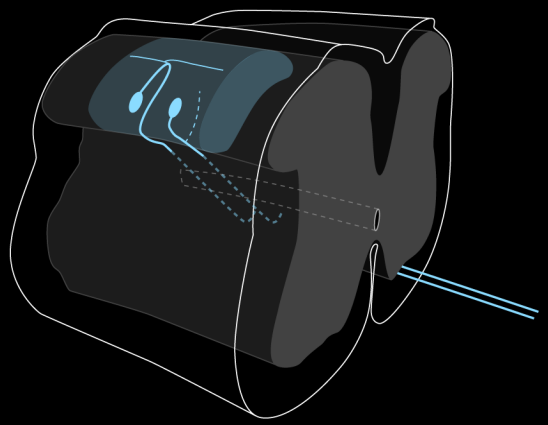
This direct inhibitory link between low-threshold afferents and **projection neurons** can function as **a postsynaptic gate** controlling the nociceptive information flow in the spinal cord

Local axon collaterals of ALT-projection neurons





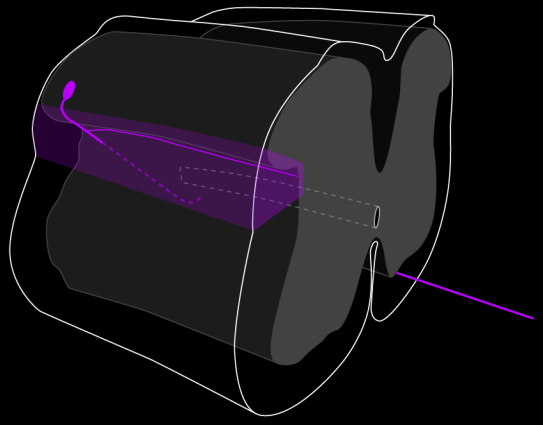
Axon collaterals of ALT-projection neurons



Dorsal Collateral Type I & II

Project to laminae I or II–IV of the same segment

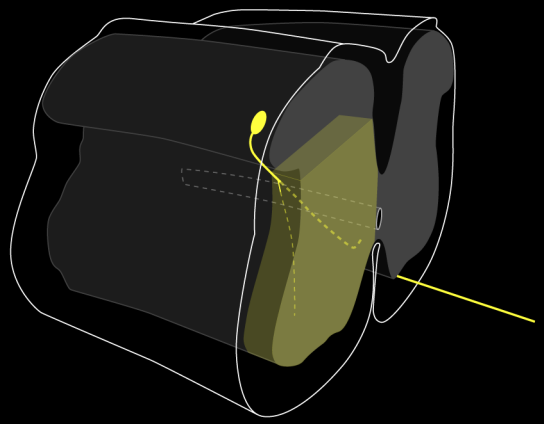
- Local segmental circuits



Lateral Collateral Type

Project to rostral and caudal segments

- Intersegmental connections
- Propriospinal projections

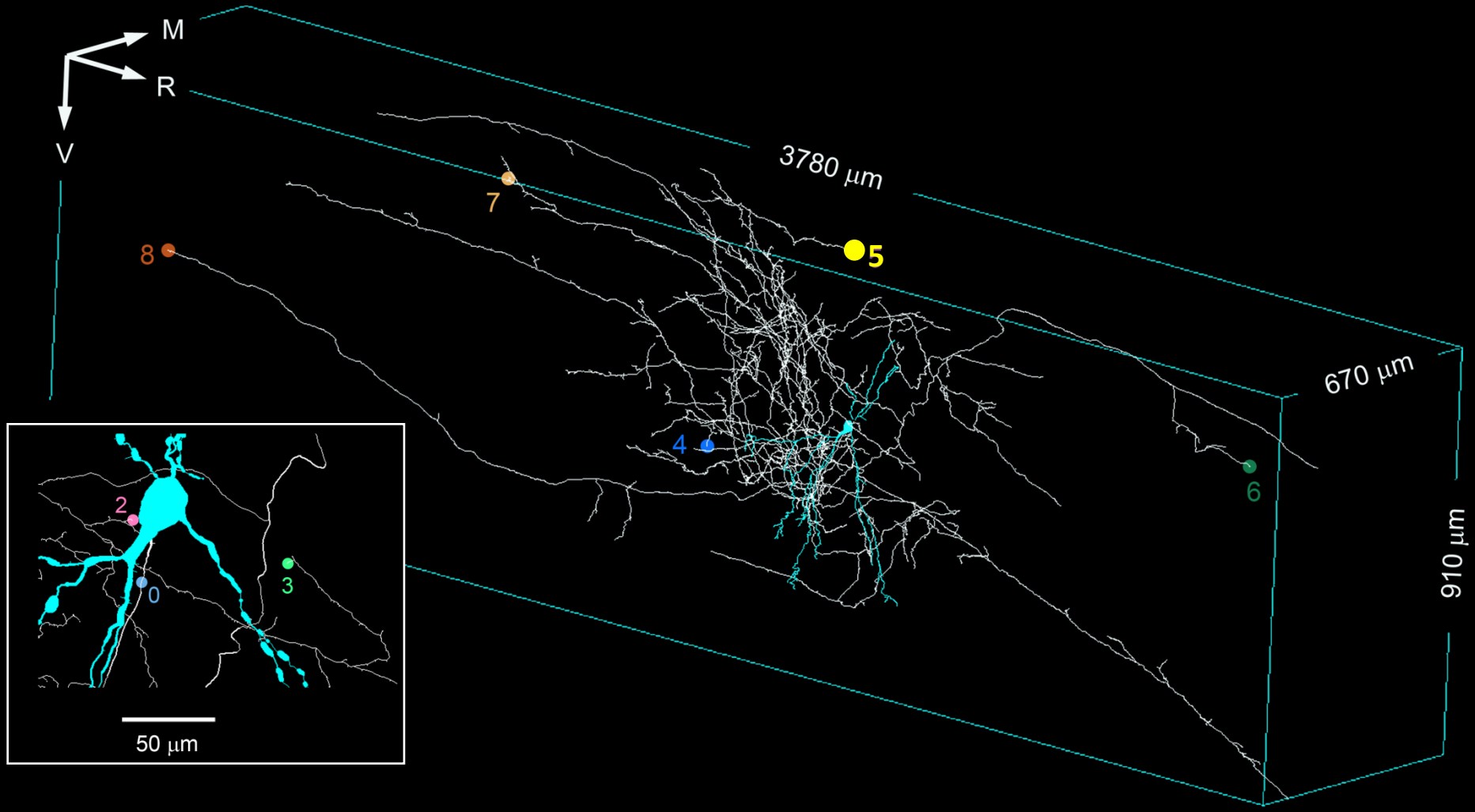


Ventral Collateral Type

Project to laminae V-VII

- Intrasegmental connections with deep laminae
- Can link parallel pain pathways originating from lamina I and lamina V

Axon of a local-circuit neuron in 3D

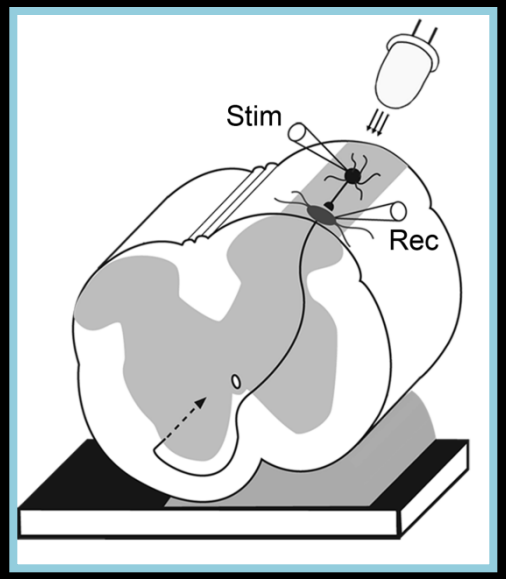


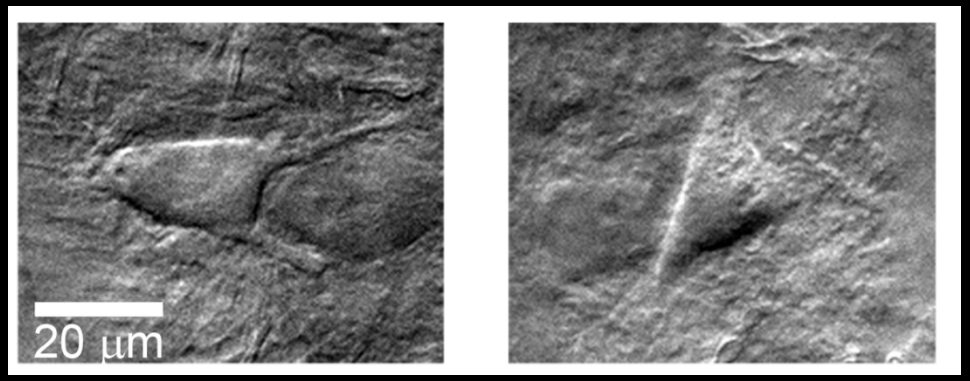
Conclusions:

Lamina I ALT-projection neurons, besides their principal role, can also function as local-circuit and propriospinal neurons participating in intra- and intersegmental processing

Lamina I local-circuit neurons form intersegmental as well as interlaminar connections and may control large numbers of neurons, providing anatomical substrate for rostrocaudal "processing units" in the dorsal horn

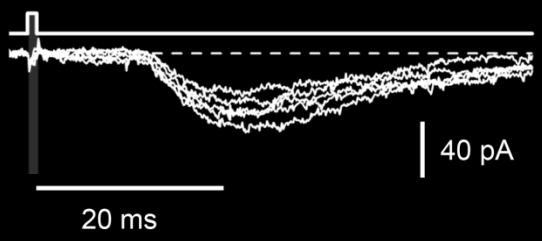
Connections between lamina I neurons



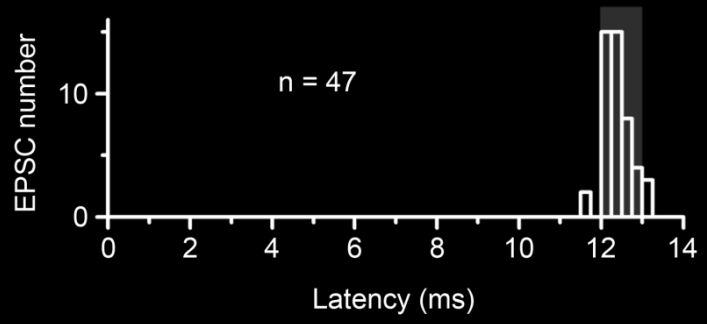


Lamina I projection neurons in isolated spinal cord

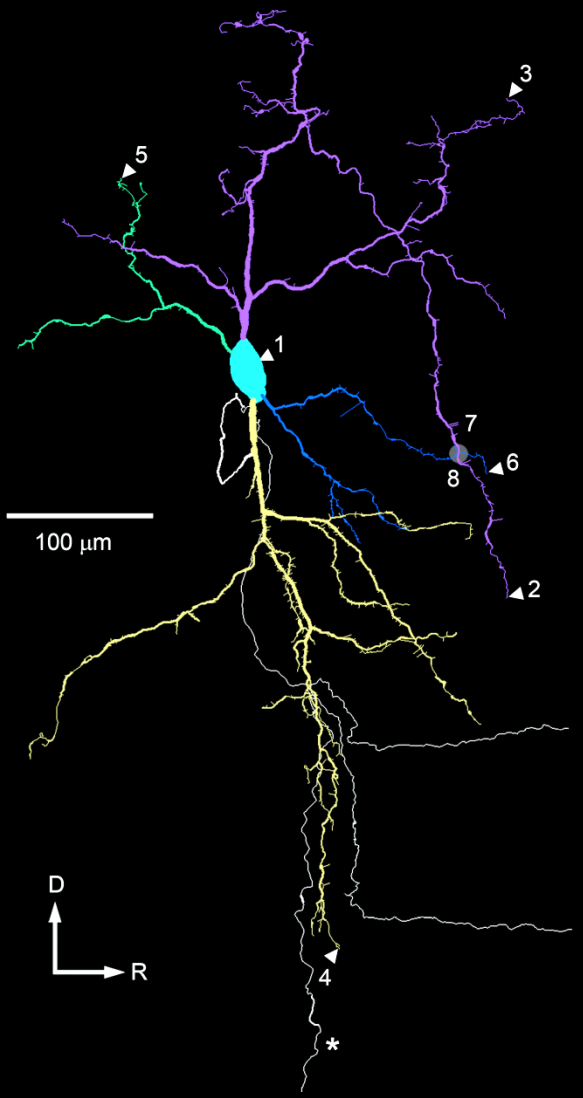
Monosynaptic EPSCs



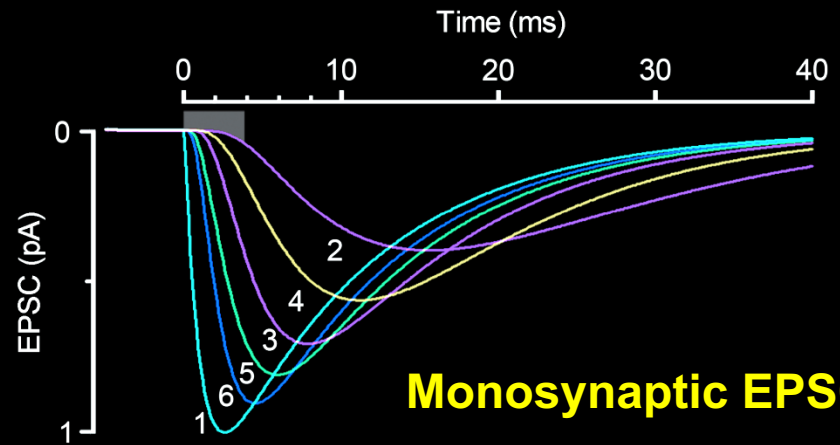
Latency of 12.4 ms



Dendritic delay … is 4 ms at most

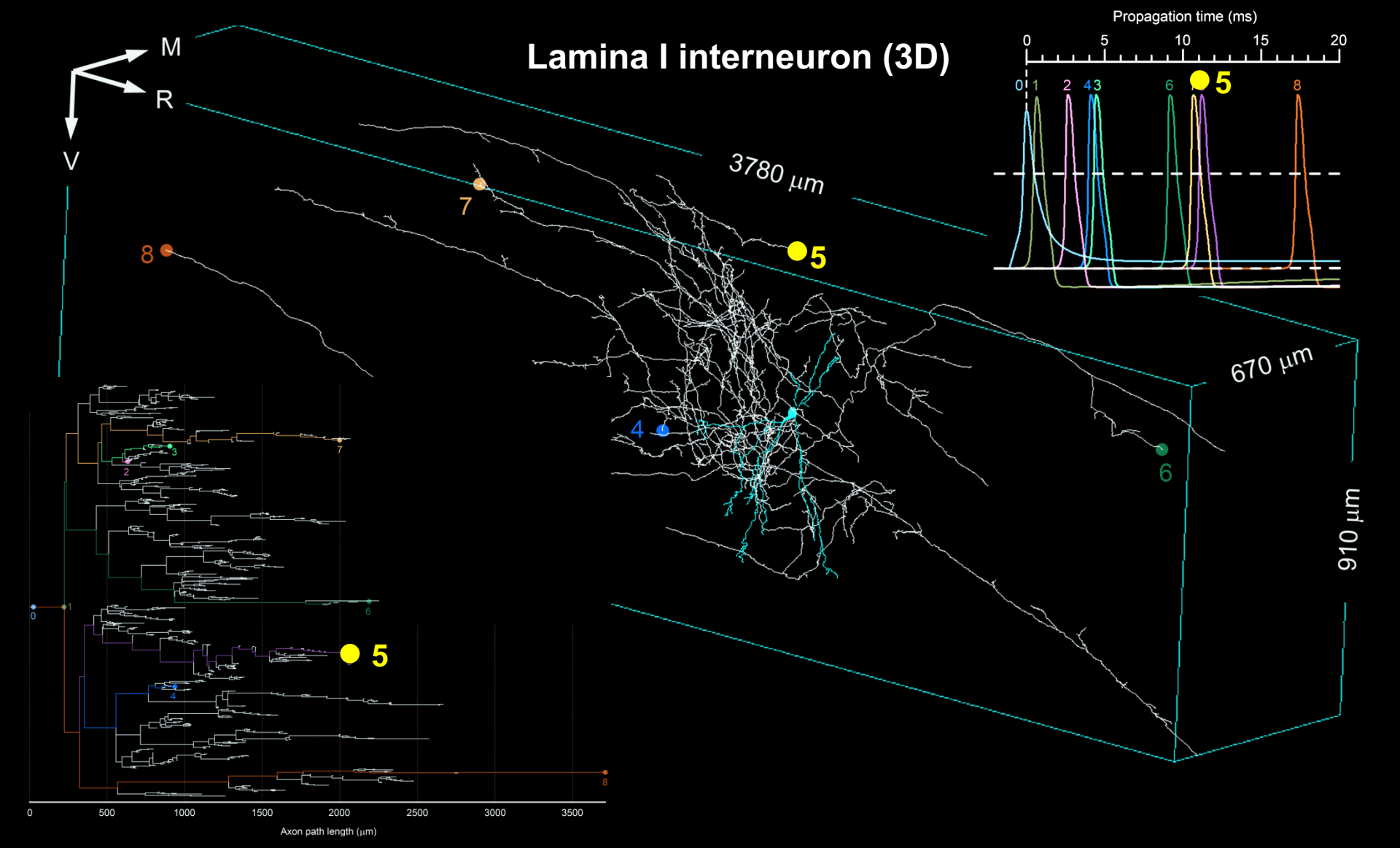


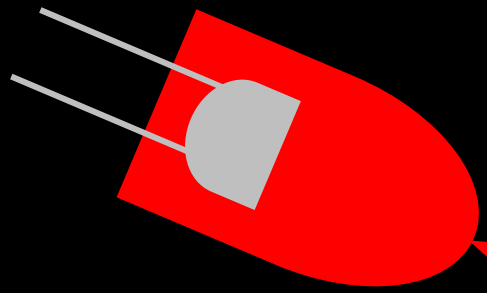
Lamina I projection neuron (3D)



Monosynaptic EPSCs

Axonal propagation can be long





Elisabete Fernandes

Liliana Luz

Peter Szucs

Vitor Pinto