Identification and Validation of Targets for Chronic Pain Treatment

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Prevalence of Chronic Pain

19% of the European population suffer from chronic pain (VAS ≥ 5, range 0 ... 10)

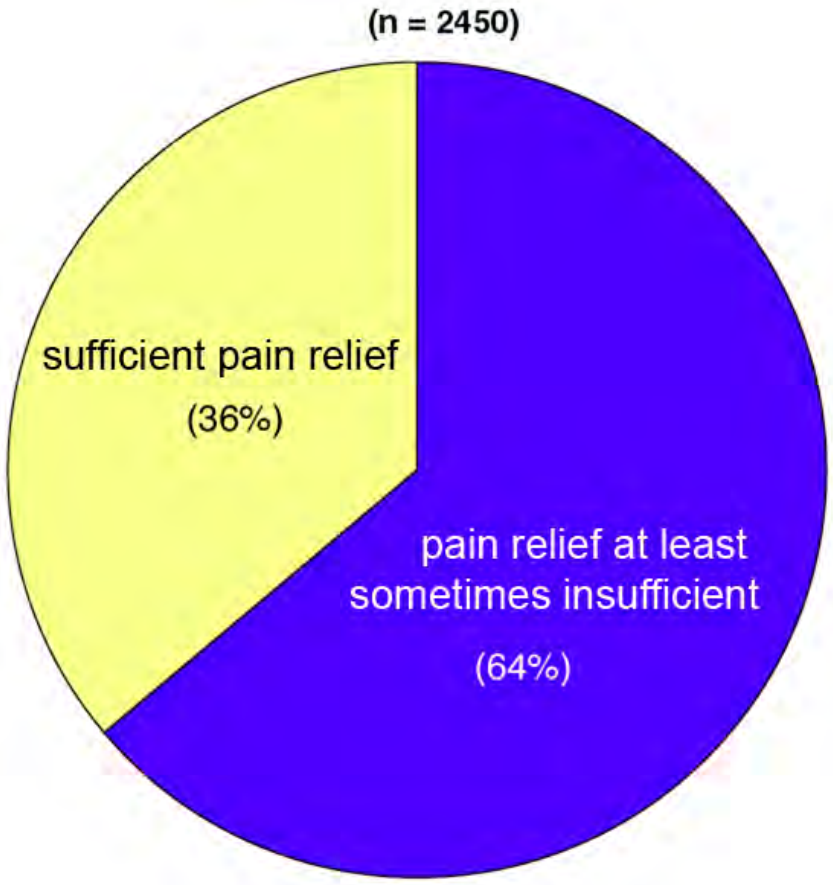
33% of these patients report strong pain (VAS ≥ 8 - 10)

In 59% of these patients pain lasted for at least 5 years.

* Telephone interviews with 46'392 persons from 15 European countries and from Israel
** longer than 6 months, VAS (0-10): ≥ 5
*** VAS (0-10): 8-10

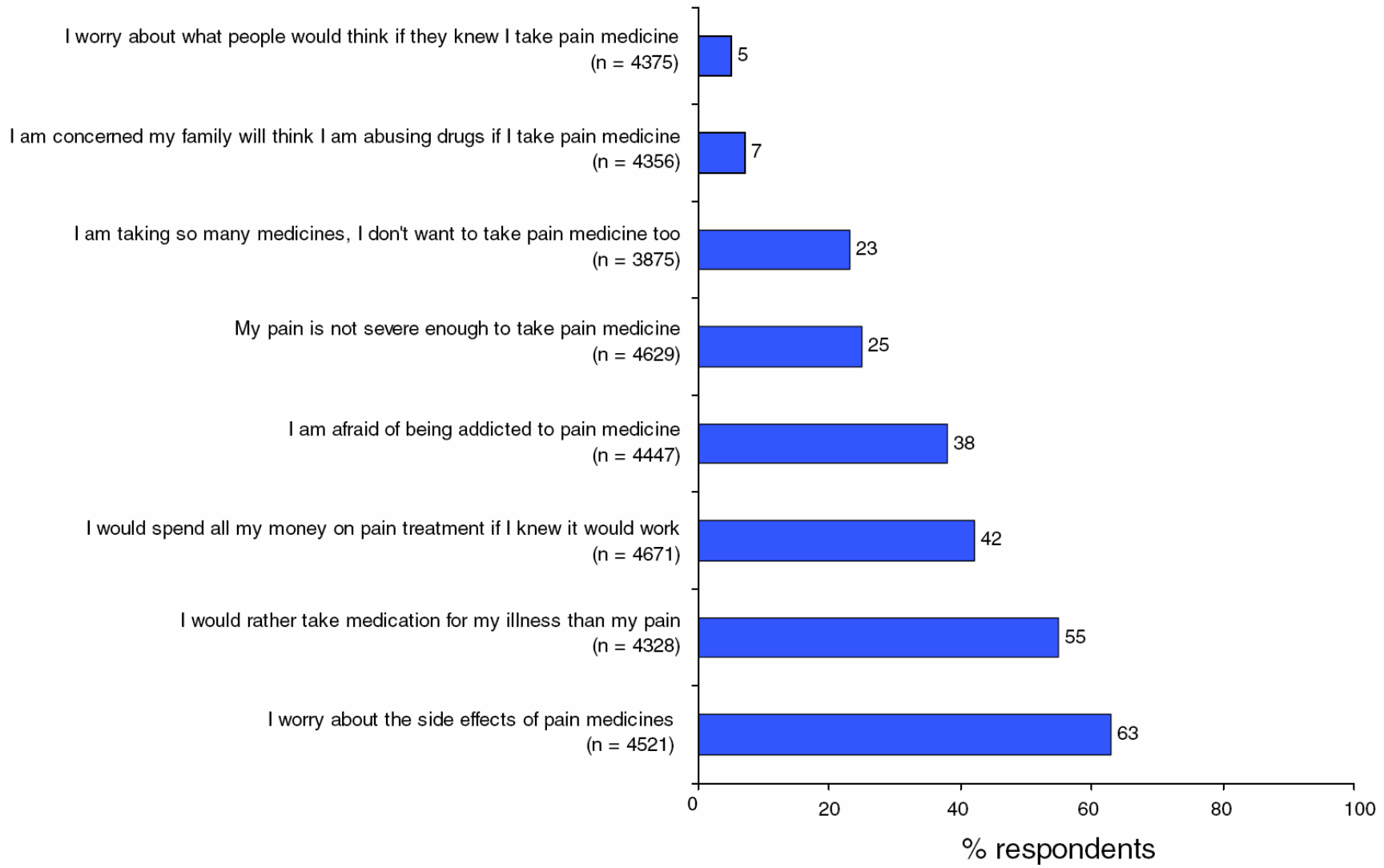
Breivik et al., *Eur J Pain* 2006

Satisfaction with Pain Medication



Breivik et al., *Eur J Pain* 2006

Patients Concerns about Pain Medication



Breivik et al., *Eur J Pain* 2006

Examples for Sources of Chronic Pain

- Inflammation

rheumatoid arthritis

- Nerve damage

chronic regional pain syndrome

- Trauma

Zur Anzeige wird der QuickTime™ Dekompressor „TIFF (LZW)“ benötigt.

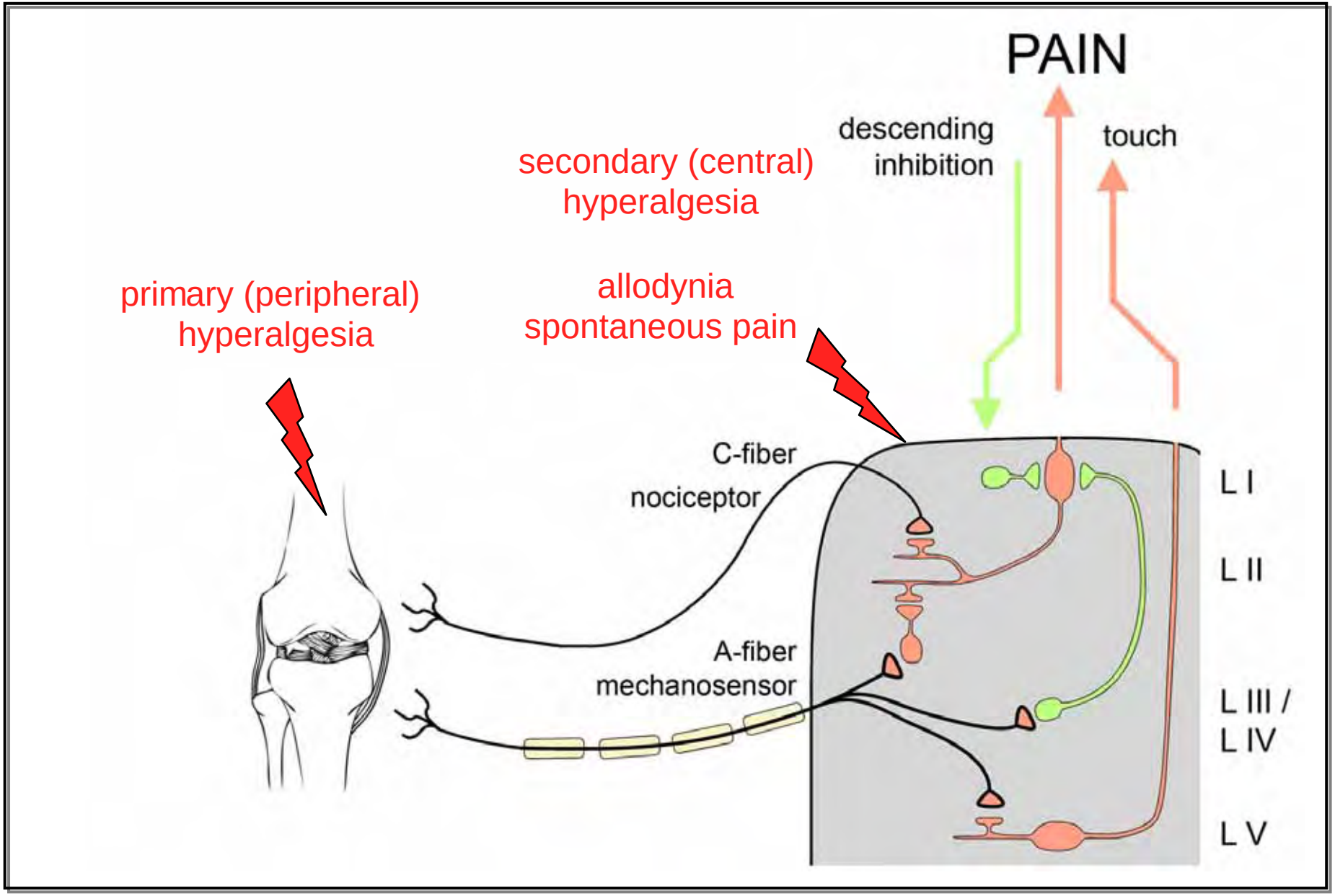
amputation

Acute Pain - Chronic Pain

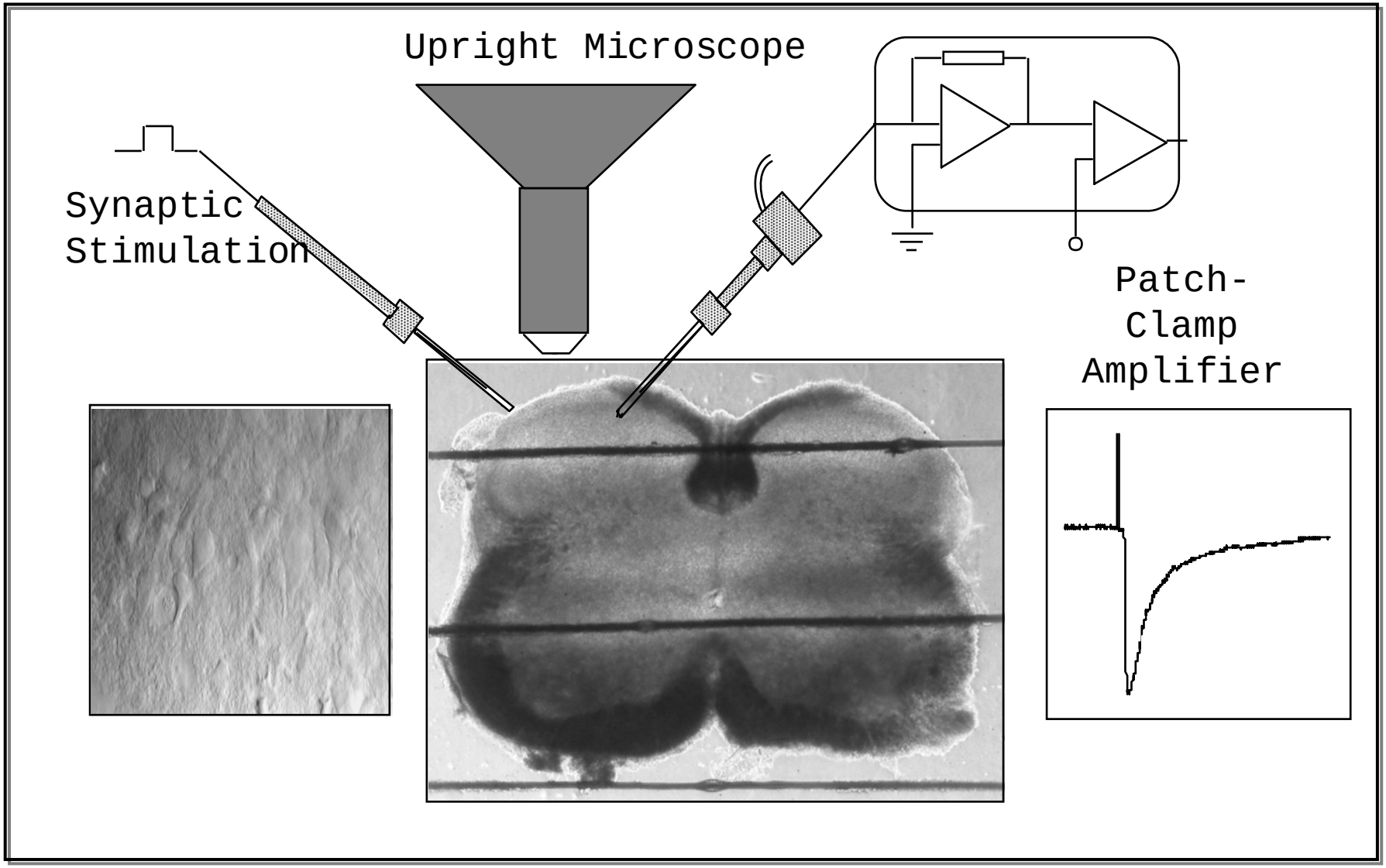
Acute Pain	Chronic Pain
Evoked by adequate stimuli, e.g. mechanical stress noxious heat acidosis	Evoked by in-adequate stimuli hyperalgesia allodynia spontaneous pain
Correlates with intensity and duration of the stimulus	Outlasts peripheral stimulation (inflammation or tissue repair)

Chronic pain is a form of maladaptive CNS plasticity

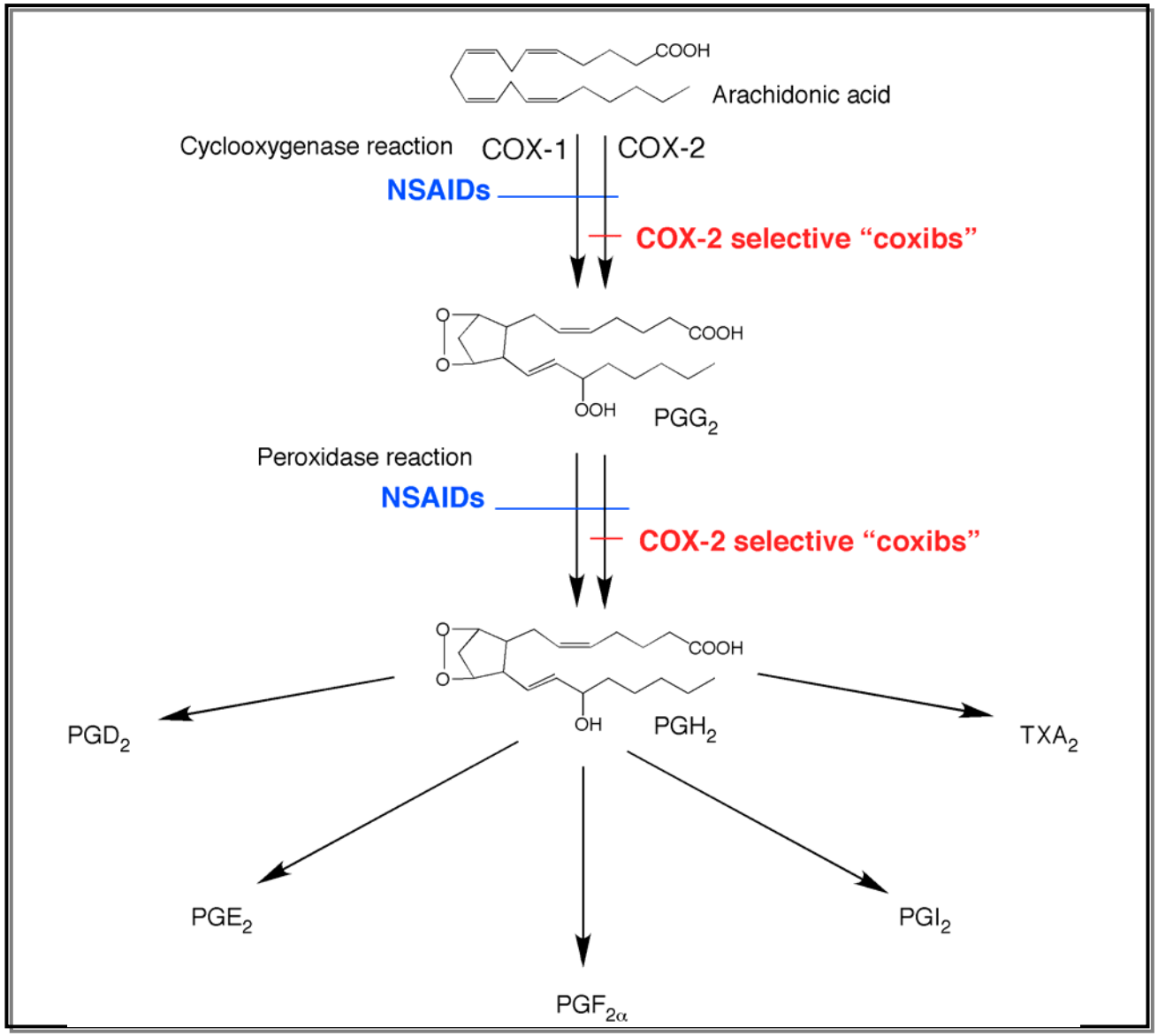
Peripheral and Central Pain Sensitization



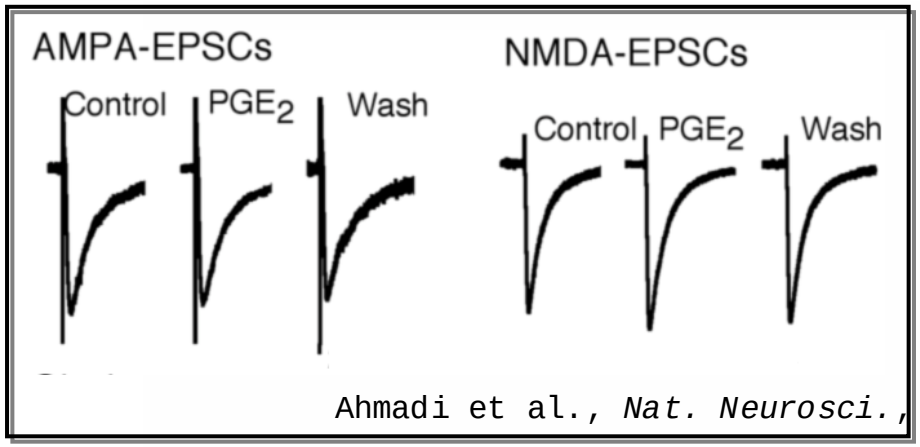
Patch-Clamp Recordings from Neurons in a Transverse Rat Spinal Cord Slice Preparation



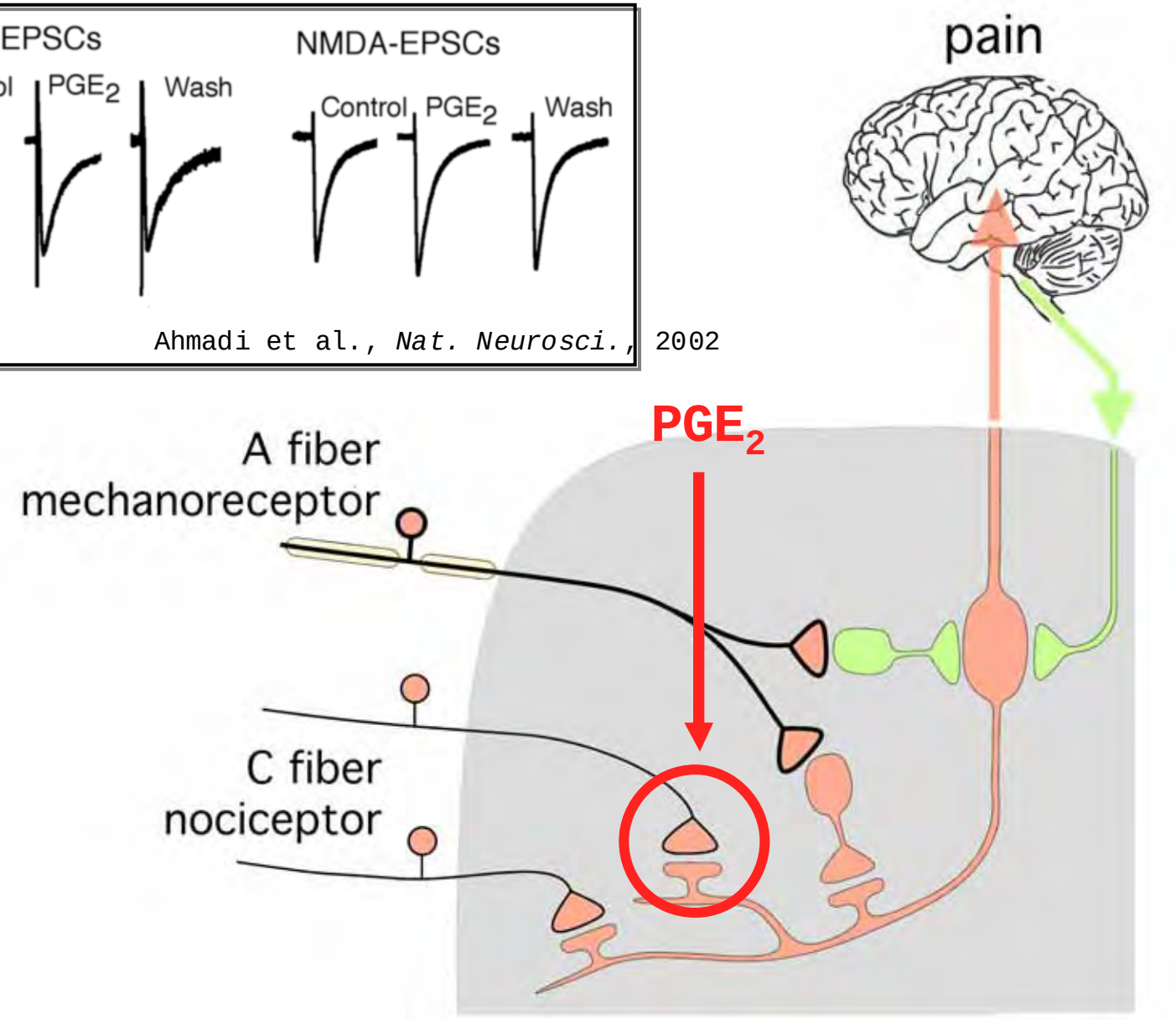
Biologically Active Prostanoids



Do Prostaglandins Affect Dorsal Horn Synapses?



Ahmadi et al., *Nat. Neurosci.*, 2002



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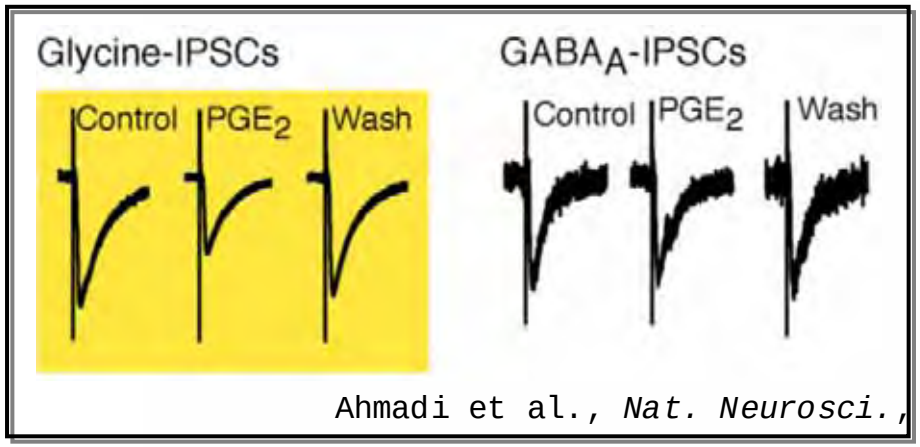
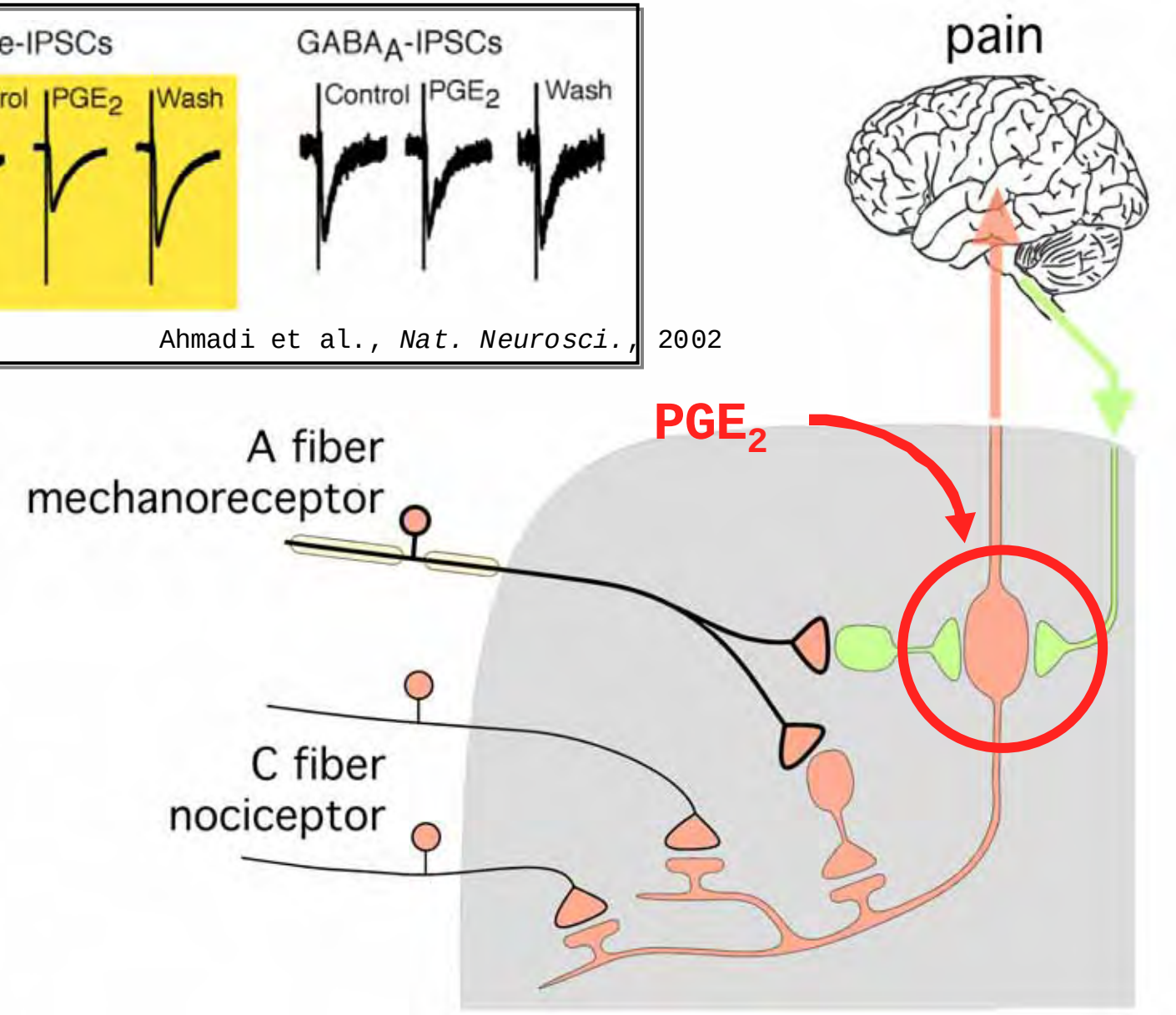
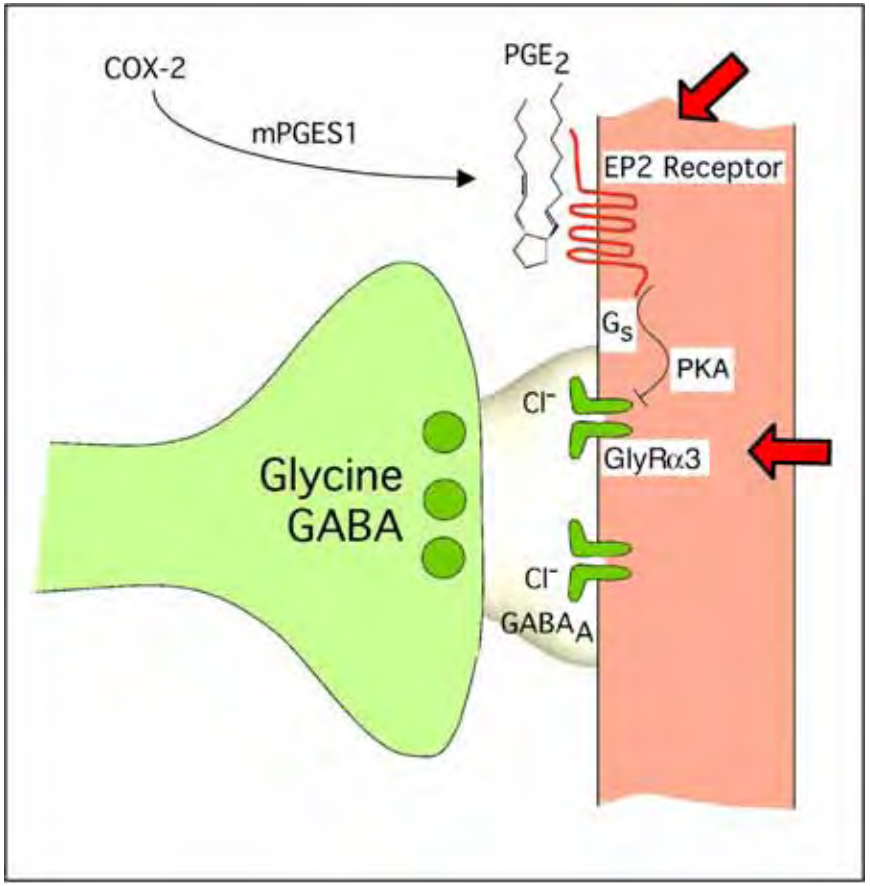
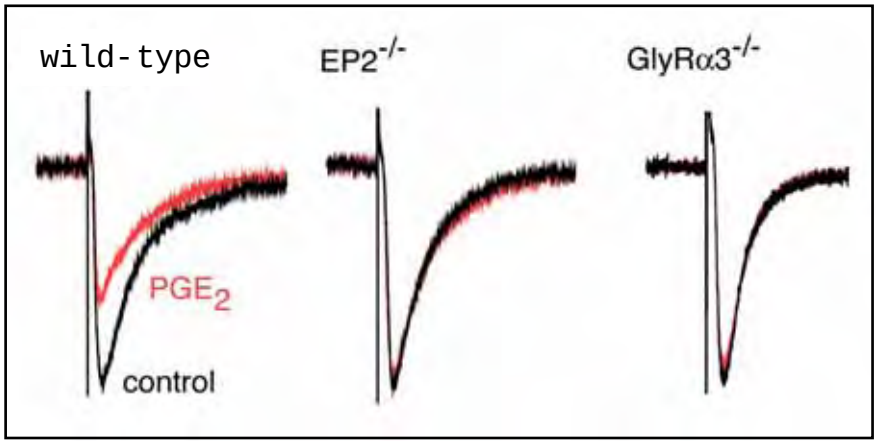


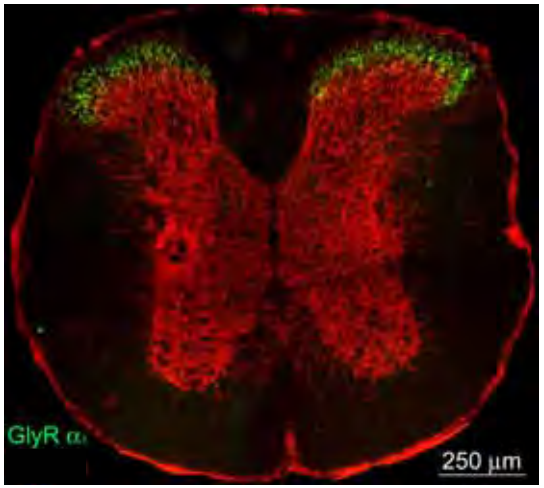
Ahmadi et al., *Nat. Neurosci.*, 2002



Spinal Neuroplasticity and Pain: Disinhibition

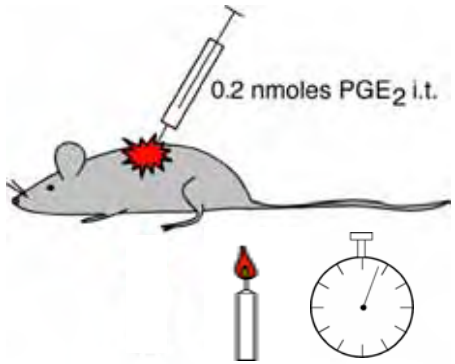


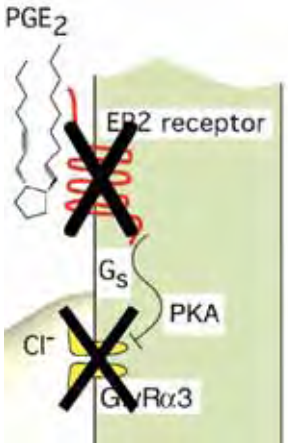


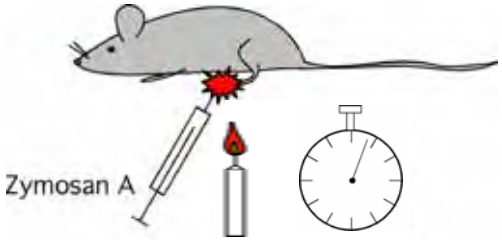


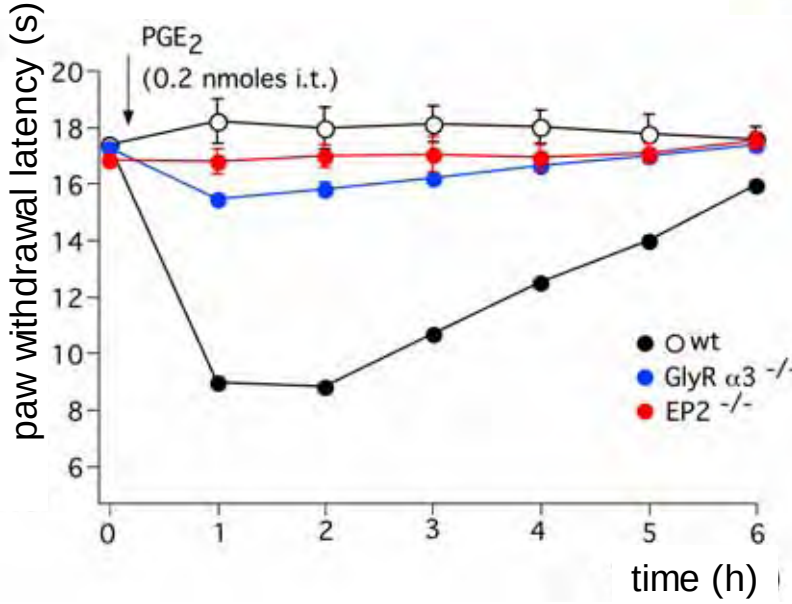
Harvey et al., *Science* 2004
Reinold et al., *J. Clin. Invest.* 2005

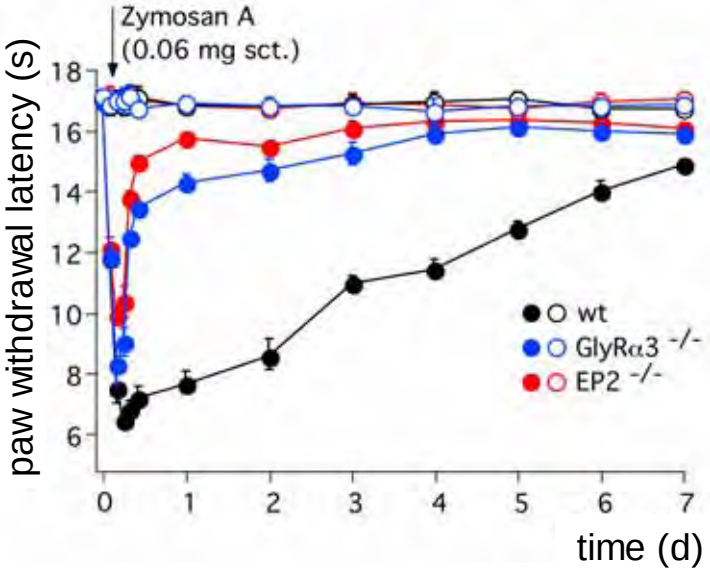
EP2 and GlyRα3 Mediate the Central Component of Inflammatory Pain





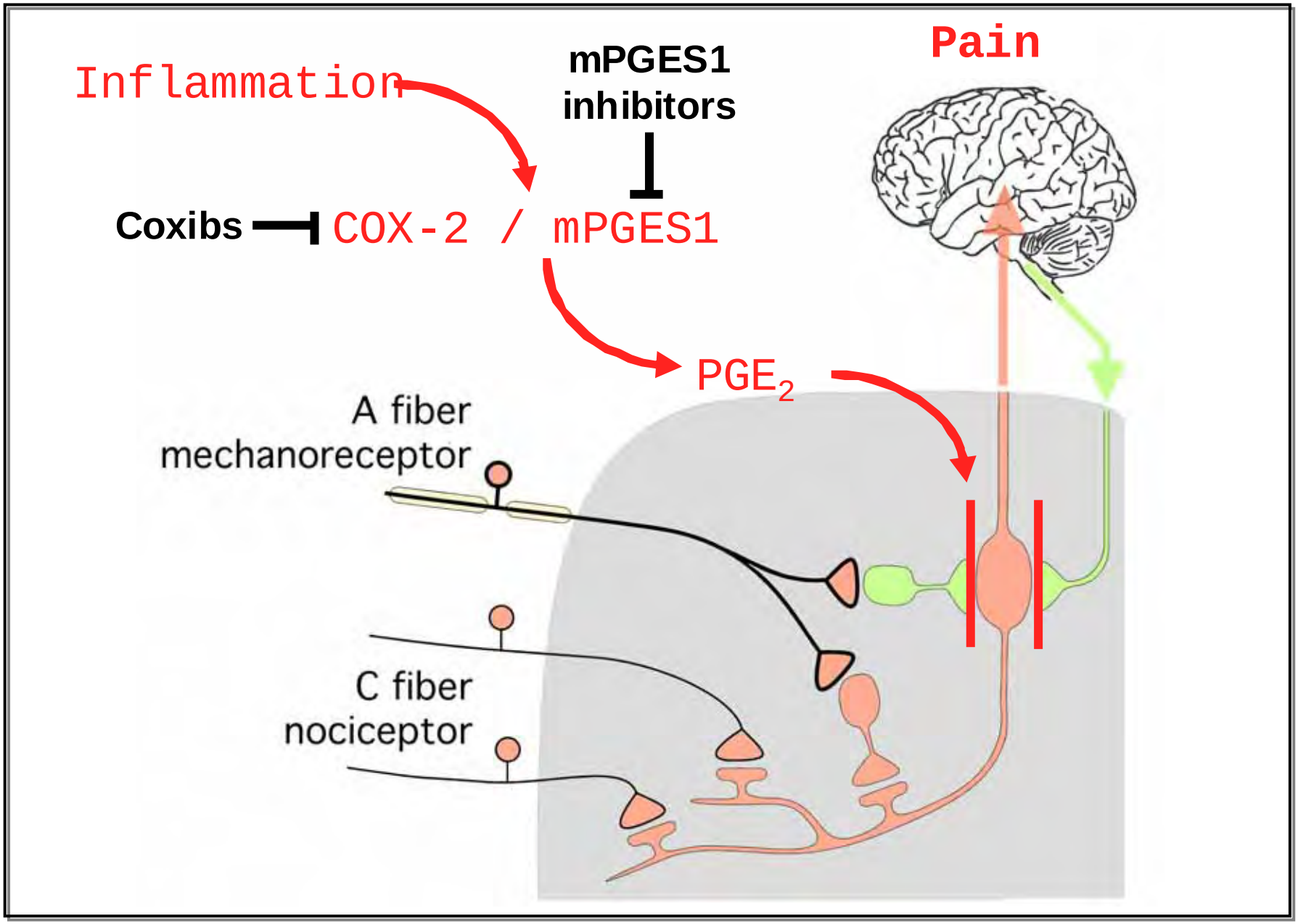




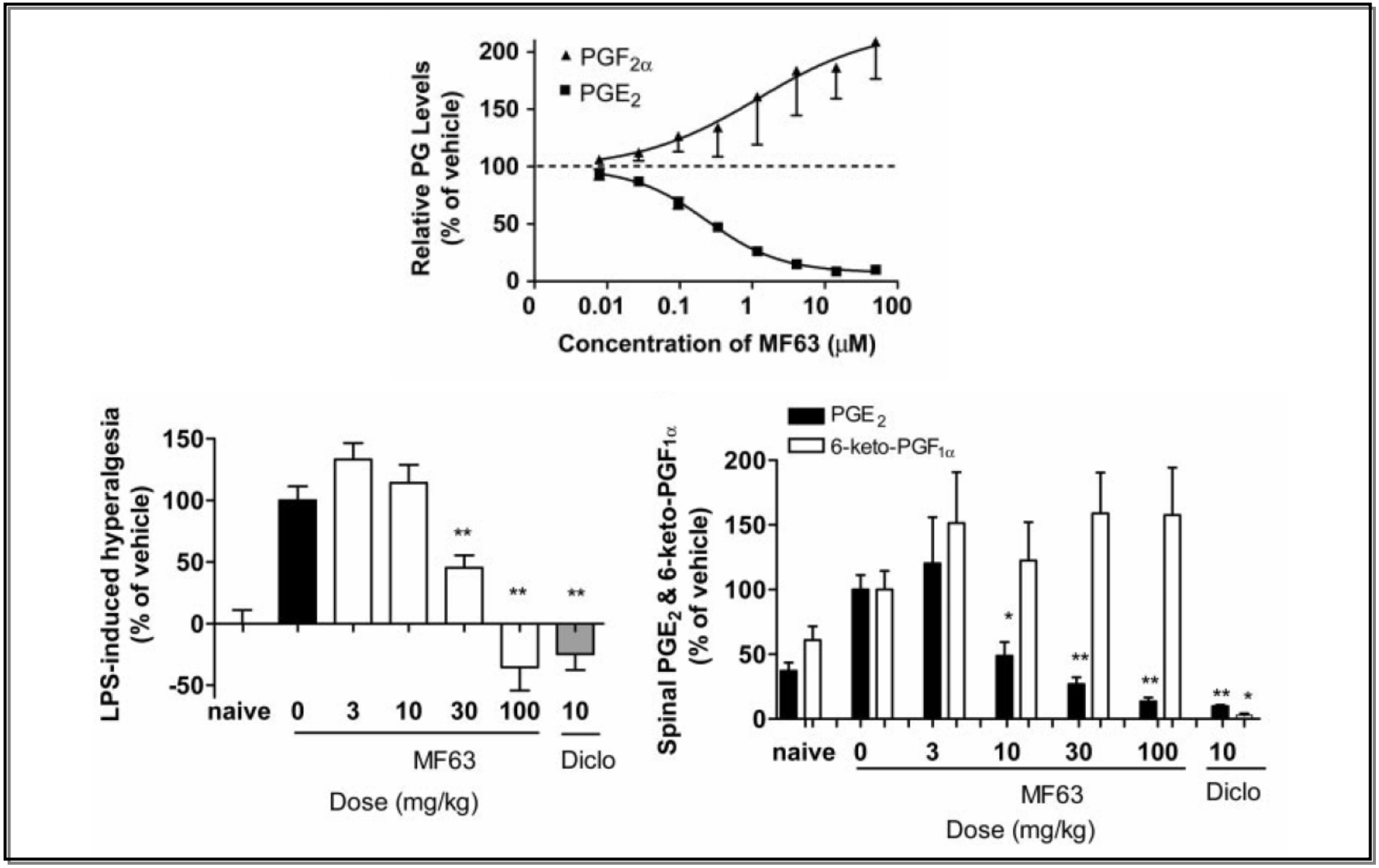


Harvey et al., *Science* 2004
Reinold et al., *J. Clin. Invest.* 2005

Dis-Inhibition in Inflammatory Pain

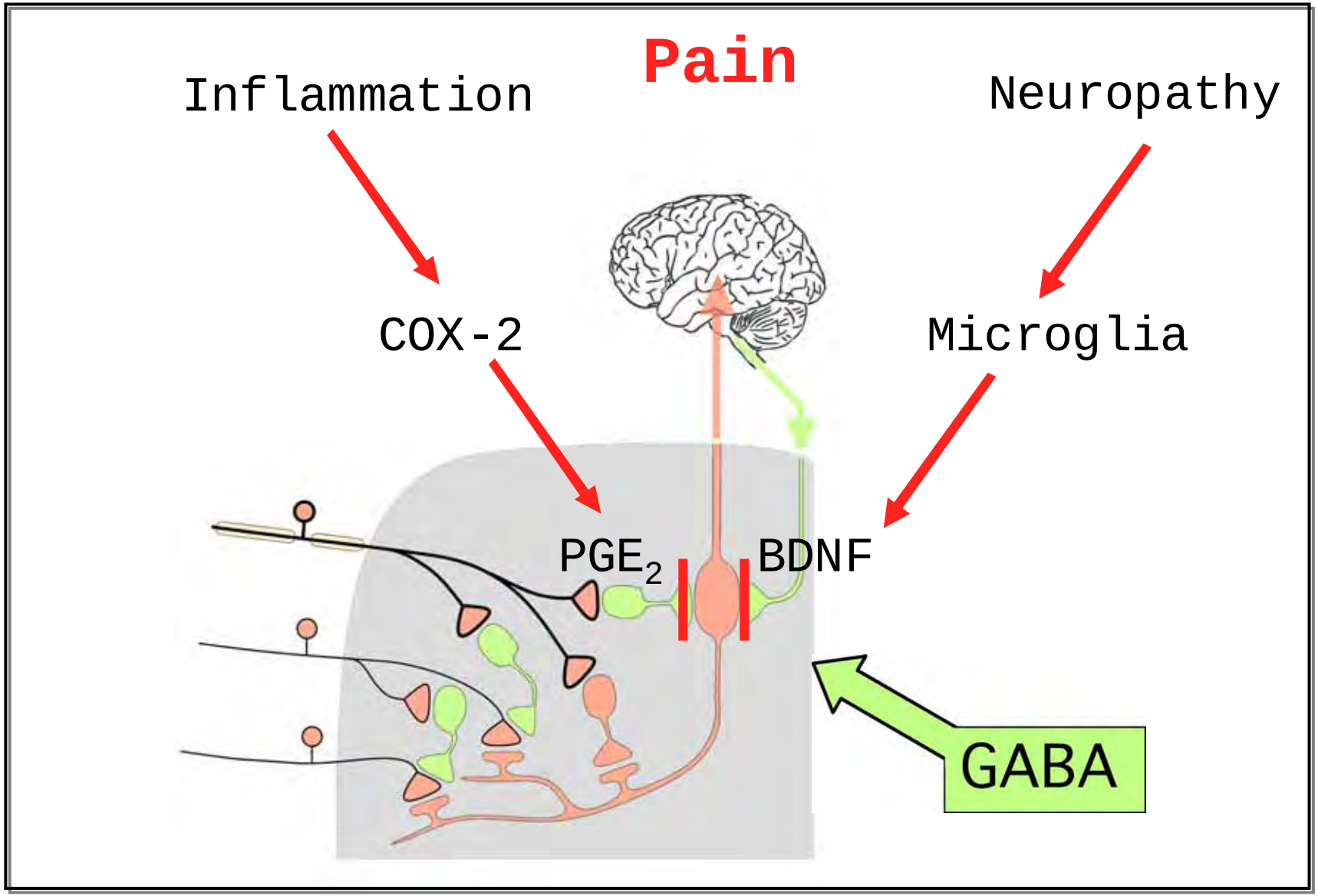


mPGES-1 Inhibition in Inflammatory Pain

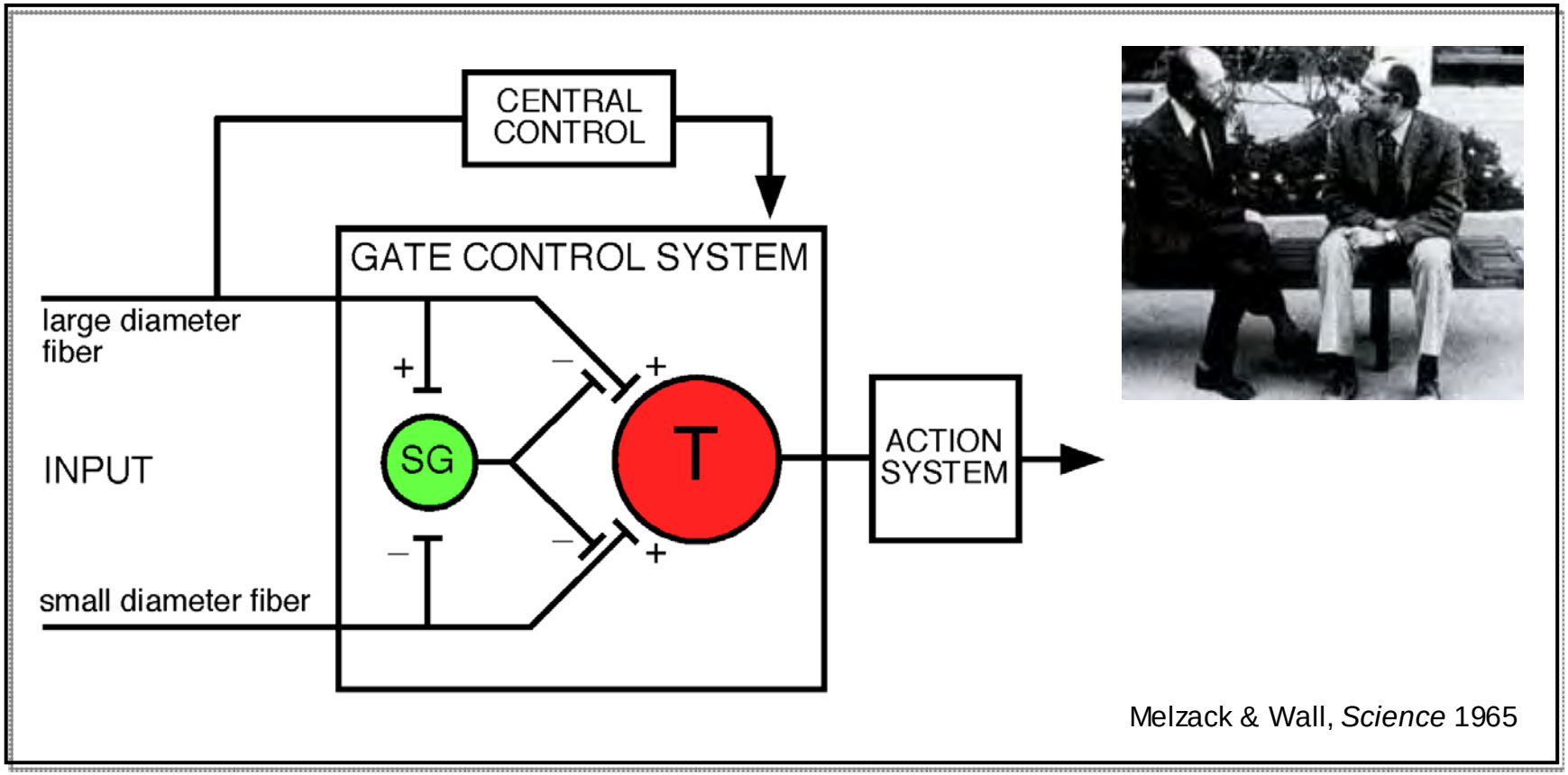


Xu et al., *JPET*, 2008

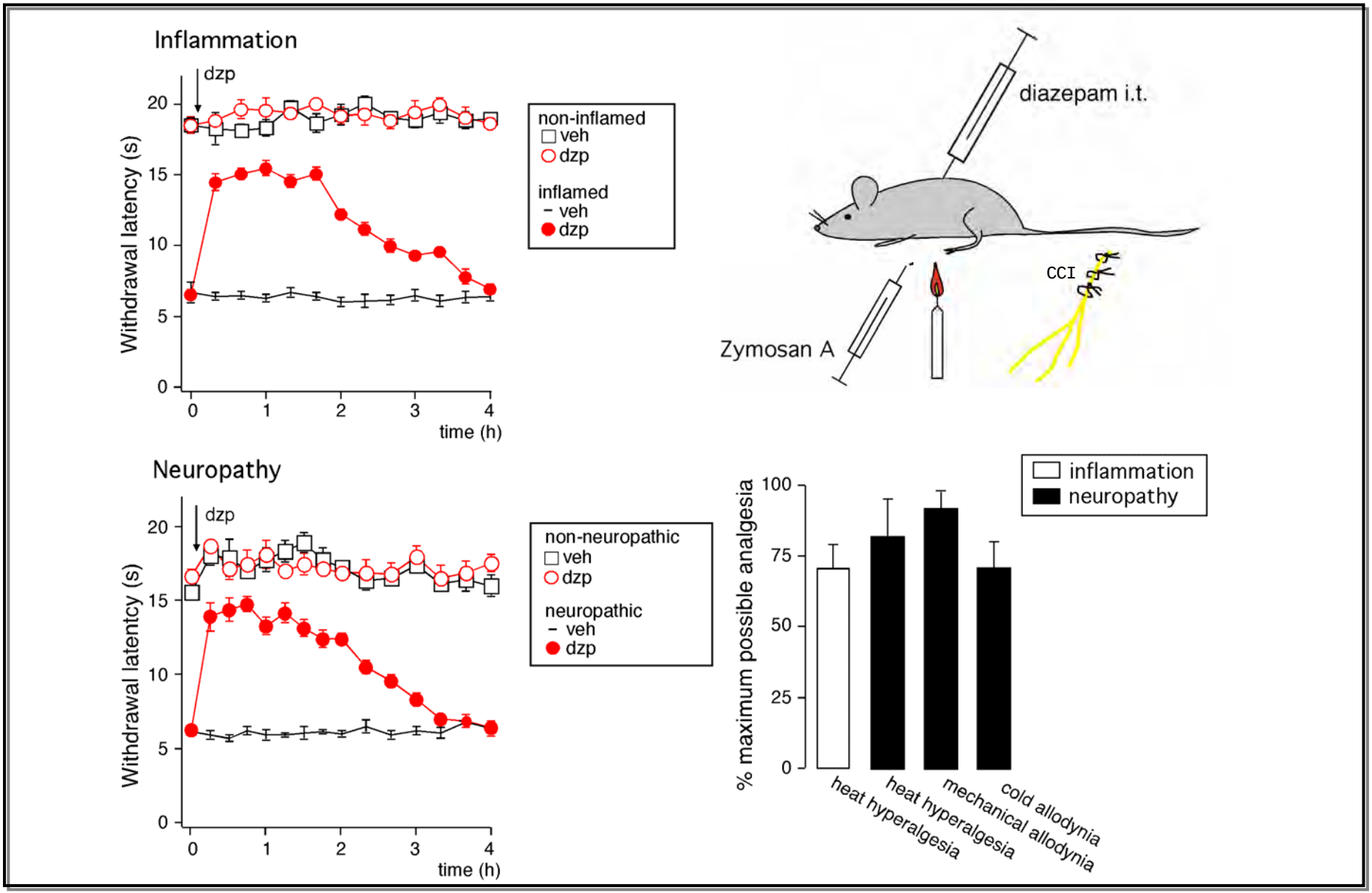
The Dorsal Horn Pain Filter: Impairment and Repair



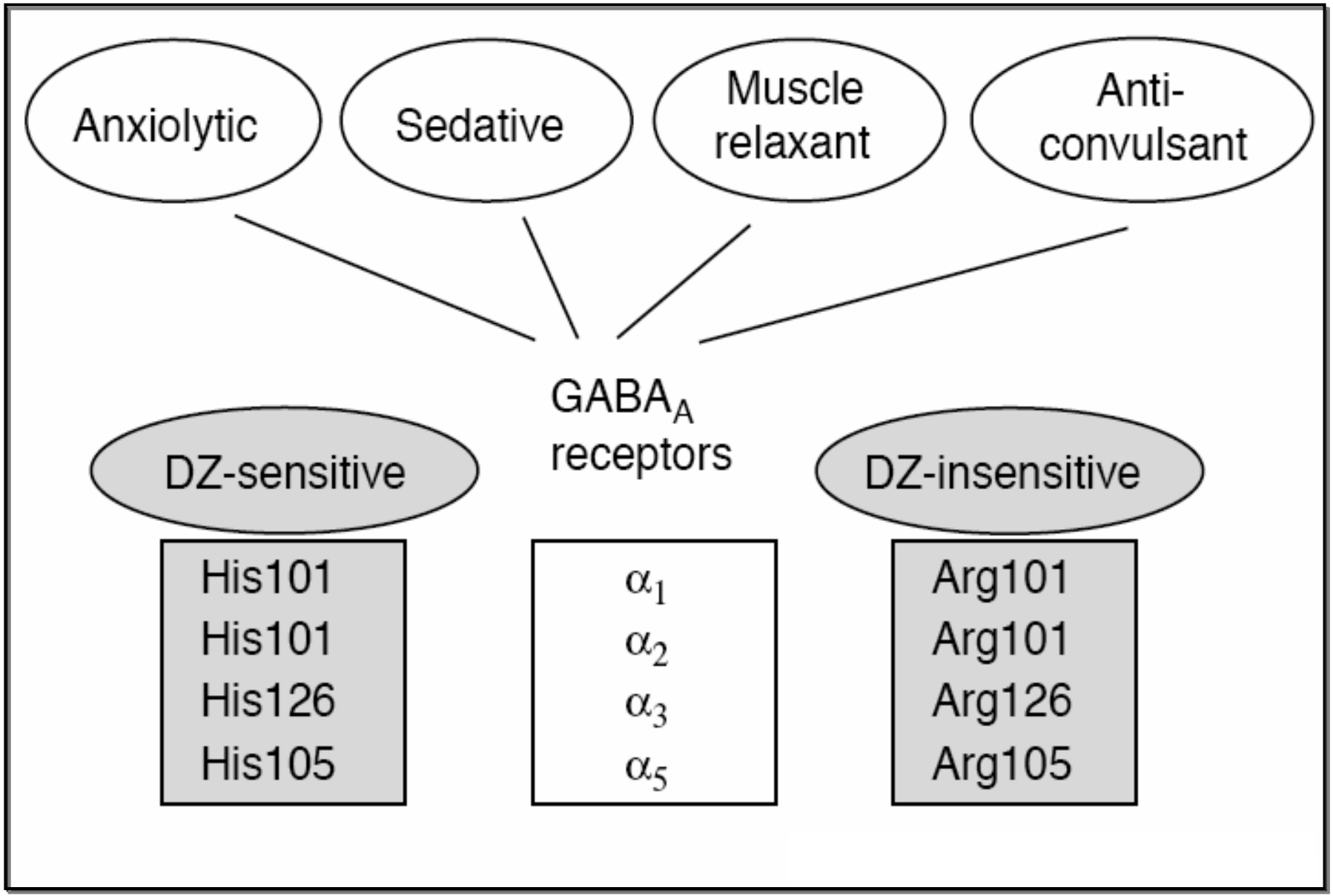
Gate-Control Theory of Pain



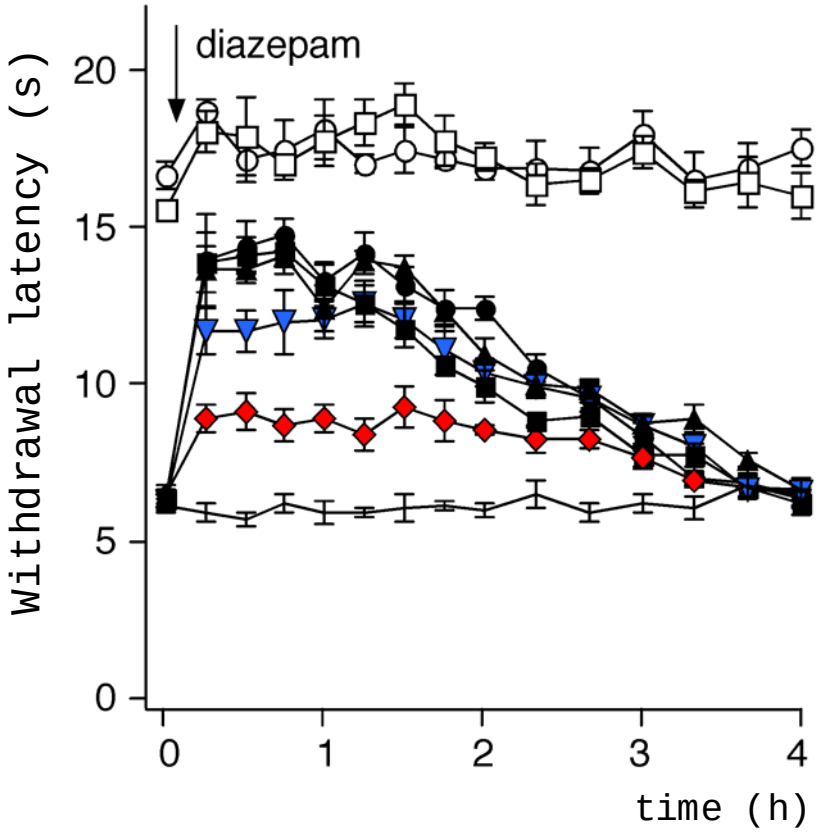
Facilitation of GABAergic Inhibition Reverses Hyperalgesia

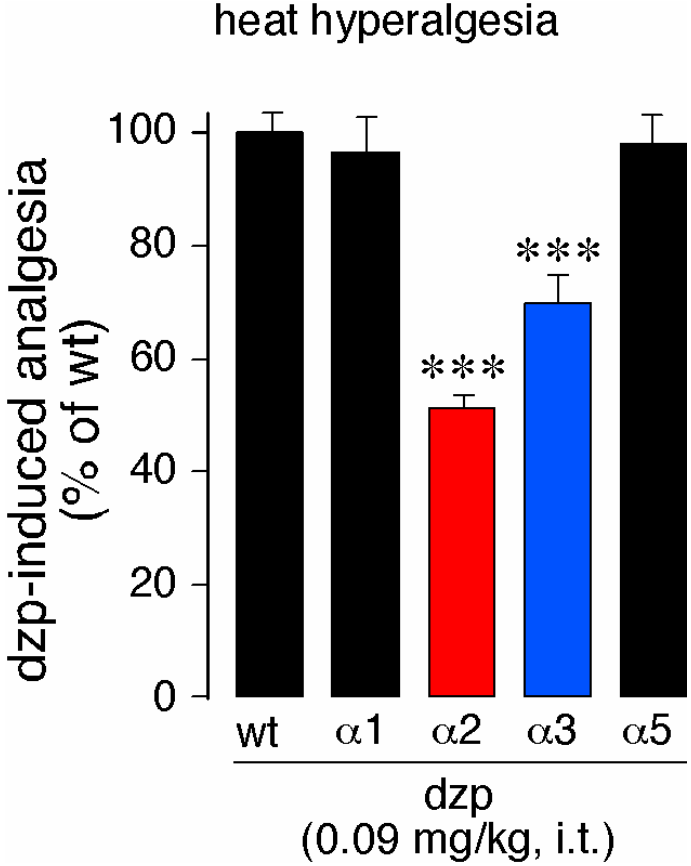


Subtype-Selective "Benzodiazepines": L-838,417



$GABA_A$ Receptor Subtypes and Spinal Analgesia - Inflammatory Pain





Katharina Hösl & Heiko Reinold
in Knabl et al., *Nature* 2008

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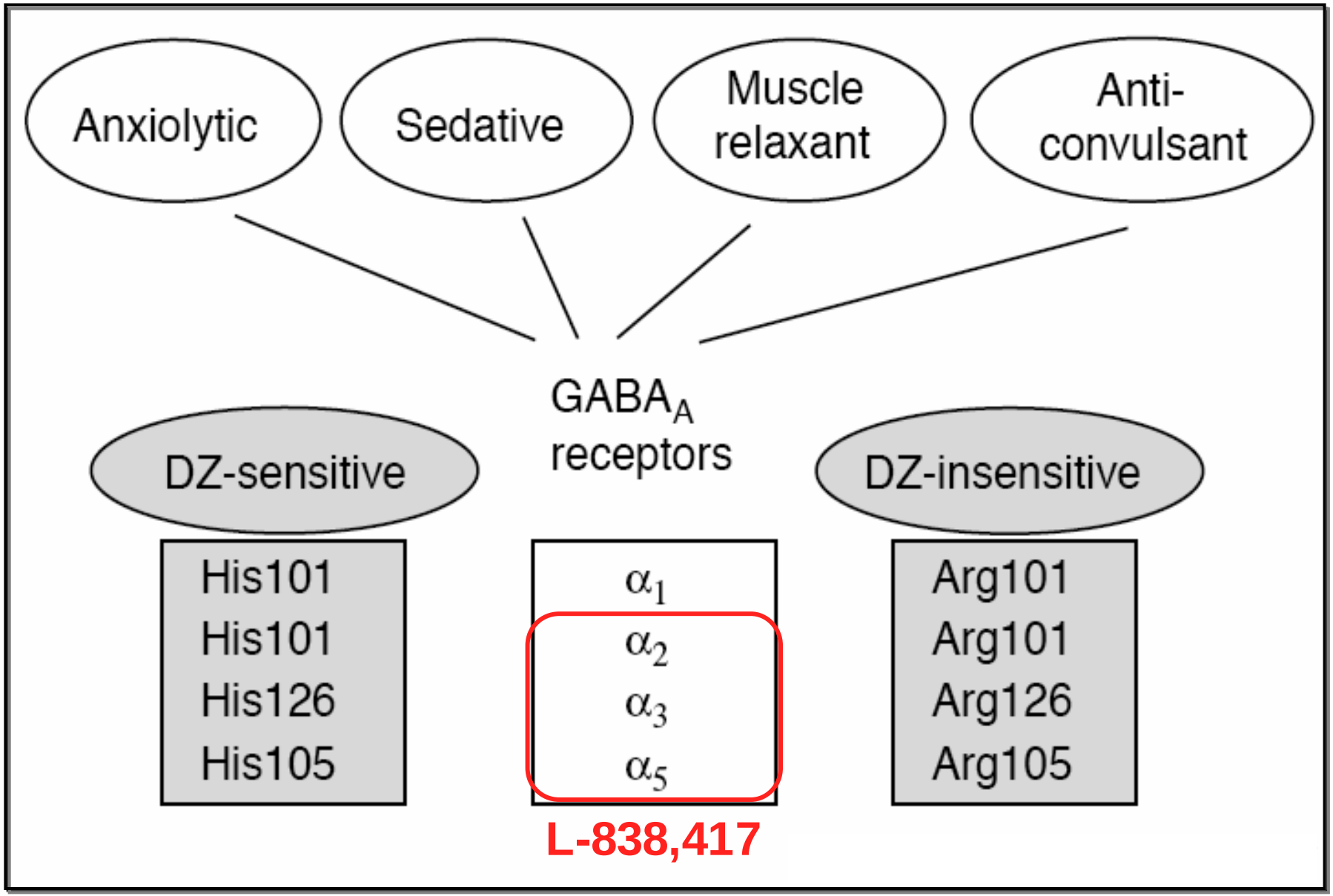
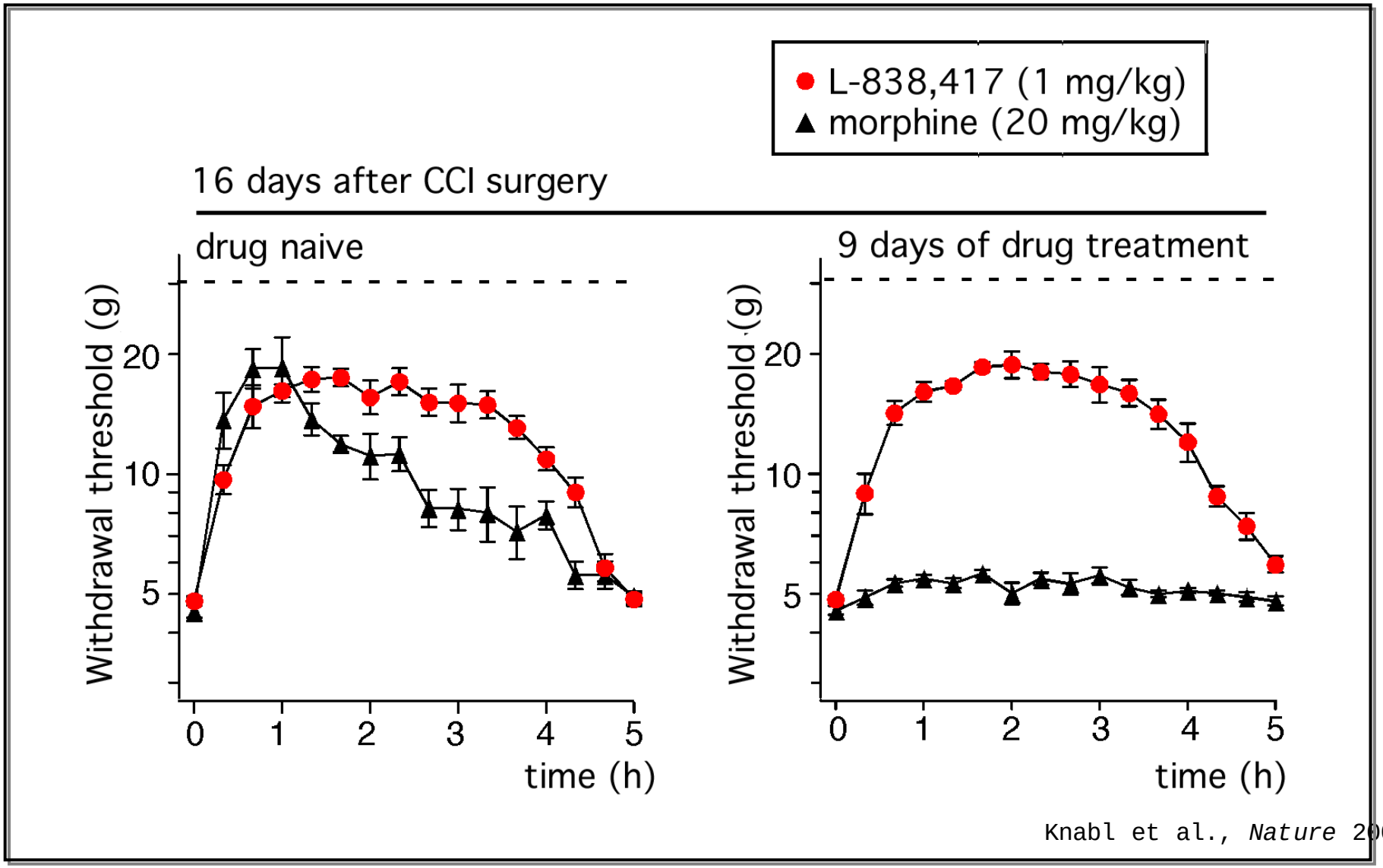
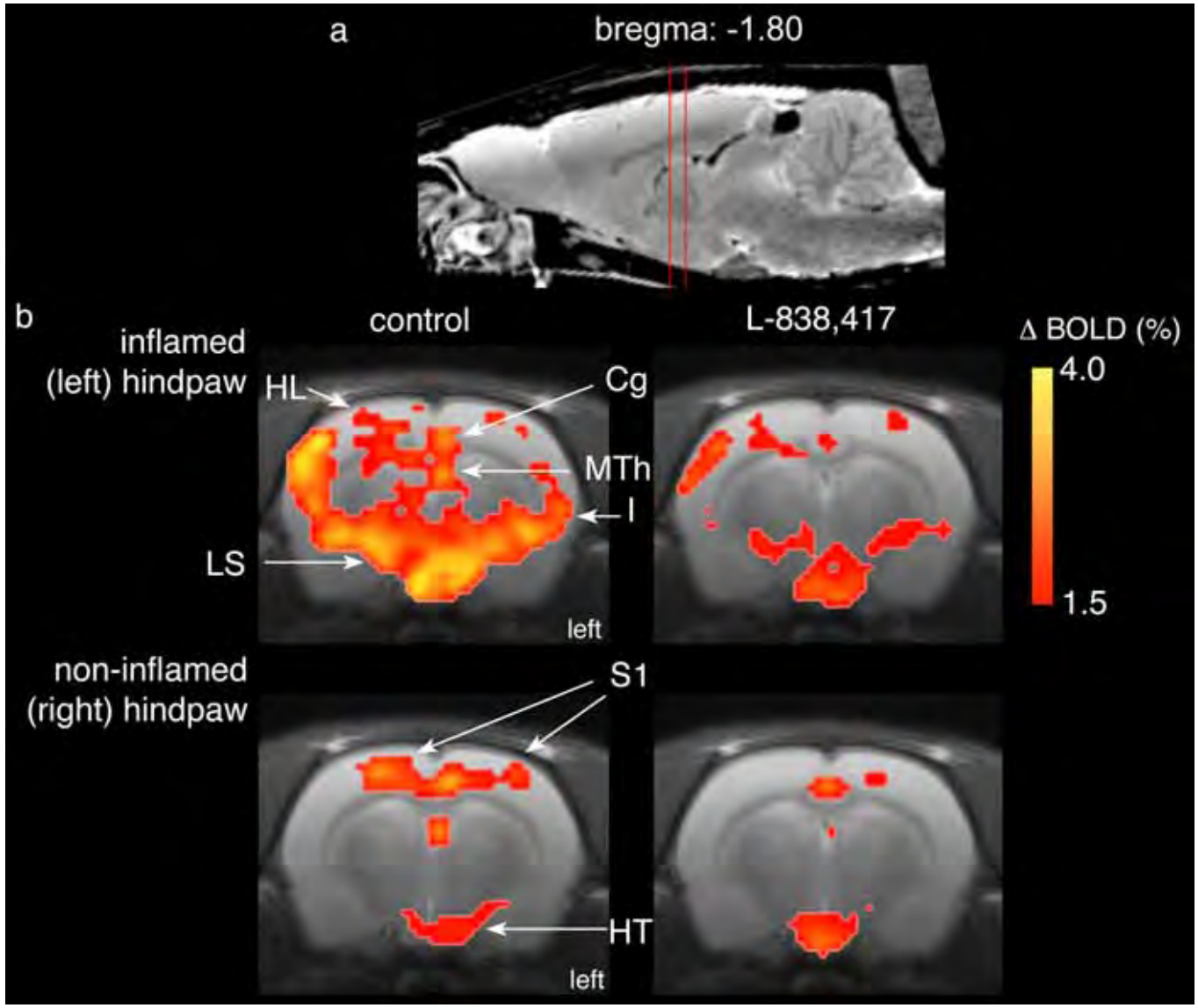


L-838,417 versus Morphine



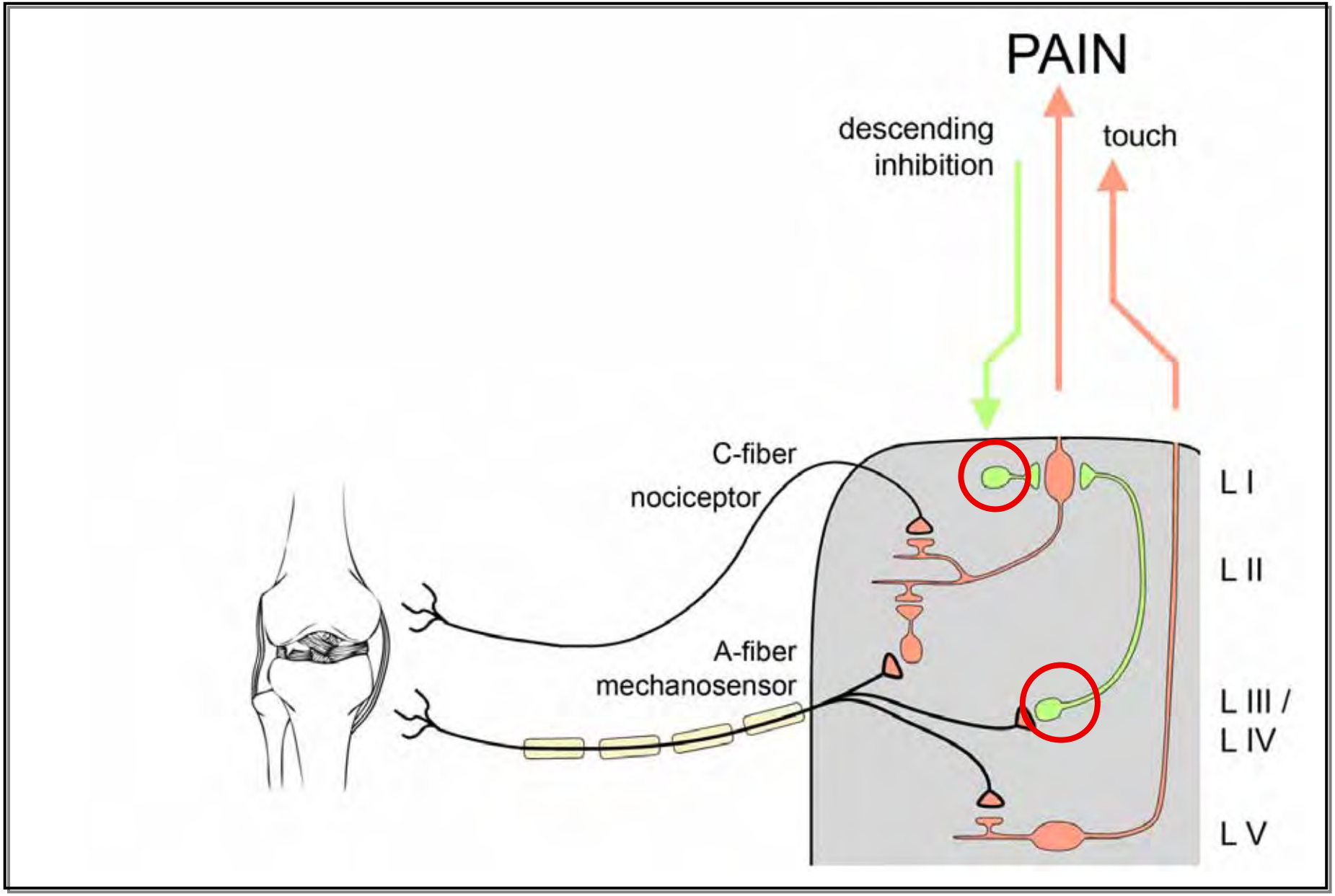
Knabl et al., *Nature* 2008

L-838‘417: fMRI in Hyperalgesic Rats

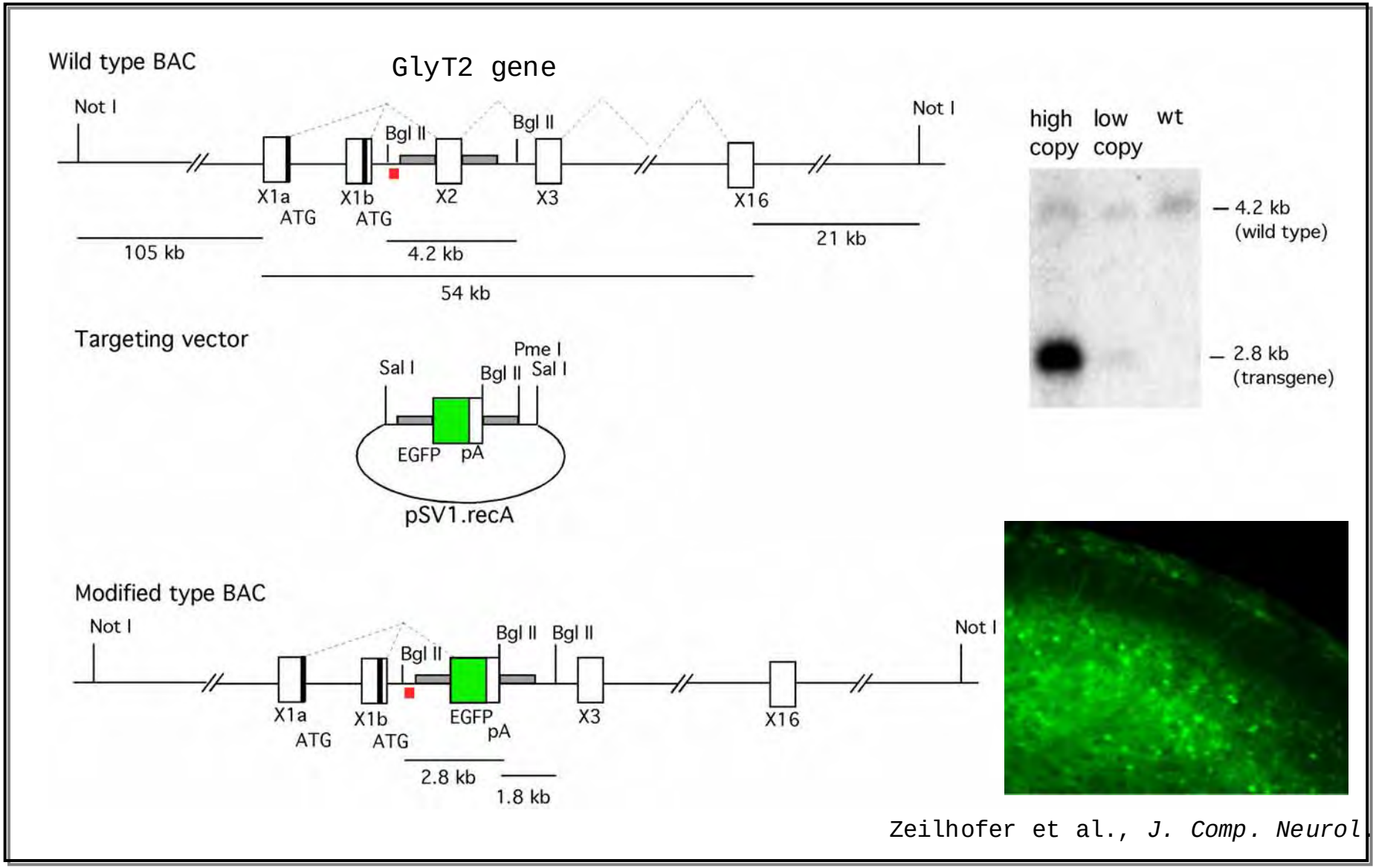


Andreas Hess in:
Knabl et al., *Nature*, 2008

Pain Control by Inhibitory Interneurons

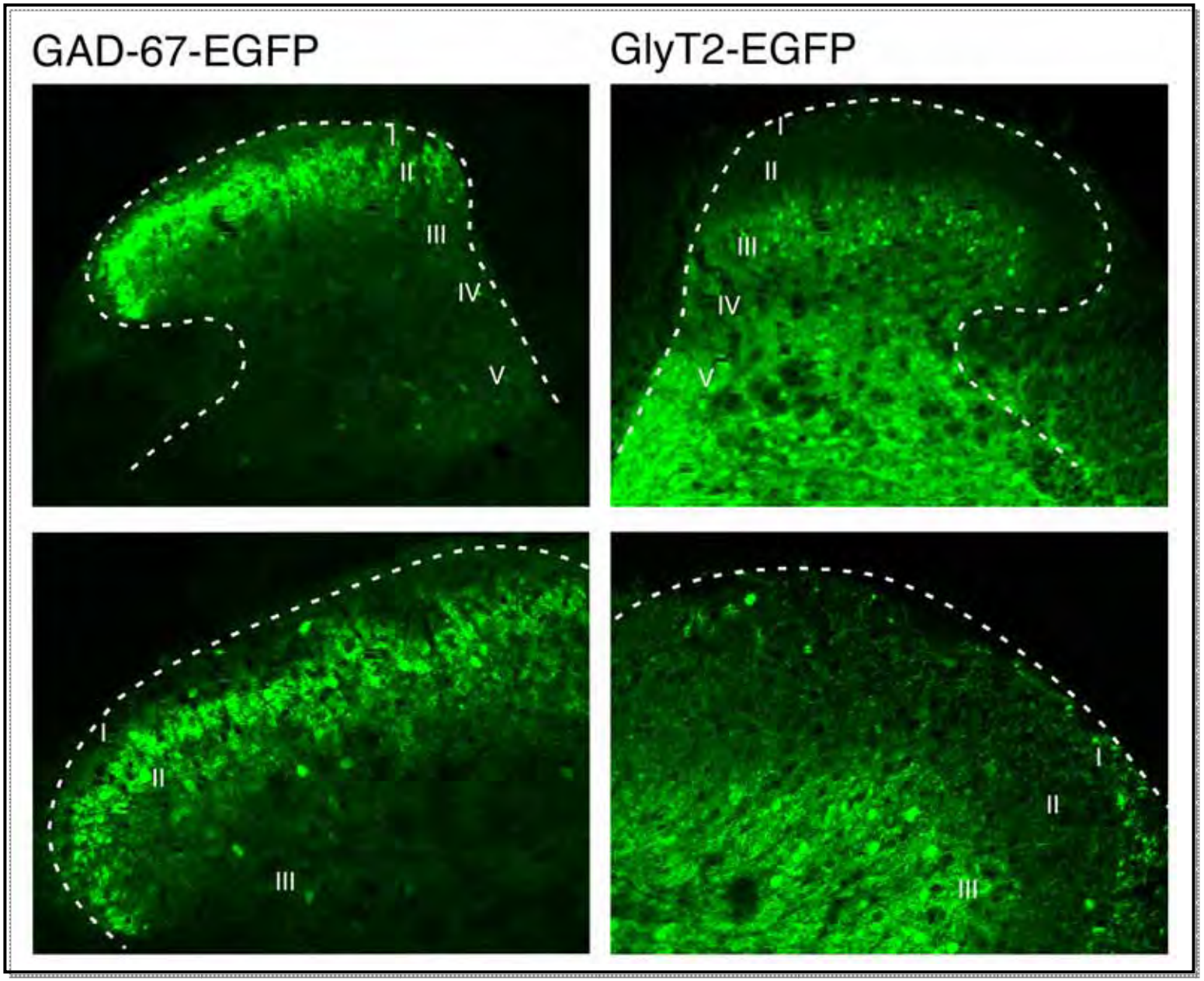


Generation of BAC Transgenic Mice Expressing EGFP in Neuronal Subpopulations



Zeilhofer et al., *J. Comp. Neurol.*,

Inhibitory Neurons in the Spinal Dorsal Horn



Transcriptom of dorsal horn inhibitory cells

- *GlyT2*-EGFP
- *GAD67*-EGFP
- *ppN/OFQ*-EGFP

Inhibitory interneuron-specific gene deletion

- *GlyT2*-cre
- *GAD67*-cre

Association studies

- postoperative hyperalgesia
- migraine