Fortbildung Privatklinik Obach 2013

Aspekte im Umgang mit Schmerzkrankheiten

Pathologie rezeptorischer Schmerzen *and new aspects of pain pathophysiology*

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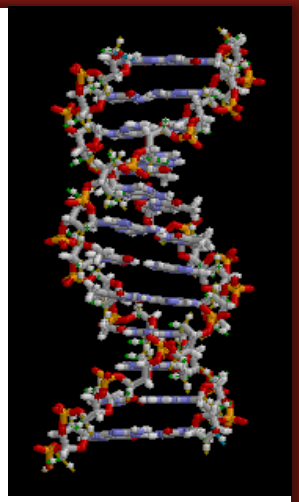
Anesthesiology Dpt, CHUV, Lausanne

Congenital insensitivity to pain

Gabby

- From Oprah Winfrey's talk show:
- "When she was a baby Gabby started chewing her hand…
  … it looked mangled and nasty, like raw hamburger"
  - > to pull out all of her teeth
- "she poke her own eye out"
  - > to wear protective eye goggles to spare the second eye

Rare genetic occurrence?



- Yes
  - But why is it interesting?
    - Give powerful directions for pathophysiology
    - Patient will soon come to the visit with their exons screened

…maybe mutations are not so rare

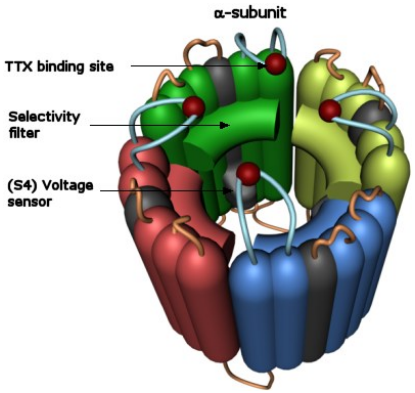
Nav1.7 example

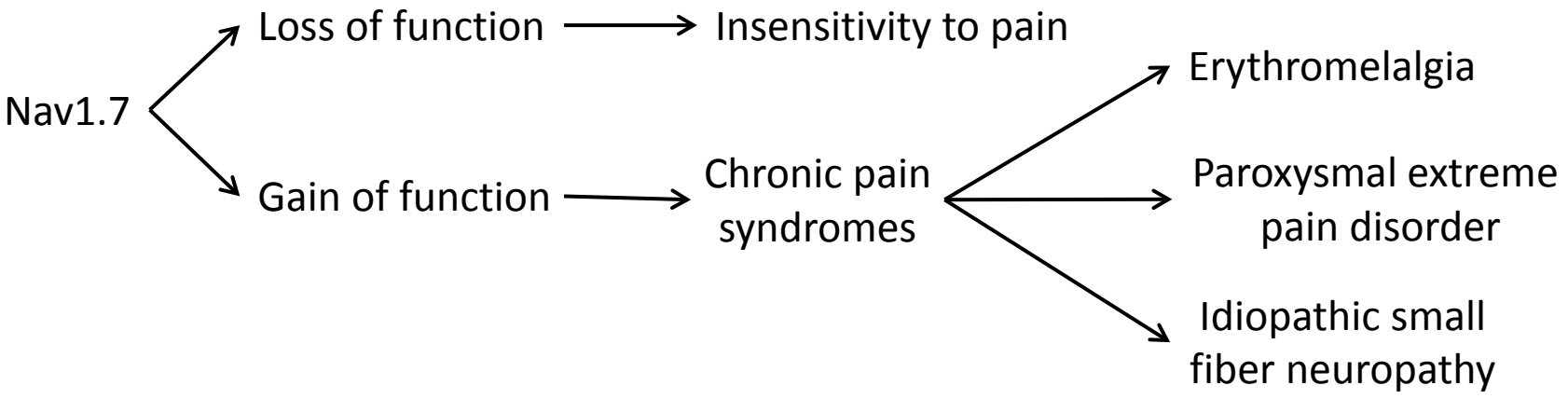
nature Vol 444|14 December 2006|doi:10.1038/nature05413

ARTICLES

An *SCN9A* channelopathy causes congenital inability to experience pain

- Sodium channels
  - Initiation and transmission of action potentials
  - 9 isoforms Nav1.1-9
  - SCN9A for Nav1.7-> mostly on nociceptors

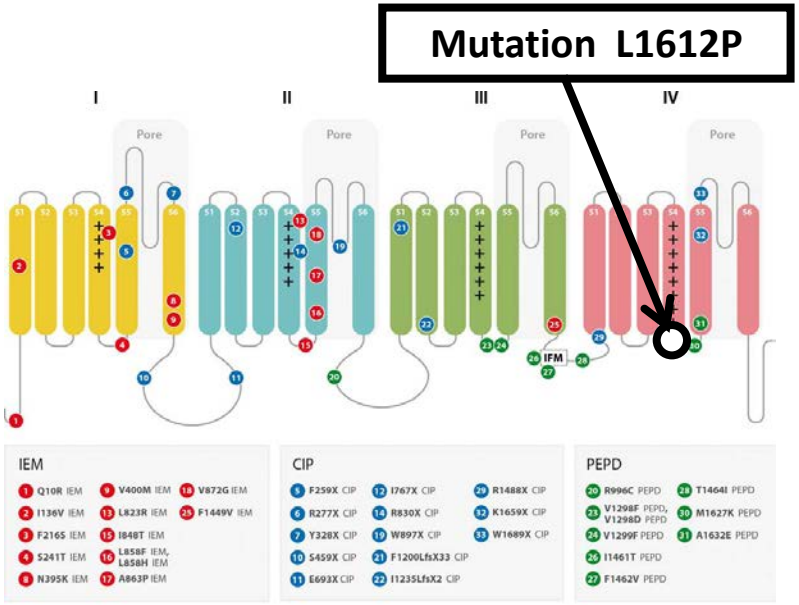


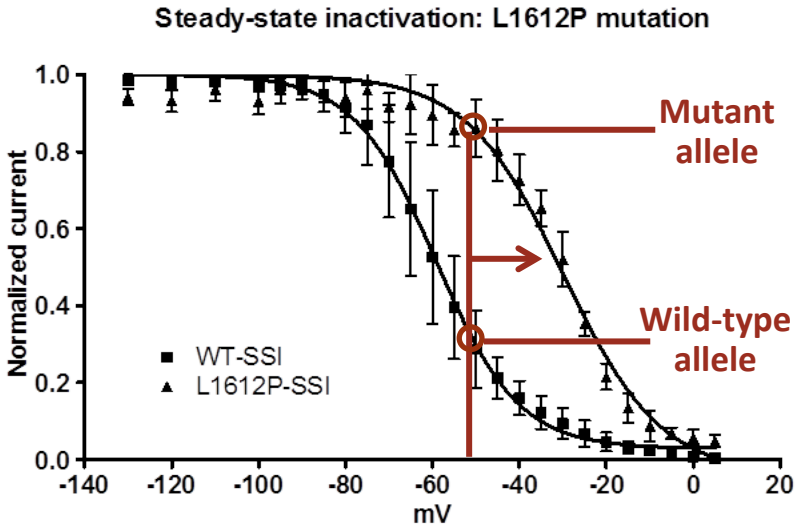


Faber CJ, *Annals of Neurology* 2012

And even locally mutated

- Newly described mutation in the Nav1.7 gene:
  - In a family from Lausanne
  - Suffering from PEPD, currently followed at the CHUV
  - Translational study with in vitro hyperexcitability





Coll: Dr C. Wider, Department of Clinical Neuroscience, CHUV

Magic bullet on Nav1.7?

Toxins

ProTx-II

Tarantula: *Thrixopelma prurient*

From last month:

Centipede

PNAS

Discovery of a selective $Na_V1.7$ inhibitor from centipede venom with analgesic efficacy exceeding morphine in rodent pain models

Shilong Yang[a,b,1], Yao Xiao[a,b,1], Di Kang[a,b,1], Jie Liu[a,b], Yuan Li[a,b], Eivind A. B. Undheim[c], Julie K. Klint[c], Mingqiang Rong[a,2], Ren Lai[a,2], and Glenn F. King[c,2]

[a]Key Laboratory of Animal Models and Human Disease Mechanisms, Kunming Institute of Zoology, Chinese Academy of Sciences and Yunnan Province, Kunming 650223, Yunnan, China; [b]Graduate School of Chinese Academy of Sciences, Beijing 100009, China; and [c]Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The University of Queensland, St. Lucia, QLD 4072, Australia

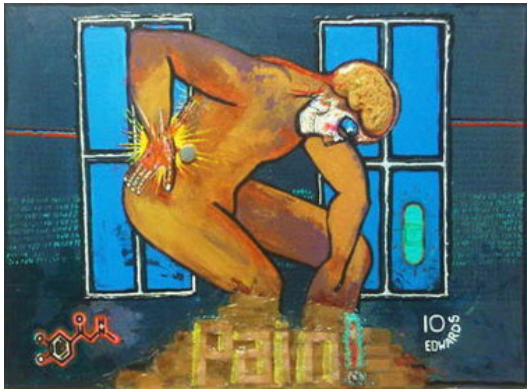
Edited* by Baldomero M. Olivera, University of Utah, Salt Lake City, UT, and approved September 4, 2013 (received for review April 3, 2013)

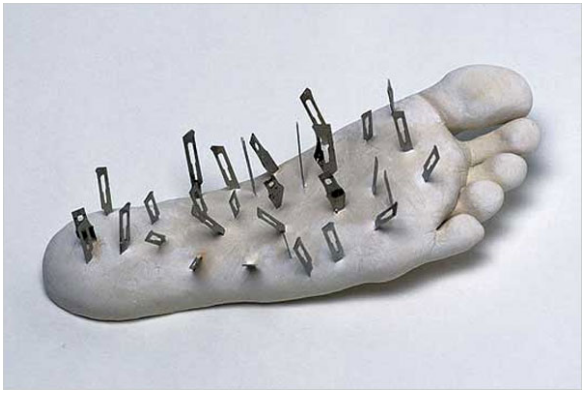
Definition of pain

- IASP – International Association for the Study of Pain
- Defines pain as:

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

2 dimensions





Pictures from: http://www.painexhibit.com/, from chronic pain patients

Blue

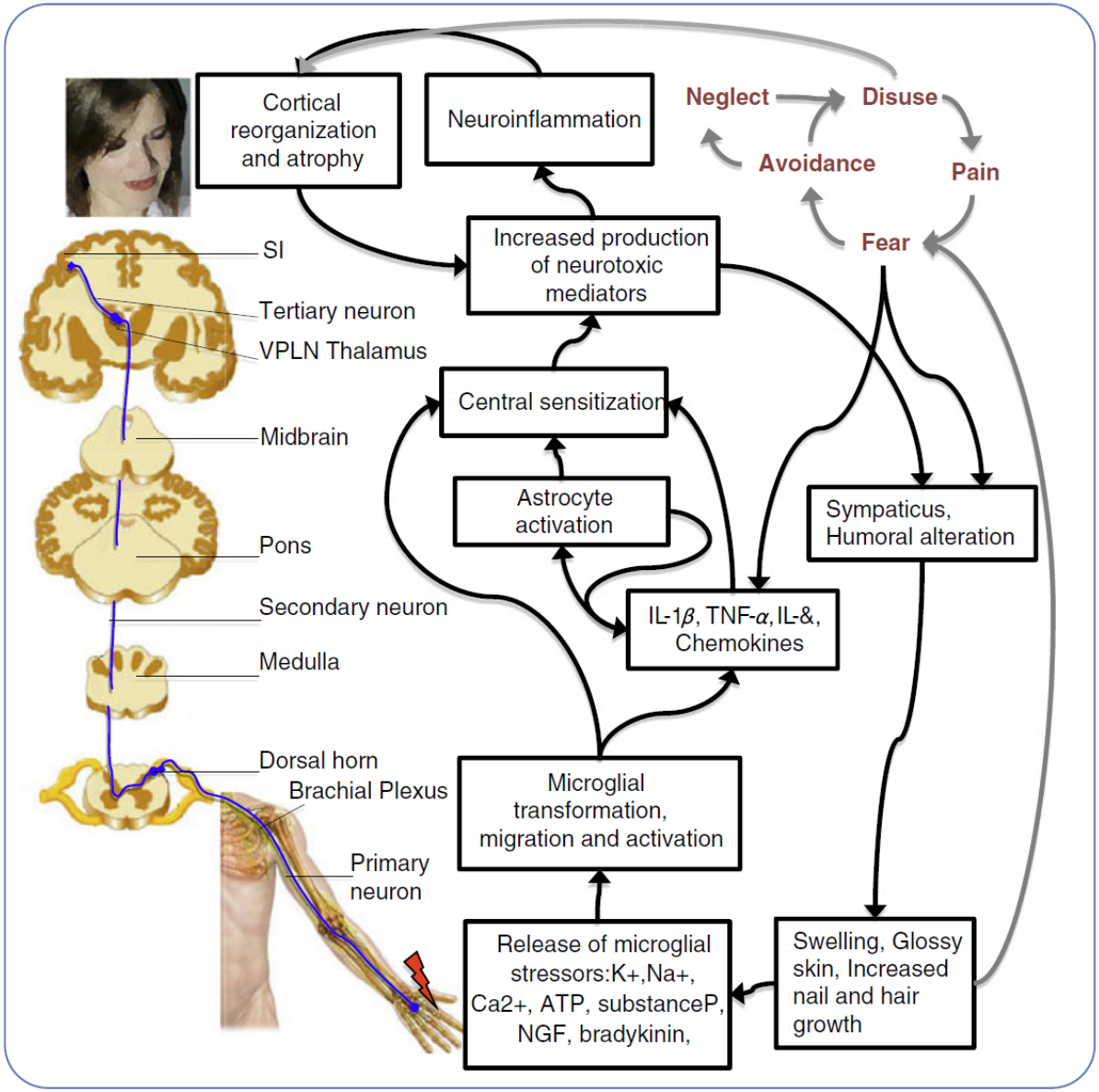
Nociceptive pathway

Black

Biochemical cascade

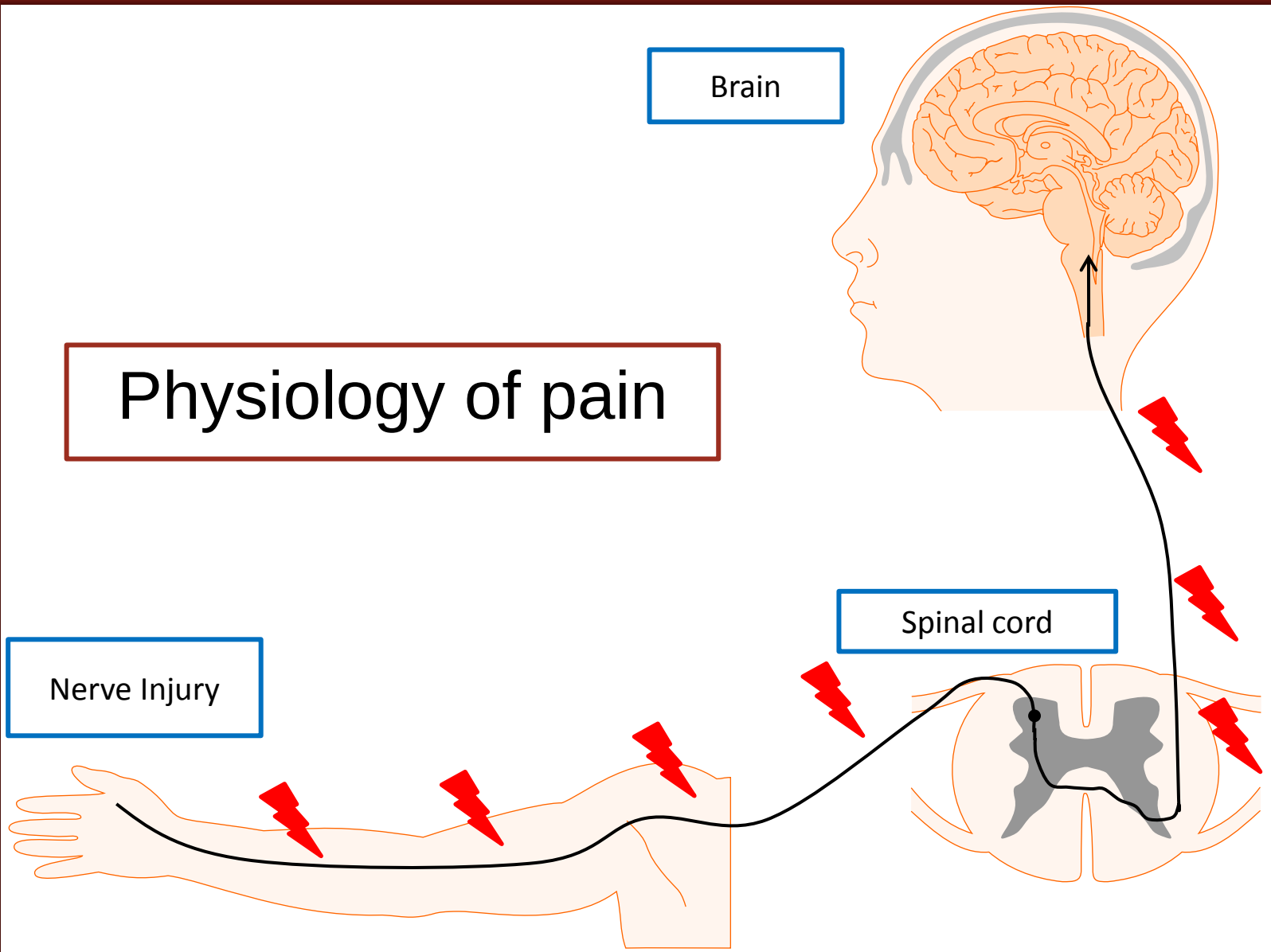
Gray

Psychosocial circuits



Linnman C, *J Neuroimmune Pharmacol* 2013

Physiology of pain



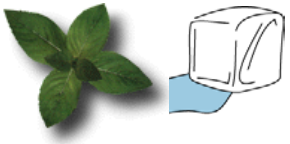
Peripheral receptors

Stimulus

Various nature

TRPV1
TRPV2

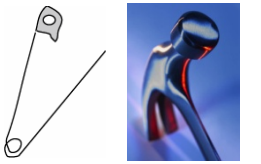
Heat



TRPM8
TRPA1

Cold

Thermosensitivity



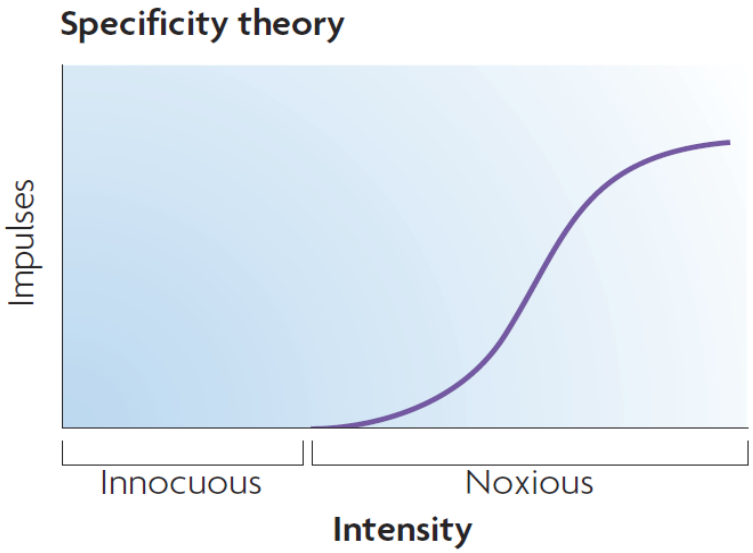
DEG/ENaC
DRASIC
TREK-1
TRPN1

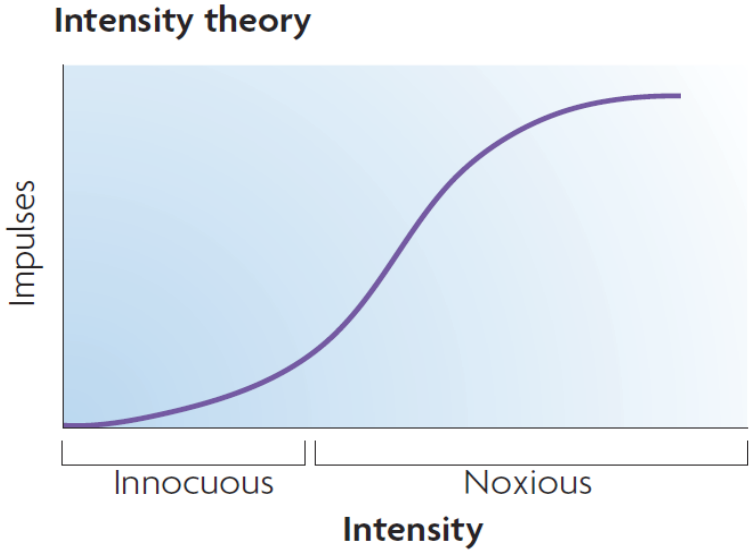
Mechanical

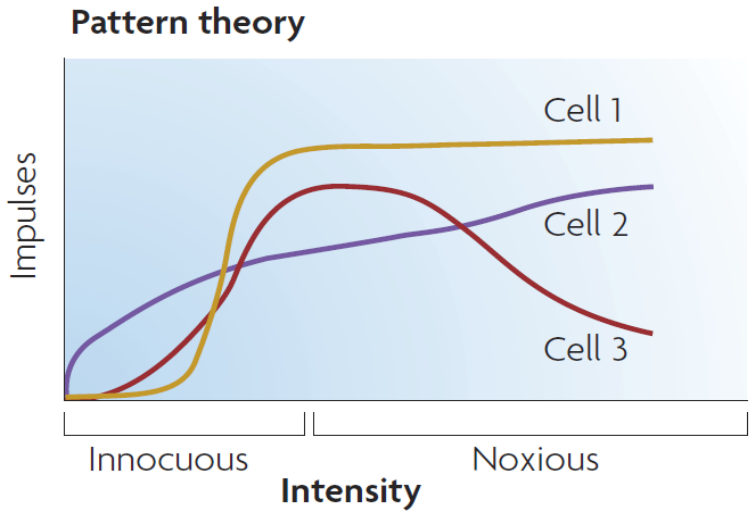
ASICs
P2X3

Chemical

Specificity is not a general principle

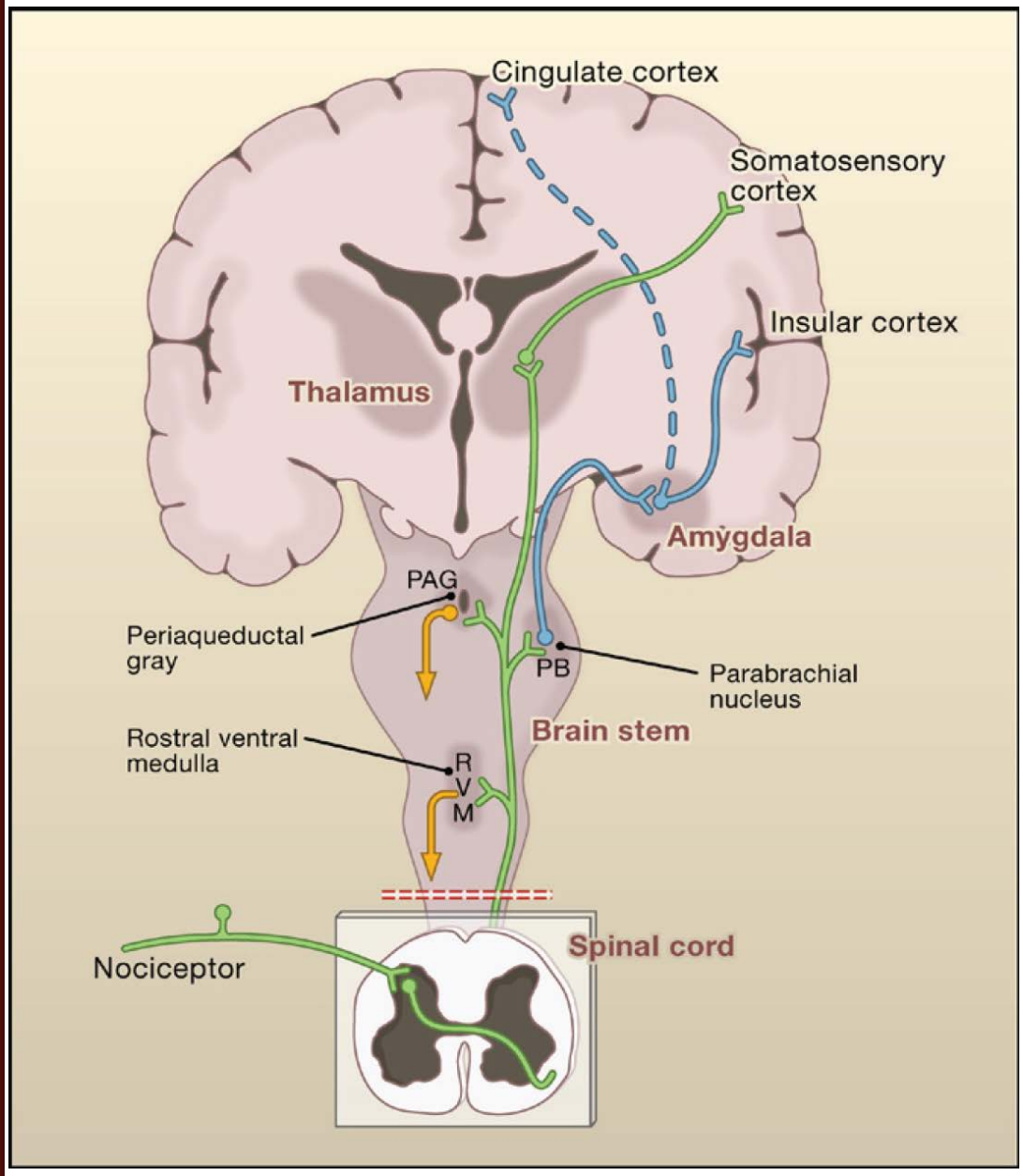






- Receptors are polymodal
- Different receptors on same fibers

Perl ER, *Nature Reviews Neuroscience* 2007



Anatomy of pain

-Nociceptor

to spinal cord

-Secondary neuron

to thalamus

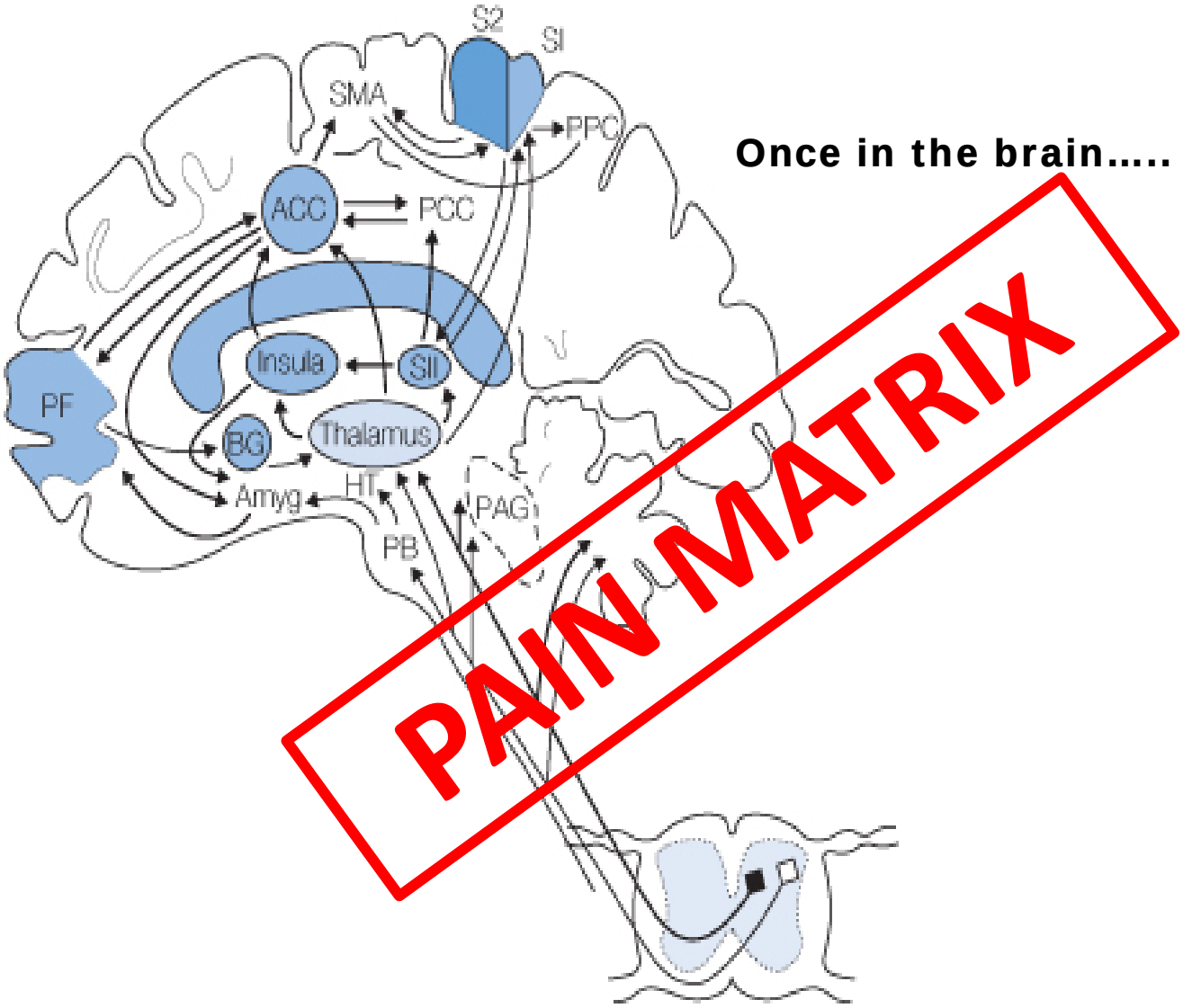
-Third neuron

to cortex

Also…

descending pathways

Basbaum AI, *Cell* 2009

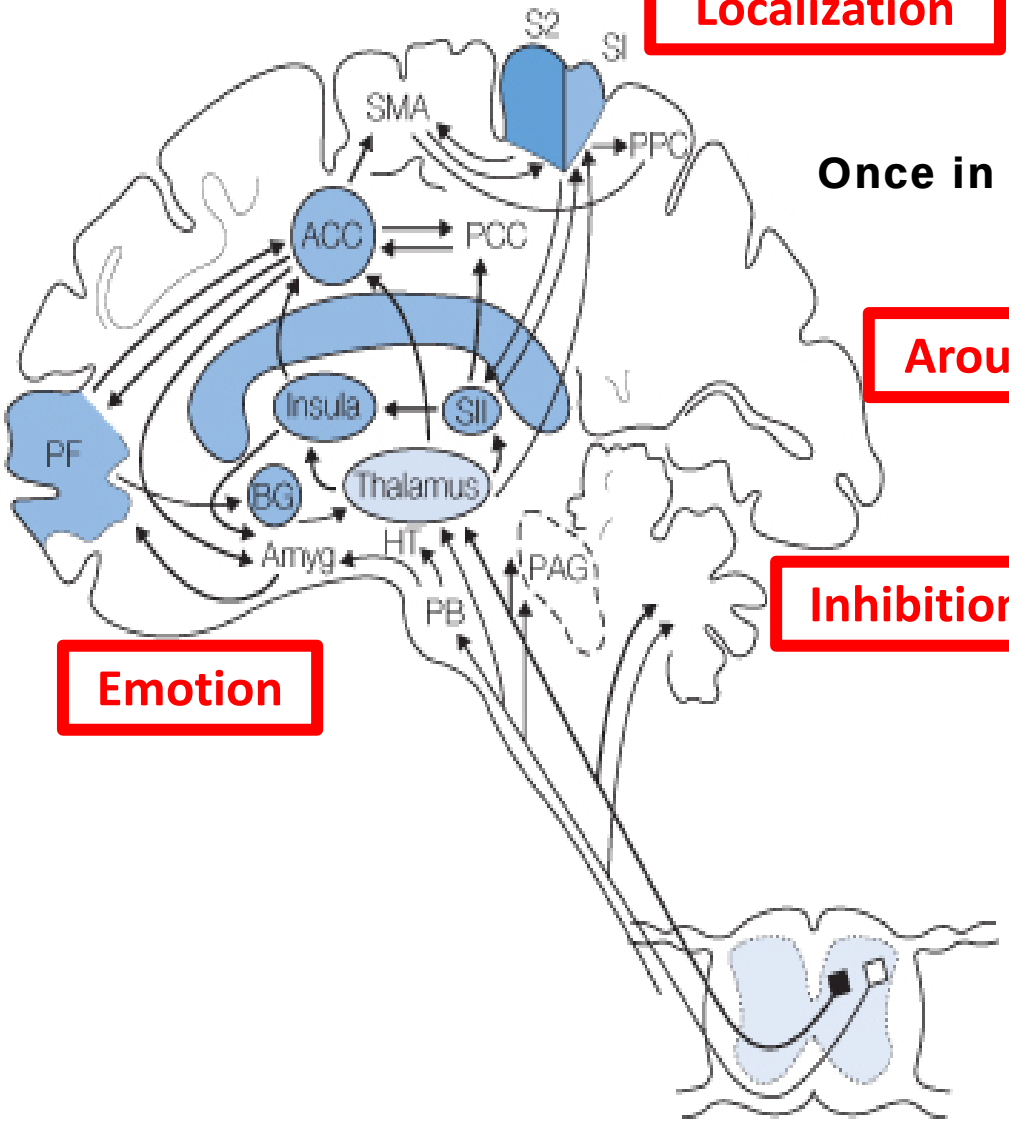


Once in the brain.....

PAIN MATRIX

Apkarain AV, *European Journal of pain* 2005

Localization



Once in the brain…..

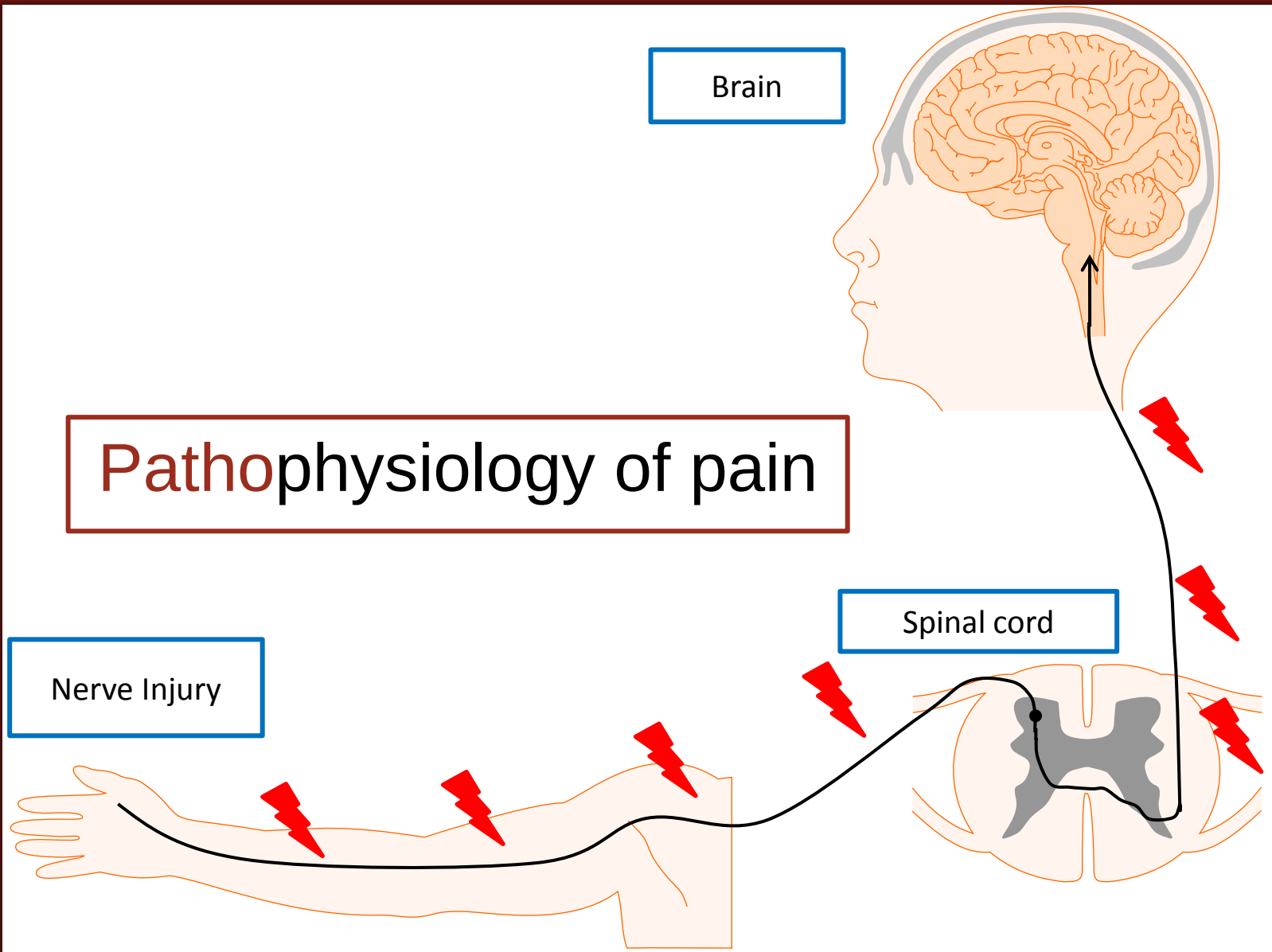
Arousal

Inhibition

Emotion

Apkarain AV, *European Journal of pain* 2005

Pathophysiology of pain

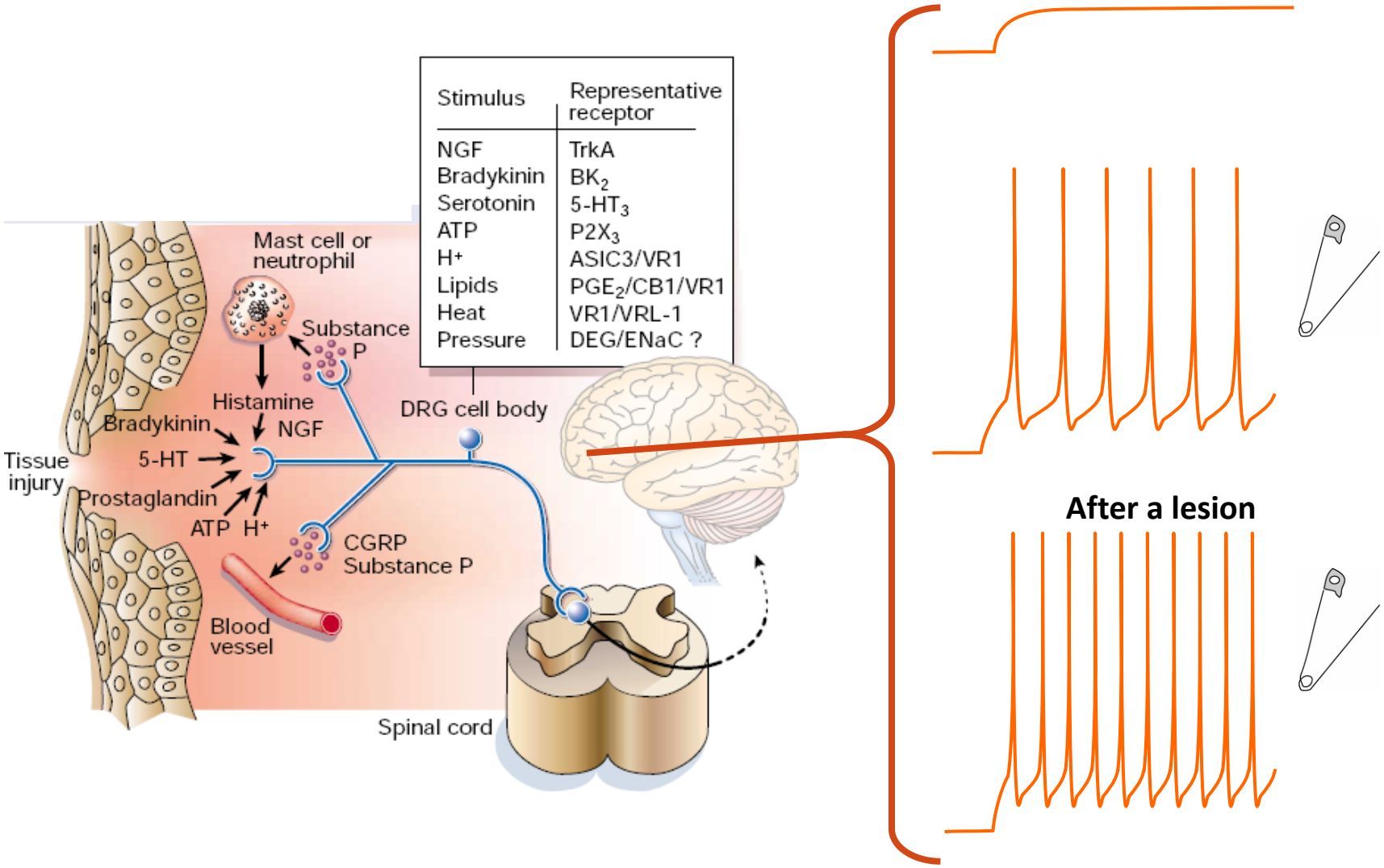


What are new mechanisms?

Mechanisms of neuropathic pain

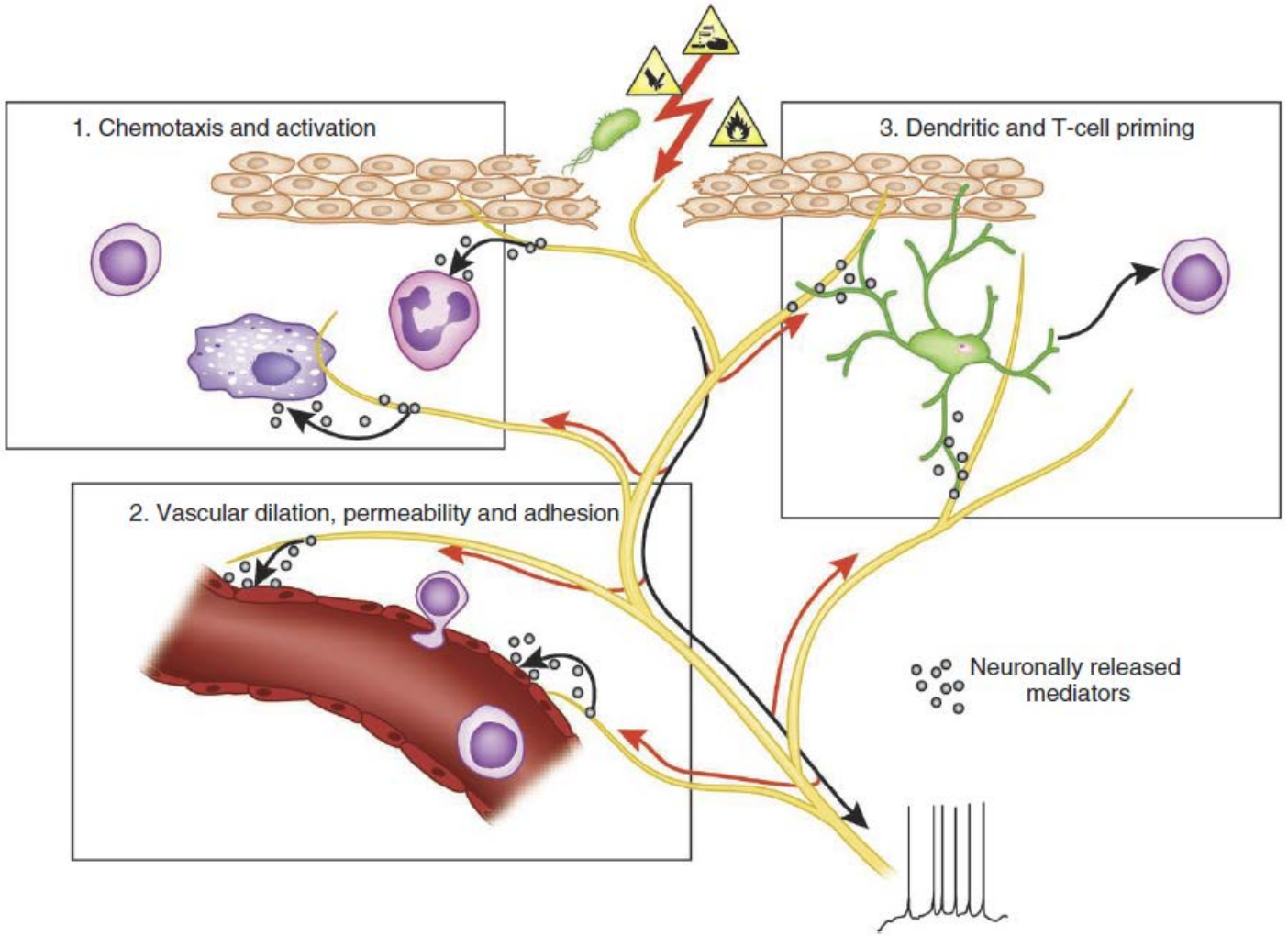
- Sensitization processes
- Microglial activation
- Disinhibition

Peripheral sensitization



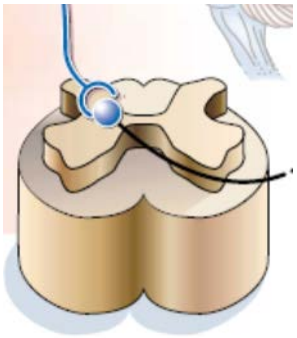
Julius D, *Nature* 2001

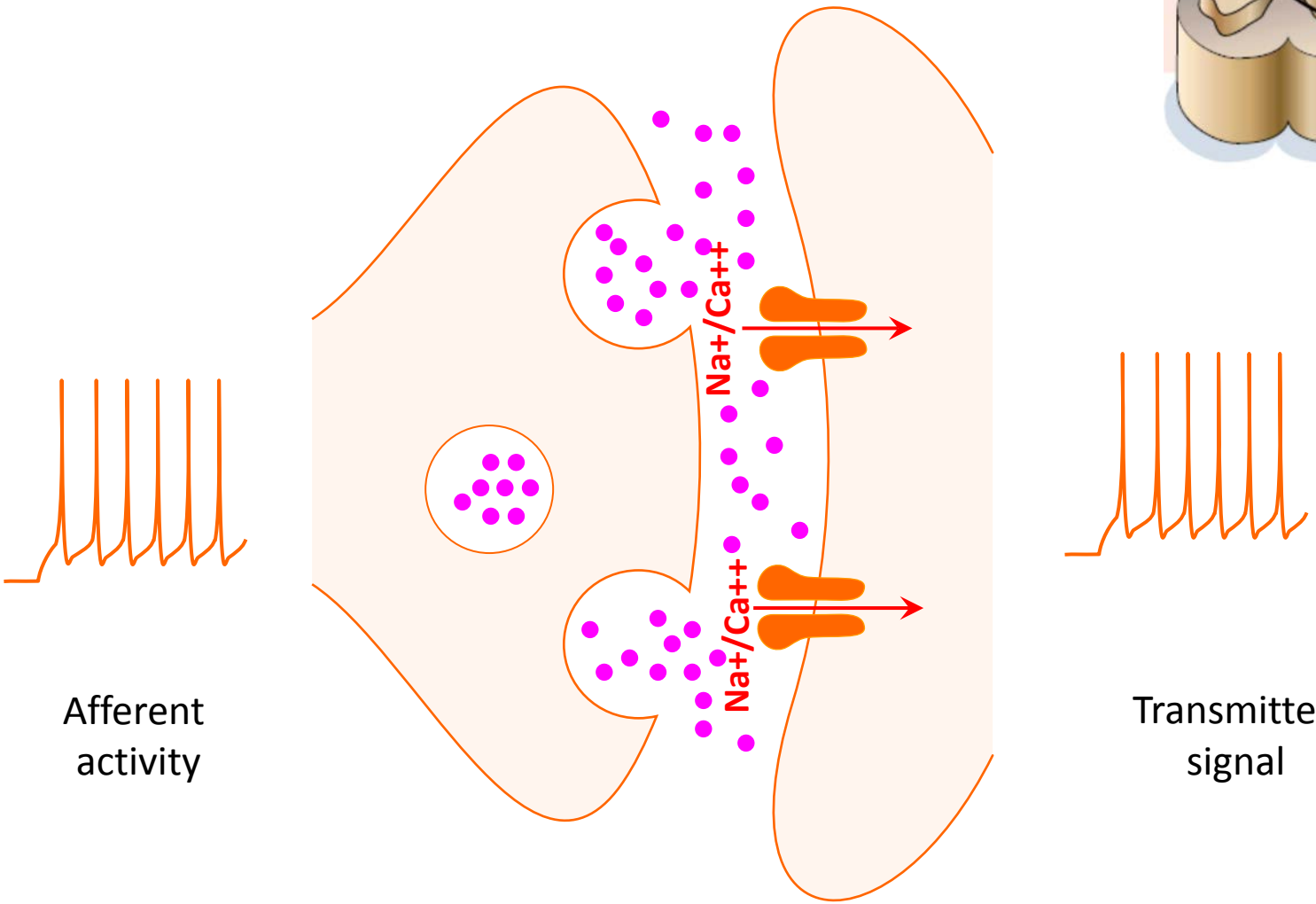
Neurogenic inflammation and neuroimmune interaction



Chiu IM, *Nature Neuroscience* 2012

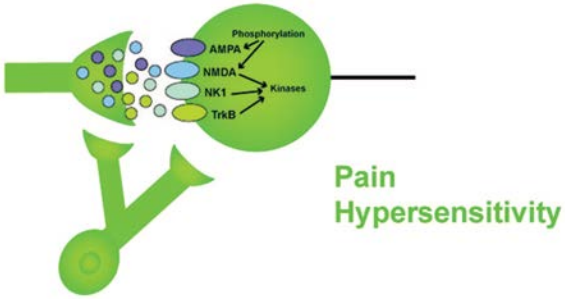
Transmission -> spinal cord



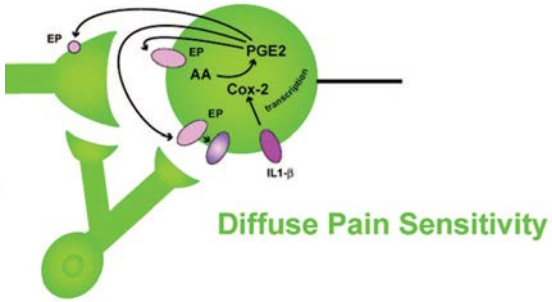


Central sensitization

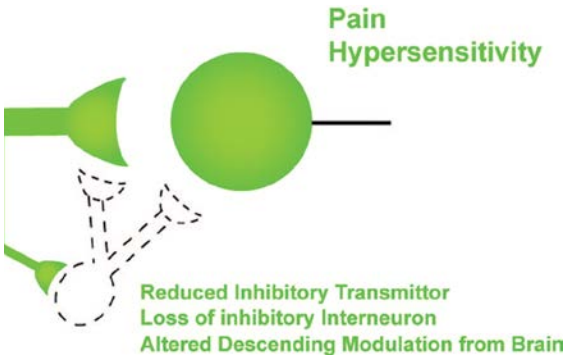
Acute phase



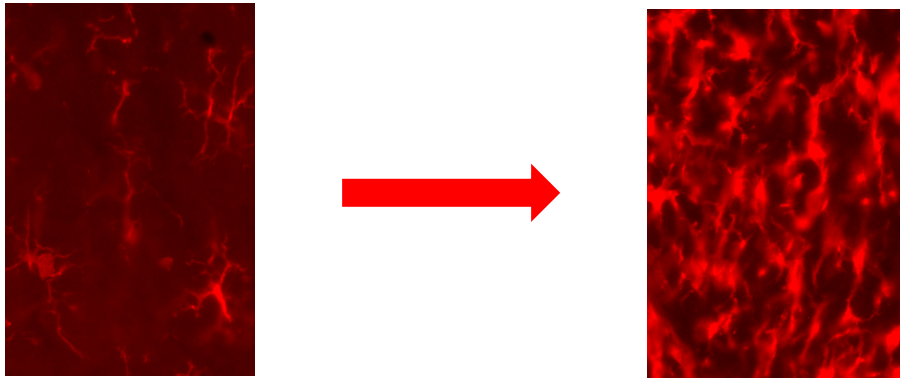
Late phase



Dishinibition



And microglial activation….



Woolf CJ, *Anesthesiology* 2007

Normal transmission

Afferent activity

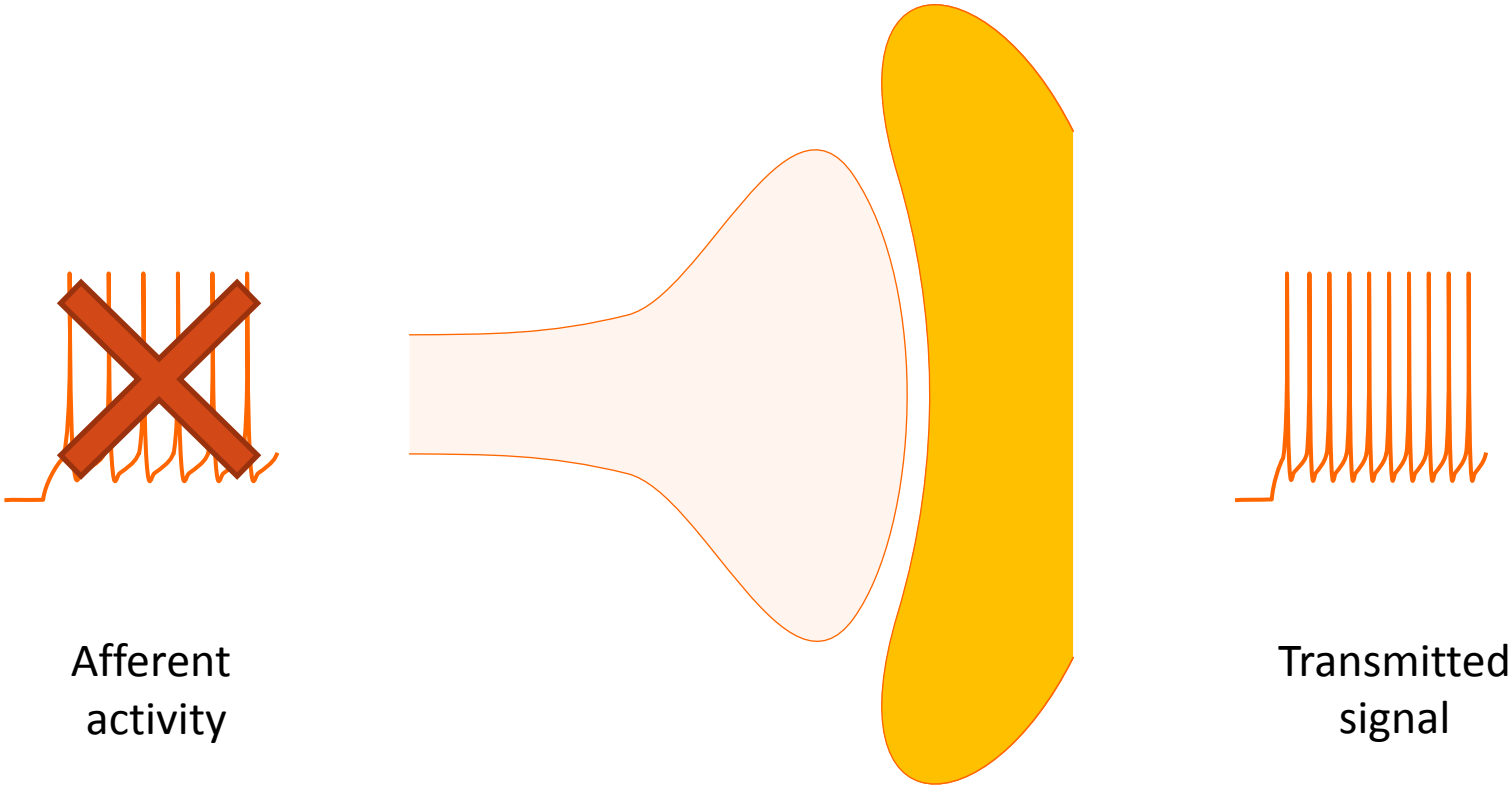
Transmitted signal

Increased gain through central sensitization

Afferent activity

Transmitted signal

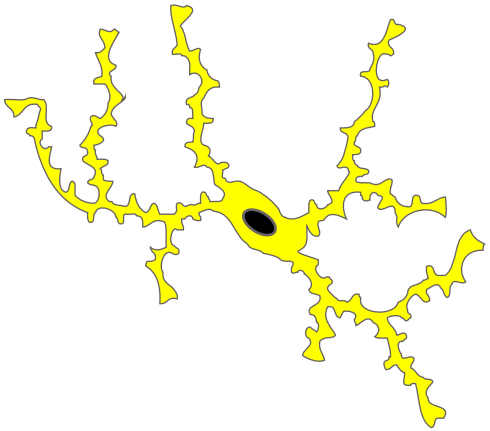
Increased gain through central sensitization



Afferent activity

Transmitted signal

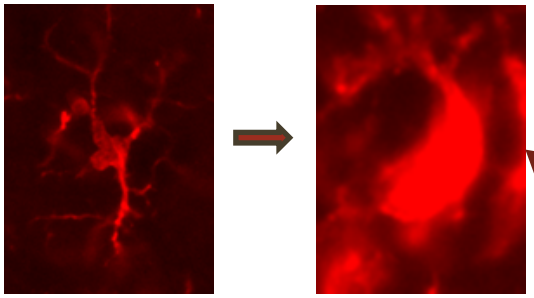
Glia – glial cells - neuroglia



- Non-neuronal cells
  - Maintain homeostasis
  - Form myelin
  - Provide support and protection
- Divided into
  - Microglia:
    - Derived from the monocyte-macrophage lineage
    - Invade the CNS during the embryonic period
  - Macroglia:
    - Astrocytes and oligodendrocyte mainly

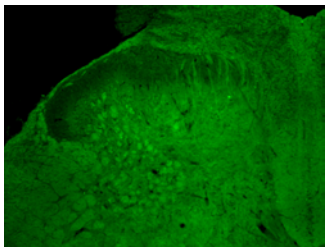
"Activation" of microglia in the spinal cord

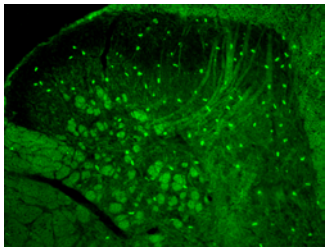
Morphology



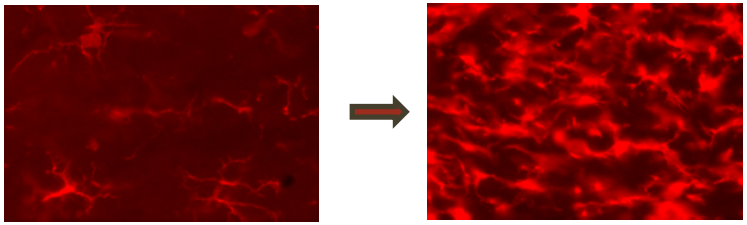
Microglial changes 2 days after sciatic nerve injury

Proliferation

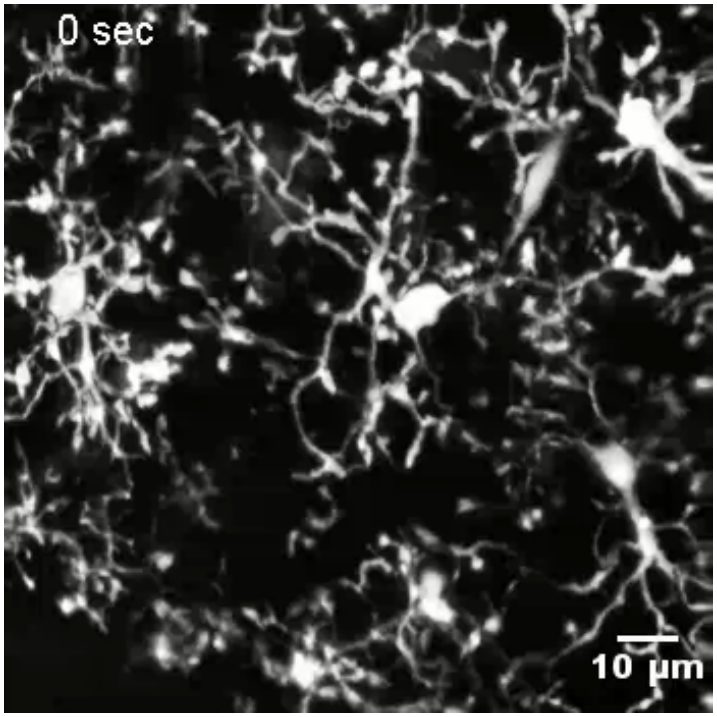


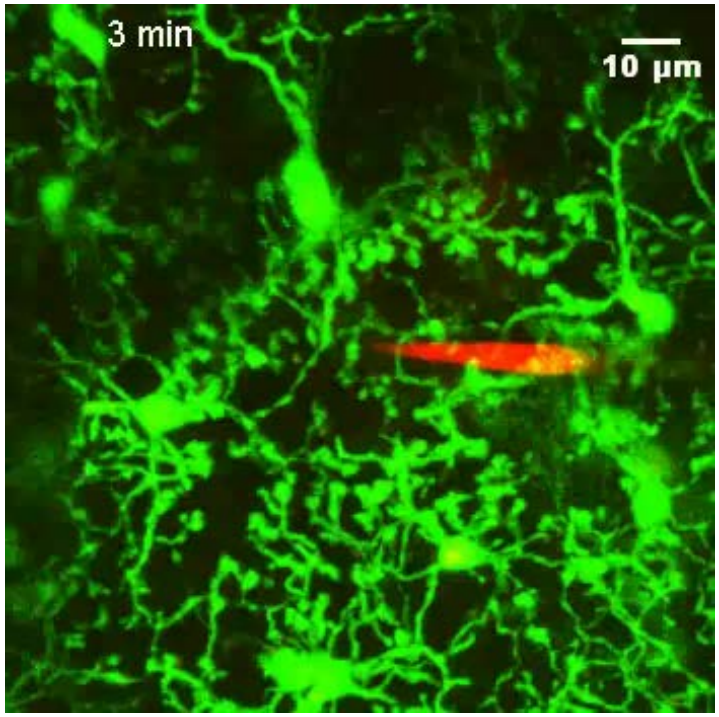


Marker

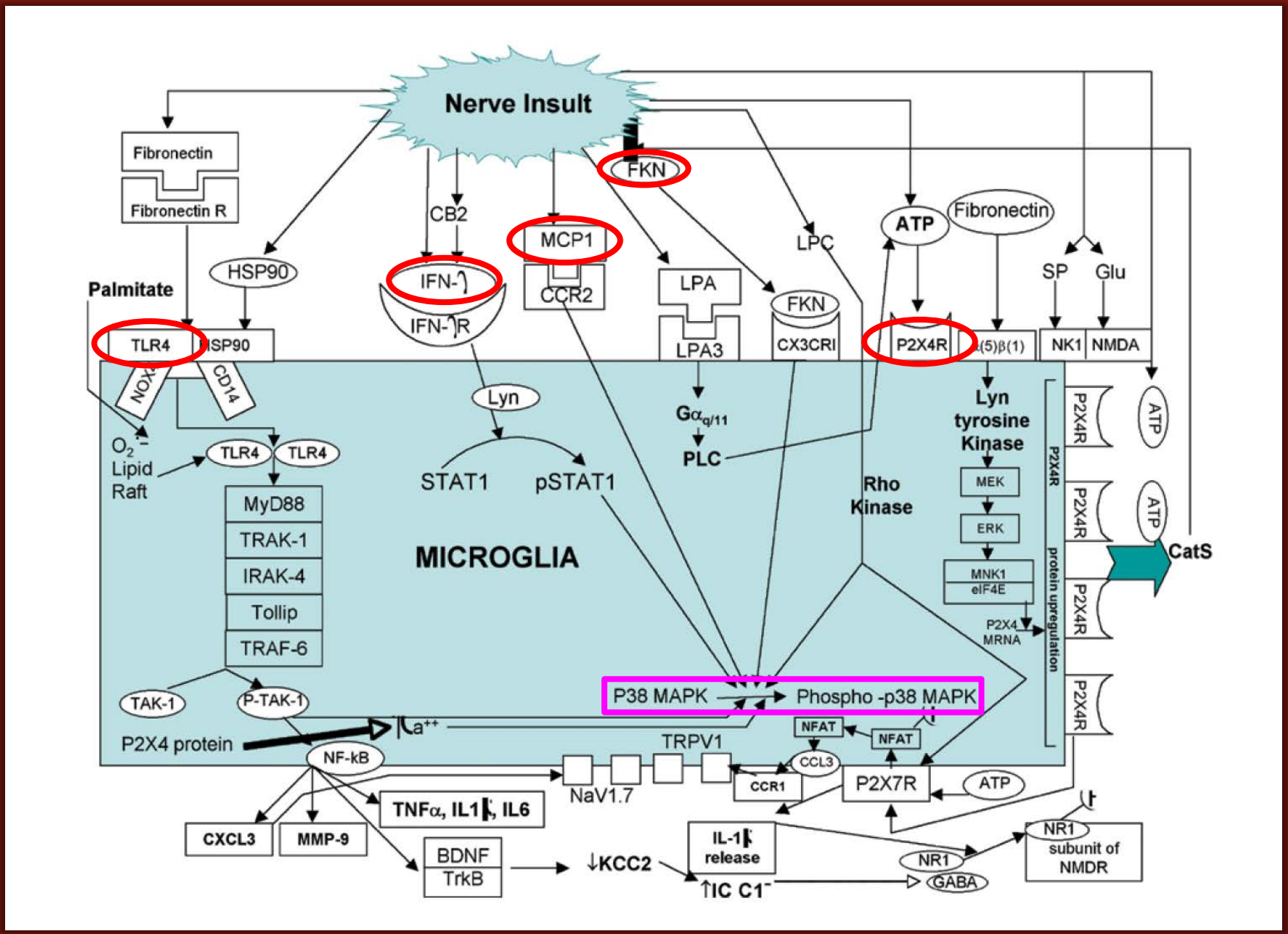


Surveilling versus reactive?



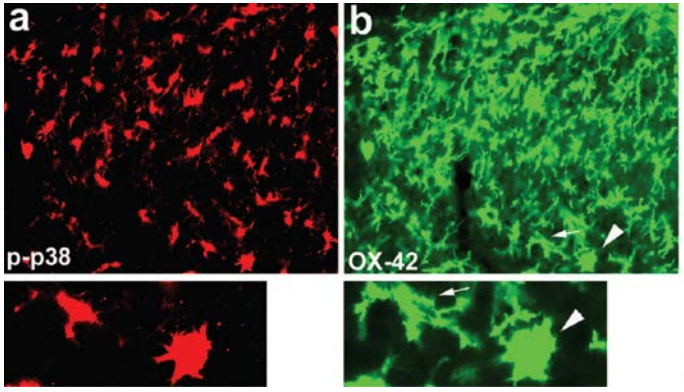


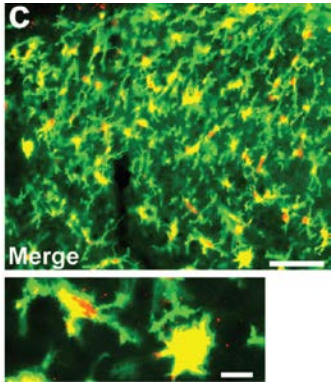
Davalos D, *Nature Neuroscience* 2005

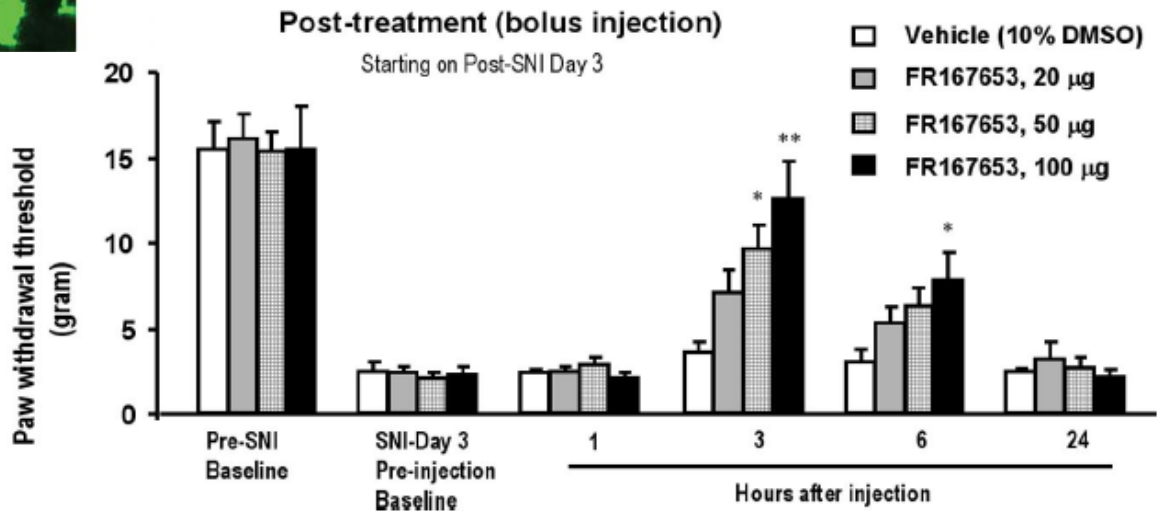


Smith HS, *Pain Physician* 2010

p38 inhibition relieves neuropathic pain

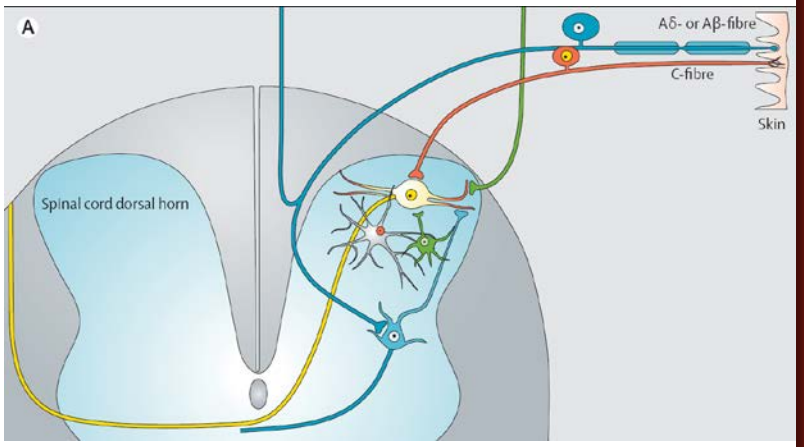






Wen YR, *Anesthesiology* 2007

Summary of mechanisms



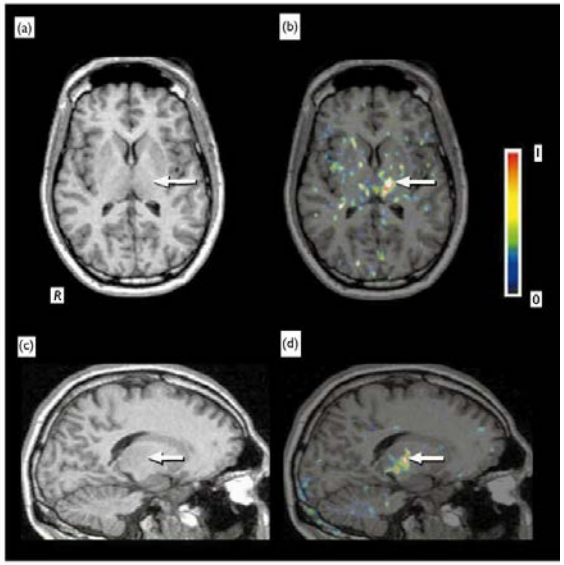
- ***Peripheral sensitization***
  - Hyperexcitability
- ***Central sensitization***
  - Increased excitability in DH neuron
  - Decreased inhibition
    - Death / dysregulation of inhibitory neurons
    - Modulation of descending inhibition
  - Glial activation
    - Microglia
    - Astrocytes

Baron R, *Lancet Neurology*, 2010

Microglia in human?

PET imaging, ^{11}C-PK111957

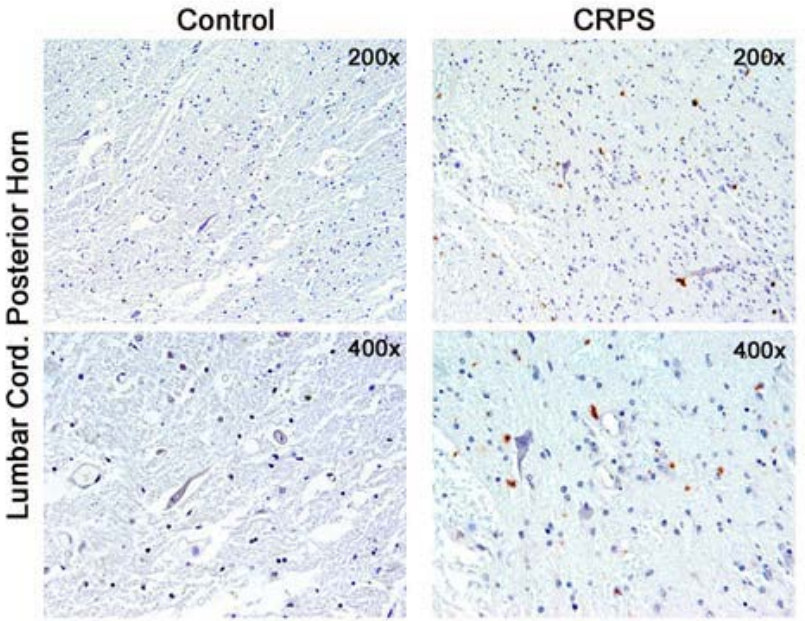
- Patients with nerve injury
- Thalamus contralateral
- Up to 2 decades
- Nerve injury vs pain?



Banati RB, *Neuroreport* 2001

Autopsy study

- Increase microglial staining (CD68)
- Maximum in ipsilateral side of lumbar dorsal horn
- CRPS
  - (complex regional pain syndrome)



Del Valle L, *Brain behavior and immunity* 2008

Microglia in human?

- Is microglia activated in human?
  - Not clearly demonstrated in pain
  - But in other neurodegenerative diseases
- Treatment?
  - Minocycline: currently used to treat acne
    - Proved efficient in animal pain models
    - Clinical trials ongoing for neurological diseases
  - For pain:
    - Martinez V, *Pain* 2013
      - Lumbar discectomy, not efficient on pain reduction at 3 months
      - maybe subgroup analysis
    - Sumracki NM, *PlosOne* 2013
      - Reduction of pain in sciatica, tendancy, 18 patients
    - Postoperative intercostal neuralgia (3/2011) (clinicaltrial.gov)

Clinical studies, p38

- Dilmapimod
  - Phase II, reduced average daily pain vs placebo
  - Anand P, *European Journal of Pain* 2011
- Losmapimod
  - 2 Phase II studies
    - No alleviation in patients with lumbosacral pain
    - No significant reduction in patients with peripheral nerve injury
      - Ostenfeld T, *European Journal of Pain* 2013

Reviewed in Gosselin RD, *FCDR-Central Nervous System* 2013

Thoughts to conclude …

- We know quite a lot
  - But we are very poor with treatment

- Why?
  - Translation to human
    - Same mechanisms?
      - Not yet much info about microglia in human
  - Wrong treatment to the wrong person
    - Mechanism-based therapy
  - No drug available
    - Drugs used in lab are not for clinic
      - Minocycline unspecific and maybe not best microglia blocker

CHUV & UNIL Lausanne

Pain Center

Anesthesiology Dpt

- Isabelle Decosterd

Head of department

Christian Kern

Thank you

Duke University

Medical Center

(Former: Harvard Medical School)

- Ru-Rong Ji

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IASP early career grant 2011
Swiss Society Anesthesiology

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