Neurobiology of joint pain
Neurobiologie von Gelenkschmerzen

Hans-Georg Schaible
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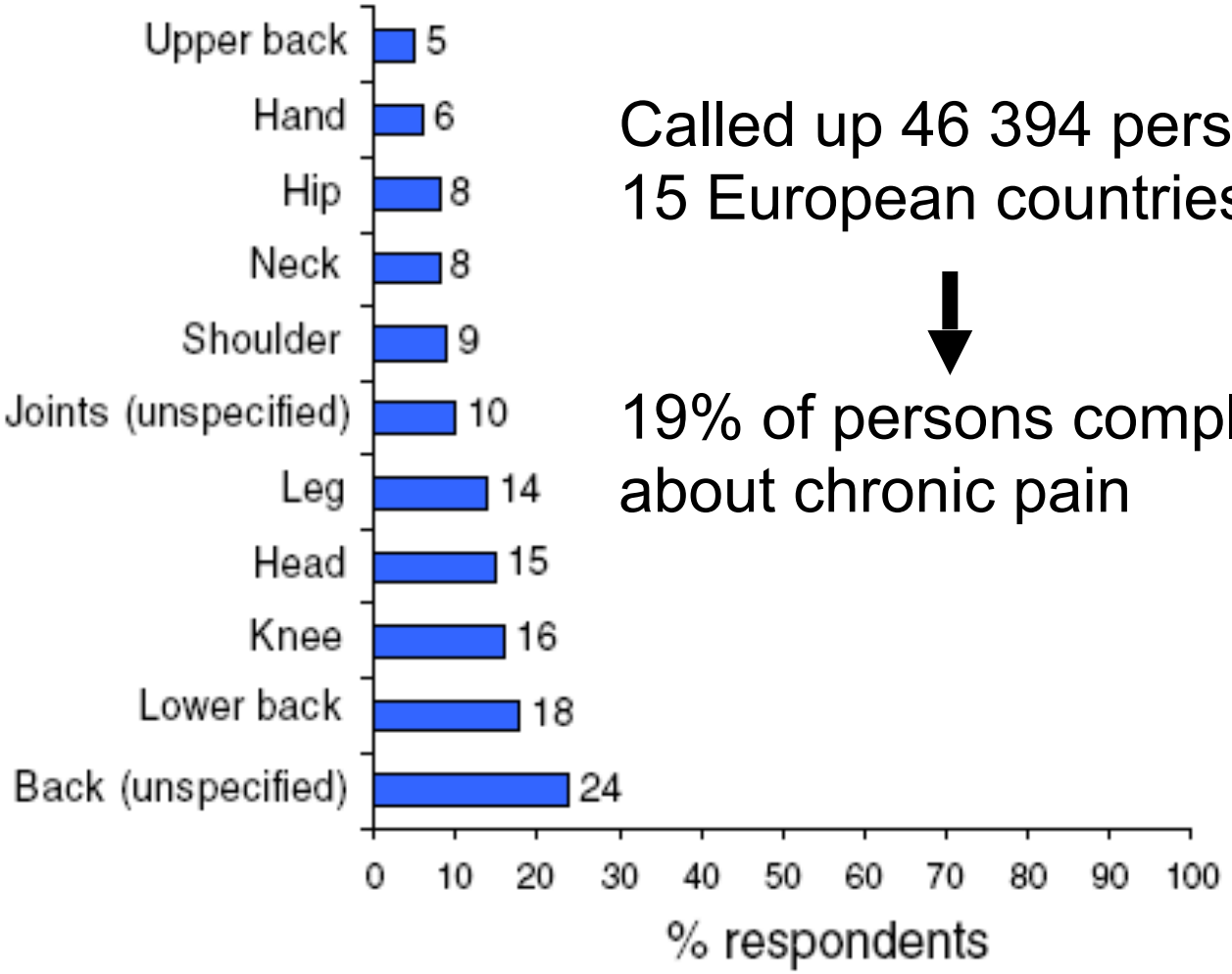
Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment

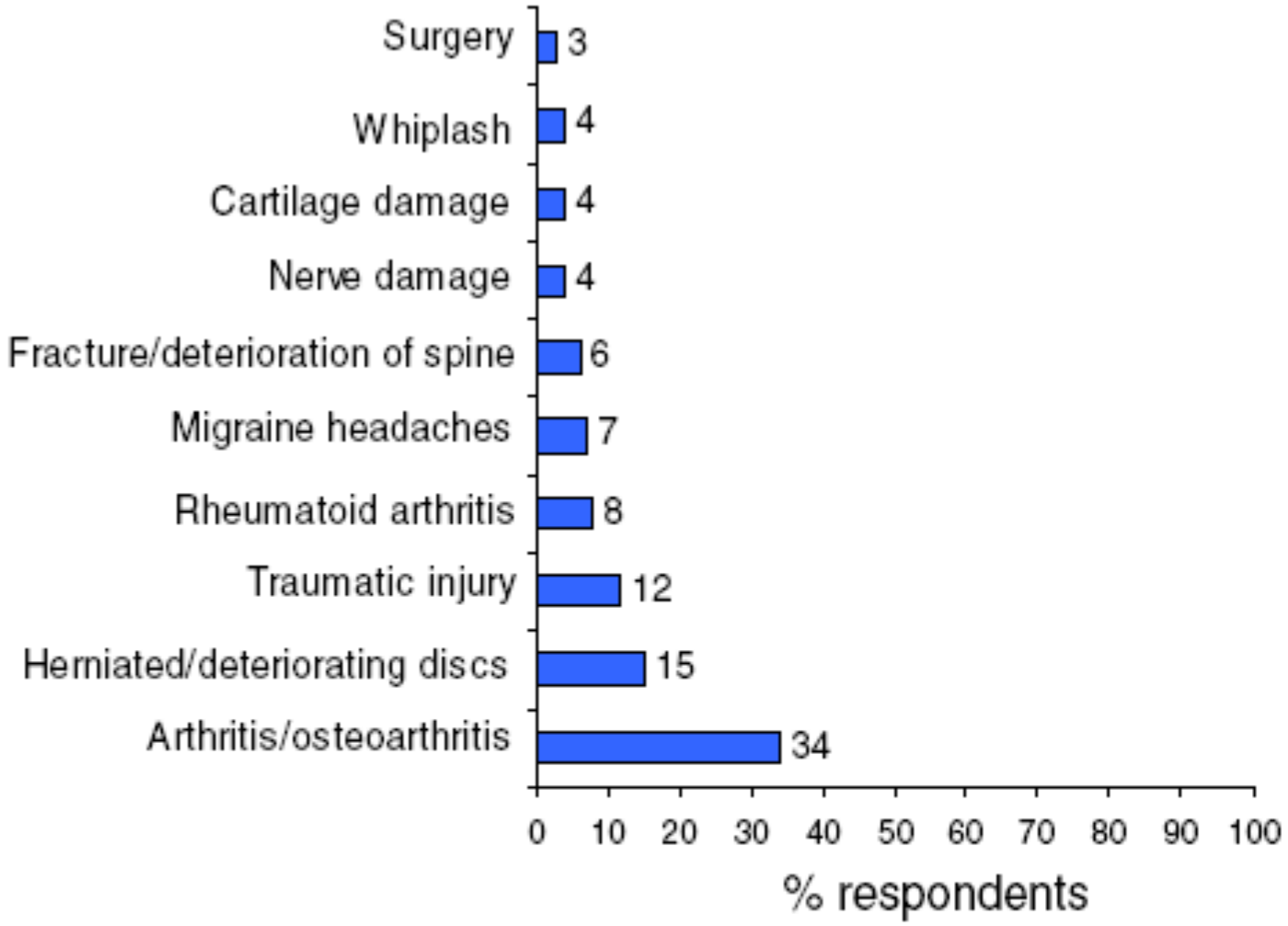


Called up 46 394 persons in 15 European countries

19% of persons complained about chronic pain

Breivik et al., Eur J Pain 10: 287-333 (2006)

Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment



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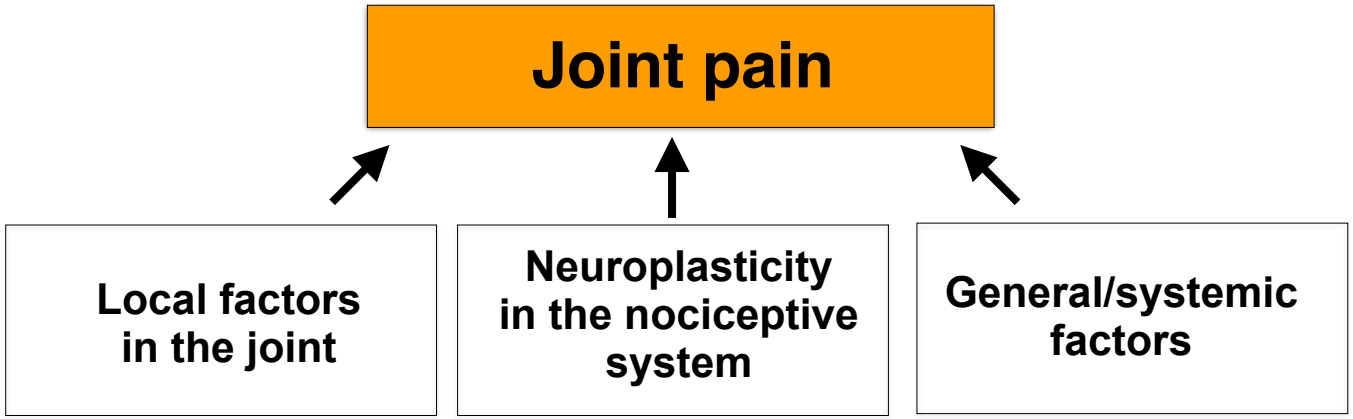
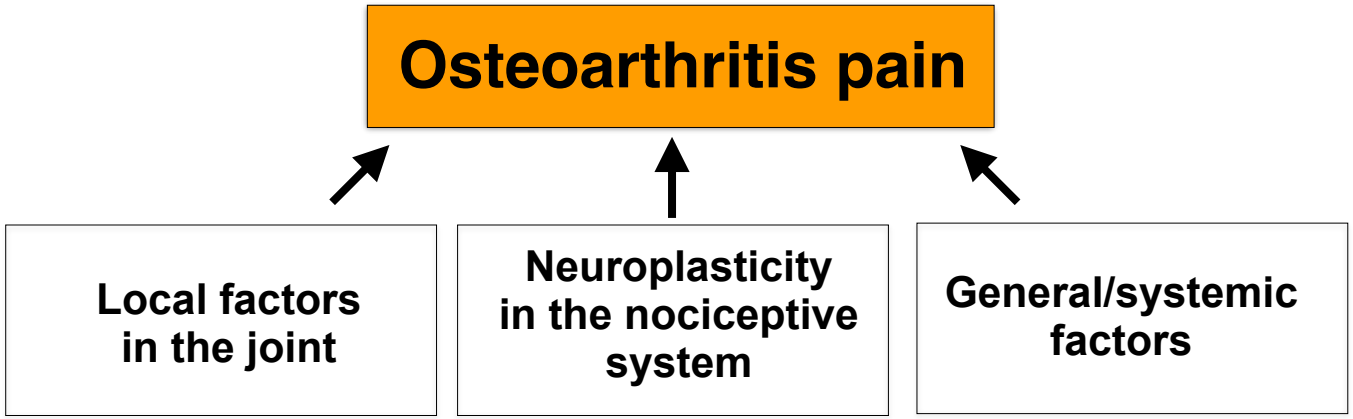


Eitner, Hofmann, Schaible, Front Mol Neurosci 10, 349 (2017)



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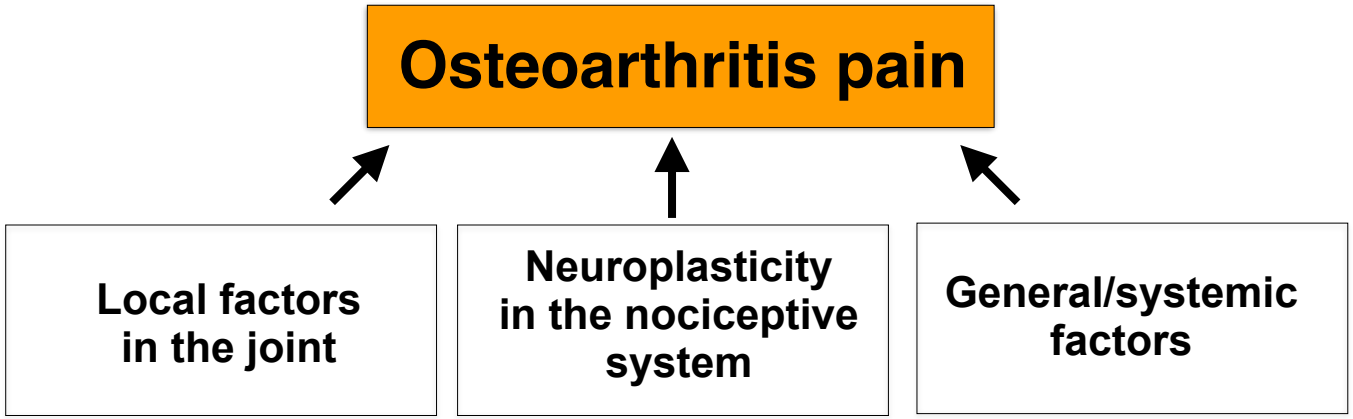

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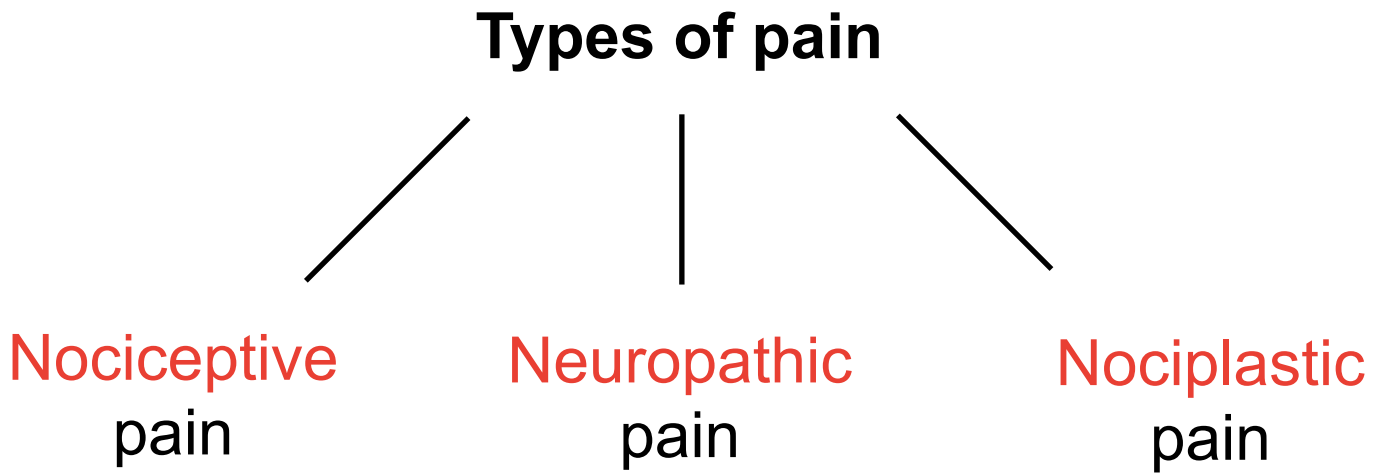
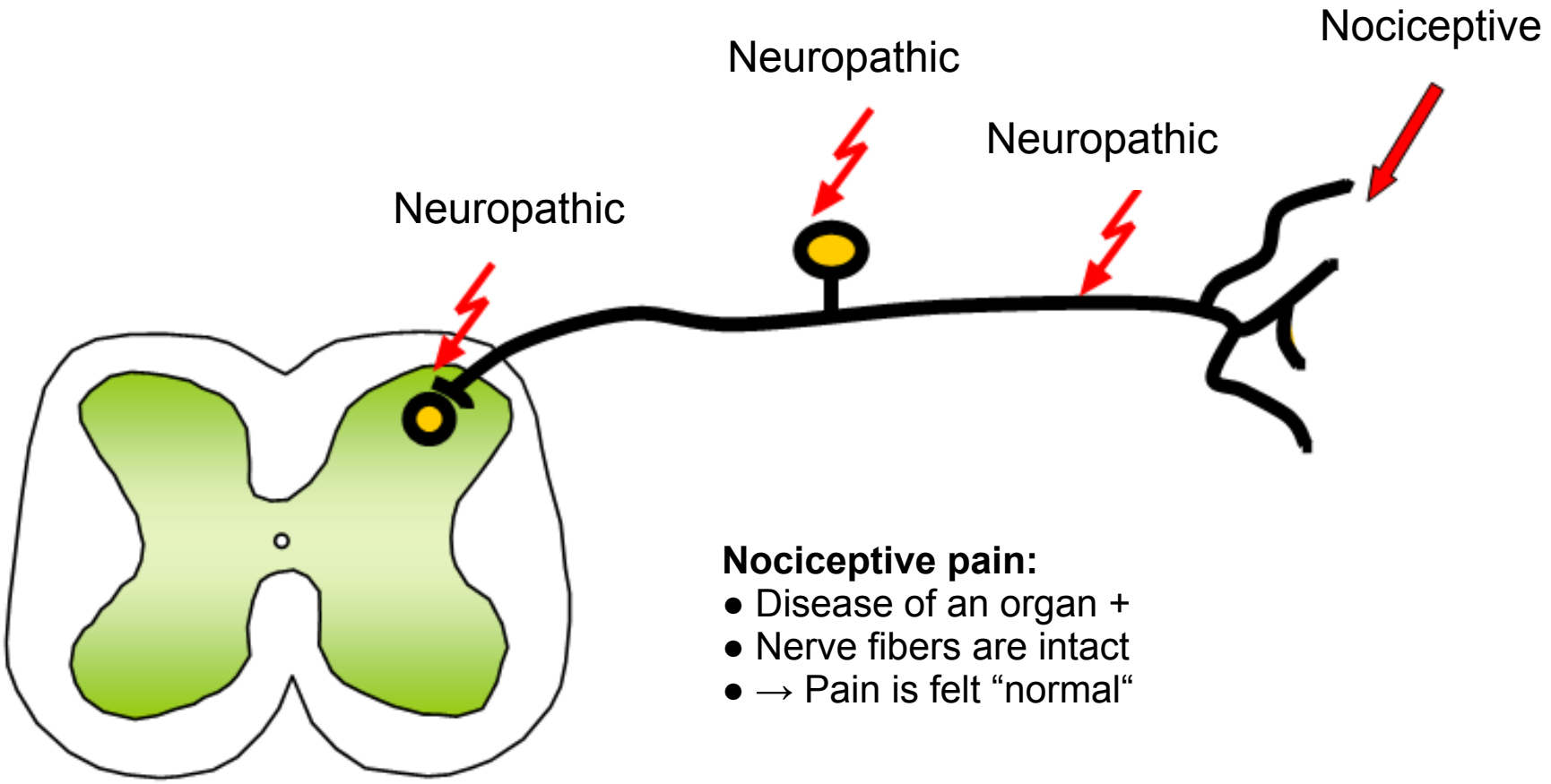

Types of pain
Nociceptive pain
Neuropathic pain
Nociplastic pain

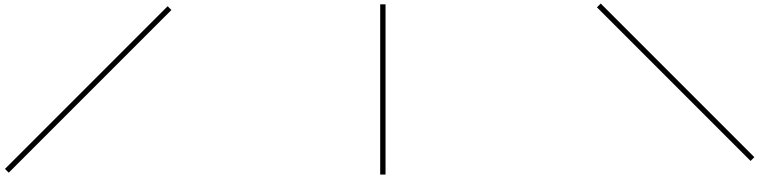
Nociceptive pain – neuropathic pain



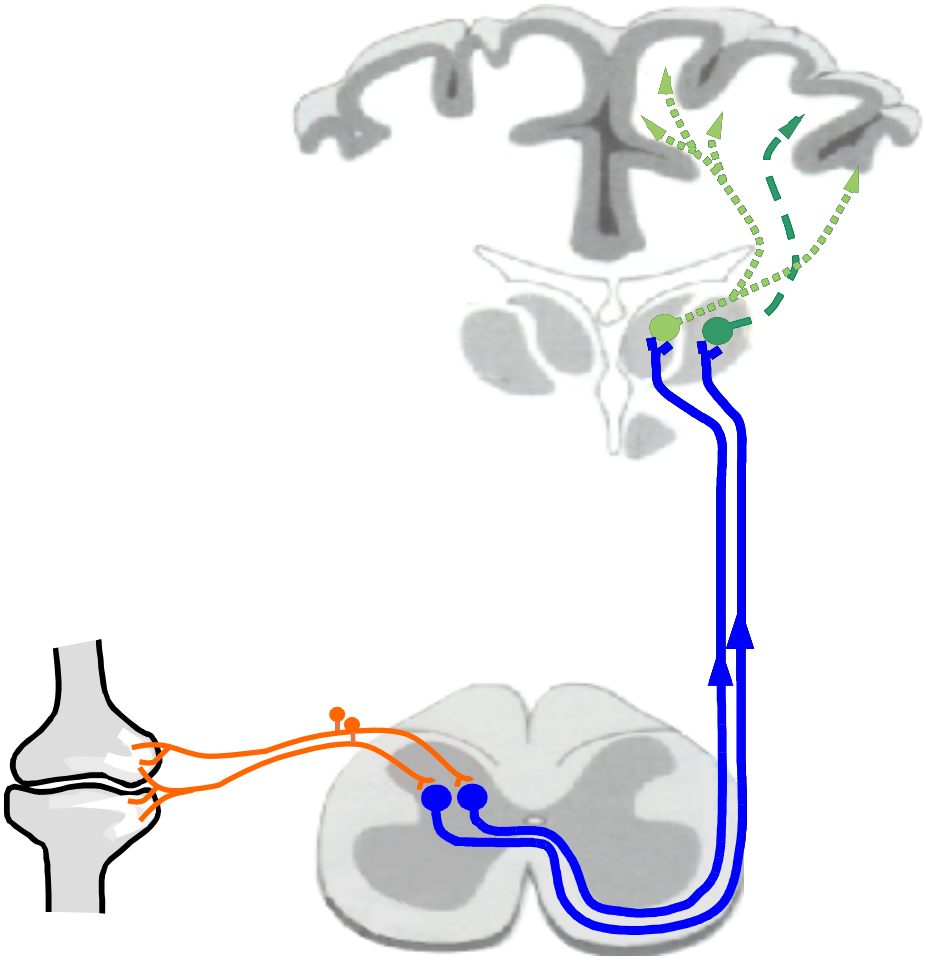
Nociceptive pain:
- Disease of an organ +
- Nerve fibers are intact
- → Pain is felt “normal“

Neuropathic pain:
- Disease of an organ +/0
- Nerve fibers are damaged/affected
- → Pain is felt “abnormal“

Types of pain in joint pain



Nociceptive pain	Neuropathic pain	Nociplastic pain
+++	+	?



Supraspinal level

- **Activation of the pain matrix**
- **Reduction of the grey matter**
- **Descending inhibition ↓**

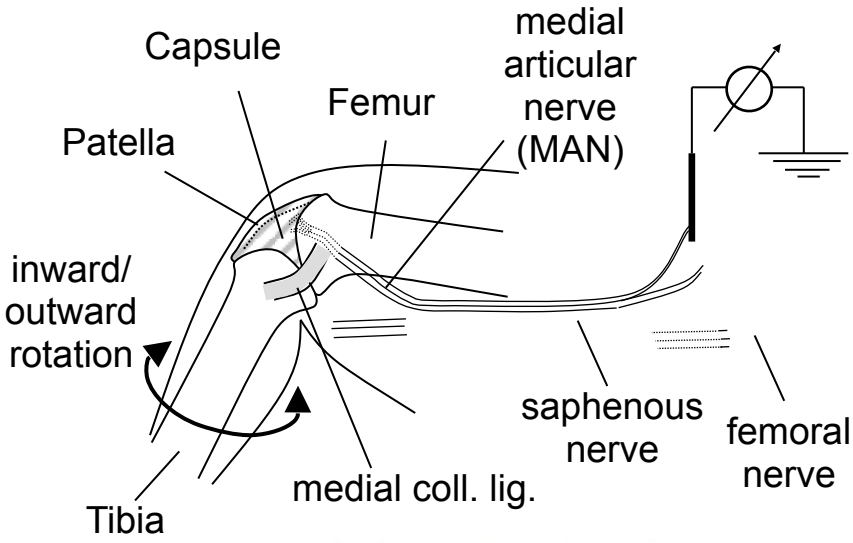
Spinal level

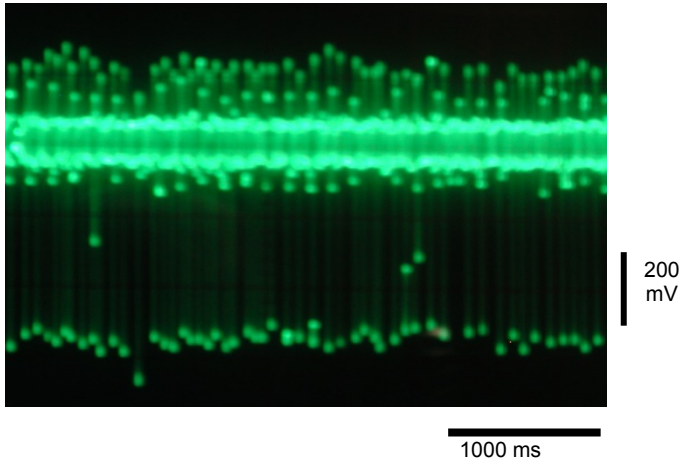
- **Spinal Sensitization**
- **Glia activation**

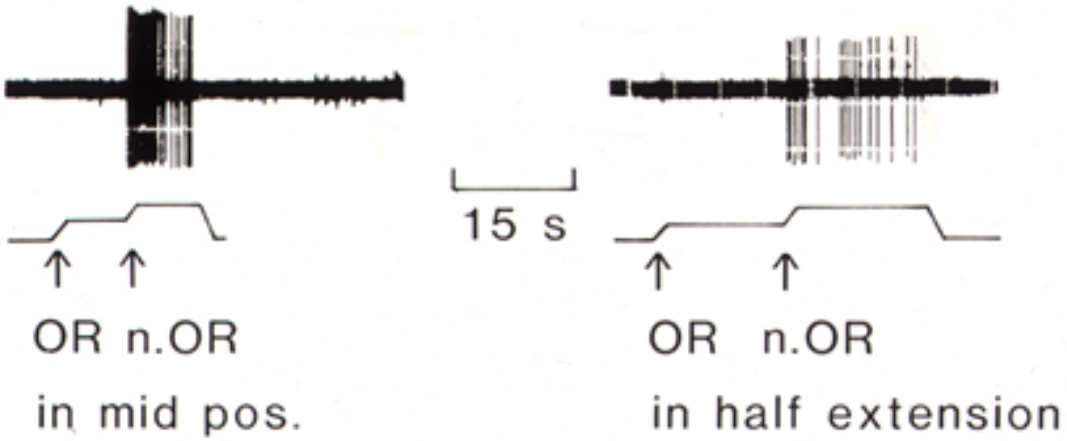
Peripheral level

- **Peripheral Sensitization**

Nociceptors of the joint

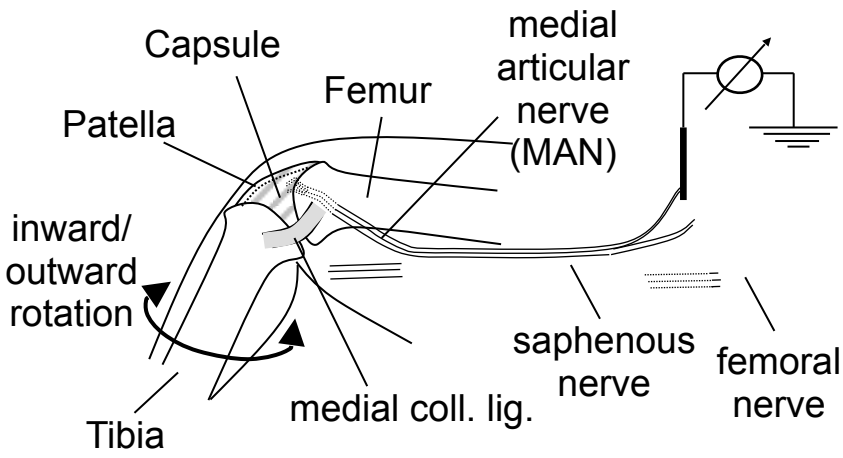


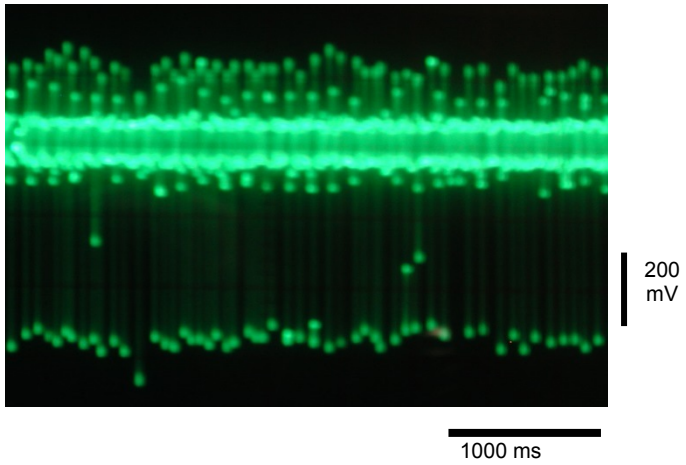


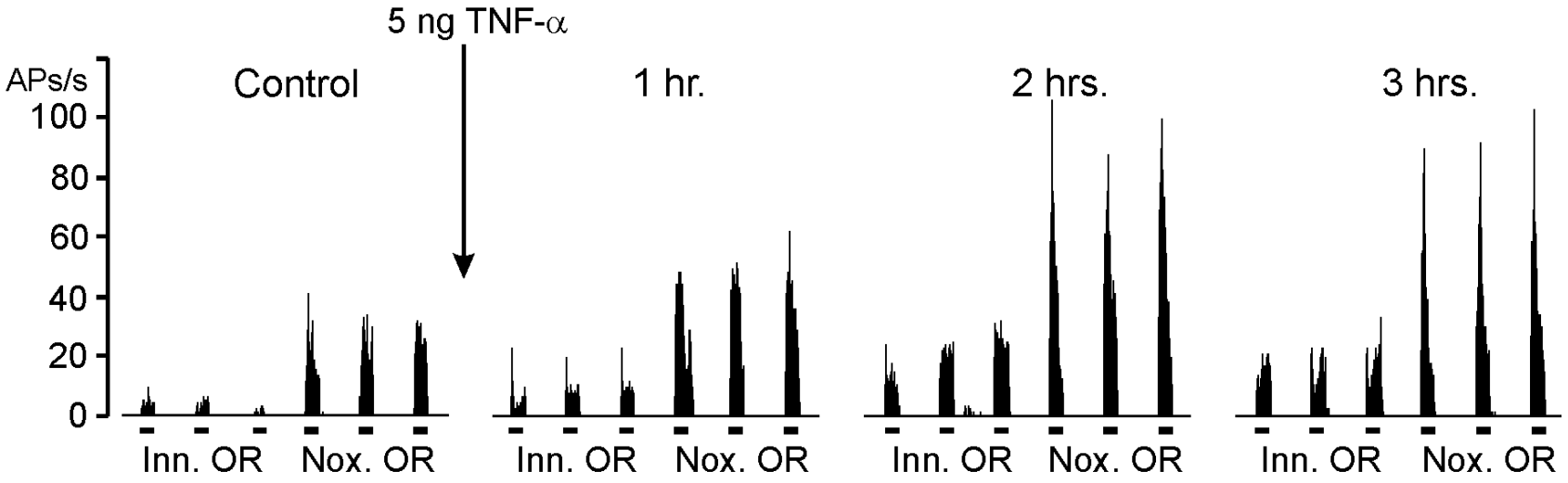


Schaible and Schmidt, Schaible and Richter

Sensitization of a nociceptor by TNF for mechanical stimuli

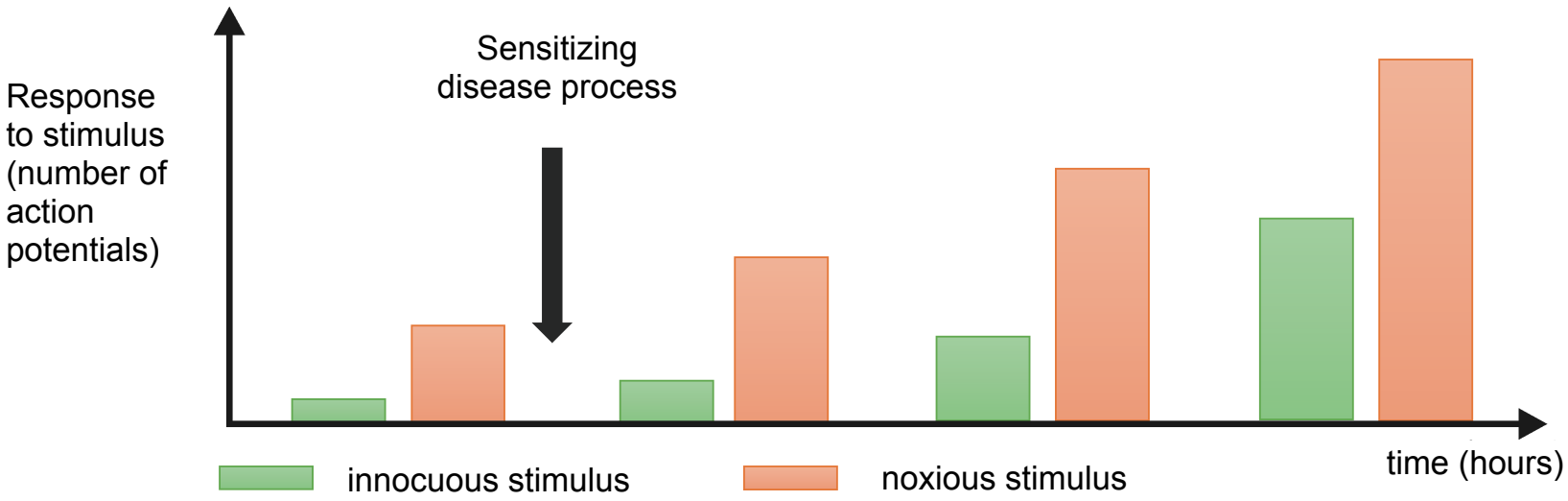






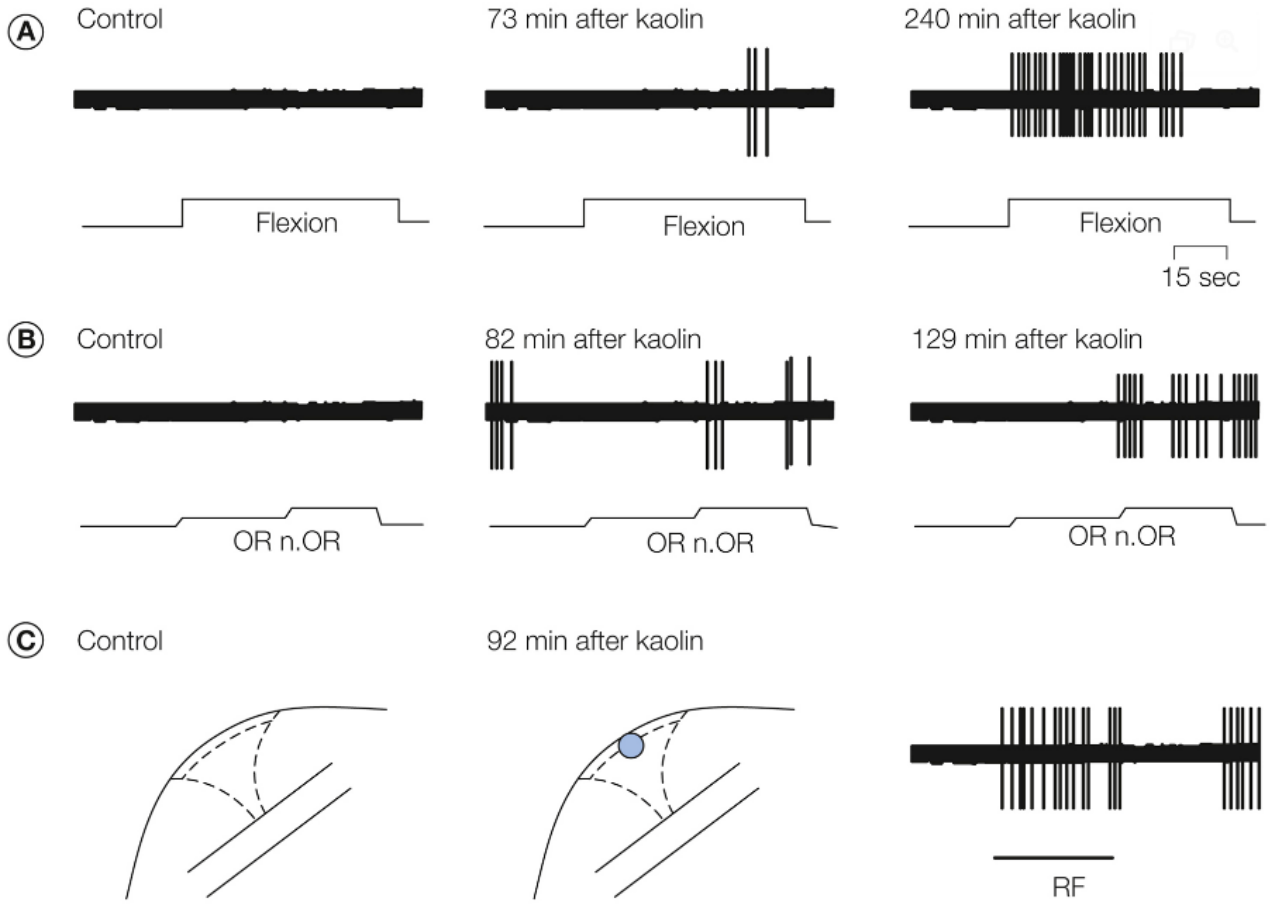
Richter et al., Arthritis Rheum 62, 3806-3814 (2010)

Sensitization of nociceptors



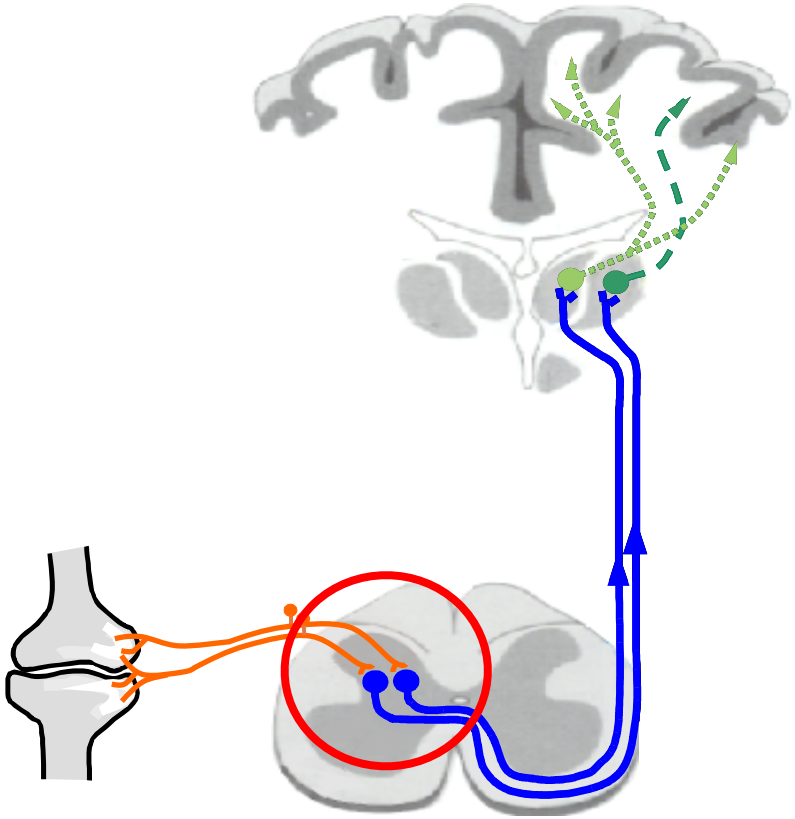
Schaible, Schmerz.Therapie 5, 18-24 (2022)

Silent nociceptors of the joint

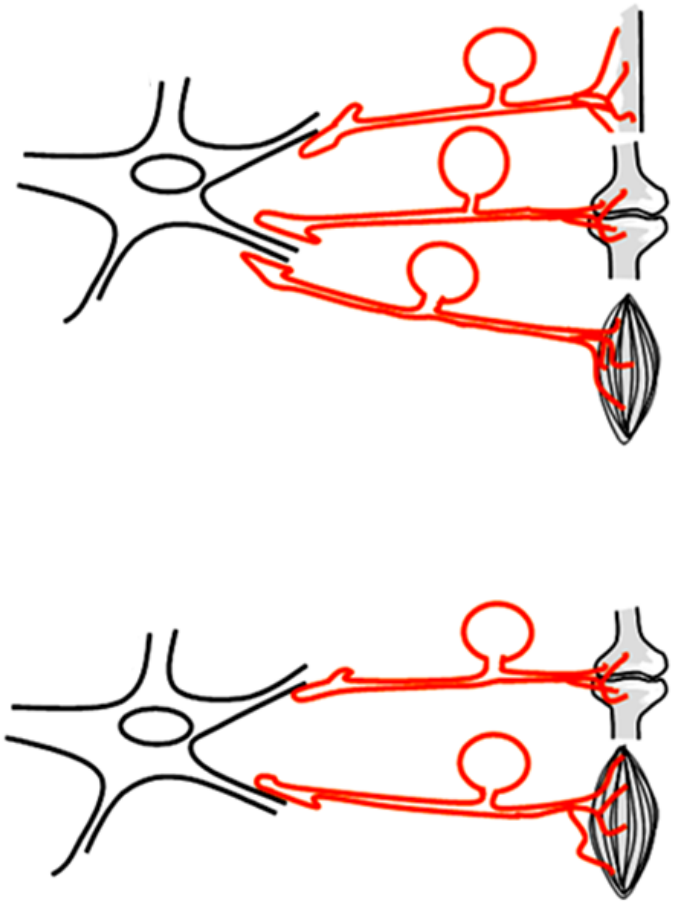


Schaible and Schmidt, J Neurophysiol 60, 2180-2195 (1988)

Spinal mechanisms of joint pain



Spinal convergence of afferents



Schaible, in Physiologie des Menschen (2019)

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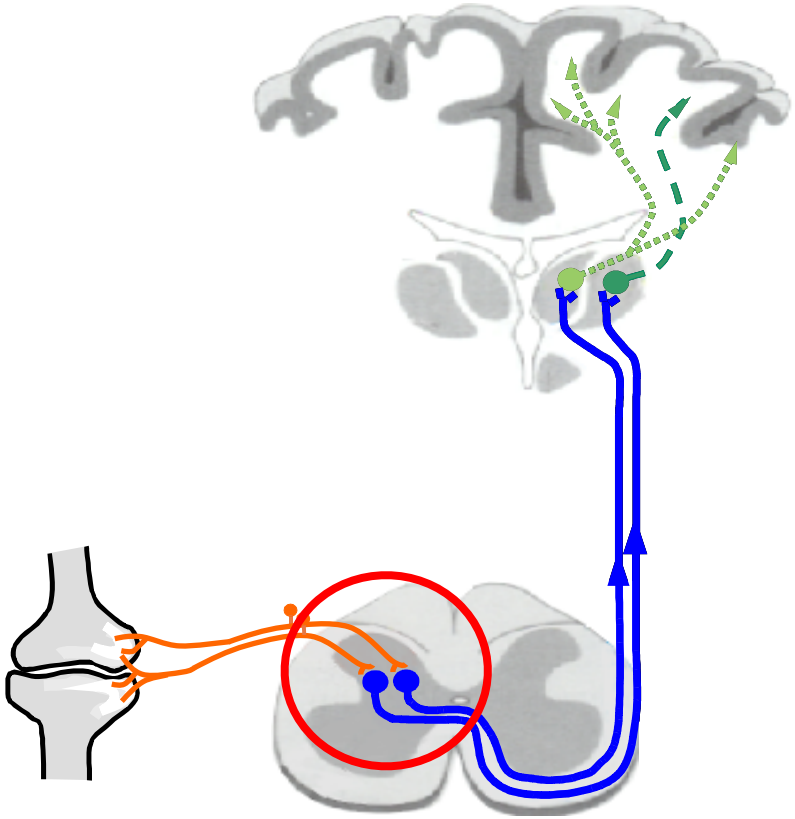

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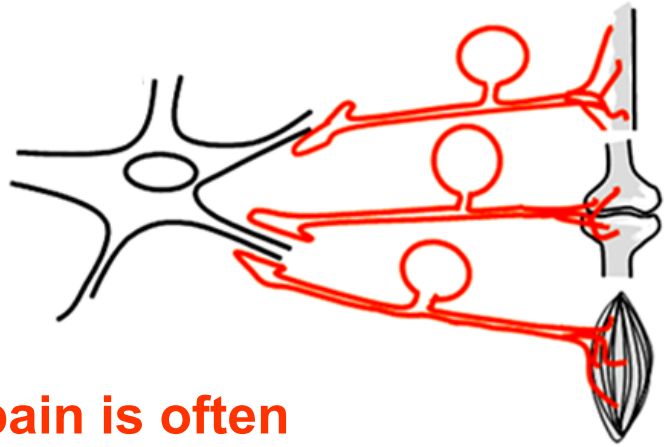
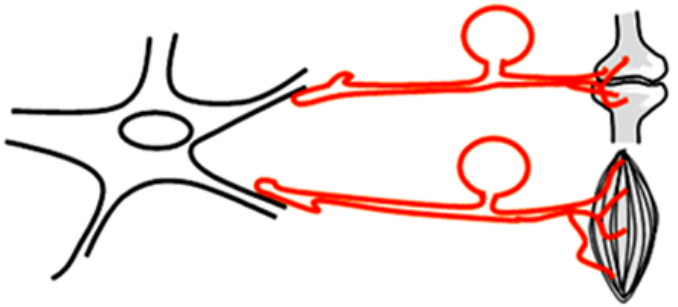
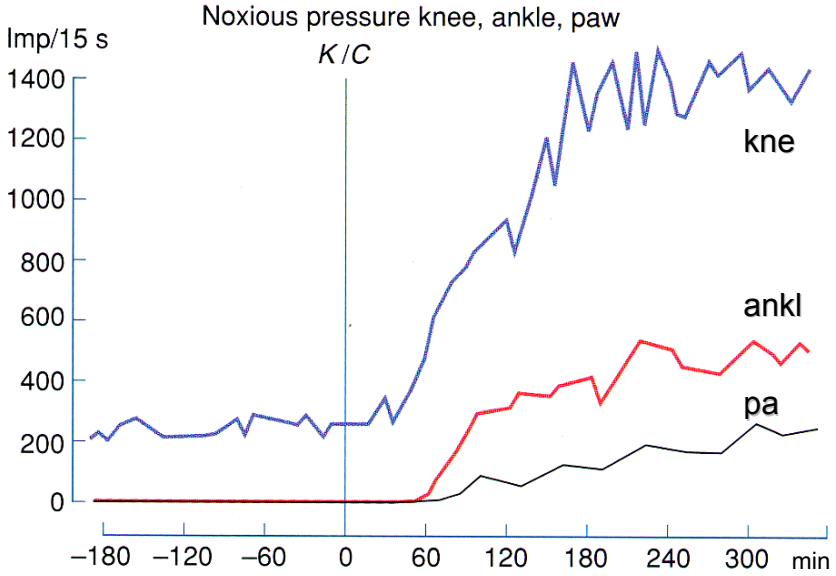


Joint pain is often badly localized or even referred

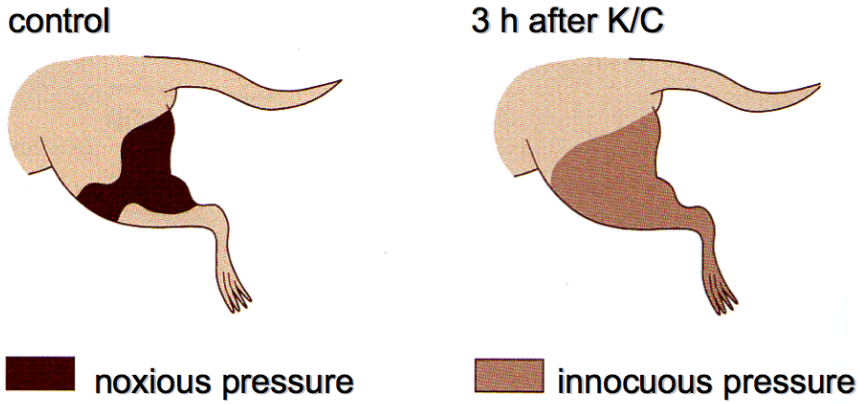


Schaible, in Physiologie des Menschen (2019)

Sensitization of a spinal cord neuron

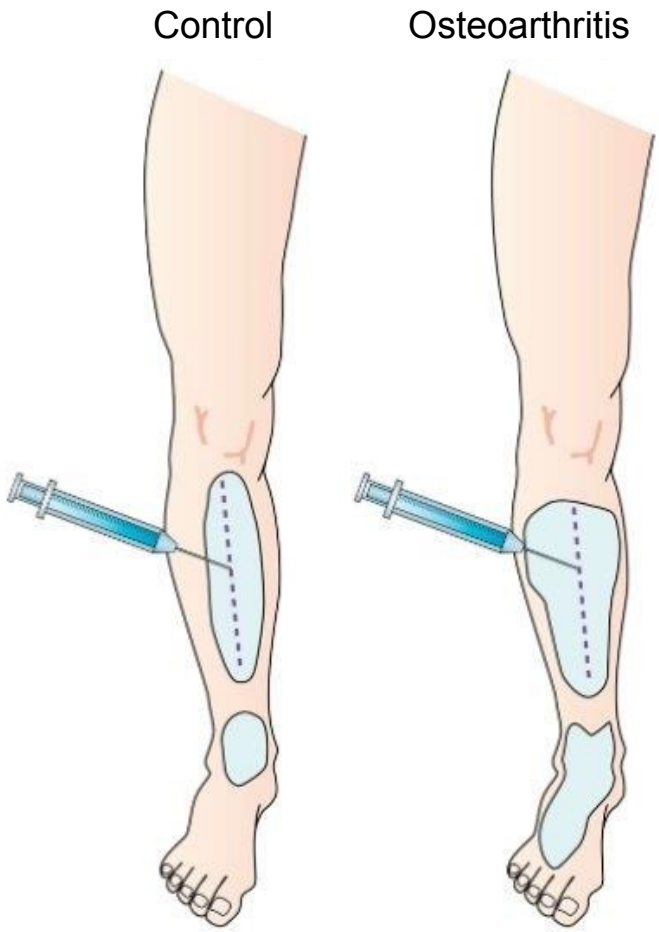


Receptive field size



Neugebauer et al., J Neurophysiol (1993)

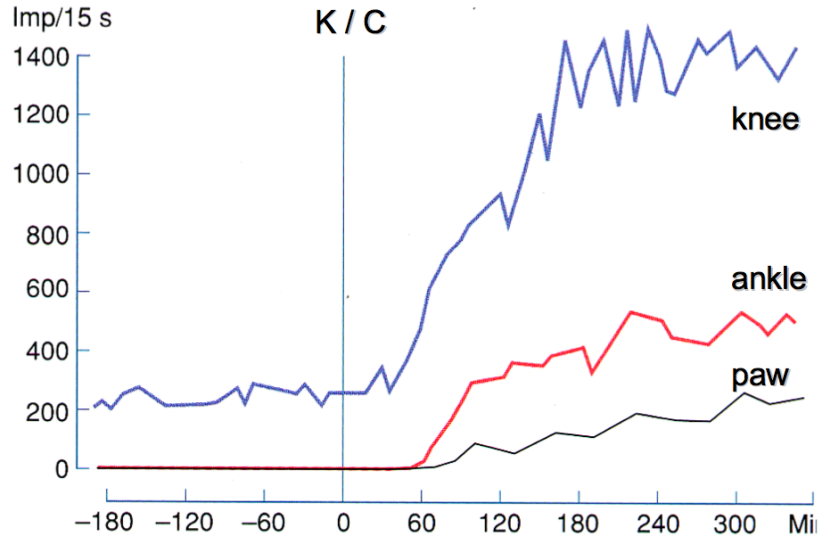
Pain area in humans



Hypertonic saline (6%)
in tibial anterior muscle

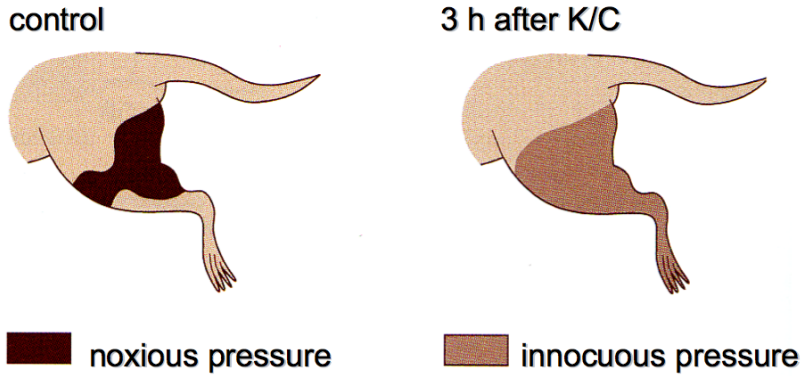
Arendt-Nielsen et al.

Noxious pressure knee, ankle, paw



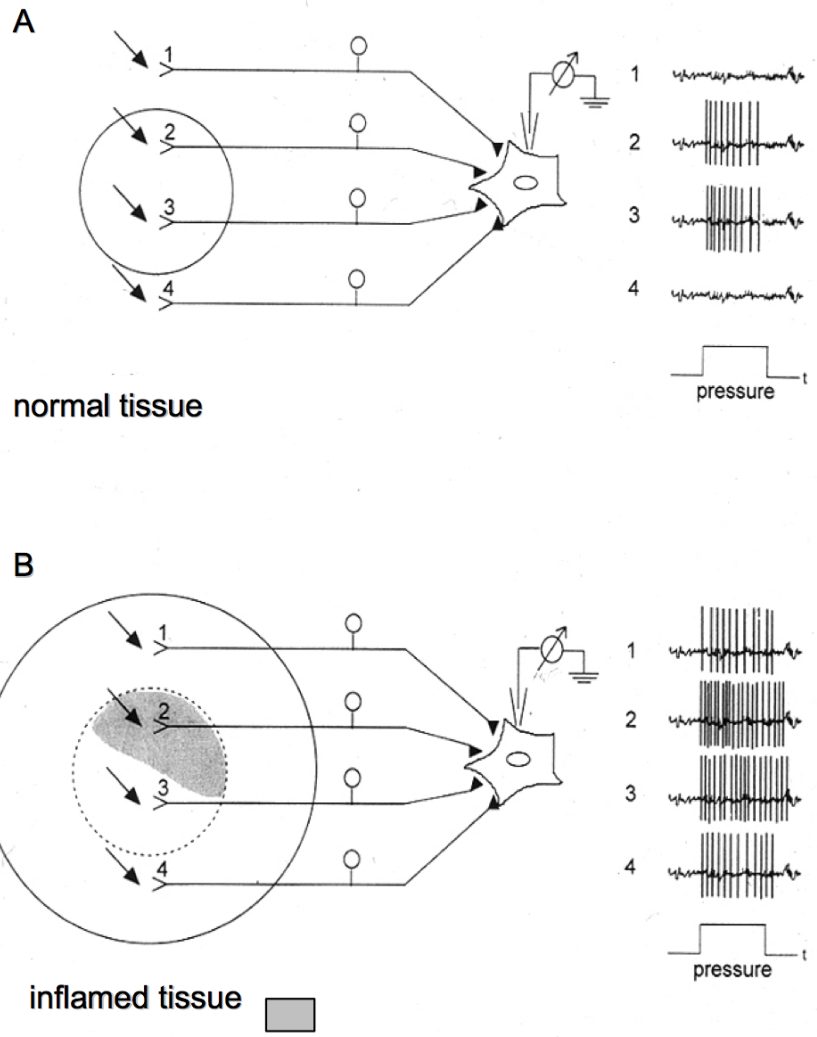
(a)

Receptive field size



(b) (c)

Sensitization of a spinal cord neuron



Neugebauer et al., J Neurophysiol (1993)

Schaible, in Physiologie des Menschen (2019)

Peripheral and central sensitization

Secondary hyperalgesia

central sensitization

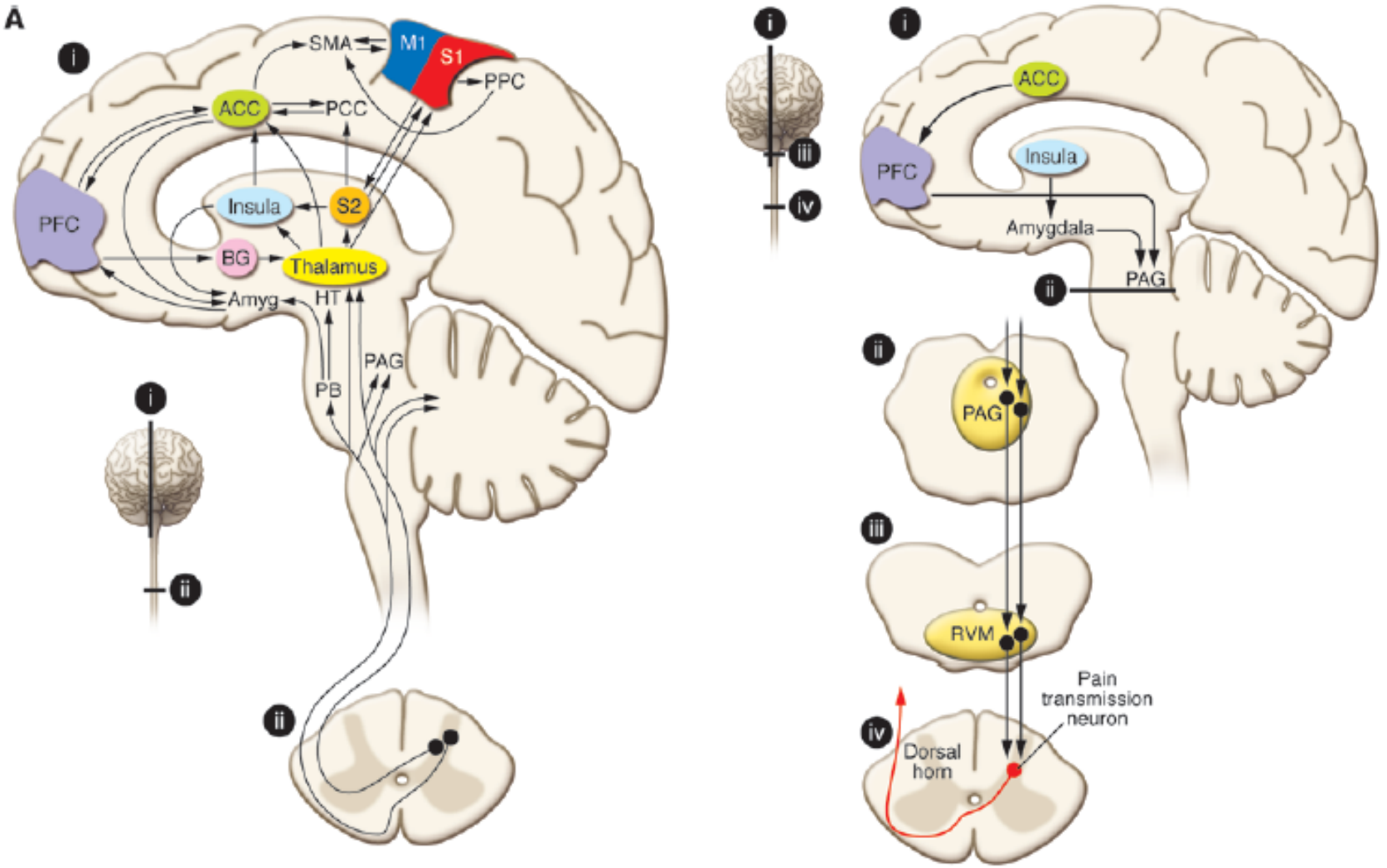
Primary hyperalgesia

peripheral and central sensitzation

Secondary hyperalgesia

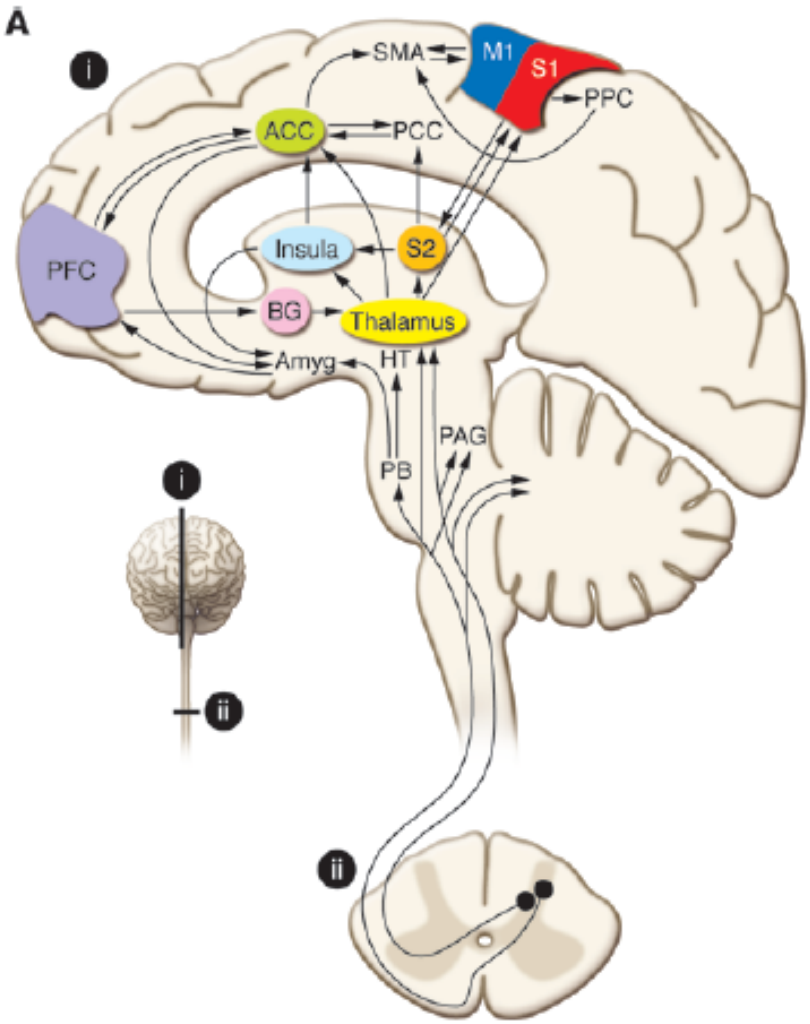
central sensitization

The processing of pain in the brain



Schweinhardt and Bushnell, J Clin Invest 120, 3788-3797 (2010)

The processing of pain in the brain



Cortex S1 and S2:

Processing of sensory discriminative aspects of pain

Insula, anterior cingulate cortex (ACC), prefrontal cortex (PFC):

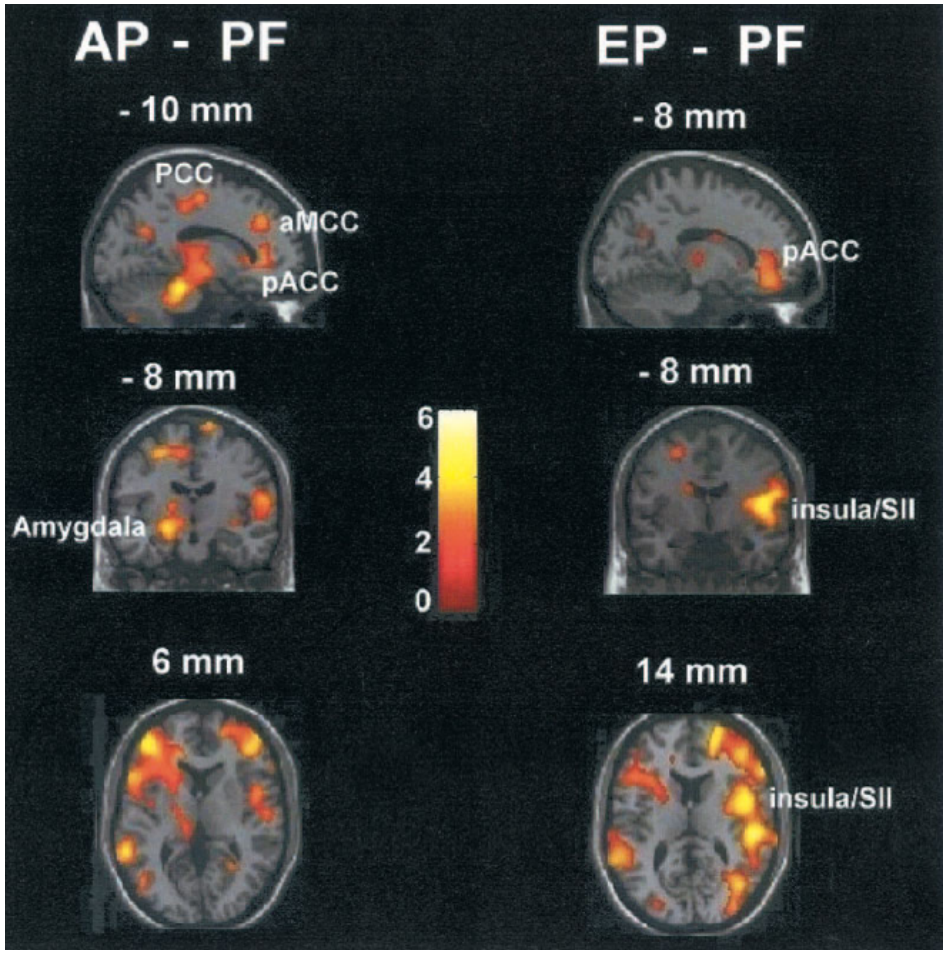
Processing of the affective emotional aspects of pain

Amygdala:

Processing of emotion fear

Schweinhardt and Bushnell, J Clin Invest 120, 3788-3797 (2010)

Central processing of joint pain

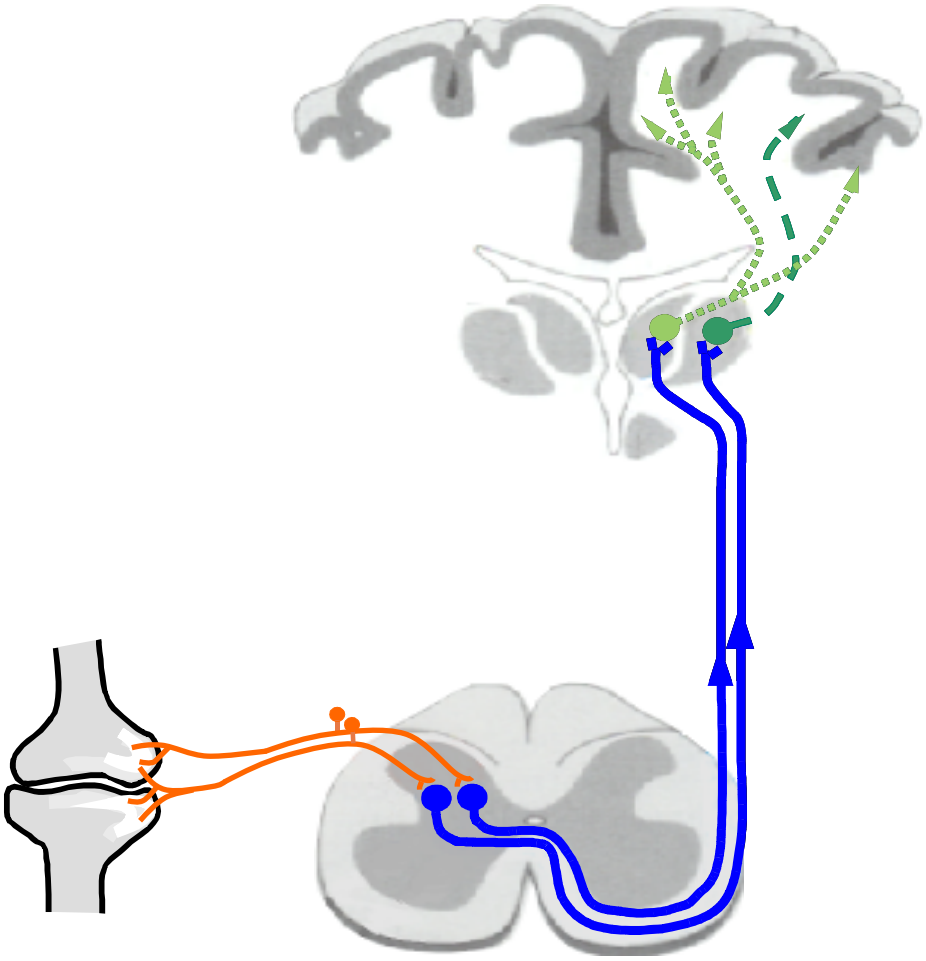


AP
arthritic pain condition
(physical stimulation of arthritic knee)

PF
pain-free condition

EP
experimental pain condition
(heat stimulation of skin over arthritic knee)

Kulkarni et al., Arthritis Rheum 56, 1345-1354 (2007)



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Peripheral level

- **Peripheral Sensitization**

“Atrophy“ of the gray matter of the cortical “pain matrix“

Prefrontal Cortex, Gyrus cinguli anterior (ACC), Insula

- Chronic back pain
- Fibromyalgia
- Osteoarthritis
- Ankylosing spondylitis
- Headache
- Irritable bowel syndrome
- Complex regional brain syndrome (CRPS)

Structural changes of the white matter (Interruption of pathways ?)

The cortical „atrophy“ is reversible upon successful pain therapy

- Chronic back pain

  Seminowicz et al., J Neuroscience (2011)

- Posttraumatic headache

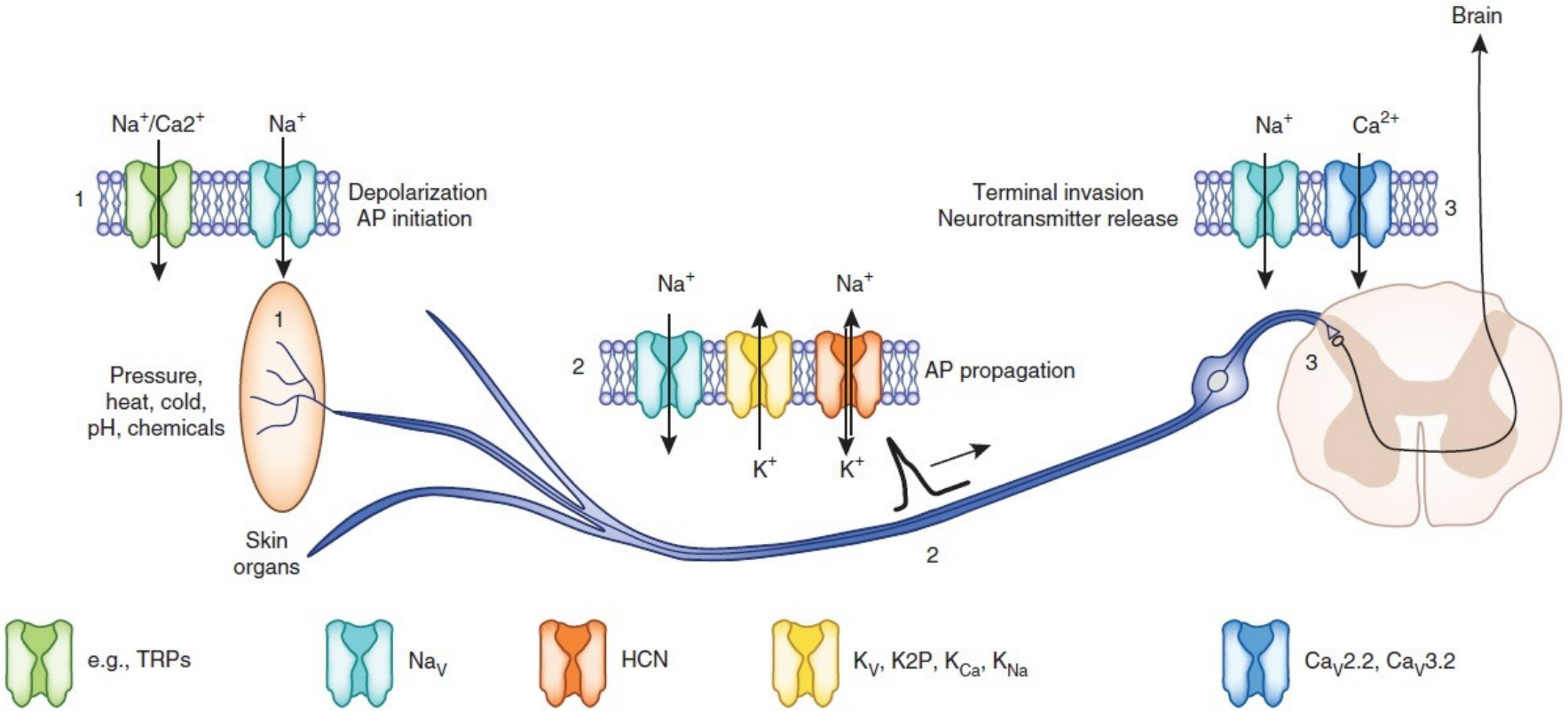
  Obermann et al., Neurology (2009)

- Osteoarthritis

  Rodriguez-Raecke et al., J Neurosci (2009)
  Gwilym et al., Arthritis Rheum (2010)

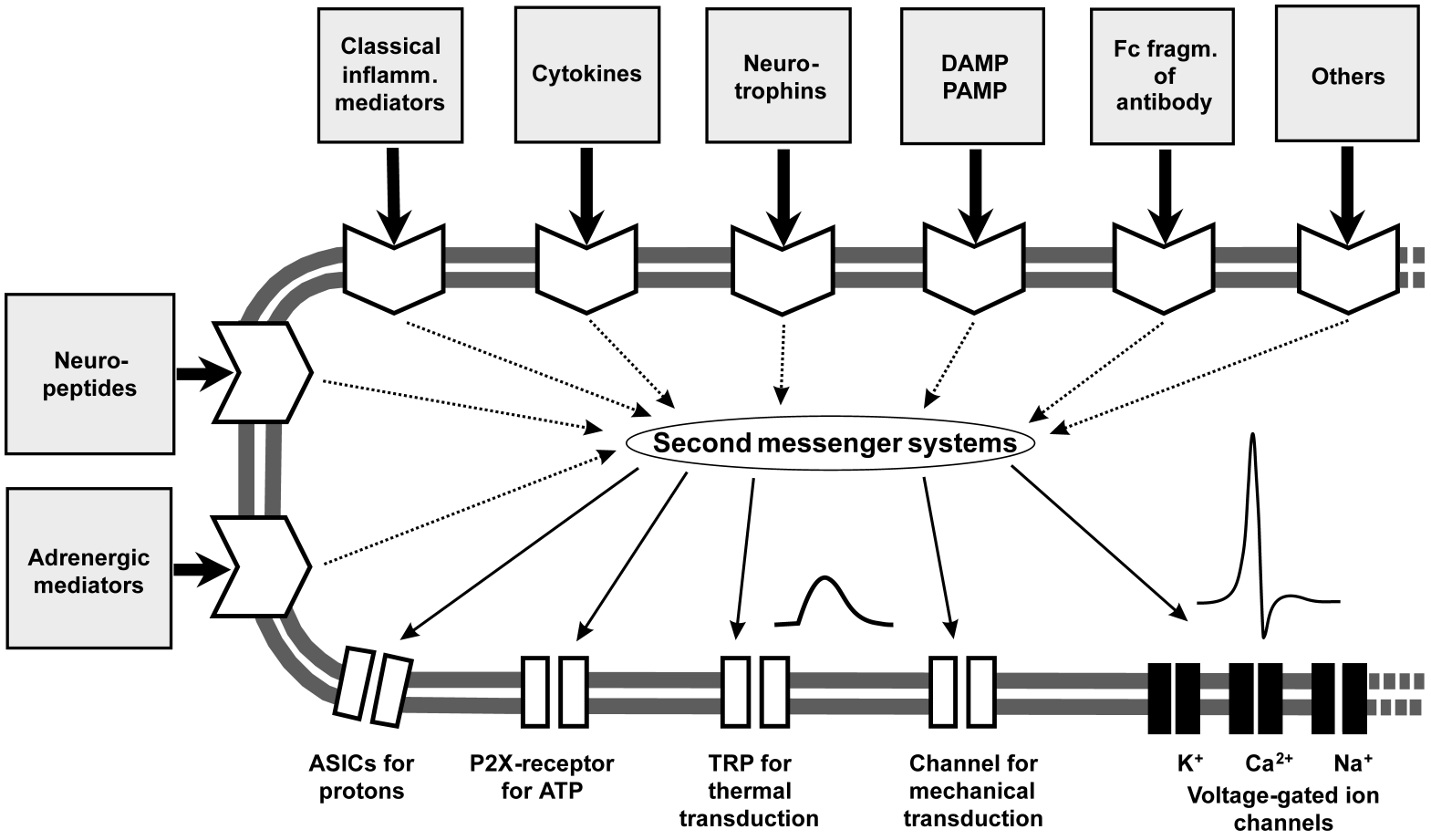
Molecular mechanisms of peripheral sensitization and central sensitization

Ion channels in nociceptors



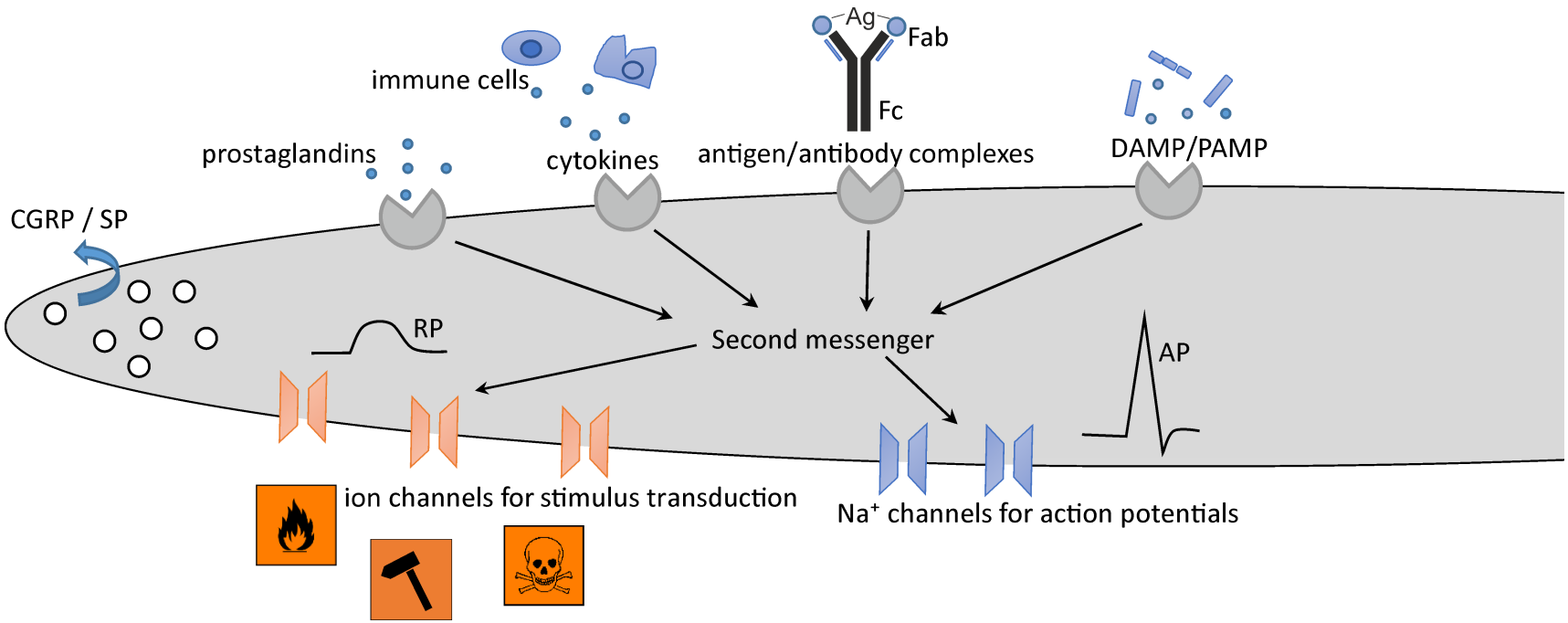
Waxman and Zamponi, Nature Neuroscience 17, 153-163 (2014)

Sensory ending of a nociceptor



modified from Schaible et al., Arthritis Res Ther 13, 210 (2011)

Effects of the immune system on nociceptors

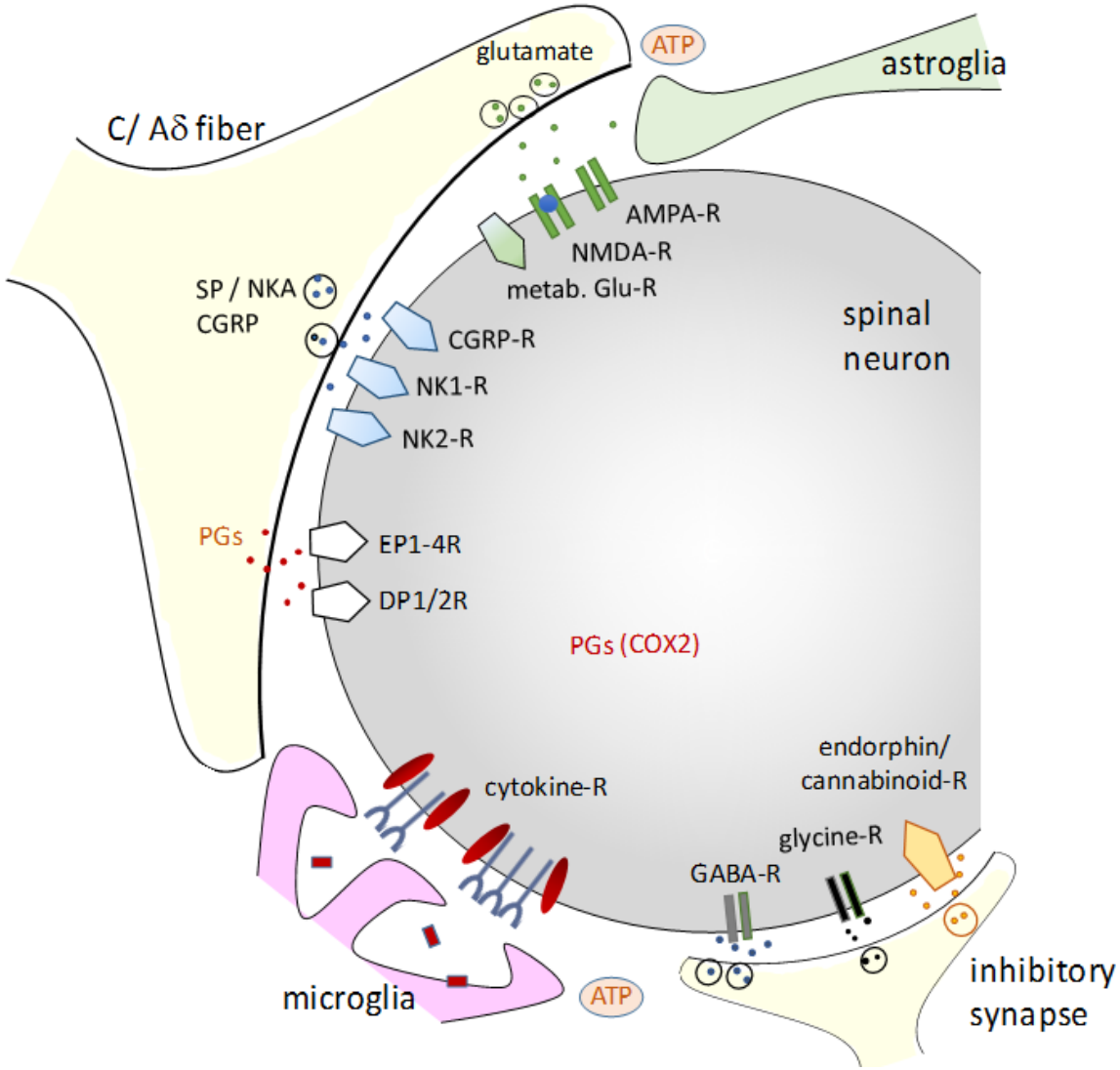


DAMP: Damage-associated molecular pattern

PAMP: Pathogen-associated molecular pattern

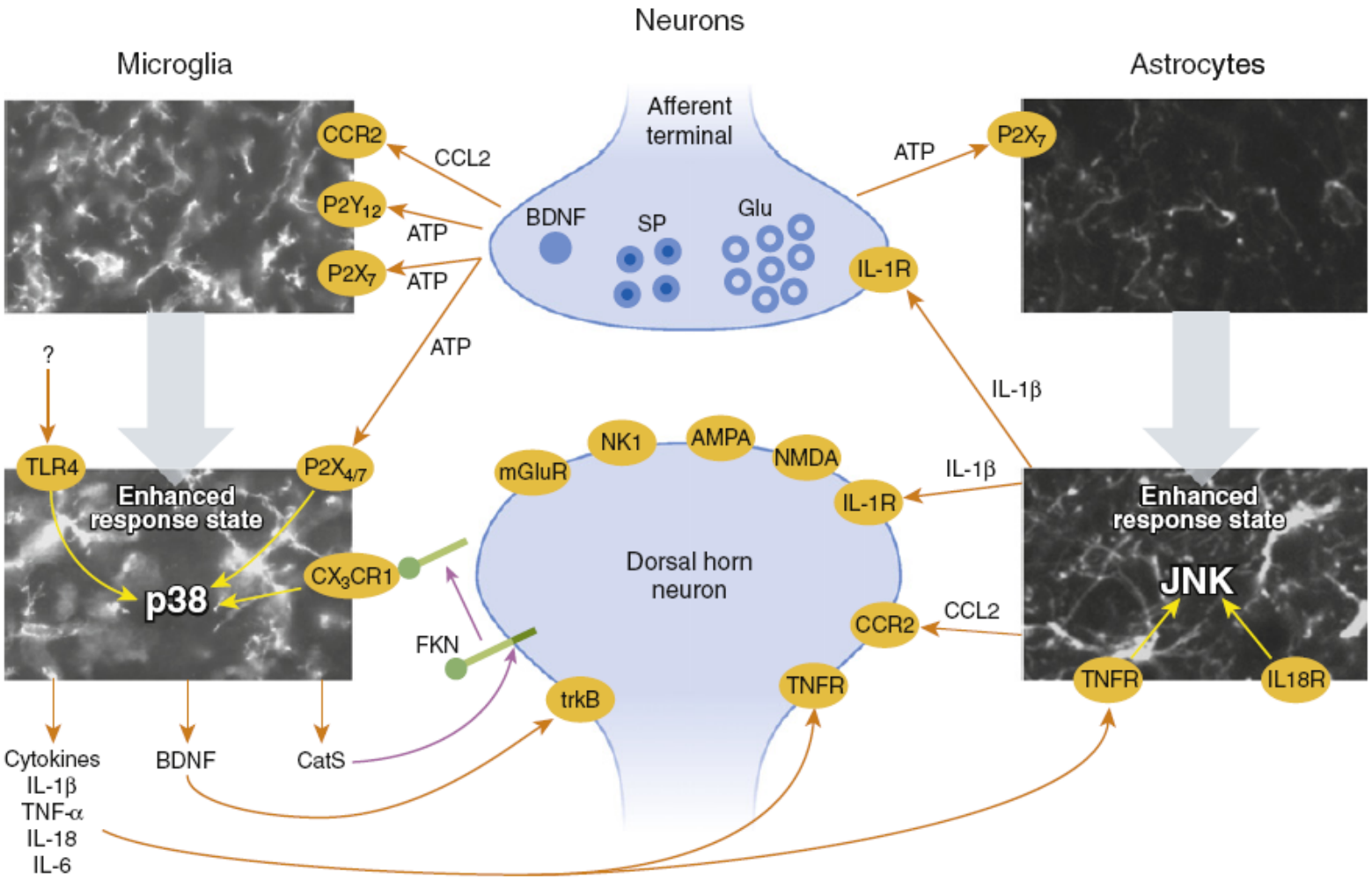
Schaible H-G, Schmerz.Therapie 5, 18-24 (2022)

Synaptic processing of nociceptive input in the spinal cord



Schaible et al., J Neurochemistry (2023)

Activation of microglia and astroglia in pain states



McMahon and Malcangio, Neuron (2009)

Microglia:

resting (quiescent) state → activated state (microgliosis)

Nerval injury, inflammation

release of mediators e.g. TNF, IL-1ß

Astroglia:

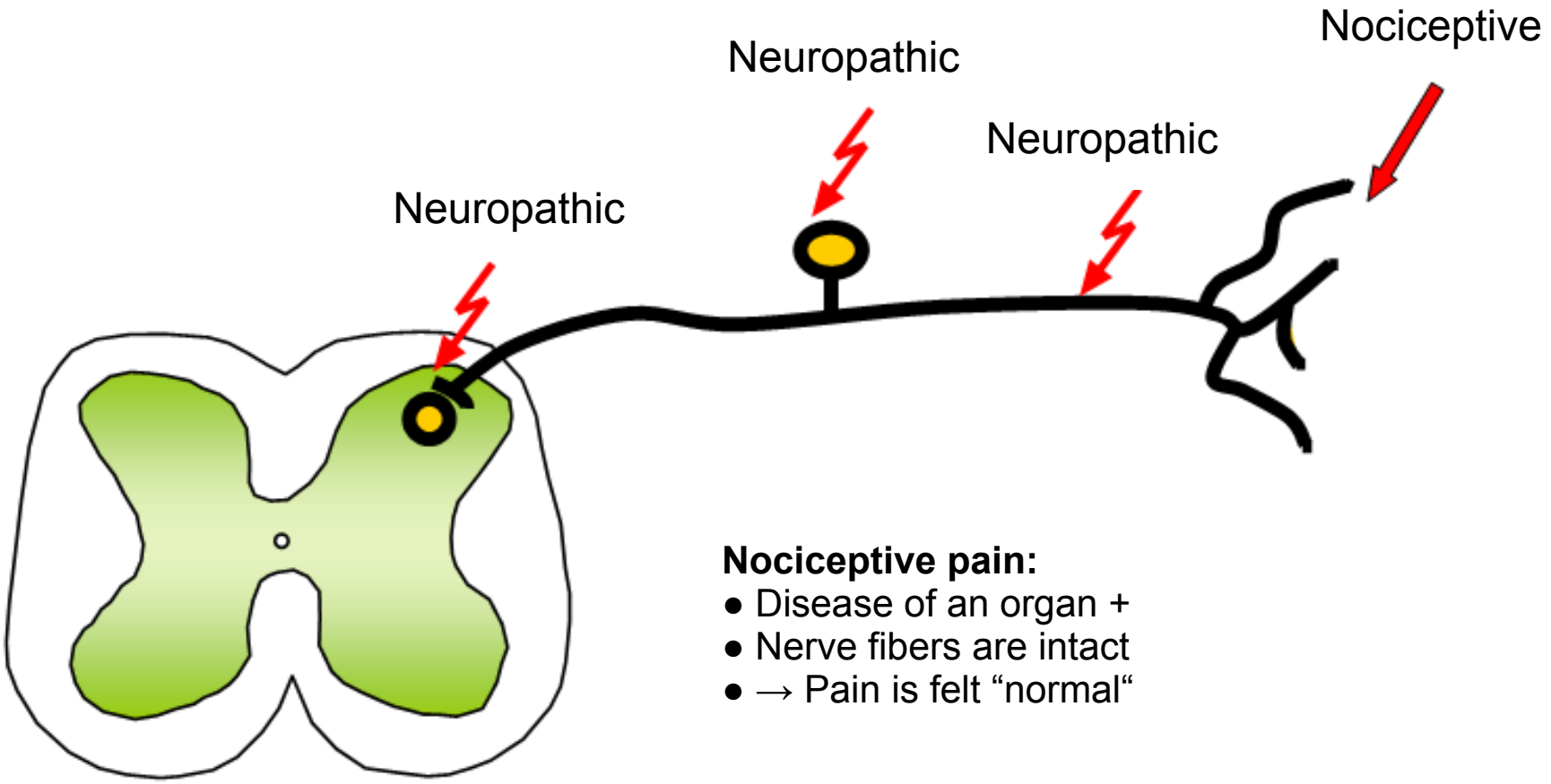
active (quiescent) state → reactive state (astrogliosis)

Nerval injury, inflammation

decrease of glutamate transporters GLT1 and GLAST

Old et al., Pain Control, Handbook of Experimental Pharmacology 227, 145-170 (2015)

Nociceptive pain – neuropathic pain



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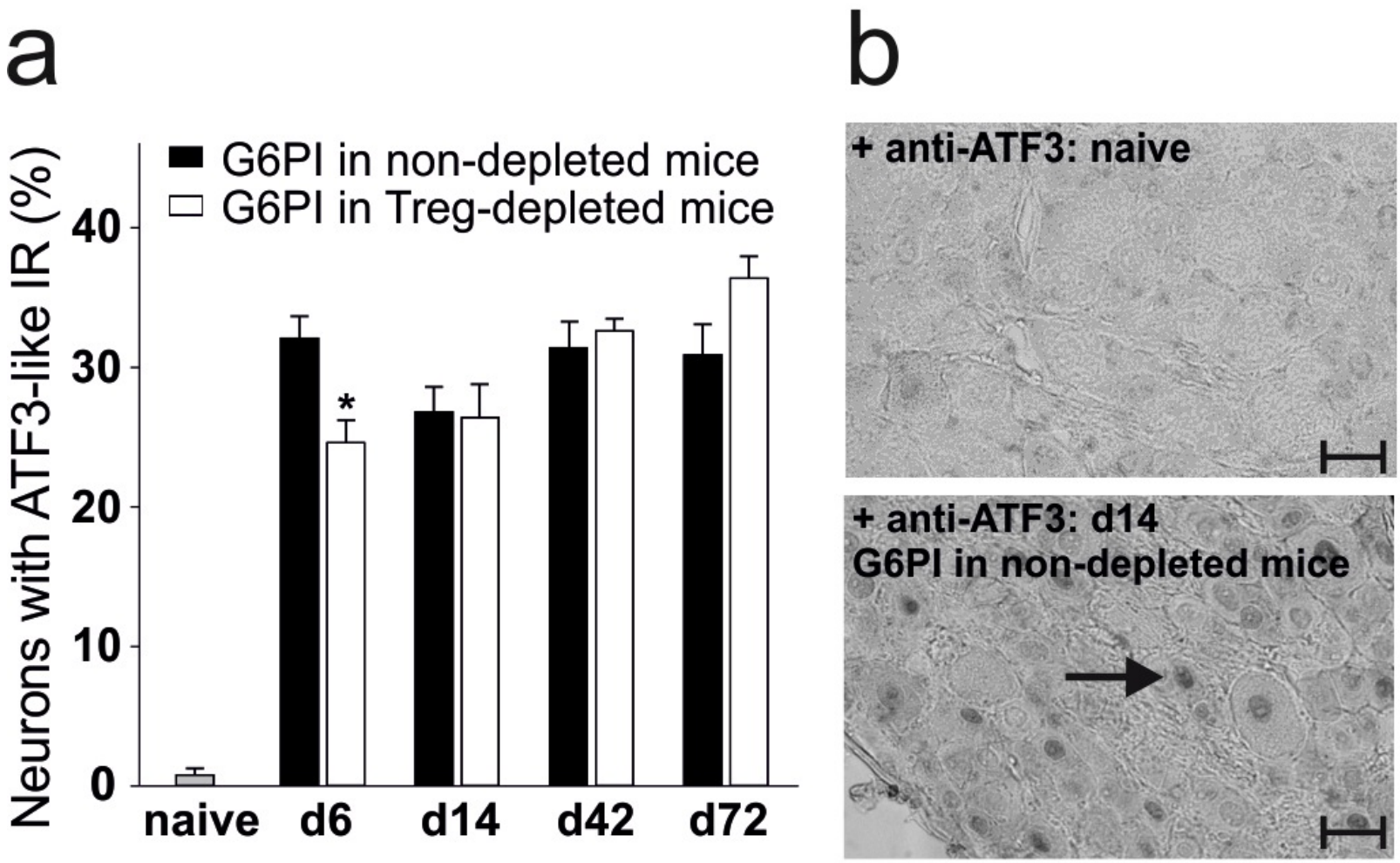
Glucose-6-Phosphat-Isomerase-induced arthritis



Ebbinghaus et al., Arthritis Rheumatol 71, 2016-2026 (2019)

Summary

Joint pain should be seen at three levels: the local factors in the joint, neuroplasticity in the nociceptive system, and general/systemic factors such as genetic, psychological, ans social factors as well as metabolic diseases

Joint pain is primarily n ociceptive pain. Neuropathic components may contribute. Nociplastic pain is under discussion for some pain states

During joint diseases, changes of neuroplasticity are induced at all levels of the nervous system

Major mechanisms of neuroplasticity are peripheral and central sensitization, reduction of descending inhibition, and local atrophies in areas processing pain

The immune system has a strong impact on the nociceptive system in the periphery as well as in the central nervous system

UNIVERSITÄTSKLINIKUM jena

Neurobiology of joint pain

Hans-Georg Schaible, Institute of Physiology 1/Neurophysiology, Universitätsklinikum Jena, Jena, Germany

Joint diseases such as osteoarthritis and rheumatoid arthritis are among the most frequent causes of pain. In general musculoskeletal pain is a major burden in the society. Three levels have to be considered: local processes in the joint (e.g. inflammatory changes, bone destruction, cartilage degradation), neuroplasticity of the nociceptive system, and systemic/general factors (e.g. genetic, psychological factors, comorbidities). This lecture will focus on the neuroplasticity of the nociceptive system. Most pains are thought to be nociceptive, but neuropathic pain components may contribute to the chronic pain states. In addition, nociplastic pain was proposed to be a separate pain category. Nociceptive pain mechanisms are characterized by sensitization of the nociceptive system. Sensitization is defined as hyperesponsiveness of nociceptive neurons resulting in the lowering of excitation threshold such that normally innocuous stimuli evoke pain, and in the increase of the responses to noxious stimulation. Both peripheral sensitization (sensitization of peripheral nociceptors) and central sensitization (in particular spinal sensitization) are prominent mechanisms of nociceptive pain. Both in the periphery and in the spinal cord, immune mechanisms significantly contribute to neuronal sensitization. In particular spinal sensitization is also supported by a reduction of descending inhibition. Both in inflammatory joint diseases and in osteoarthritis, sensory neurons may exhibit signs of neuronal challenge, e.g. upregulation of ATF3, a marker of damaged neurons. Damaged neurons may generate ectopic discharges and action potentials in the absence of stimulation. Neuropathic mechanisms my contribute to the pain phenotype and pain chronification. In addition to peripheral and spinal mechanisms of sensitization, changes in the brain characterize chronic pain states. Imaging data in humans have provided evidence for so-called atrophies (thinning of the cortex in areas involved in pain processing) and for processes of reorganization. Moreover, the amygdala, a limbic structure involved in the generation of emotions such as fear, are directly activated by pain pathways.