Master Biologie-Santé
HAV919V

Pulsed radiofrequency in a pain context

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DEFINITION

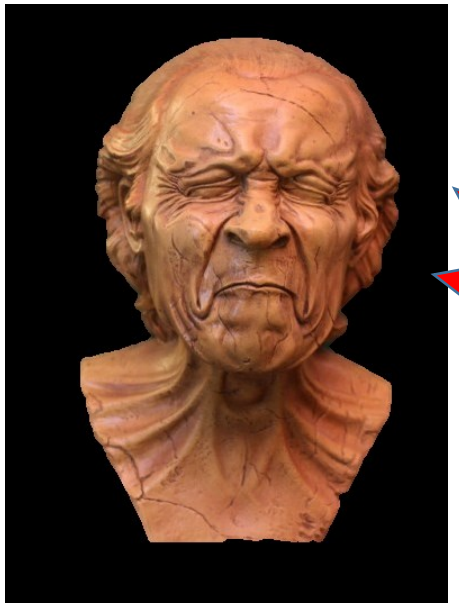
International Association for the Study of Pain
IASP
Working together for pain relief

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

Sensory discriminative component

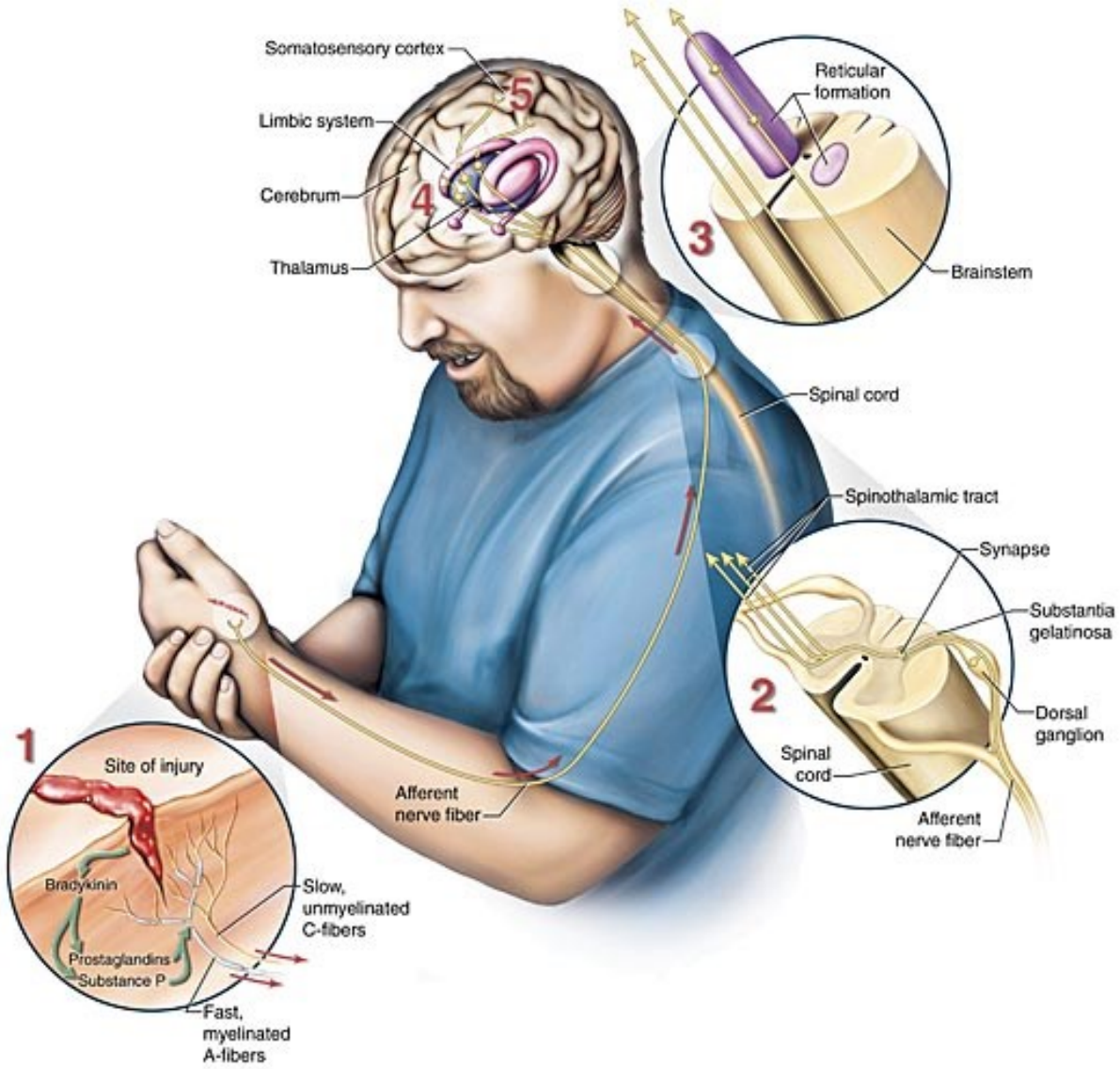
+

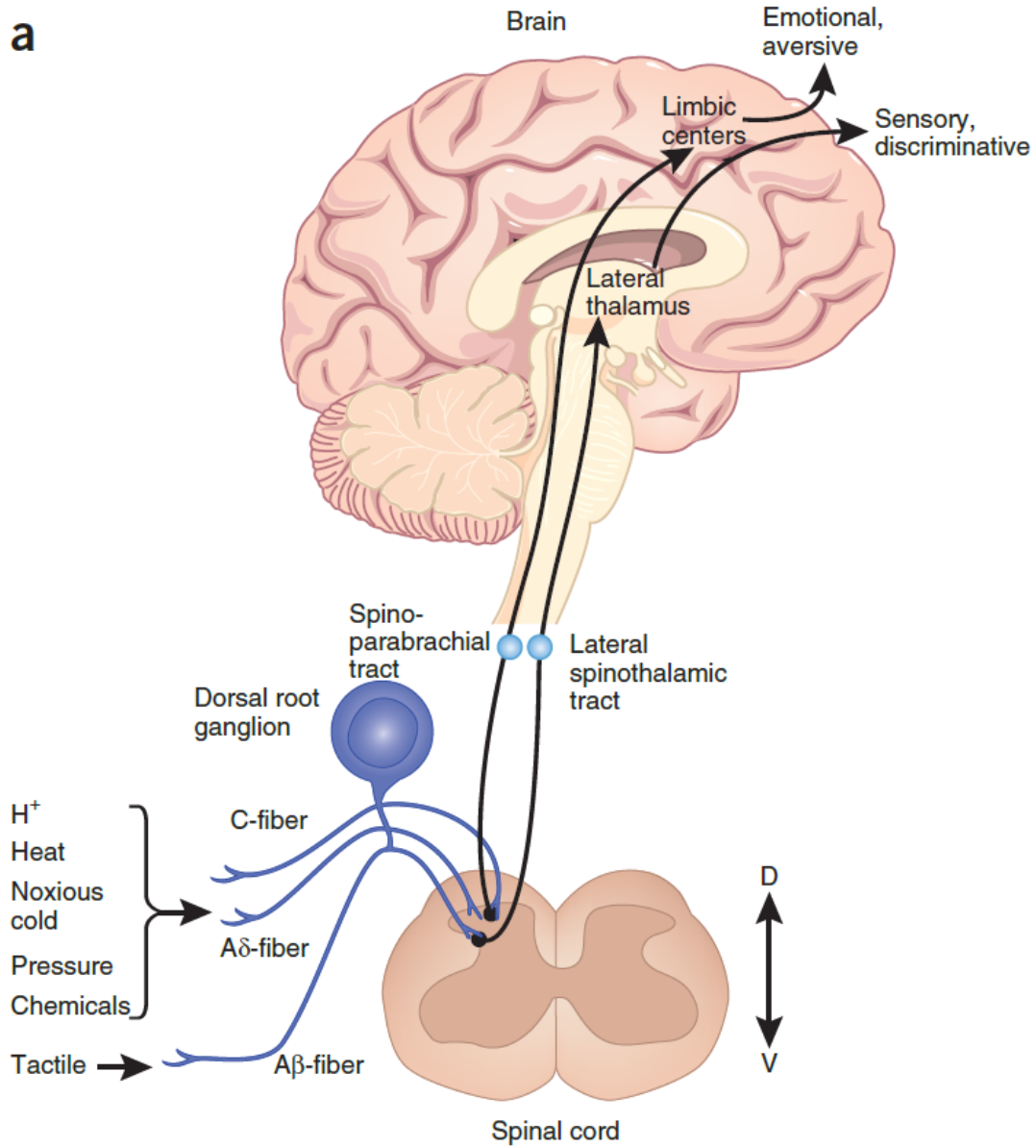
Emotional component



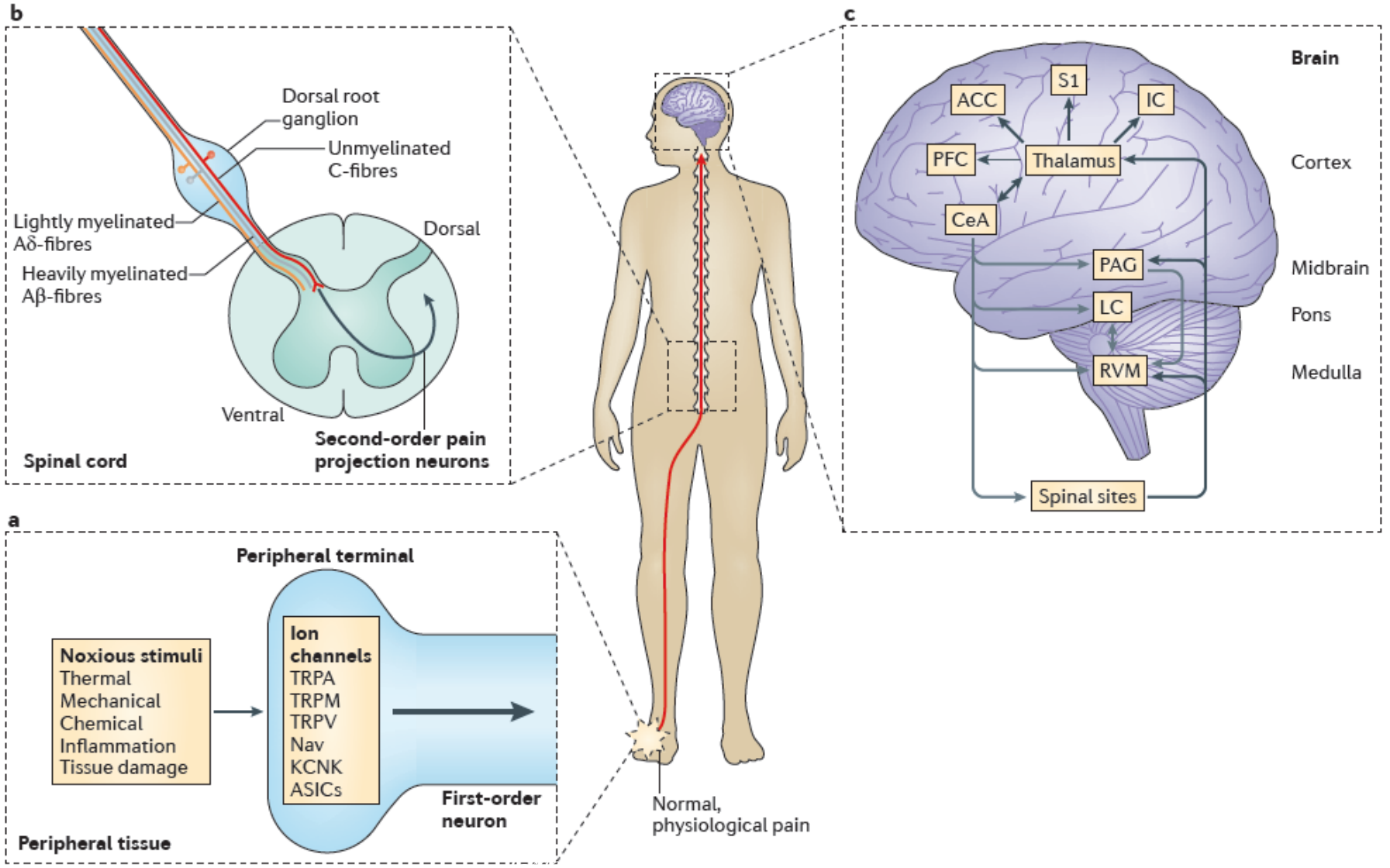
PAIN

NOCICEPTIVE SYSTEM

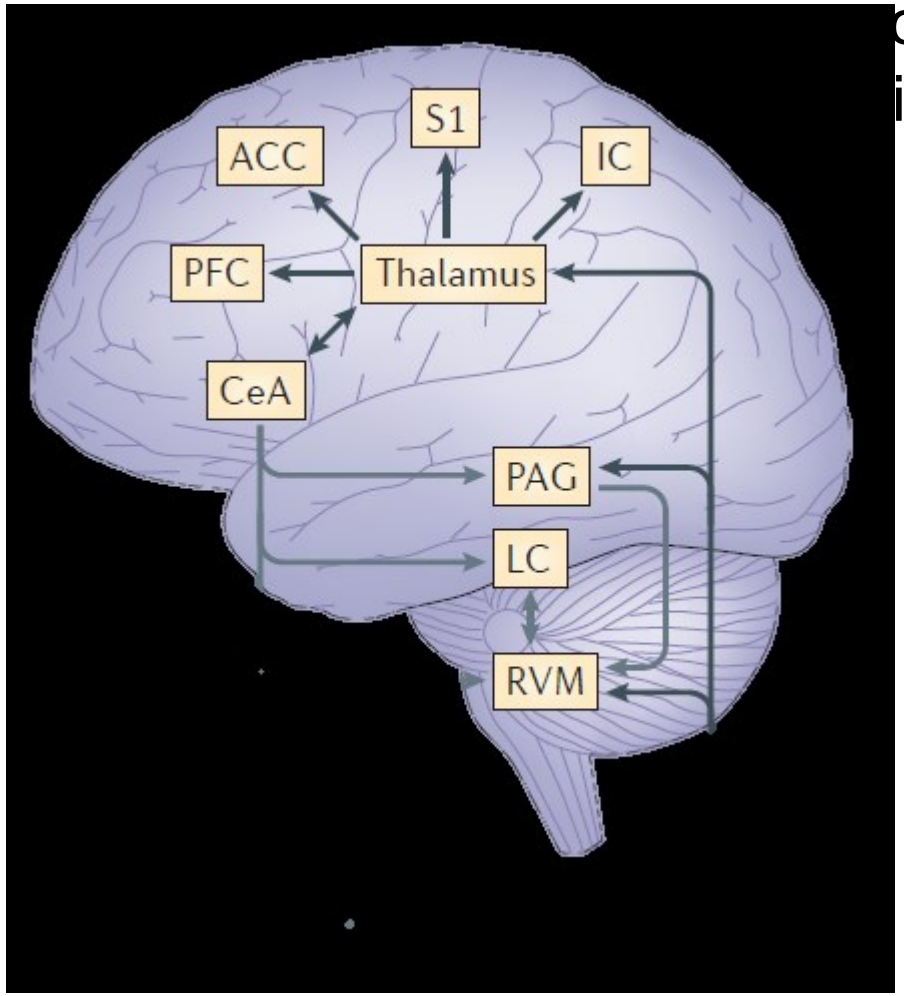




NOCICEPTIVE SYSTEM



NOCICEPTIVE SYSTEM



Third-order neurons from the thalamus project to several ortical and subcortical regions that encode sensory-iscriminative, emotional and cognitive aspects of pain.

Association between sensory-discriminative and emotional components of pain

Grace et al., Pathological pain and the neuroimmune interface. Nat Rev Immuno, 2014.

NOCICEPTIVE SYSTEM

Facilitatory systems

PGE2
Glutamate
CGRP
SP
NGF

Inhibitory systems

GABA
Glycine
Endogenous opioids

\+

Sensitization

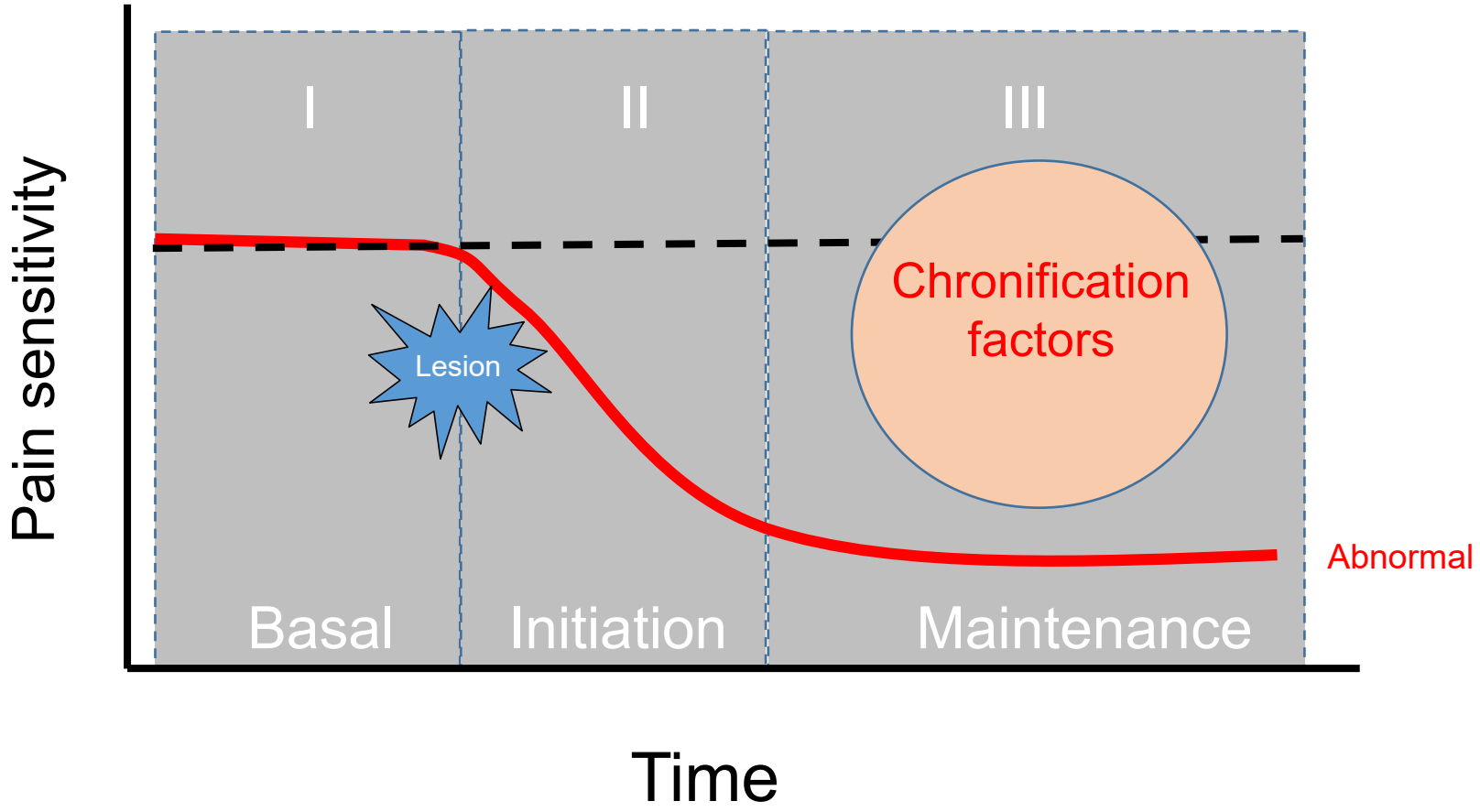
PAIN

\-

Inhibition/extinction

PATHOPHYSIOLOGY OF PAIN

Chronic pain development



PATHOPHYSIOLOGY OF PAIN

- 116 million adults in the U.S. and 20% of the adult European population

- The annual cost of chronic pain is $560–635 billion in the U.S (higher than the costs of cardiovascular diseases, cancers, and diabetes combined)

- Classification of chronic pain

  - Nociceptive pain

    Damage to body tissue or disease

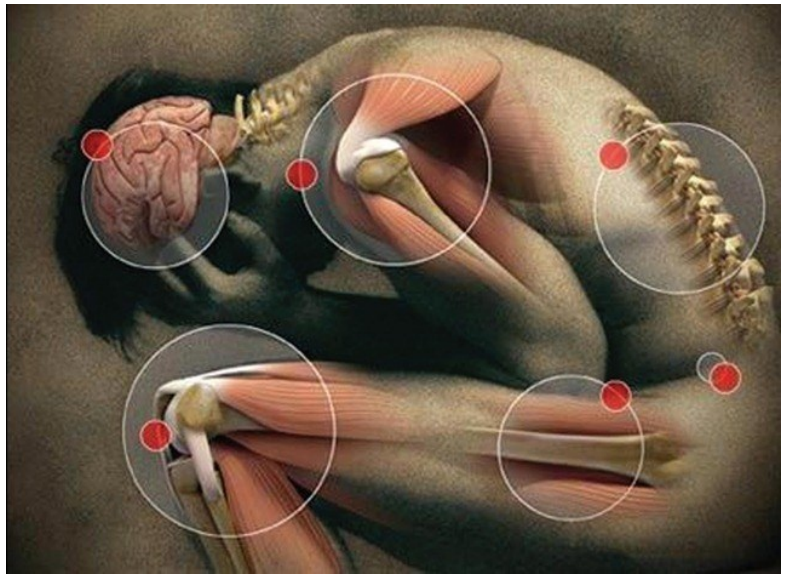
  - Neuropathic pain

    Dysfonction of the PNS or CNS

  - Psychogenic pain

    No apparent lesion

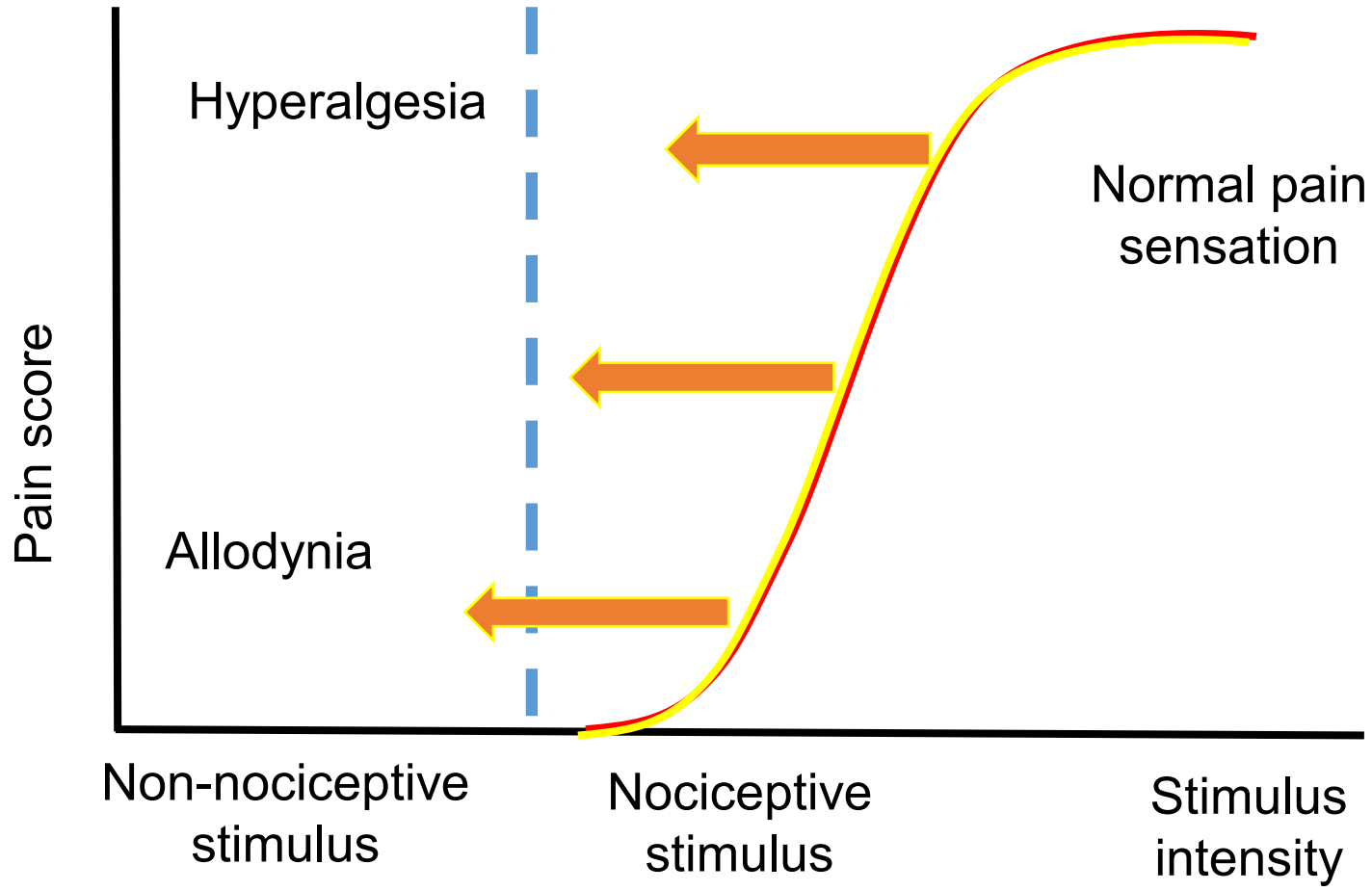
PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



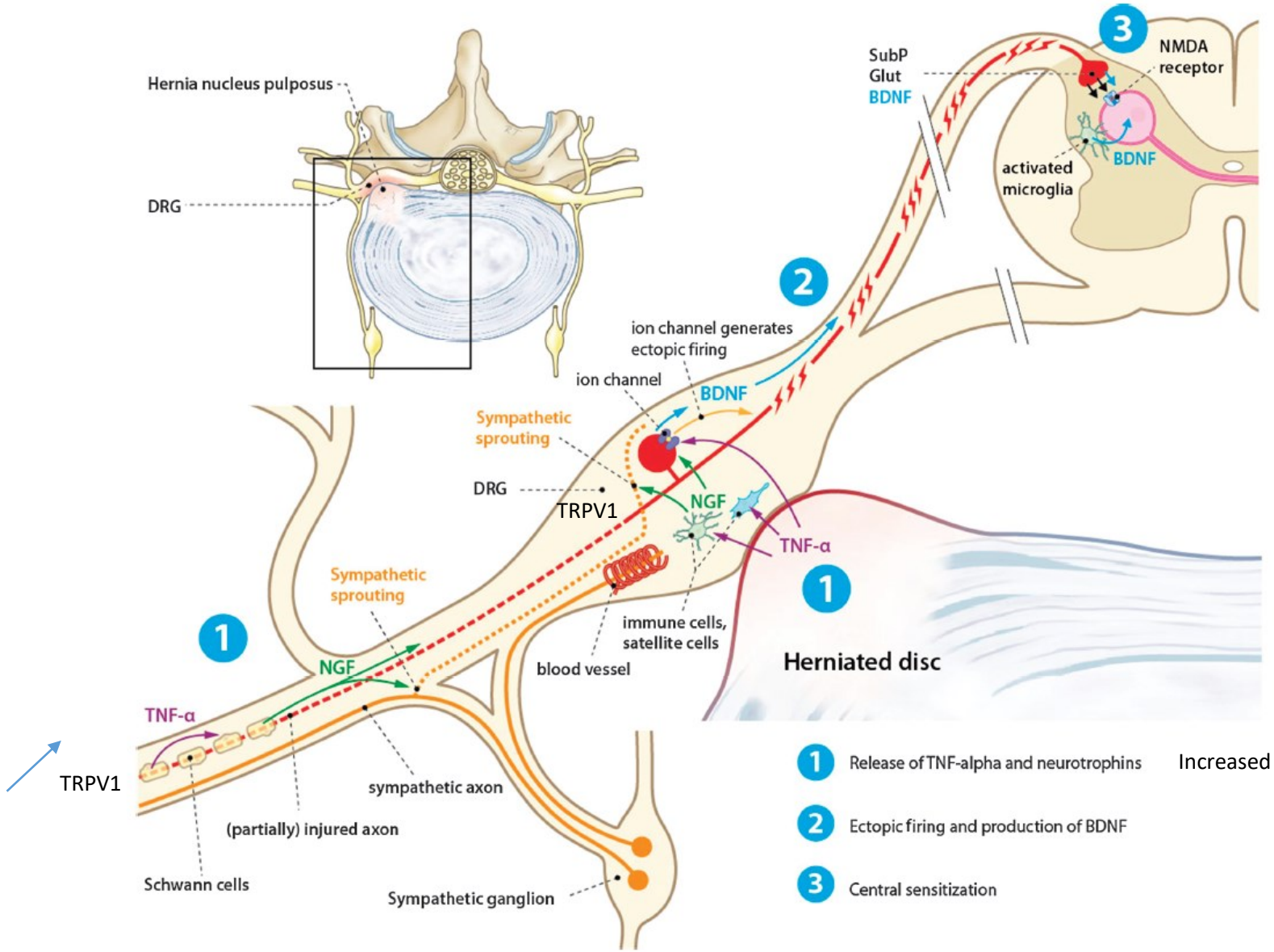
- Chronic disease affecting 7% of the population
  (surgery, chemotherapy, alcohol, HIV, diabetes…)
- No specific treatment
- Resistance to the treatments in about 50%-65% of the patients
- Difficult to diagnose

↳Identify pathophysiological mechanisms to propose innovative therapeutic strategies

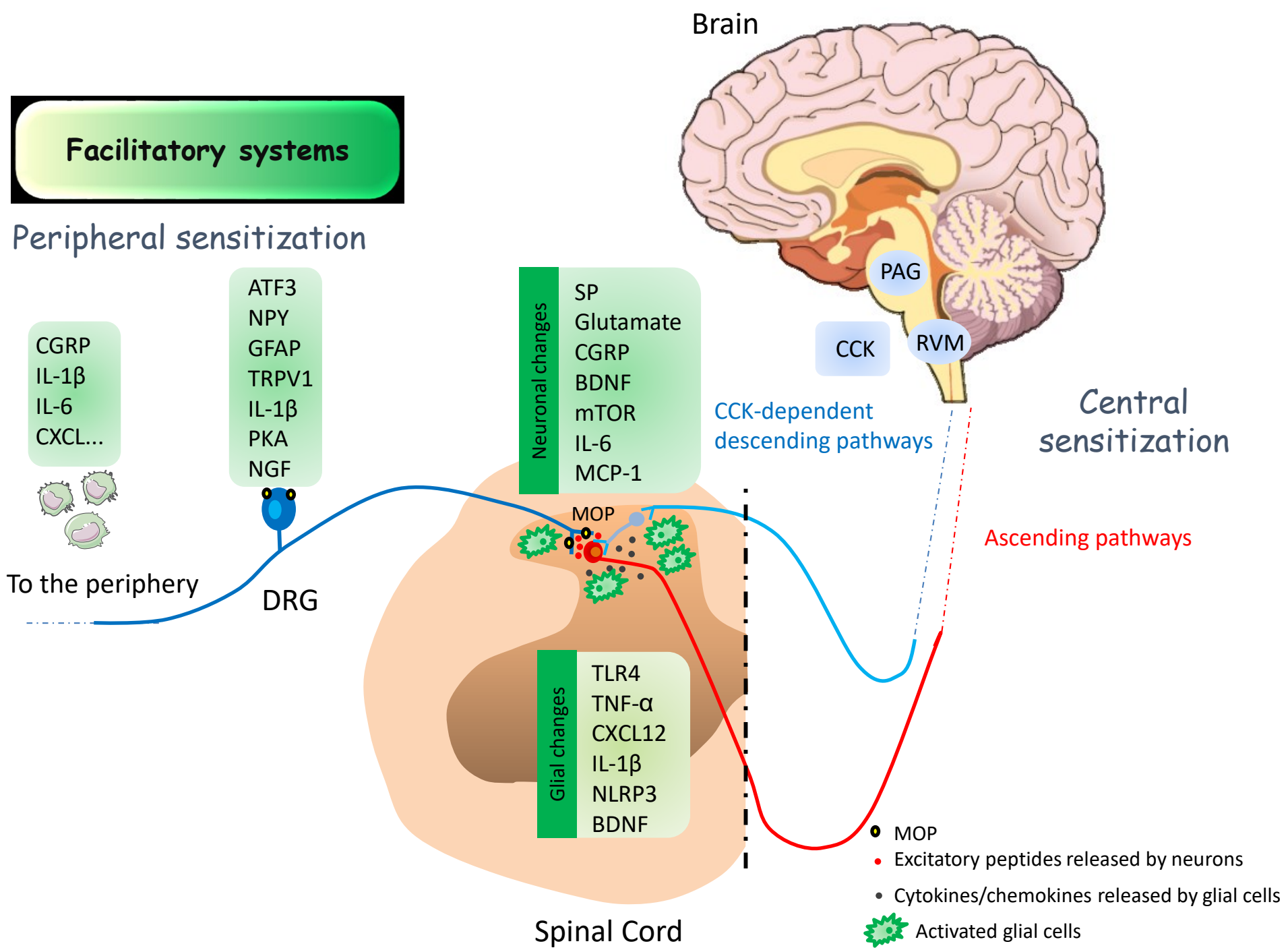
PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



Increased expression of ionotropic receptor

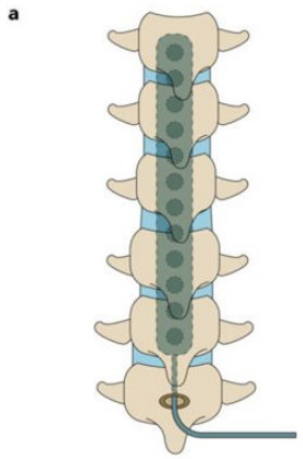

Facilitatory systems
Peripheral sensitization
Brain
PAG
RVM
CCK
CCK-dependent
descending pathways
Central
sensitization
Ascending pathways
CGRP
IL-1β
IL-6
CXCL...
ATF3
NPY
GFAP
TRPV1
IL-1β
PKA
NGF
Neuronal changes
SP
Glutamate
CGRP
BDNF
mTOR
IL-6
MCP-1
MOP
To the periphery
DRG
Glial changes
TLR4
TNF-α
CXCL12
IL-1β
NLRP3
BDNF
Spinal Cord
MOP
Excitatory peptides released by neurons
Cytokines/chemokines released by glial cells
Activated glial cells

TREATMENT OF NEUROPATHIC PAIN

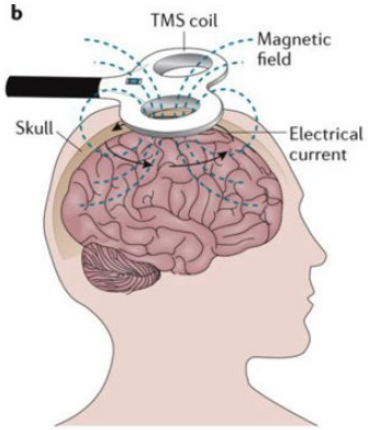
Drug treatments

- Tricyclic antidepressants
- Serotonin-noradrenaline reuptake inhibitors
- Calcium channel α2δ ligands
- Topical lidocaine
- Capsaicin high-concentration patch (8%)
- Opioids
- Neurotoxin

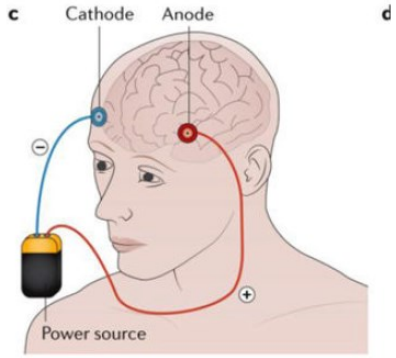
Interventional treatments



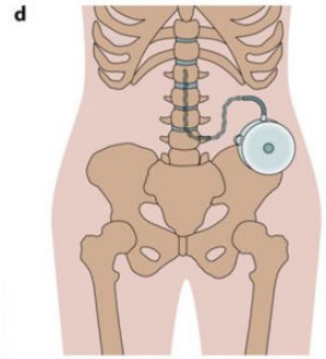
Spinal cord stimulation



transcranial magnetic stimulation



Deep brain stimulation high-frequency chronic intracranial stimulation

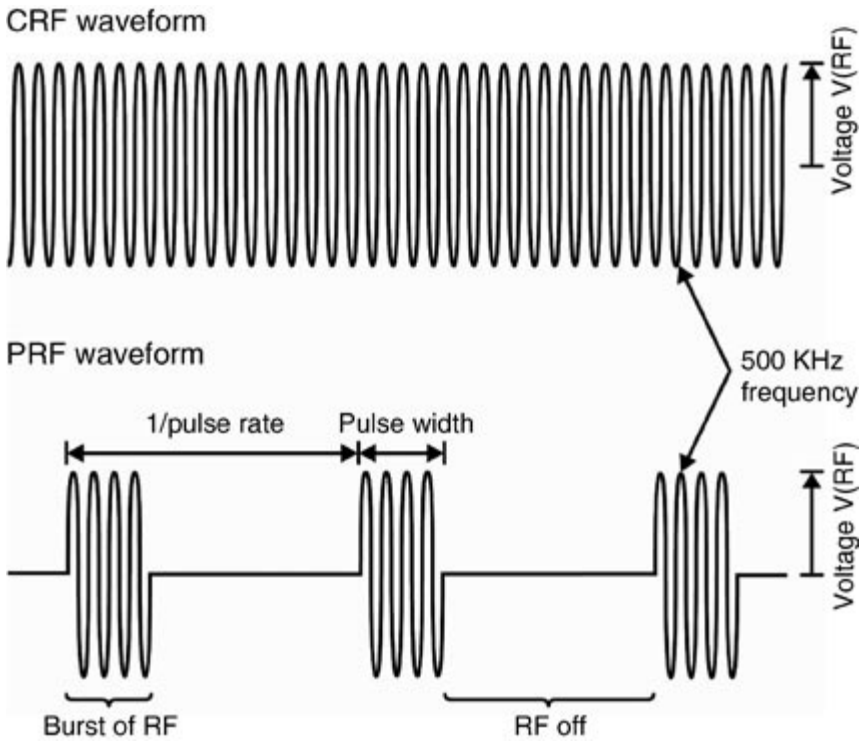


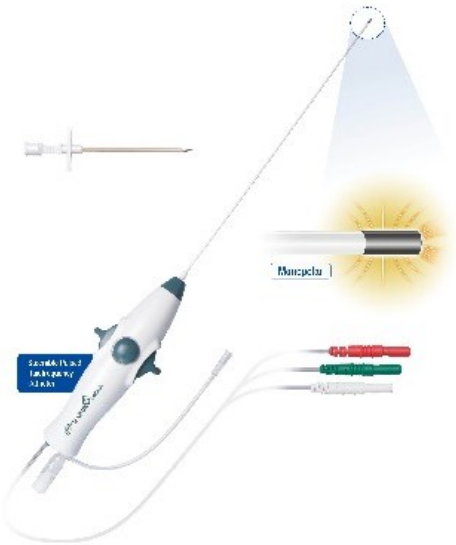
Intrathecal treatments

PULSED RADIOFREQUENCY

- Pulsed radiofrequency (PRF) is a form of electromagnetic stimulation that has clinically been used to treat symptoms such as cardiac arrhythmias, bone fracture, oedema etc…

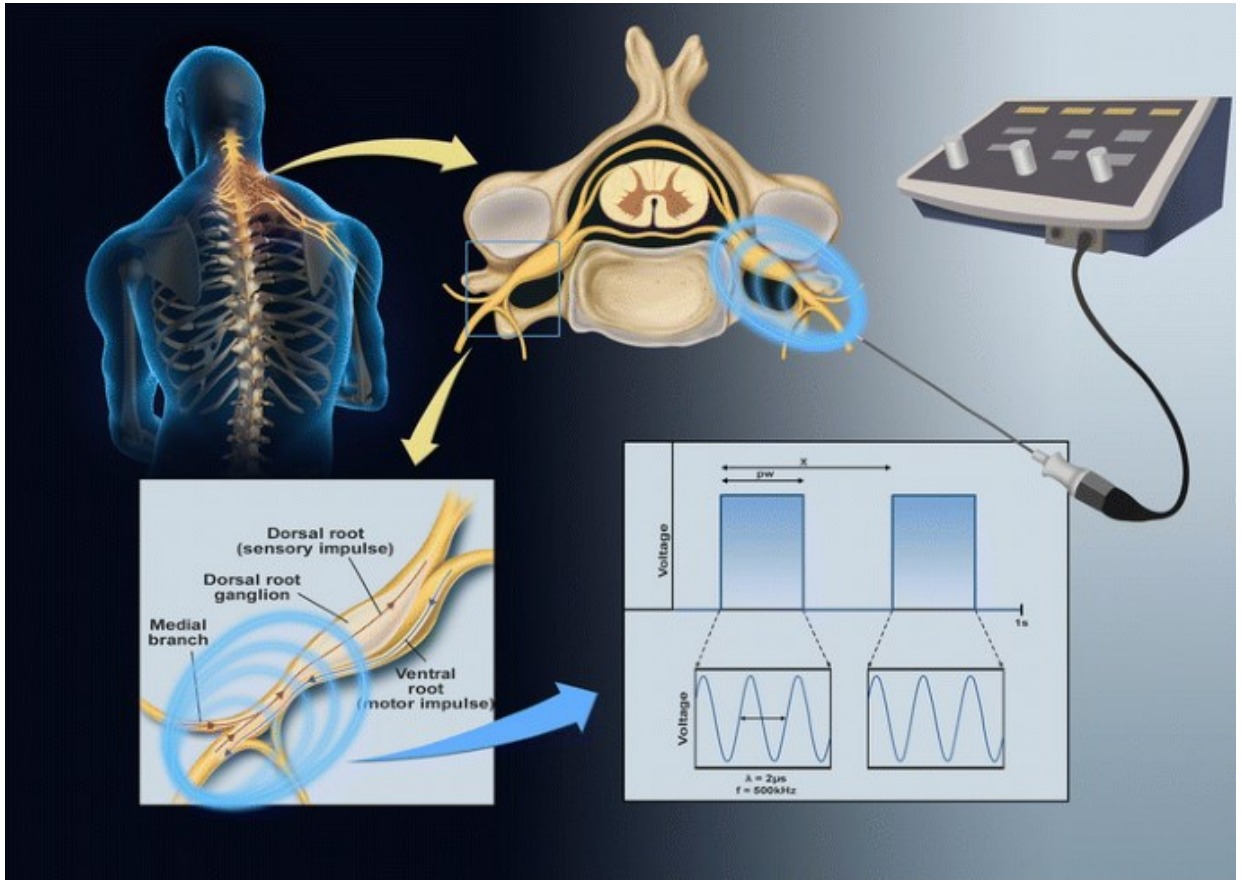
- PRF is a technique in which electromagnetic waves are applied close to the tissue to be treated for periods of between 2 and 8 min, with a raise of mean temperature to a maximum of 42 °C



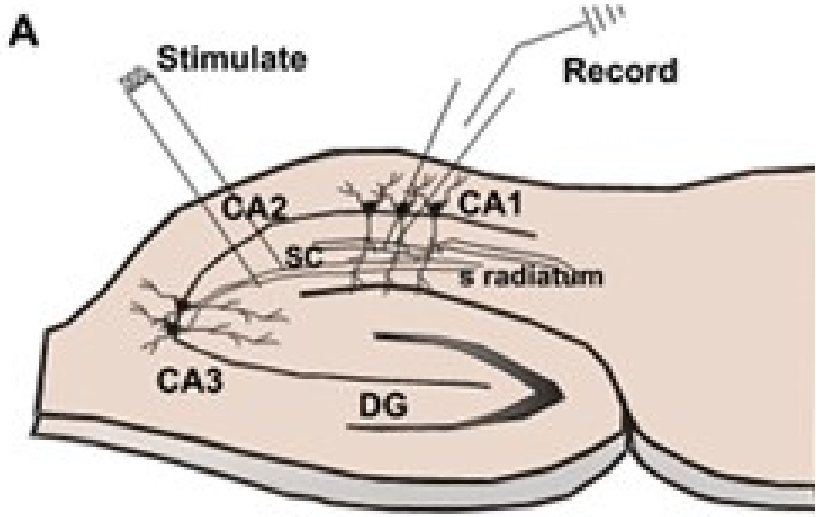


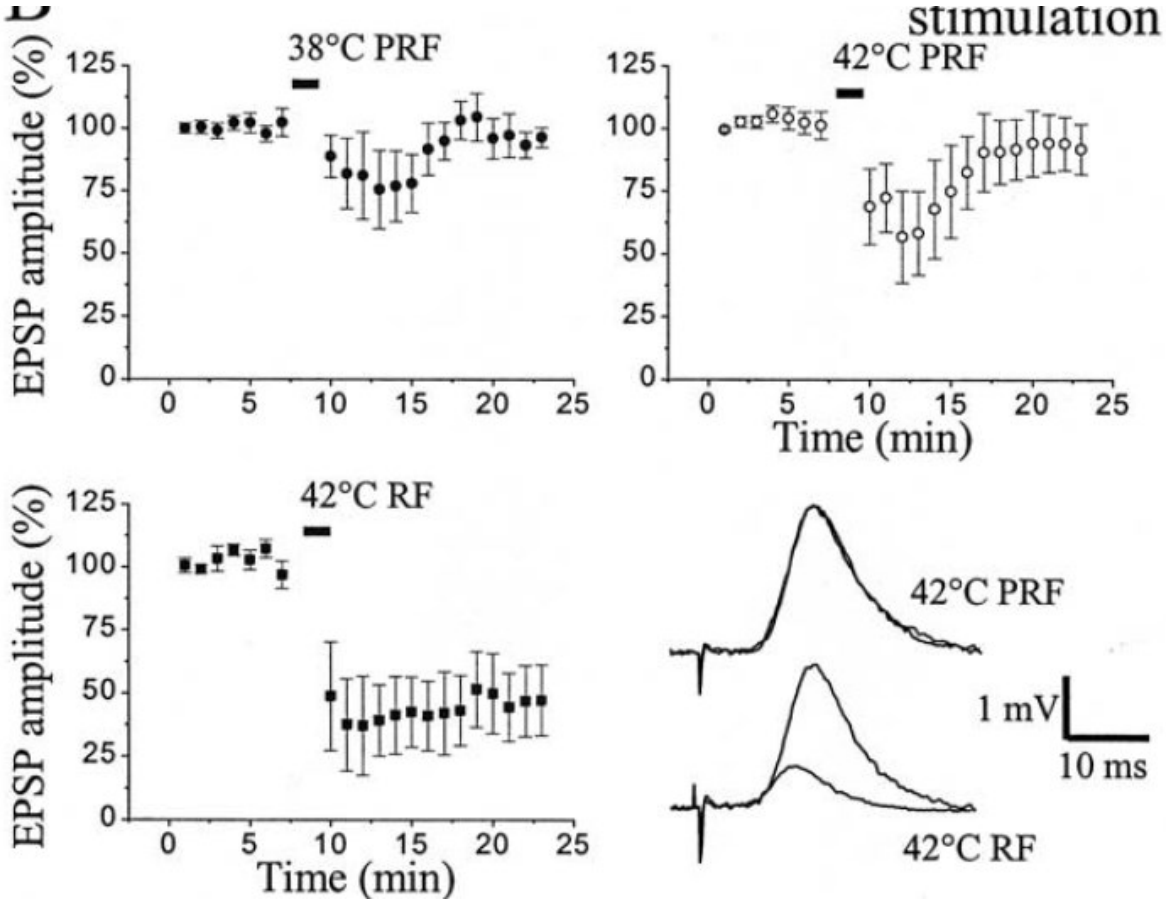
PULSED RADIOFREQUENCY

PRF has been used for the management of chronic pain, especially peripheral neuropathic pain. The electromagnetic waves (20 ms pulses of 500 kHz) produced by an electrode is applied close to a dorsal root ganglion (DRG) or a sensory nerve for periods of between 2 and 8 min (maximum of 42 °C)



CELLULAR EFFECTS OF PRF



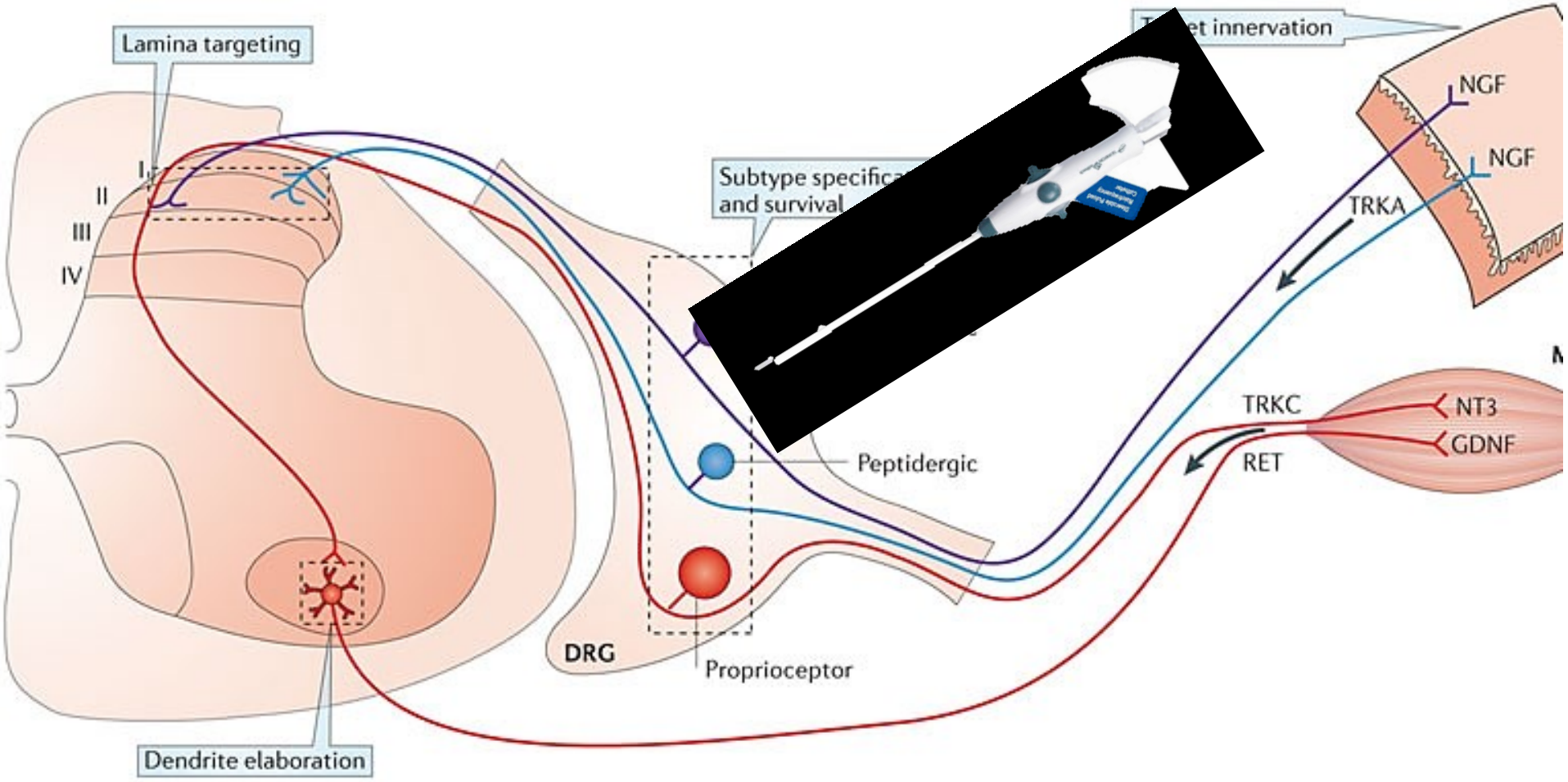


Exposure of neurons to PRF results in a transient inhibition of evoked excitatory transmission with full recovery of synaptic activity within a few minutes, whereas continuous radiofrequency results in a lasting blockade that does not recover during the next 15 to 30 minutes

Cahana A. et al., The Journal of Pain, Vol 4, No 4 (May), 2003: pp 197-202

CELLULAR EFFECTS OF PRF

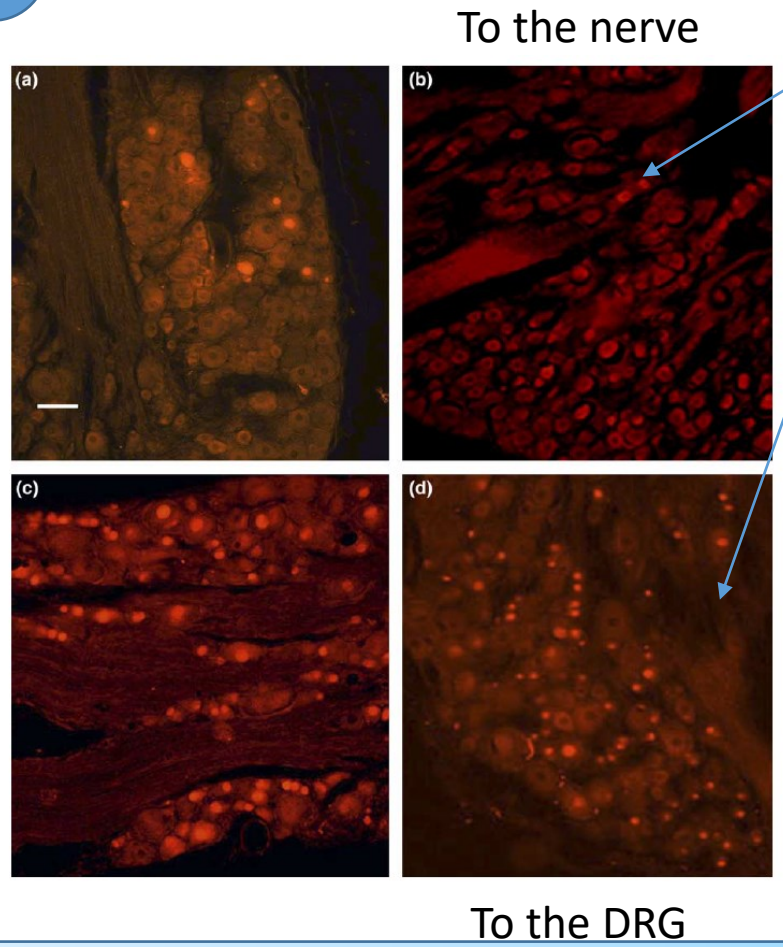
Sub-populations of neurons in the DRG

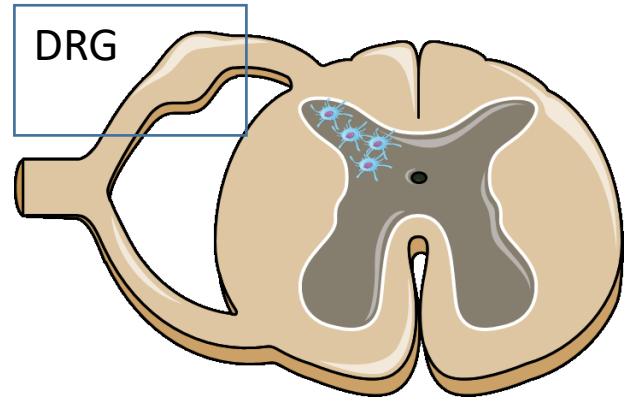


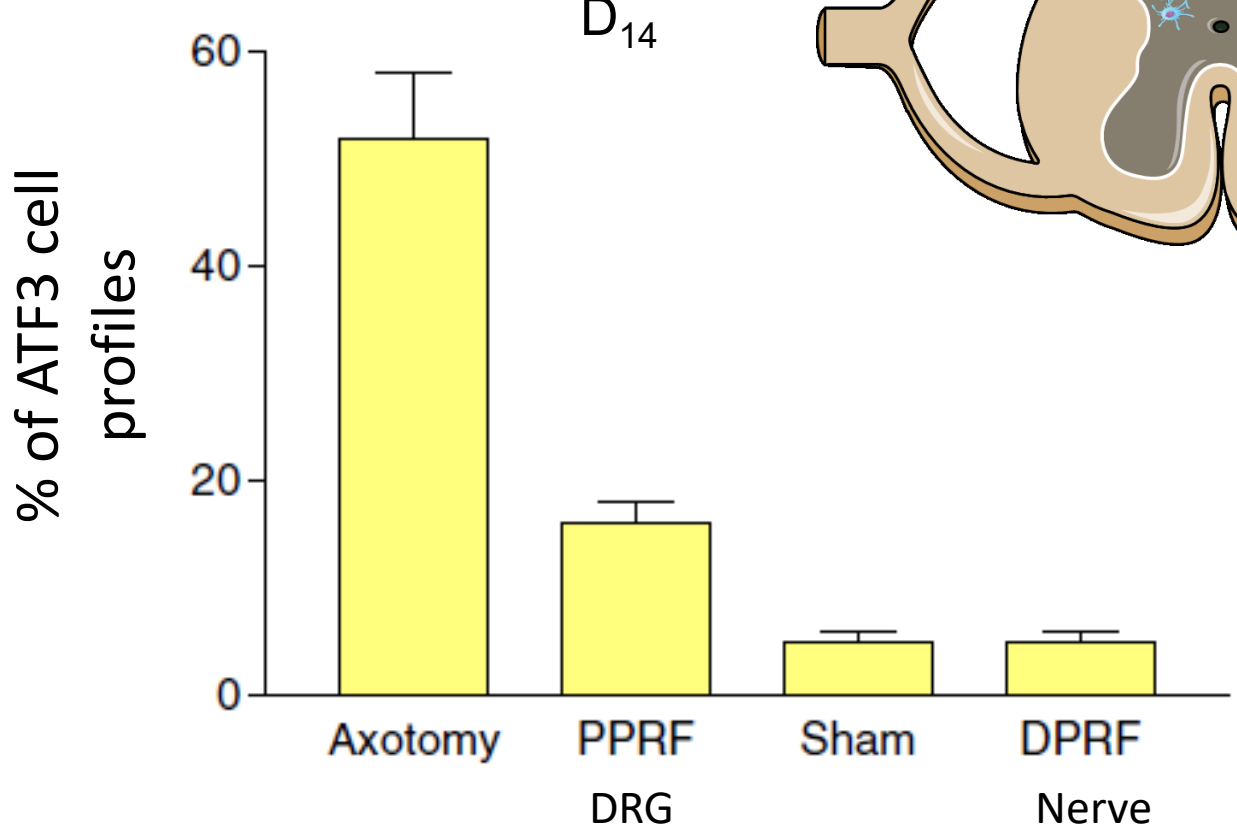
Harrington and Ginty. Long-distance retrograde neurotrophic factor signalling in neurons. Nature Reviews Neurosci, 2013.

CELLULAR EFFECTS OF PRF

1 PRF and DRG





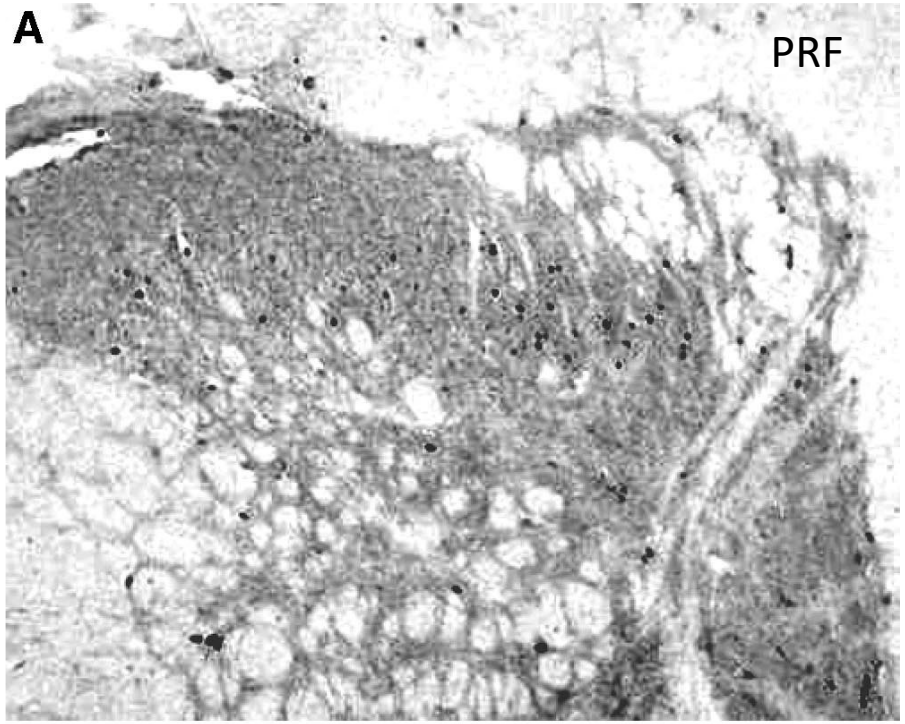


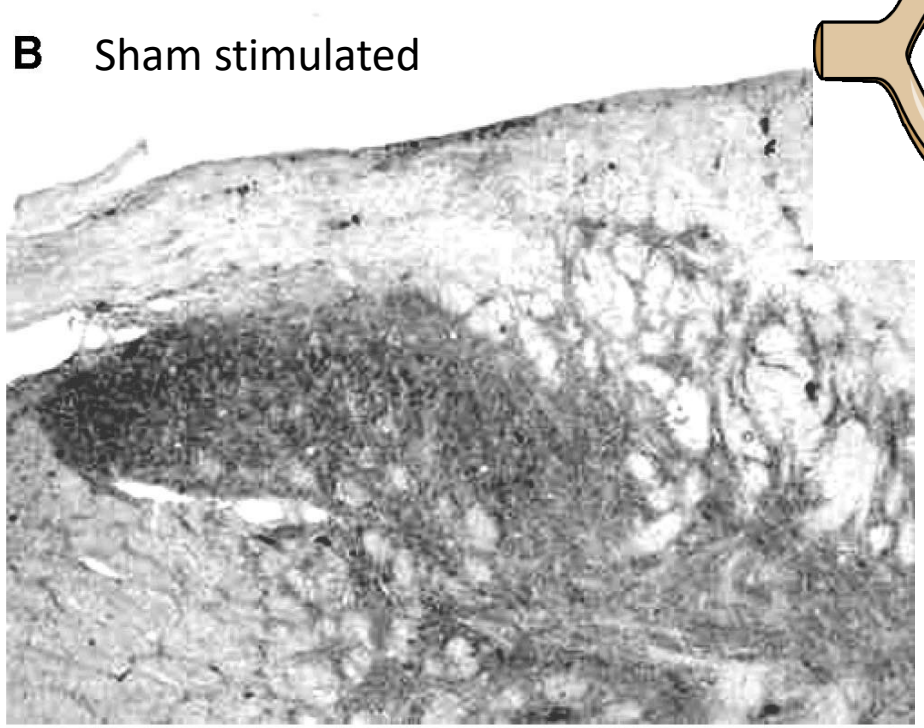
The activation of neuronal stress marker ATF3 by PRF demonstrates the cellular effects of PRF on sensory neurons specifically in the non-myelinated neurons

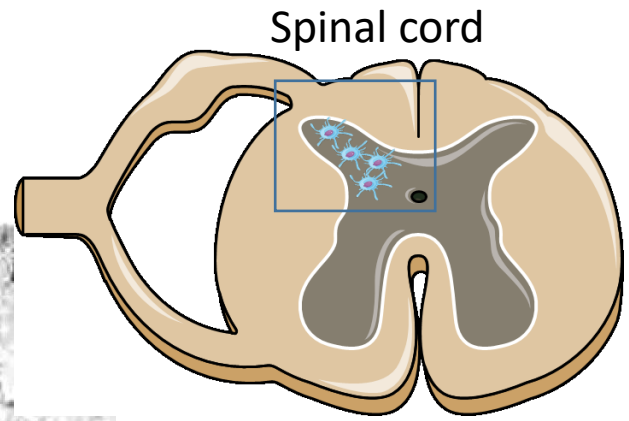
Hamann W. et al., European Journal of Pain 10 (2006) 171–176

CELLULAR EFFECTS OF PRF

2 PRF and Spinal cord







A late neuronal activity in the dorsal horn after exposure of the cervical DRG to different radiofrequency modalities. The observation that c-fos was present 7 days after stimulation suggests sustained activation in prain processing.

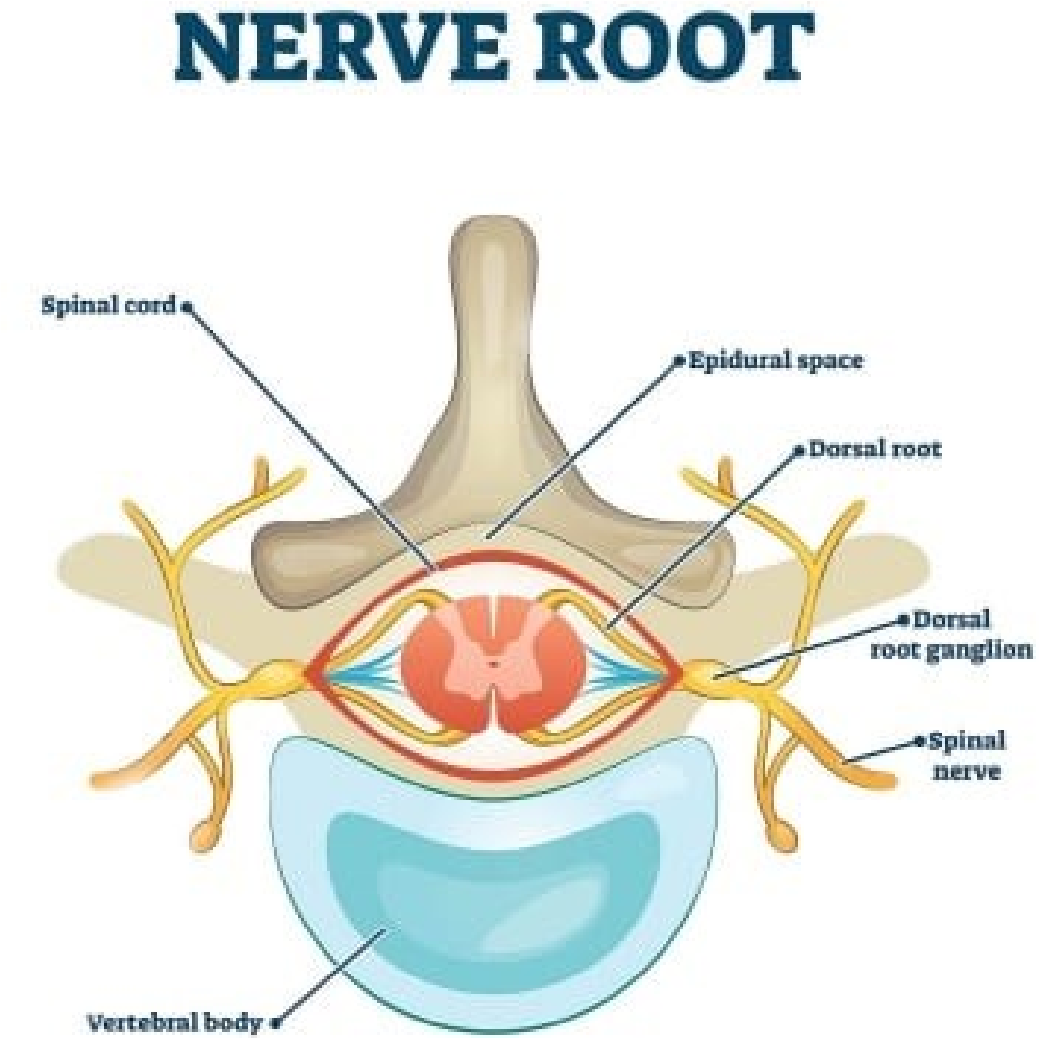
Van Zundert et al. Anesthesiology, 2005

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

- It has been reported that the biological effect of PRF was unlikely to be related to an overt thermal damage and appears to be selective in that it targets the group of neurons whose axons are the small-diameter C and Aδ nociceptive fibers.
- PRF alters synaptic transmission as evidenced by the reduction in post-synaptic excitatory transmission
- Similarly, a morphological evaluation of the rabbit DRG 2 weeks after sham, continuous radiofrequency or PRF, illustrated no pathological findings in control and sham-operated group, minimal morphological changes in the PRF group, and neurodestruction in the continuous RF group

PRF demonstrates cellular effects and its use seems to be safe

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Effects of PRF on DRG

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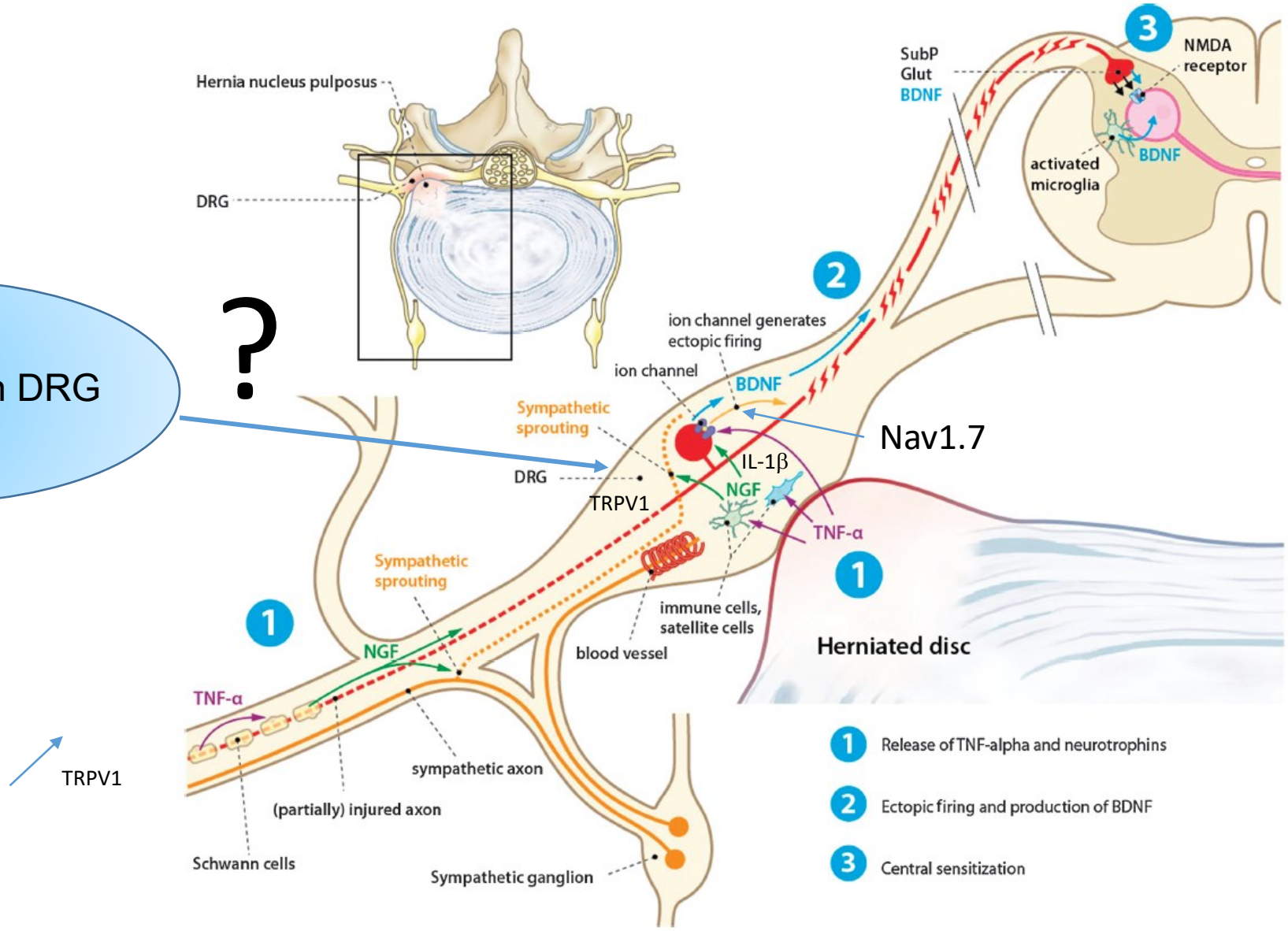
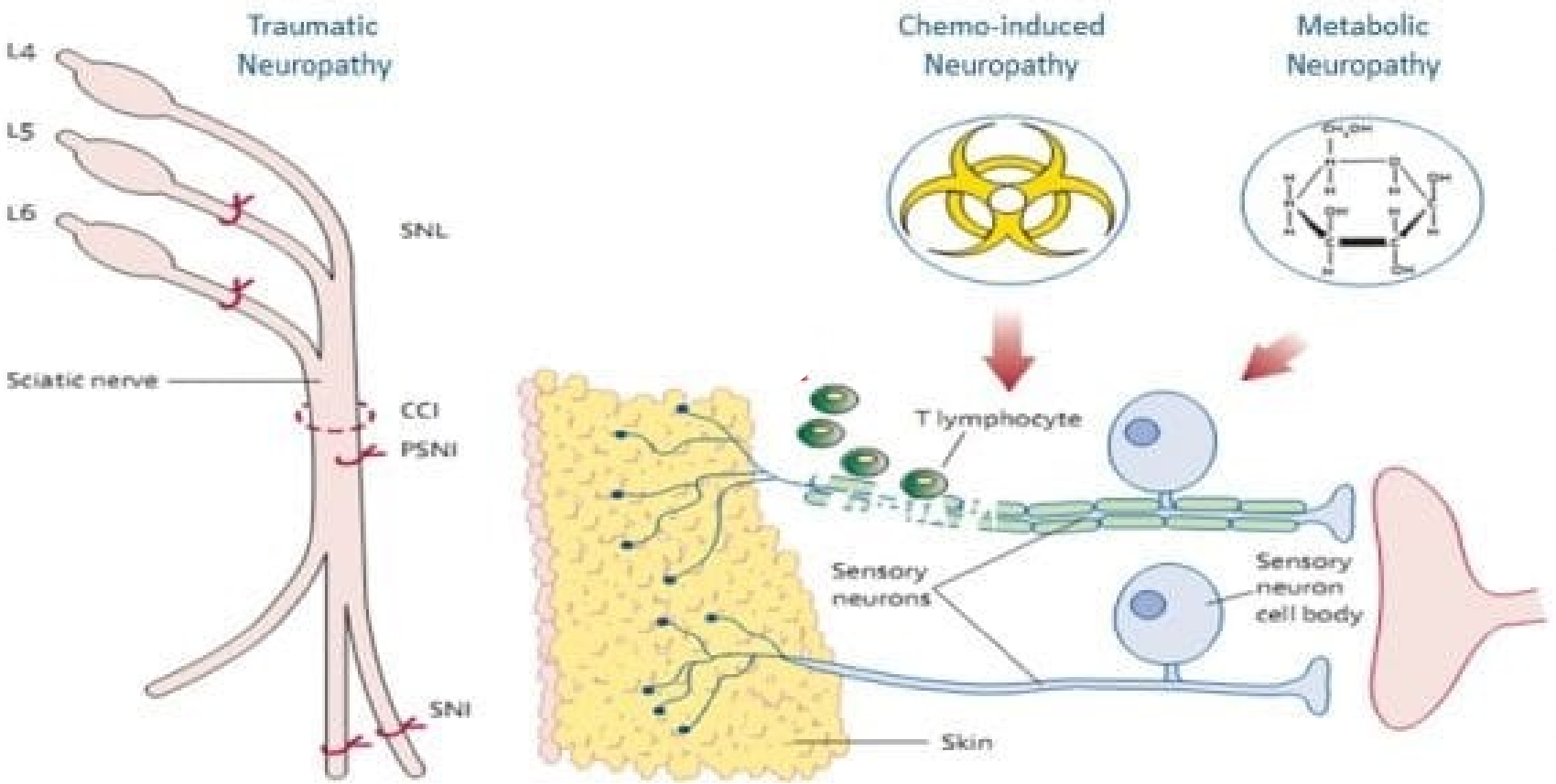
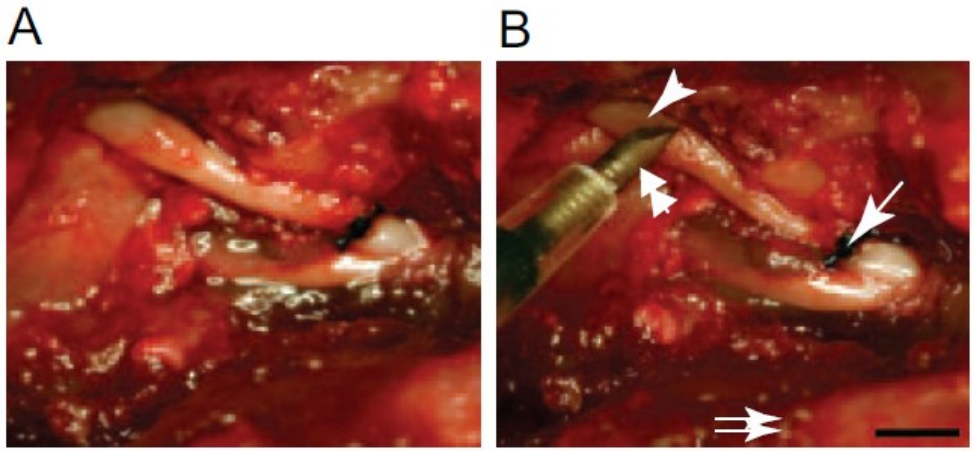


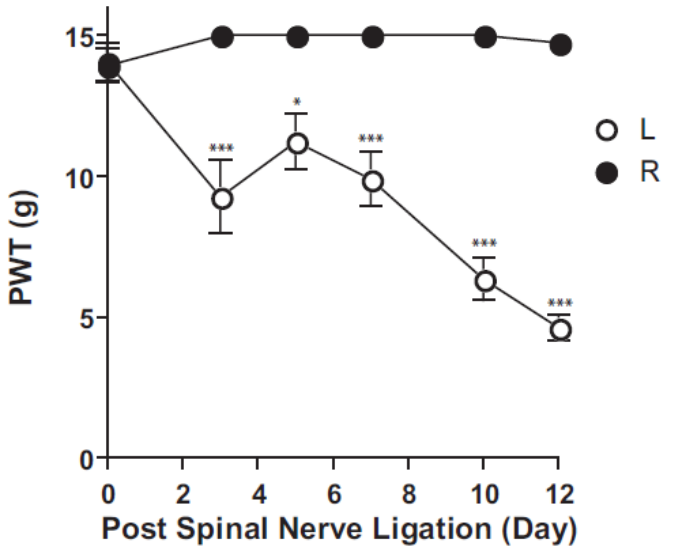
PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



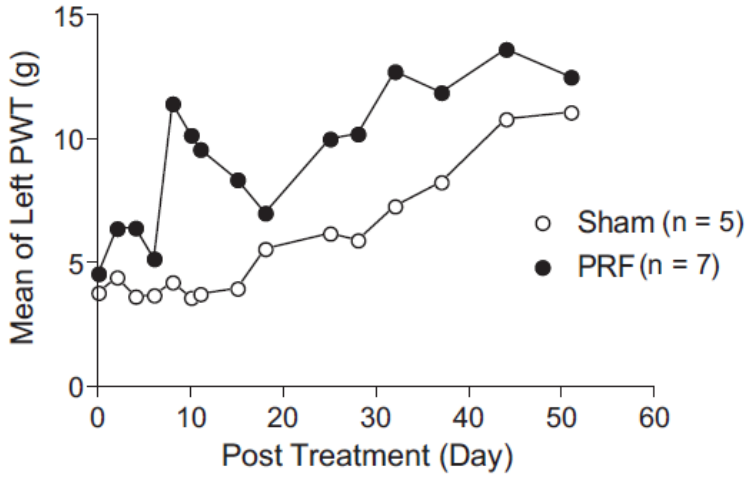
Different animal models of nerve injury-induced pain-related behaviors

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



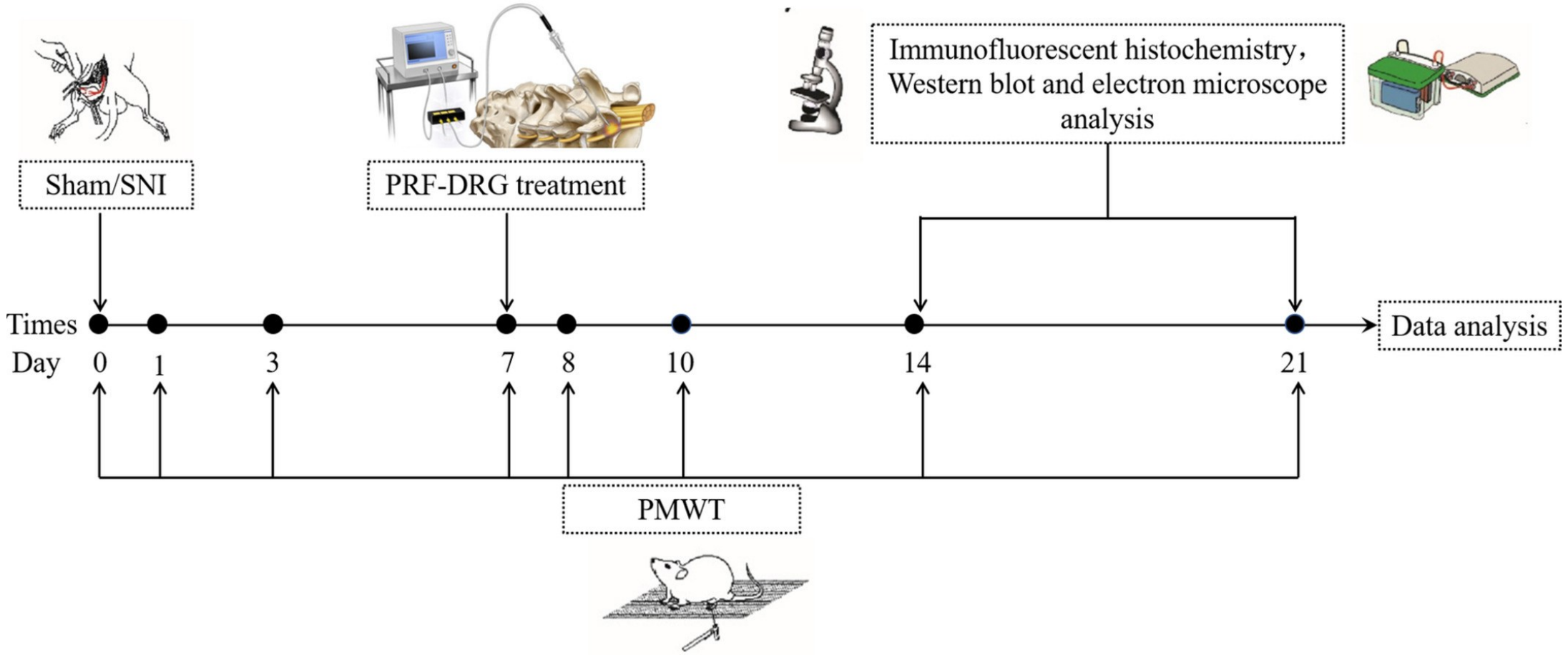


PRF protocol: the DRG was exposed to approximately 25-V (peak voltage), 500-kHz RF pulses for 20 milliseconds. The pulses were delivered at a rate of 2 Hz for a period of 120 seconds. Temperature was limited to 42°C.



Danielle M Perret Anesth Analg. 2011 September ; 113(3): 610–616

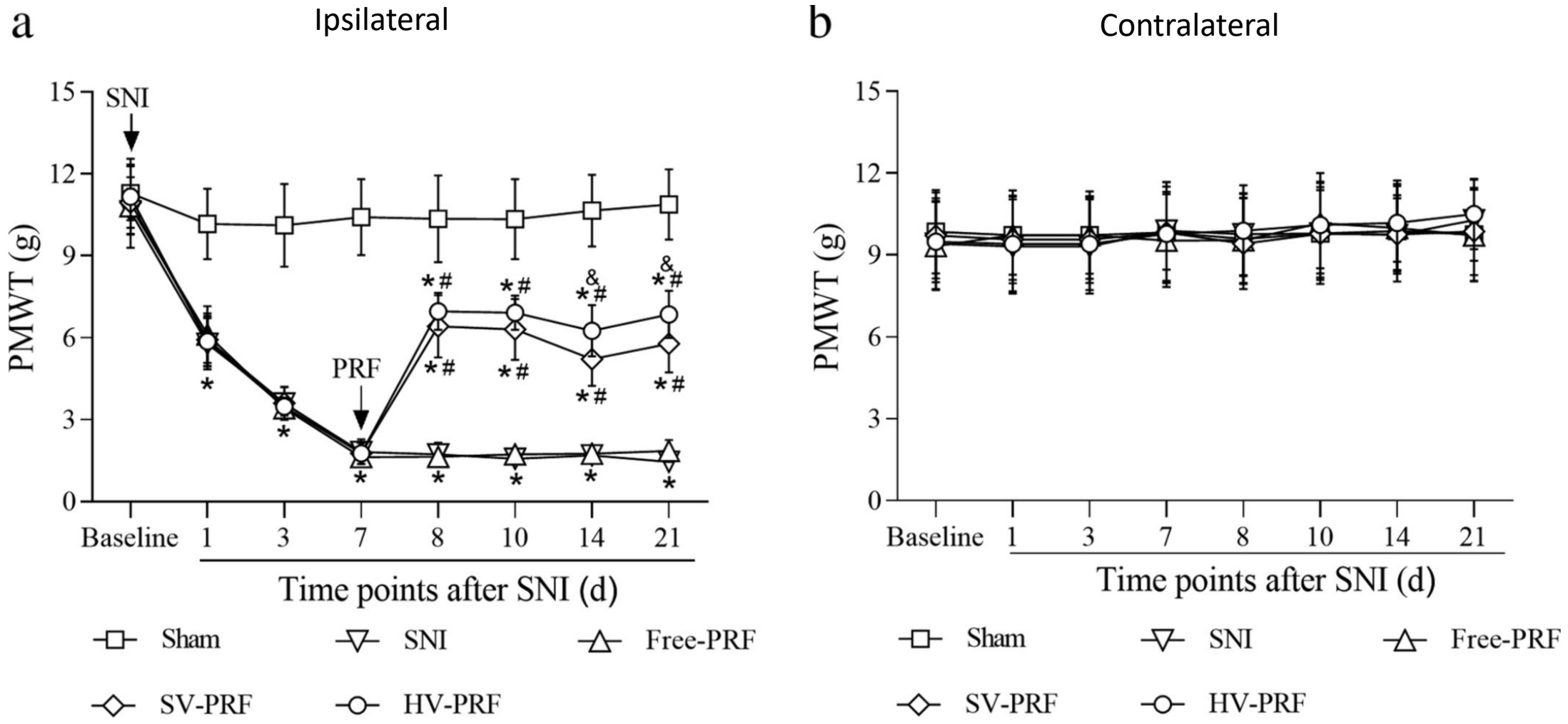
PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



PRF Protocol: the pulse rate of 2 Hz, the voltage of 45 V (for the SV-PRF group) or 85 V (for the HV-PRF group), the maximum temperature of 42°C, the pulse width of 20 msec, and total stimulated time of 6 min.

Zhisen Dai Neuromodulation: 2022 Oct;25(7):980-988

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

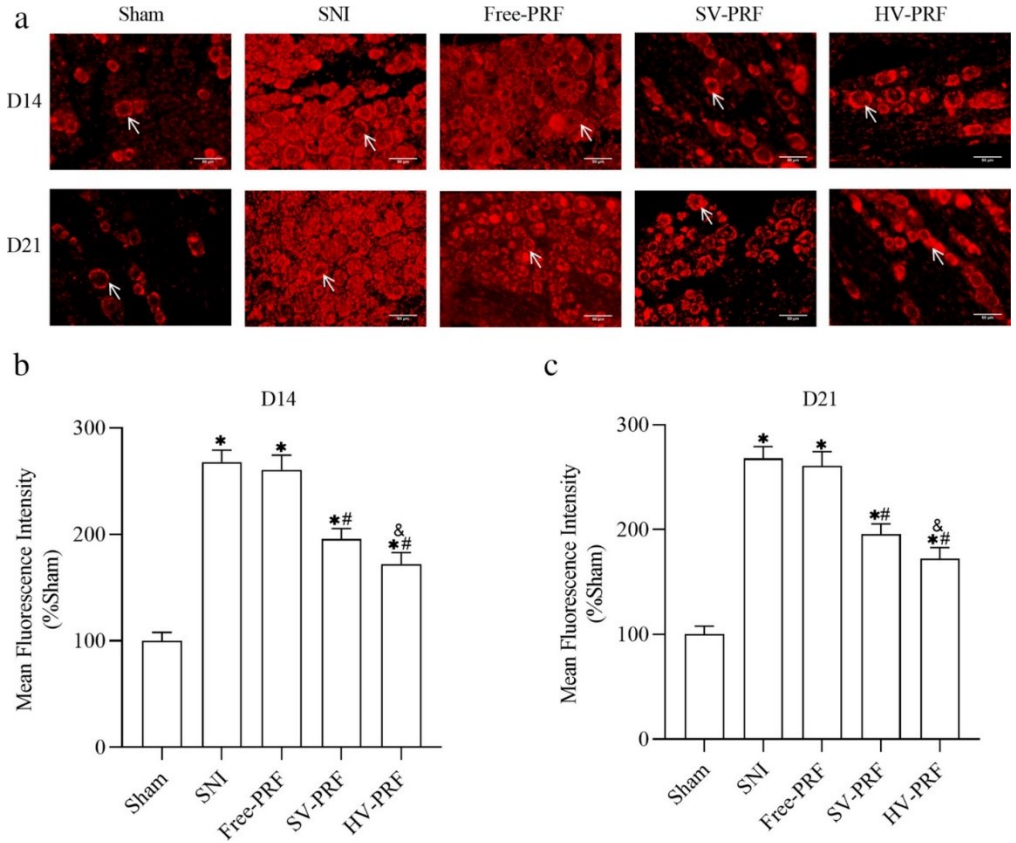


Effects of pulsed radiofrequency reduces mechanical pain hypersensitivity produced by nerve injury.

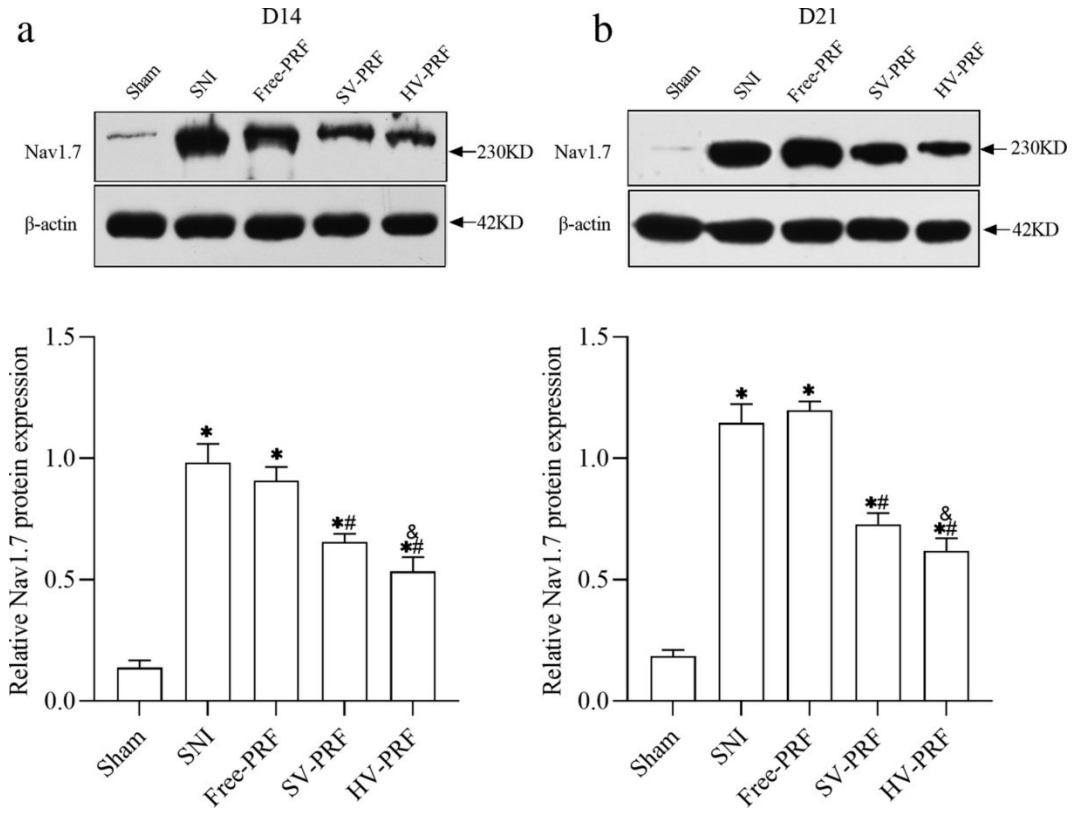
Zhisen Dai Neuromodulation: 2022 Oct;25(7):980-988

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

1 PRF and DRG



Nav1.7



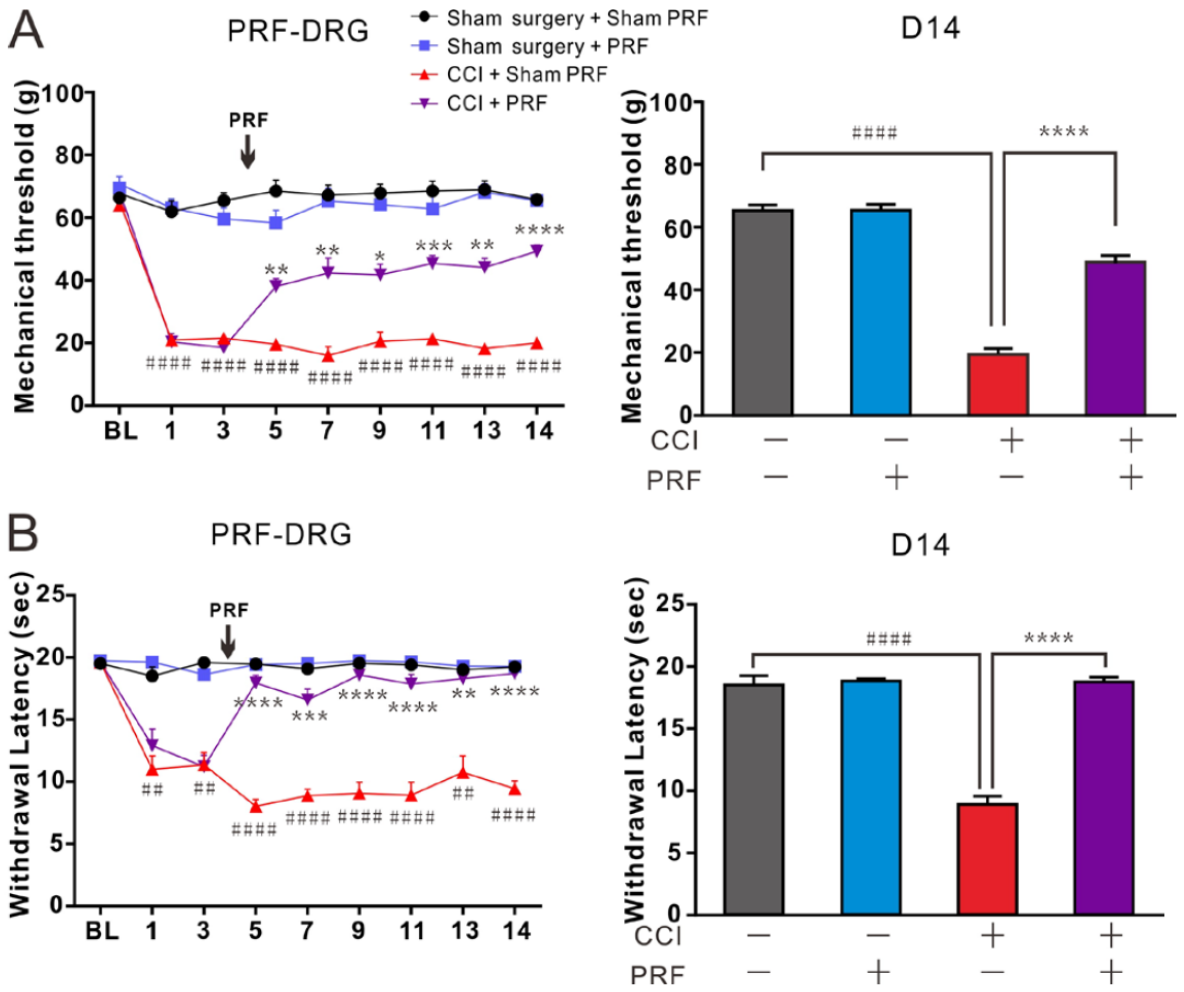
Effects of high-voltage pulsed radiofrequency on the expression of Nav1.7 level of the DRG in rats with spared nerve injury.

Zhisen Dai Neuromodulation: 2022 Oct;25(7):980-988

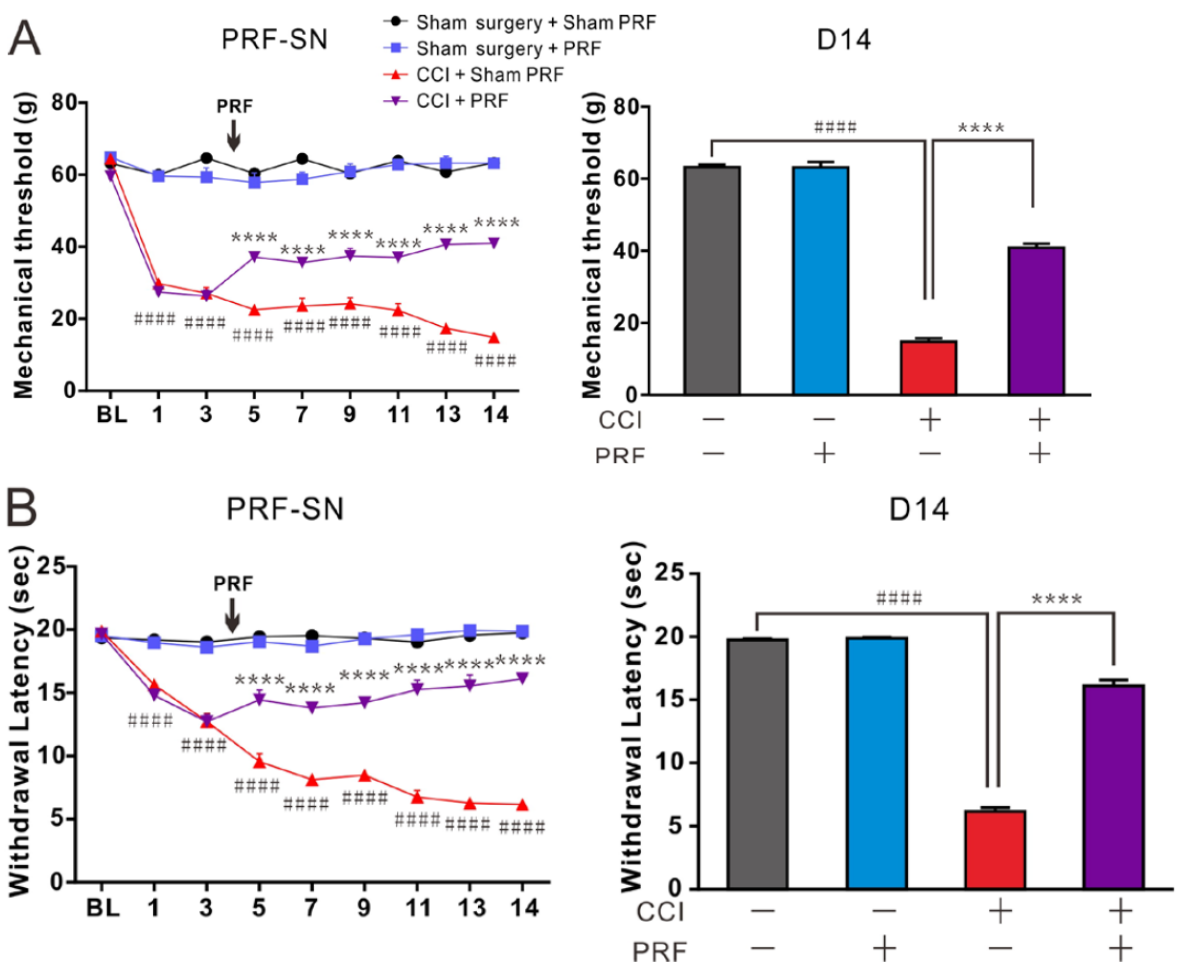
PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

1 PRF and DRG

DRG stimulation



Sciatic nerve stimulation



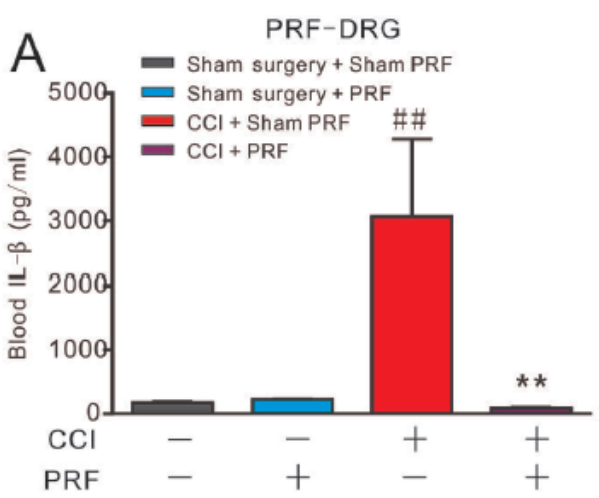
*Jiang R, et al. Reg Anesth Pain Med 2019;**44**:742–746*

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

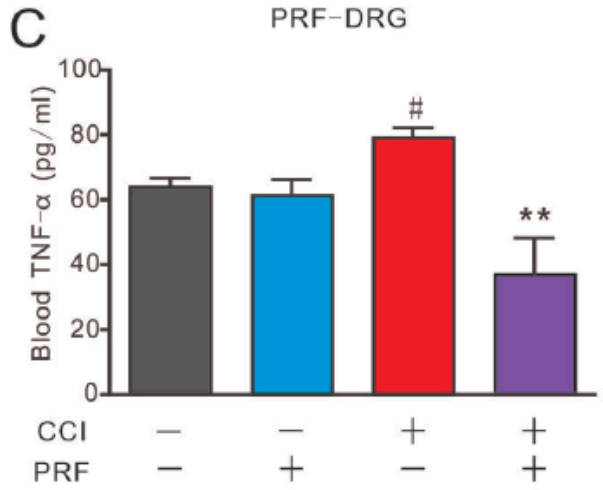
1 PRF and DRG

DRG stimulation

IL-1β

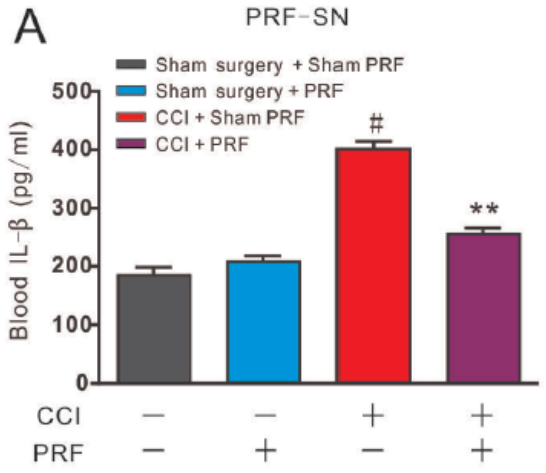


TNFα

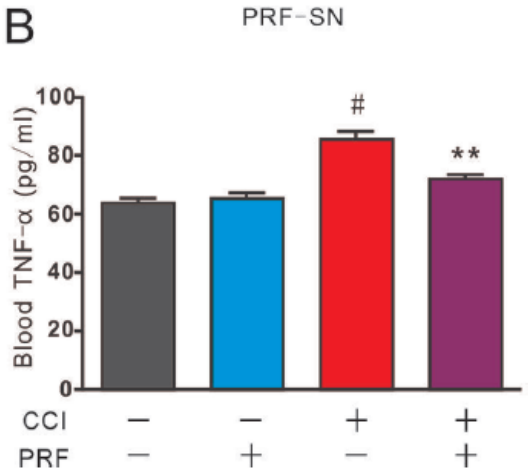


Sciatic nerve stimulation

IL-1β



TNFα

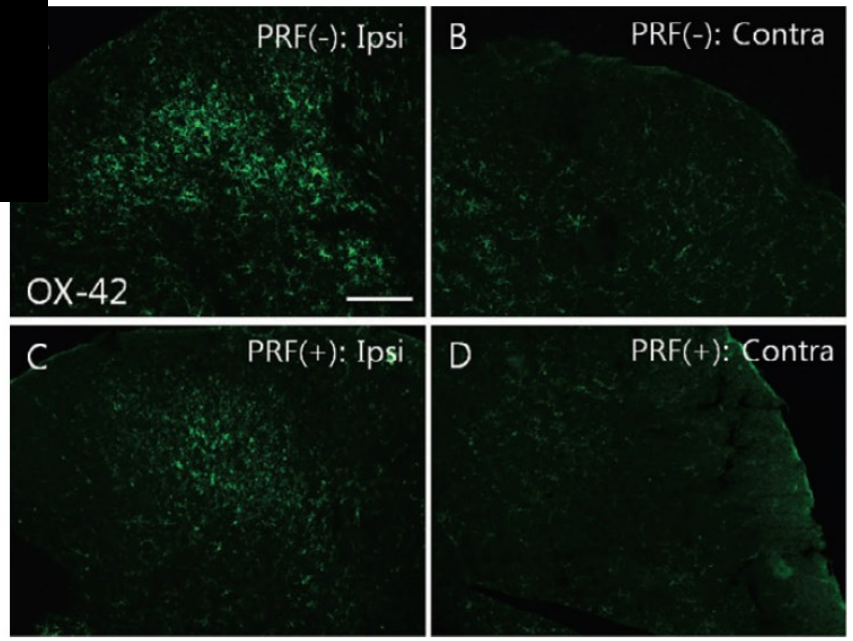


PRF decreases the up-regulation of IL-1β and TNFα produced by nerve injury suggesting that PRF may reduce neuroinflammatory mechanisms responsible for the beneficial effects of PRF in neuropathic pain.

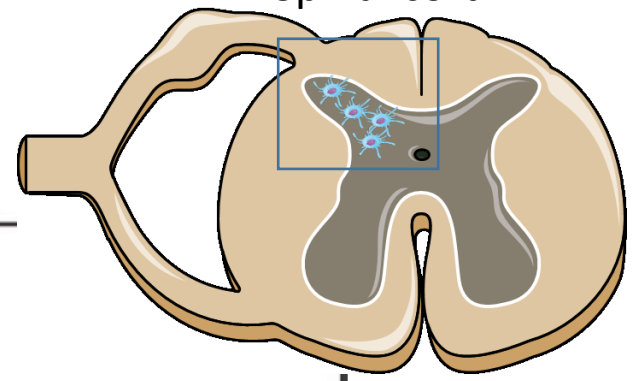
*Jiang R, et al. Reg Anesth Pain Med 2019;**44**:742–746*

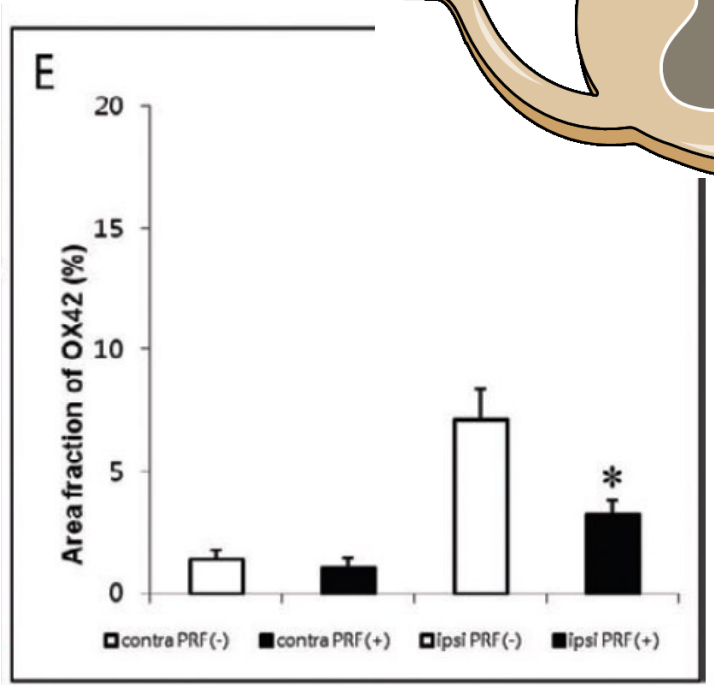
PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

2 PRF and Spinal cord



Spinal cord



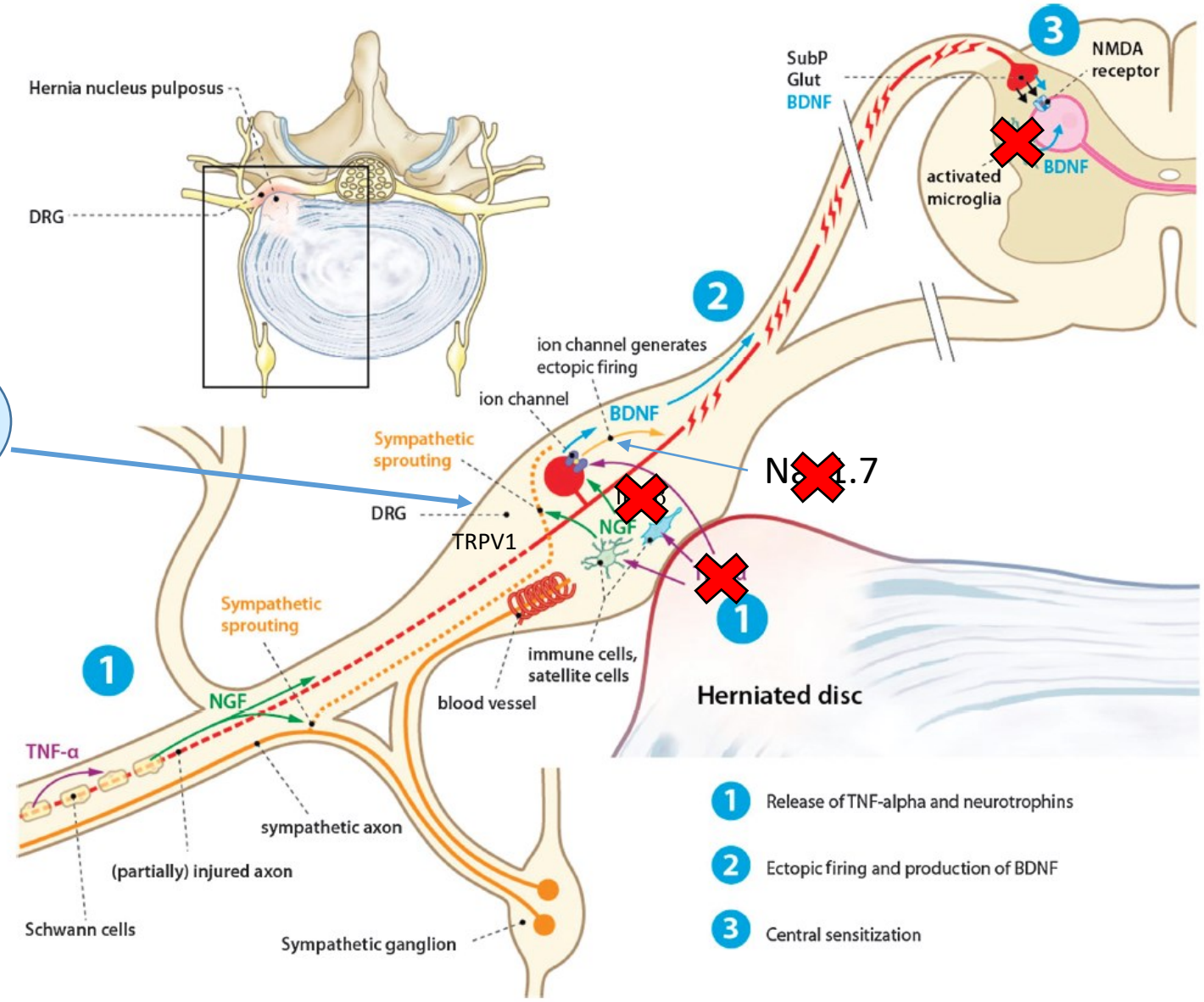


At 12 days after PRF, the increase of the immunoreactivity for OX42-positive microglia was observed in the ipsilateral dorsal horn of the PRF (-) group and the increase was attenuated in the PRF (+) group.

Park et al. Pain Medicine 2012; 13: 1227–1234

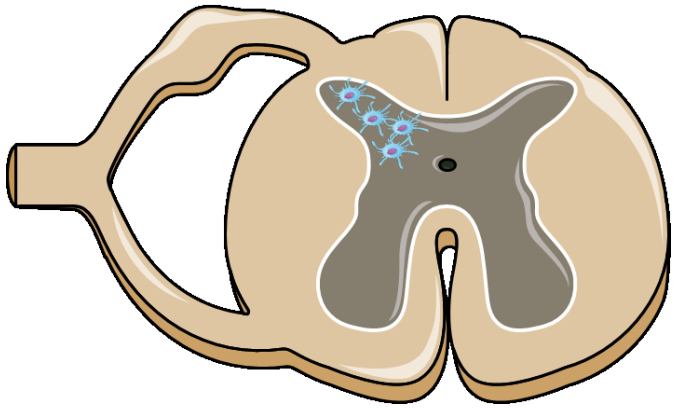
PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Effects of PRF on DRG



TRPV1

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



e 1 The met-enkephalin levels in the spinal cord of

(*n* = 16)	Met-enkephalin level (pg/mg)
Normal group	3.51 ± 0.52
Control group	3.58 ± 0.63
Sham intervention group	3.97 ± 0.75
Pulsed radiofrequency group	6.70 ± 1.76*

Note: *$P<0.05$ (RF versus normal, control, or sham intervention group).

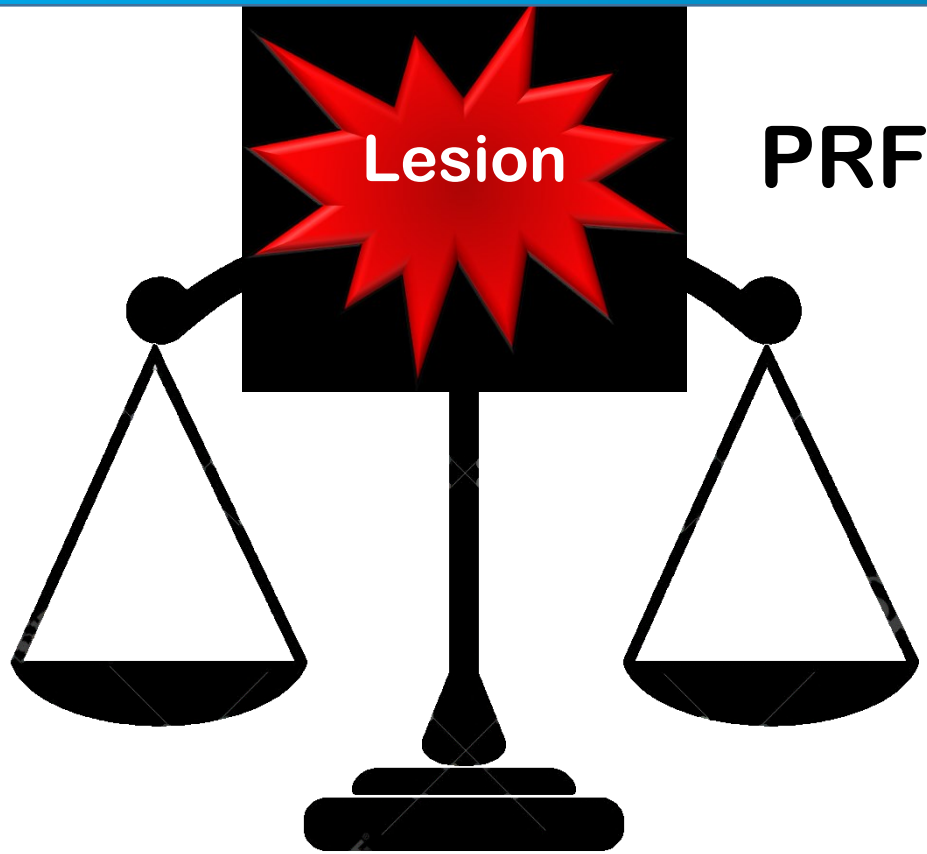
The analgesic effects of PRF seem to be due to an increased endogenous expression of met-enkephalin in the spinal cord.

Wu et al., Neurological Research 2012 VOL. 34 NO. 4

NOCICEPTIVE SYSTEM

Facilitatory systems

PGE2
Glutamate
CGRP
SP
NGF



PRF

Inhibitory systems

GABA
Glycine
Endogenous opioids

\+

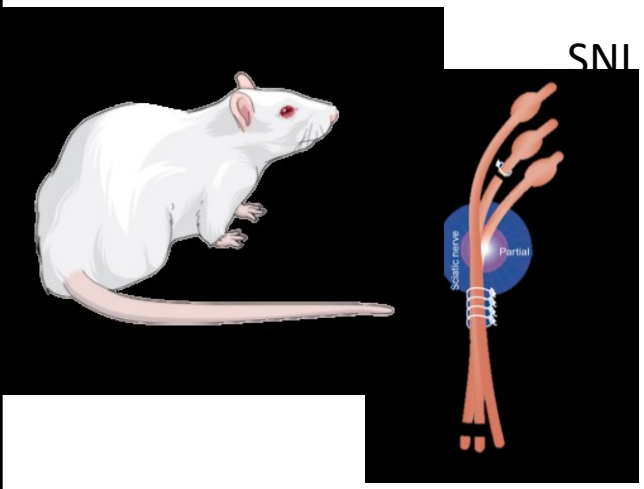
Sensitization

PAIN

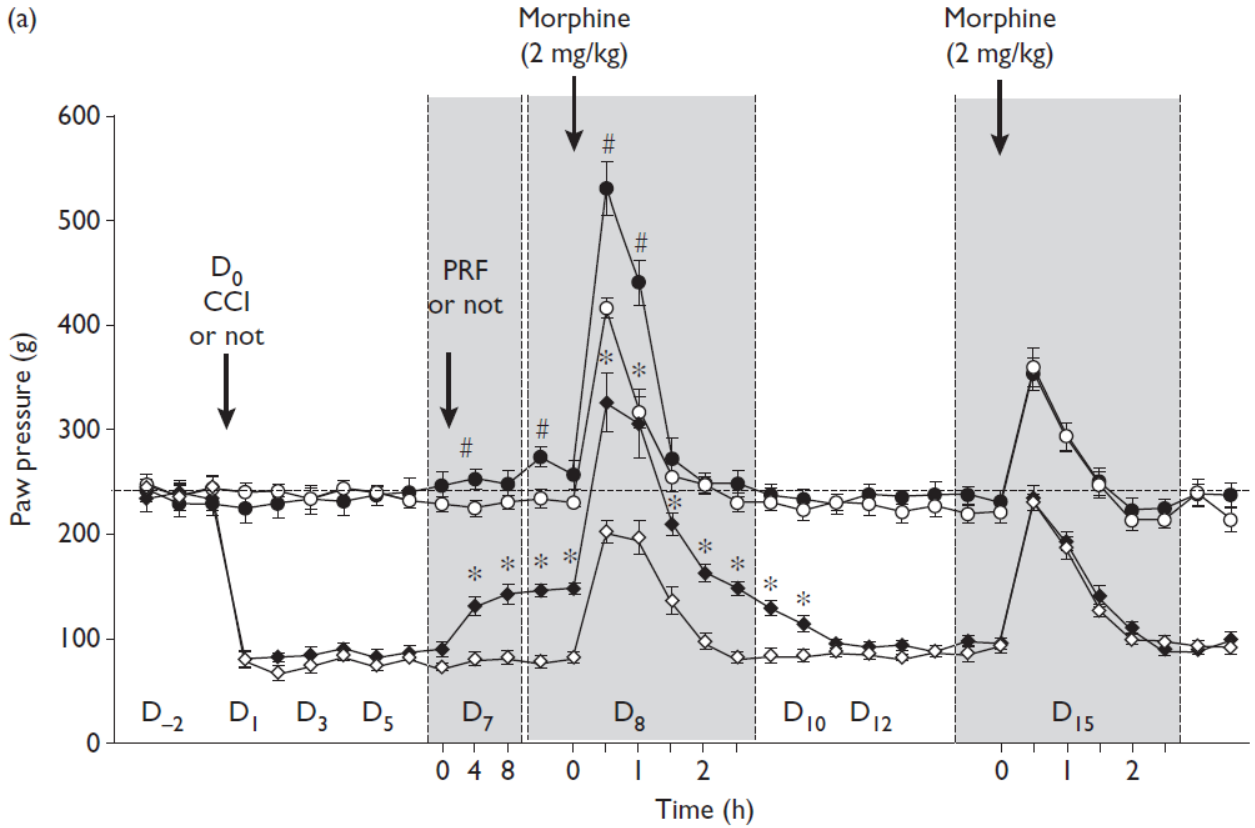
\-

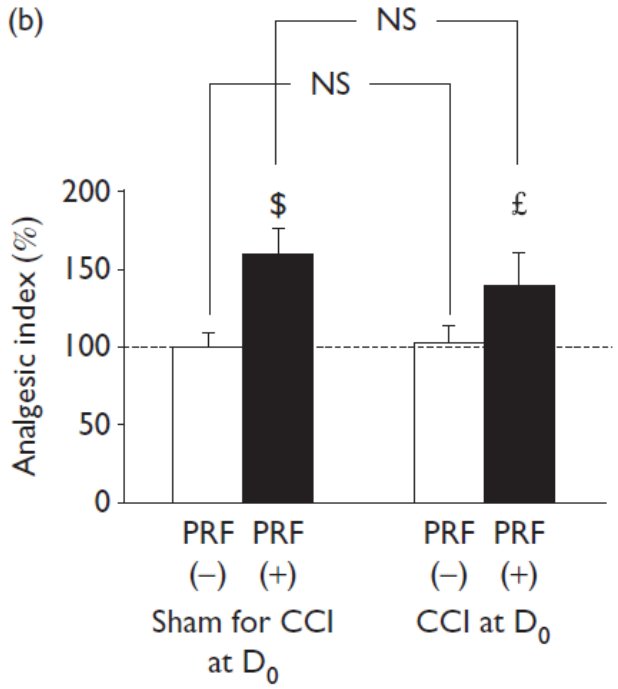
Inhibition/extinction

PRF ON PATHOPHYSIOLOGY OF NEUROPATHIC PAIN



PRF protocol: 2 Hz, 45 V, and less than 42°C for 120 s.





Laboureyras E et al., Neuroreport. 2012 Jun 20;23(9):535-9

PRF is effective in decreasing hyperalgesia induced by neuropathy and to enhance the morphine analgesic effect in these animals well known to be opioid resistant.

PRF ON NEUROPATHIC PAIN IN HUMAN

- The first published trial on PRF reported on 20 patients following failed back surgery, treated with PRF adjacent to the lumbar DRG, resulting in a decrease in visual analog scale, less disability, and an improved global effect without any postoperative discomfort.
- PRF has been used mainly for the pain management of neuropathy
- Several studies report analgesic effects in patients with peripheral neuropathic pain
- Long-term effects have been shown after short-term application of PRF

PRF ON NEUROPATHIC PAIN IN HUMAN

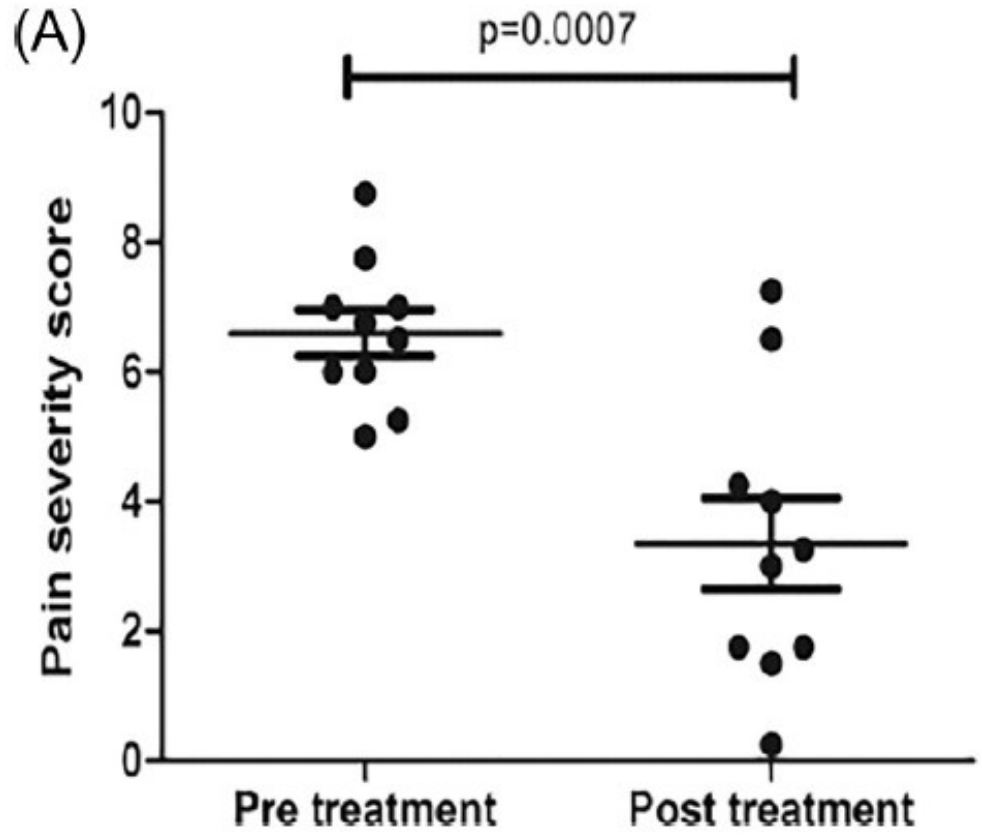
Chronic lumbosacral radicular pain

Table 1
Demographics.

Number of patients (n)	10
Age in years: Range	32–74
Male: Female	5:5
L4 Radicular pain	7
L5 Radicular pain	2
S1 Radicular pain	1
Mean duration of pain in months	8.5

PRF protocol: Two cycles of PRF was performed after application of 1 ml of 1% lignocaine with a pulse width of 20 ms, 42°C, at 2 Hz frequency for 2 min.

Evaluation 3 months after PRF



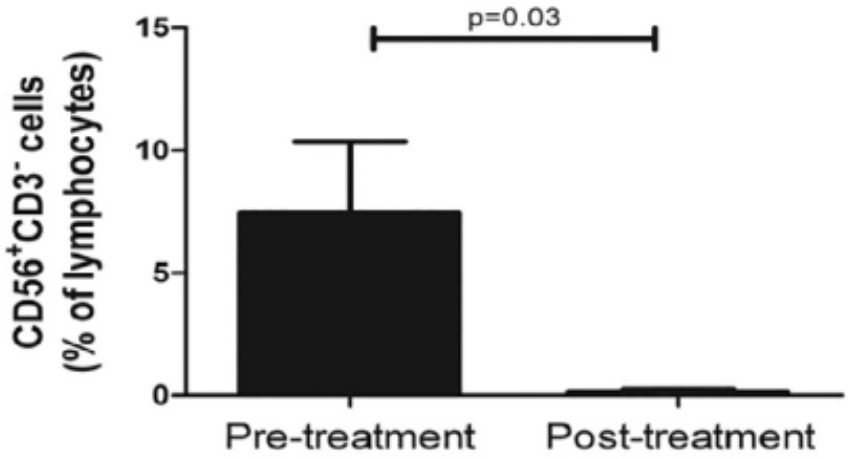
Basabjit Das et al., Brain Behavior and immunity, 2018

PRF ON NEUROPATHIC PAIN IN HUMAN

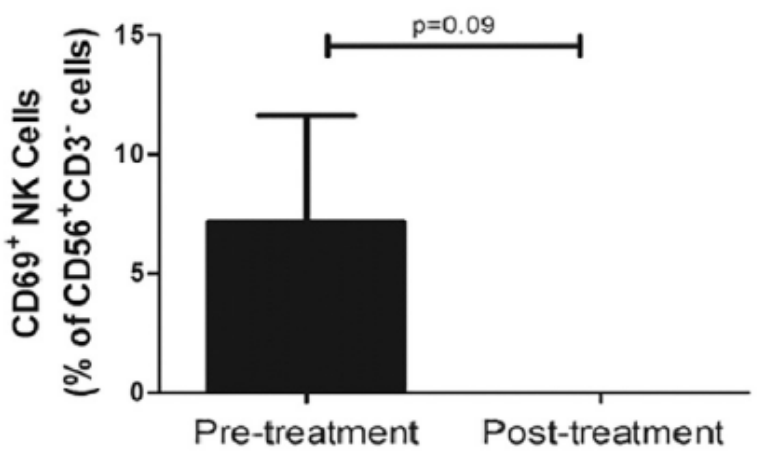
Chronic lumbosacral radicular pain

3 months after PRF

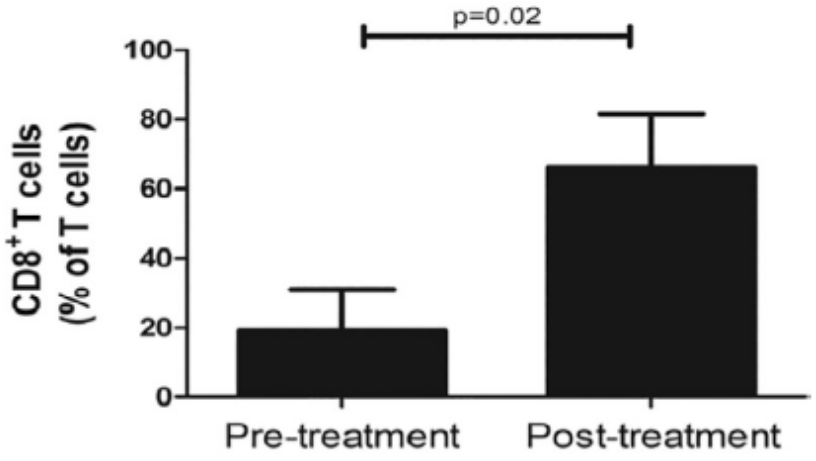
NK cells



NK cells



Lymphocyte

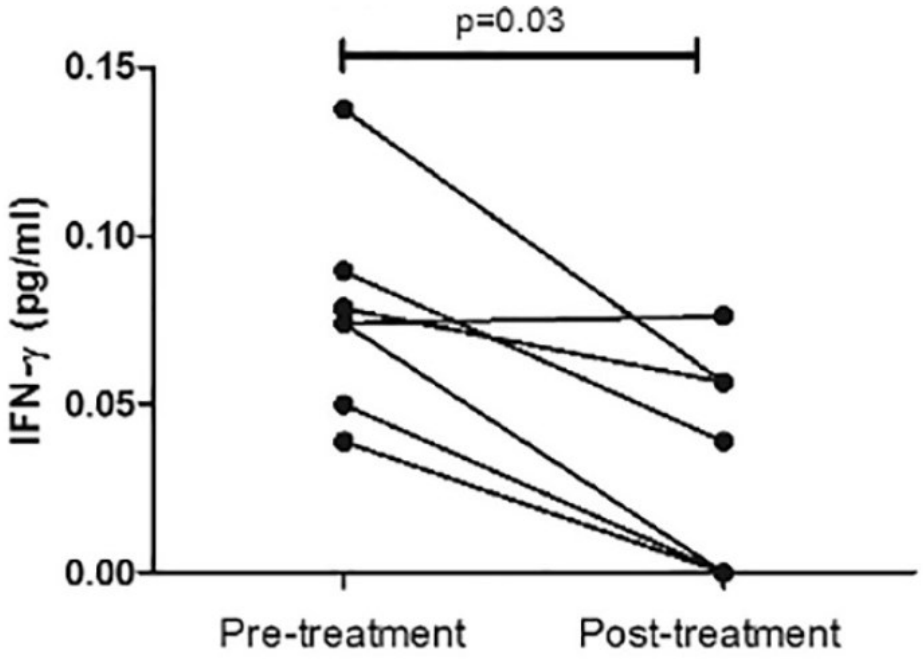


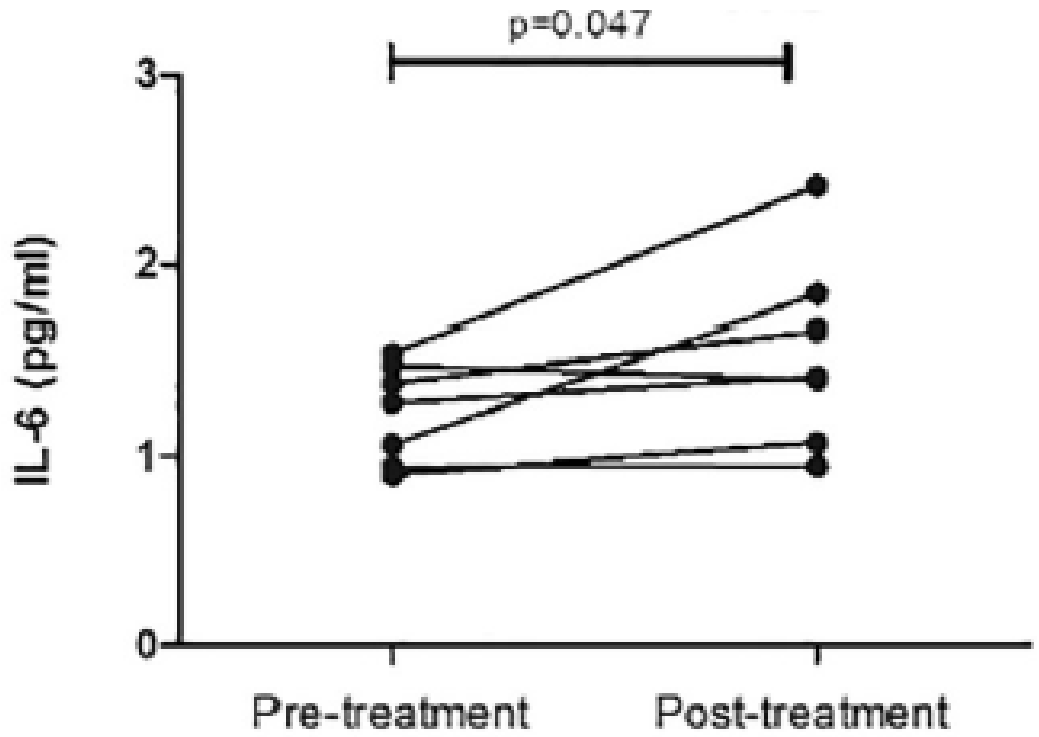
PRF treatment reduces lymphocyte and NK populations and inflammatory cytokine levels in patient CSF three months post treatment.

Basabjit Das et al., Brain Behavior and immunity, 2018

PRF ON NEUROPATHIC PAIN IN HUMAN

Chronic radicular neuropathic pain





PRF treatment reduces lymphocyte and NK populations and inflammatory cytokine levels in patient CSF three months post treatment.

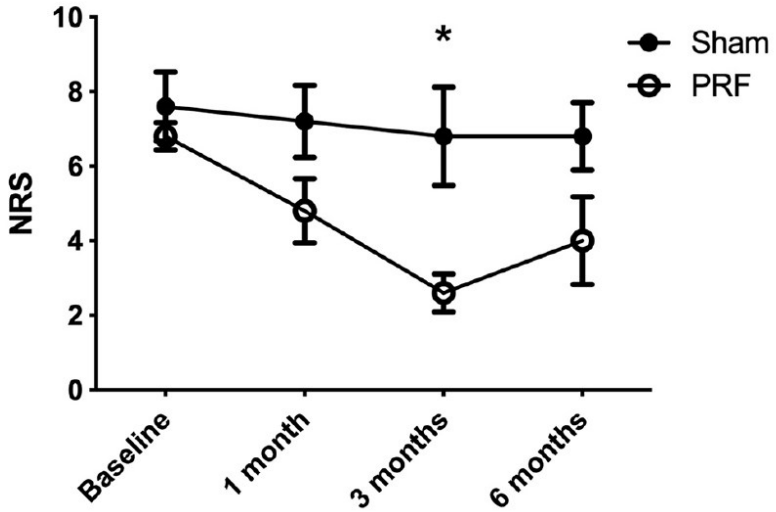
Basabjit Das et al., Brain Behavior and immunity, 2018

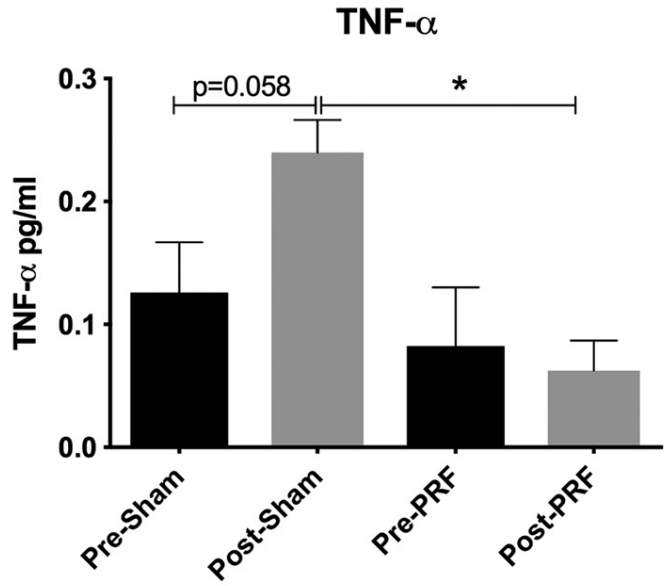
PRF ON NEUROPATHIC PAIN IN HUMAN

Chronic radicular neuropathic pain

Table 1
Demographics of Patients involved

Number of patients (n)	11
Age (years)	48 (range 35–60)
Male:Female	5:6
Side of pain, left:right	6:5
Level of DRG treated (n)	C5 (2) C6 (1) L4 (3) L5 (4) S1 (1)
Duration of pain (months)	29





PRF treatment reduces TNF alpha concentration in the CSF. This study provides further information supporting the neuroimmune concept of neuropathic pain chronicity and suggests that a PRF mechanism of action involves modulation of CSF peptides.

David Moore et al., Journal of Neuroimmunology, 2020

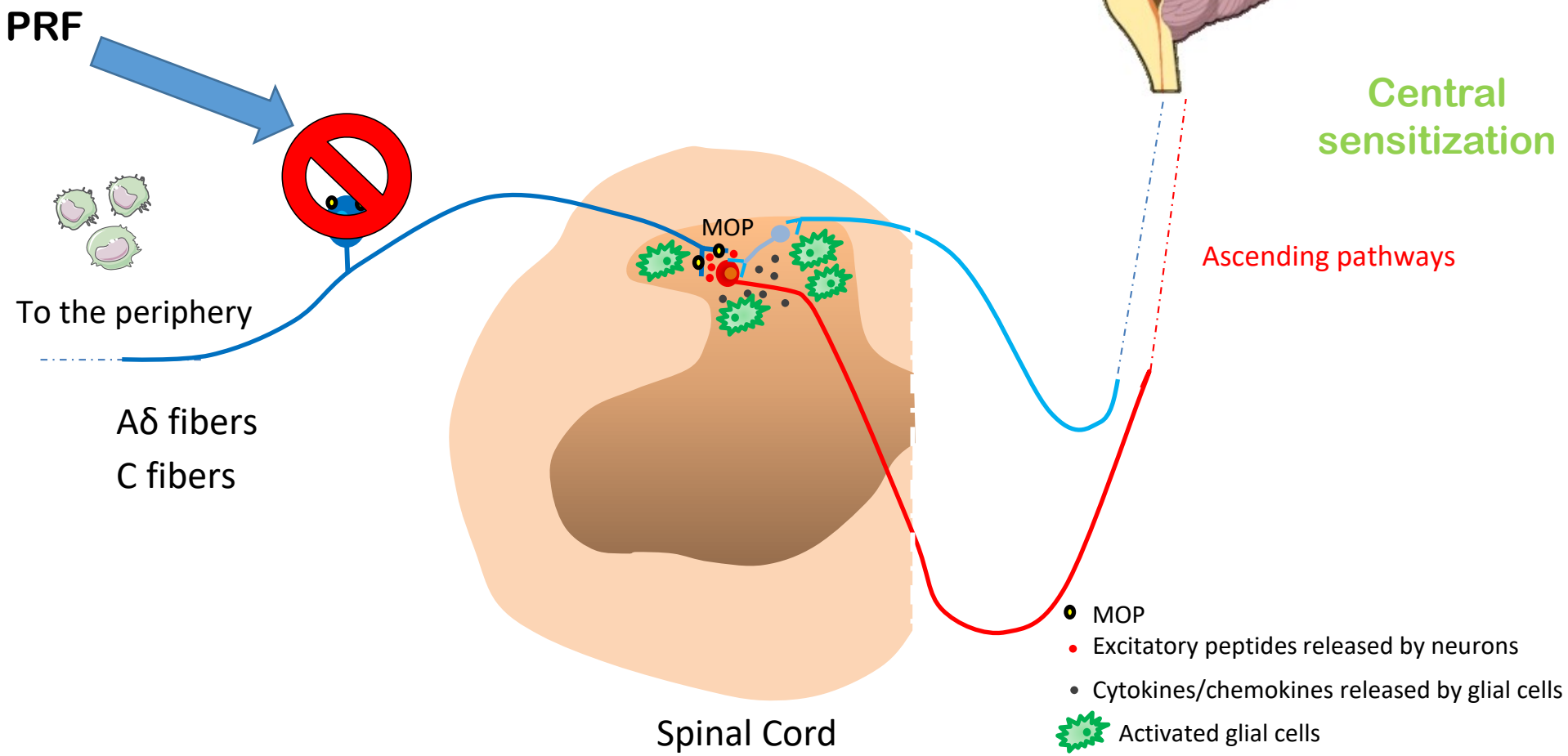
Limitations

- Most of the clinical studies are non-randomized and controlled studies
- The majority of studies included patients that have failed other therapies so these results cannot be generalized.
- PRF treatment needs to be tested in new, high-quality and large-scale trials, to confirm the efficacy of this intervention

CONCLUSION

Facilitatory systems

Peripheral sensitization



THE END