Neuromodulation의 적용과 이해

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Acute & chronic pain in MSK

- Acute
  - Tissue injury
  - Inflammation
  - Steroid
  - Operation

Aging

- Chronic
  - Inflammation (?) – Autoimmune (?)
  - Healing state of Initial tissue injury (Scar ?)
  - Instability
  - Central sensitization
  - Pain memory

Neuromodulation

Central sensitization (chat GPT)

결과

The central nervous system becomes hyperresponsive to stimuli, resulting in an amplified and prolonged pain response.

원인

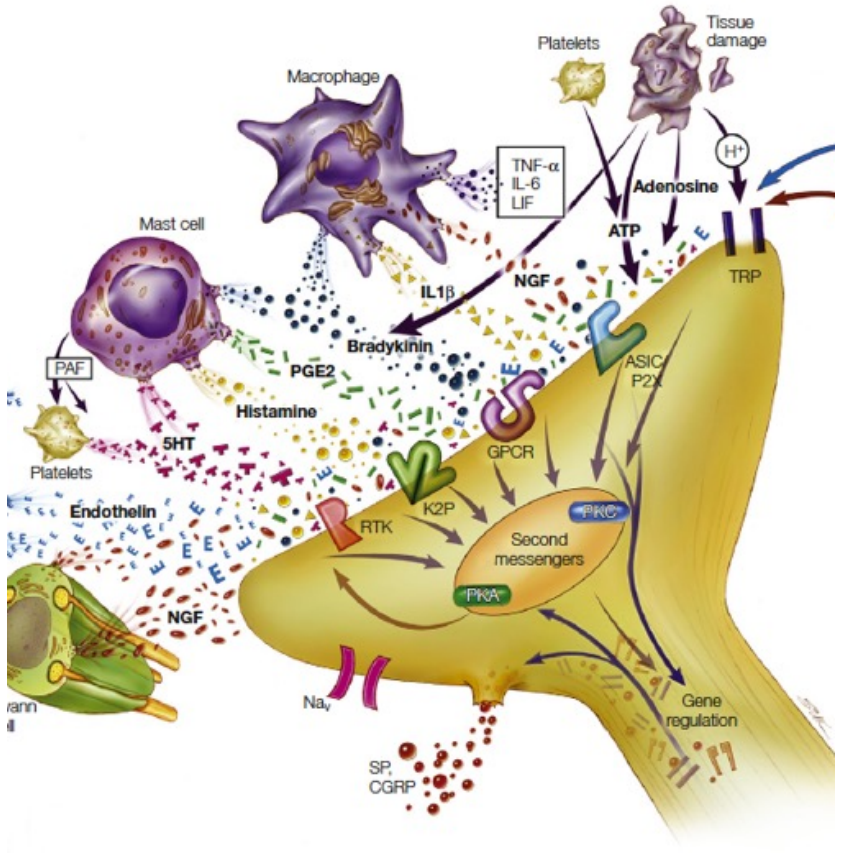
This can occur as a result of persistent or repeated nociceptive input (painful stimuli), leading to changes in the excitability of neurons in the spinal cord and brain.

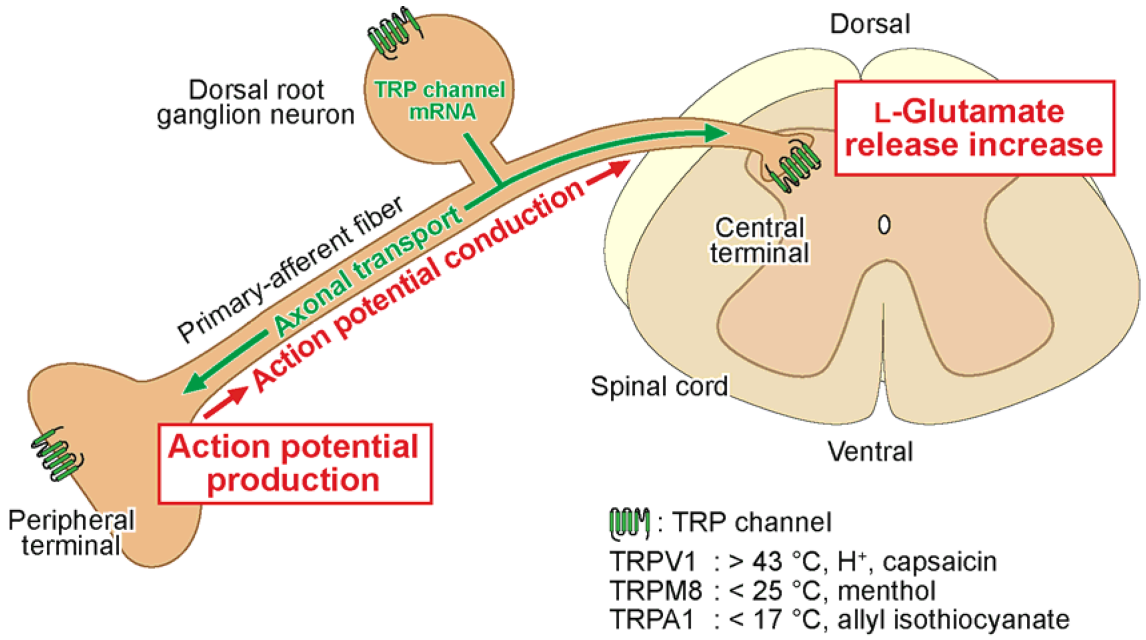
Persistent or repeated nociceptive input

- Tissue injury (antecedent but not sufficient condition)
  - Trauma – Acute nociception
  - Degeneration following injury
  - persistent instability
  - repeated nociception

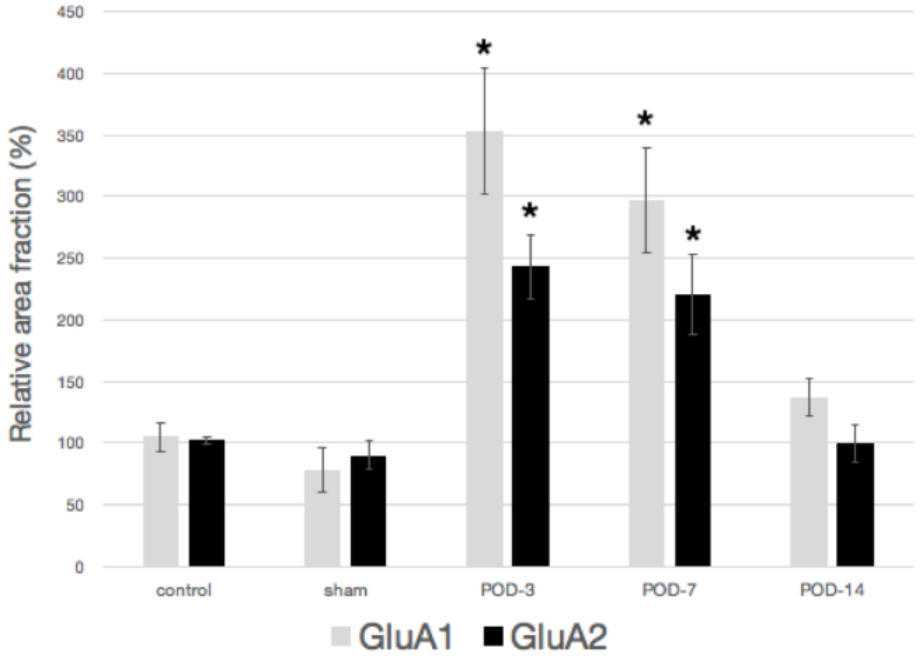
- Decreased central pain Modulation fx.
  - Chronic pain(persistent nociception)
  - Depression
  - Sedentary lifestyle

Nociception (Persistent nociception)





AMAP receptor following disc herniation rat model



Pain withdrawal threshold following disc herniation rat model

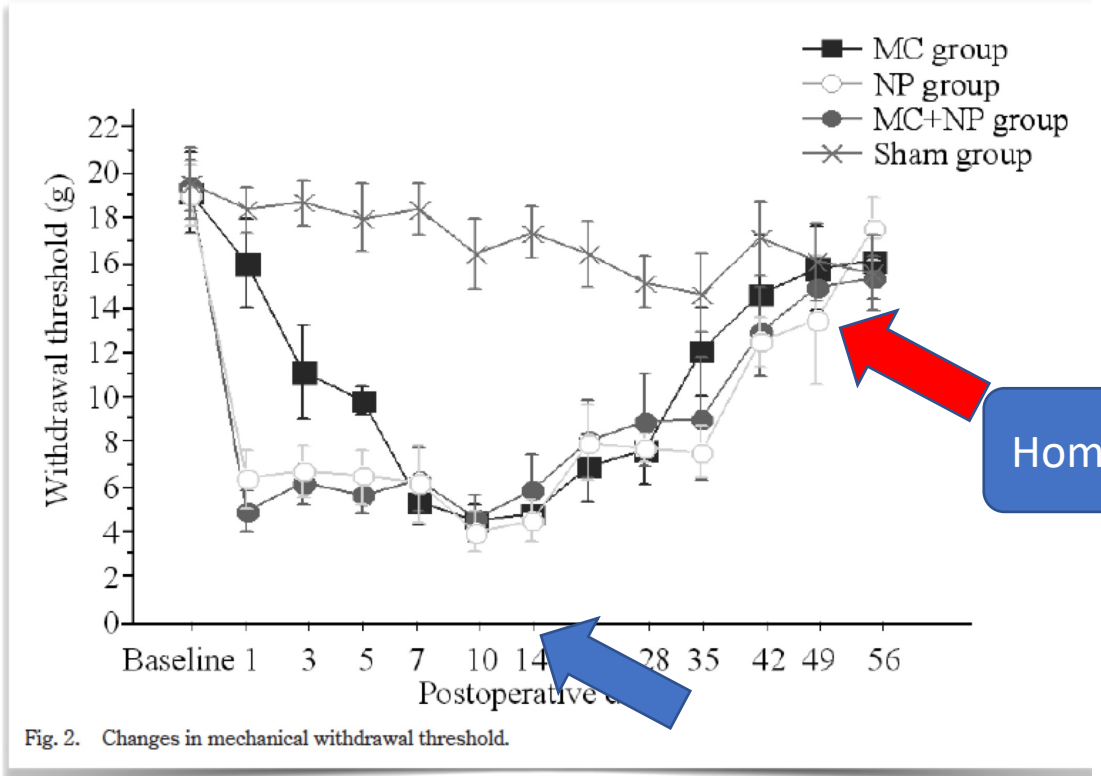
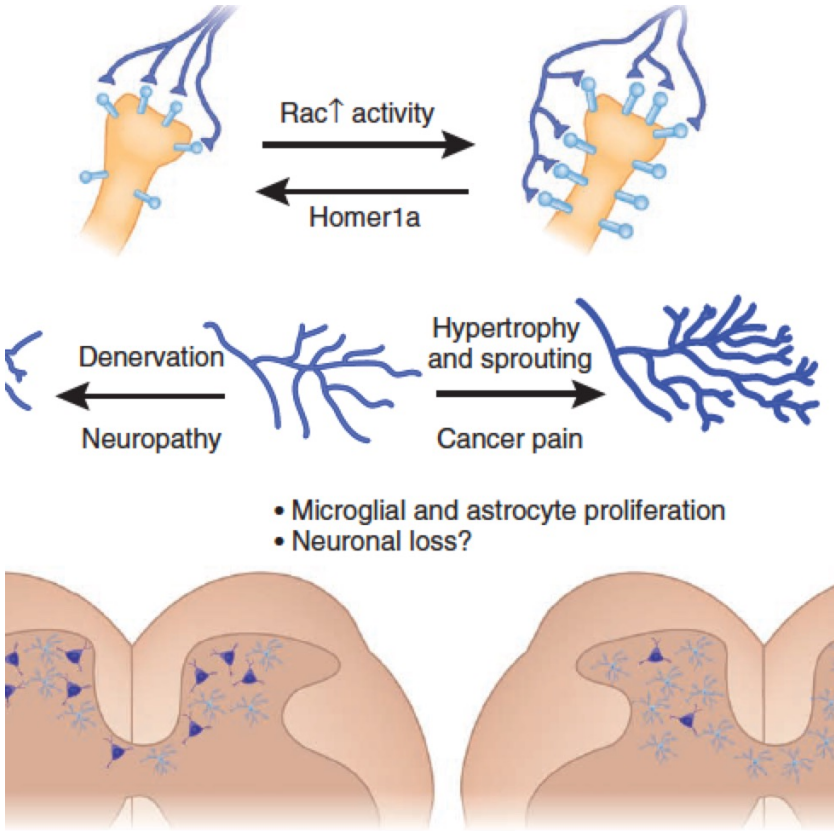


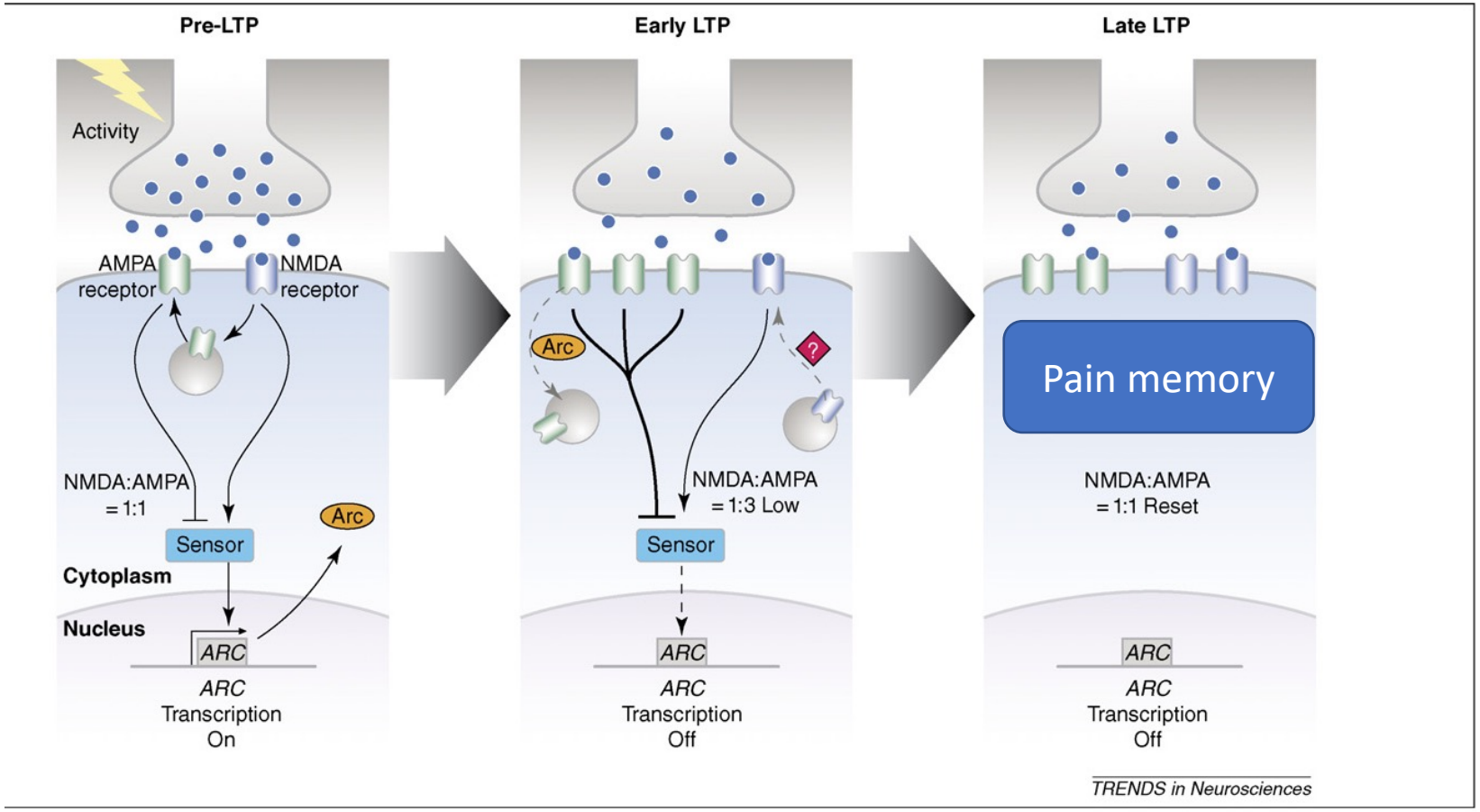
Fig. 2. Changes in mechanical withdrawal threshold.

Persistent nociception & synaptic plasticity

- Synapses are also highly dynamic structures that can change in response to different stimuli.
- This process known as synaptic plasticity.
- Synaptic plasticity alters pain sensitivity and expands the receptive field.

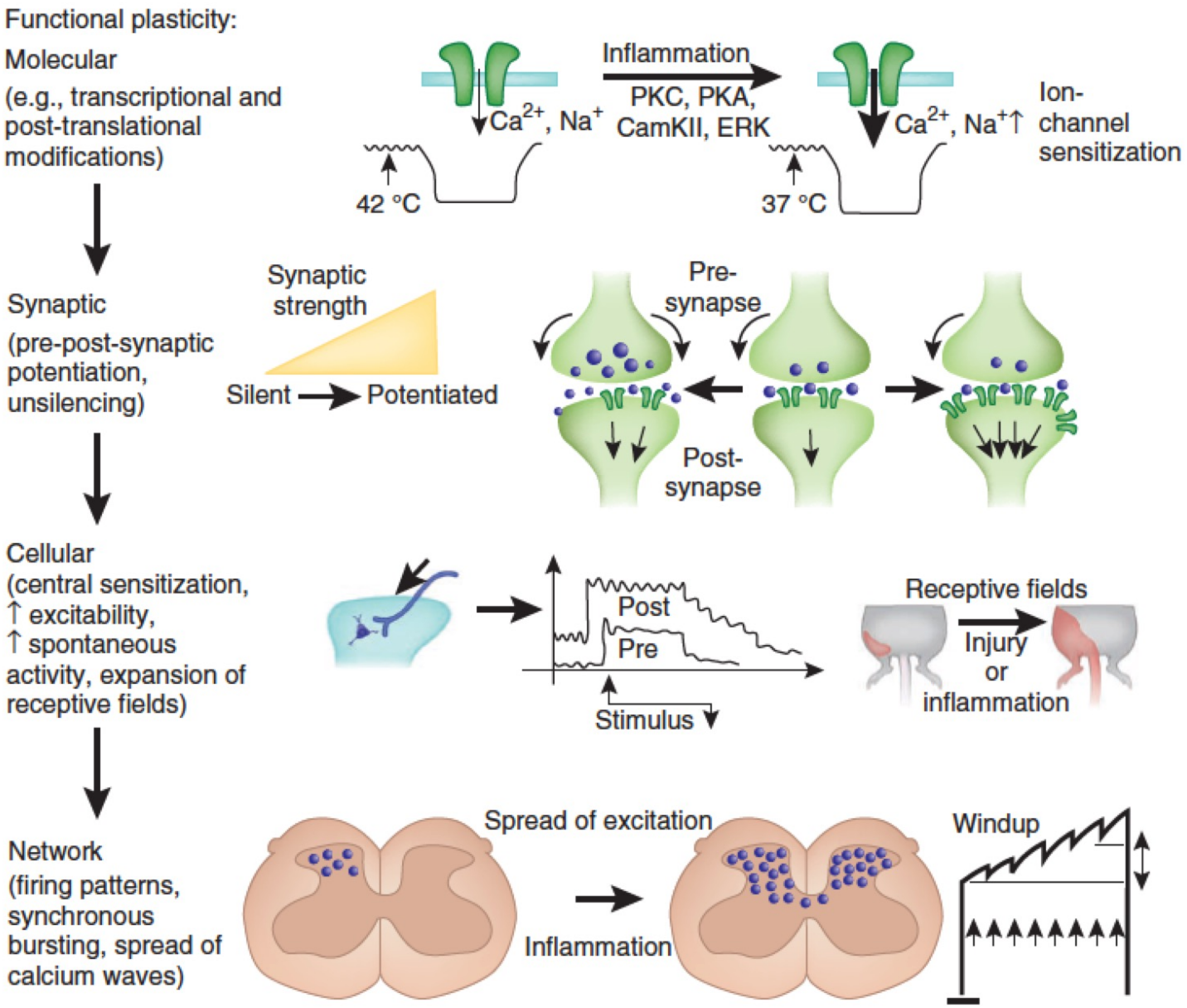


AMPA receptors and pain memory



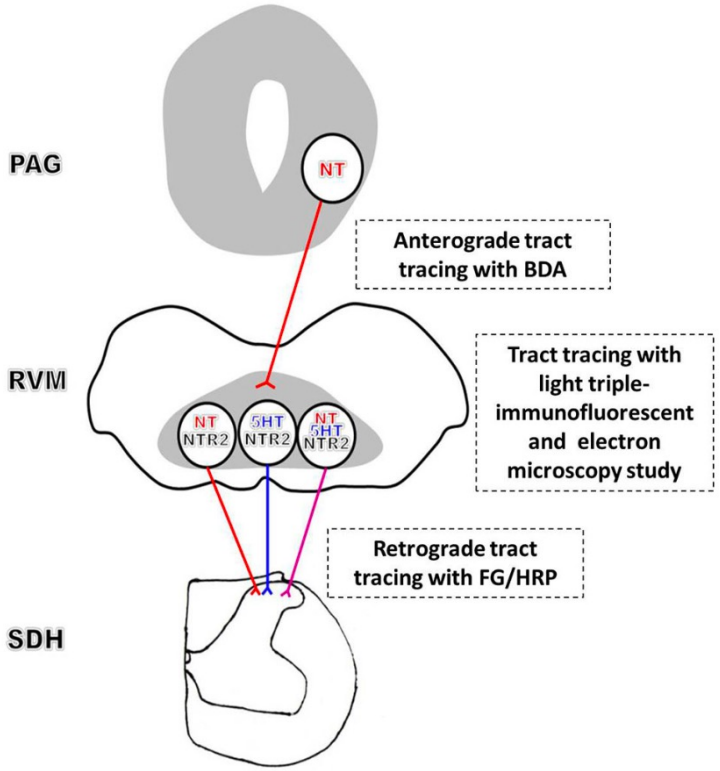
odel of the regulation of *ARC* by NMDA receptors and AMPA receptors. During synaptic activity NMDA and AMPA receptors propagate opposing signals that are

Central sensitization and pain memory



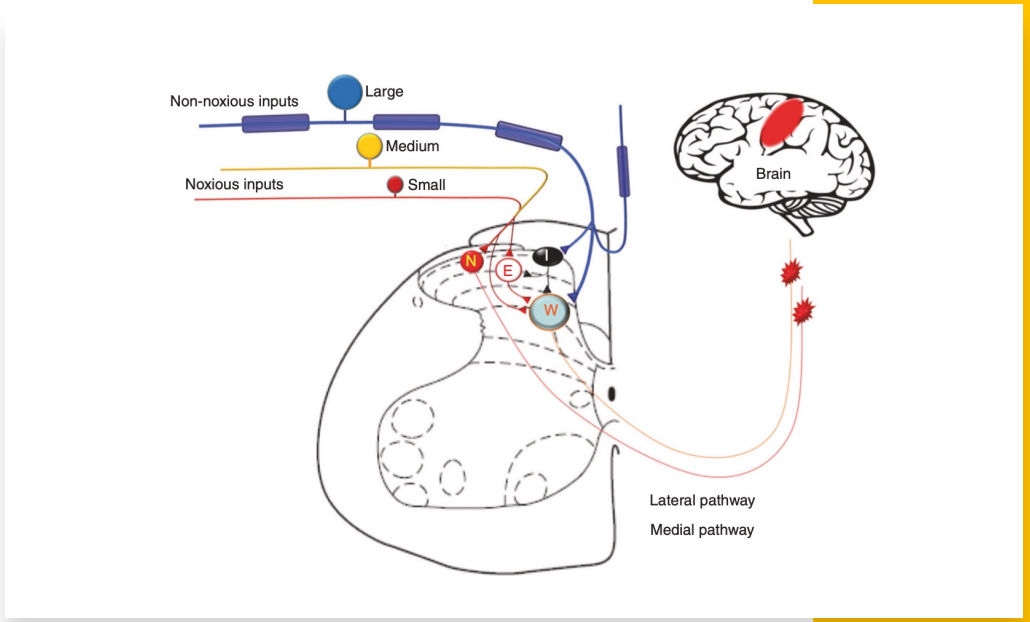
Descending pain modulation

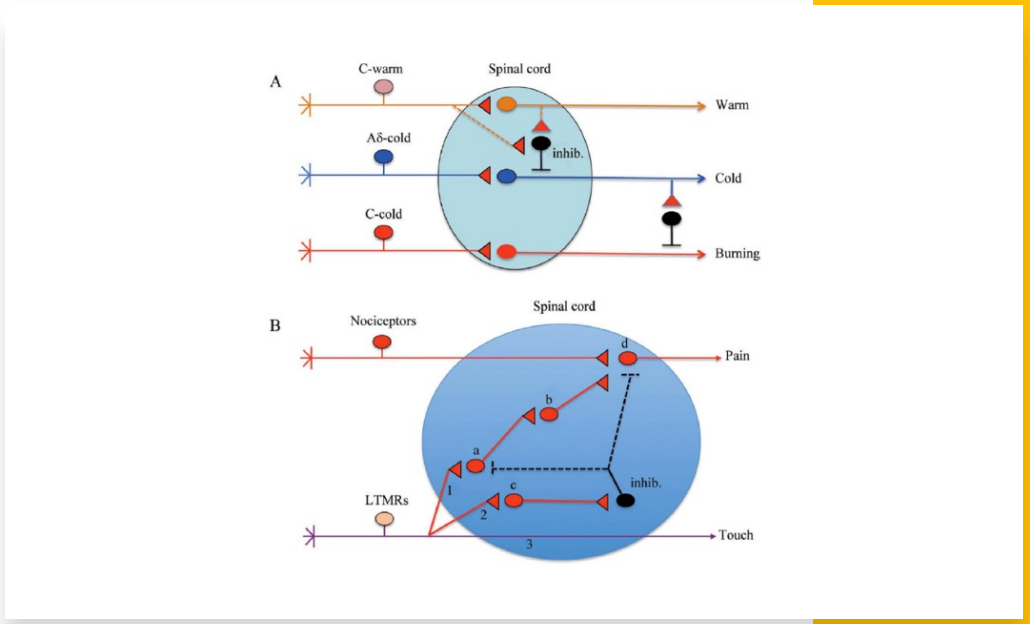
- Central pain modulation (CPM)
  - Central pain modulation refers to the ability of the central nervous system (CNS) to regulate and control the experience of pain.
  - It involves the interplay of various neuronal pathways and systems in the brain and spinal cord that influence the perception of pain.
- PAG-RVW-SDH pathway modulate pain transmission.
  - PAG: periaqueductal gray
  - RVM: the rostral ventromedial medulla
  - SDH: the spinal dorsal horn



CPM and wide dynamic range neurons on dorsal horn

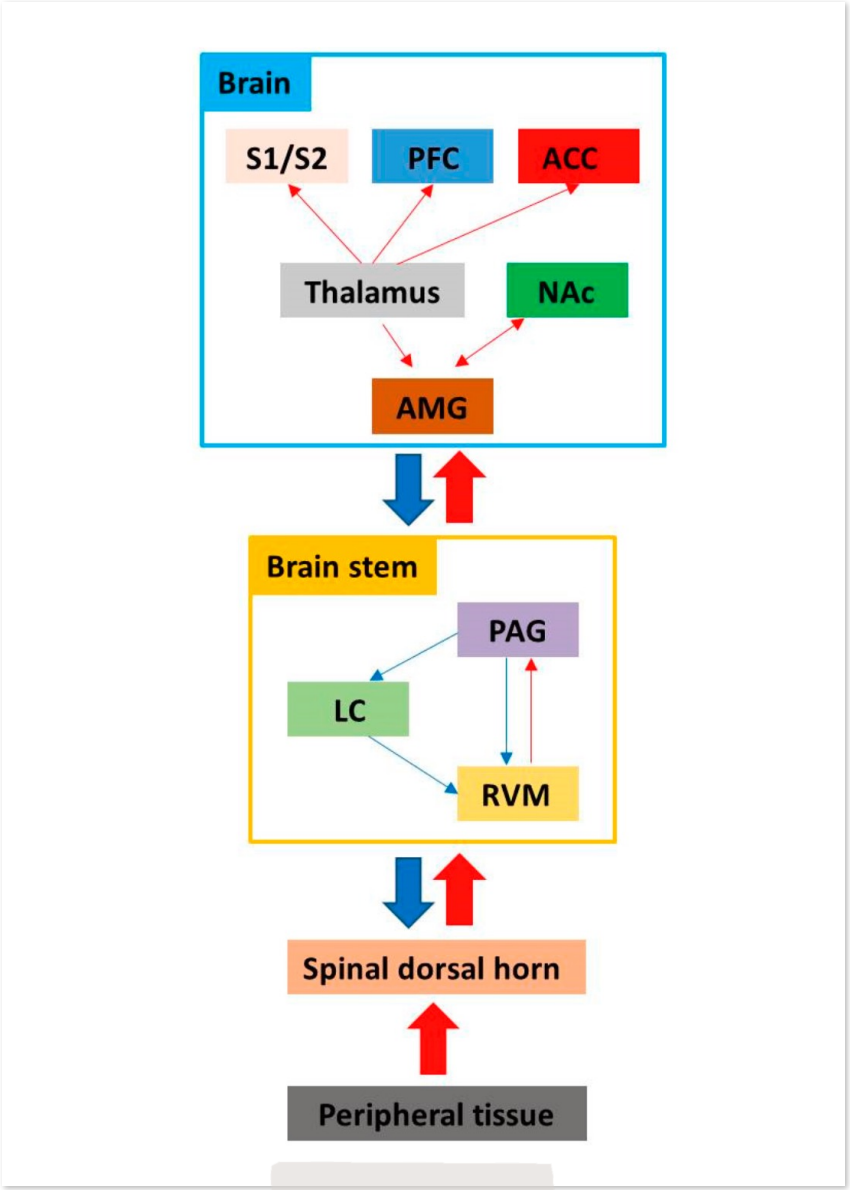
- WDR neurons receive input from multiple types of sensory receptors, including nociceptors (pain receptors), mechanoreceptors (pressure receptors), and thermoreceptors (heat and cold receptors).
- WDR neurons are also important for the process of pain modulation.
- They can inhibit or enhance the transmission of pain signals depending on the context and the overall level of pain.



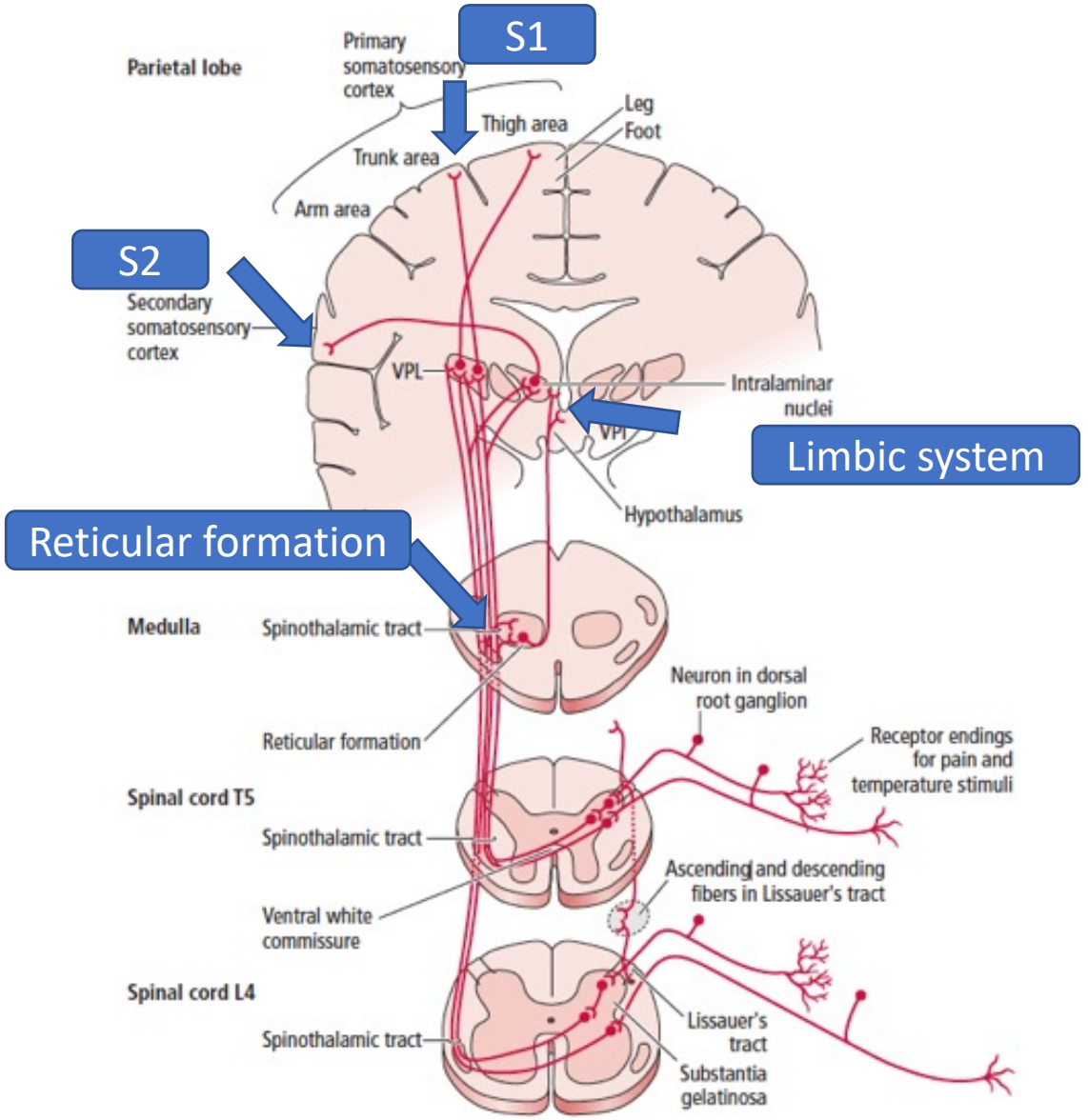


Limbic system and nociception

- Factors such as attention, emotions, and stress can alter pain modulation
- Ascending pain pathway
  - The nociception is transmitted to the somatosensory cortex and periaqueductal gray matter(PAG) .
  - Nociceptive information also is transmitted to brain areas involved in memory and affective aspects of pain, such as the amygdala, hypothalamus, PAG, and nucleus accumbens (NAc) through the spinoreticular and spinomesencephalic tracts.
- Descending pain modulatory systems
  - The PAG and rostral ventral medulla (RVM).
  - The RVM is the major output node
  - It receives input from the PAG and sends diffuse bilateral projections to the dorsal horn, terminating at multiple level

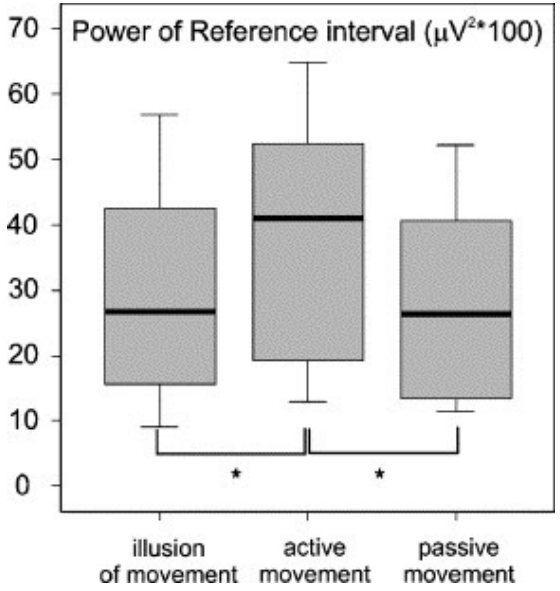


Int J Mol Sci 2019;20(13):3130


S1
S2
Limbic system
Reticular formation
Parietal lobe
Primary somatosensory cortex
Thigh area
Leg
Foot
Trunk area
Arm area
Secondary somatosensory cortex
VPL
Intralaminar nuclei
VPI
Hypothalamus
Medulla
Spinothalamic tract
Reticular formation
Neuron in dorsal root ganglion
Receptor endings for pain and temperature stimuli
Spinal cord T5
Spinothalamic tract
Ascending and descending fibers in Lissauer's tract
Ventral white commissure
Spinal cord L4
Spinothalamic tract
Lissauer's tract
Substantia gelatinosa

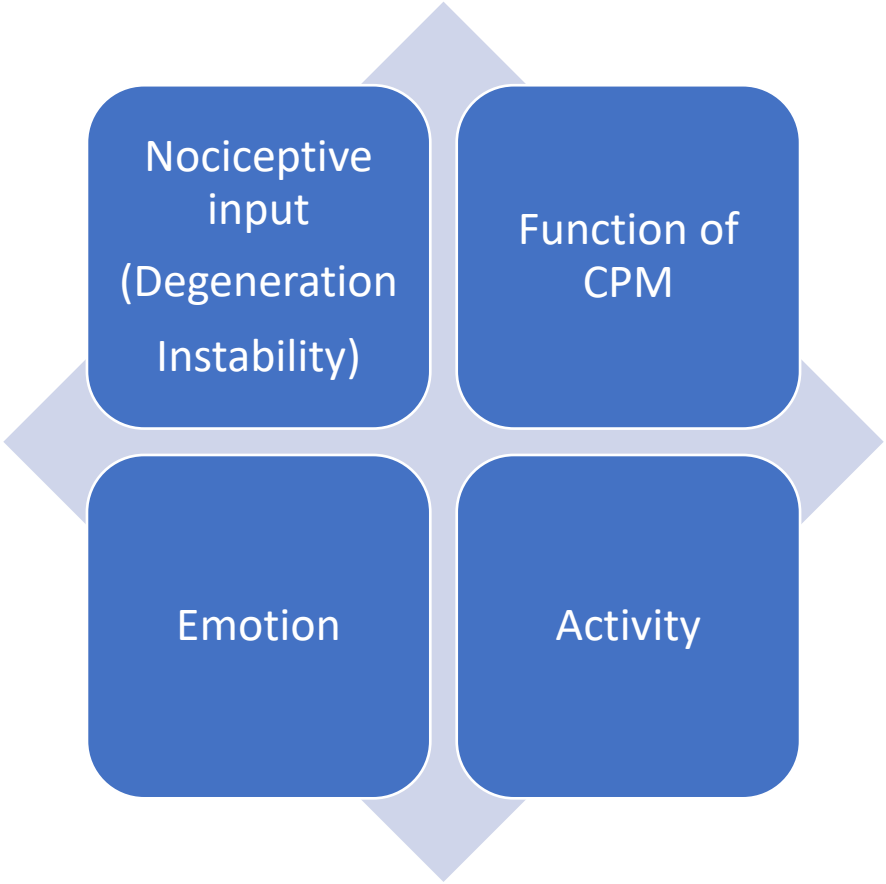
Exercise-induced hypoalgesia.

- Exercise-induced hypoalgesia refers to the phenomenon of reduced pain sensitivity that occurs after physical exercise.
- Post-movement beta synchronization(PMB) and exercise-induced hypoalgesia are two interrelated phenomena.
- Studies have shown that increased post-movement beta synchronization is associated with reduced pain perception and that physical exercise can enhance beta synchronization in pain-related brain regions.
- PMRS decreases in case of pain of various origins.



Clinical neurophysiology 2013;124(4);761

Chronic pain



Neuromodulation

WHAT IS NEUROMODULATION?

Neuromodulation is technology that acts directly upon nerves. It is the alteration—or modulation—of nerve activity by delivering electrical or pharmaceutical agents directly to a target area.

Neuromodulation devices and treatments are life changing. They affect every area of the body and treat nearly every disease or symptom from headaches to tremors to spinal cord damage to urinary incontinence. With such a broad therapeutic scope, and significant ongoing improvements in biotechnology, it is not surprising that neuromodulation is poised as a major growth industry for the next decade.

Most frequently, people think of neuromodulation in the context of chronic pain relief, the most common indication. However, there are a plethora of neuromodulation applications, such as deep brain stimulation (DBS) treatment for Parkinson's disease, sacral nerve stimulation for pelvic disorders and incontinence, and spinal cord stimulation for ischemic disorders (angina, peripheral vascular disease).

In addition, neuromodulation devices can stimulate a response where there was previously none, as in the case of a cochlear implant restoring hearing in a deaf patient.

And for every existing neuromodulatory treatment, there are many more on the horizon. An emerging technology called BrainGate Neural Interface System has been used to analyze brain signals and translate those signals into cursor movements, allowing severely motor-impaired individuals an alternate “pathway” to control a computer with thought, and offers potential for one day restoring some degree of limb movement.

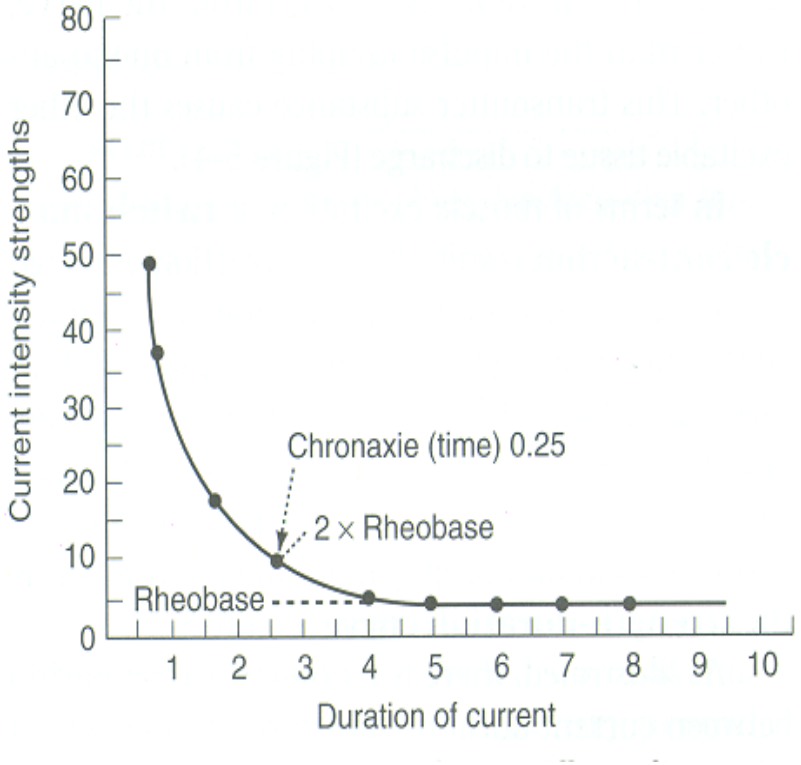
Neuromodulation for chronic pain

- Electrical delivery
  - Peripheral nerve
    - TENS
    - ESWT (?)
    - Pulsed & continuous radiofrequency
  - Spinal cord
    - Spinal cord stimulation
  - Brain
    - rTMS
    - tDCS

- Pharmaceutical agents
  - Peripheral nerve
    - Botulinum toxin
    - Alcohol block (?)
    - Nerve block
  - Spinal cord
    - Intrathecal pump

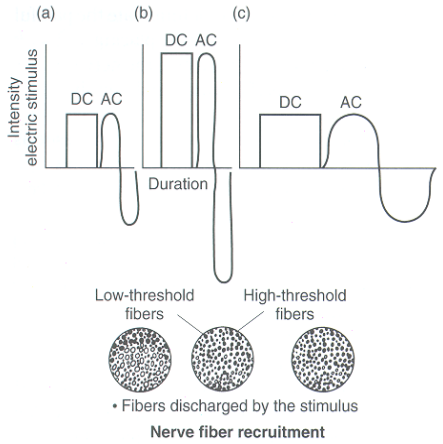
Electrical stimulation

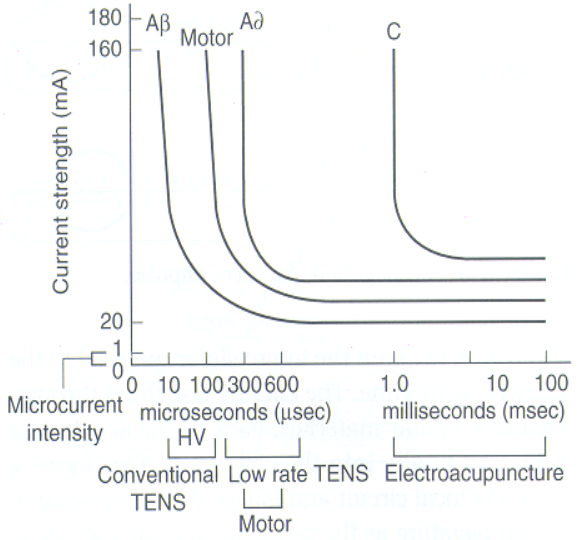
- Intensity of electrical stimuli and length of time is necessary to depolarize.
- Rheobase: minimum intensity to cause tissue excitation for maximum duration
- Chronaxie: duration required for current of twice intensity of the rheobase current



Duration and intensity

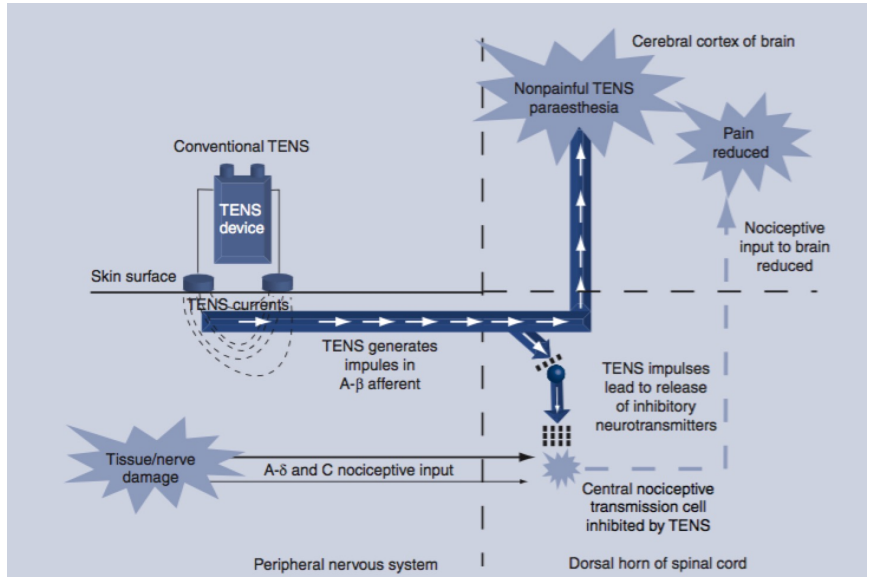
- Intensity ↑ → Current to reach deeper into the tissue, and samller fibers
- Duration ↑ → samller fibers and farther away
- Pulse width can be varied to target different fiber types
- Corresponding intensities would be necessary to create a depolarizing stimulus for any of the nerve fibers
- Aα = 50-100μs, small Aδ=150μs, C sensory= 400μs





Mechanism of TENS

- Gate control theory
  - The electrical impulses delivered by TENS activate large-diameter nerve fibers that carry non-painful sensations to the brain
  - Effectively block the transmission of pain signals from smaller, pain-sensing nerve fibers.
- Limitation
  - adaptation or habituation.
  - Effectiveness can vary depending on pain type and location.



Tolerance of TENSE

- Repeated daily administration of TENS – analgesic tolerance
- Synaptic plasticity
  - Blockade NMDA receptor during TENSE – precents the development of analgesic tolerance
  - Blockade of CCK (G-protein coupled receptors) – prevent development of opioid tolerance
- Alternating-frequency or mixed-frequency – delayed tolerance

Curr Rheuma Reports 2008;10(6);492

Scrambler therapy for chronic pain

Table 1 Summary of Scrambler Therapy trials

	Reports, by first author	Year	Patients	Condition	Results	Trial type	Comments
1	Marineo [13]	2003	11	Drug-resistant visceral pain	Substantial pain reduction	Prospective trial	
2	Sabato [24]	2005	226	Multiple chronic pain syndromes	80 % of patients with greater than a 50 % pain reduction	Prospective trial	
3	Smith [30]	2010	18	Chemotherapy-induced neuropathy	Over 50 % reduction in pain	Prospective trial	16 evaluable
4	Abdi [15]	2011	10	Back pain	28 % reduction in pain	Prospective trial	Abstract only
5	Marineo [20]	2011	52	Post-herpetic neuralgia, spinal canal stenosis, and postsurgical neuropathic pain	Pain reduced more in Scrambler arm, than the control arm at 1 and 3 months ($P < 0.0001$)	Randomized, controlled trial	Open-label trial
6	Ricci [28]	2012	82	Various cancer and non-cancer pains	Mean pain scores dropped from 6.2/10 prior to treatment to 1.6 just after completing 10 treatment days to 2.9, 2 weeks after finishing treatment.	Prospective trial	73 evaluable patients
7	Ghatak [18]	2011	8	Chronic low back pain	Pain score drop from 8.12 to 6.93; Drop in Oswestry Disability Index from 49.88 to 18.44	Prospective trial	Open label
8	Sparadeo [27]	2012	173	Chronic pain >6 months	Marked pain reduction	Clinical practice experience	91 provided 3–6 months follow-up
9	Coyne [17]	2013	39	Cancer pain syndromes, including chemotherapy-induced neuropathy	Significant pain reduction with 10 treatment days that largely lasted for 3 months	Prospective trial	
10	Smith [25]	2013	10	Post-herpetic neuralgia	95 % pain reduction, that largely lasted for 3 months	Prospective trial data	Some patients were the same as in a previous trial [18]
11	Ko [19]	2013	3	Post-herpetic neuralgia	Marked pain reduction	Clinical practice experience	
12	Park [23]	2013	3	Cancer bone metastases	Marked pain reduction	Clinical practice experience	
13	Campbell [16]	2013	14	Chemotherapy-induced neuropathy	No differences between active and placebo arms	Prospective, double-blind, placebo-controlled trial	Abstract only
14	Pachman [22]	2014	37	Chemotherapy-induced neuropathy	Average pain decreased by 53 % at end of treatment and benefit largely remained for 10 weeks after completion.	Prospective trial	Decrease in tingling and numbness, too.
15	Sparadeo [26]	2014	91	Variety of pain syndromes	Substantial pain reduction	Clinical practice experience	Consecutive patients; Some patients were the same as in a previous trial [30]
16	Moon [21]	2014	147	Variety of pain syndromes		Clinical practice experience	
17	Starkweather [29]	2015	30	Low back pain	Significant improvements in active vs control group for: (1) worse pain and pain interference states; (2) pain sensitivity measures, and (3) differential mRNA expression of 17 pain genes	Prospective, double-blind, placebo-controlled trial	
18	Notaro [31]	2015	25	Bone and visceral metastases	All patients experienced at least a 50 % drop in pain scores, with average duration of response of 7.7 weeks; improved sleep performance	Prospective trial	
19	Compagnone [33]	2015	201	Variety of pain syndromes	Reduction from mean pain score of 7.41 at baseline to 1.6 following treatment	Retrospective cohort	
20	Lee [32]	2016	20	Various cancer-related pain syndromes	Mean pain score decreased from 7.4 to 3.7 by visit 3	Prospective, single-arm	

- The developer of Scrambler Therapy participated in the initial clinical trials.
- There are no large, placebo-controlled, double-blinded clinical trials to estimate the effectiveness of Scrambler Therapy.

Support care cancer 2016;24;2807

Kilohertz frequency alternating current

- KHFAC- rapid block of nerve conduction and reversible
  - Action potential are arrested as they pass under the blocking electrode.
- Typical above 100 Hz-
  - neurotransmitter is transiently depleted at the synaptic or neuromuscular junction.
  - Thus, in a neurotransmitter depletion “block,” the axon itself is still *activated* and not blocked.
  - Skin surface – nerve block X

Neuromodulation 2014;17;242

Pulsed radiofrequency (PRF)

- Pulse Frequence= 1/x
- PW: pulse width
- Time : 120s
- Common setting
  - Pulse frequency:2Hz
  - Pulse width: 20ms
  - 45V
  - 120s

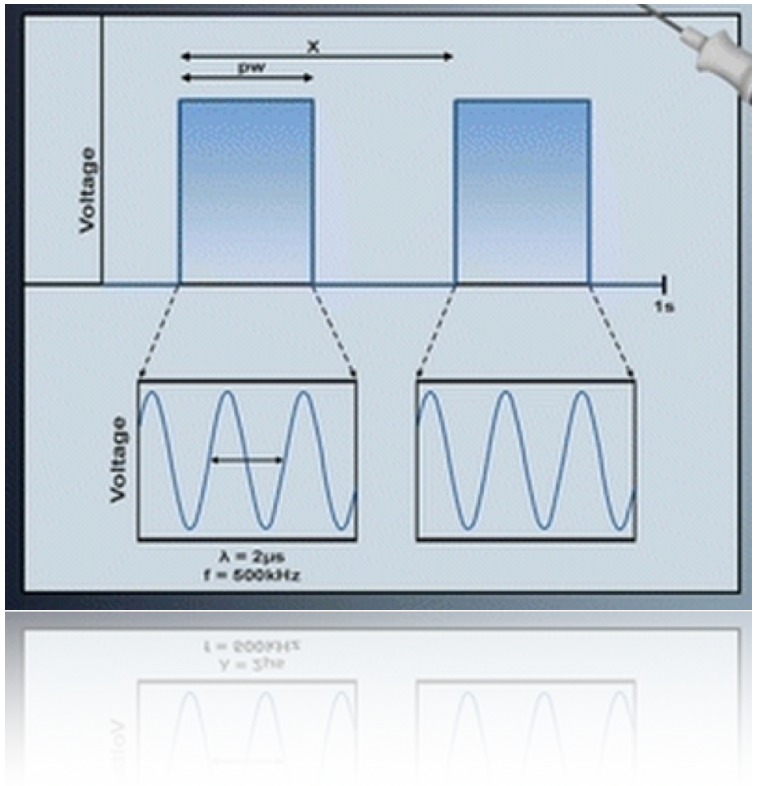
•reduce heat spike setting

•Pulse frequency:2Hz

•Pulse width: 10ms

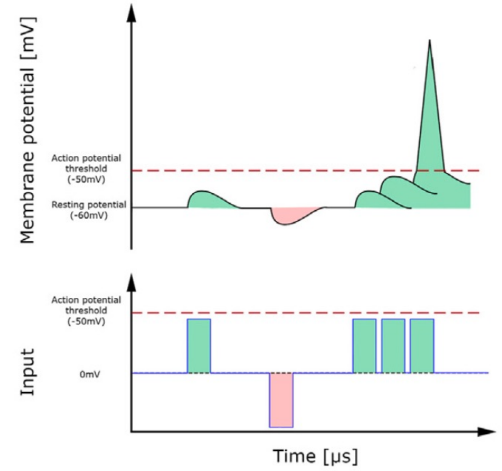
•45V

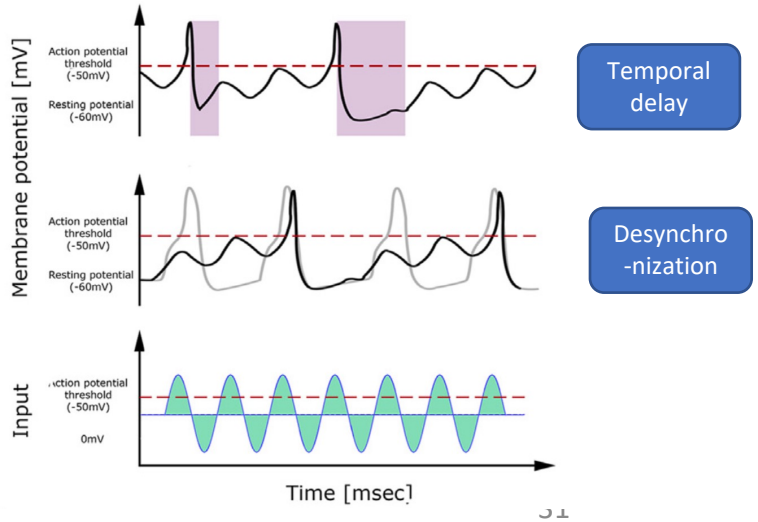
•240s



Kilohertz-frequency stimulation

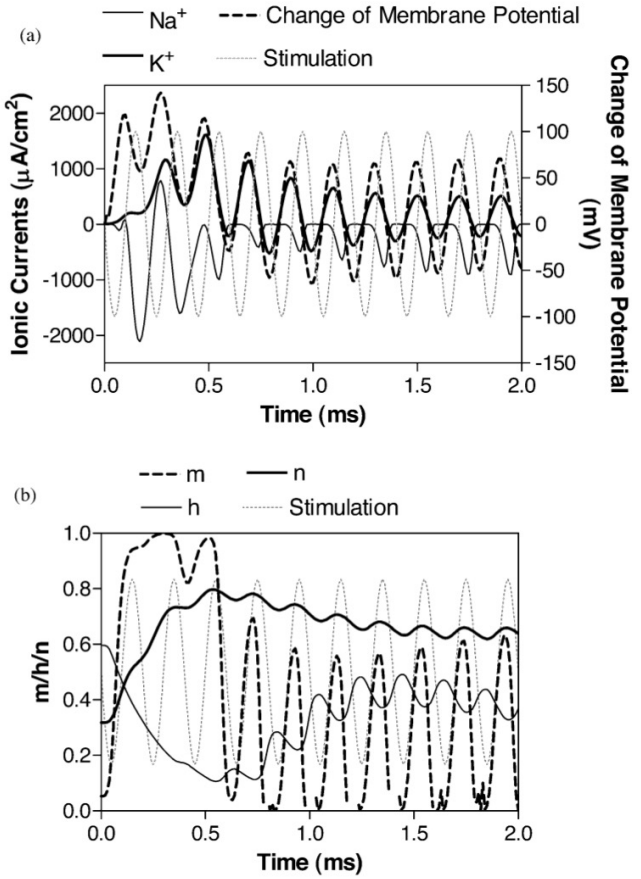
- Physiological conditions a neuron's maximum firing rate - typically 500 Hz
- The kilohertz- frequency range - supraphysiological frequencies
- Subthreshold effects
  - Facilitation: Temporal summation
  - Iinduce facilitation with each subthreshold stimulus adding to the already built-up charge
- Suprathreshold effect;
  - Desynchronization of neural firing: As a result of stochastic membrane dynamics





Conduction block of kHz

- 5 kHz, 15 mA, nerve block occurred
- Inward sodium currents cannot initiate action potentials.
- The potassium current is tightly linked to the change of membrane potential, due to the constant activation of the potassium channels
- The ensuing efflux of potassium consequently overwhelms the depolarizing sodium currents and biases the transmembrane potential towards hyperpolarization - eventually culminates in true conduction block



IEEE Transactions on neural systems and rehabilitation engineering 2005;13(3);415

Pulsed radiofrequency (PRF)

High Temperature

↓

Conventional RF
: MBB ablation,
L-Disq

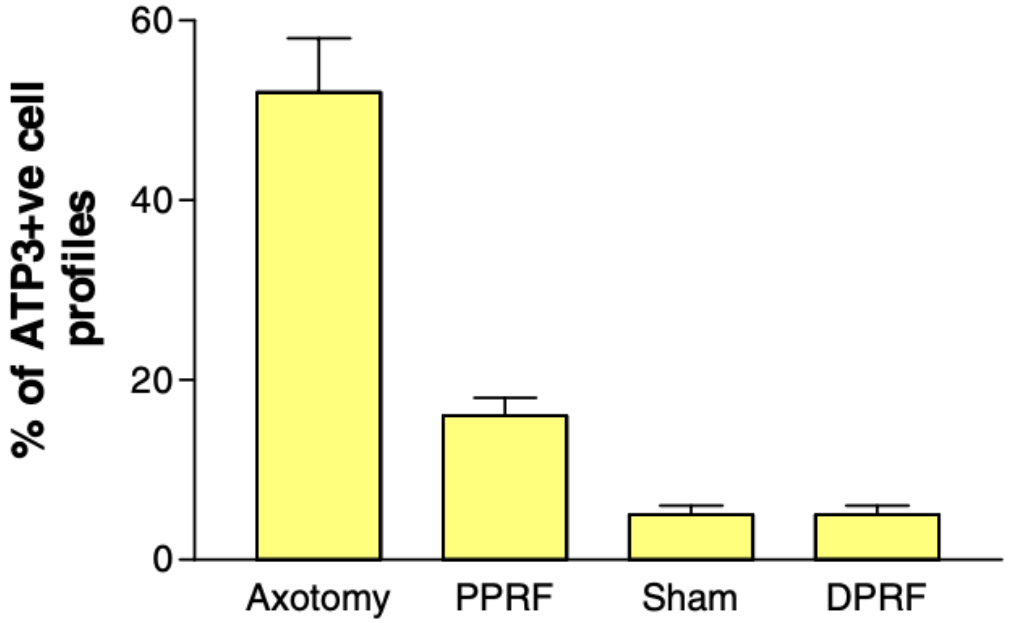
Electrical field

↓

Pulsed RF
: DRG,
Sympathetic ganglion,
Trigeminal ganglion

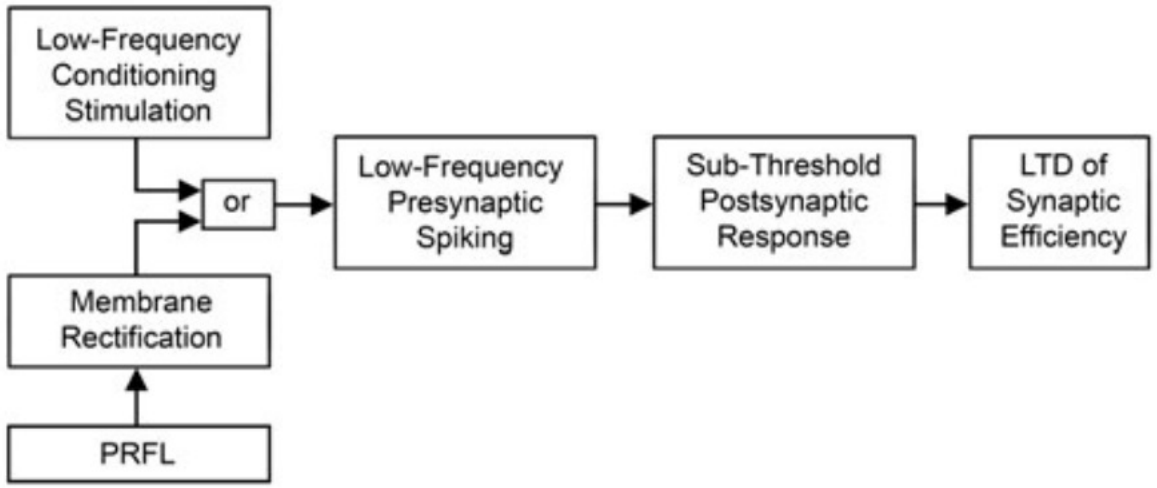
PRF at DRG

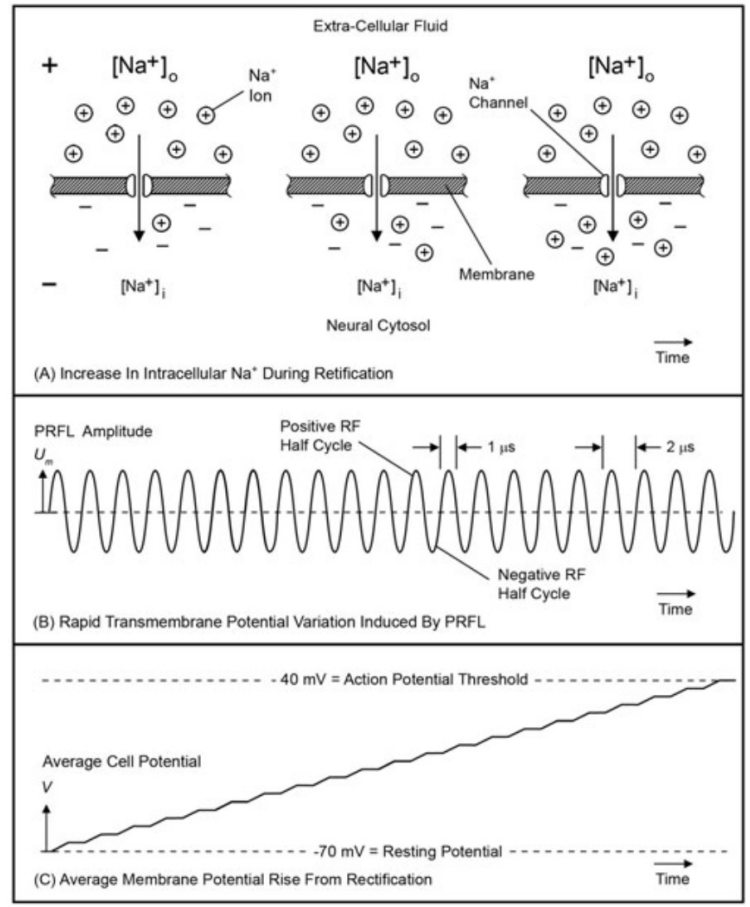
- PRF has a biological effect, unlikely to be related to overt thermal damage.
- It appears to be selective in that it targets the group of neurons whose axons are the small diameter C and Ad nociceptive fibers.
- Expression of ATF3 is regarded as a marker for nerve injur
- PRF did not produce any obvious cellular changes in the nerve or L4 DRG neurons when applied to the sciatic nerve in mid-thigh.



European J of pain 2006;10;171

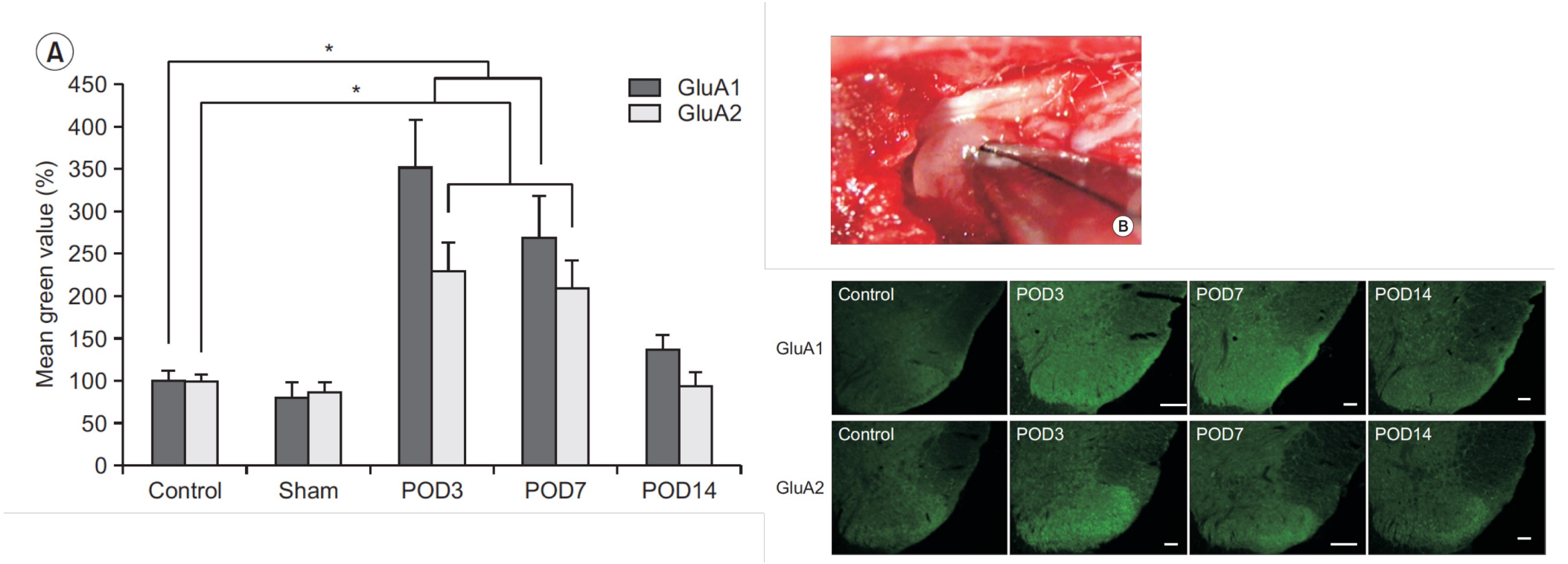
Electrical field effect of PRF





Pain medicine 2005;6(6);405

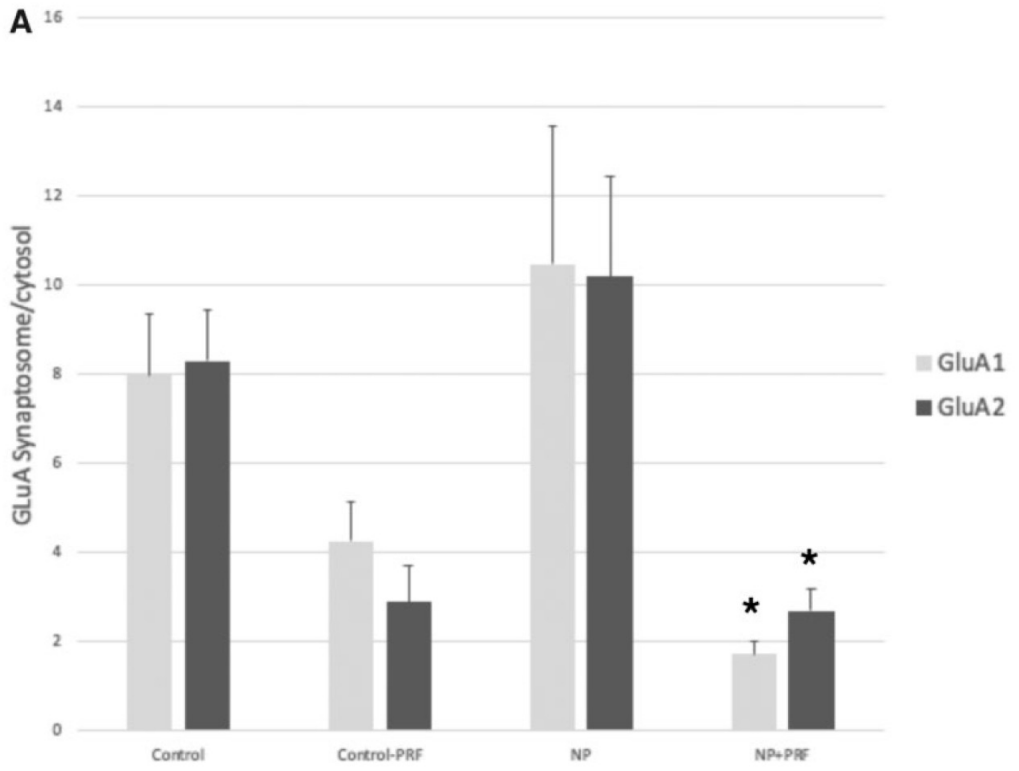
Disc herniation rat model and AMPA on dorsal horn of spinal cord



Pain medicine 2020;21(9);1913

Ratio of synaptosome to cytosol fractions of AMPA receptors

- PRF stimulation decreased the ratio of synaptosome to cytosol fractions of GluA1 and GluA2 subunit.
- The ratio in the NP+PRF group showed a statistically significant decrease compared with the NP group.



10K SCS

Study (First Author et al., Year of Publication)	Type (In Vitro, Ex Vivo, In Vivo or Clinical)	Model	Key Finding
Lee et al., 2020 [91]	In vivo and ex vivo	In vivo and ex vivo electrophysiological approaches: In vivo experiments: adult male Sprague Dawley rats Ex vivo experiments: Transgenic mice expressing green fluorescent protein in GABAergic neurons	10 kHz SCS may inhibit pain sensory processing in the spinal dorsal horn by uniquely activating inhibitory interneurons without activating dorsal column fibers, resulting in paresthesia-free pain relief.
Liao et al., 2020 [93]	In vivo, sham controlled	Spared nerve injury Sprague-Dawley rats	10 kHz SCS applied to the T10/T11 spinal cord significantly attenuated spared nerve injury-induced mechanical hyperalgesia compared with the sham stimulation group. Western blotting revealed a significant attenuation of ERK1, ERK2, JNK1, and p38 activation in the dorsal root ganglia and the spinal dorsal horn.
Liao et al., 2020 [94]	In vivo, sham controlled	Spared nerve injury Sprague-Dawley rats	10 kHz SCS treatment attenuated spared nerve injury -induced neuropathic pain and partially restored the altered glutamate uptake after spared nerve injury.
DeGroote et al., 2020 [95]	Clinical, Prospective study	Patients with FBSS treated with 10 kHz SCS; resting state functional magnetic resonance imaging (rsfMRI)	Increased strength in functional connectivity between the left dorsolateral prefrontal cortex and the right anterior insula significantly correlated with the minimum clinically important difference value of the Pittsburgh sleep quality index.
DeGroote et al., 2020 [96]	Clinical, prospective	Patients with FBSS treated with 10 kHz SCS; neuroimaging MRI (Voxel-Based Morphometry Diffeomorphic Anatomical Registration Through Exponentiated Lie)	10 kHz SCS influences structural brain regions over time. The volume of the hippocampus decreased bilaterally after three months with a positive correlation with back pain intensity.
Telkes et al., 2020 [97]	Clinical, prospective	Patients with FBSS treated with 10 kHz SCS; electroencephalogram (EEG)	Stronger relative alpha power in the somatosensory region. Shift in peak frequency from theta to alpha Rhythms compared to baseline. Changes in ODI scores positively correlated with alpha/theta peak power ratio in frontal and somatosensory regions.

Biomedicines 2021;9;644

Research

JAMA | Original Investigation

Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery
A Randomized Clinical Trial

Sozaburo Hara, MD; Hege Andresen, RN, MSc; Ole Solheim, MD, PhD; Sven M. Carlsen, MD, PhD; Terje Sundstrøm, MD, PhD; Greger Lønne, MD, PhD; Vetle V. Lønne, MD; Kristin Taraldsen, PT, PhD; Erling A. Tronvik, MD, PhD; Lise R. Øie, MD, PhD; Agnete M. Gulati, MD, PhD; Lisa M. Sagberg, RN, PhD; Asgeir S. Jakola, MD, PhD; Tore K. Solberg, MD, PhD; Øystein P. Nygaard, MD, PhD; Øyvind O. Salvesen, MSc, PhD; Sasha Gulati, MD, PhD

IMPORTANCE The use of spinal cord stimulation for chronic pain after lumbar spine surgery is increasing, yet rigorous evidence of its efficacy is lacking.

OBJECTIVE To investigate the efficacy of spinal cord burst stimulation, which involves the placement of an implantable pulse generator connected to electrodes with leads that travel into the epidural space posterior to the spinal cord dorsal columns, in patients with chronic radiculopathy after surgery for degenerative lumbar spine disorders.

DESIGN, SETTING, AND PARTICIPANTS This placebo-controlled, crossover, randomized clinical trial in 50 patients was conducted at St Olavs University Hospital in Norway, with study enrollment from September 5, 2018, through April 28, 2021. The date of final follow-up was May 20, 2022.

INTERVENTIONS Patients underwent two 3-month periods with spinal cord burst stimulation and two 3-month periods with placebo stimulation in a randomized order. Burst stimulation consisted of closely spaced, high-frequency electrical stimuli delivered to the spinal cord. The stimulus consisted of a 40-Hz burst mode of constant-current stimuli with 4 spikes per burst and an amplitude corresponding to 50% to 70% of the paresthesia perception threshold.

MAIN OUTCOMES AND MEASURES The primary outcome was difference in change from baseline in the self-reported Oswestry Disability Index (ODI; range, 0 points [no disability] to 100 points [maximum disability]; the minimal clinically important difference was 10 points) score between periods with burst stimulation and placebo stimulation. The secondary outcomes were leg and back pain, quality of life, physical activity levels, and adverse events.

RESULTS Among 50 patients who were randomized (mean age, 52.2 [SD, 9.9] years; 27 [54%] were women), 47 (94%) had at least 1 follow-up ODI score and 42 (84%) completed all stimulation randomization periods and ODI measurements. The mean ODI score at baseline was 44.7 points and the mean changes in ODI score were −10.6 points for the burst stimulation periods and −9.3 points for the placebo stimulation periods, resulting in a mean between-group difference of −1.3 points (95% CI, −3.9 to 1.3 points; $P = .32$). None of the prespecified secondary outcomes showed a significant difference. Nine patients (18%) experienced adverse events, including 4 (8%) who required surgical revision of the implanted system.

CONCLUSIONS AND RELEVANCE Among patients with chronic radicular pain after lumbar spine surgery, spinal cord burst stimulation, compared with placebo stimulation, after placement of a spinal cord stimulator resulted in no significant difference in the change from baseline in self-reported back pain–related disability.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03546738

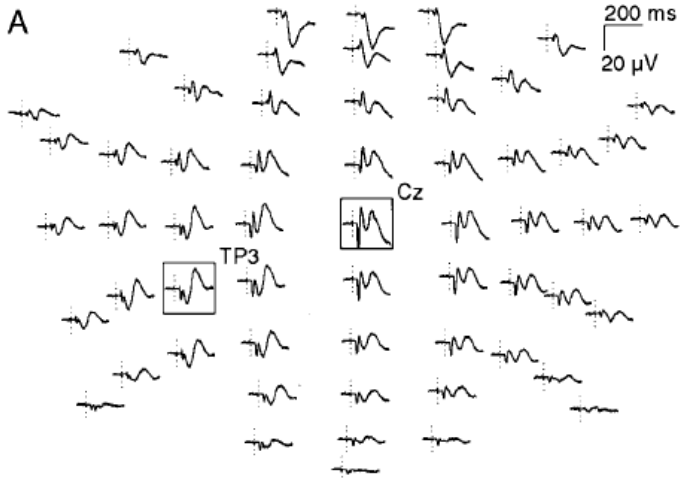
Visual Abstract

Supplemental content

CONCLUSIONS AND RELEVANCE Among patients with chronic radicular pain after lumbar spine surgery, spinal cord burst stimulation, compared with placebo stimulation, after placement of a spinal cord stimulator resulted in no significant difference in the change from baseline in self-reported back pain–related disability.

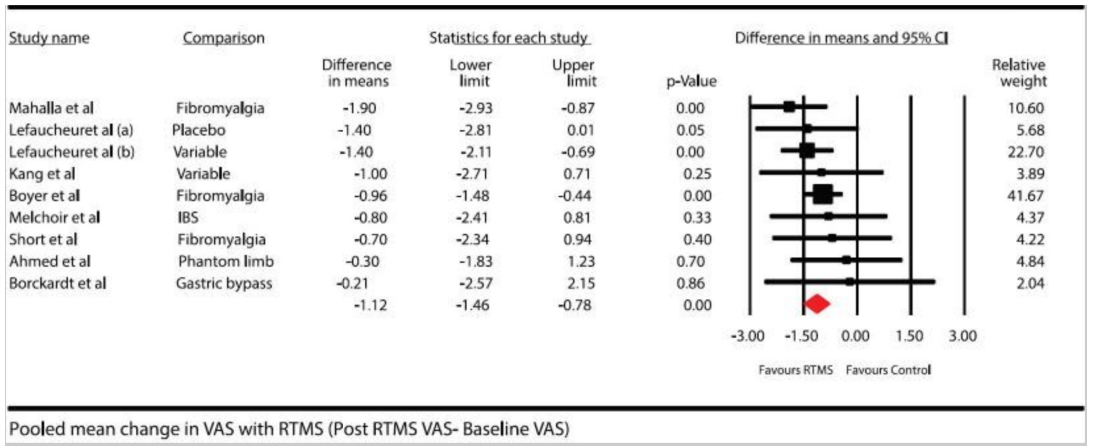
Post-movement beta synchronization (PMBS)

- Beta wave : frequency range between 12.5 and 30Hz.
- Movement is followed by a short-lasting beta synchronization: exercise related synchronization (ERS).
- 20Hz beta thythm is located in the motor area.
- PMRS decreases in case of pain of various origins.
- The motor cortex stimulation (MCS: implanted mode) restores partially the physiological PMBS pattern improving defective cortical inhibition with reduction of thalamic hyperactivity.



rTMS in chronic pain

- rTMS showed efficacy in meta-analysis.
- rTMS VS rTMS with conventional pain treatment.
- rTMS frequency: 10 -20 Hz.
- Session: 2 – 10 session, 1000 – 4000/session
- The duration and frequency of rTMS is presently highly variable.

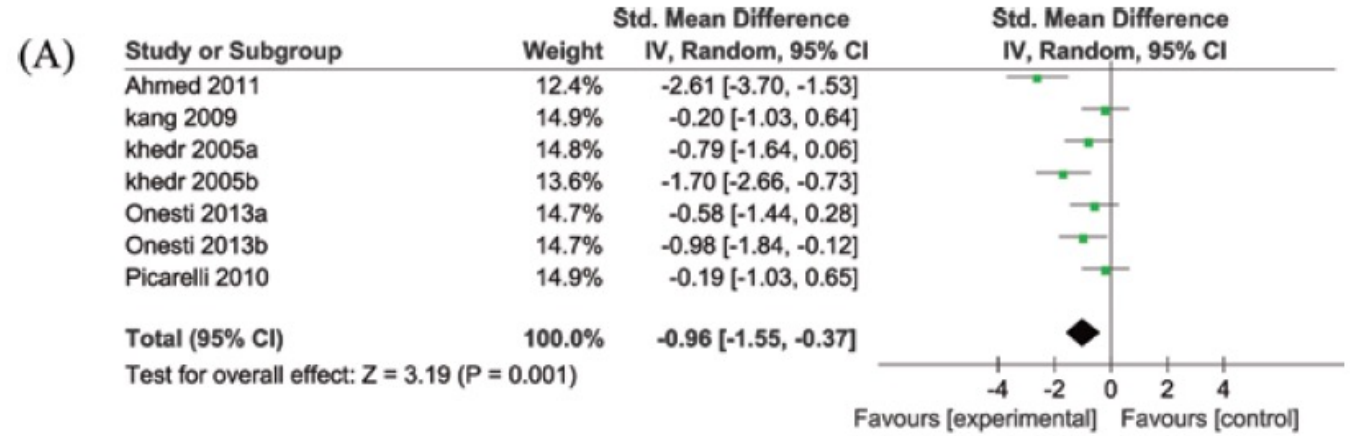


Study name	Comparison	Statistics for each study: Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Mahalla et al	Fibromyalgia	-1.90	-2.93	-0.87	0.00	10.60
Lefaucheuret al (a)	Placebo	-1.40	-2.81	0.01	0.05	5.68
Lefaucheuret al (b)	Variable	-1.40	-2.11	-0.69	0.00	22.70
Kang et al	Variable	-1.00	-2.71	0.71	0.25	3.89
Boyer et al	Fibromyalgia	-0.96	-1.48	-0.44	0.00	41.67
Melchoir et al	IBS	-0.80	-2.41	0.81	0.33	4.37
Short et al	Fibromyalgia	-0.70	-2.34	0.94	0.40	4.22
Ahmed et al	Phantom limb	-0.30	-1.83	1.23	0.70	4.84
Borckardt et al	Gastric bypass	-0.21	-2.57	2.15	0.86	2.04
		-1.12	-1.46	-0.78	0.00	

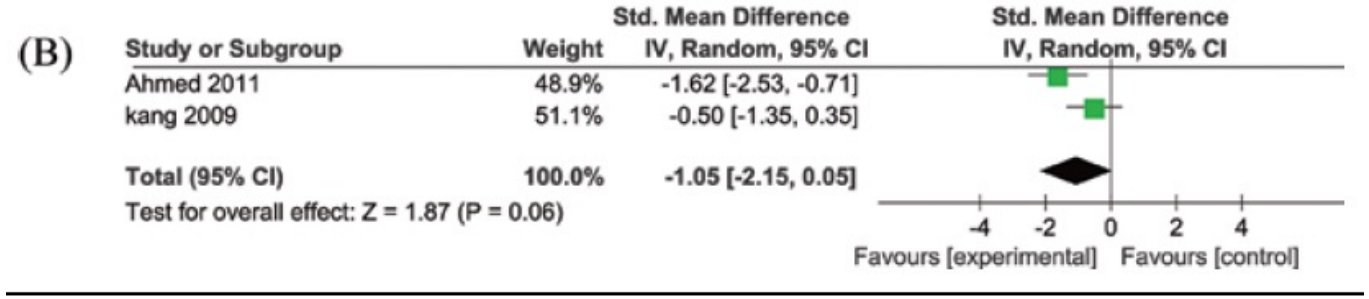
Pooled mean change in VAS with RTMS (Post RTMS VAS- Baseline VAS)

Long-term analgesic effect (?) following rTMS

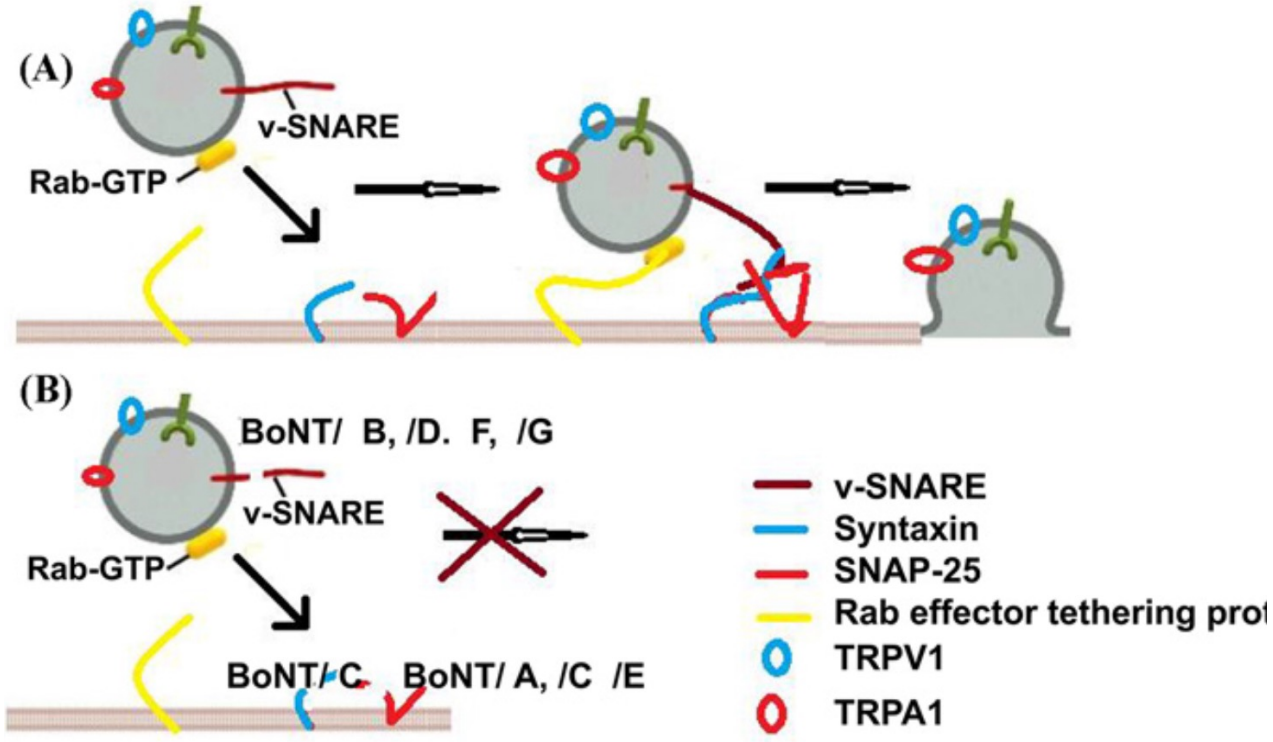
One month F/U



Two months F/U

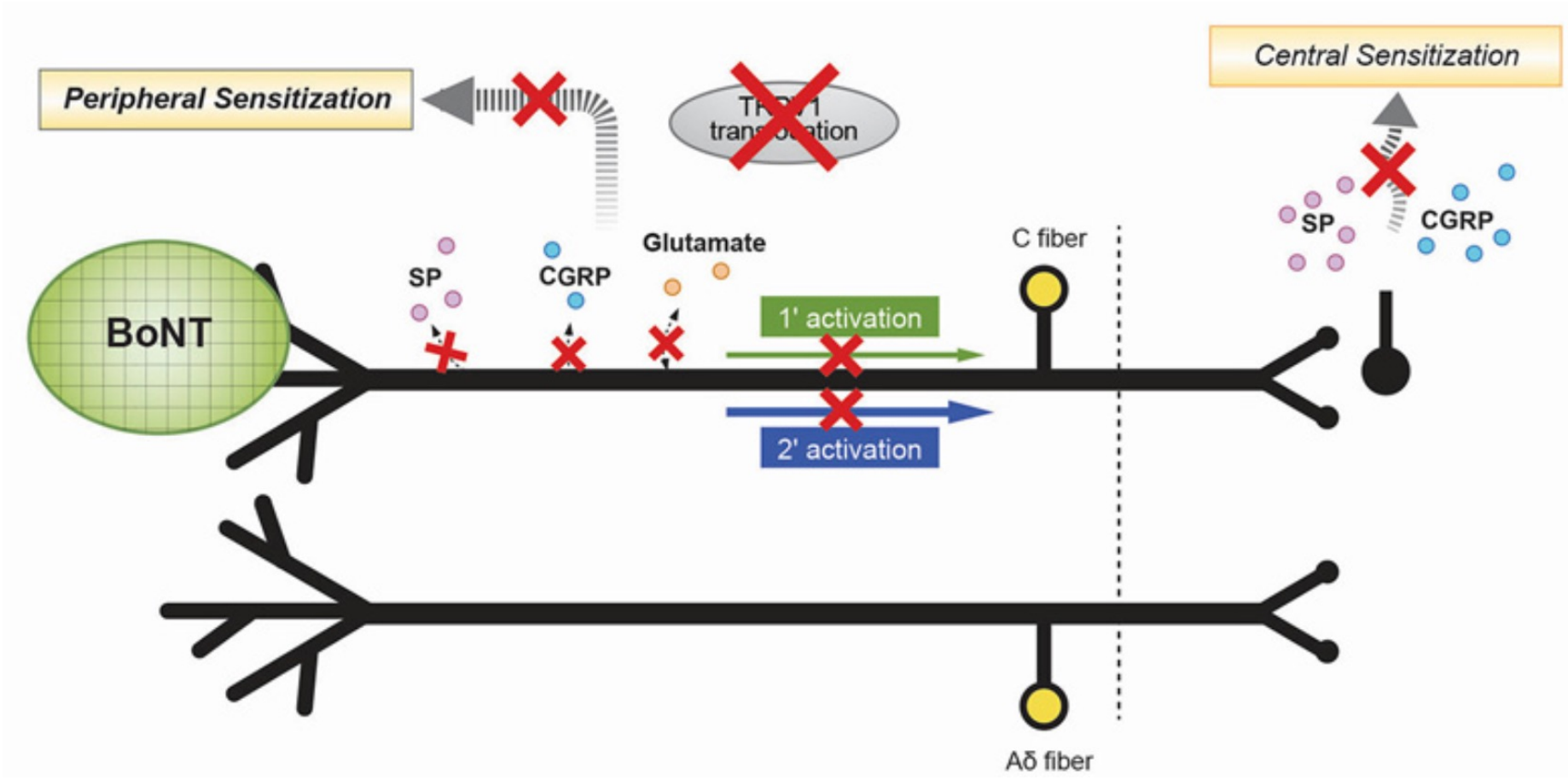


BoNT at synaptic vesicle



- sensory receptor from synaptic vesicle through regular fusion process.
- Exocytosis process at the synapse is not only involved in neurotransmitter release, but also populates presynaptic regions with several pain receptors.
- Inhibition of fusion vesicles reduces number of pain receptors at the synapse.

Antinociceptive activity



Neuronal signaling 2018;2(3)

Studies assessing efficacy of botulinum toxin

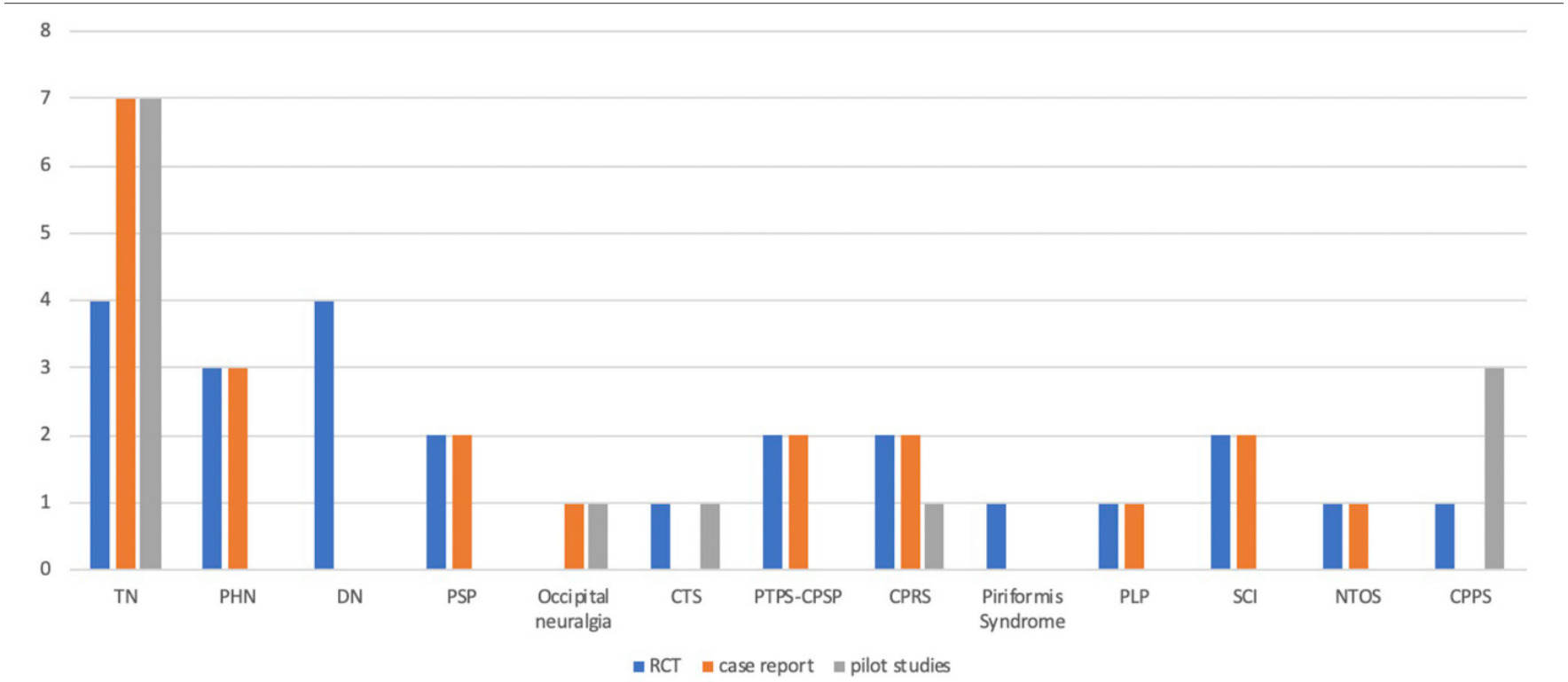


FIGURE 1 | Studies assessing the efficacy of botulinum toxin in different types of neuropathic pain. TN: trigeminal neuralgia; PHN: post-herpetic neuralgia; DN: diabetic neuropathy; PSP: post-stroke pain; CTS: carpal tunnel syndrome; PTPS: post-thoracotomy pain syndrome; CPSP: chronic post-surgical pain; CPRS: complex regional pain syndrome; PLP: phantom limb pain; SCI: spinal cord injury; NTOS: neurogenic thoracic outlet syndrome; CPPS: Chronic pelvic pain syndrome.

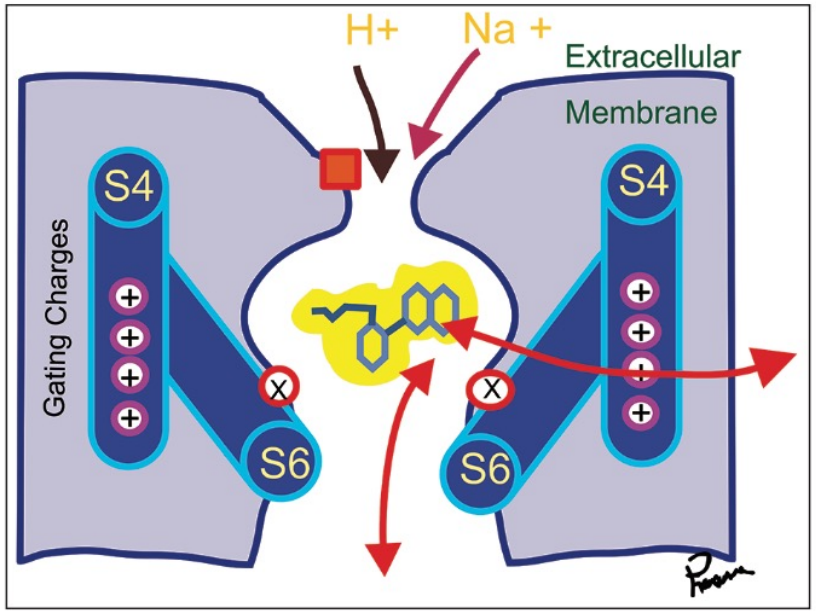
Frontiers in neurology 2020;11;716

Studies assessing efficacy of botulinum toxin

- Botulinum toxin could represent a promising therapeutic tool for NP for its documented efficacy and tolerability in a wide range of NP conditions
- BoNT/A seems helpful in particular in trigeminal neuralgia, post-herpetic neuralgia, painful diabetic neuropathy, occipital neuralgia, post-surgical pain and in SCI-related pain.
- No major safety issue emerged in the studies reported

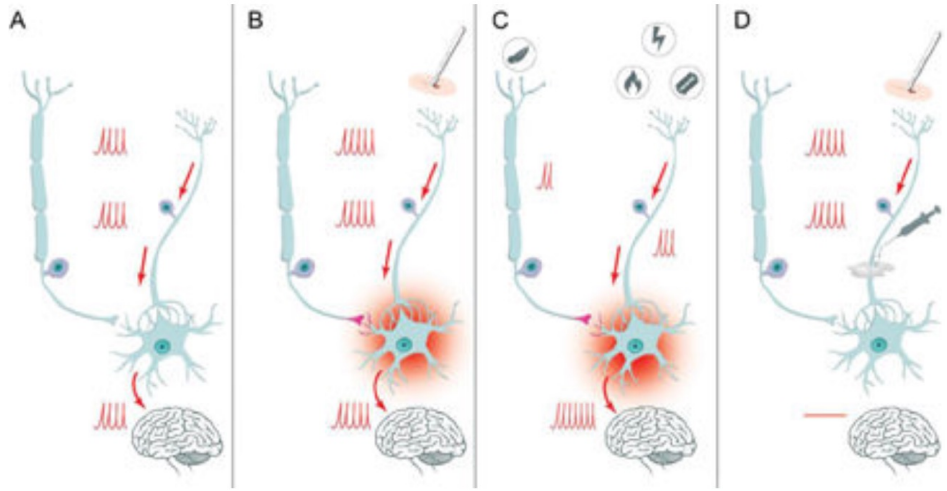
Local anesthetics

- Na channels play a vital role in impulse propagation
- The NaV channel as a bell-shaped transmembrane glycoprotein with 4 domains, D1-D4.
- Only the open state can conduct Na ions through them.
- Specific sites of the NaV channel for sensing voltage and binding Las.
- Local anesthetics (LAs) reduce the permeability of cell membranes to Na+, avoiding membrane depolarization, and thus blocking neural conduction of painful stimulation.



Regional anesthesia prevent central sensitization

- Central sensitization, can be mitigated or prevented by blocking the barrage of pain signals with local anesthetics, preventing the development of persistent pain after surgery.

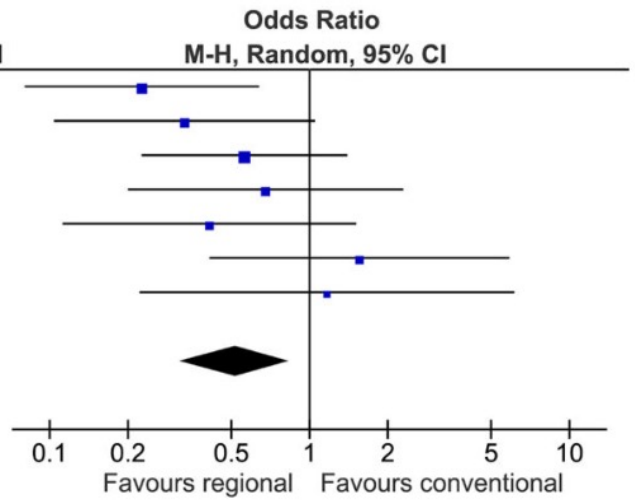


The seven randomized trials investigating regional anesthesia for the prevention of prevention of persistent postoperative pain after thoracotomy

Study or Subgroup	Favours regional Events	Total	Conventional Pain Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Lu 2008	9	62	12	28	17.9%	0.23 [0.08, 0.63]
Senturk 2002	25	46	18	23	14.9%	0.33 [0.10, 1.04]
Ju 2008	16	38	22	39	22.0%	0.56 [0.23, 1.39]
Can 2013	9	40	6	20	13.6%	0.68 [0.20, 2.27]
Comez 2015	6	40	6	20	12.1%	0.41 [0.11, 1.50]
Liu 2015	6	60	4	60	11.7%	1.56 [0.42, 5.82]
Katz 1996	7	13	5	10	7.8%	1.17 [0.22, 6.08]
Total (95% CI)		**299**		**200**	**100.0%**	**0.52 [0.32, 0.84]**
Total events	78		73			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.01$, df = 6 (P = 0.32); $I^2 = 14\%$

Test for overall effect: Z = 2.67 (P = 0.008)



J clin anesth 2019;55;116

Pain Physician 2010; 13:437-450 • ISSN 1533-3159

Randomized Trial

Comparative Outcomes of a 2-Year Follow-Up of Cervical Medial Branch Blocks in Management of Chronic Neck Pain: A Randomized, Double-Blind Controlled Trial

Laxmaiah Manchikanti, MD[1], Vijay Singh, MD[2], Frank J.E. Falco, MD[3], Kimberly A. Cash, RT[1], and Bert Fellows, MA[1]

- Group I consisted of cervical medial branch blocks with bupivacaine only
- Group II consisted of cervical medial branch blocks with bupivacaine and steroid.

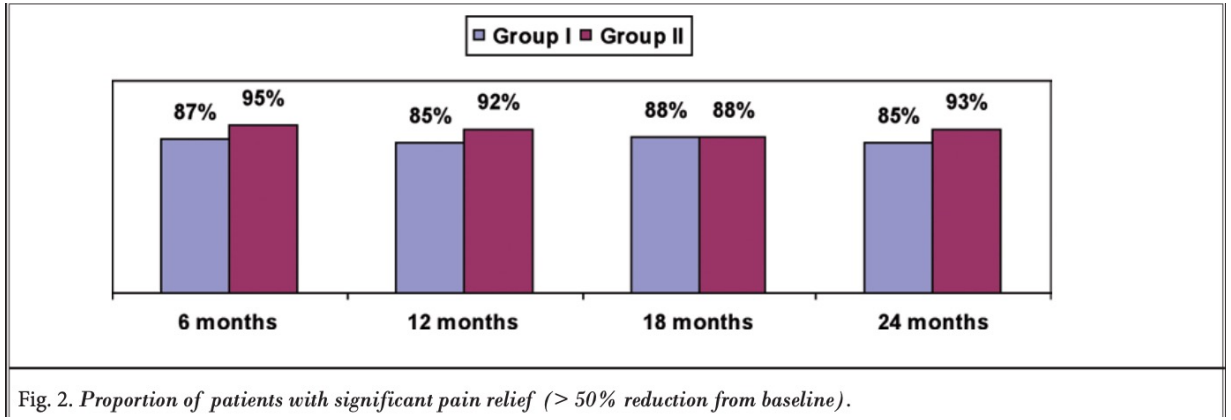
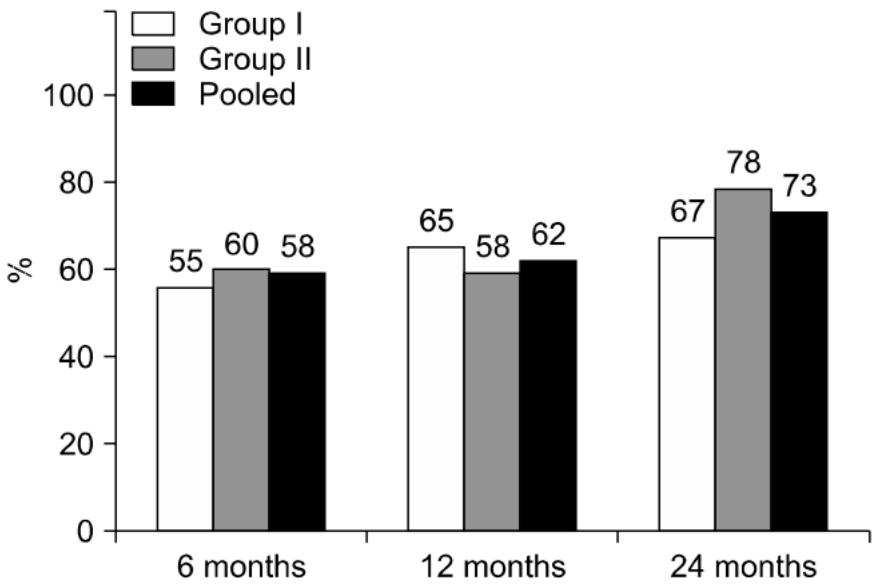


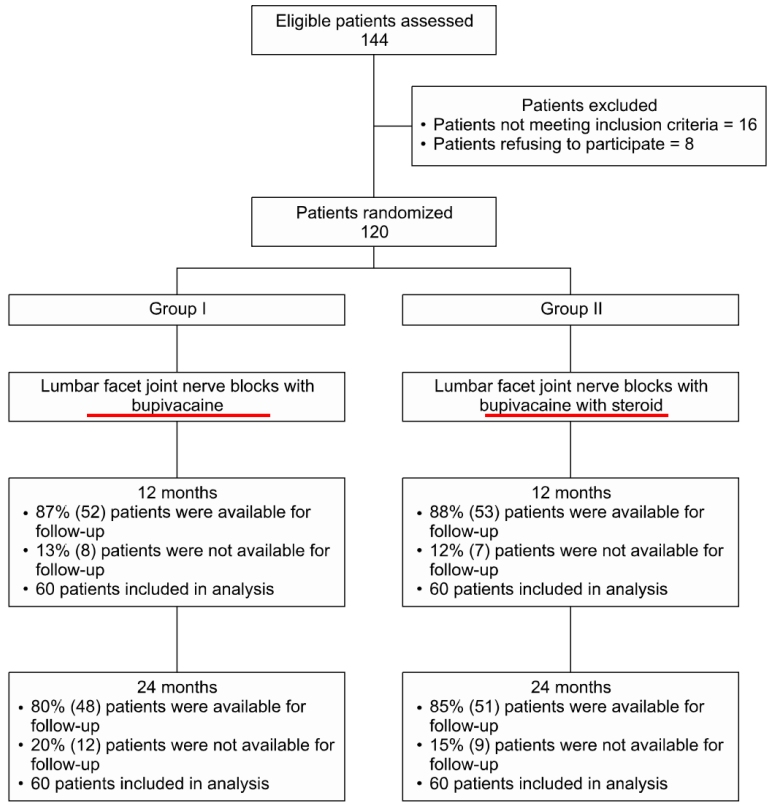
Fig. 2. *Proportion of patients with significant pain relief (> 50% reduction from baseline).*

Therapeutic lumbar facet joint nerve blocks in the treatment of chronic low back pain: on RCT

- lumbar facet joint nerve blocks in the treatment of chronic low back pain shows clinical effectiveness



NRS ≥ 50% reduction from baseline



KJP 2018;31(1);27

Inflammation & healing (or scar)

- Vasoconstriction
- Platelet aggregation
- Leucocyte migration

- Early-neutrophil chemoattract release
- Late macrophages
- Phagocytosis

- Fibroblast. proliferation
- Collagen synthesis
- ECM reorganization
- Angiogenssis
- Granulation formation

- Remodeling
- Increase in tensile. strength of wound