Neuromodulation: Neuroelectric Medicine

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Conflicts of Interest

- None

- Some topics may be off label use

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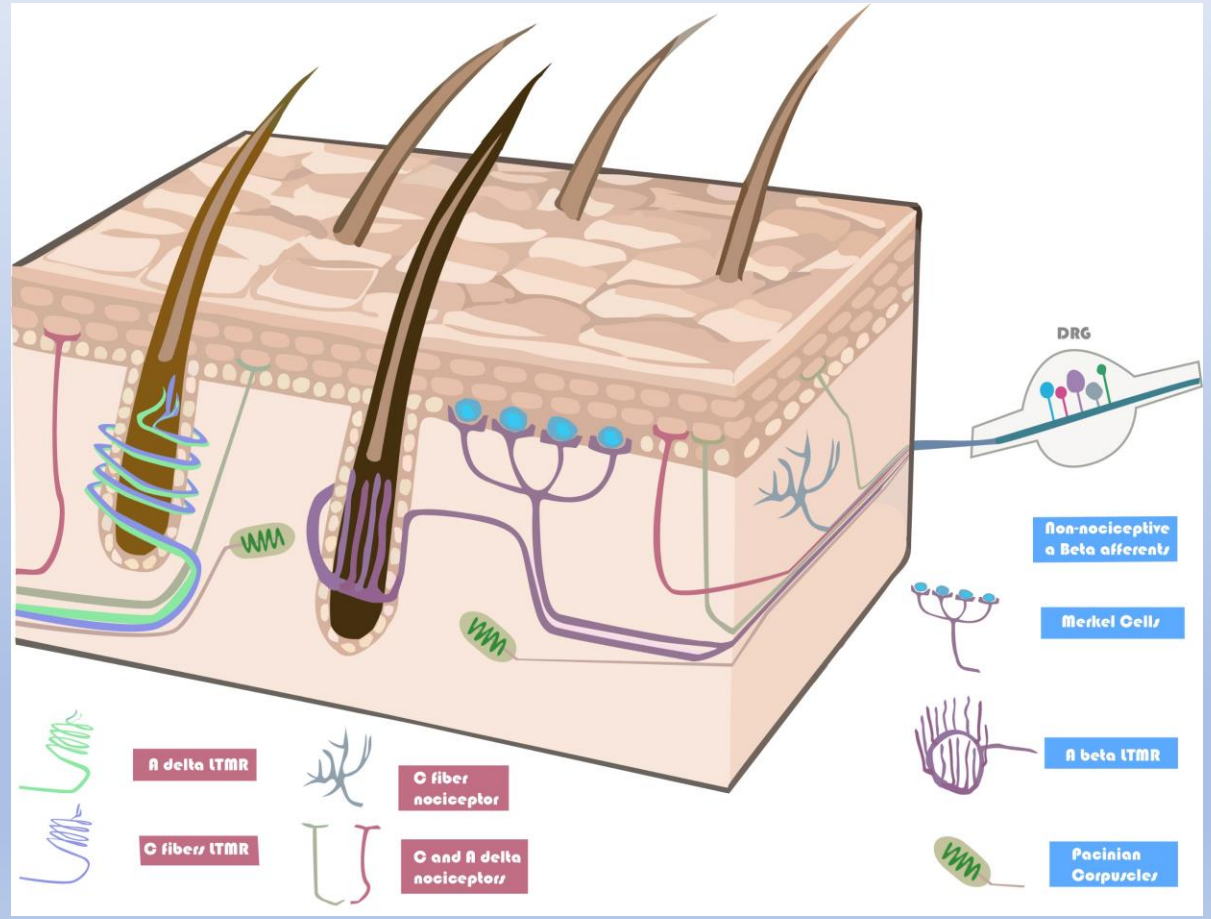
Outline

- Neuroanatomy and Neurophysiology
- How we use electrical energy to manipulate our nervous system
- Review of mechanisms
  - Tonic
  - High Frequency
  - DRG
- Use electrical energy to manipulate our nervous system

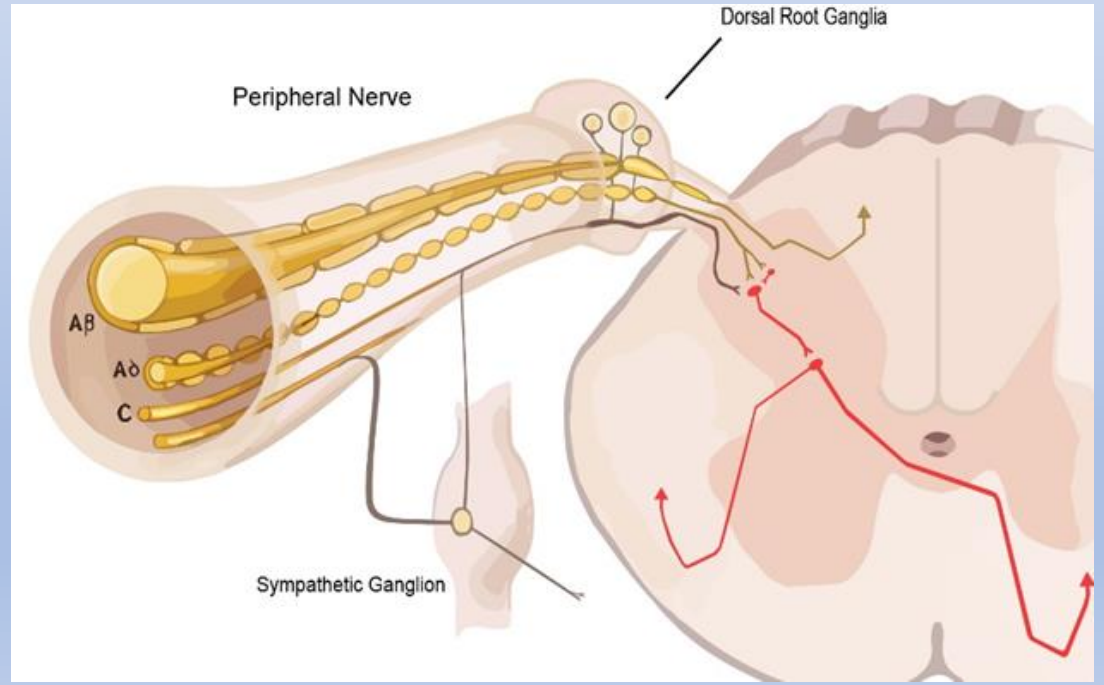
The Skin



- Most afferent fibers are A delta and C fibers from the skin
- Multiple receptors that respond to different stimuli
- Receptor threshold

Nerve Fiber Types

- Receptors with varying threshold potentials transport sensation through specialized nerve fibers

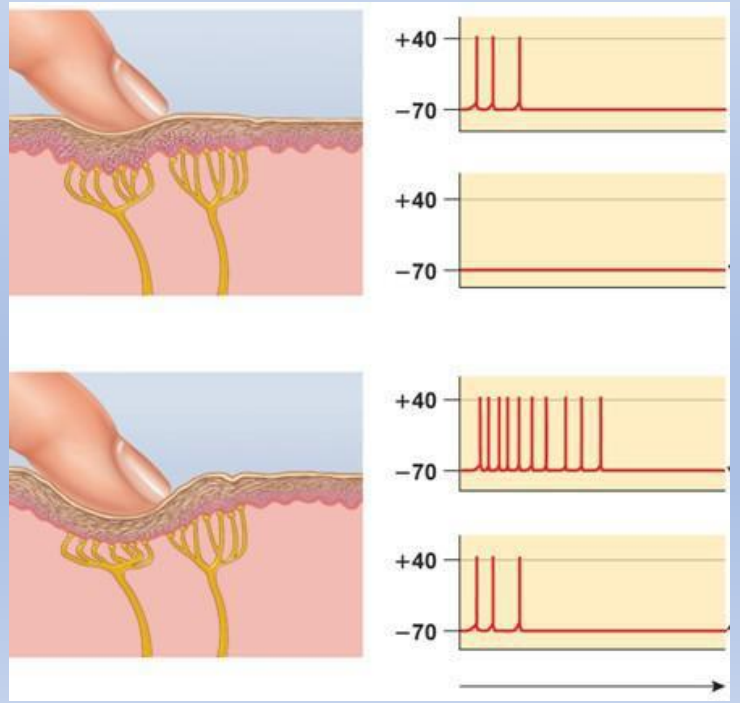


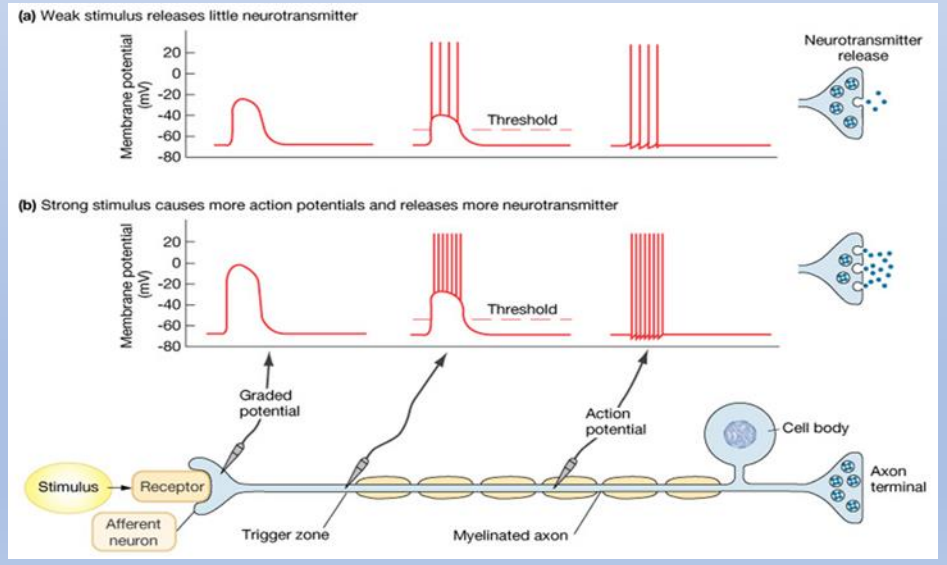
Type of Nerve Fiber	Information Carried	Myelin Sheath?	Diameter Um	Conduction Speed (m/s)
A-alpha	Propriocepti on	Myelinated	13 - 20	80 - 120
A-beta	Touch	Myelinated	6 - 12	35 - 90
A-delta	Pain (mechanical and thermal)	Myelinated	1 - 5	5 - 40
C	Pain (mechanical, thermal, and chmical)	Non-Myelinated	0.2 - 1.5	0.5 - 2

How does our nervous system 'code' sensation?

- Receptors receive input and when threshold is reached an action potential is propagated
- But how does the intensity of the signal determined?

Frequency





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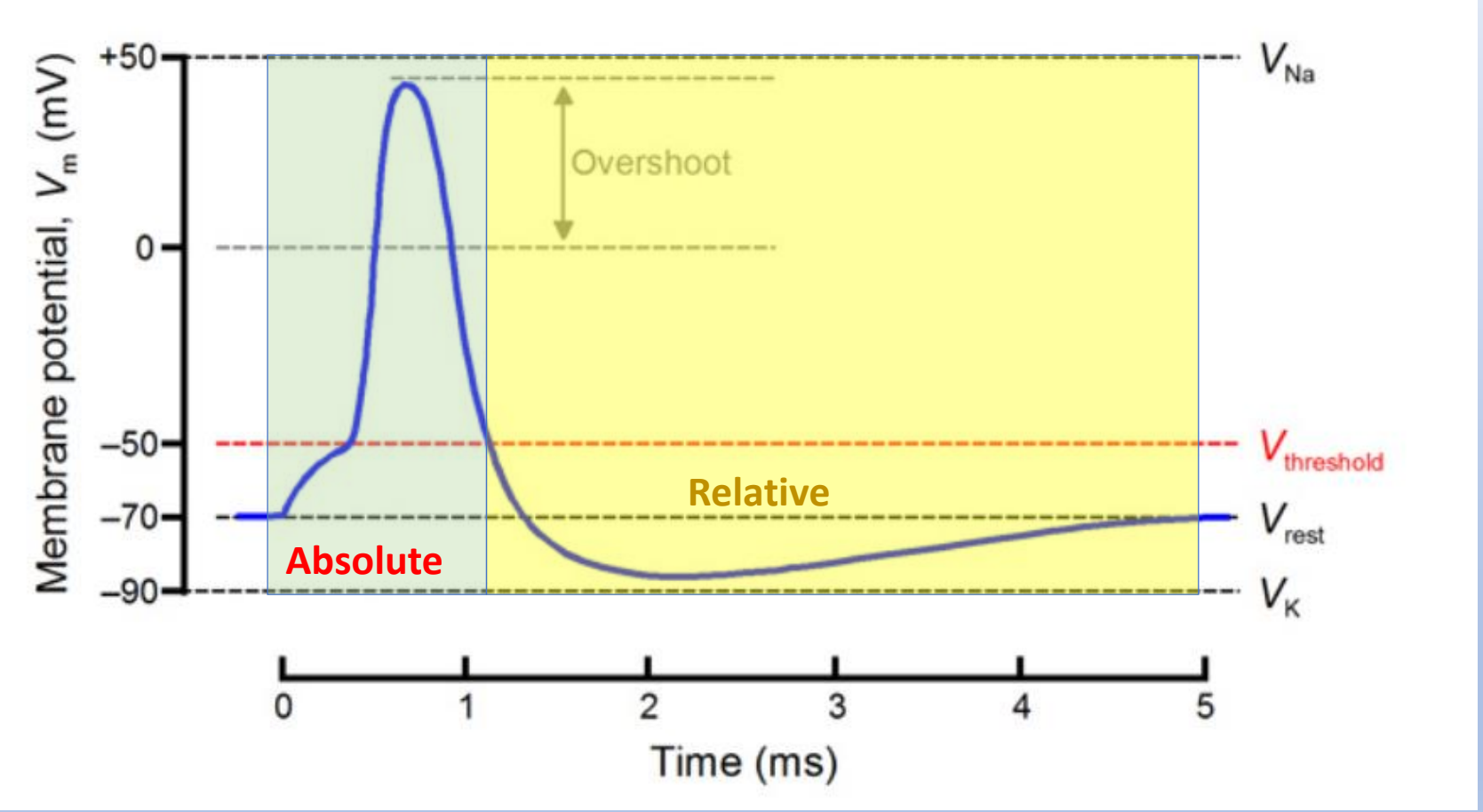
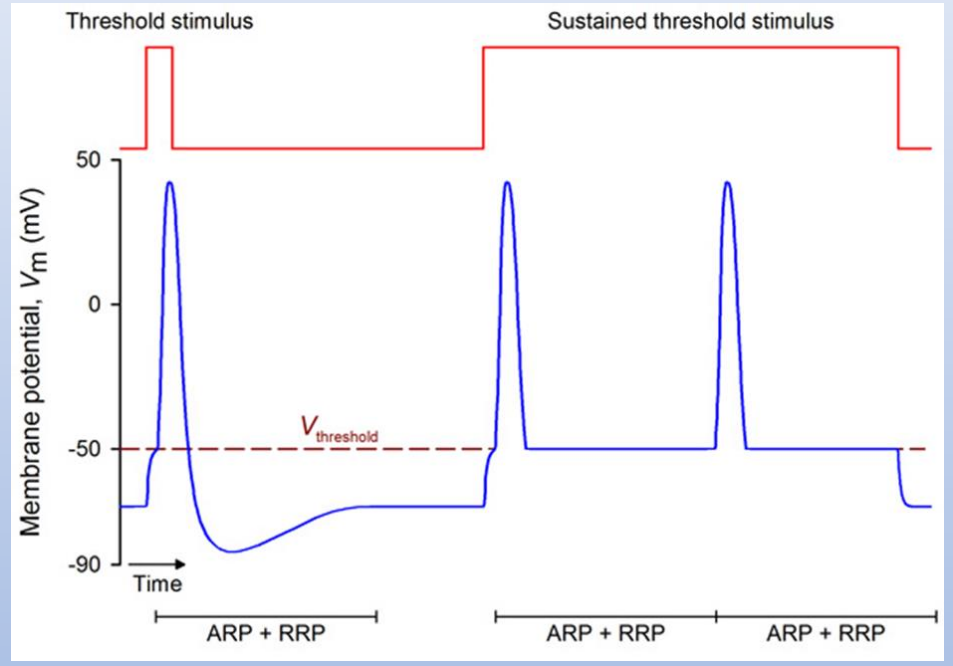
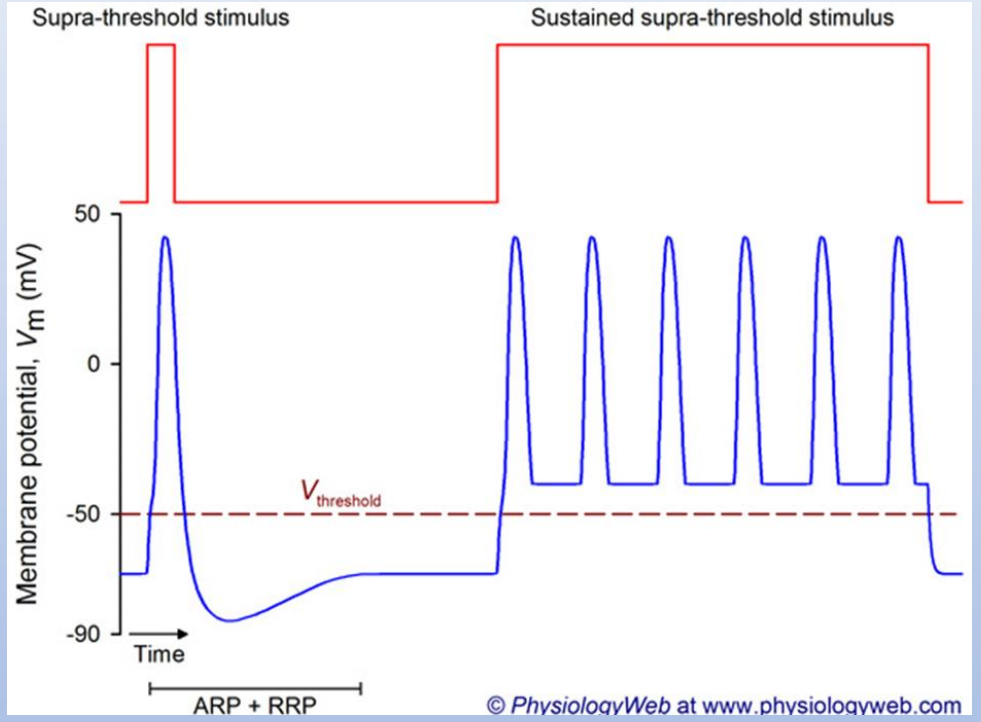
Action Potential



Stimulus coding/ Maximum activation



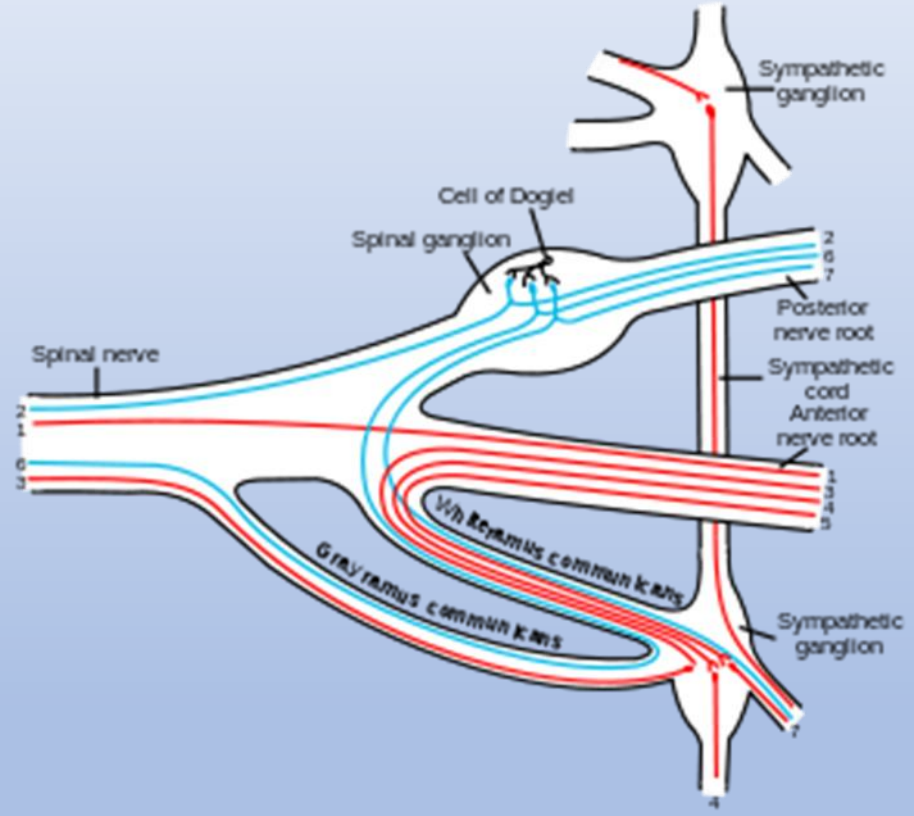


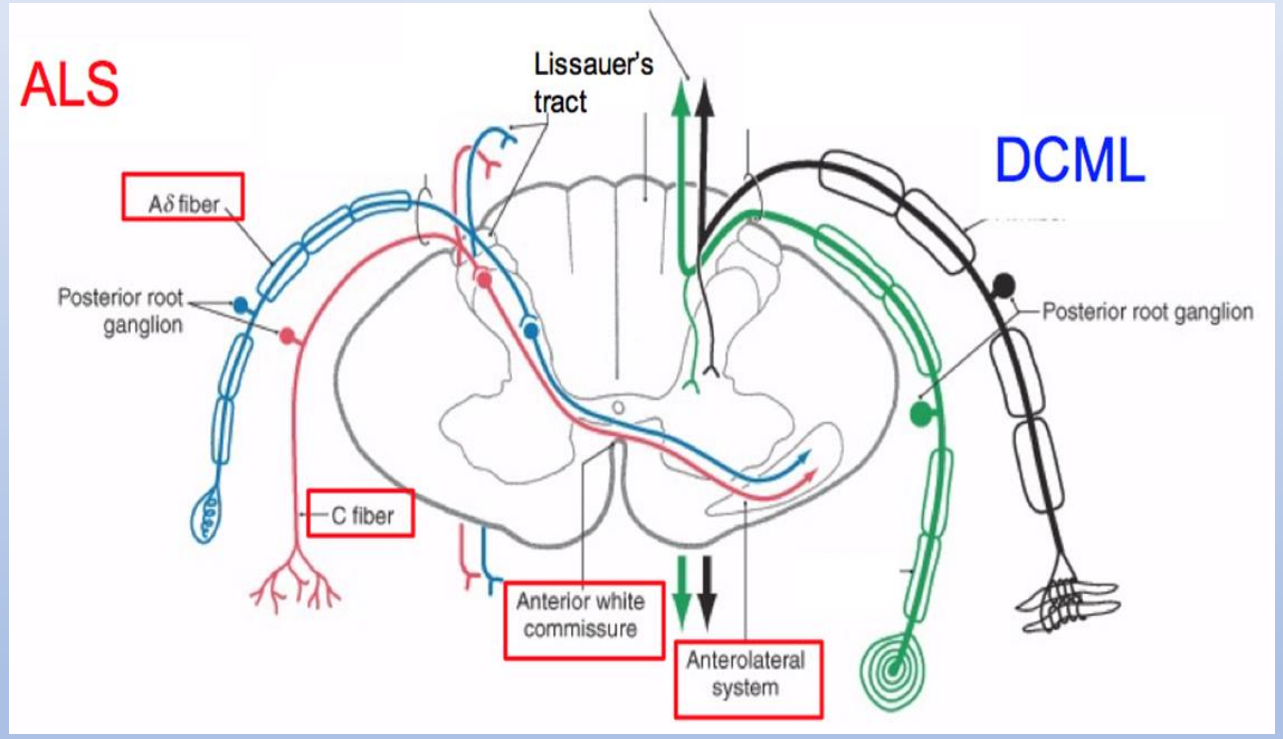
$$\frac{1\,\text{cycle}}{5\,\text{ms}} \times \frac{1000\,\text{ms}}{1\,\text{s}} = \frac{200\,\text{cycles}}{\text{s}} = 200\,\text{Hz}$$

$$\frac{1\,\text{cycle}}{2\,\text{ms}} \times \frac{1000\,\text{ms}}{1\,\text{s}} = \frac{500\,\text{cycles}}{\text{s}} = 500\,\text{Hz}$$

$$\frac{1\,\text{cycle}}{1\,\text{ms}} \times \frac{1000\,\text{ms}}{1\,\text{s}} = \frac{1000\,\text{cycles}}{\text{s}} = 1000\,\text{Hz}$$

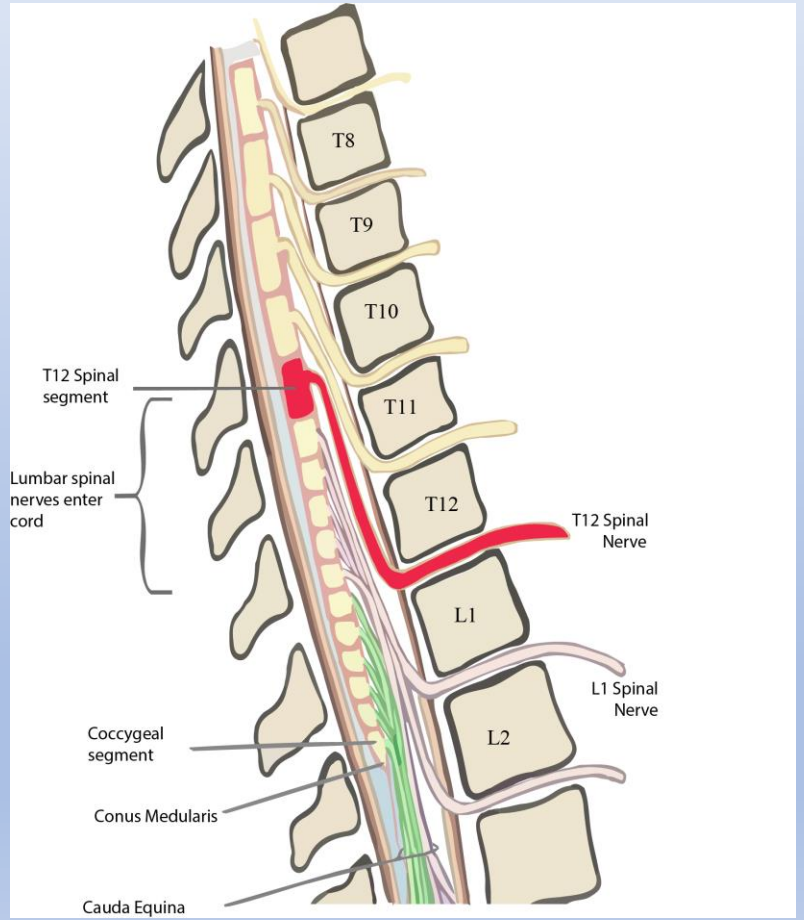
Neural Transmission

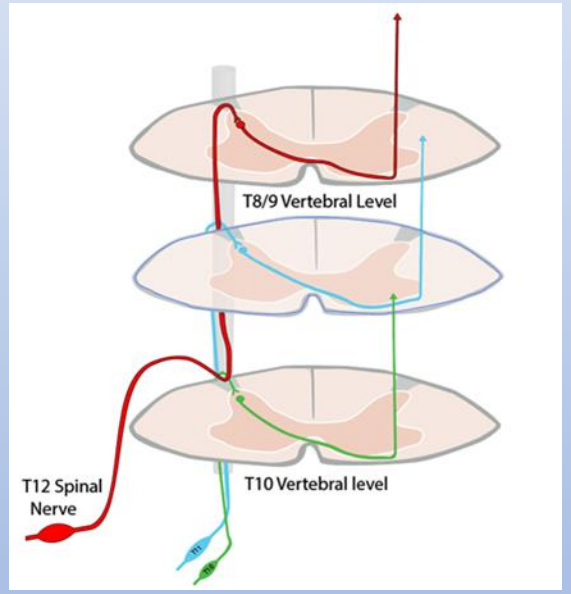




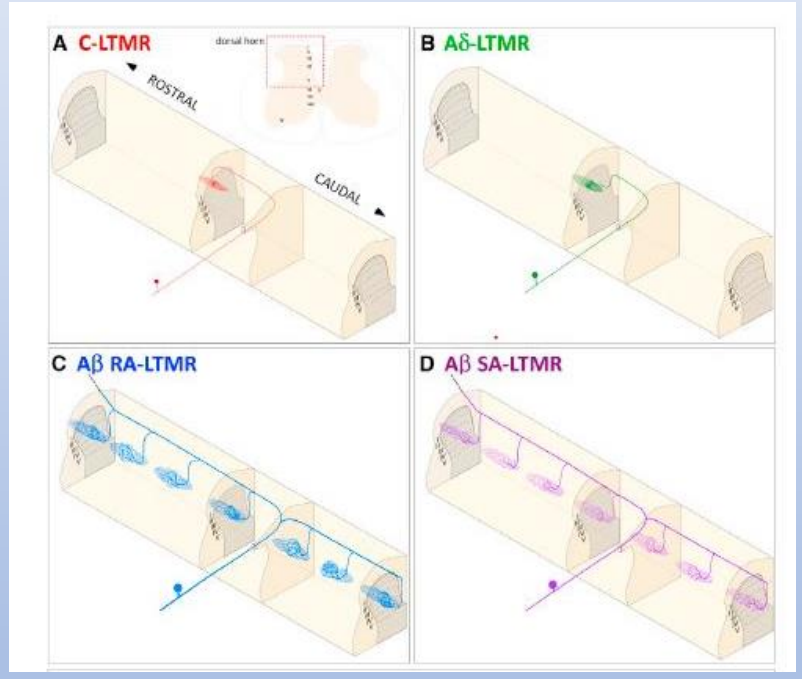
Posterior rootlet - Afferent Fibers
Anterior rootlet - Efferent Fibers

Neural Transmission





Brown Sequard Syndrome



A beta fibers enter into the Dorsal Columns with collaterals into lamina 2-3 and Lamina 5

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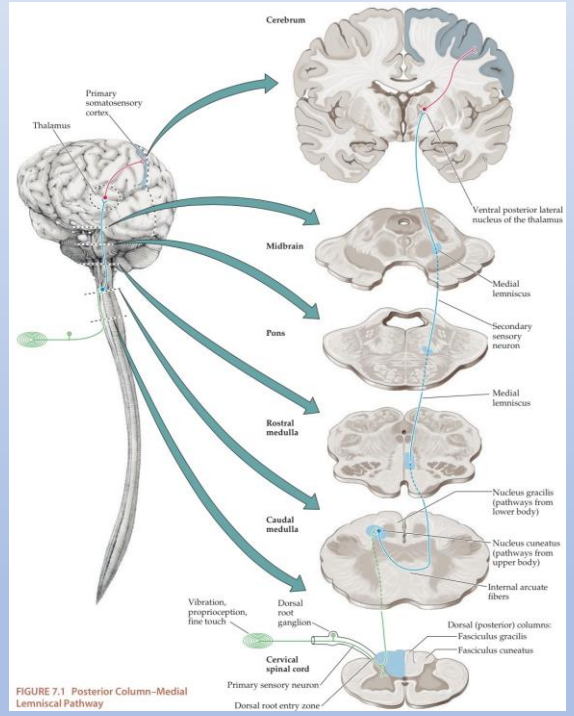
Ascending Tracts

Dorsal Column

1st Order Neuron-
- Periphery to Nucleus Cunetus and Gracilis in Medulla
- Collateral branches connect within Dorsal Horn

2nd Order Neuron-
- Medial lemniscus to VPL of Thalmus

3rd Order Neuron-
- VPL to Primary Sensory Cortext

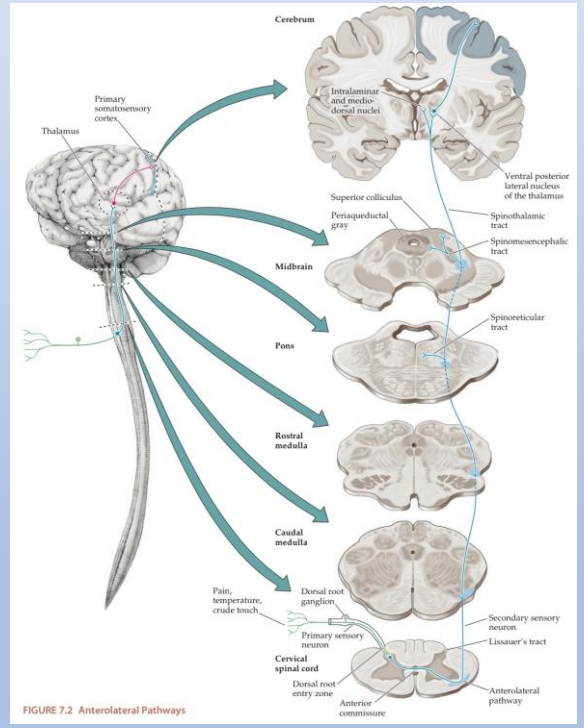


Spinothalamic Tract

1st Order Neuron-
- Periphery to DH

2nd Order Neuron-
- STT to VPL of Thalmus

3rd Order Neuron-
- VPL to Primary Sensory Cortex



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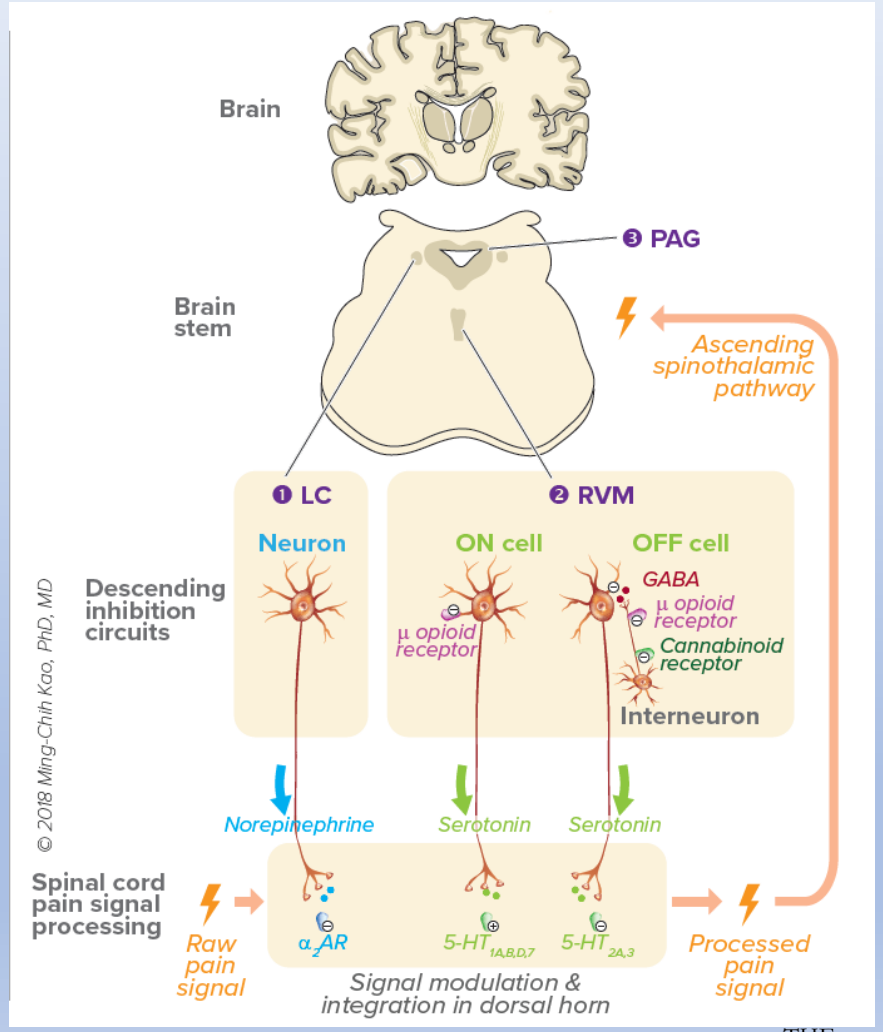
Descending Inhibition

Orthodromic effects

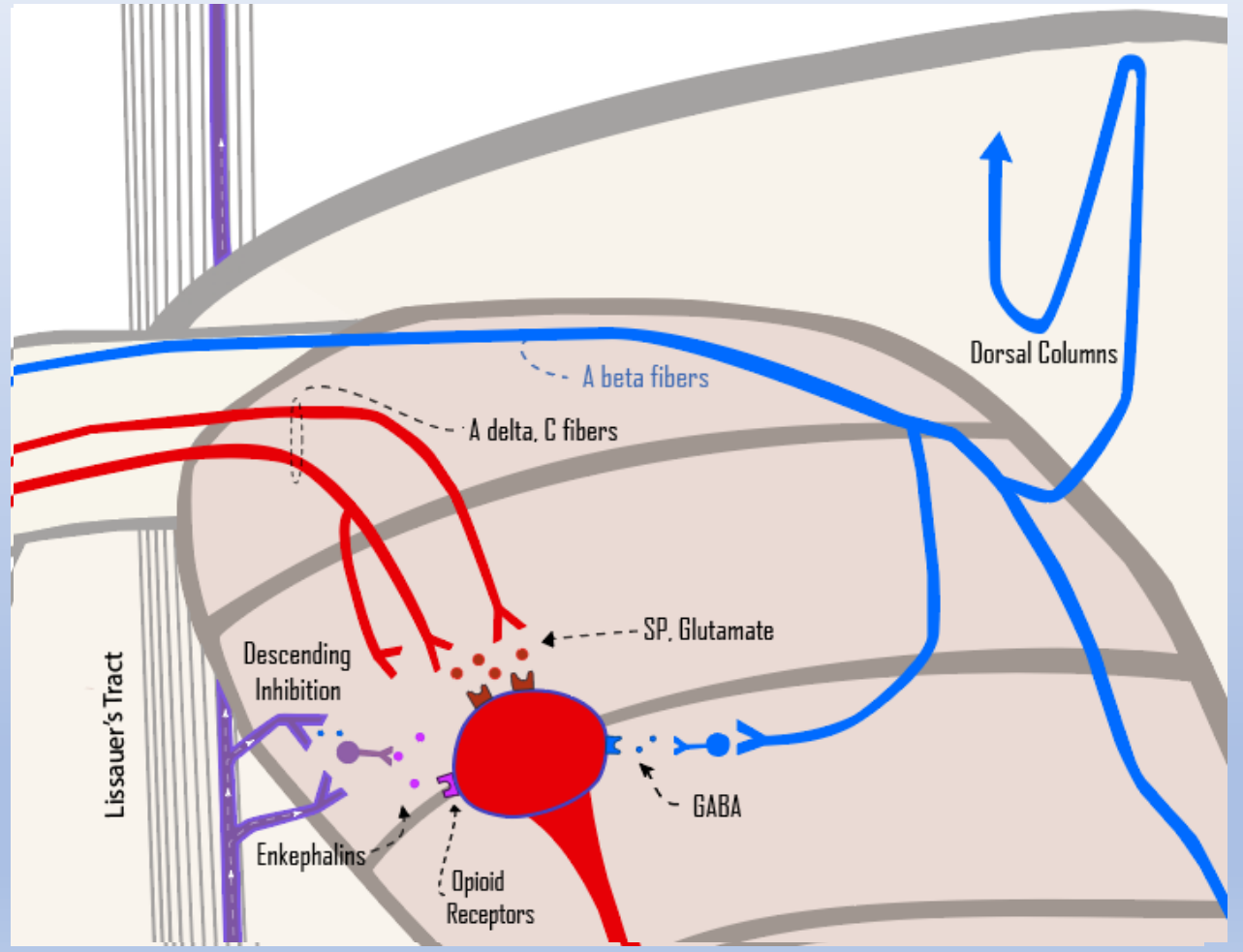
- Locus Coeruleus - NE
- Rostroventral Medulla-5-HT
- Peri-aqueductal gray
  - Integrates emotional and autonomic inputs
  - Coordinates descending inhibition
  - Opioids



Dorsal Horn Processing

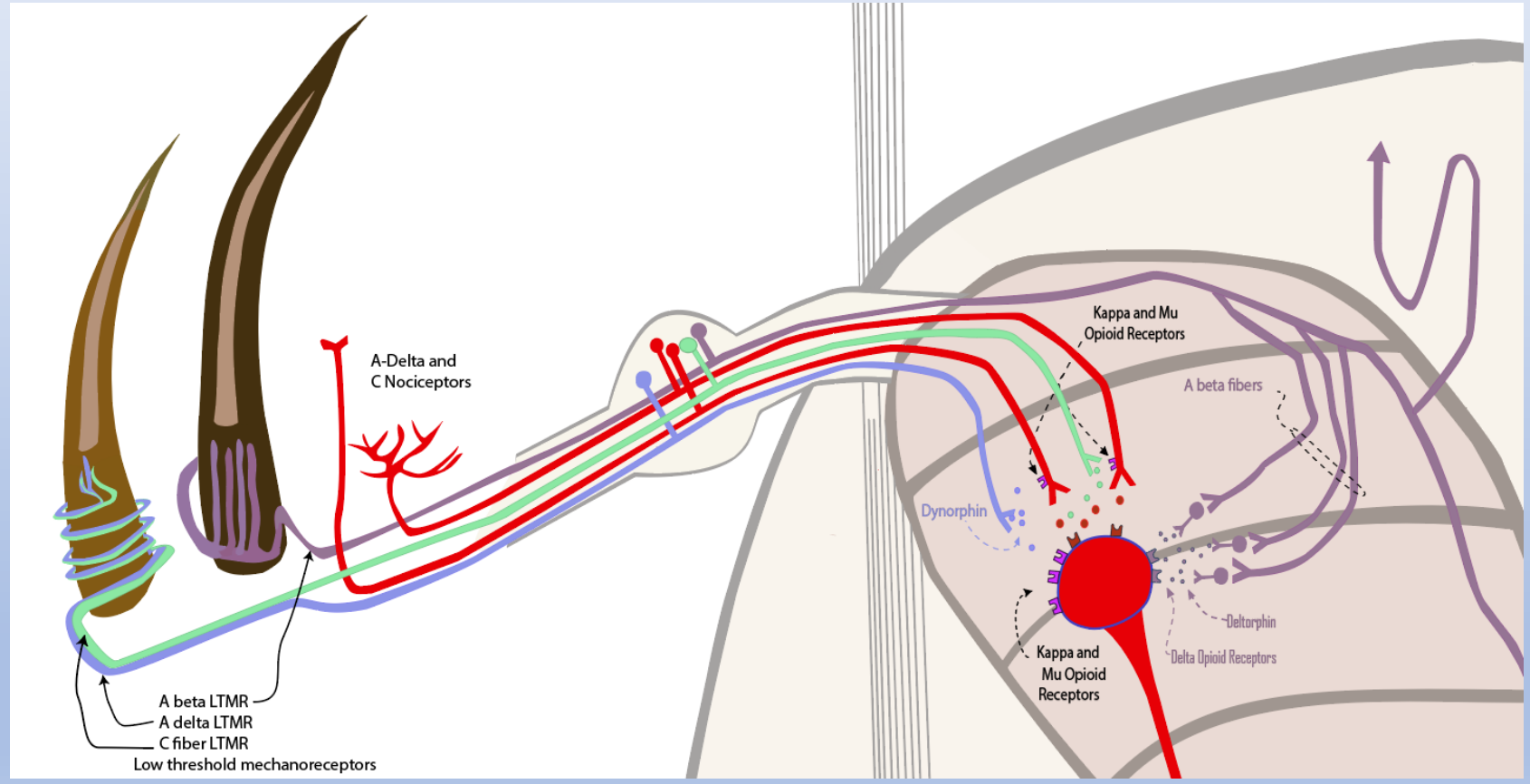
- Substance P, Glutamate excitatory neurotransmitters
- GABA, Glycine Inihibitory neurotransmitters
- Descending Inhibition
  - RVM, LC
  - Enkephalins on Opioid Receptors
  - Mechanical Pain
  - 5-HT, NE

- Medications:
  Tricyclic Medications
  Clonidine
  Opioids (Mu receptors)
  Tramadol (Mu, 5 HT, NE)
  Tapendalol



Touch/Pain and the Opioid Receptors

- Touch/Pain is a fine tuned process which is an accumulation of excitatory and inhibitory input
- Kappa, Delta, and Mu opioid receptors are pivotal in this process
- Inhibit pre- synaptically and post synaptically



Cortical Pathways

- Lateral Pathway
  - Localization of pain
- Medial Pathway-
  - Affective aspect of pain
  - Mood, affect, depression etc.

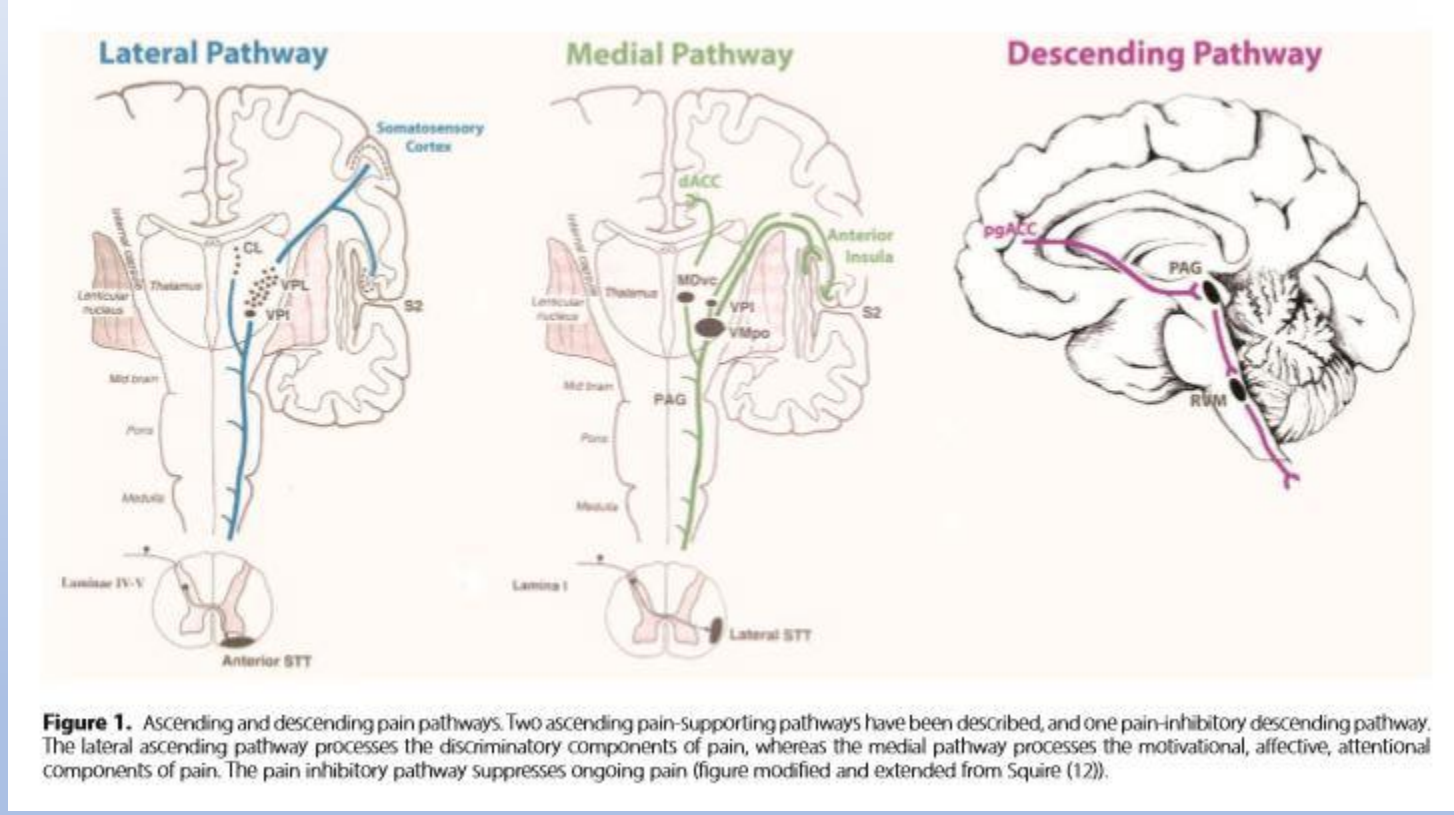


Figure 1. Ascending and descending pain pathways. Two ascending pain-supporting pathways have been described, and one pain-inhibitory descending pathway. The lateral ascending pathway processes the discriminatory components of pain, whereas the medial pathway processes the motivational, affective, attentional components of pain. The pain inhibitory pathway suppresses ongoing pain (figure modified and extended from Squire (12)).

Spinal Cord Stimulation

How does it work?

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First SCS

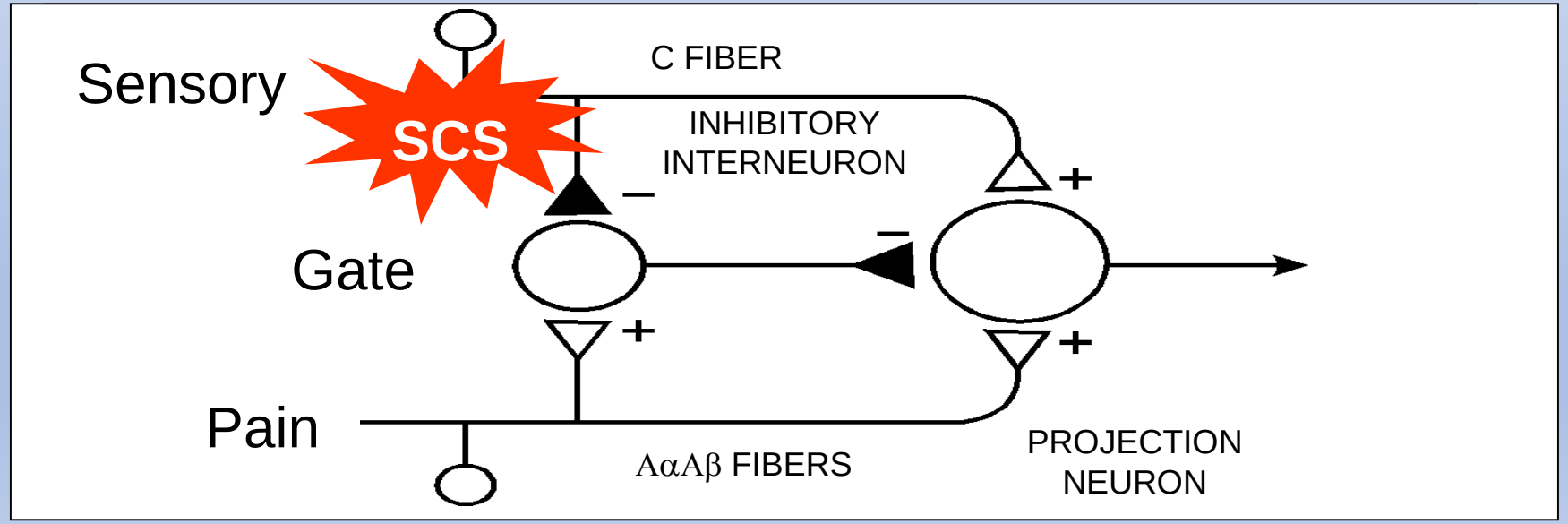
C. Norman Shealy, MD, 1967
CWRU

- Originally called DCS (dorsal column stimulator) in the mistaken belief that the primary stimulation was of the dorsal columns
  - His paper was turned down by Journal of Neurosurgery
- Barolat introduced the term Spinal Cord Stimulation (SCS) in 1999

Shealy CN, Mortimer JT, Reswick JB. **Electrical inhibition of pain by stimulation of the dorsal columns. Preliminary clinical report**. *Anesth Analg (Cleve)* 1967;46:489–91

Gate Control Theory

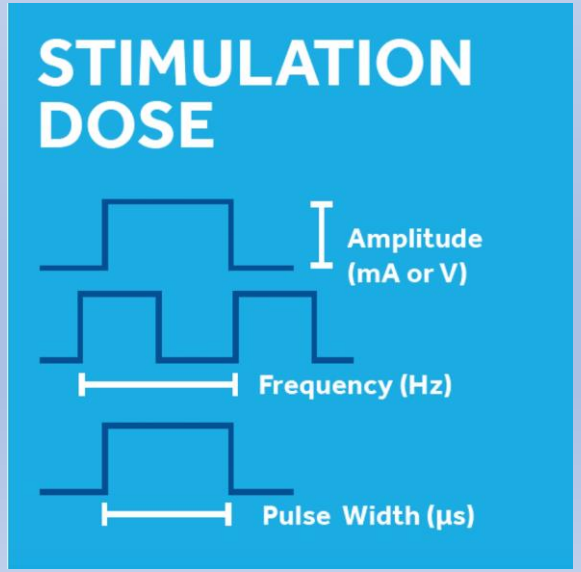
- When sensory impulses are greater than pain impulses
- “Gate” in the spinal cord closes preventing the pain signal from reaching the brain

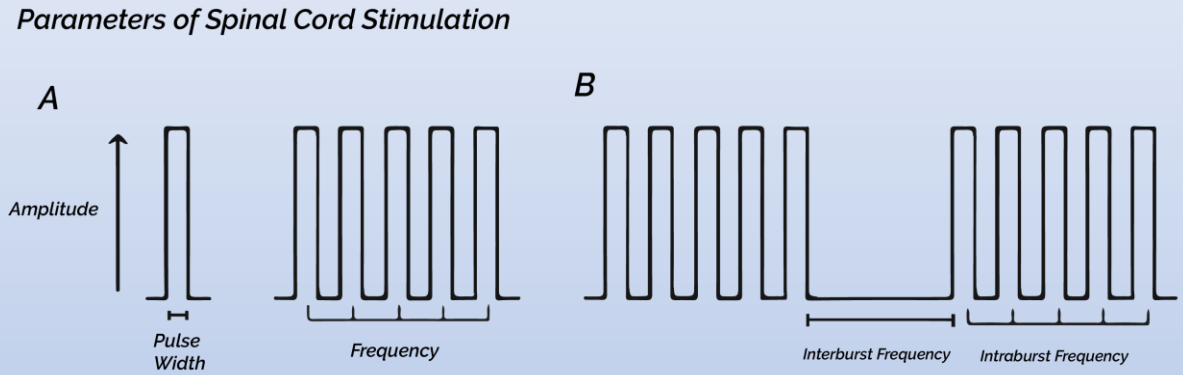


Melzack and Wall, 1968

What are basics of SCS

- Frequency (Hz)
- Pulse width (us)
- Amplitude(mA or V)





Terminology

- Pulse = Amplitude, Frequency, and waveform
- Charge= Amplitude x PW
- Charge/S= Amplitude x PW x Frequency

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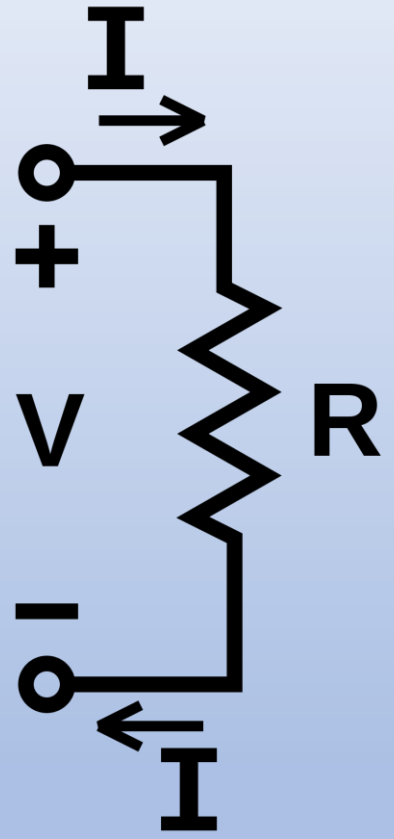
Ohm's Law

- **<u>Voltage-controlled (VC) systems:</u>** Voltage (V) is fixed; variations in impedance (R) cause a change in current.

- **<u>Current-controlled (CC) systems:</u>** the current (I) is set; variations in impedance(R) cause a change in voltage.

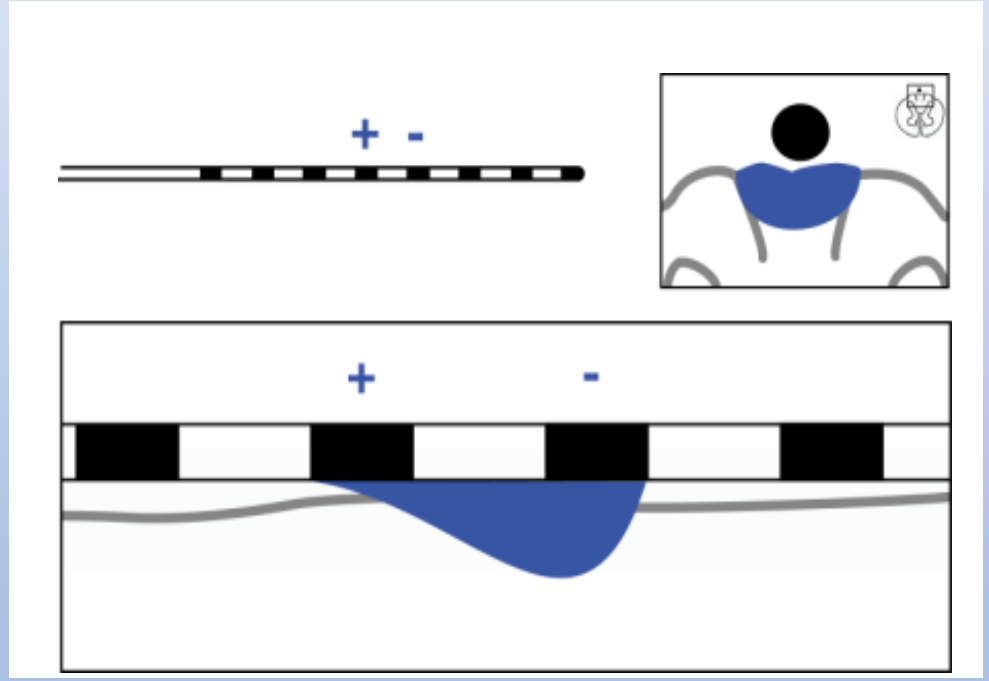


V=IR

Miller et al., 2016; Schade et al., 2010

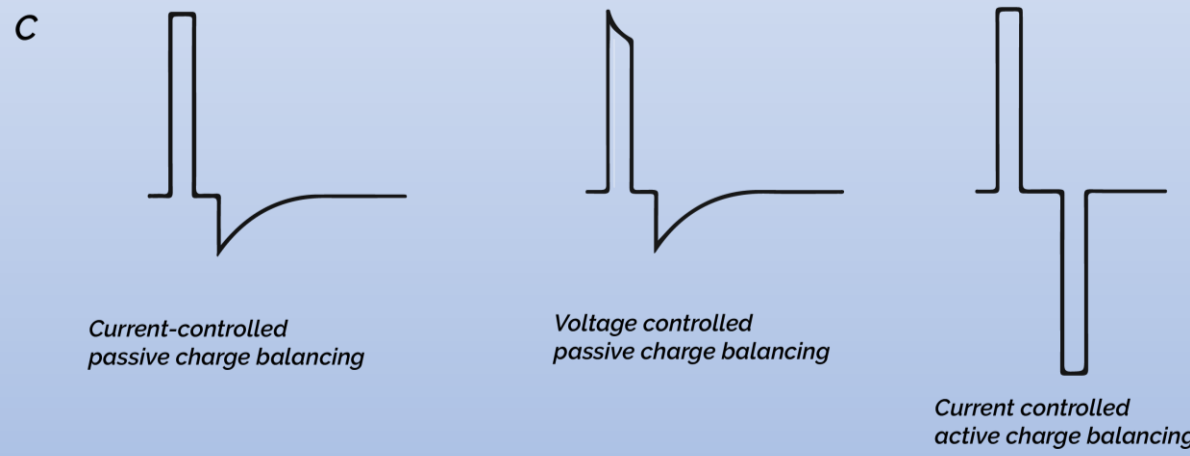
Electrophysiologic Mechanisms of SCS

- Current flows from Cathode (-) to Anode (+) resulting in neuronal depolarization at Cathode (-) and hyperpolarization at Anode (+)
- Electrical parameters are adjusted during programming including electrode polarity, Frequency (Hz), Amplitude (V or ma), and Pulse Width (µs)
- Potential segmental conductance blockade of spinothalamic tracts

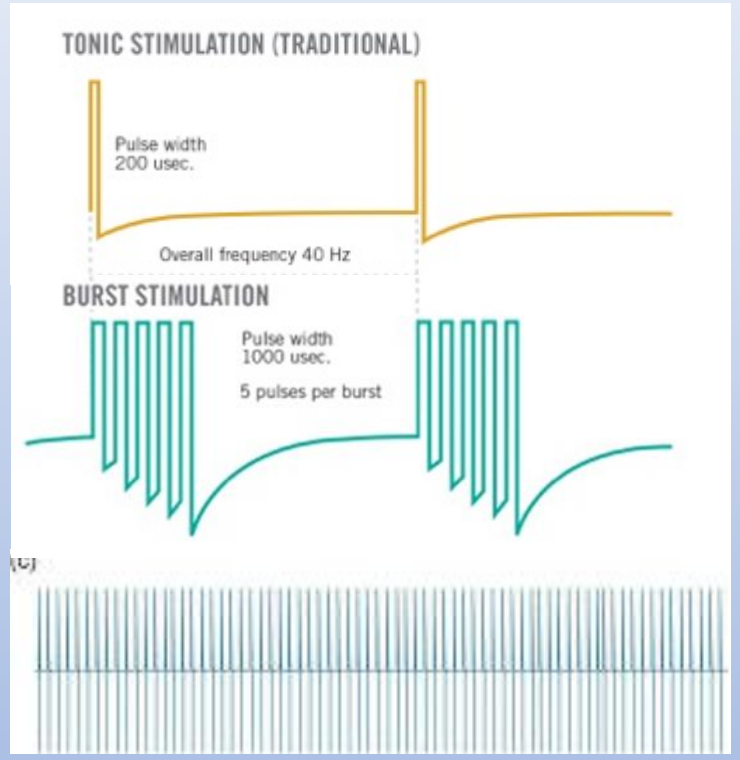


Charge Balance

- Active Charge Balance: Symmetric, biphasic pulse.
- Passive Charge Balance: Asymmetric pulse.
- In either Charge Balance strategy: the initial pulse is followed by equal and opposite current movement to return the net charge to baseline; this avoids buildup of charge in the tissue, which may lead to injury if allowed to accumulate.



Waveforms



- Recurrent Electrical Impulse delivered at certain parameters
- PARESTHESIA Dependent
- A variation of tonic stimulation:
- Amplitude is 60% threshold = NO PARESTHESIA
- High Frequency >1200 Hz
- 10K
- NO PARESTHESIA

	Frequency	Pulse width	Amplitude
Tonic	50 Hz	500 us	3.0-4.0 mA
Burst	40Hz	140-300 us	60% threshold
HF	10,000Hz	30 us	2.2 mA

Tonic Stimulation

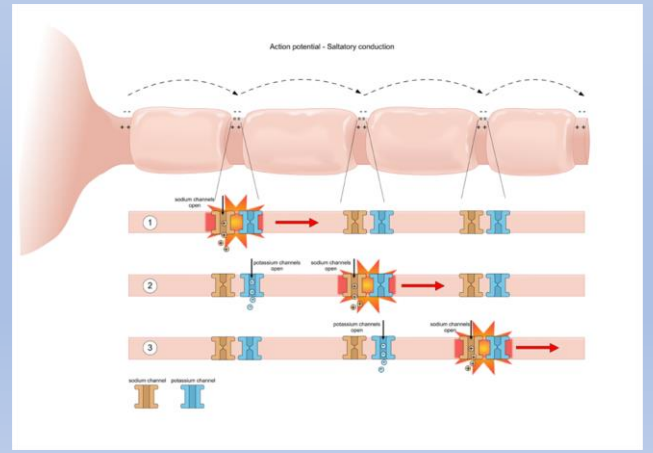
- 1967-present
- Improvements in electrode configuration
- Improvements in IPG design and battery life
- Better coverage of the low back
- ‘The 50/50 club’

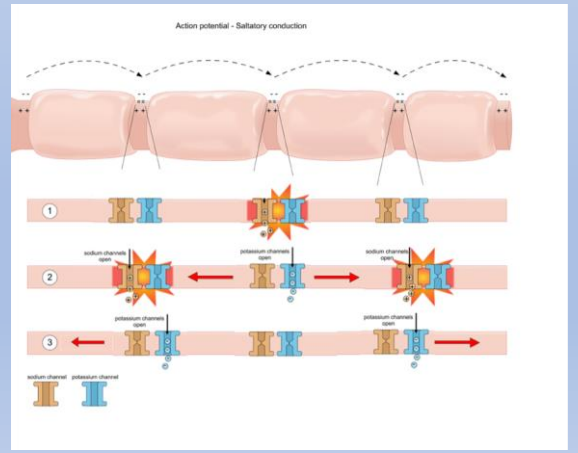
How does Tonic SCS work?

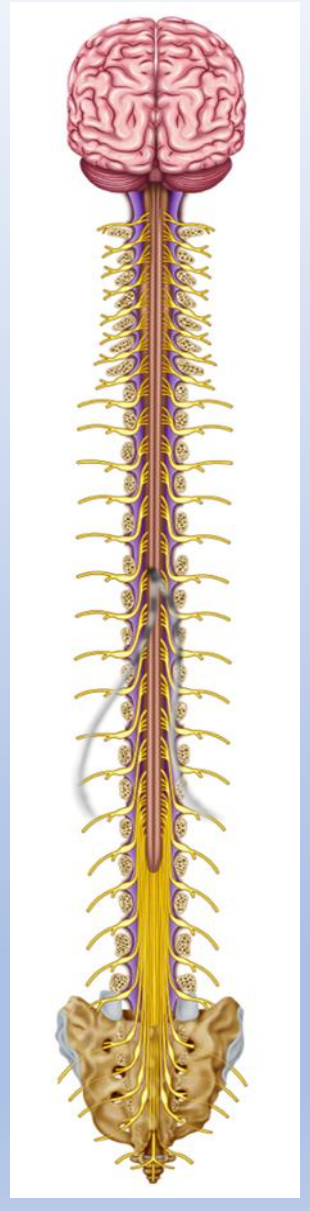
What are the currently accepted MOA's?

- 1. **Orthodromic**
  - Ab-fibers directly projecting to the Dorsal Column Nuclei and then further connected to the periaqueductal gray and the thalamus.

- 2. **Antidromic**
  - A beta collaterals activate interneurons to inhibit wide dynamic range (WDR) neurons in the dorsal horn.







West & Wolstencroft, 1983; Holsheimer, 2002.

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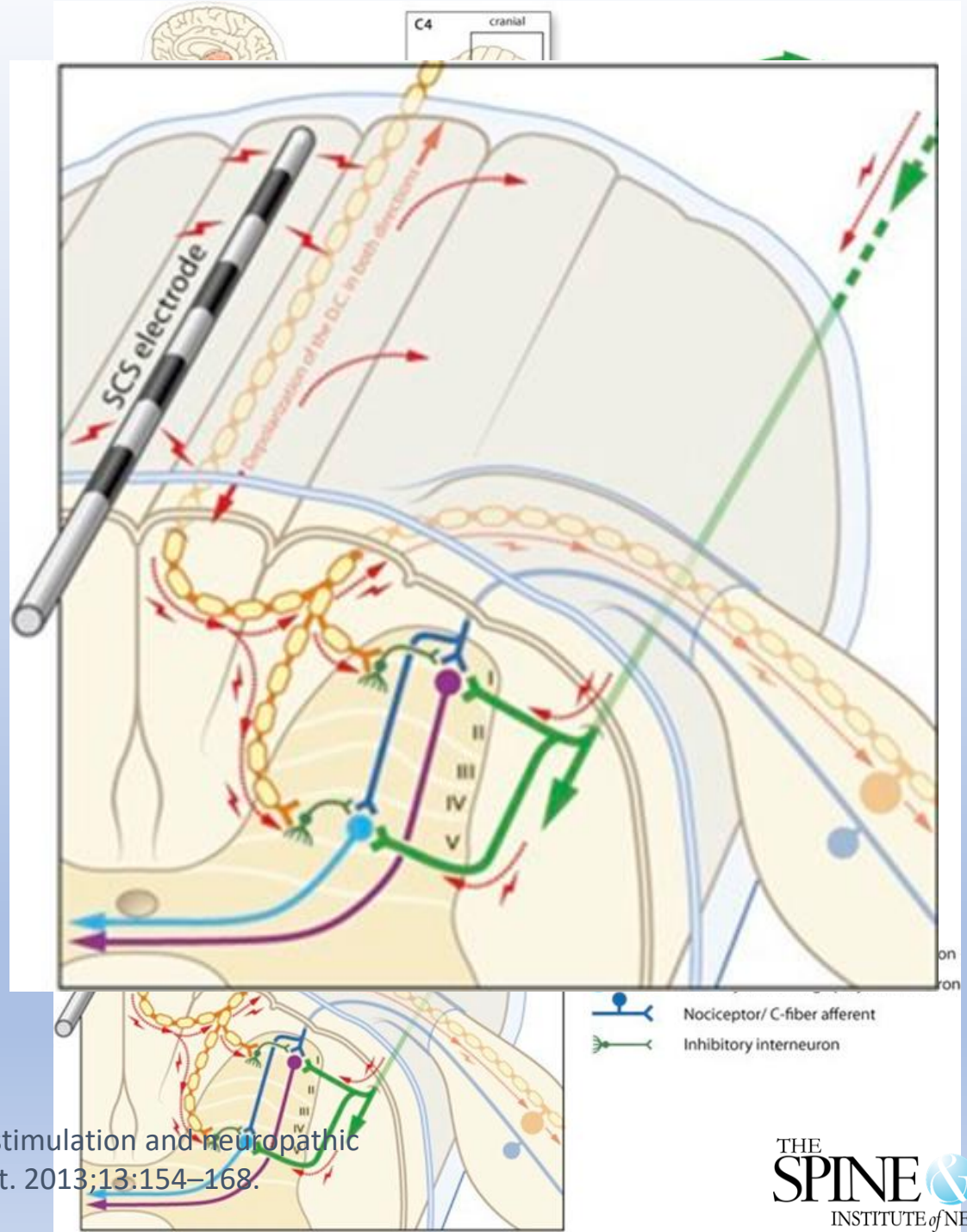
Segmental Mechanism of Action

-Orthodromic effects

-Antidromic effects

- Gate Control Theory
- A-beta fibers
- Deep Layers in DH
- Pain fibers superficial DH



Smits H, van Kleef M, Holsheimer J, Joosten EA. Experimental spinal cord stimulation and neuropathic pain: mechanism of action, technical aspects, and effectiveness. Pain Pract. 2013;13:154–168.

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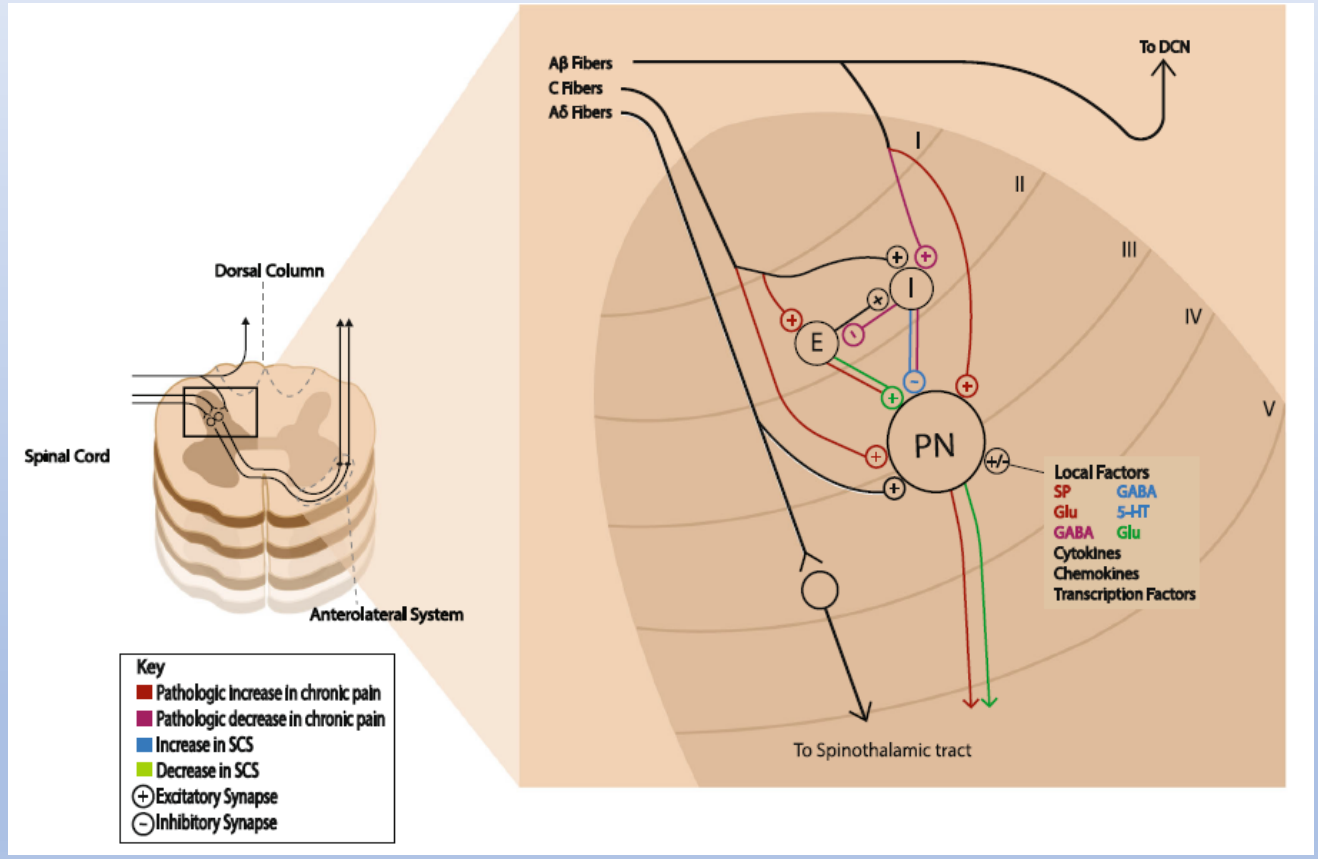
Mechanism of tonic, paresthesia based SCS

Antidromic- Within the DH

- Increased GABA
- Decrease in glutamate
  - via presynaptic GABA inhibition is critical to improvement in allodynic rat models

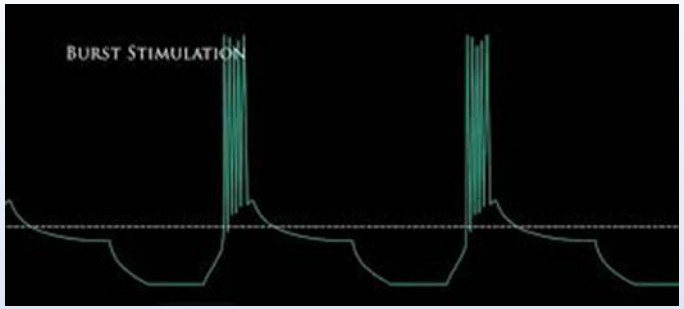
Orthodromic- Supraspinal mechanisms

- Descending inhibition activated
- Increased Seratonin and NE in DH



Yakhnitsa et al., 1999; Cui et al., 1996; Stiller et al., 1995
Caylor et al. Spinal cord stimulation in chronic pain: evidence and theory for mechanism of action. Bioelectric Medicine 2019

Burst DR

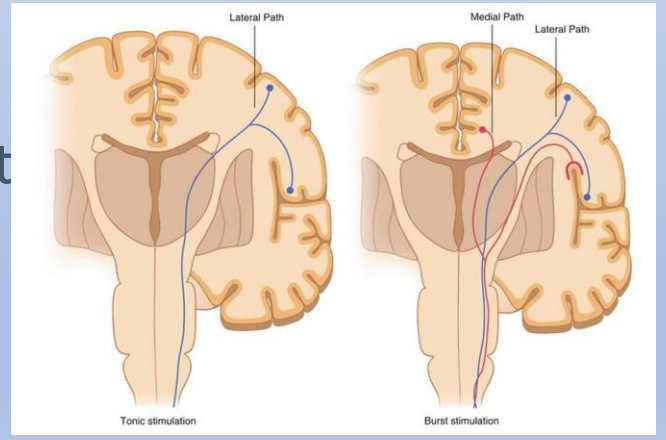


- A variation of tonic stimulation that is paresthesia free

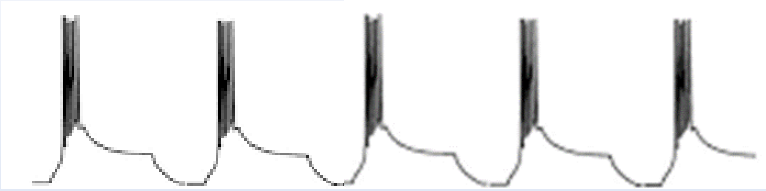
	Frequency	Pulse width	Amplitude	Delivered Pulse Frequency	Burst Pulse width
Tonic	50 Hz	500 us	3.0-4.0 mA		
Burst	40Hz	140-300 us	60% threshold	500HZ	1 ms

Potential Mechanisms of Action:

- More natural means of stimulating neurons
- Different neurochemical pathways in the dorsal horn (not
- Testing does not show activity in dorsal column nuclei
- Potentially working at locations that tonic SCS does not
- Supraspinal mechanisms- Medial vs Lateral Pathway



Crosby, N.D., et al., *Burst and Tonic Spinal Cord Stimulation Differentially Activate GABAergic Mechanisms to Attenuate Pain in a Rat Model of Cervical Radiculopathy.* IEEE Trans Biomed Eng, 2015. **62**(6): p. 1604-13.
Tang, R., et al., *Comparison of burst and tonic spinal cord stimulation on spinal neuralprocessing in an animal model.* Neuromodulation, 2014. **17**(2): p. 143-51.



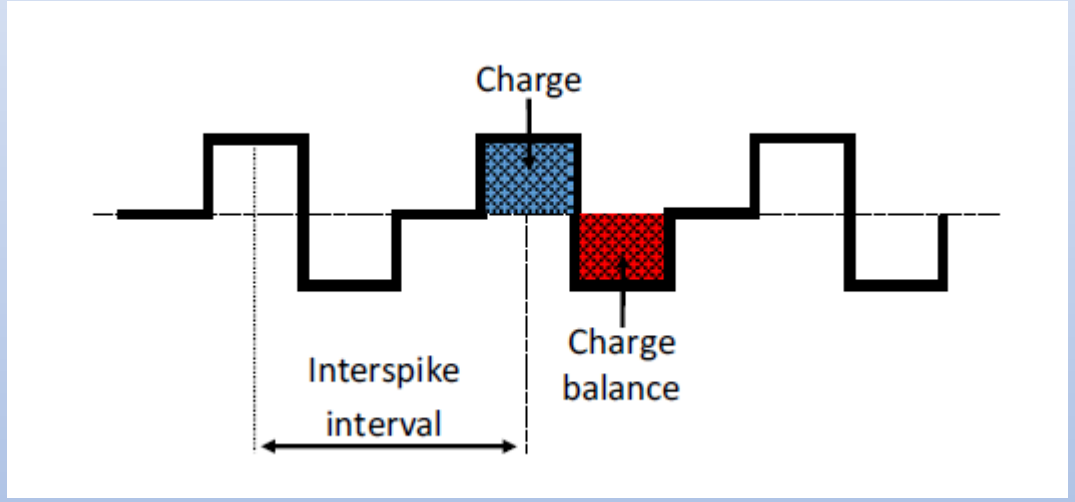
Burst DR vs Burst

Burst DR

- Passive charge balance
- Axon given 1ms to balance membrane through cellular mechanisms

Burst

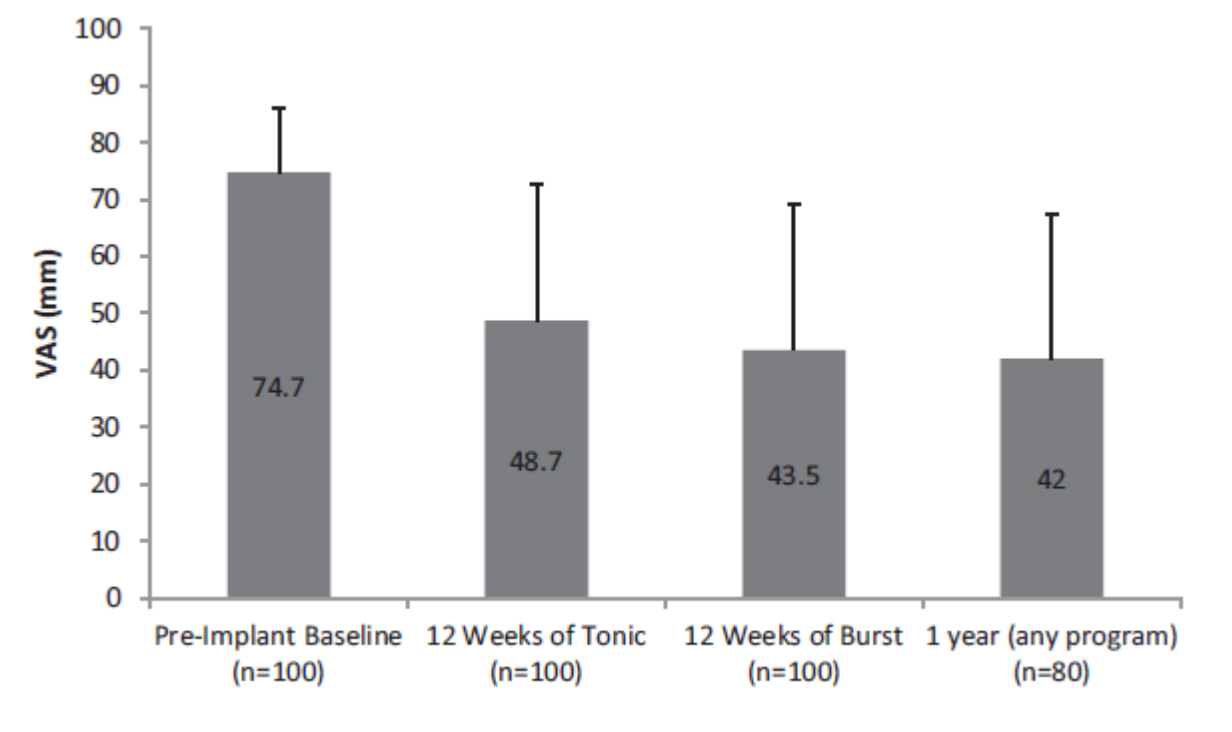
- Other systems do not allow passive recharge
- Active charge balance by flipping anode and cathode



Is there a difference?

Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective,Randomized Controlled Trial Using a Novel Burst Waveform
Deer T, Slavin K, Amirdelfan K, North R, Burton A, Tearwood T, Tavel E, Staats P, Faloqwski S, Pope J, Justiz R, Fabi A, Taghva A, Paicius R, Houden T, Wilson D

Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective,Randomized Controlled Trial Using a Novel Burst Waveform



Minimal Change in VAS Burst vs Tonic
Patients preferred subthreshold, paresthesia free stimulation

Patients preferred paresthesia free

- Deer et. al. **Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform.** Neuromodulation. 2018 Jan;21(1):56-66. doi: 10.1111/ner.12698. Epub 2017 Sep 29.

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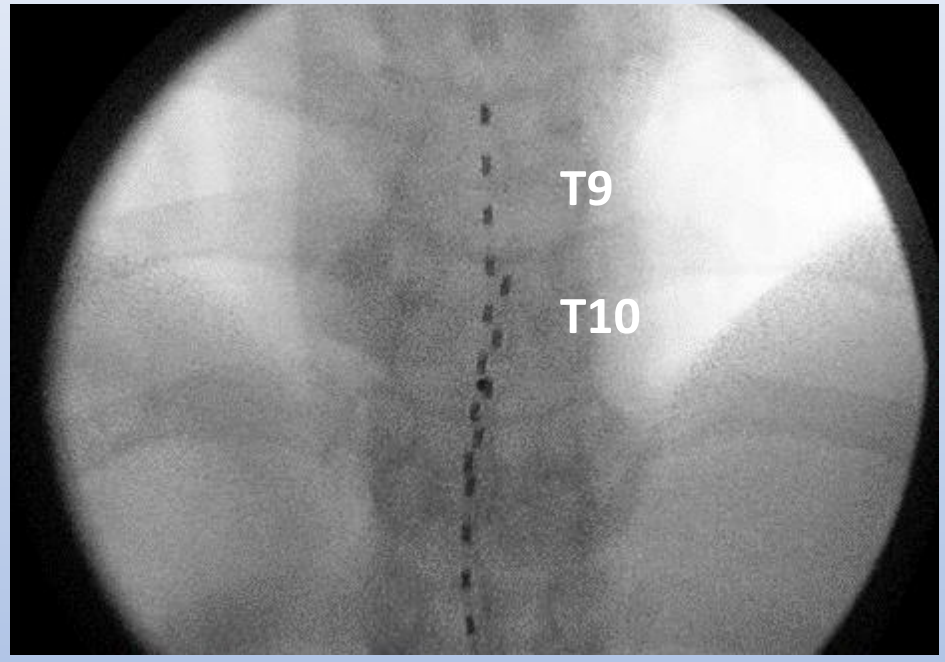
High Frequency Stimulation (HF-10 SCS)

- Sweet Spot T9-10
- Proprietary algorithm
- Paresthesia Free



HF-10 SCS

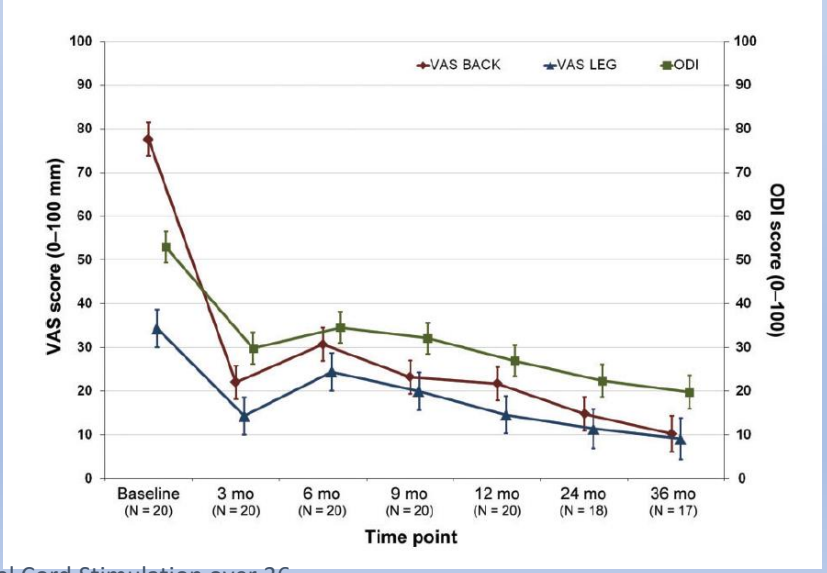
Senza Study

- 198 pts HF-10 vs SCS
- 93% trial to implant
- Low back HF-10 VAS 7.8 to 2.4
- Disability improvements and satisfaction HF>scs

- 3 months:
  - HF
    - 84.5% for back pain
    - 83.1% for leg pain
  - Tonic
    - 43.8% for back pain
    - 55.5% for leg pain
- 24-months
  - HF
    - 76.5% for back pain
    - 72.9% for leg pain
  - Tonic
    - 49.3% for back pain
    - 49.3% for leg pain

10 K for No previous spine surgery

- Pain intensity measured on an average VAS decreased from a baseline of 7.9 to 1.1 at 36 months



Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36 Months. Al-Kaisy, A, Palmisani S, Smith T, Carganillo R, Houghton R, Pang D, Burgoyne W, Lam K, Lucas J

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HF-10 SCS

- Multiple studies proving good evidence and efficacy

High frequency (10 kHz) or burst spinal cord stimulation in failed back surgery syndrome patients with predominant back pain: preliminary data from a prospective observational study. Kinfe TM, Pintea B, Link C, et al. Neuromodulation. 2016;19:268–275.

Long-term improvements in chronic axial low back pain patients without previous spinal surgery: a cohort analysis of 10-kHz highfrequency spinal cord stimulation over 36 months. Al-Kaisy A, Palmisani S, Smith TE, et al.

High frequency spinal cord stimulation at 10 kHz for the treatment of chronic pain: 6-month Australian clinical experience. Russo M, Verrills P, Mitchell B, Salmon J, Barnard A, Santarelli D. Pain Physician. 2016;19:267–280

High-frequency spinal cord stimulation. Rapcan R, Mlaka J, Venglarcik M, Vinklerova V, Gajdos M, Illes R. Bratisl Lek Listy. 2015;116:354–356.

10 kHz cervical SCS for chronic neck and upper limb pain: 12 months' results. El Majdoub F, Neudorfer C, Richter R, Schieferdecker S, Maarouf M. Annals of Clinical and Translational Neurology. Sept 2019 doi:10.1002/acn3.50915

HF-10 SCS

- PROCO study
  - RCT demonstrating equivalent pain relief with SCS at 1, 4, 7 and 10 KHz SCS
- FBSS HF vs SCS
  - 55 patients 1 year follow up
  - No difference in outcomes
- Anectodal Clinical Experience not entirely consistent with published industry funded data
- High energy output on spinal cord
- Typically requires daily recharging

Thomson SJ, Tavakkolizadeh M, Love-Jones S, Patel NK, Gu JW, Bains A, Doan Q, Moffitt M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation. 2018 Jan;21(1):67-76

De Andres J, Monsalve-Dolz V, Fabregat-Cid G, et al. Prospective, randomized blind effect-on-outcome study of conventional vs high-frequency spinal cord stimulation in patients with pain and disability due to failed back surgery syndrome. Pain Med. 2017;18Zannou AL, Khadka N, Truong DQ, Zhang T, Esteller R, Hershey B, Bikson M. Temperature increases by kilohertz frequency spinal cord stimulation. Brain Stimul. 2019;12(1):62–72.

HF-10 SCS

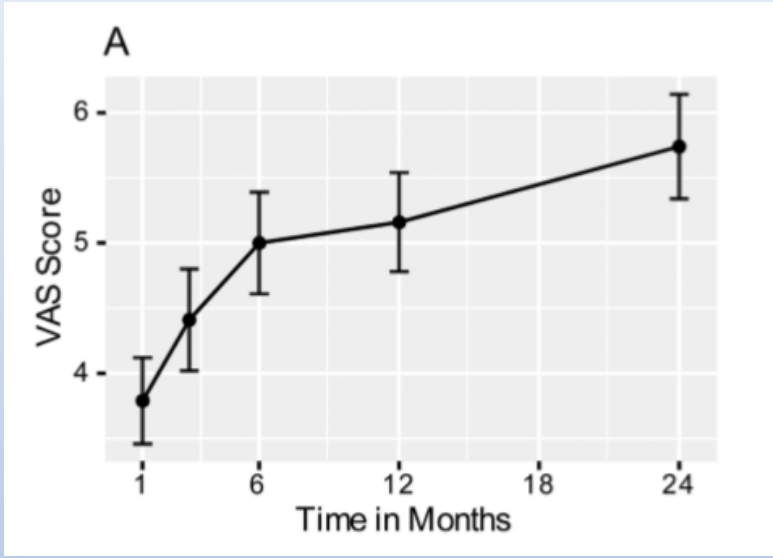
- Not through Conduction block on spinal cord
  - 10K on peripheral nerve → conduction block
- Several ‘working hypotheses’ have been proposed via animal and computational models that include
  - Wide dynamic range (WDR) neuron modulation
  - Dorsal horn fiber recruitment
  - Local depolarization blockade

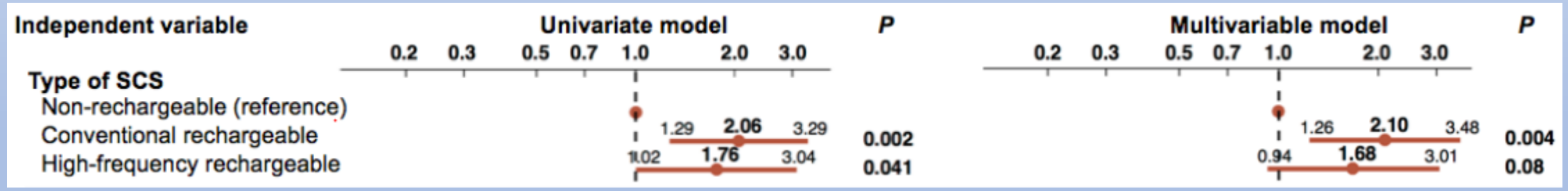
Kilgore KL, Bhadra N. Nerve conduction block utilizing high-frequency alternating current. Med Biol Eng Comput. 2004;42:394–406.
Lempka SF, McIntyre CC, Kilgore KL, Machado AG. Computational analysis of kilohertz frequency spinal cord stimulation for chronic pain management. Anesthesiology. 2015;122:1362–1376.
Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation. 2014;17:226–234.
Crosby ND, Janik JJ, Grill WM. Modulation of activity and conduction in single dorsal column axons by kilohertz-frequency spinal cord stimulation. J Neurophysiol.2017;117:136–147.

Loss of Efficacy

- No predictive factors

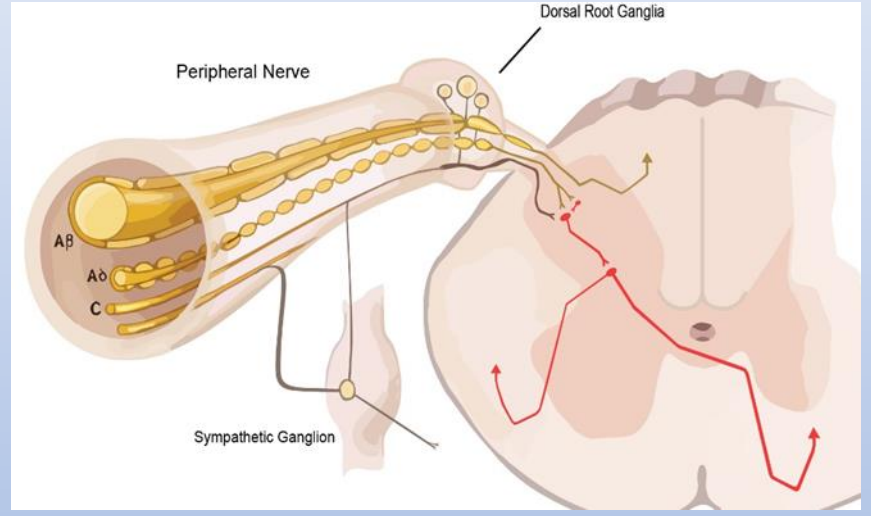
Explant Rate 7% Annually
#1 loss of efficacy

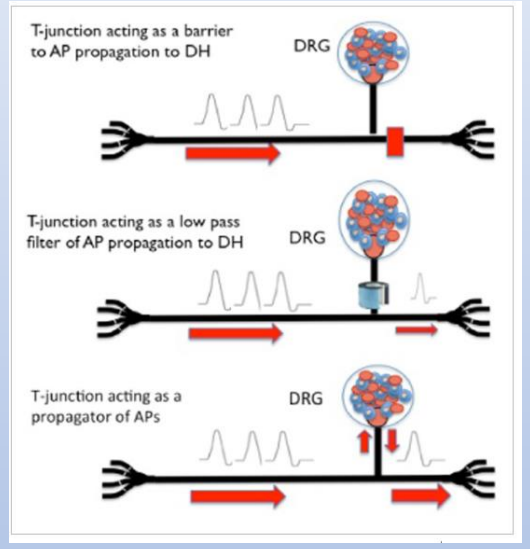


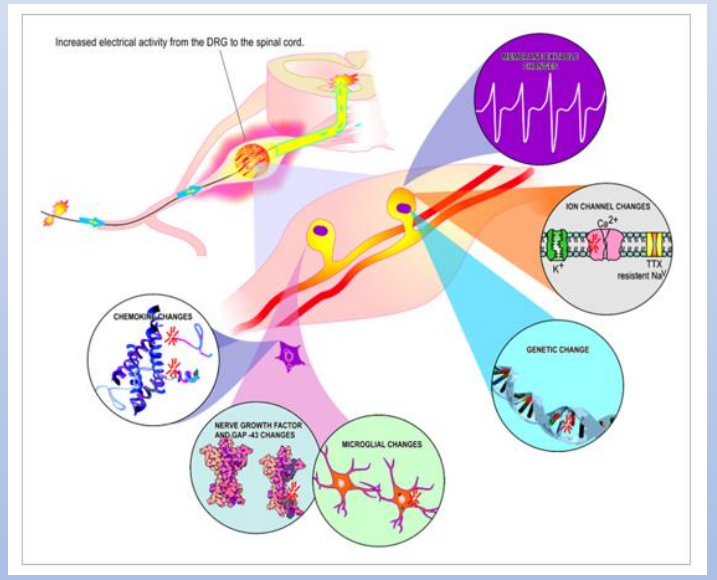


Auidi et al. Loss of Efficacy to Spinal Cord Stimulator Therapy: Clinical Evidence and Possible Causes. Pain Physician 2017
Van Buyten JP et al. International SCS Effectiveness Study: Long-Term Outcomes of the Therapy in 956 Implants. Neuromodulation 2017 Oct;20(7):642-649.

MOA at level of DRG



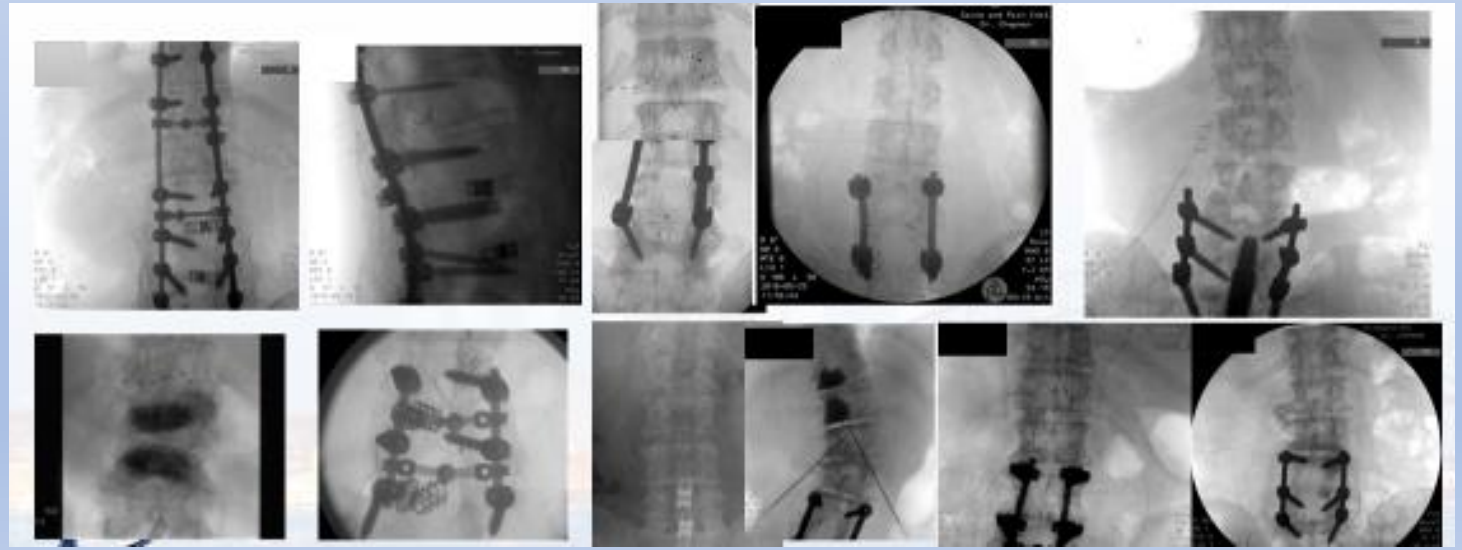


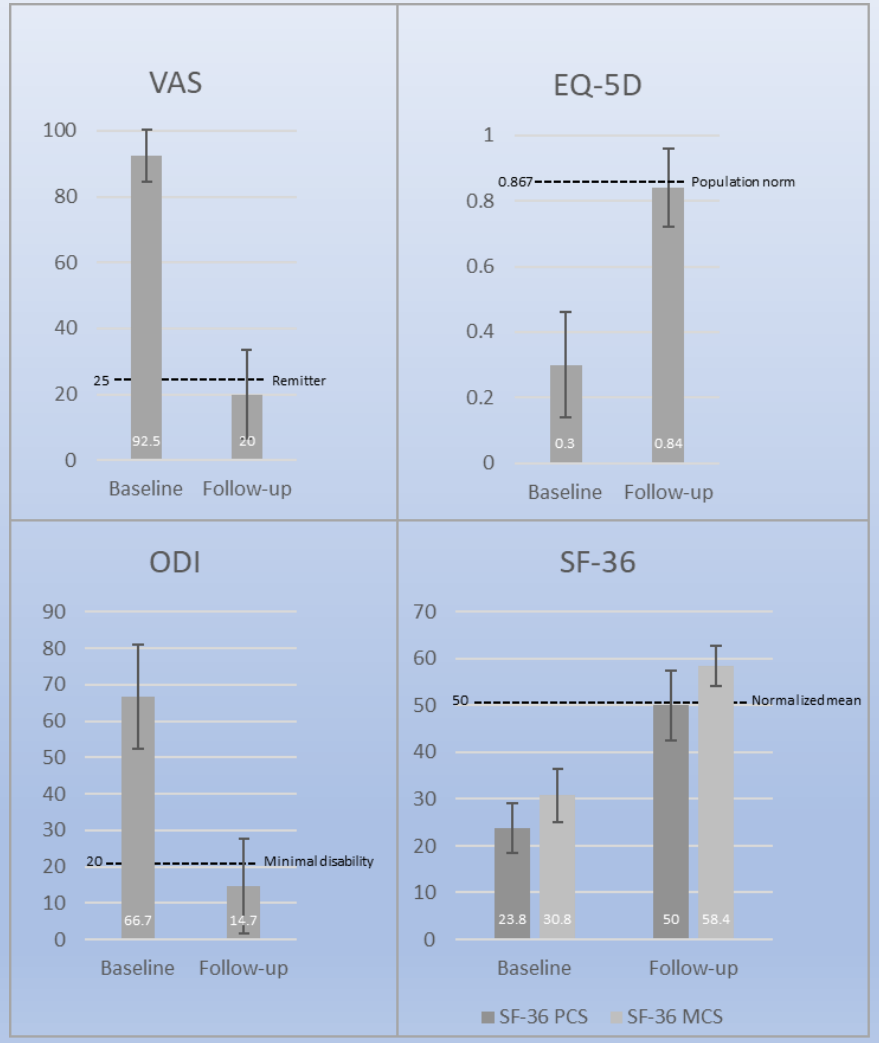


Krames E. The Dorsal Root Ganglion in Chronic Pain and as a Target for Neuromodulation: A Review. Neuromodulation 2015

DRG T12 for Axial Low Back Pain

- Case series 17 patients
- Over 100 currently implanted
- 0-24 months
- No clinical loss of efficacy
- No explants to date





Chapman K, Groenen P, Patel K, Vissers K, van Helmond N. T12 Dorsal Root Ganglion Spinal Cord Stimulation to Treat Chronic Low Back Pain: a Case Series

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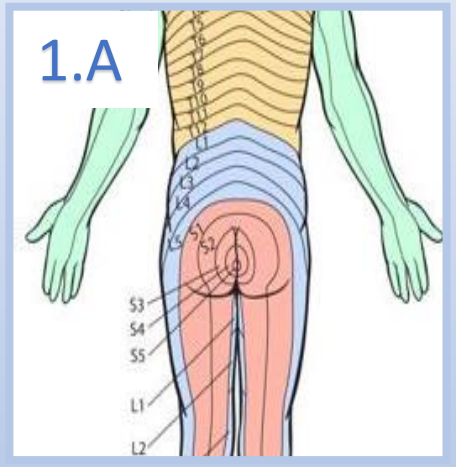
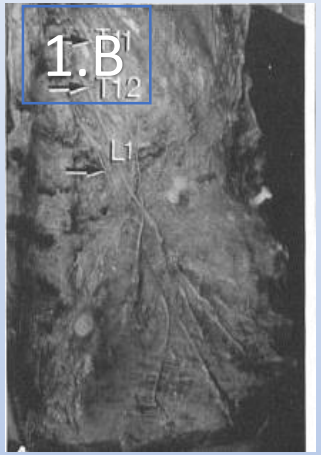
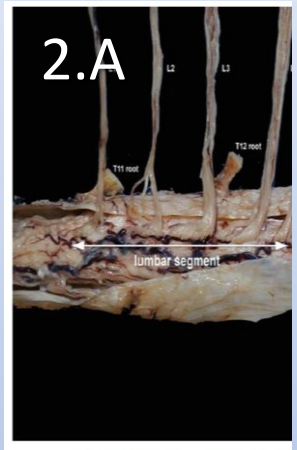
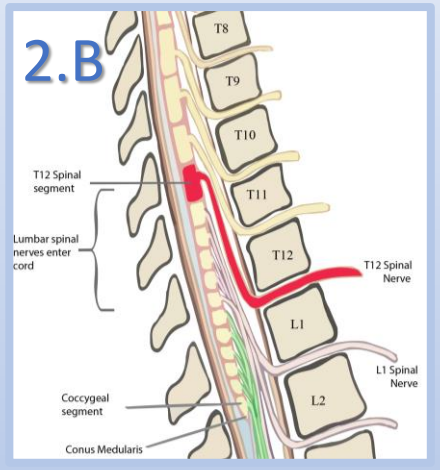
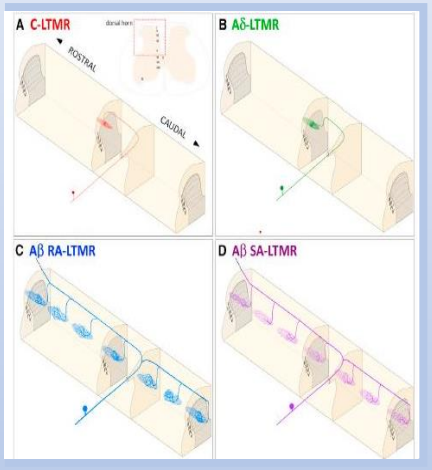
The pathways and processes underlying spinal transmission of low back pain: observations from dorsal root ganglion stimulation treatment

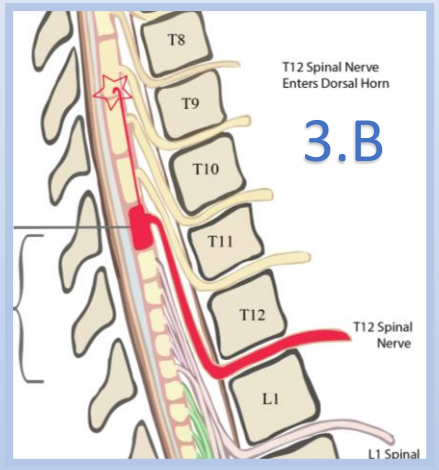


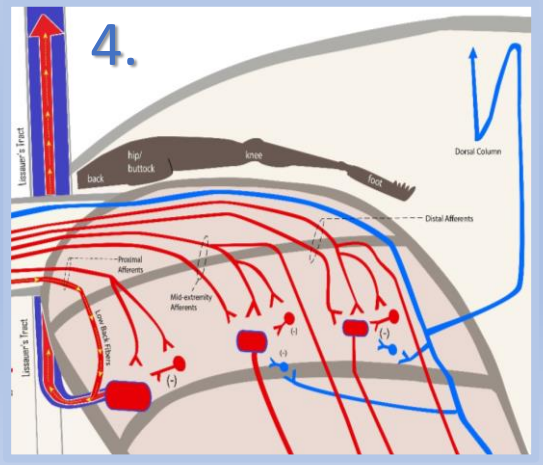


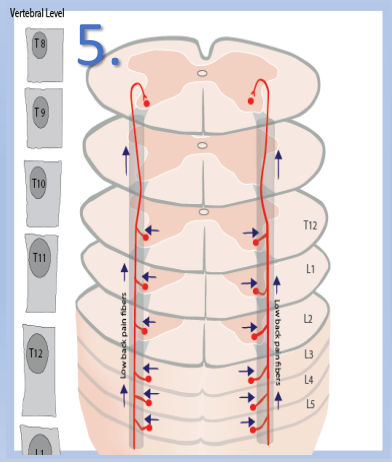


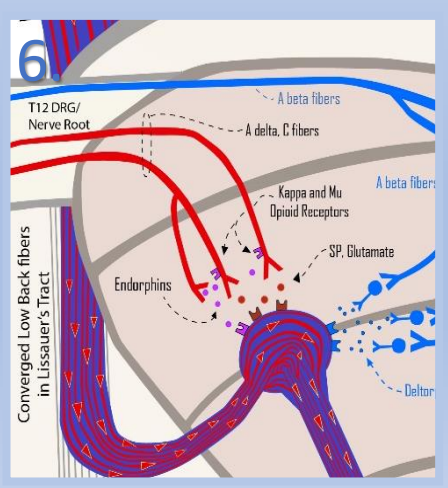


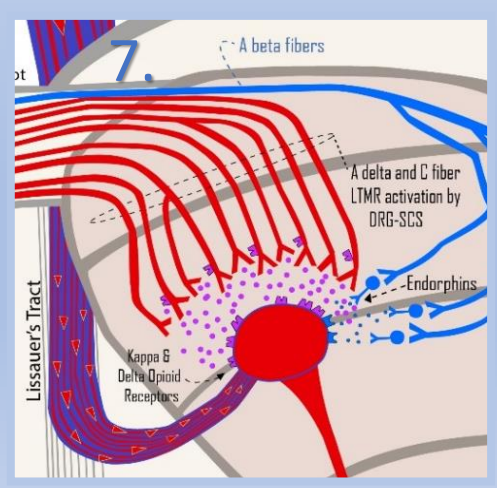












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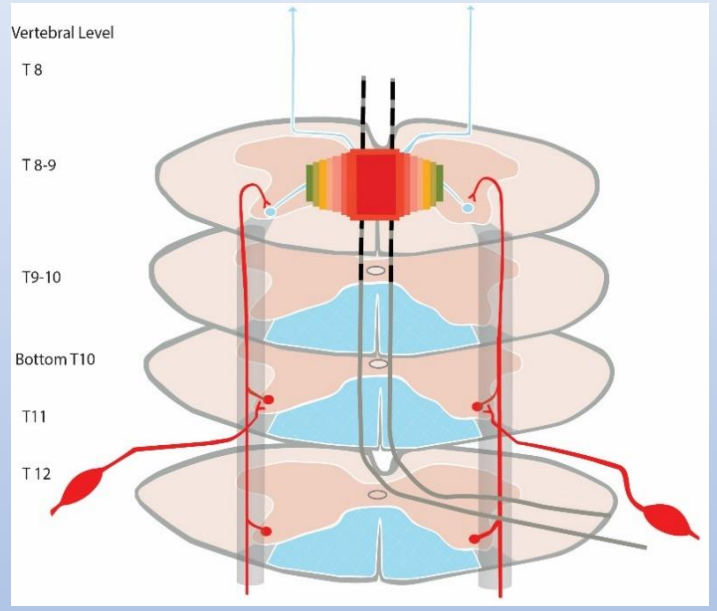
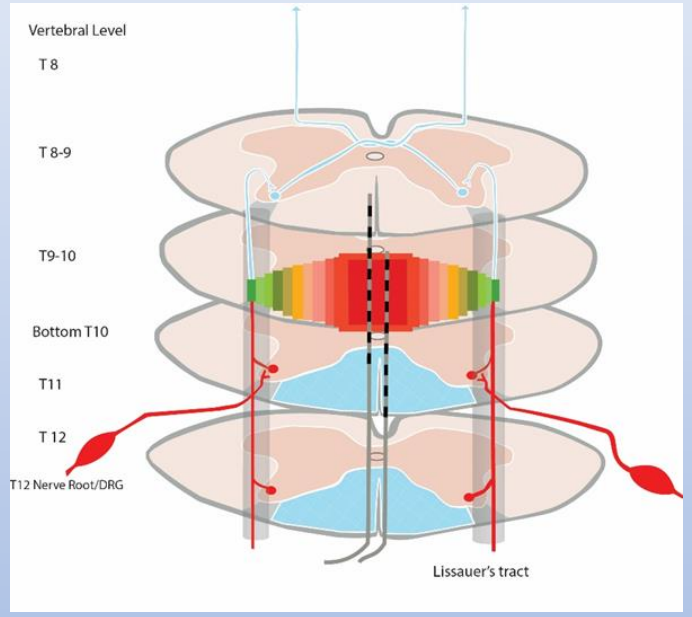
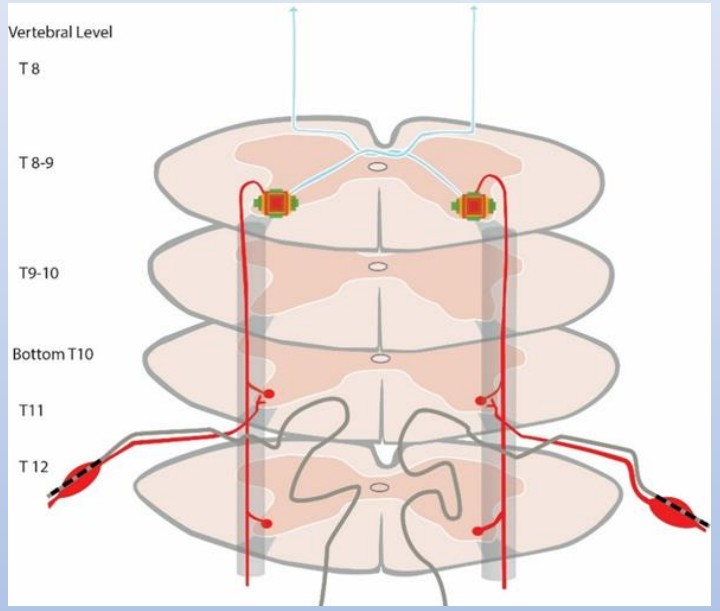
DRG Stimulation

- Access to all afferent nerve input
- At DRG effects
- Effects at levels of convergence
- Potential for improved outcomes
- Further studies are warranted

Energy consumption







	Frequency (Hz)	Pulse width (us)	Amplitude (mA)	Charge/Sec =mA * PW * Hz
DRG-S	4	260	0.725	754
Tonic SCS	50	400	3.5	70,000
HF10	10,000	30	2.5	750,000

DRG-S on patient who reached endpoint of 4Hz without clinically significant decreases in VAS or ODI. Also listed are average settings for Tonic SCS and HF-10 SCS.
Charge/Second = Amplitude (mA) x Pulse Width (us) x Frequency (Hz).

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Conclusions

Over last 5 years spinal cord stimulation has advanced greatly

- Our understanding of the mechanism of action of the various forms of neuromodulation need further elucidation
- Without understanding the fundamental knowledge of the nervous system we can never understand how to improve our treatments

Questions?

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Chapmanken@SpinePainNY.com

Ask about the WIP visiting Scholar Program

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