Novel Approaches to Understanding and Treating Spinal Cord Injury Neuropathic Pain

Dr. Scott Falci
Founder, Chief Medical Officer, CEO

Nociceptive Pain

- Pain experienced from injury to body tissues
- Resolves after tissue healing
- Protective

Neuropathic Pain

- Pain that occurs subsequent to injury or malfunction of nerves in the brain, spinal cord, or peripheral nerves (those that go to regions of the body such as the arms and legs)

- Common Pain Descriptors: sharp, burning, electrical, stabbing, pins-and-needles, squeezing, crushing, pressure

Pain Characteristics

- Spontaneous/Non-Evoked: pain that occurs spontaneously without obvious cause

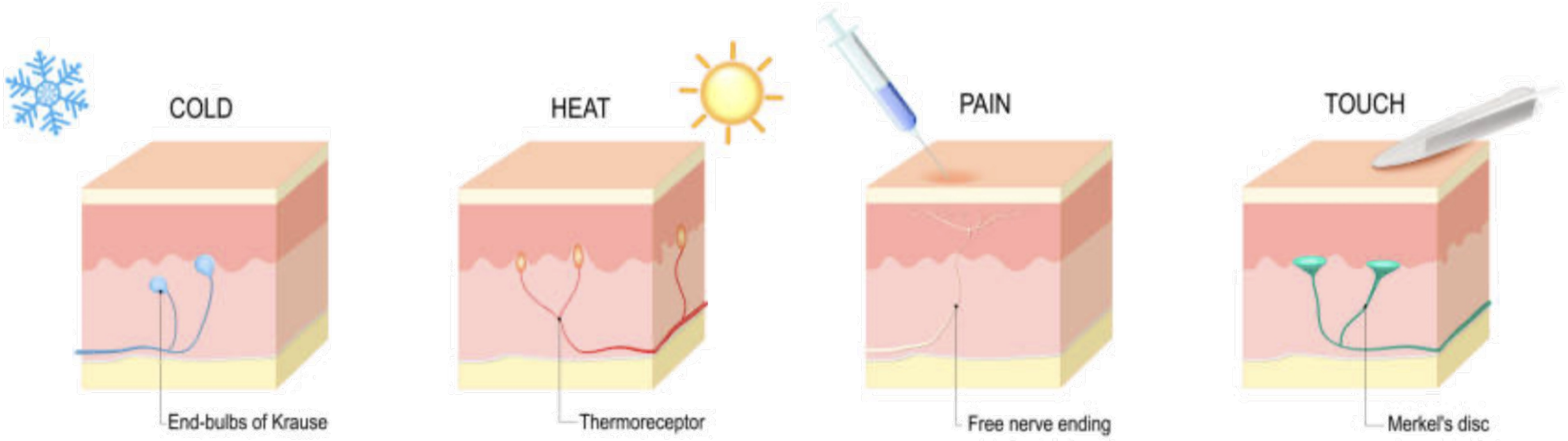
- Allodynia: normal non-painful stimulus such as light touch perceived as painful

- Hyperalgesia: painful stimulus perceived with greater intensity than normal

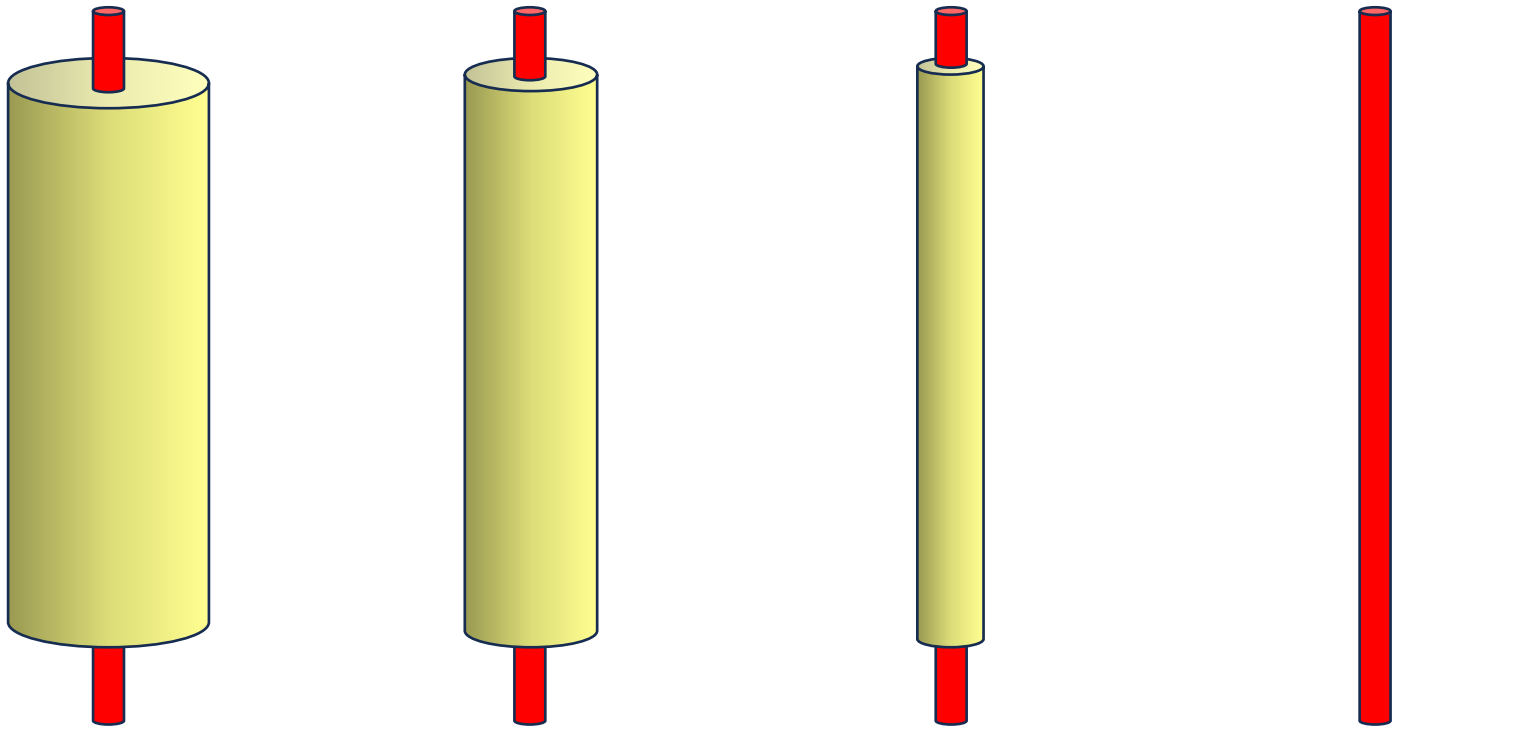
Clinical Considerations for SCI Neuropathic Pain

- Neuropathic pain is amongst the most disabling of sequelae of spinal cord injury (SCI)
- Prevalence estimated from 65%-80%
- These pains are always perceived in body regions of complete sensory loss or partial sensory loss
- Respond poorly to opioid and NSAID medications

Cutaneous Receptors

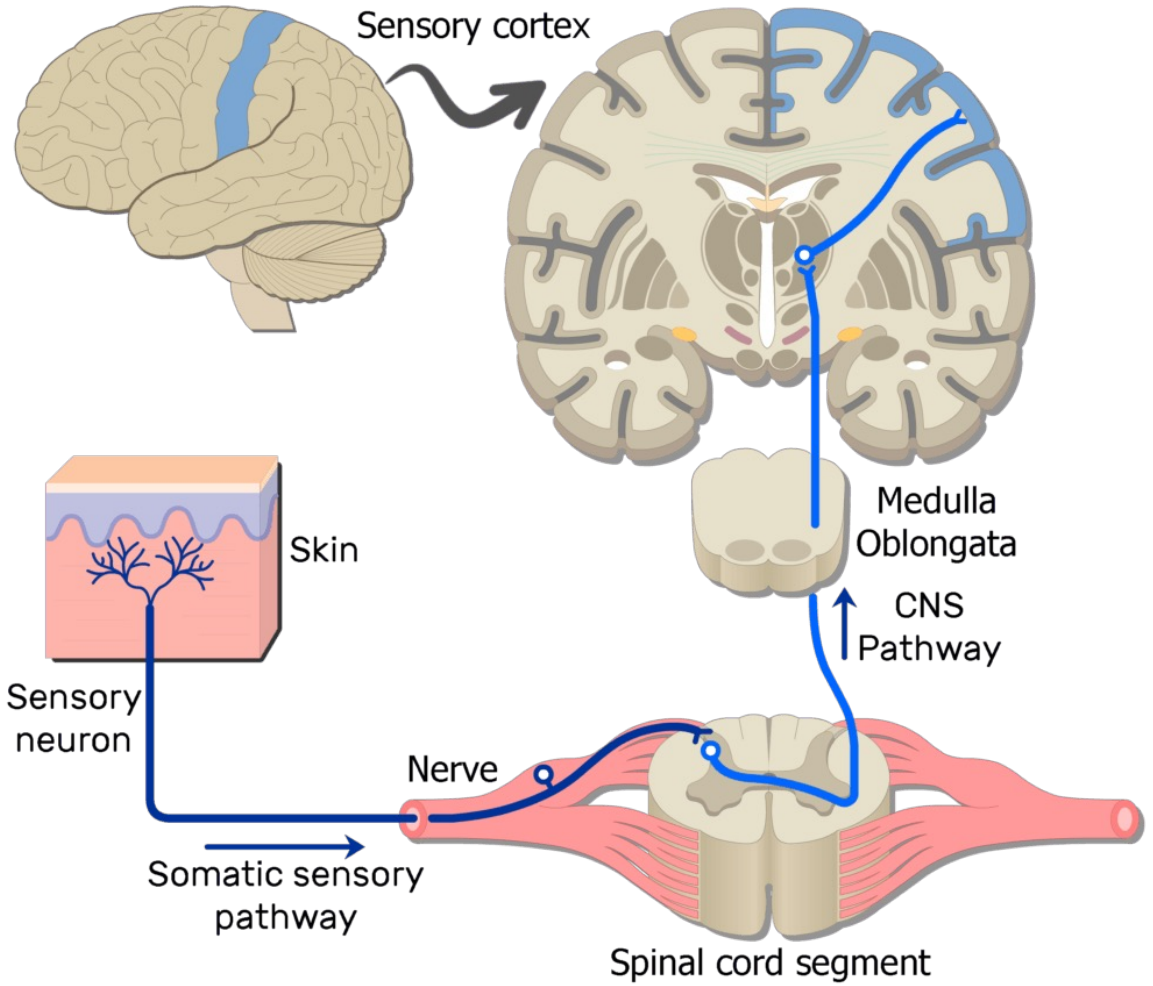


Nerve Fibers



A-alpha A-beta A-delta C-nerve Fibers

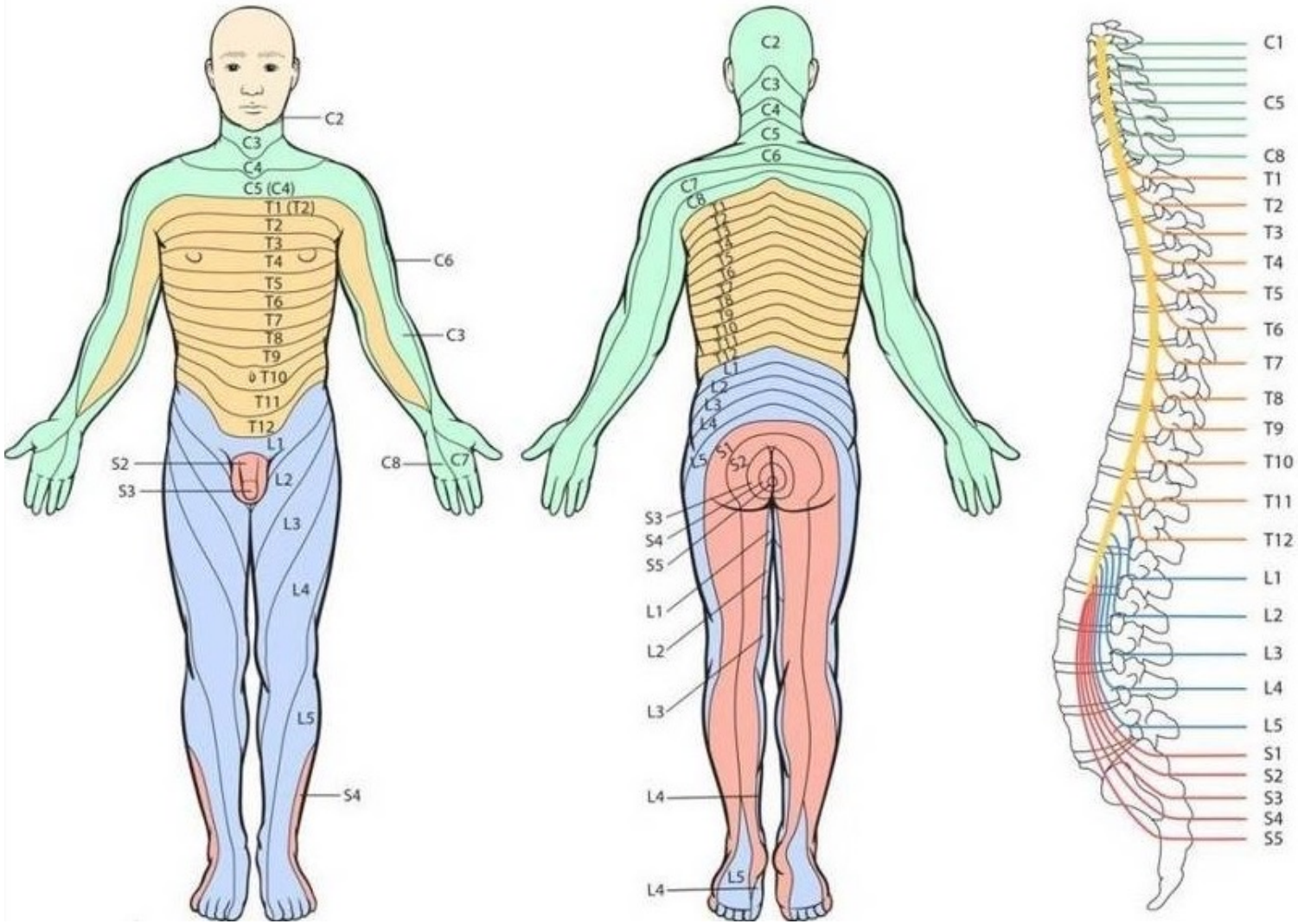
Sensory Perception



Source: Scott A. Sheffield (2022) "Pain pathway: interactive diagram"

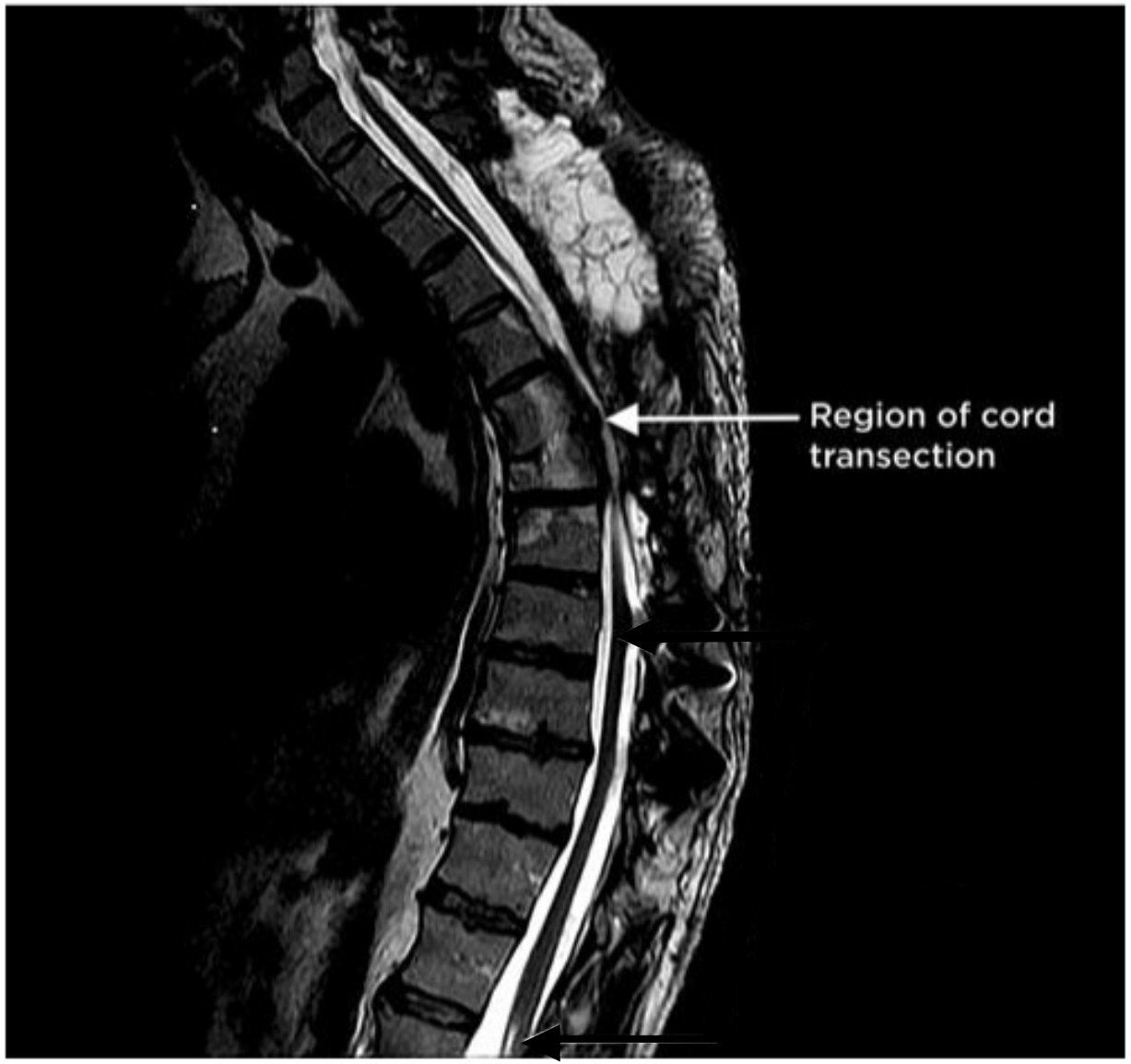
The Human Body Is Segmented in Dermatomes

Specific parts of the spinal cord innervate specific regions of the body – both motor and sensory functions



MRI of an Injured Spinal Cord: Sensory Sequelae After Injury

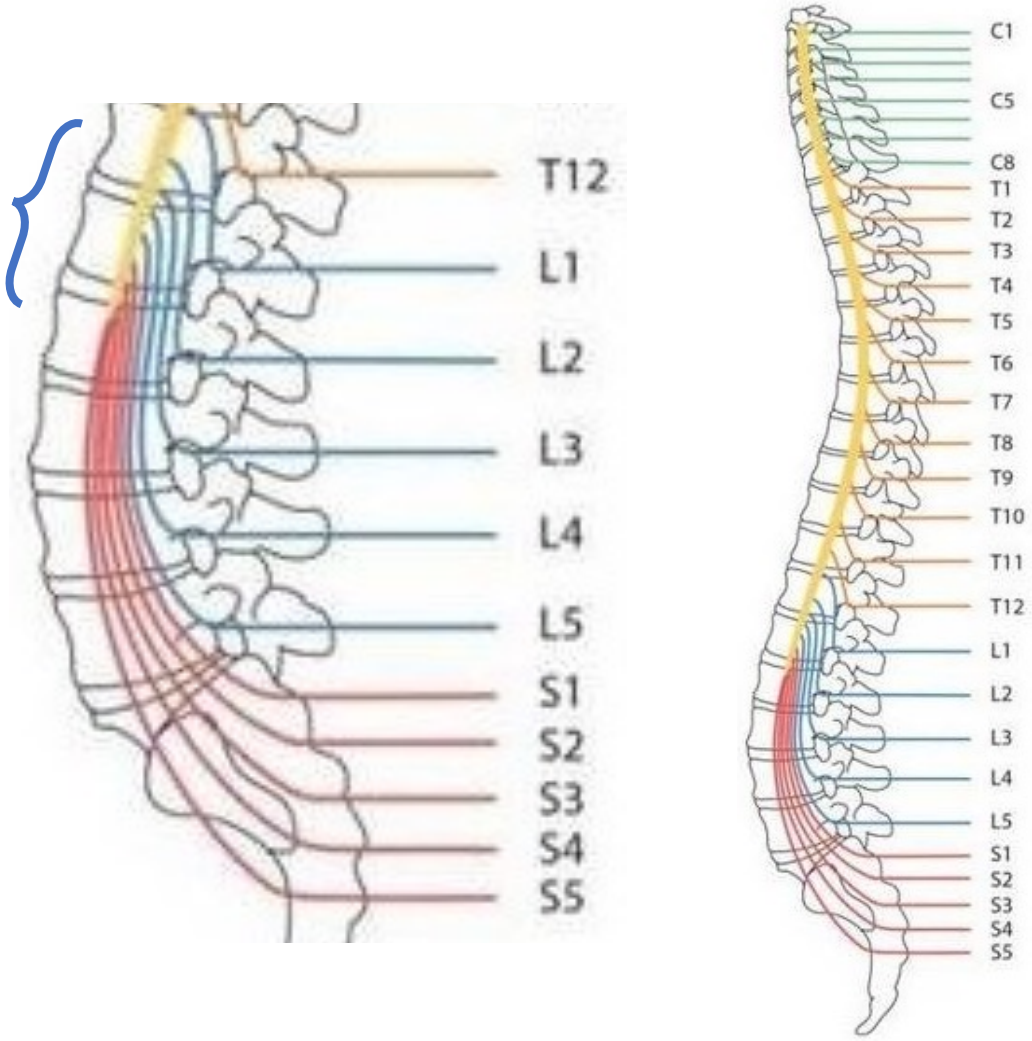
- Loss of sensation and strength below injury
- In 80% of patients, spontaneous pain occurs in regions of sensory loss two weeks to two months post-injury
- Spinal cord transection at injury site fails to relieve pain
- Opioids/NSAIDS do not relieve pain



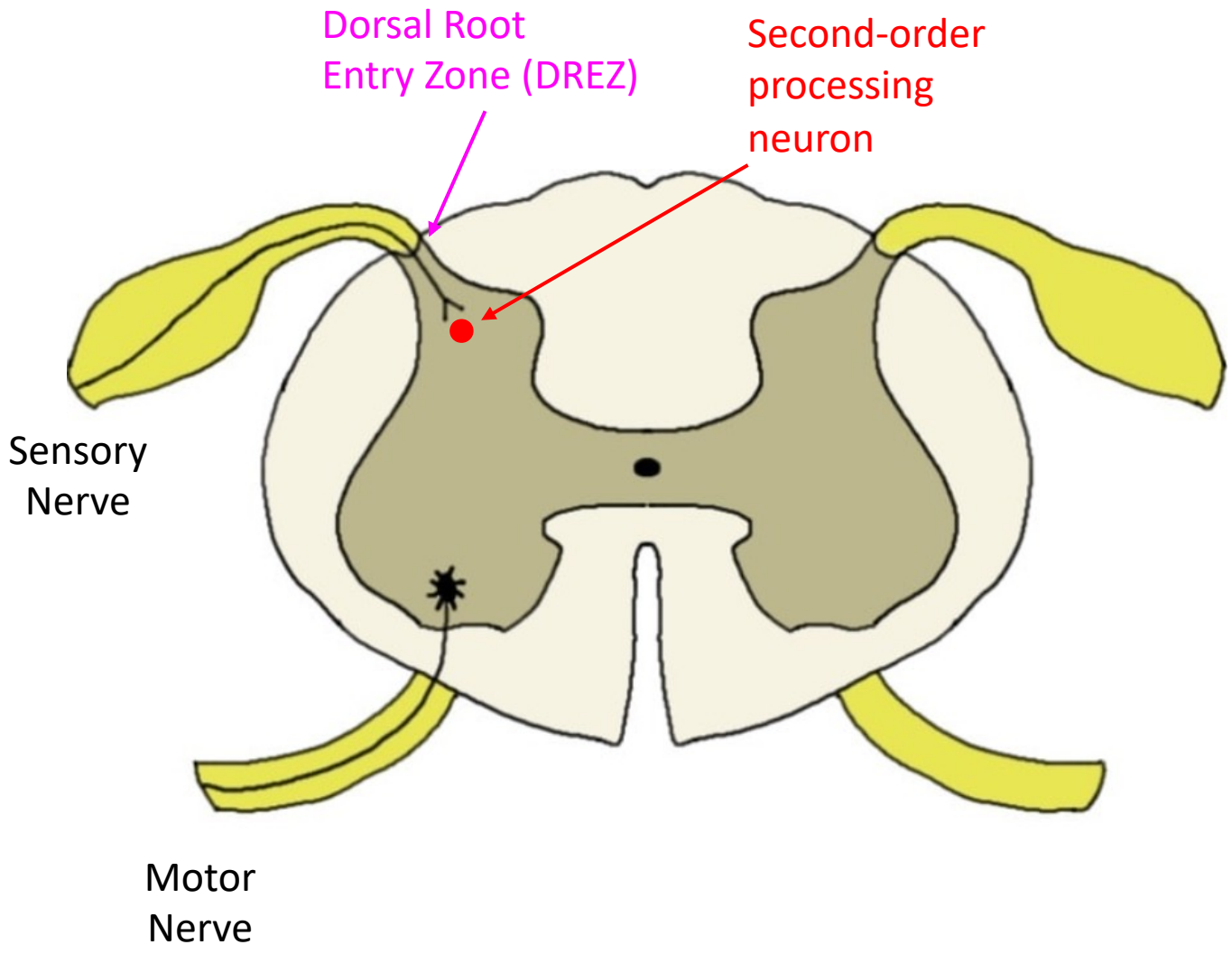
What is the mechanism for this pain?

- Injuries are very common to *spinal cord* levels L2 – S5 (the conus) and cause loss of sensation and motor function in legs, bowels, bladder

- Could spontaneous electrical hyperactivity in DREZs located immediately above the injured conus cause these pains perceived below the level of injury?



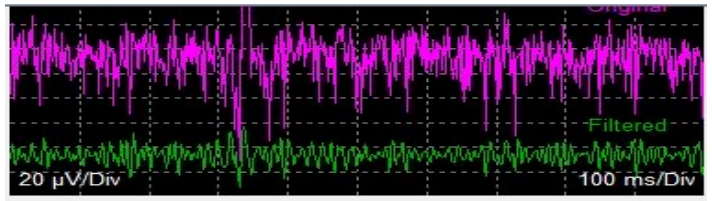
Location of Pain-Processing Neurons in the DREZ

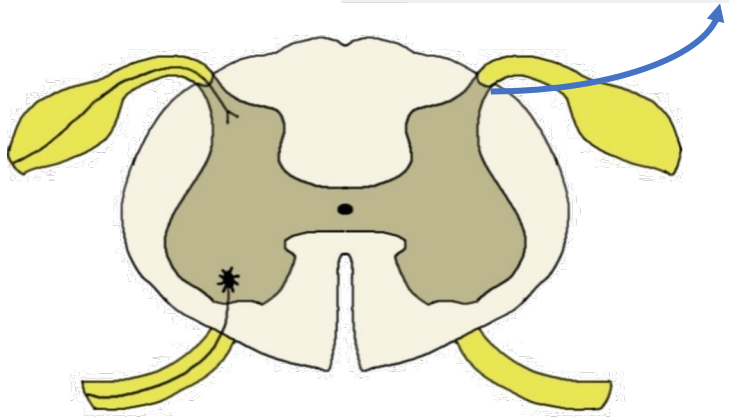


DREZ Electrical Hyperactivity in Conus Injuries

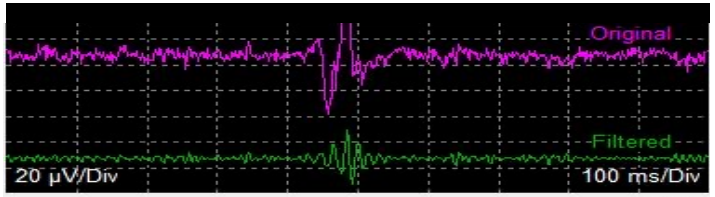
- DREZ electrical hyperactivity is found in one or more DREZs above the level of injury
- Ablation of these electrically hyperactive DREZ regions leads to 100% relief of pain in 85% of patients
- DREZ regions of electrical hyperactivity were correlated with C-fiber deafferentation

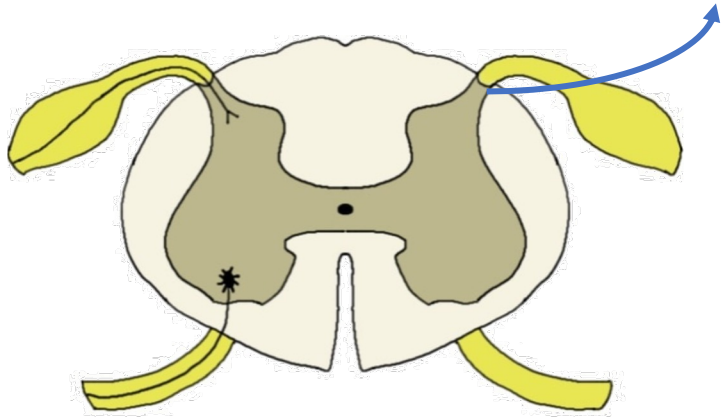
Hyperactive DREZ





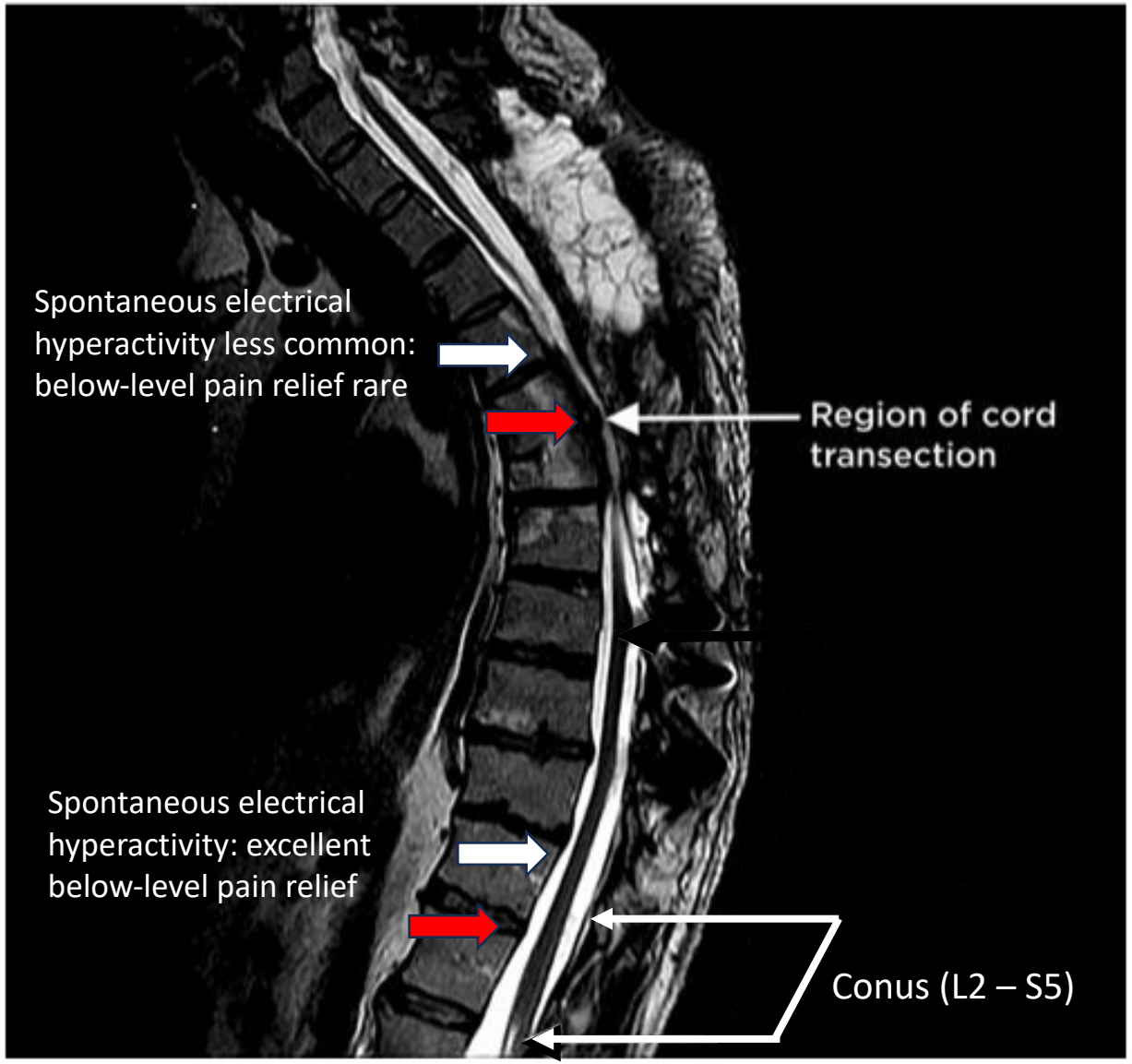
Normal DREZ



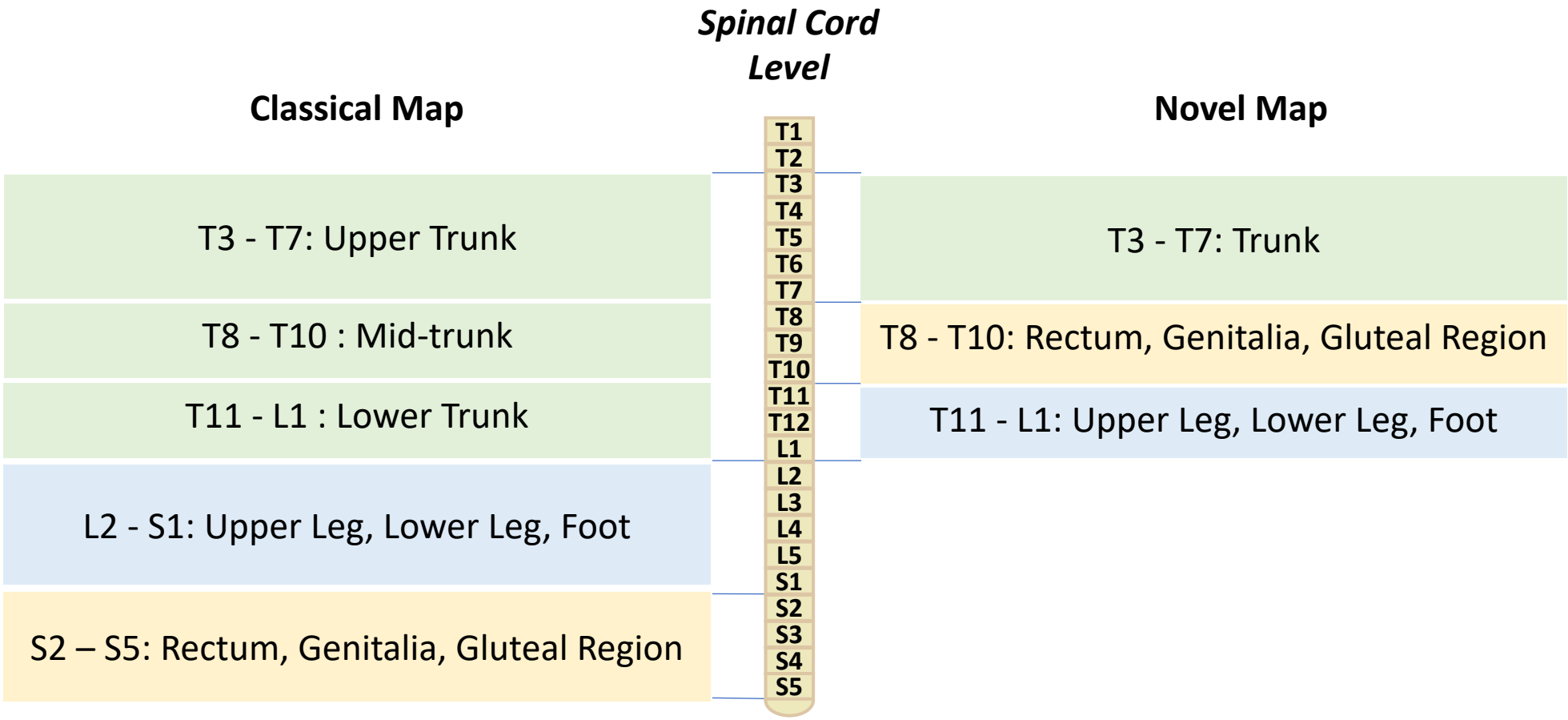


DREZ Electrical Hyperactivity in Injuries Above the Conus

- Electrical hyperactivity often not found
- When DREZ electrical hyperactivity found, ablation rarely led to pain relief
- Why did surgeries fail for injuries above the conus?

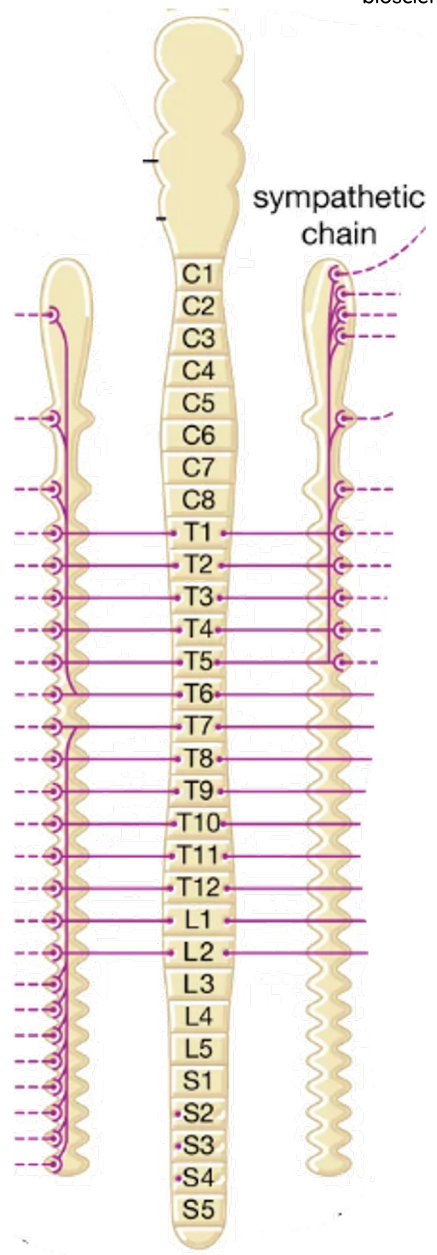


Creation of Novel Spinal Cord Map of DREZ Electrical Hyperactivity and Body Regions of Pain Perception



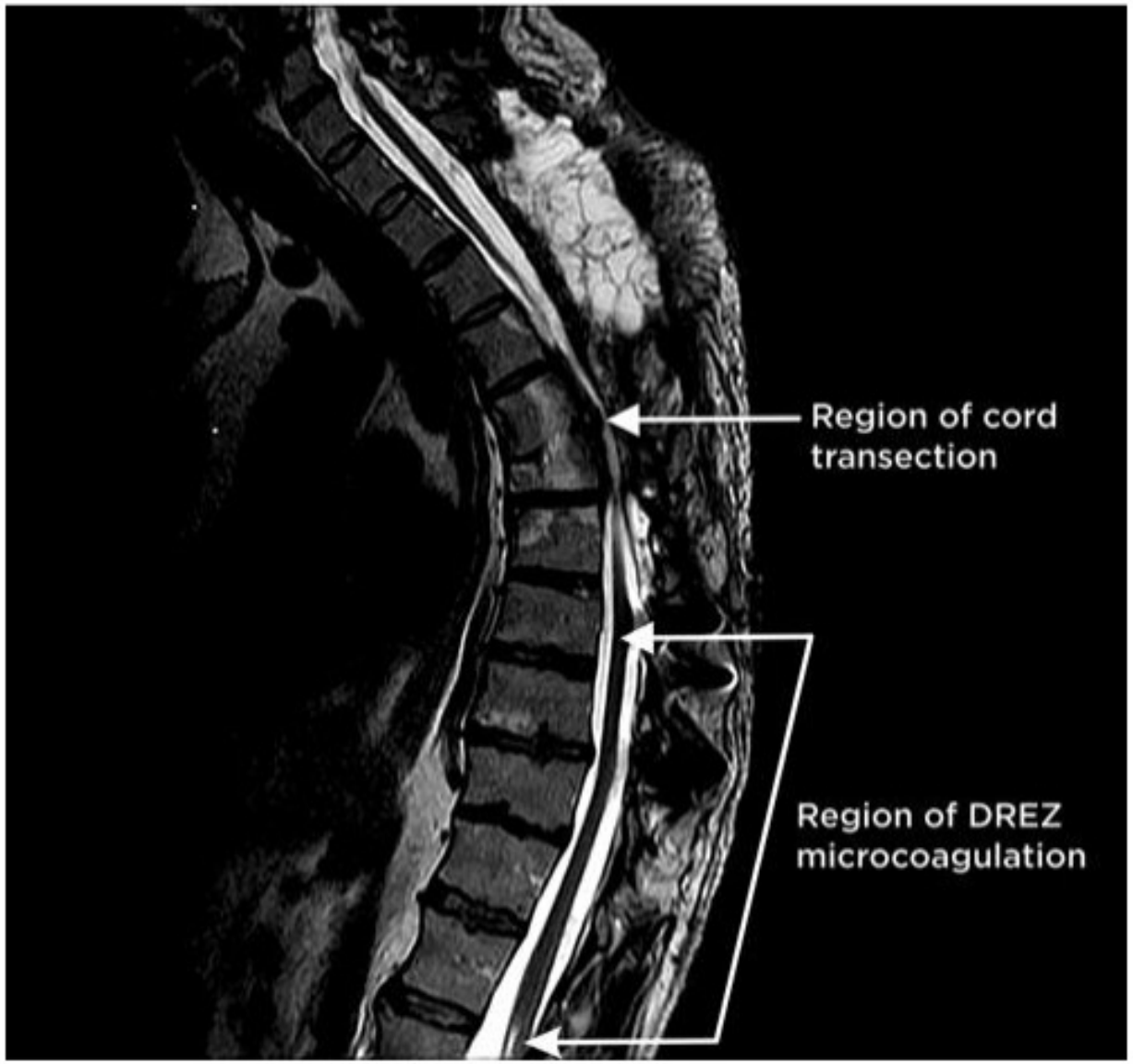
The Novel Maps Aligns with Patterns of Sympathetic Innervation

Classical Map	*Spinal Cord Level*	Novel Map
T3 - T7: Upper Trunk	T1 T2 T3 T4 T5 T6 T7	T3 - T7: Trunk
T8 - T10 : Mid-trunk	T8 T9 T10	T8 - T10: Rectum, Genitalia, Gluteal Region
T11 - L1 : Lower Trunk	T11 T12 L1	T11 - L1: Upper Leg, Lower Leg, Foot
L2 - S1: Upper Leg, Lower Leg, Foot	L2 L3 L4 L5 S1	
S2 – S5: Rectum, Genitalia, Gluteal Region	S2 S3 S4 S5	



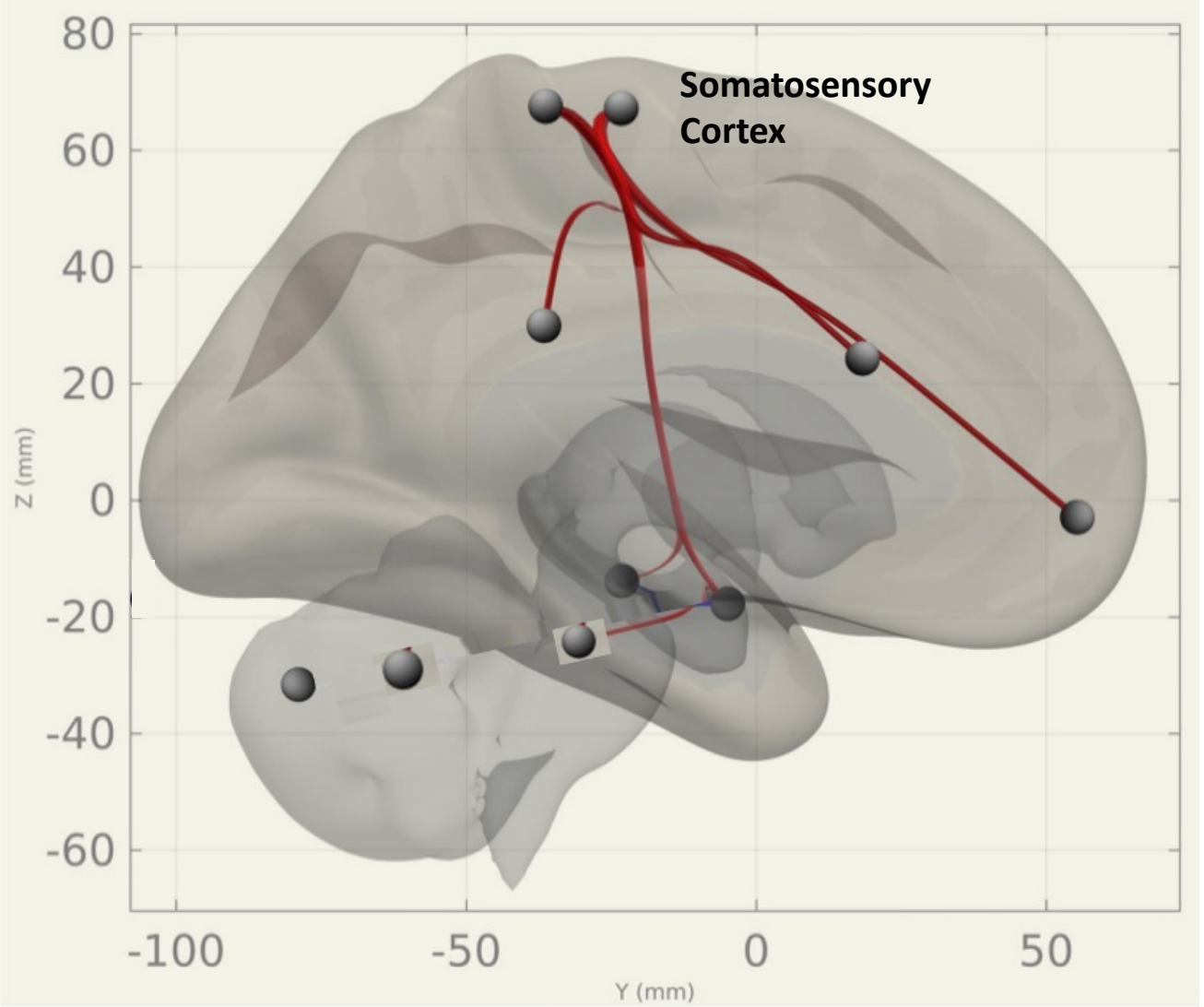
DREZ Electrical Hyperactivity Below the Level of Spinal Cord Injury Can Generate Pain Corresponding to the Novel Map

- If the sympathetic nervous system allows pain signals to route around the injury site, perhaps electrical hyperactivity *below* the injury is causing pain…
- Ablating this hyperactive tissue relieves pain: 100% relief of pain in 85% of patients
- Spinal cord injury can lead to DREZ hyperactivity both above and below the level of injury and resulting pain
- This hyperactivity is strongly correlated with loss of c-fiber pain inputs



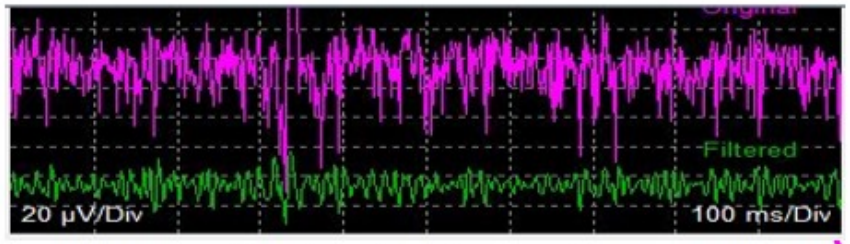
fMRI of the Brain: Changes in Sympathetic Nervous System Connectivity after Surgery to the DREZ

- Red lines indicate increased communication among brain centers associated with the sympathetic nervous system following DREZ surgery
- These patterns of communication resemble those seen in a normal, pain-free state



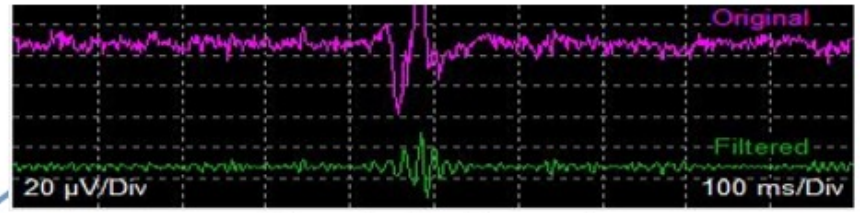
DREZ Surgery Procedure

Hot Tissue



Electrically Hyperactive

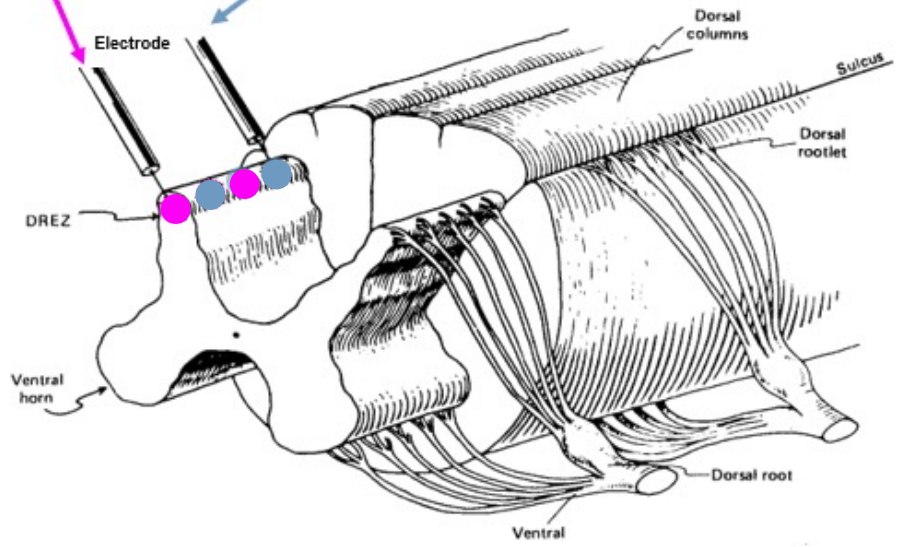
Cold Tissue



Electrically Normal

Spontaneous electrical hyperactivity even in areas of the spinal cord that innervate parts of the body that have no sensation and are paralyzed

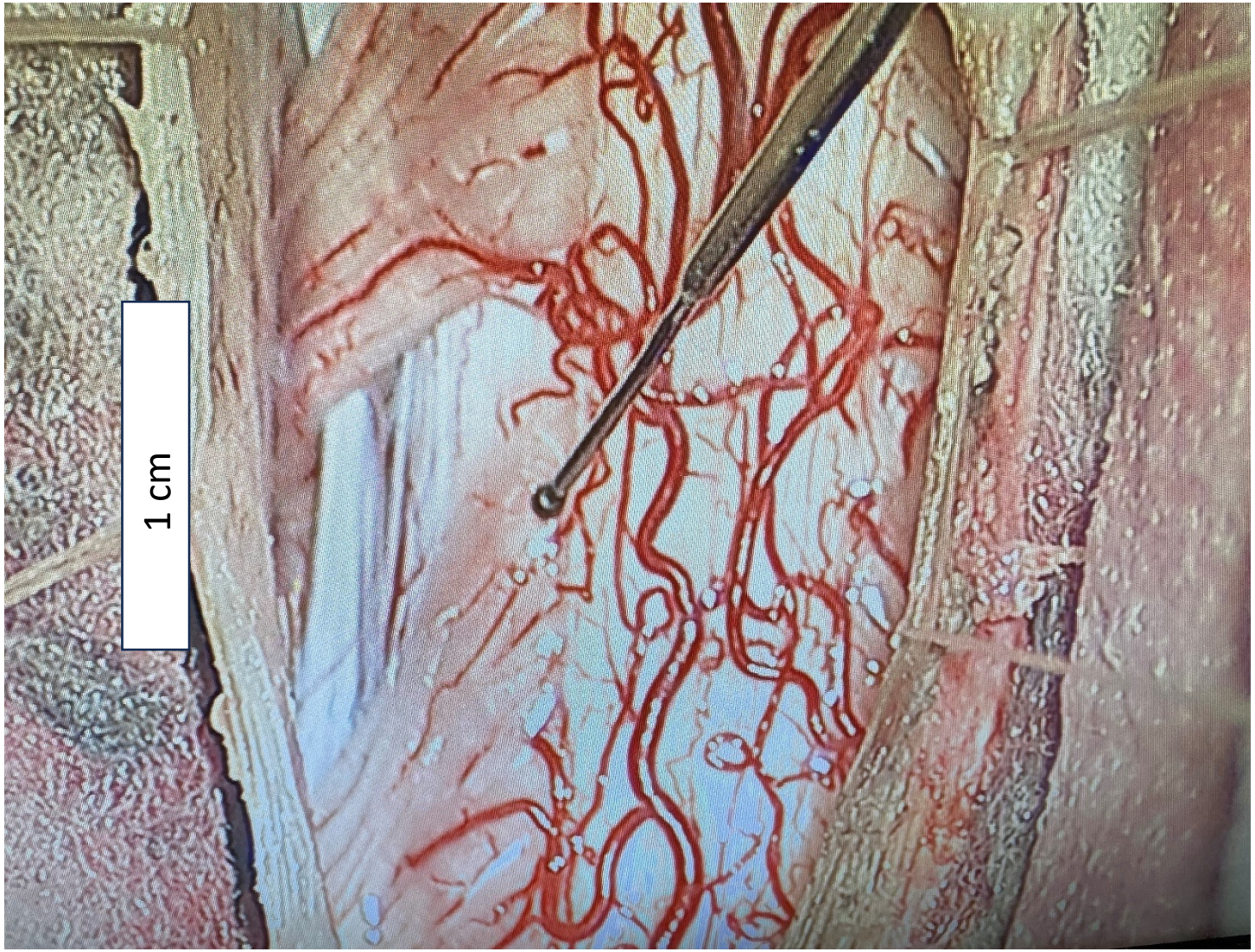
Strongly correlated with c-fiber deafferentation



Interspersed electrically quiescent DREZ tissue

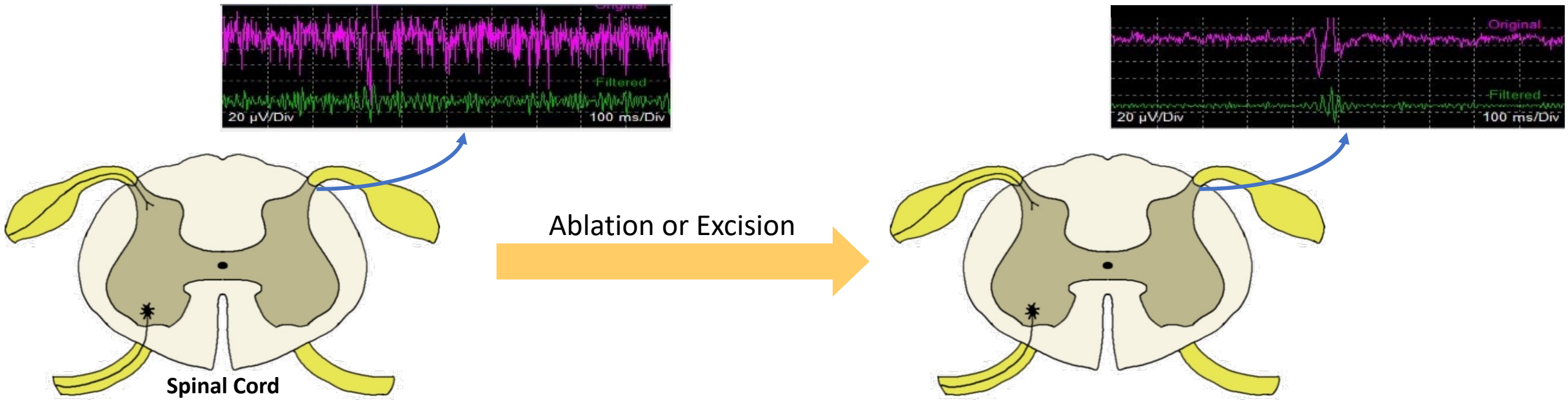
Source (traces): Falci, Indeck and Barnkow (2018)

Operative Image of Spinal Cord and DREZ

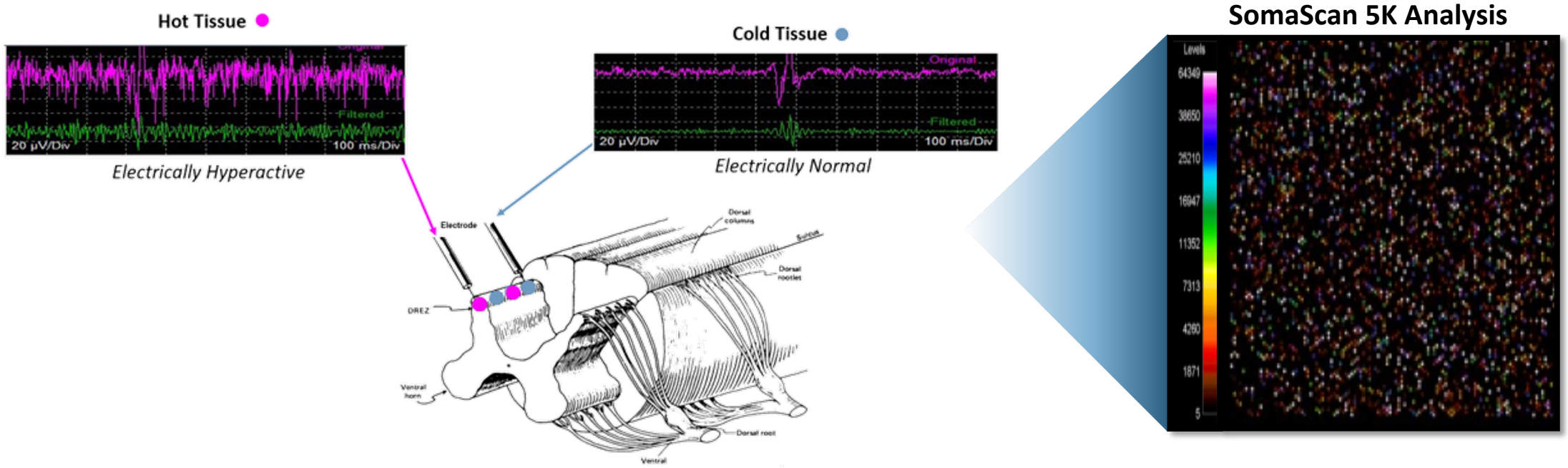


Surgery for Spinal Cord Injury Pain Relief

Ablation of electrically hyperactive DREZs results in complete (100%) pain relief in 85% of patients across hundreds of surgeries

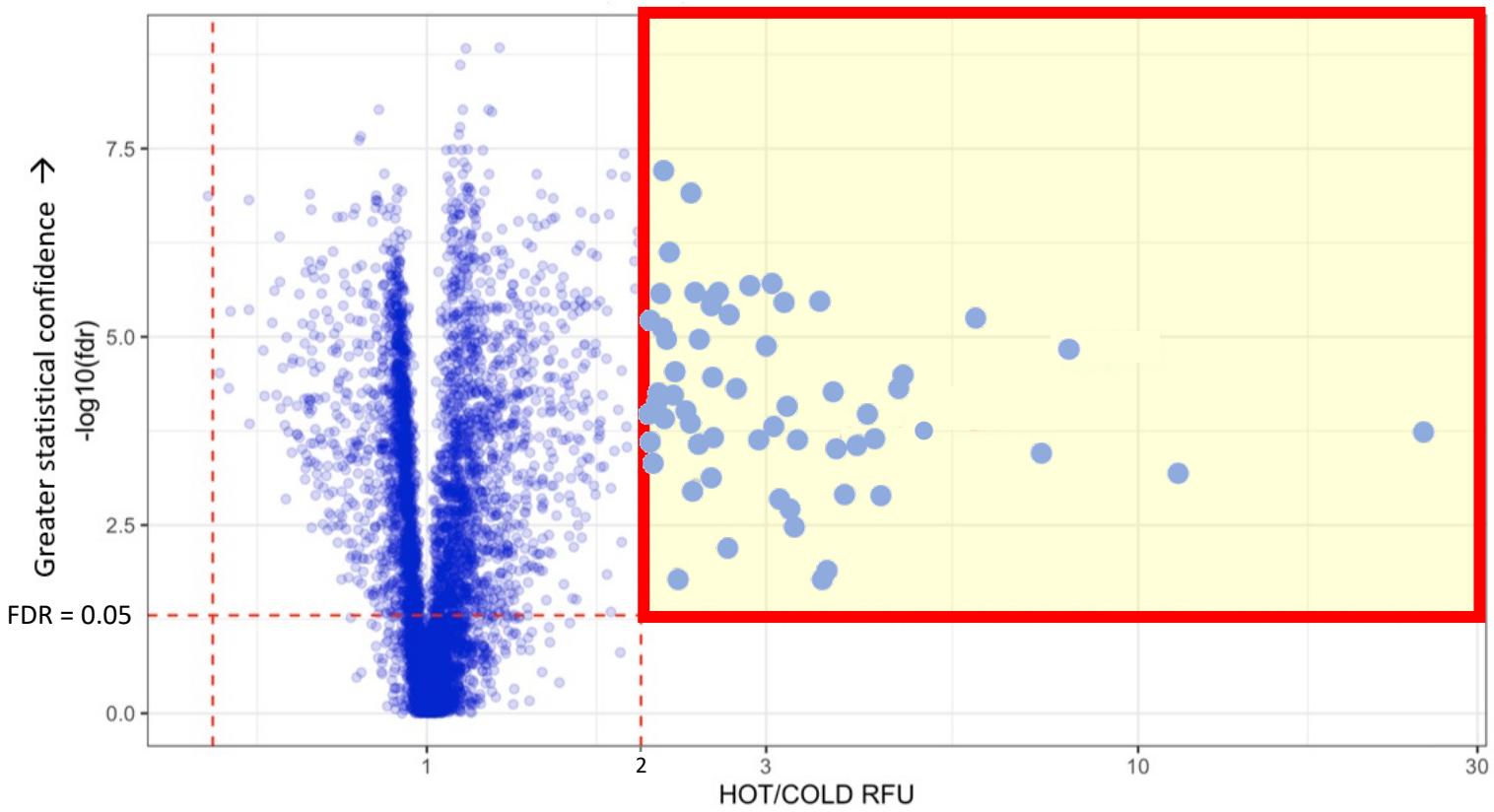


Proteomic Analysis of Electrically Hyperactive DREZ Tissue as a Platform for Drug Target Discovery



- Approach: Excise Hot ● and interspersed Cold ● tissue samples from within pain-causal DREZs before ablation to identify proteins that are differentially expressed, may drive pain, and could become drug targets
- Method: Analyze Hot and Cold tissue samples using the SomaScan 5K proteomics platform to measure approximately 5,000 proteins
- Results: about 1% of the proteins measured on the SomaScan 5K assay were identified as potential targets
- Future analyses will use the SomaScan 11K assay to examine approximately twice as many proteins

SomaScan 5K Reveals Differentially Abundant Proteins in Hot vs. Cold Tissue – Initial Focus on The Red Box



Increasing protein abundance in electrically hyperactive tissue →

n = 10 patients, 107 samples total

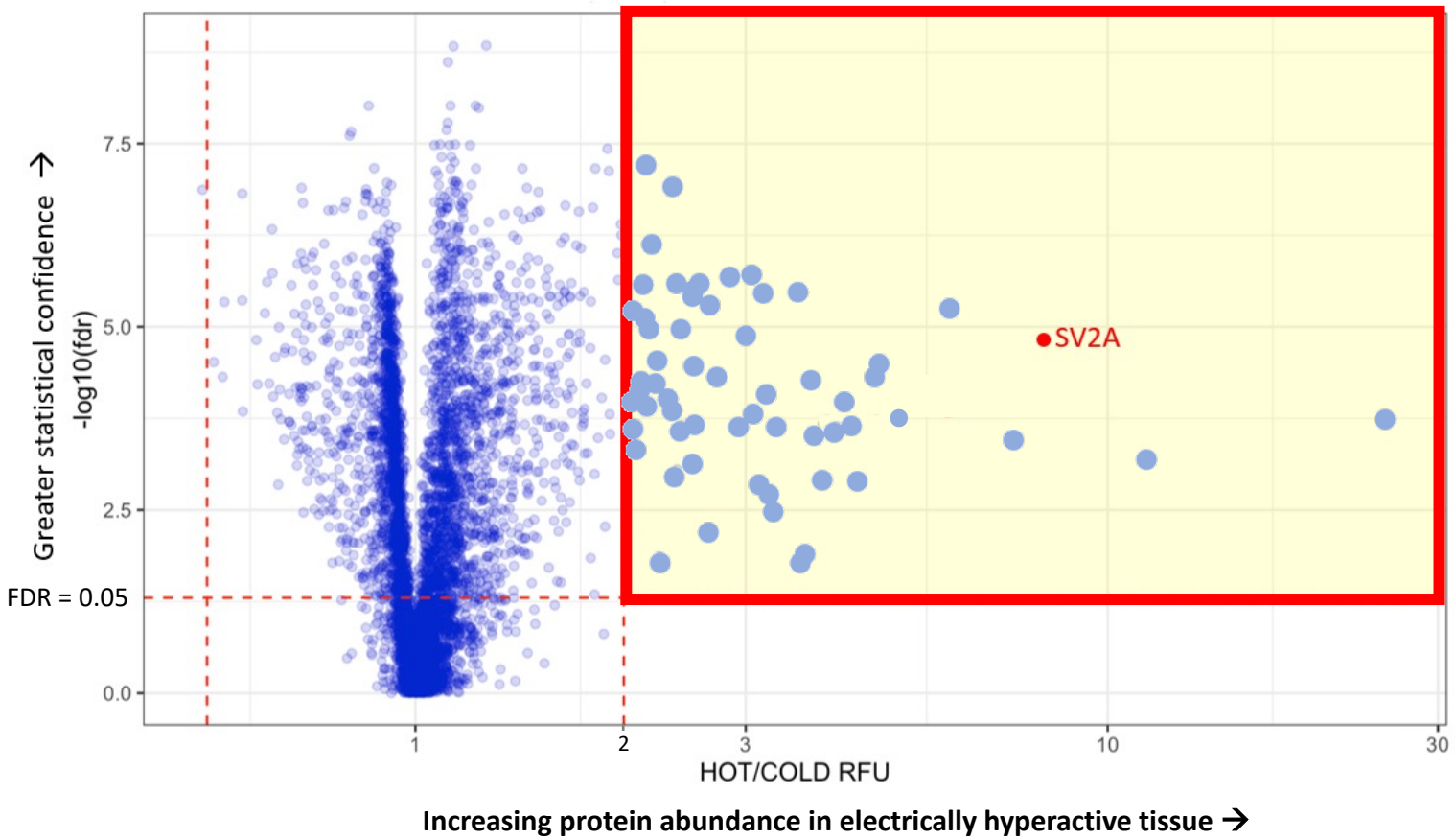
Red Box: proteins that are at least twice as abundant in hot tissue and have a false discovery rate <0.05

Other potential targets lie outside the red box

Each dot represents one protein; FDR = false discovery rate

TenZero's First Proof of Concept: SomaScan Identifies SV2A as a Possible Target for Neuropathic Pain

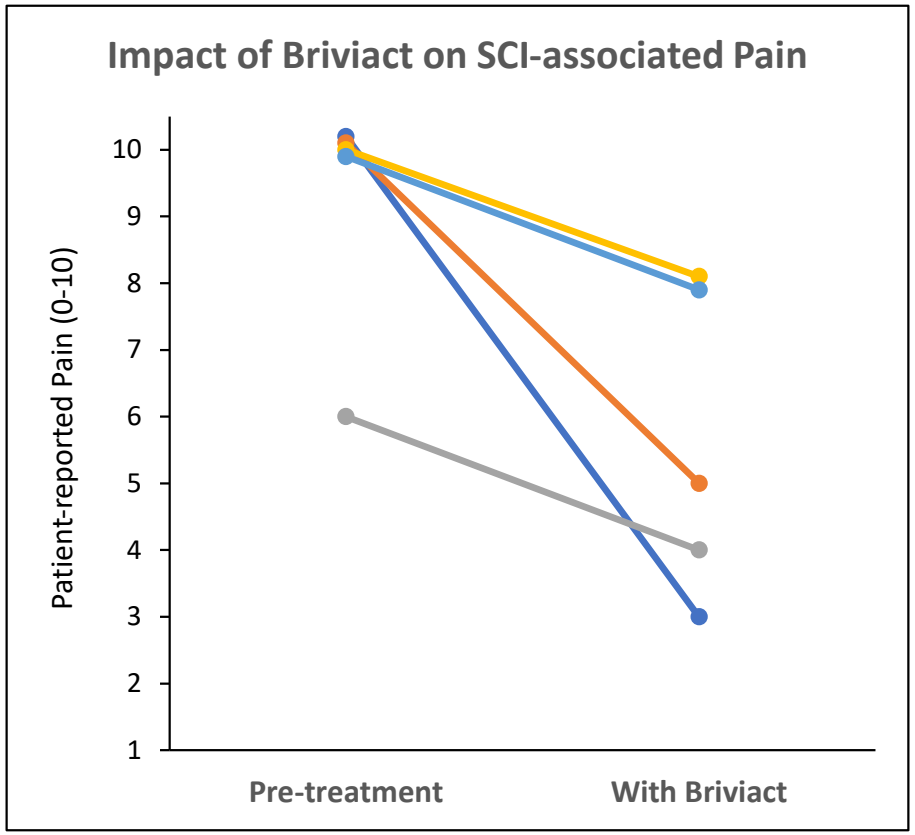
- Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A)
- Brivaracetam approved in 2016 for the treatment of certain forms of epilepsy
- Compassionate use study
  - Eight spinal cord injury patients with severe neuropathic pain
  - Pain refractory to pharmacological management by opioids, NSAIDS, Lyrica, Neurontin, antidepressants
  - Treated with brivaracetam: 75 to 300 mg/day



Brivaracetam Compassionate Use Successes

Pre-treatment

- "Severe continuous burning pains and painful hypersensitivity to touch: arms, trunk, legs"
- "Sharp, burning, electrical pains throughout the arms, trunk, and lower extremities; painful hypersensitivity"
- "Refractory to opioids, Lyrica, Neurontin, anti-depressants" – no therapeutic options
- 10 = near-suicidal pain

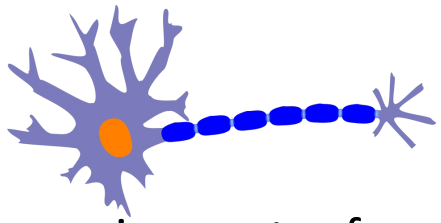


With Brivaracetam

- "Fully engaged in life activities"
- "Could wear clothes without pain"
- "Pain relief continues two years later"
- "Attempted dose reductions led to incremental increases in pain"
- Two of these five patients voluntarily reduced their use of opioids

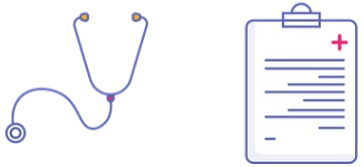
- **Targeting SV2A with brivaracetam brought relief to 5 of 8 patients suffering from intractable pain**
- **Recently completed placebo-controlled Phase 2 study trial with 20 patients showed an average 2.6-point decrease in pain**
- **Phase 3 study in progress**
- **More therapeutic options – and combinations – are needed**

Beyond SCI – Addressing All Neuropathic Pain



Neurobiology

- DREZ is the processing center for virtually all pain signals
- Common mechanism across many types of neuropathic pain: c-fiber deafferentation
- Hyperactivity in the DREZ *creates* the full range of pain sensations
- Insights from rodent neuropathic pain models
  - Both central and peripheral injuries lead to DREZ hyperactivity and chronic pain
  - Chronic pain is associated with proteomic changes in the DREZ



Clinical Experience

- Pain descriptors (burning, stabbing, electrical shock) are consistent across SCI and other types of neuropathic pain, suggesting a common underlying mechanism
- Opioids generally fail to relieve neuropathic pain despite their effectiveness against acute pain

Targeting causal proteins in electrically hyperactive DREZ tissue may address diabetes-associated neuropathic pain, fibromyalgia, multiple sclerosis, failed back syndrome, chemotherapy-induced neuropathic pain…

Developing Innovative Drugs for Neuropathic Pain

- Limited progress in treating neuropathic pain over the past 30 years
- Animal models do not adequately represent human neuropathic pain
- Strongest analgesics – opioids – have limited effectiveness and myriad negative effects
- TenZero Biosciences' focus
  - Build on our emerging mechanistic understanding of *human* neuropathic pain
  - Unprecedented number of potential new targets for neuropathic pain
  - Exploring new approaches to identifying drugs directed toward diverse targets
  - Committed to working with established leaders in pharma to deliver novel therapeutics across multiple indications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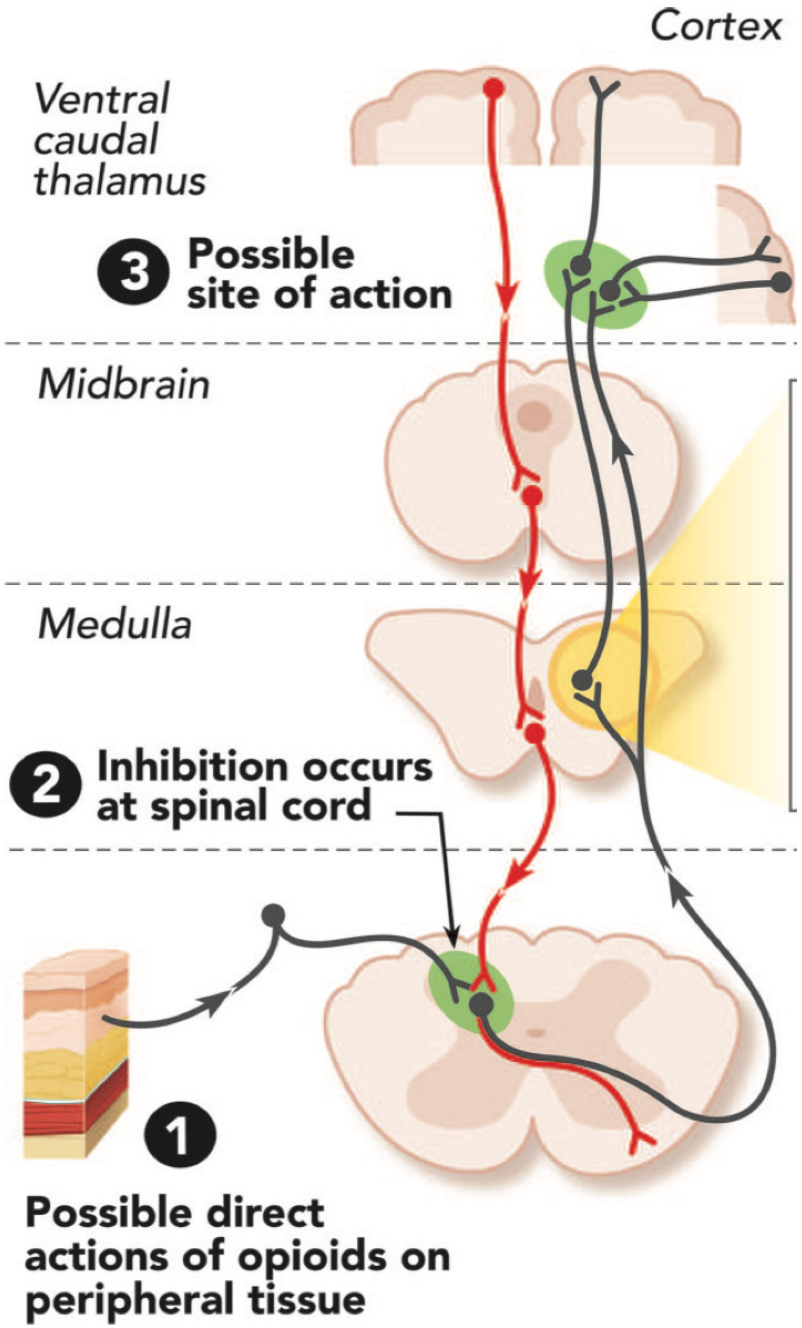
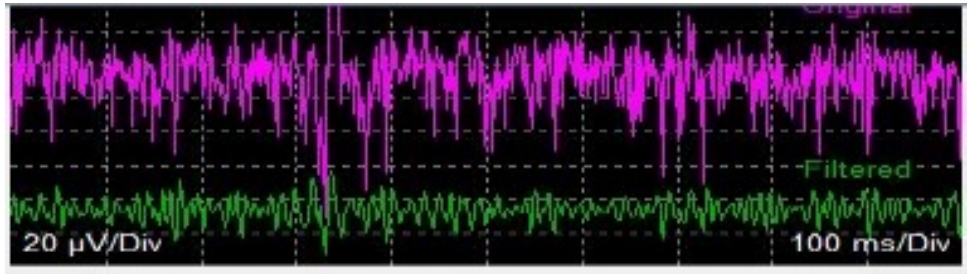

Cortex
Ventral caudal thalamus
3 Possible site of action
Midbrain
Medulla
2 Inhibition occurs at spinal cord
1
Possible direct actions of opioids on peripheral tissue

Spinal Cord in Response to a Pain Stimulus



Higher frequency and higher energy electrical activity

Reverts to quiescent state when stimulus ceases…