# Neuropathic Pain after Spinal Cord Injury

Zaman Mirzadeh MD PhD

Assistant Professor of Neurosurgery
Barrow Neurological Institute
Phoenix, AZ

# Disclosures

none

# Overview

*Impact of SCI pain*

*Pain types*

*Pain pathway anatomy*

*SCI pain mechanisms*

*Therapeutic options*

# Scope of the problem

## Frequency and Severity of 7 symptoms in SCI patients

| Symptom* | Frequency of Occurrence (% >1) | Frequency of Severe Symptom (% >6) | Average Severity (mean ± SD) |
|---|---|---|---|
| Pain | 84 | 35 | 4.17±3.08 |
| Weakness | 64 | 18 | 3.21±3.10 |
| Fatigue | 67 | 18 | 3.23±2.91 |
| Numbness | 66 | 38 | 4.41±3.89 |
| Memory loss | 27 | 5 | 1.11±2.14 |
| Vision loss | 27 | 4 | 0.99±1.96 |
| Shortness of breath | 34 | 8 | 1.52±2.61 |

*All symptoms rated by respondents on a 0 (none) to 10 (very severe) scale.

## Correlation coefficients between Symptom Severity and Patient Function

| Symptom | Community Integration (CIQ) | | | Psychologic Functioning (SF-36 mental health scale) |
|---|---|---|---|---|
| | Home Competency | Social Integration | Productive Activity | |
| Pain | −.05 | −.33* | −.16 | −.40* |
| Weakness | −.15 | −.33* | −.14 | −.32* |
| Fatigue | −.09 | −.31* | −.17 | −.34* |
| Numbness | −.03 | −.11 | −.14 | −.23 |
| Memory loss | −.13 | −.32* | −.11 | −.34* |
| Vision loss | .01 | .00 | −.08 | −.08 |
| Dyspnea (shortness of breath) | −.06 | −.02 | −.19 | −.18 |

*$P<.002$.

MP Jensen et al., 2007

# Types of pain after SCI

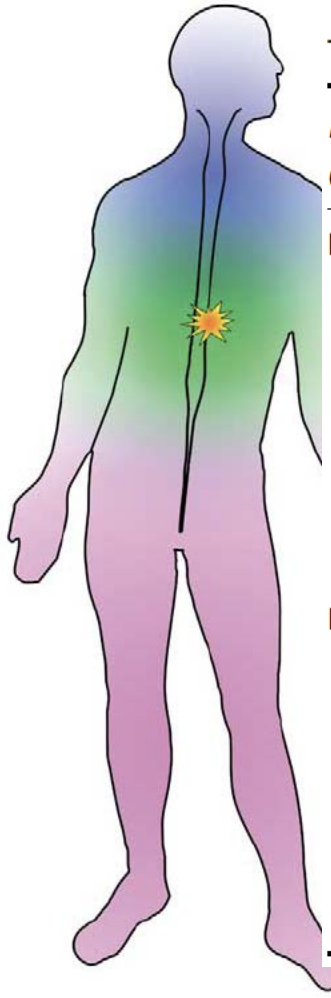


**Table 1** Proposed IASP classification of pain following SCI

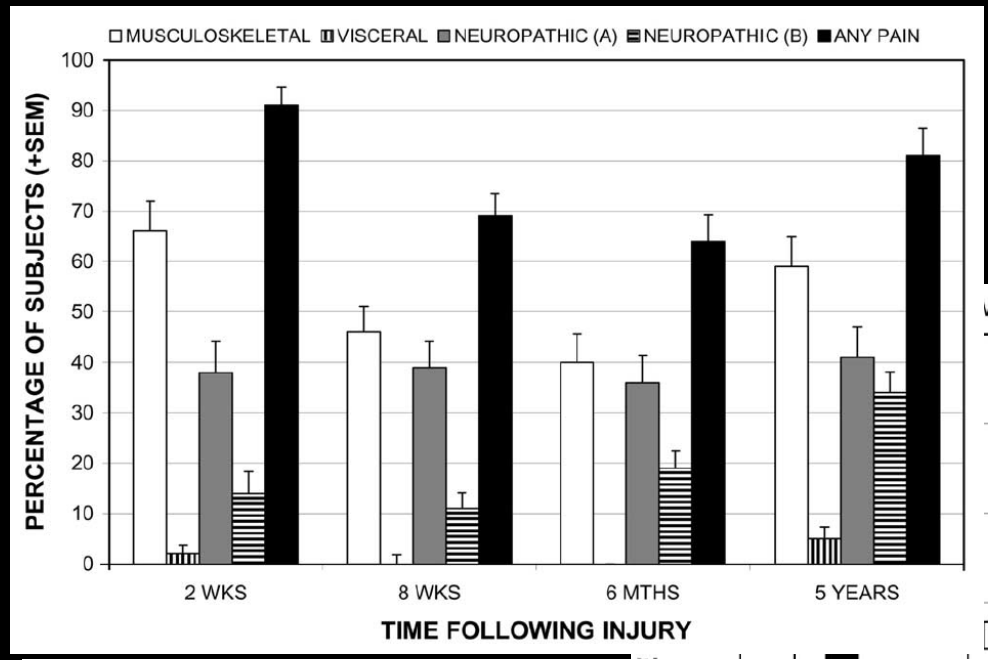
| *Broad type (Tier 1)* | *Broad system (Tier 2)* | *Specific structures/pathology (Tier 3)* |
|---|---|---|
| Nociceptive | Musculoskeletal | Bone, joint, muscle trauma or inflammation<br>Mechanical instability<br>Muscle spasm<br>Secondary overuse syndromes |
| | Visceral | Renal calculus, bowel, sphincter dysfunction, etc.<br>Dysreflexic headache |
| Neuropathic | Above level | Compressive mononeuropathies<br>Complex regional pain syndromes |
| | At level | Nerve root compression (including cauda equina)<br>Syringomyelia<br>Spinal cord trauma/ischemia |
| | Below level | Spinal cord trauma/ischemia |

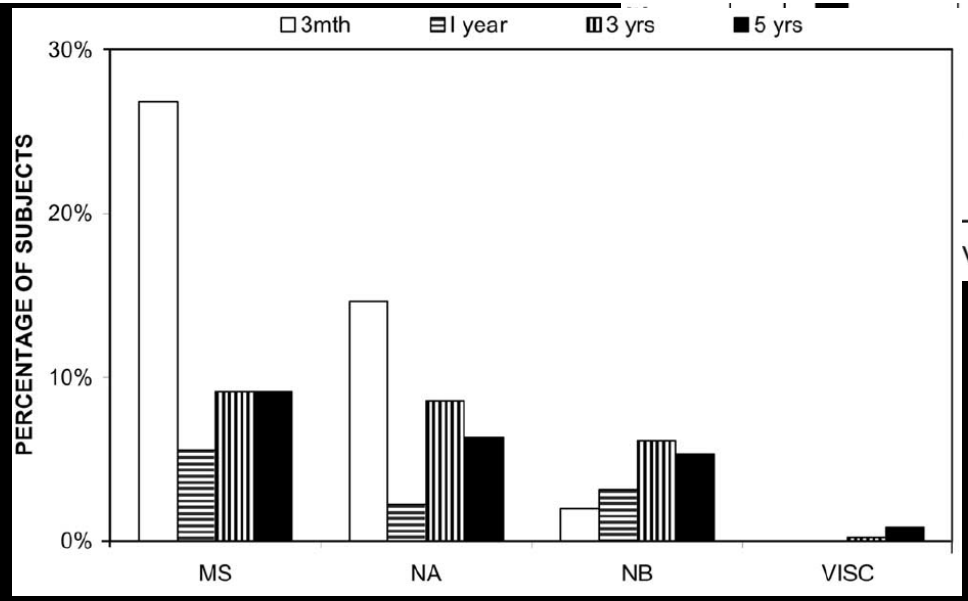
Siddall, 2009, Spinal Cord

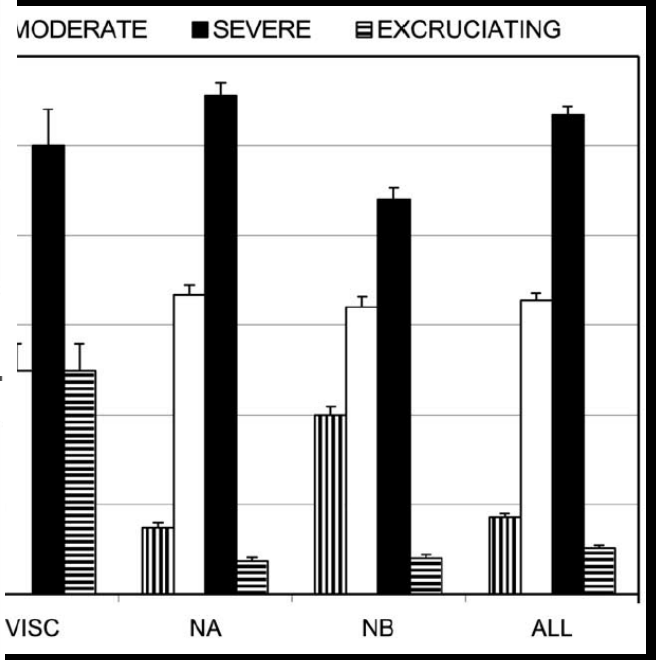
Waxman et al., 2006, Trends Neurosci

BARROW Neurological Institute

# Types of pain after SCI



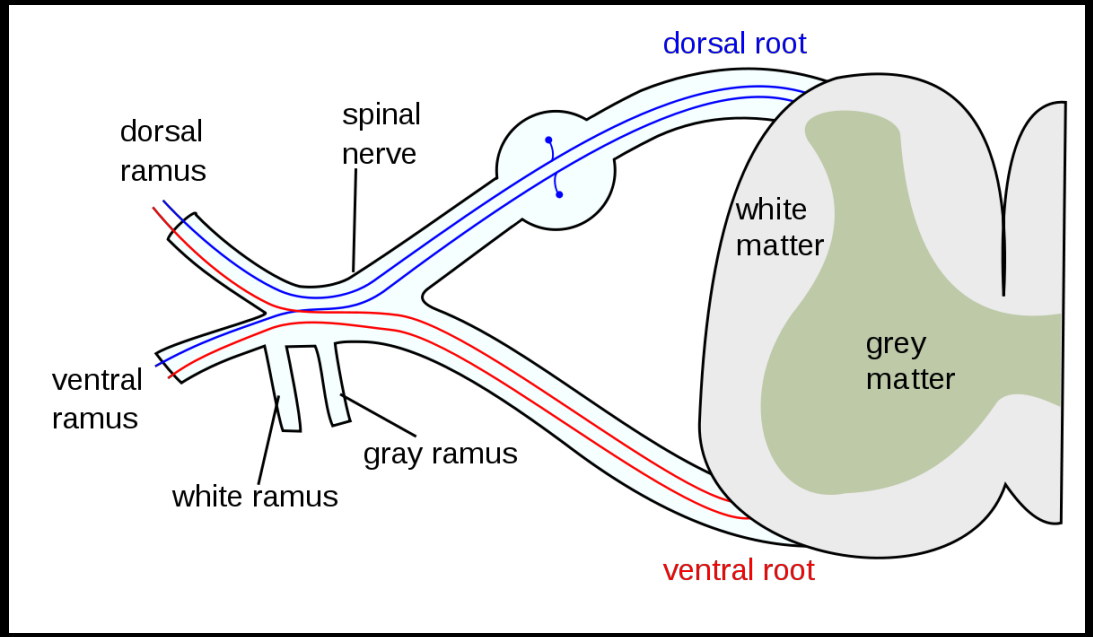




Siddall et al., 2003, Pain

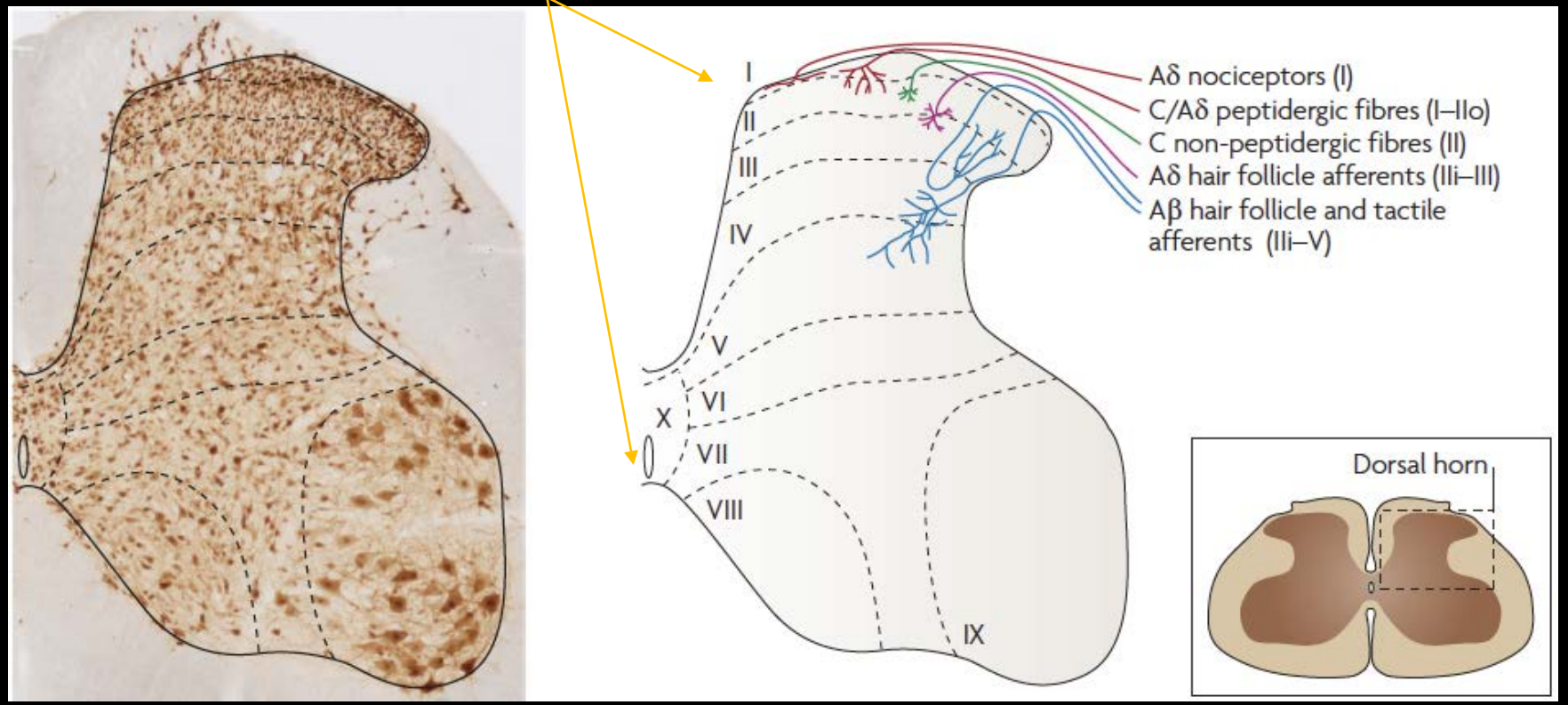
# The pain pathway: peripheral anatomy

Nociception is the process by which intense thermal, mechanical, or chemical stimuli are detected by a subpopulation of peripheral nerve fibers, called nociceptors (Basbaum and Jessell, 2000)



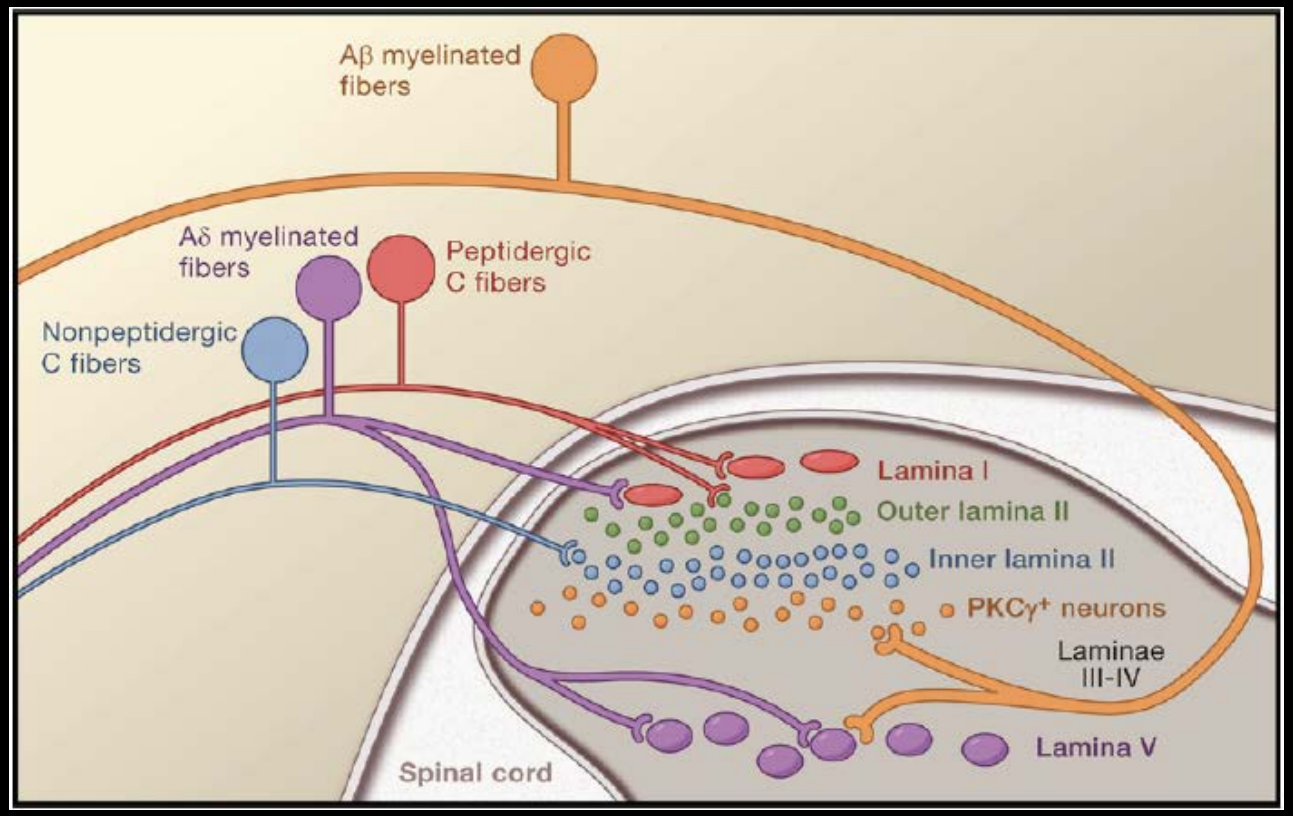
# Nociceptor projections are stratified to specific laminae in the spinal cord dorsal horn

Rexed's laminae




Todd et al., 2010

# Nociceptor projections are stratified to specific laminae in the spinal cord dorsal horn

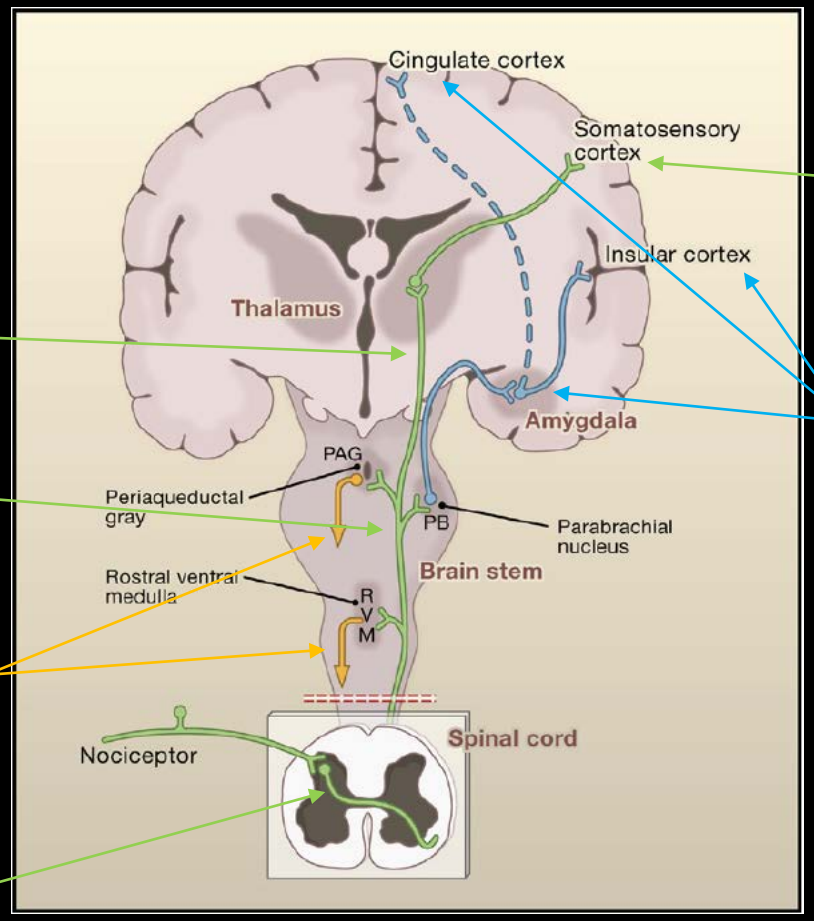



Electrophysiological studies of dorsal horn neurons:

- Lamina I neurons primarily responsive to noxious stimuli (Aδ and C afferents)
- Lamina III and IV neurons primarily responsive to innocuous stimuli (Aβ)
- Lamina V neurons with convergent nonnoxious and noxious input via direct (monosynaptic) Aβ and Aδ and indirect (polysynaptic) C fiber inputs→ *Wide Dynamic Range Neurons (WDR)*

Basbaum et al., 2009

# Supraspinal projections and pain processing




Sensory-discriminative pain

aversive/emotional properties of pain experience

Spinothalamic tract

Spinoreticulothalamic tract

Descending modulation: Periaqueductal grey & rostral ventral medulla

Projection neurons in laminae I & V constitute major output from dorsal horn to brain

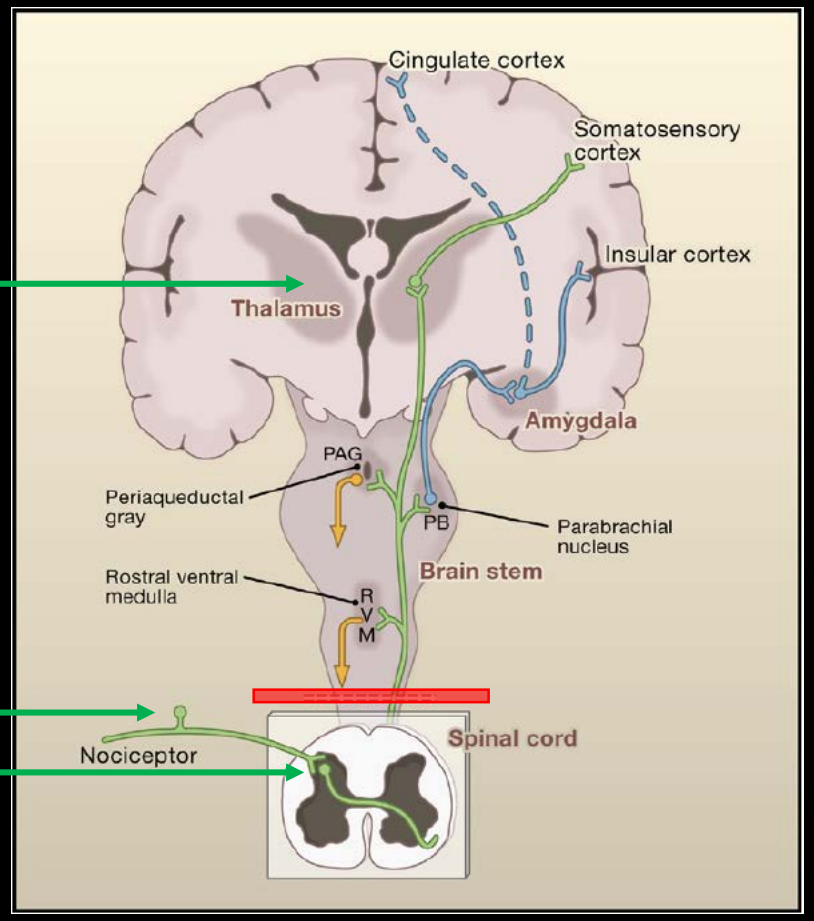
Basbaum et al., 2009

# Mechanisms of neuropathic pain after SCI

Brain

Peripheral

Spinal cord

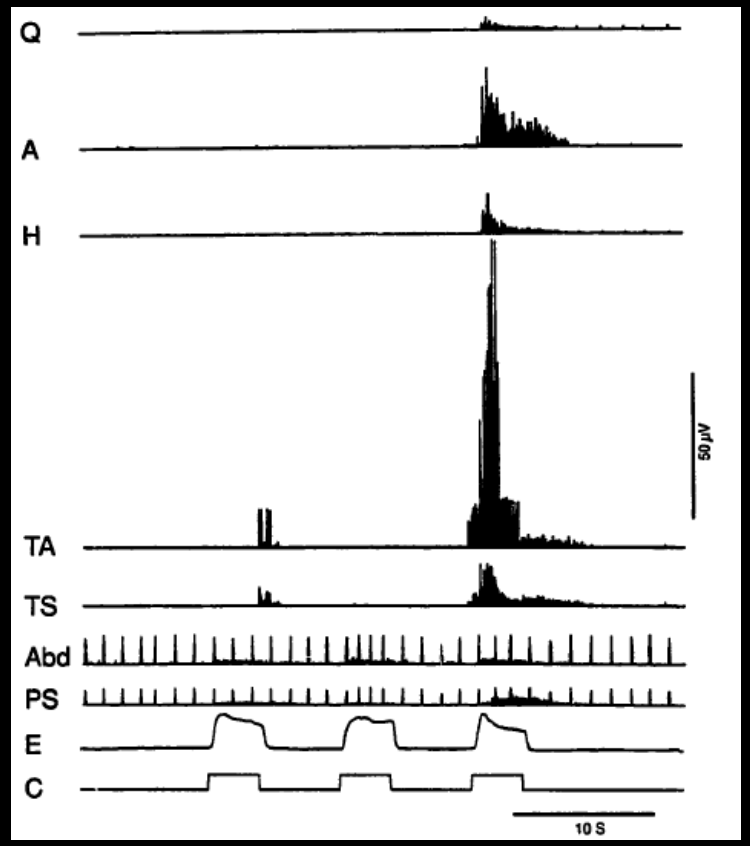



Basbaum et al., 2009

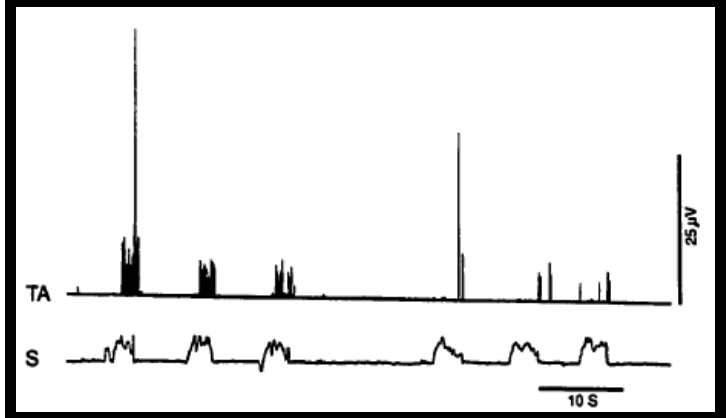
# Peripheral mechanisms of neuropathic pain following SCI

## "Discomplete" SCI is common

74 of 88 clinically complete SCI patients (84%) had discomplete injuries on Brain Motor Control Assessment



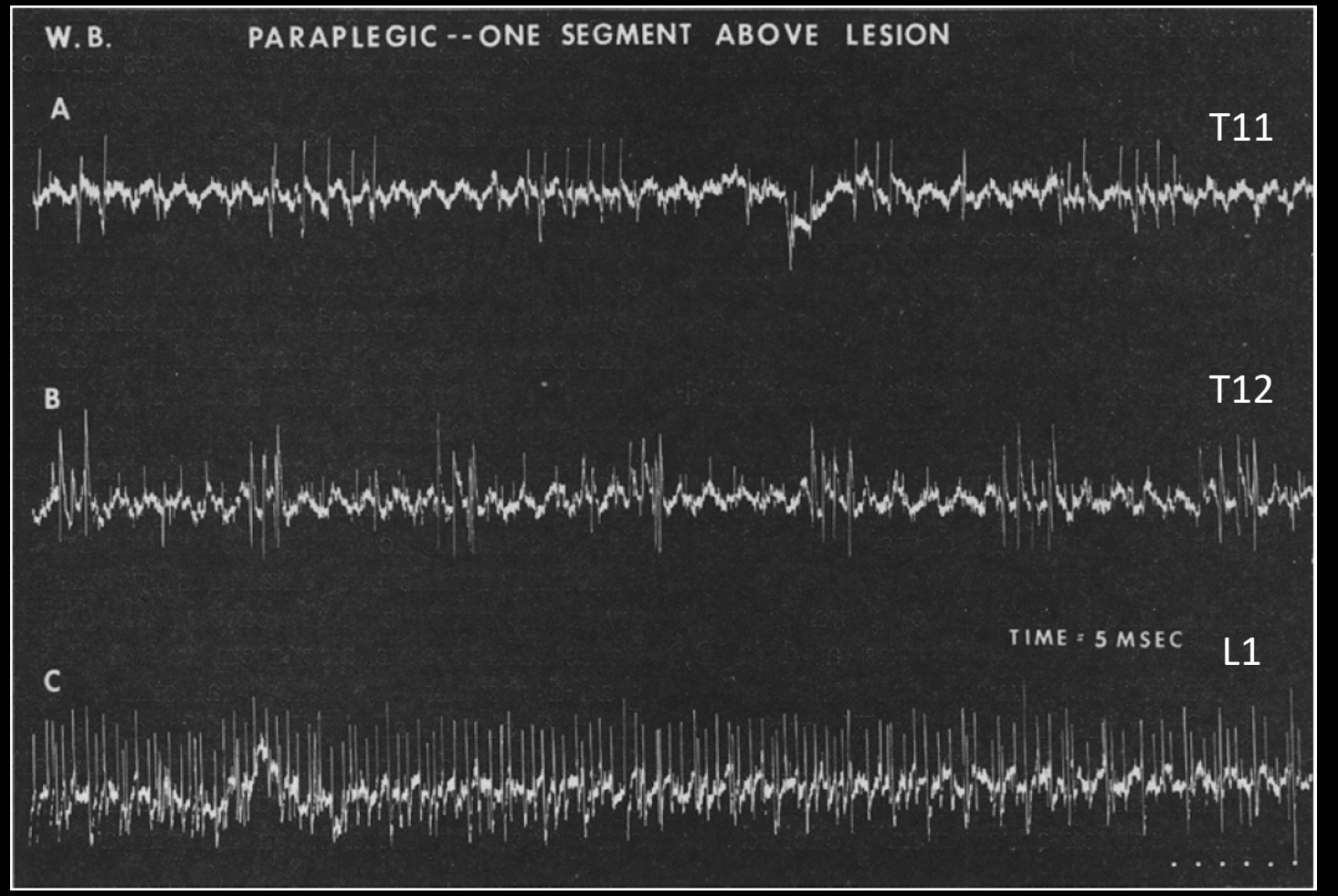

Jendrassik maneuver elicits EMG activity below lesion




Voluntary suppression of plantar withdrawal reflex

Sherwood et al., 1992, J Neurol Sci

# Spinal mechanisms of neuropathic pain following SCI



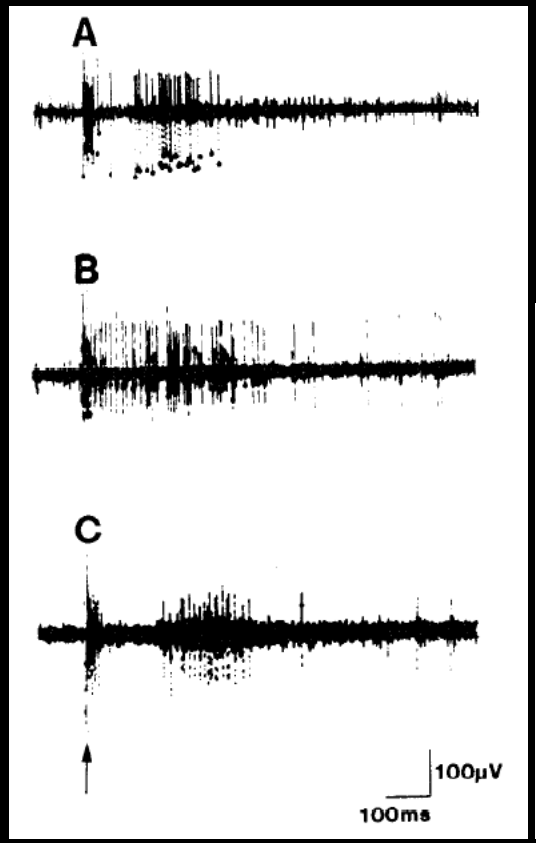

Patient with L1 sensory/motor level

"These cells also seem to lose their graded response to peripheral stimuli and fire with abnormally prolonged bursts to any suprathreshold stimulus. This might be analogous to the long-lasting, diffuse pain which our patient reported when his partially innervated thighs were stimulated."

Loeser et al., 1968, J Neurosurg

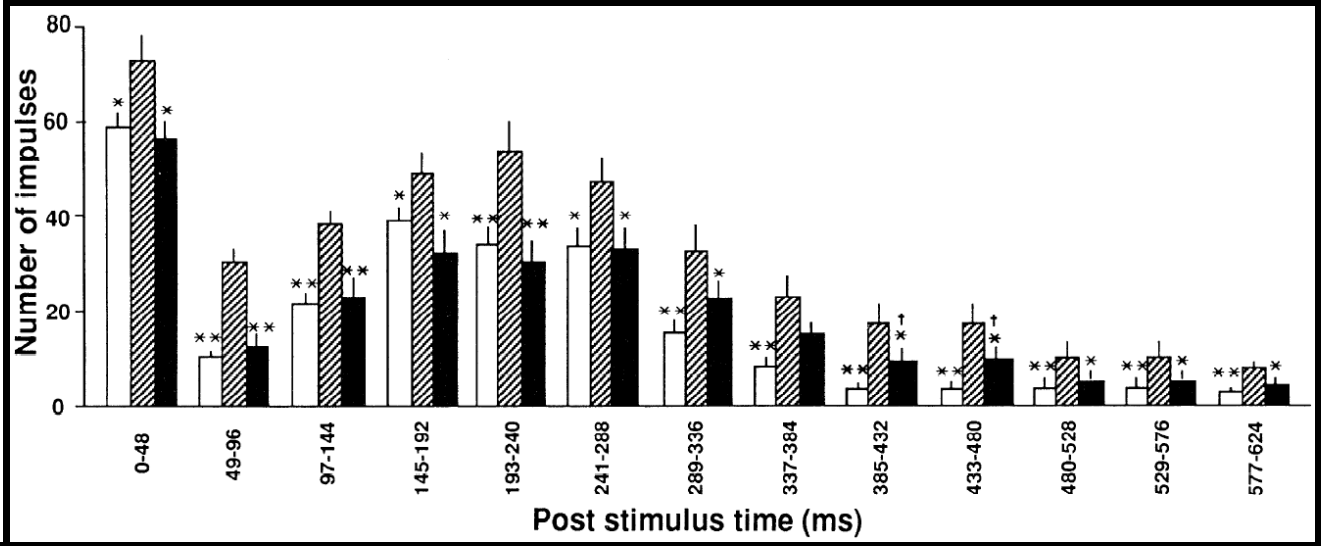
# Spinal mechanisms of neuropathic pain following SCI

Separation and Aδ and C input




WDR neuron response to subcutaneous electrical stimulation

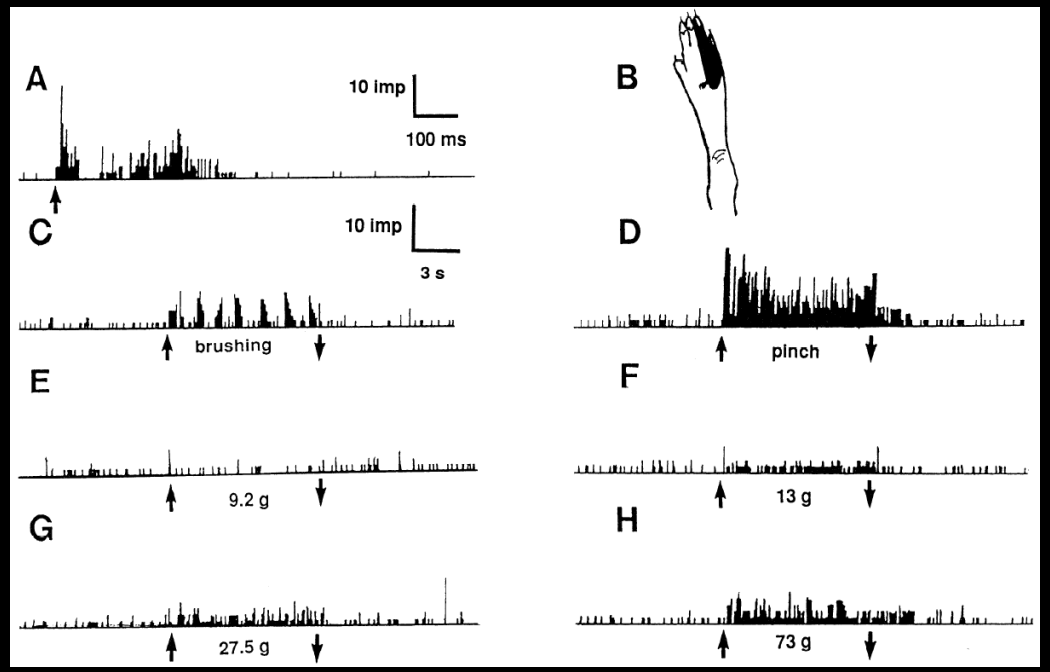
A) Normal
B) 2d after transient SC ischemia (period of allodynia)
C) 15d after transient SC ischemia (recovery from allodynia)

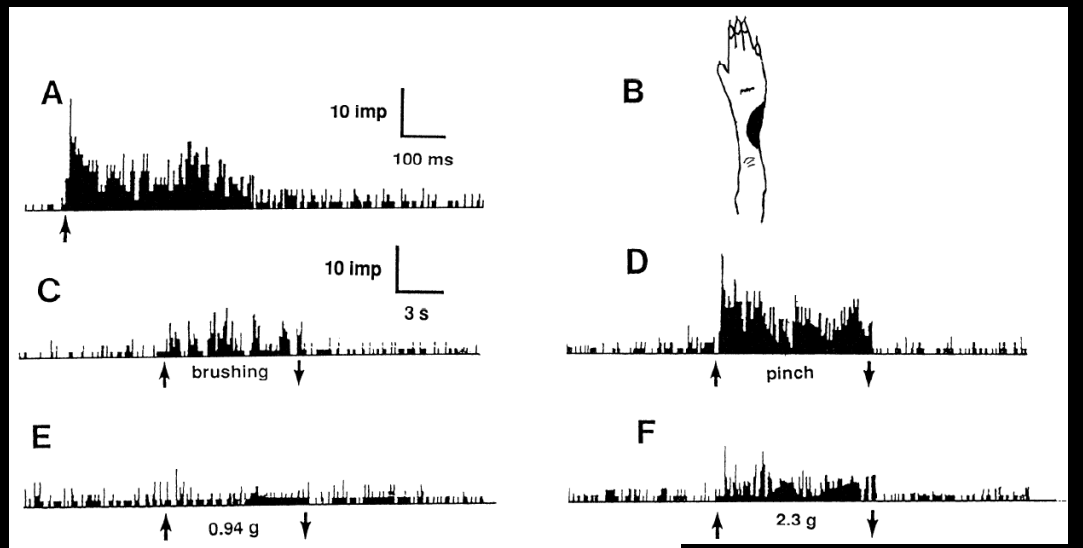


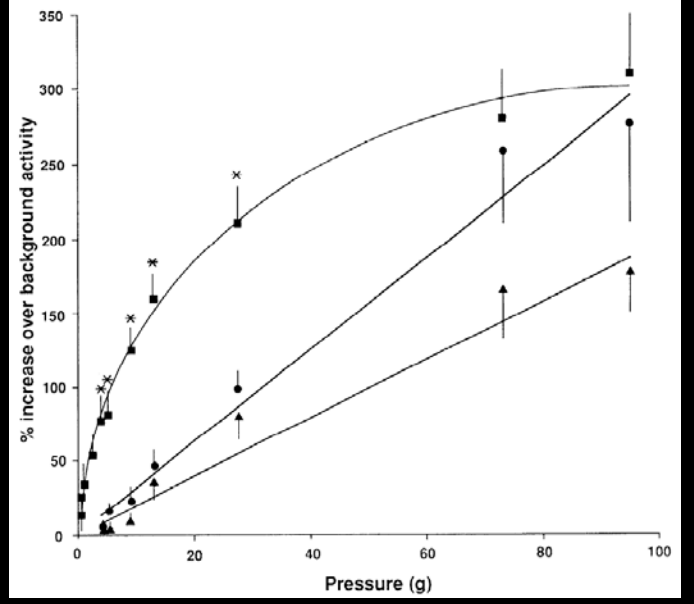

Hao et al., 1992, J Neurophys.

# Spinal mechanisms of neuropathic pain following SCI

## WDR neuron response to graded mechanical stimuli

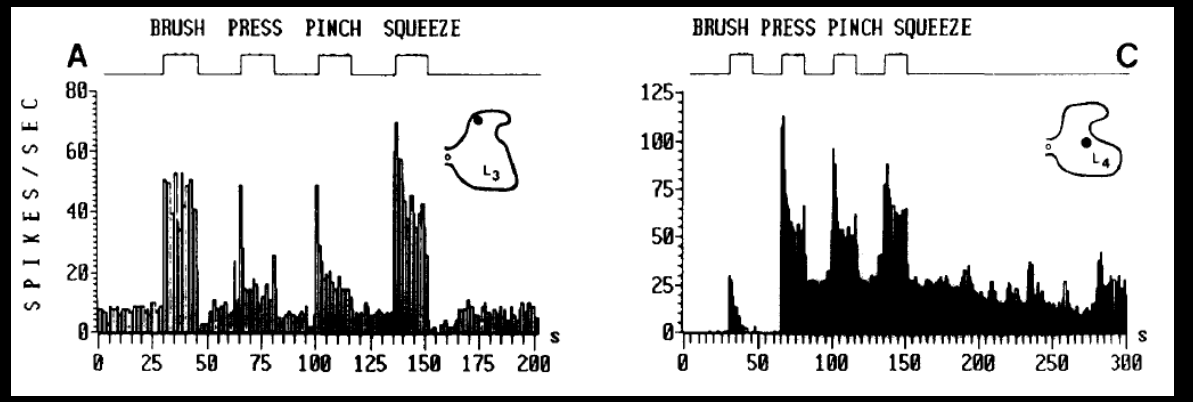


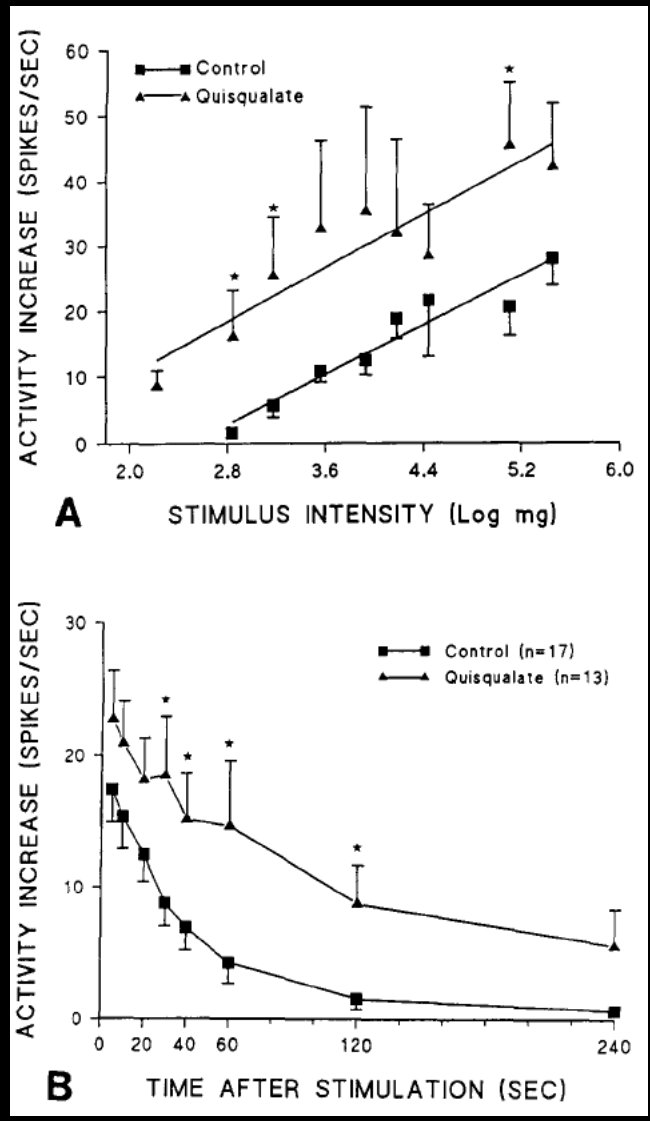

Hao et al., 1992, J Neurophys.

# Spinal mechanisms of neuropathic pain following SCI




Changes in Dorsal Horn Nociceptive Neuron Responses:

↑proportion of cells responding to noxious stimulation
↑spontaneous discharges/background activity
↑evoked activity to innocuous and noxious stimuli
↑after-discharges following stimulation




Yezierski et al., 1993, Neurosci Lett
Waxman et al., 2006, Trends Neurosci

BARROW
Neurological Institute

# Spinal mechanisms of neuropathic pain following SCI

Changes in dorsal horn neuron response properties are associated with other cellular and molecular changes in the spinal cord after SCI:

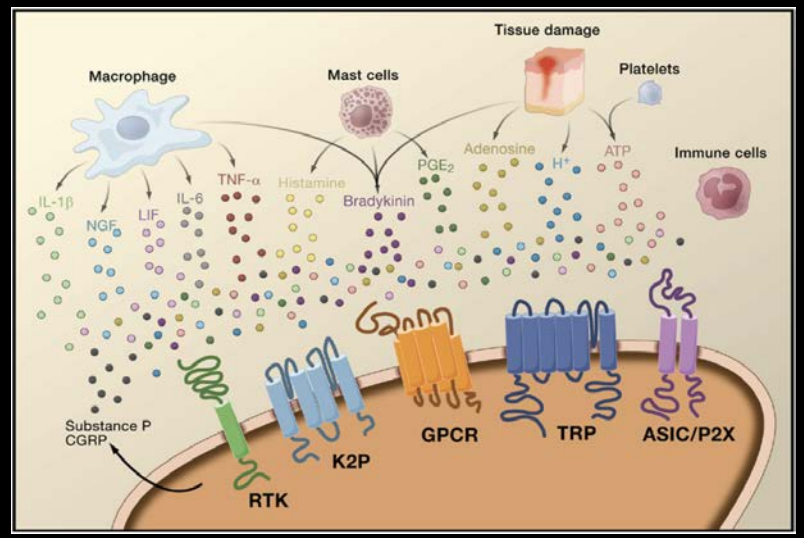
Circuit Reorganization

Glial Activation

Molecular expression changes

Glutamate/Seratonin receptor signaling
Loss of GABAergic inhibition

Cytokine/Prostaglandin release

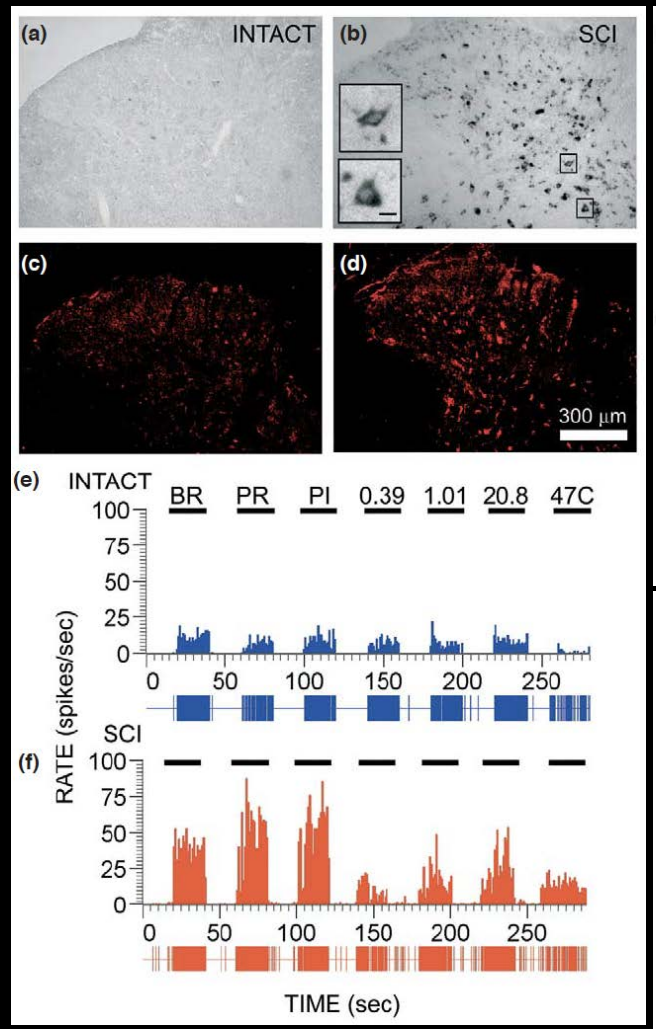


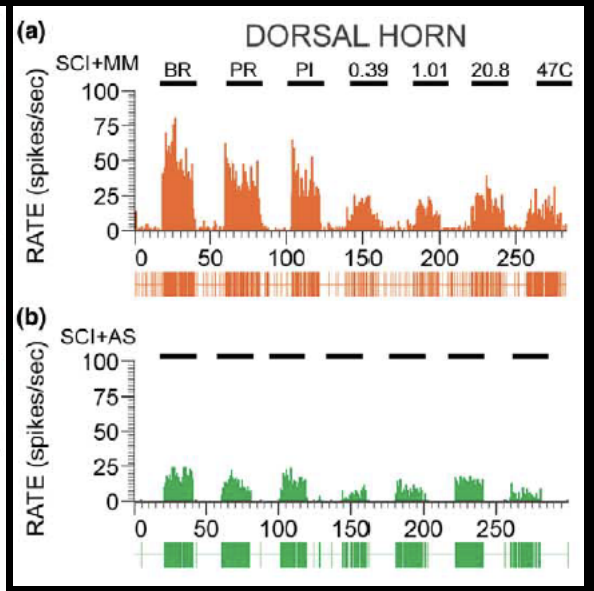

Voltage-gated Na Channel 1.3

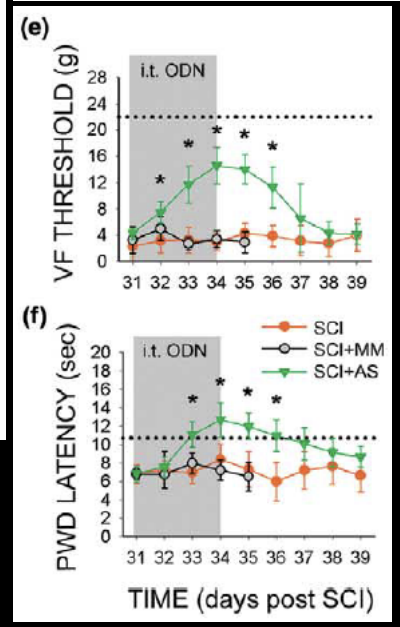
- Rapid recovery from inactivation
- Persistent depolarizing current in response to small subthreshold stimuli


Drew et al., 2004, Pain
Hains et al, 2003, Exp Brain Res
Mills et al, 2002, J Neurotrauma
Hains et al, 2003, J Neurosci
Hains et al, 2005, Brain

# Spinal mechanisms of neuropathic pain following SCI




Molecular expression changes

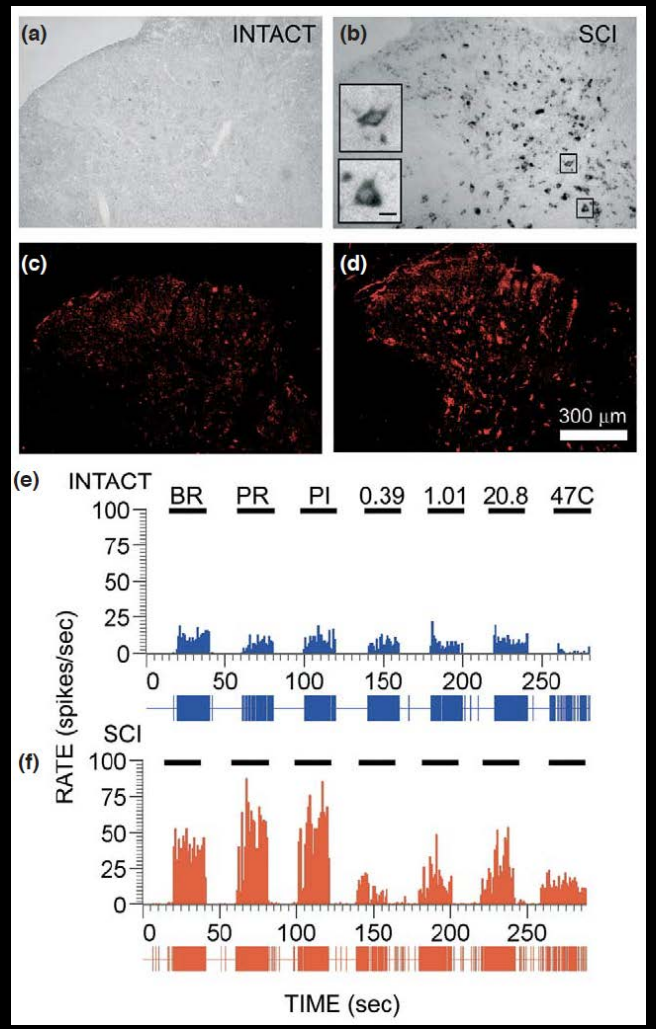
Voltage-gated Na Channel 1.3

- Rapid recovery from inactivation
- Persistent depolarizing current in response to small subthreshold stimuli

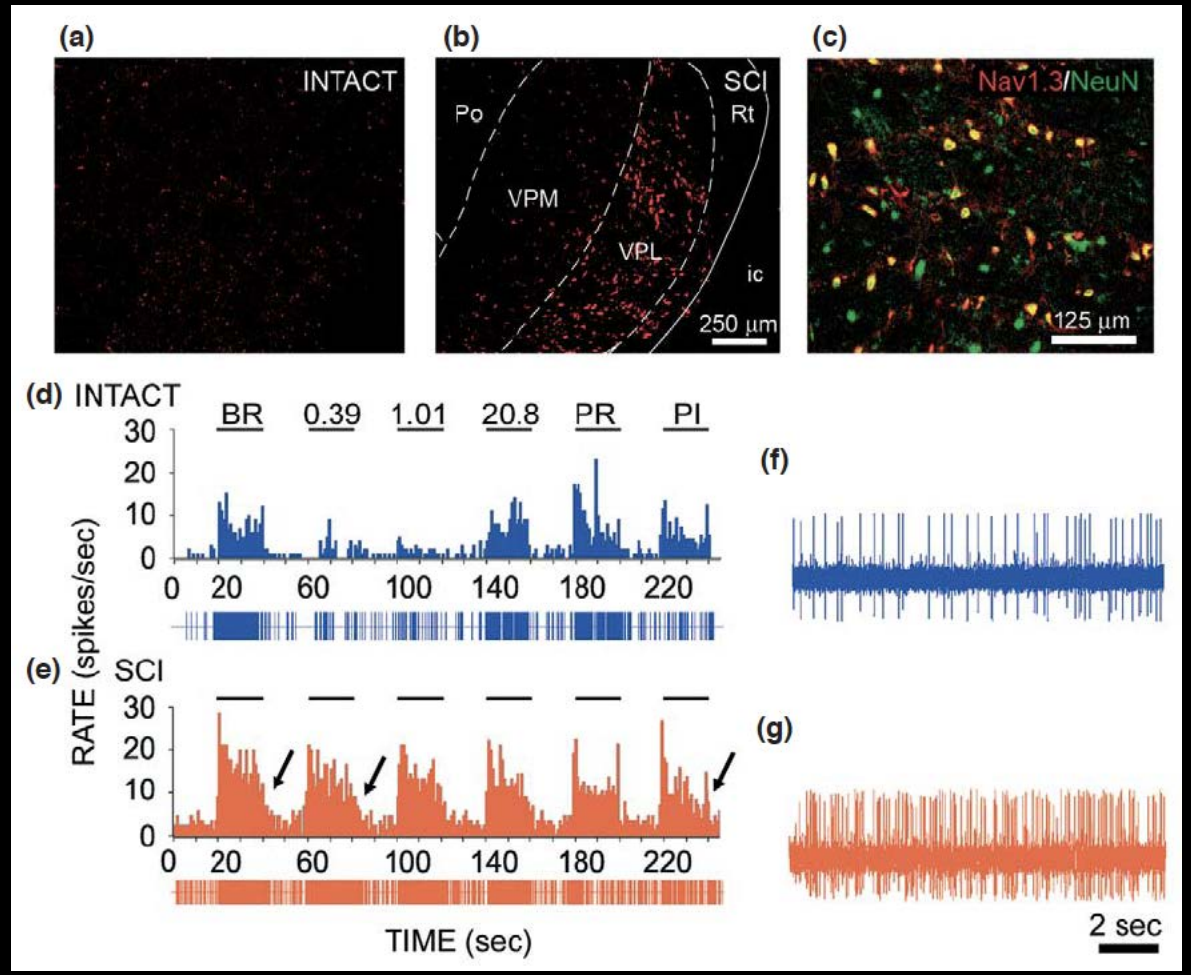
Drew et al., 2004, Pain
Hains et al, 2003, Exp Brain Res
Mills et al, 2002, J Neurotrauma
Hains et al, 2003, J Neurosci
Hains et al, 2005, Brain

BARROW Neurological Institute

# Spinal mechanisms of neuropathic pain following SCI




Similar hyperactivity observed in sensory thalamic neurons




Drew et al., 2004, Pain
Hains et al, 2003, Exp Brain Res
Mills et al, 2002, J Neurotrauma
Hains et al, 2003, J Neurosci
Hains et al, 2005, Brain

# Brain mechanisms of neuropathic pain following SCI

Cha
Neu sory
Nuc

**PHANTOM BODY PAIN IN PARAPLEGICS: EVIDENCE FOR A CENTRAL "PATTERN GENERATING MECHANISM" FOR PAIN**

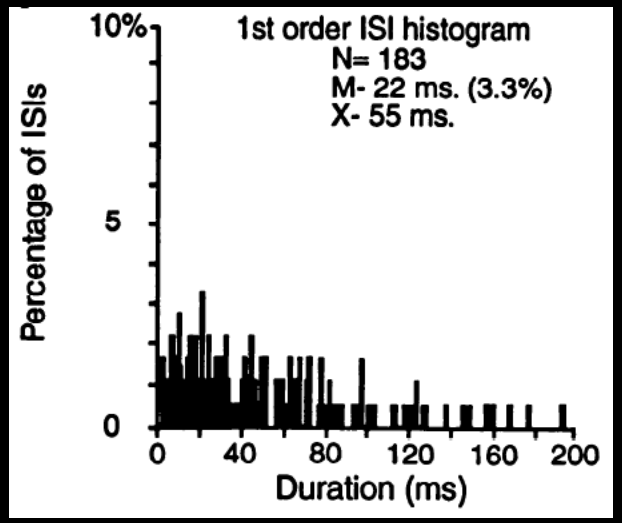
RONALD MELZACK and JOHN D. LOESER

F. A. I SKY
Depart iversity,
Baltim oronto,
Toront

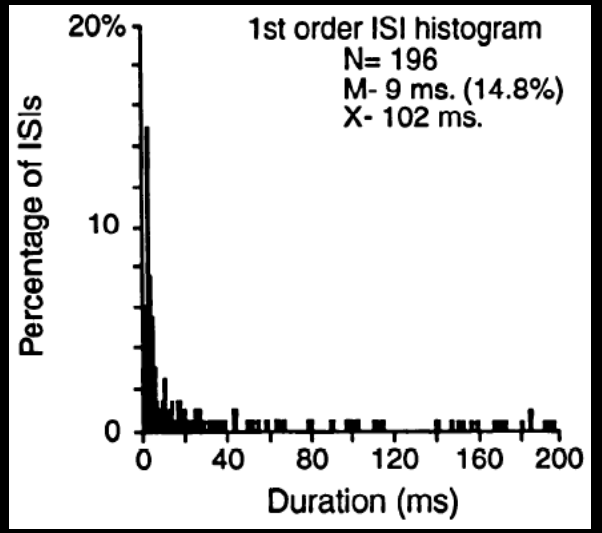
*Department of Psychology, McGill University, Montreal, Que. (Canada) and Department of Neurological Surgery, University of Washington, School of Medicine, Seattle, Wash. 98195 (U.S.A.)*

(Accepted May 24th, 1977)

Single unit recordings from sensory thalamus (Vc)




movement disorder patients




SCI patients

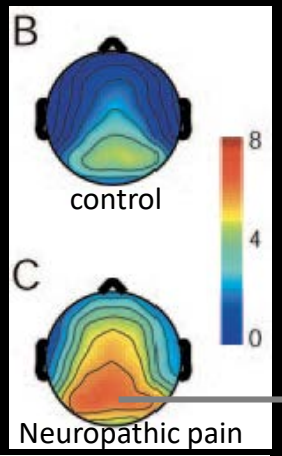
Neurons in sensory thalamus (Vc) display high-frequency bursting pattern of activity after SCI

BARROW Neurological Institute

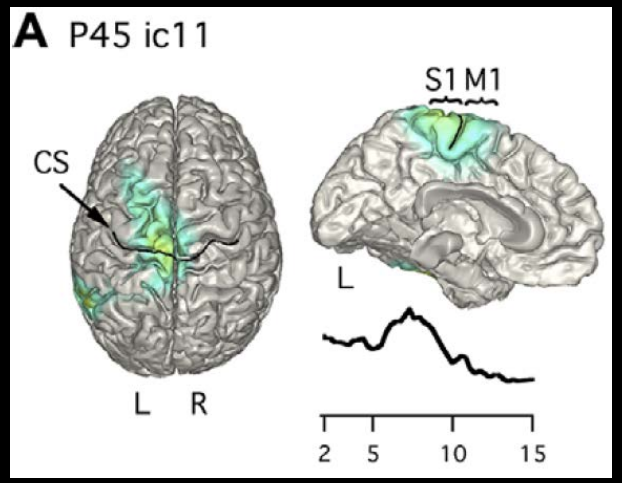
# Brain mechanisms of neuropathic pain following SCI

Thalamocortical Dysrhythmia (TCD): *a centralized pain echo*
abnormal resonant interaction between thalamus and cortex that results in widespread coherence in low frequency (theta) activity

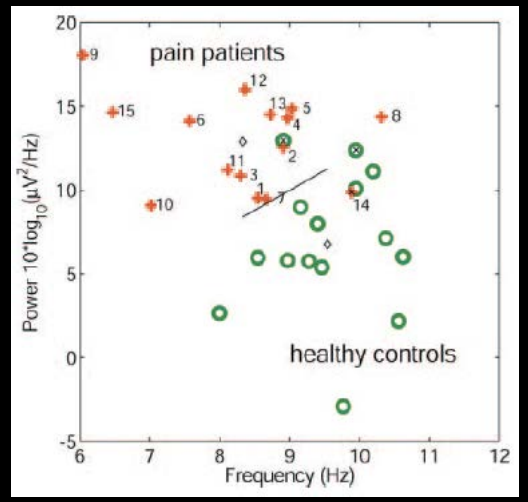
Theta-alpha EEG power distribution

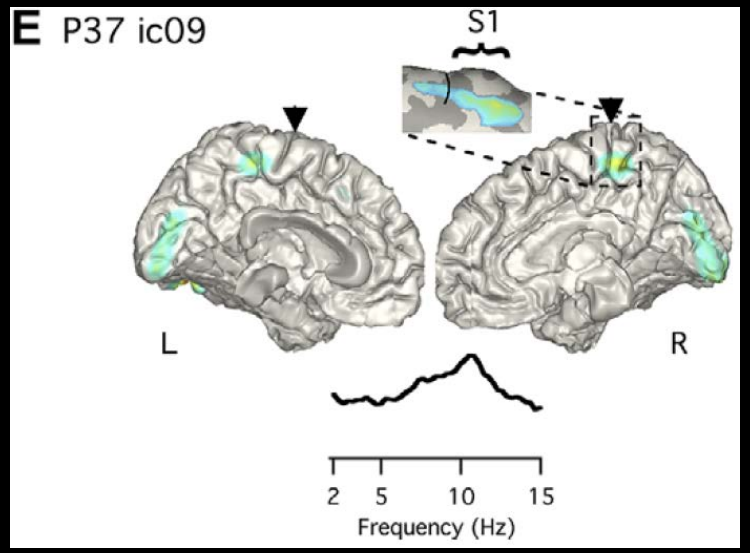



Localization using ICA




Woman with right forearm/wrist pain




Woman with bilateral foot/ankle pain

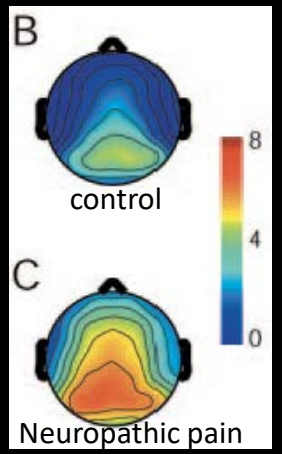
Boord et al., 2008, Spinal Cord

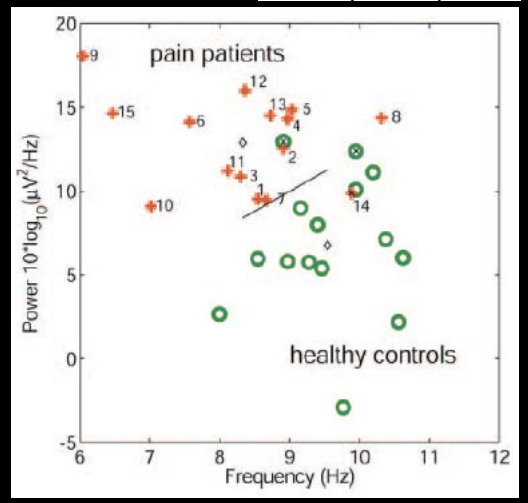
BARROW Neurological Institute

# Brain mechanisms of neuropathic pain following SCI

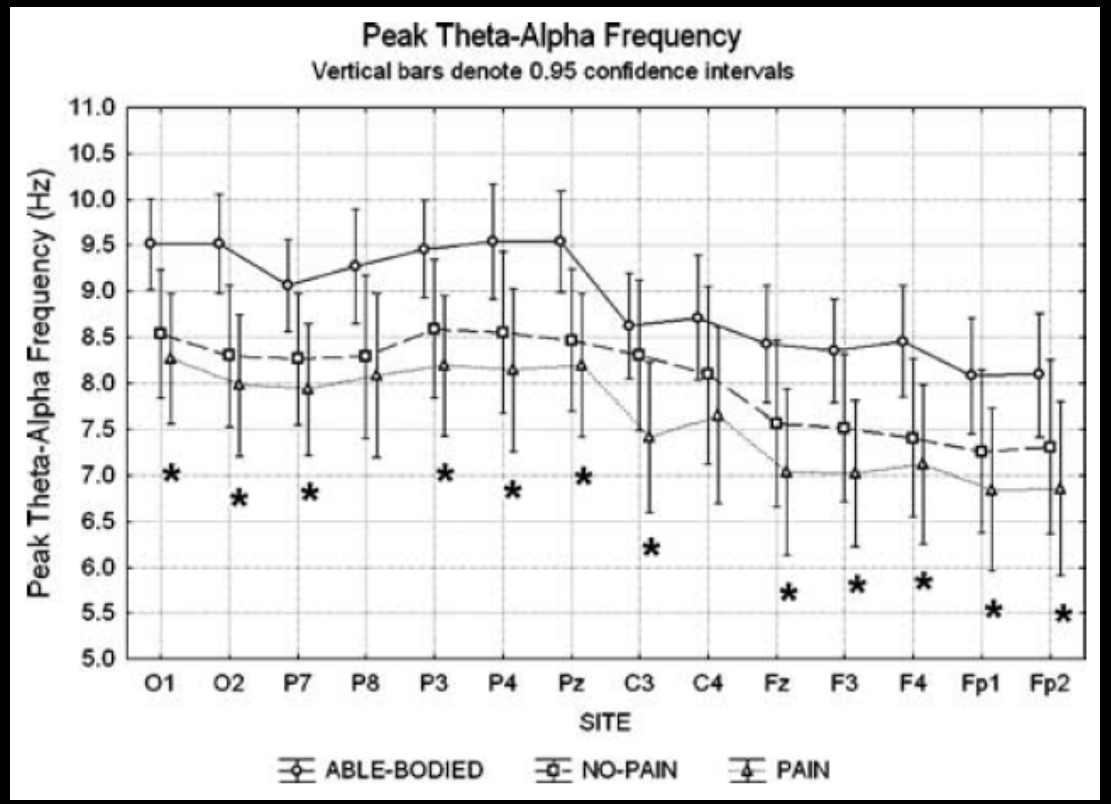
Thalamocortical Dysrhythmia (TCD): *a centralized pain echo*
abnormal resonant interaction between thalamus and cortex that results in widespread coherence in low frequency (theta) activity

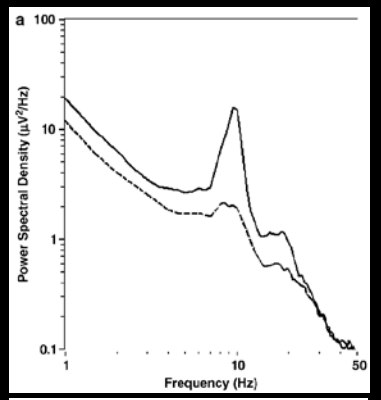
Theta-alpha EEG power distribution



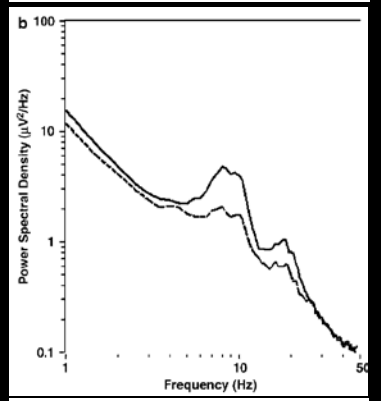




## TCD in SCI neuropathic pain

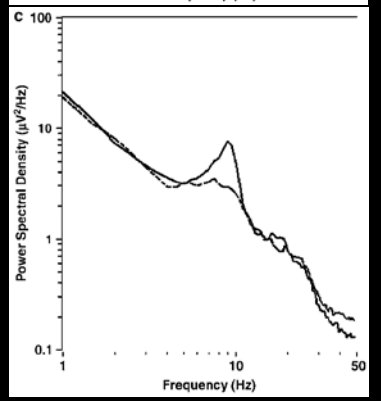



SC intact




SCI no pain

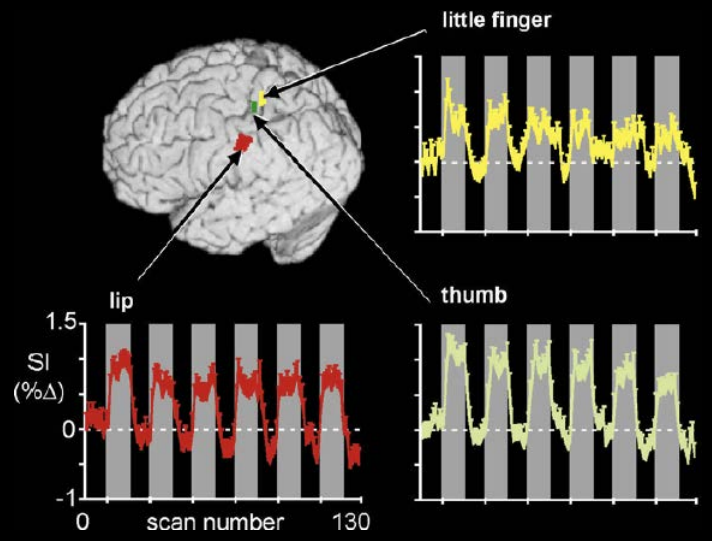


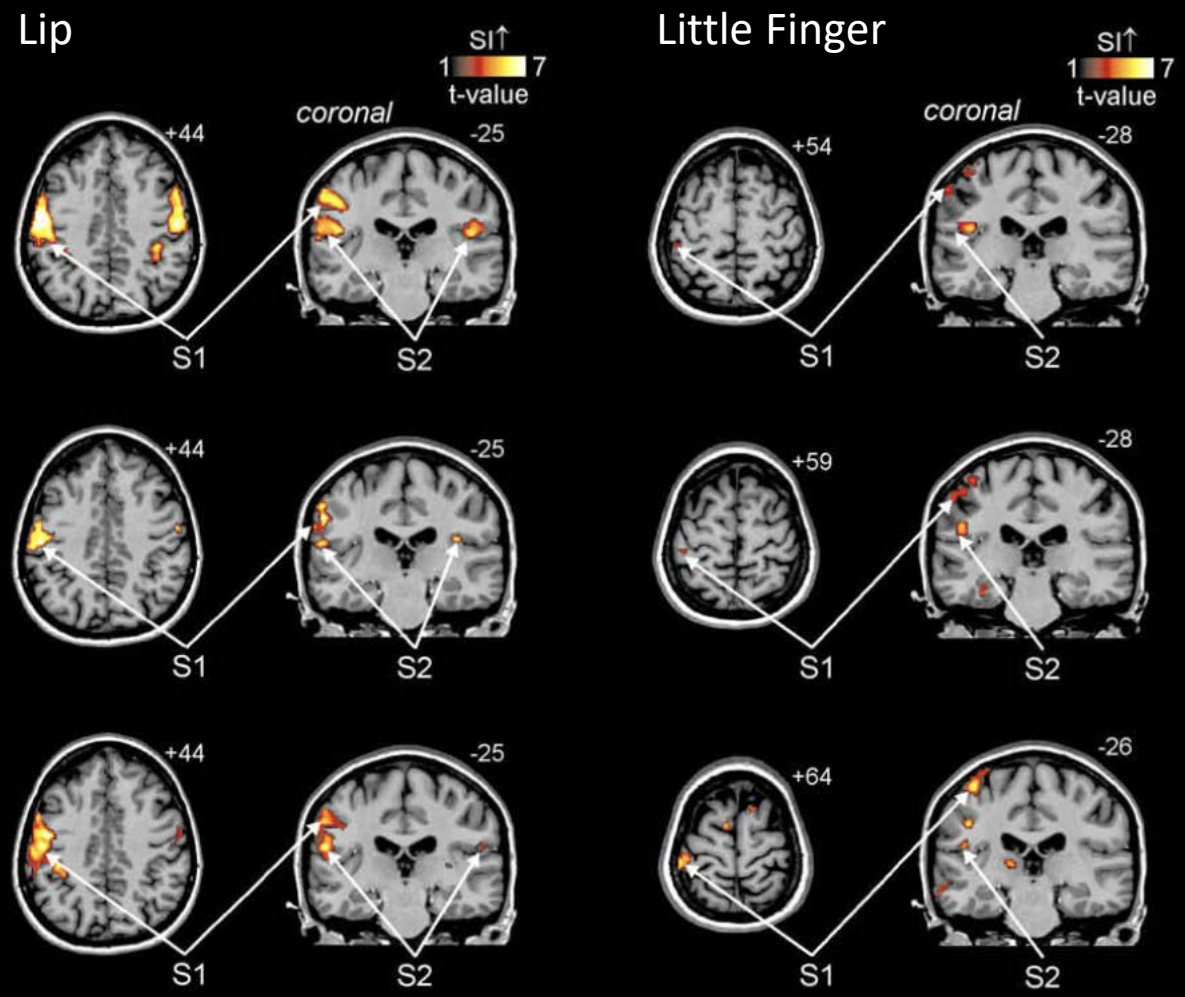

SCI pain

Boord et al., 2008, Spinal Cord

# Brain mechanisms of neuropathic pain following SCI

## Cortical reorganization associated with SCI neuropathic pain intensity



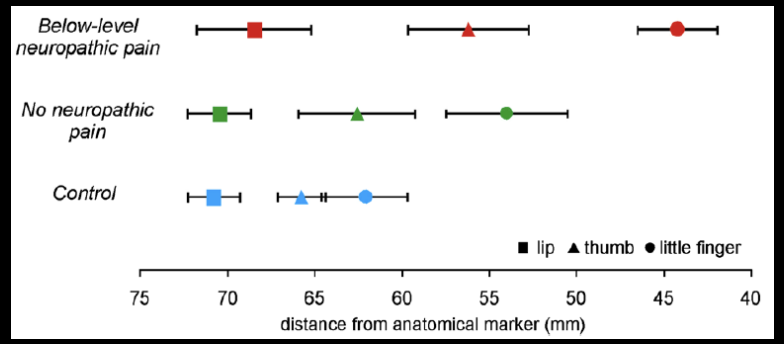



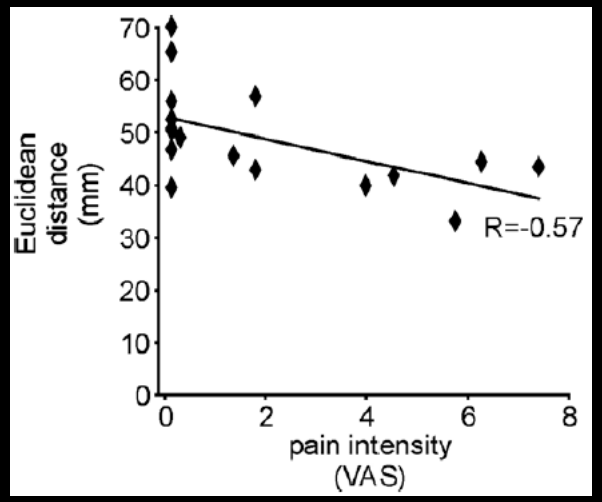

Wrigley et al., 2009, Pain

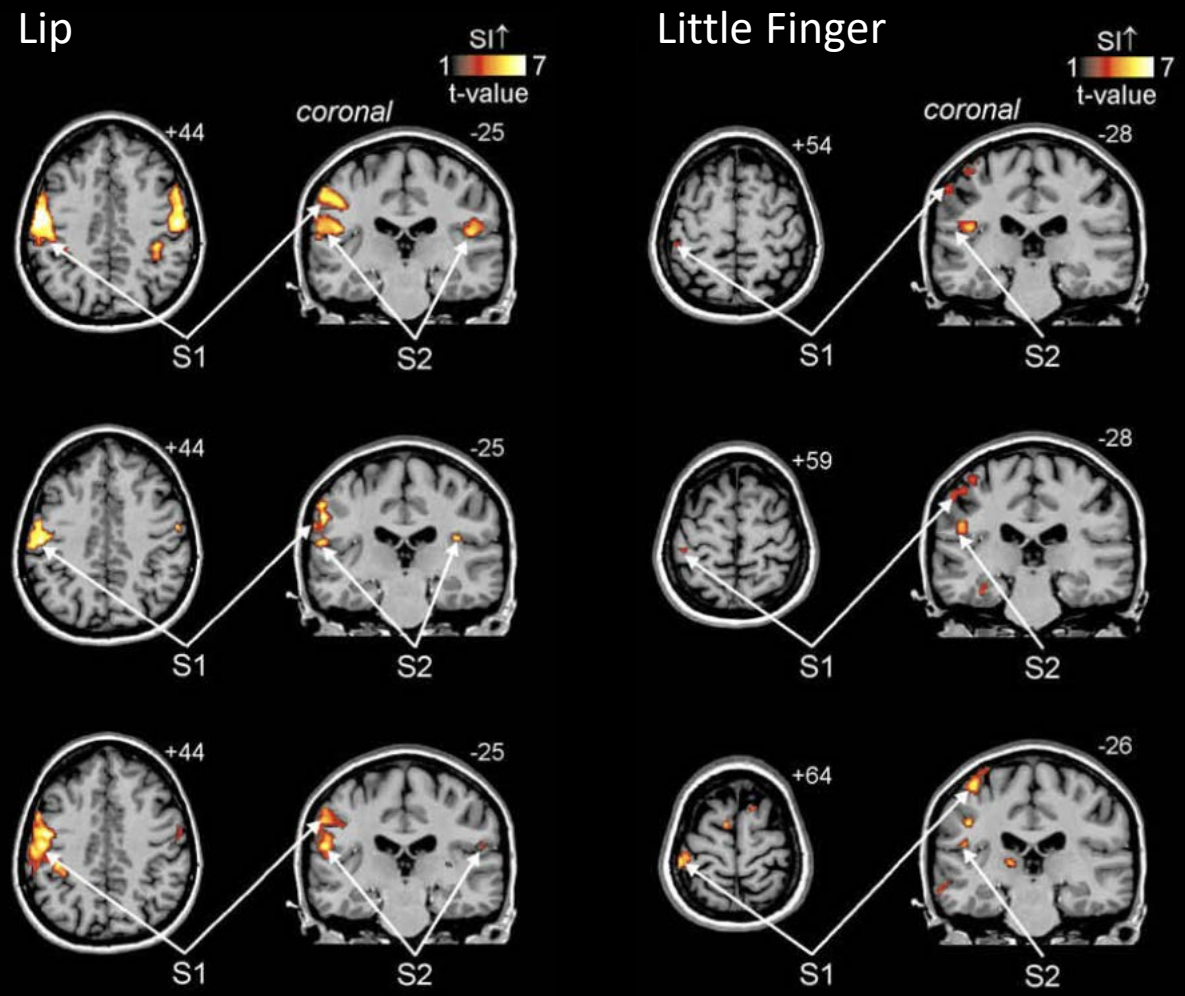
BARROW Neurological Institute

# Brain mechanisms of neuropathic pain following SCI

## Cortical reorganization associated with SCI neuropathic pain intensity




Wrigley et al., 2009, Pain

BARROW Neurological Institute

# Thank you

BARROW
Neurological Institute®