

# EDS & Pain



Norman Marcus, M.D.  
Director, Norman Marcus Pain Institute  
Clinical Associate Professor of Anesthesiology and Psychiatry  
Director, Division of Muscle Pain Research  
NYU School of Medicine

Six clinical types  
Defective Metabolism of Collagen  
(Tenascin-X)

EDS Type III (Joint Hypermobility)  
and Classic Type represent 90% of  
all EDS cases.

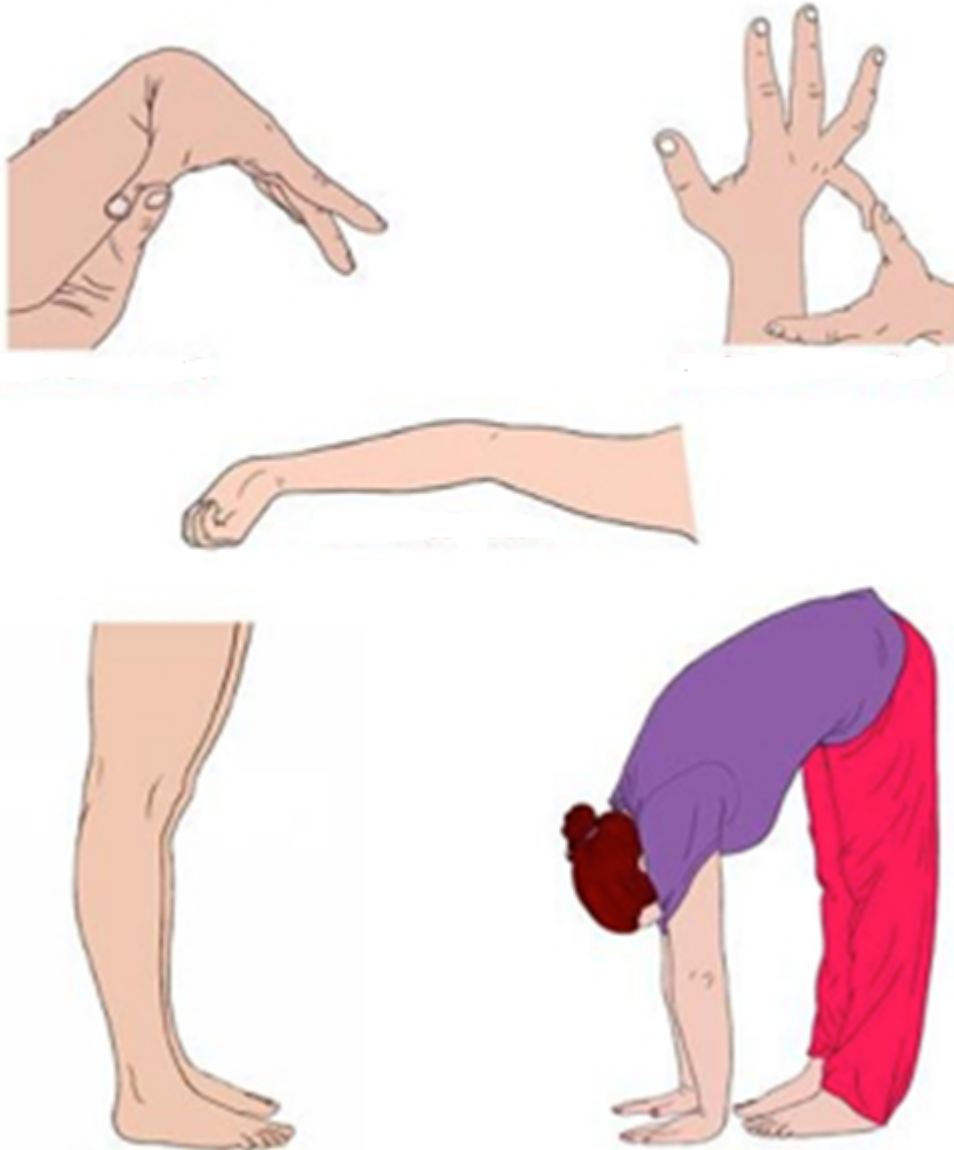
Fragile and stretchy (hyperelastic)  
skin

Unstable and loose  
(hypermobile) joints

Fragile blood vessels and  
body tissues

## THE BEIGHTON SCORE

( 4 / 9 = HYPERMOBILITY )



Clinical  
Diagnosis

No genetic  
test



# Common History with Joint Hypermobility

- Assets
  - Athletic activity/gymnastics
  - Dancing
- Liabilities
  - Joint instability
  - Pain



The majority of patients will at some point in adulthood begin to experience diffuse pain and subjective stiffness.

# Symptoms

## 79 patients (8 men, 71 women)

*Medication, Surgery, and Physiotherapy Among Patients With the Hypermobility Type of Ehler-Danlos Syndrome (Rombaut,, et al, 2011)*

Joint Pain	100%
Joint Dislocation	96.3%
Joint Lock	11.1%
Joint Swelling	3.7%
Muscular Pain	29.6%
Muscle Cramp	66.7%
Muscle Stiffness	7.4%
Muscle Weakness	14.8%
Tendinitis	25.9%
Headache	29.6%
Fatigue	25.9%
Bad physical condition	22.2%
Impaired Balance	3.7%

Pain	100%
Joint Problems	84.8%
Muscle Problems	64.6%
Skin Fragility	63.3%
Dysautonomia	58.2%
Fatigue	49.4%
Headache	36.7%
Neurologic Sxs	29.1%
Infections/Illnesses	27.8%
Cardiorespir. Sx	16.5%
Sleeping Problems	16.5%
Exercise Intol.	15.2%
Inflammation	15.2%
Cognitive Problems	10.1%
Logopedic Problem	7.6%

## 32 patients (all women)

*Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type (Rombaut, et al, 2010)*

# Locations of Pain

Location	Joint Pain (%)	Joint Dislocation (%)
Finger	59.4	44.4
Wrist	48.1	33.3
Elbow	14.8	14.8
Shoulder	85.2	63
Jaw	25.9	18.5
Neck	59.3	
Back	7.8	
Pelvis/Hip	66.7	48.1
Knee	81.5	40.7
Ankle & Foot	77.8	51.9
Toe	11.1	3.7

Rombaut, L., et al., *Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers–Danlos syndrome hypermobility type*. Disability & Rehabilitation, 2010. **32**(16): p. 1339-1345.

# Various Treatments

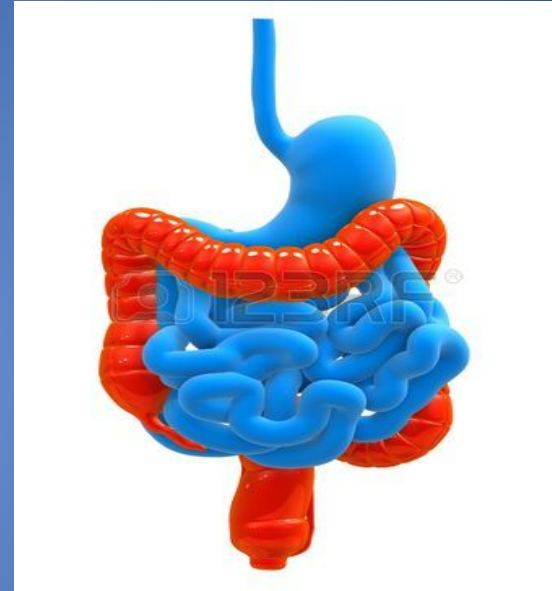
- Medication
  - NSAIDs
  - Opioids
  - Antidepressants
  - Sedatives/Benzos
  - Cardiovascular
  - Pulmonary
- Surgery
- Physiotherapy
  - Strength Training
  - Massage
  - Stabilization Training
  - Electrotherapy
  - Manual Therapy
  - Aquatic Therapy
  - Heat Therapy
  - Stretching



# WHAT IS PAIN?

## PAIN PRODUCING STIMULI

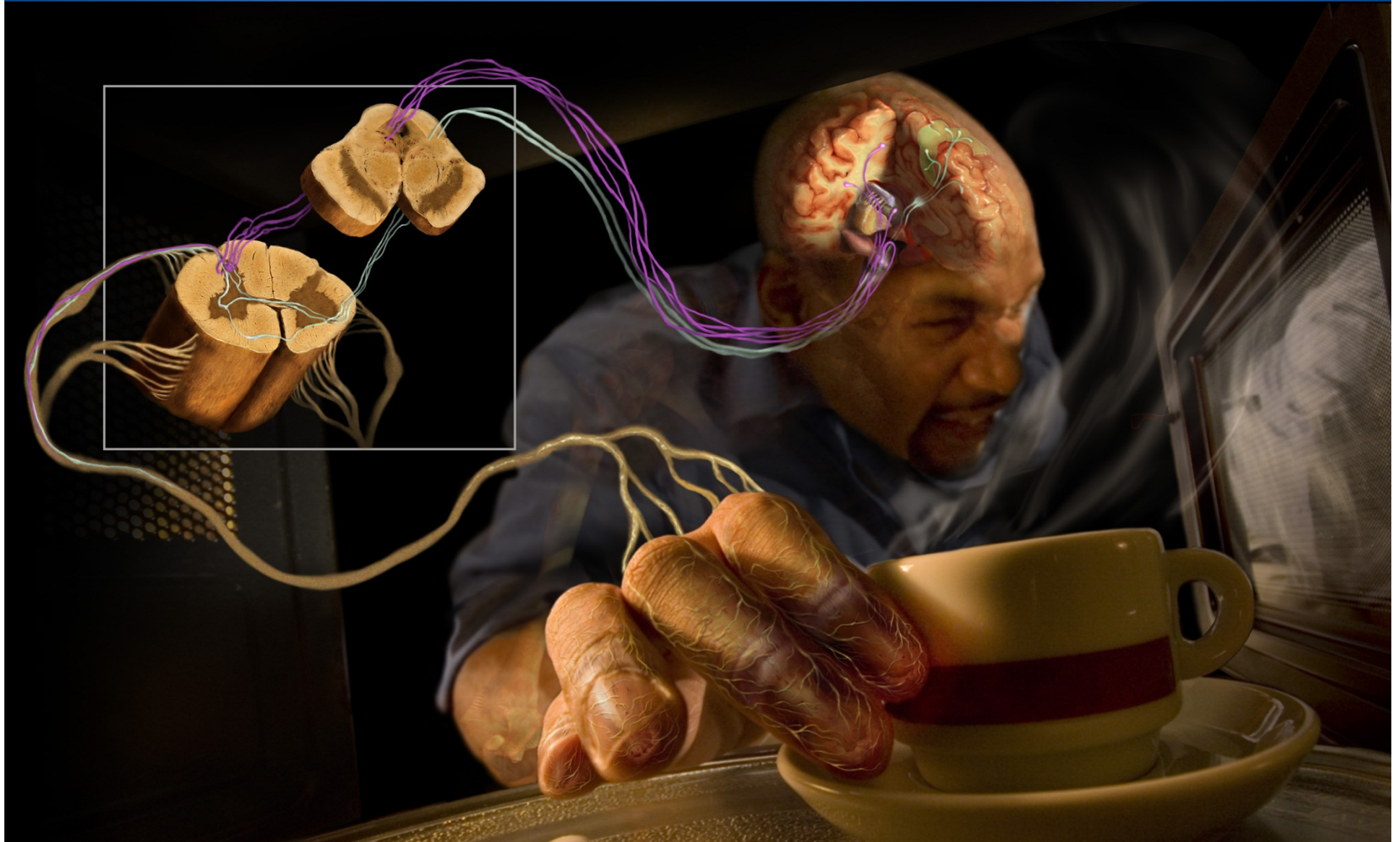
- Internal
  - Distension
  - Spasm
  - inflammation
- External
  - Pricking, cutting, crushing,
  - burning, freezing





What is pain?

# Nociceptive/Pain Pathways



# ACUTE PAIN

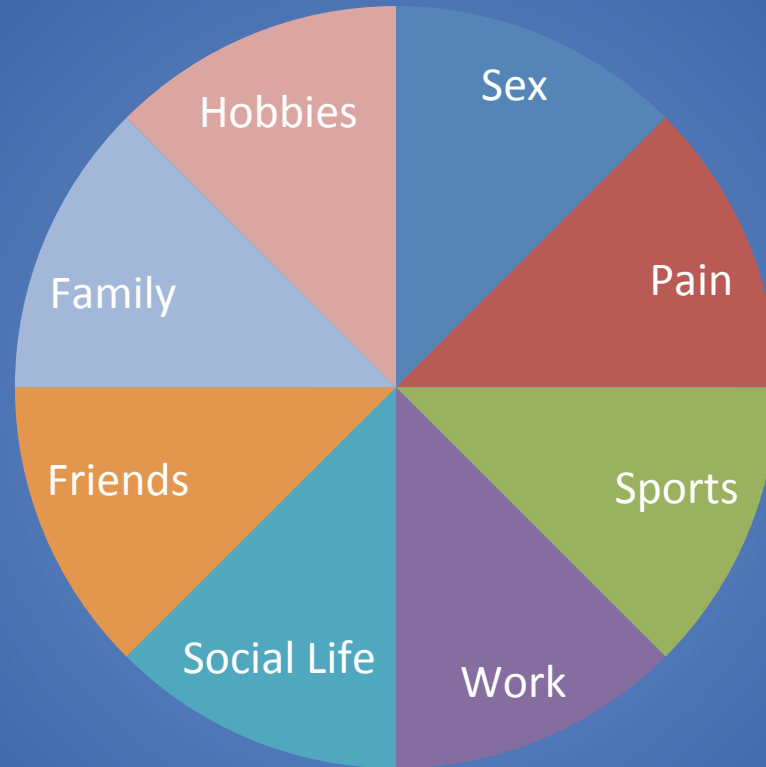
- Recent onset
- Usually in proportion to amount of tissue damage

# ACUTE PAIN

- Patient appears in distress
- Increased heart rate
- Increased blood pressure
- Increased respiratory rate
- Increased sweating
- Dilated pupils
- Characterized as:

Throbbing, Shooting, Sharp, Aching, Cutting,  
Stabbing, Twisting, Pulling, Tingling, Shooting,  
Squeezing, Burning







**Behavior**

**Suffering**

**Pain**

**Sensation of  
Tissue Damage**



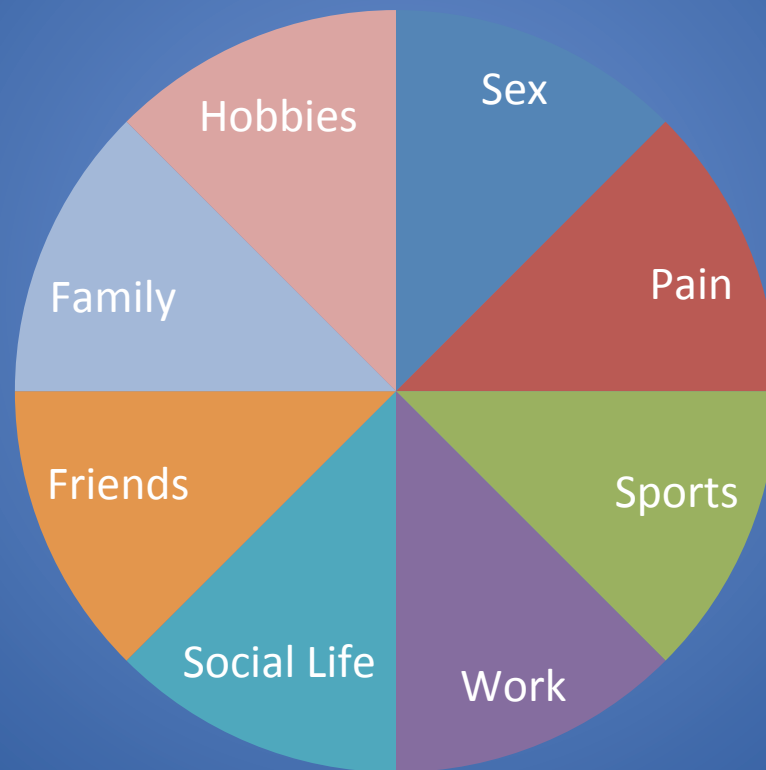
# Chronic Pain

May not appear in distress

## Descriptors

- Killing
- Torturing
- Unbearable
- Too much to bear
- Overwhelming
- Consumes my life
- You can't understand
- What did I do to deserve this?
- Why is G-d Punishing Me?
- I can't go on living like this
- When will it end?
- I want to die
- Nobody can take this kind of pain

# Life with Pain



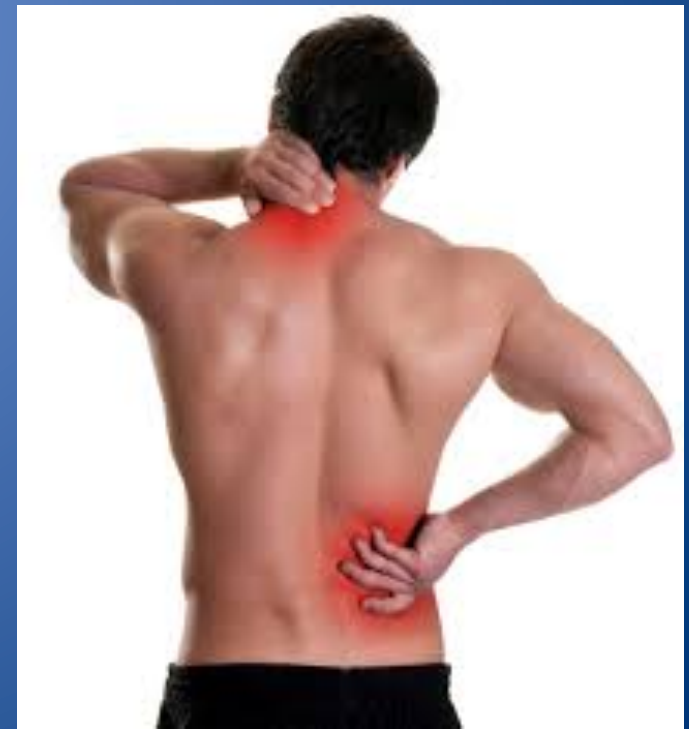
Life of Pain



Pain

# Typical Pain Presentations in the General Population

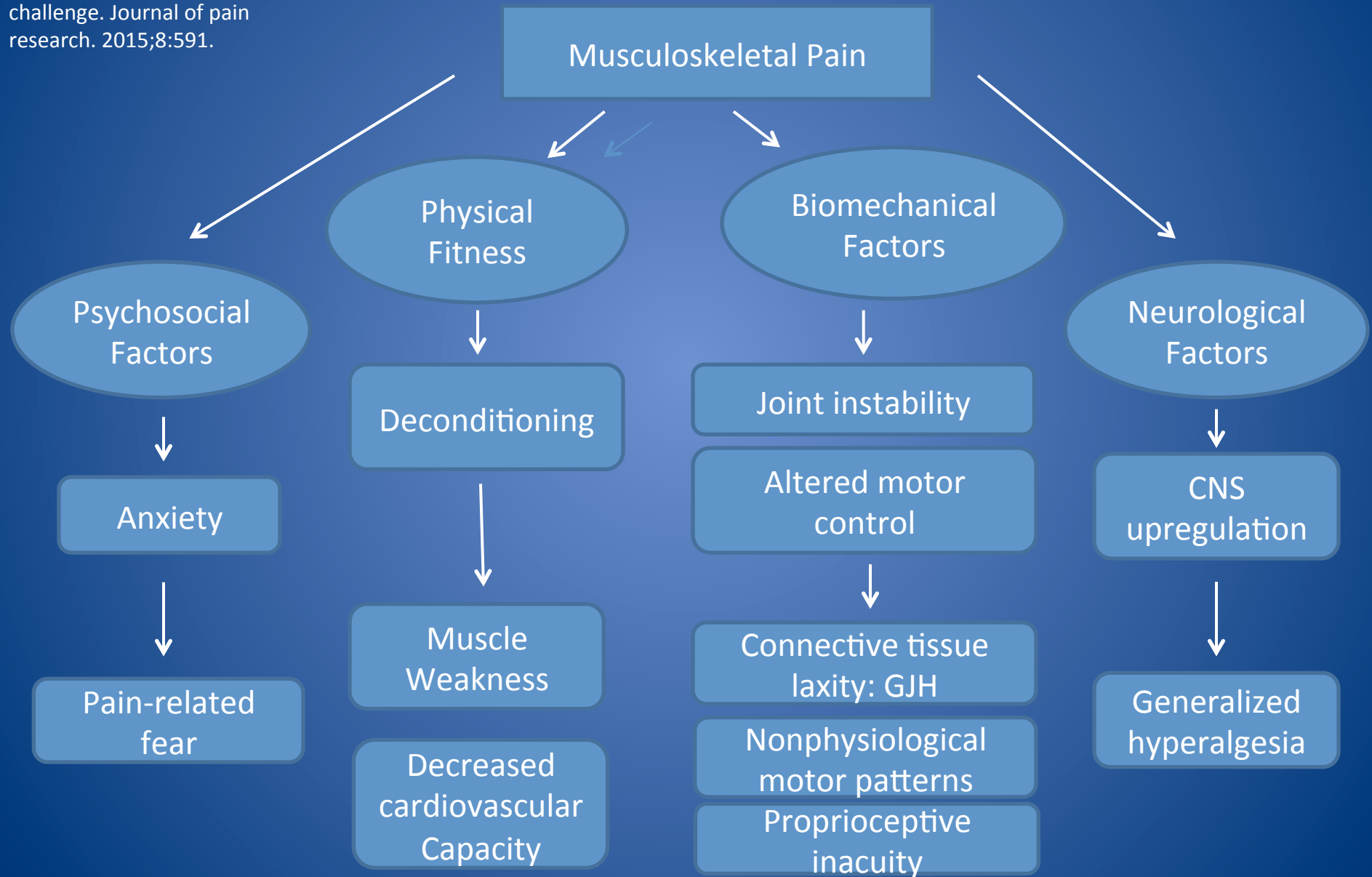
- Low Back Pain
- Headache
- TMJ
- Neck and Shoulder



Why do patients with EDS have  
pain?

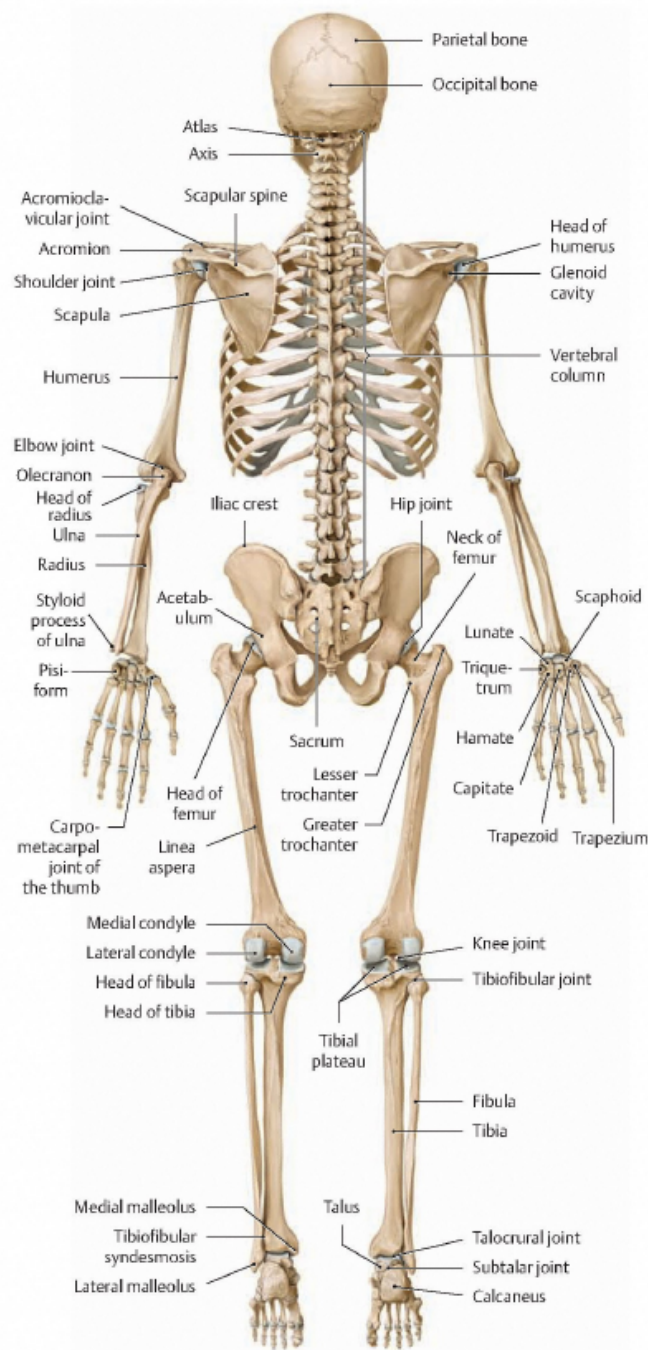
Scheper MC, de Vries JE, Verbunt J, Engelbert RH. Chronic pain in hypermobility syndrome and Ehlers–Danlos syndrome (hypermobility type): it is a challenge. Journal of pain research. 2015;8:591.

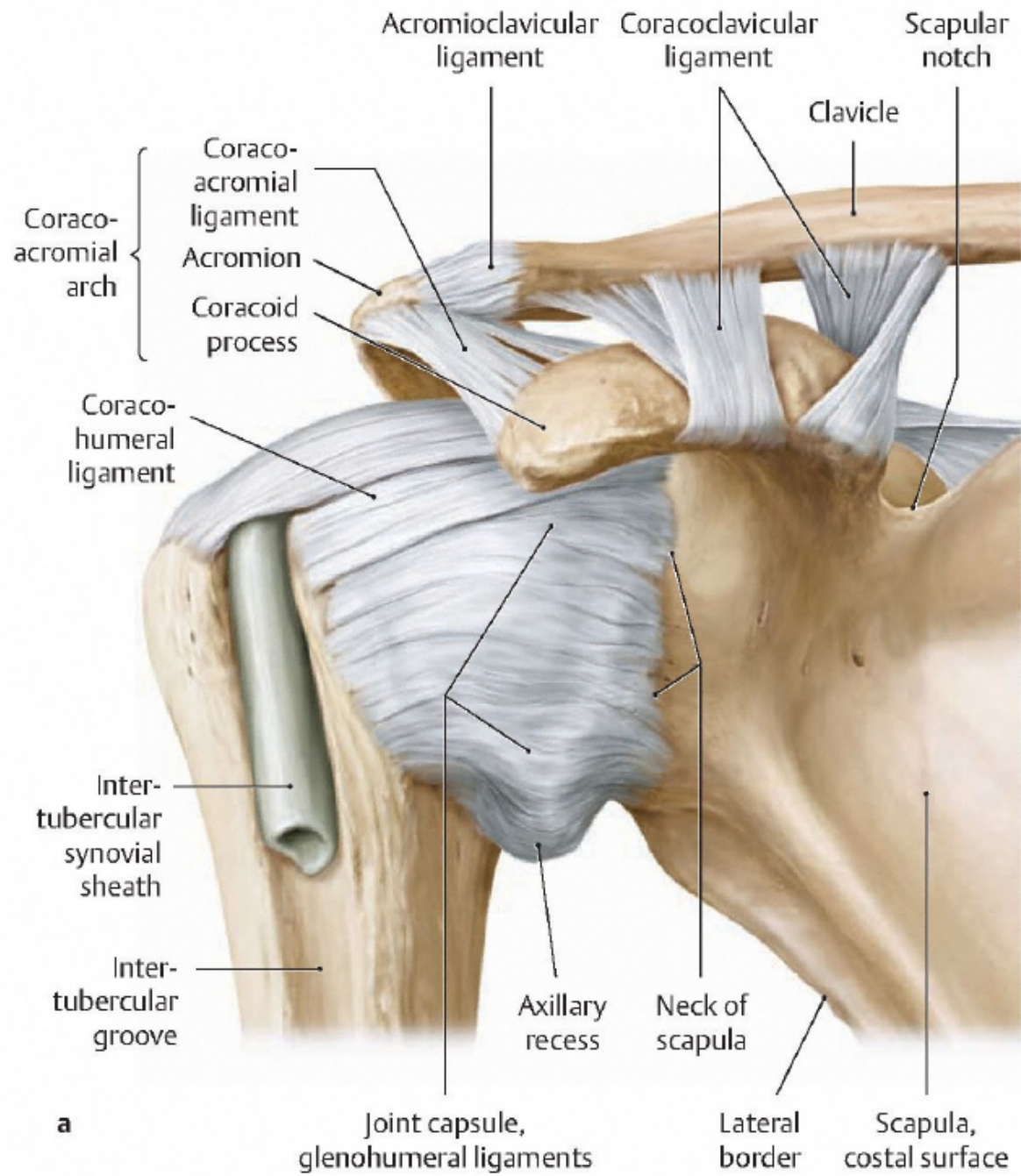
# Pain Mechanisms

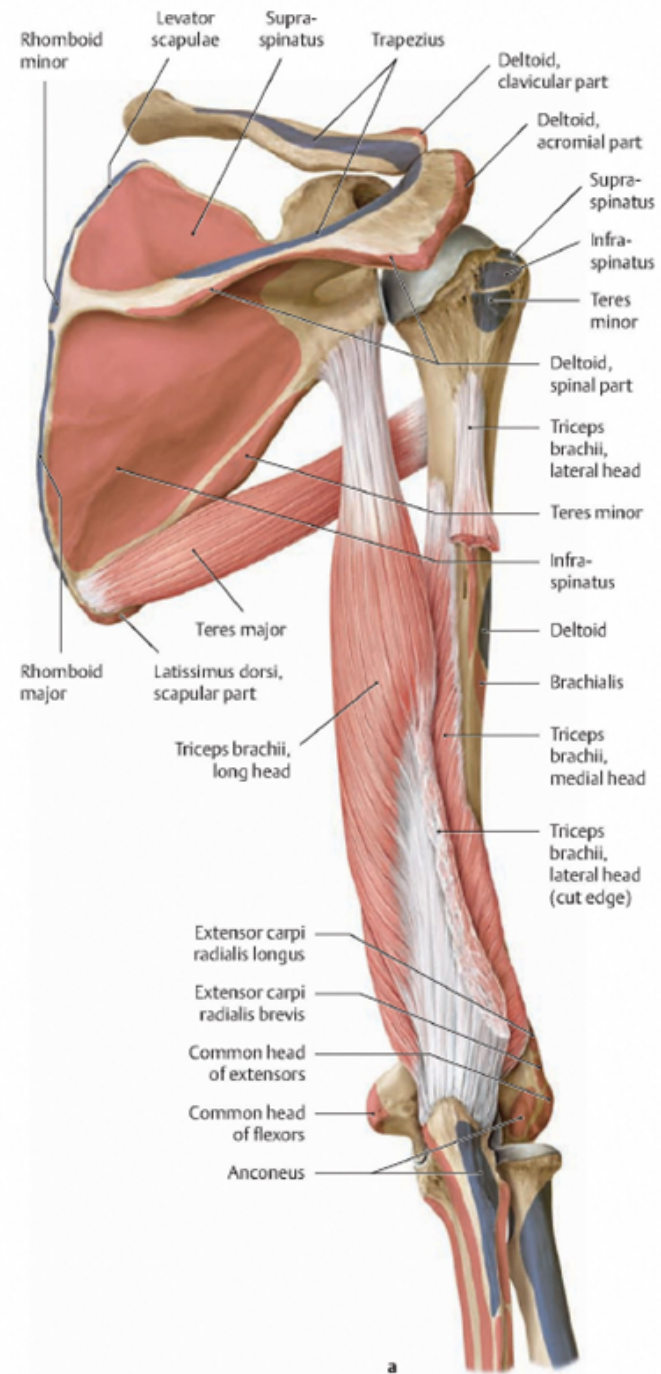




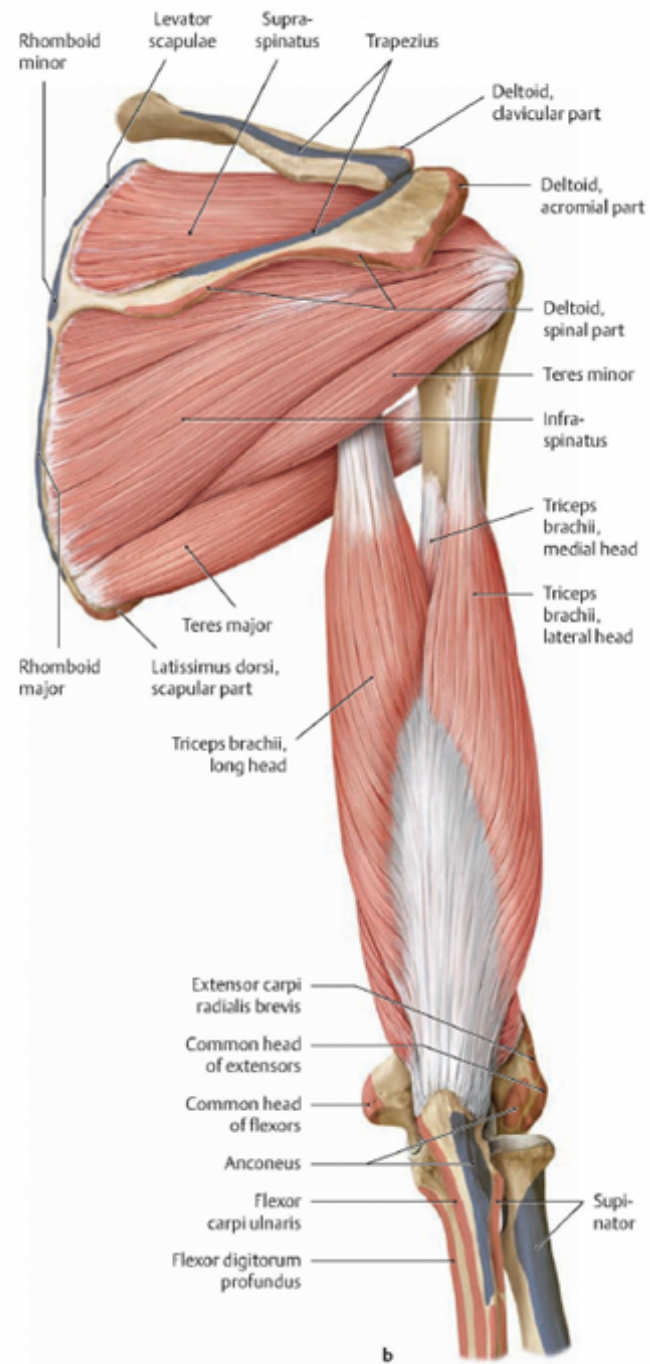
Could painful muscles surrounding  
loose joints be a source of EDS  
related pain?

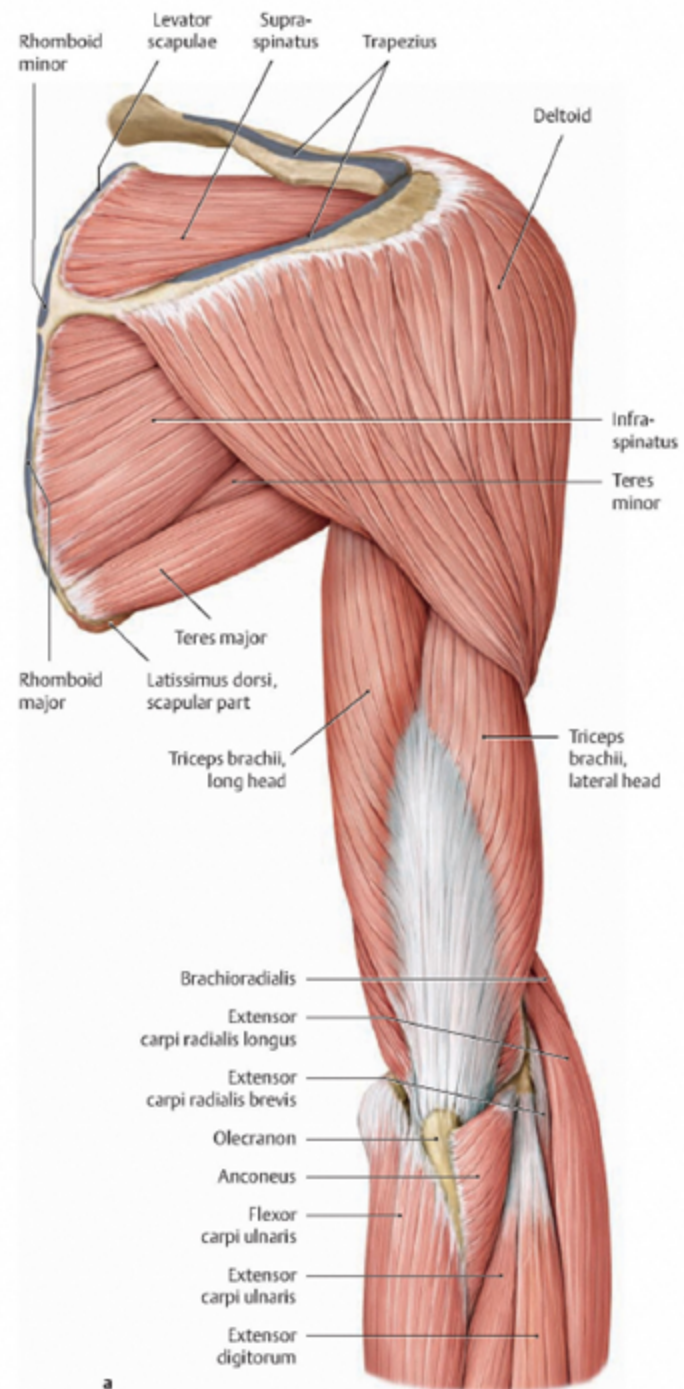




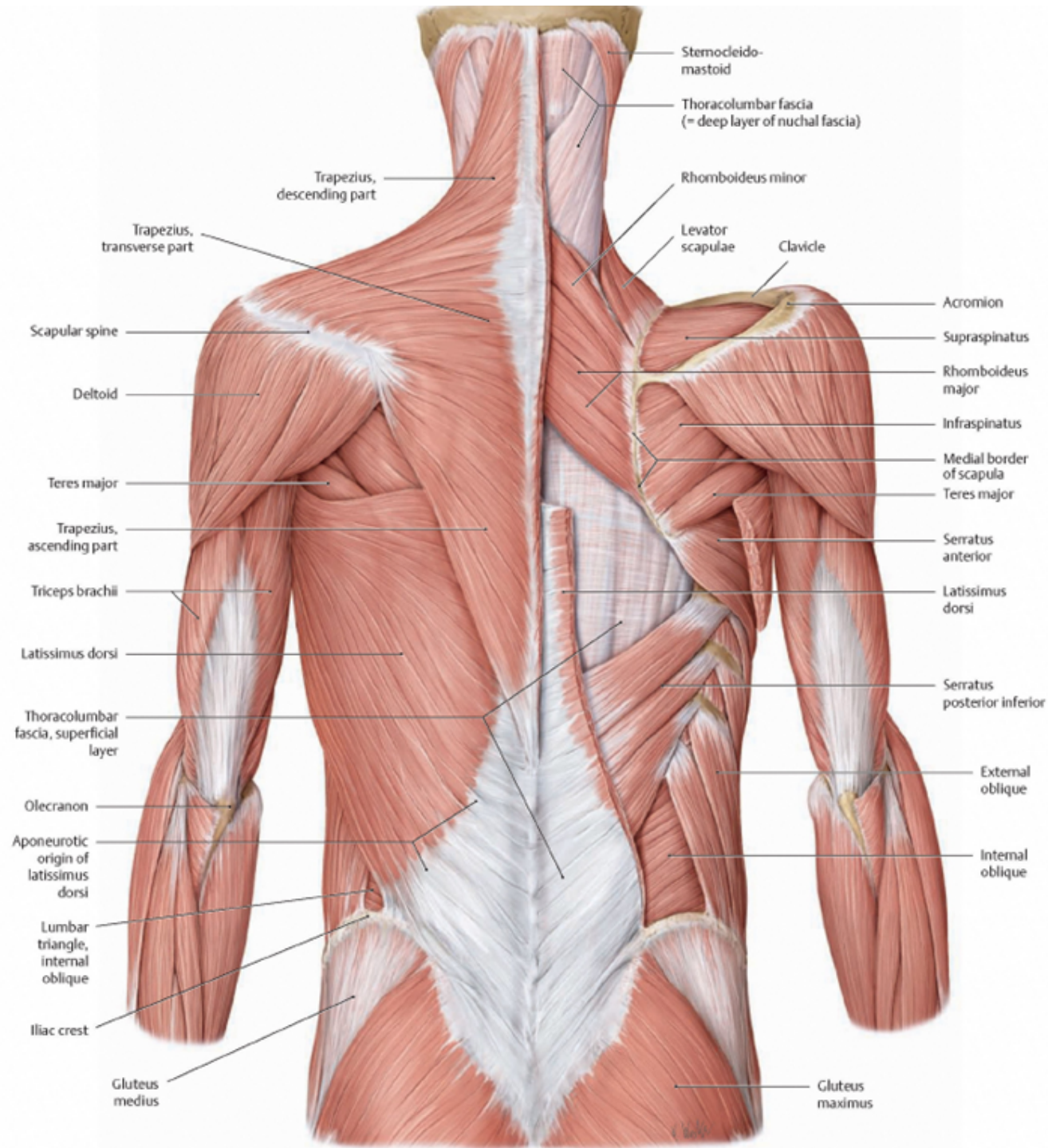










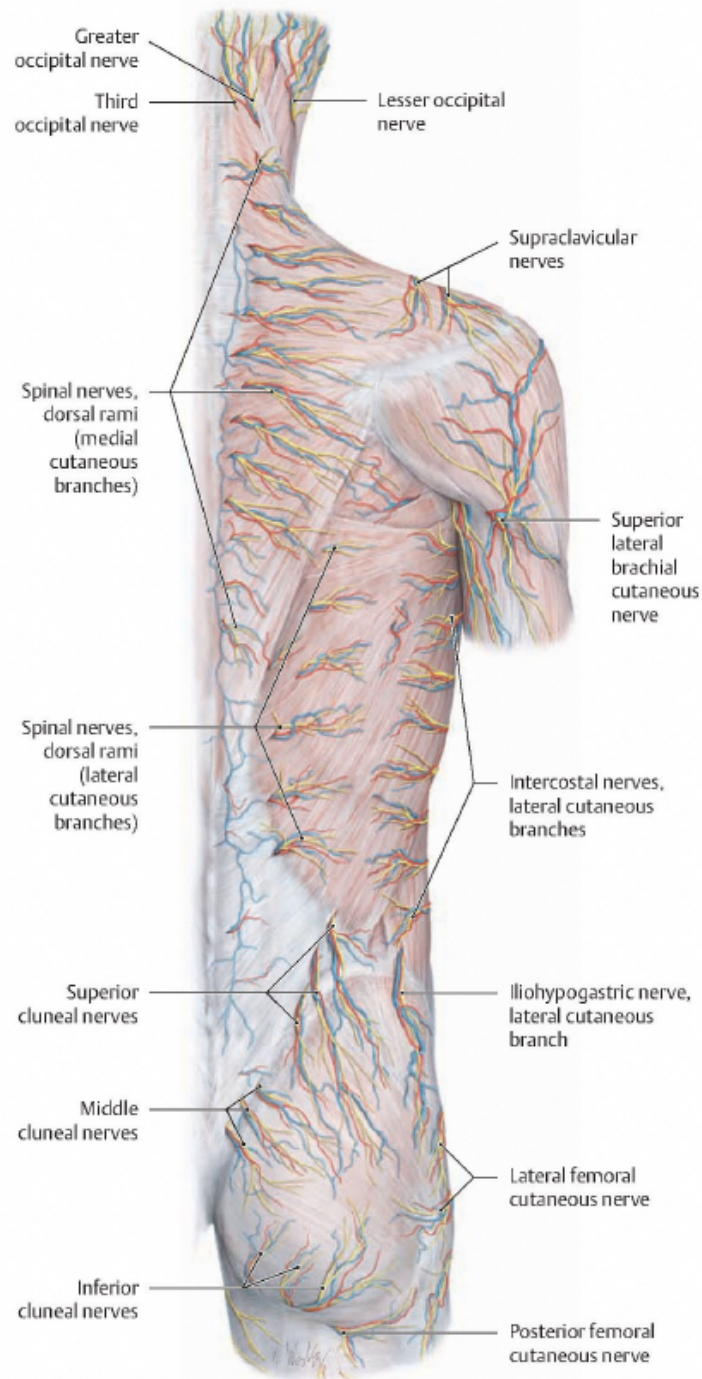


Tightened muscles stabilize  
loose joints.

Should muscles around the  
unstable joints therefore be  
considered as a significant  
source of pain in EDS?

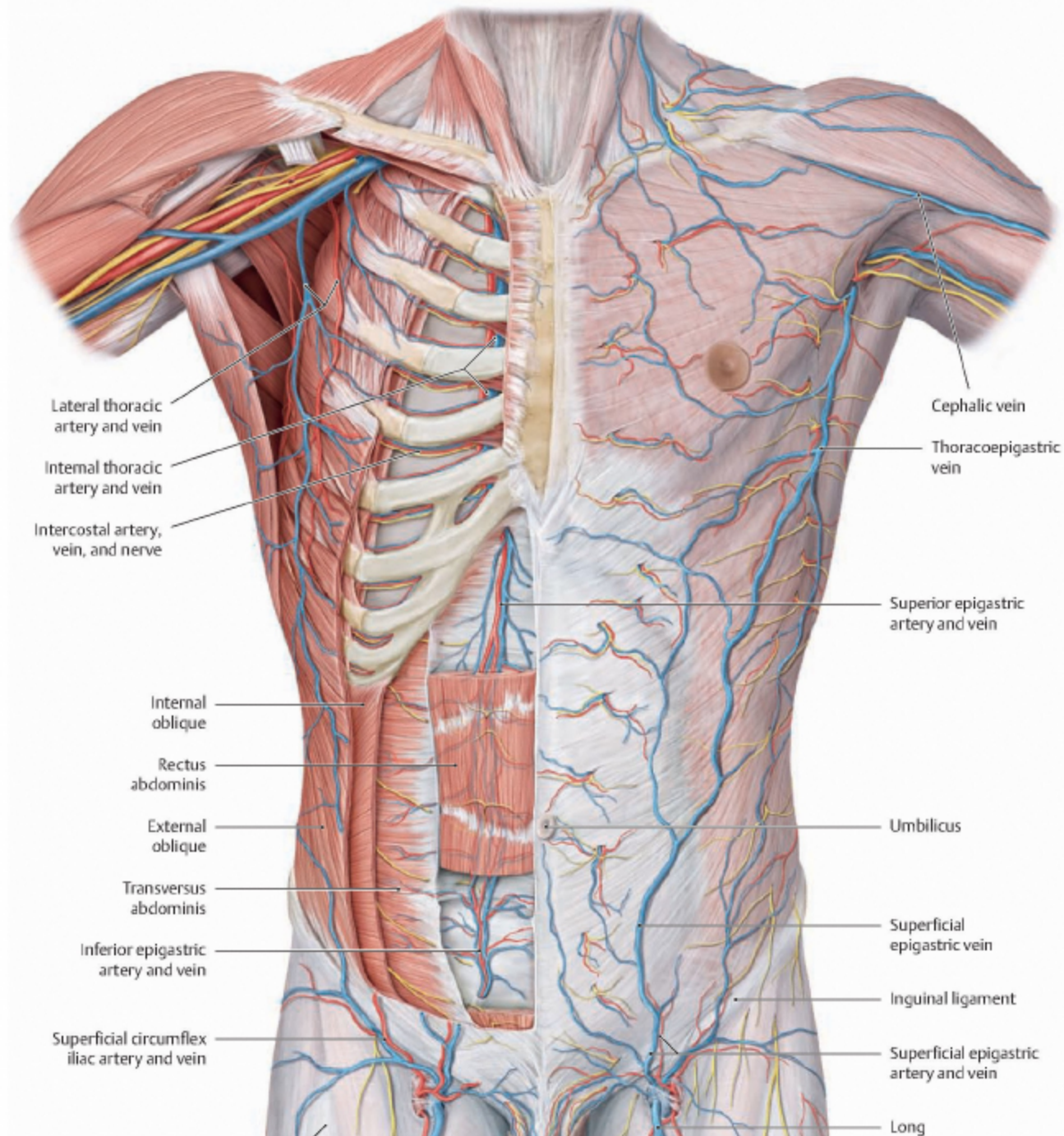
# Muscles and Blood Vessels

- Muscles and blood vessels



# Muscles, Blood Vessels, and Nerves



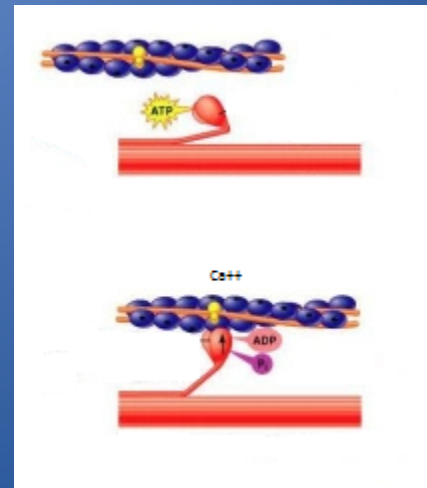


# Oxygen and Muscle Pain

Constricted blood vessels inhibit the flow of blood and deliver **less oxygen**:

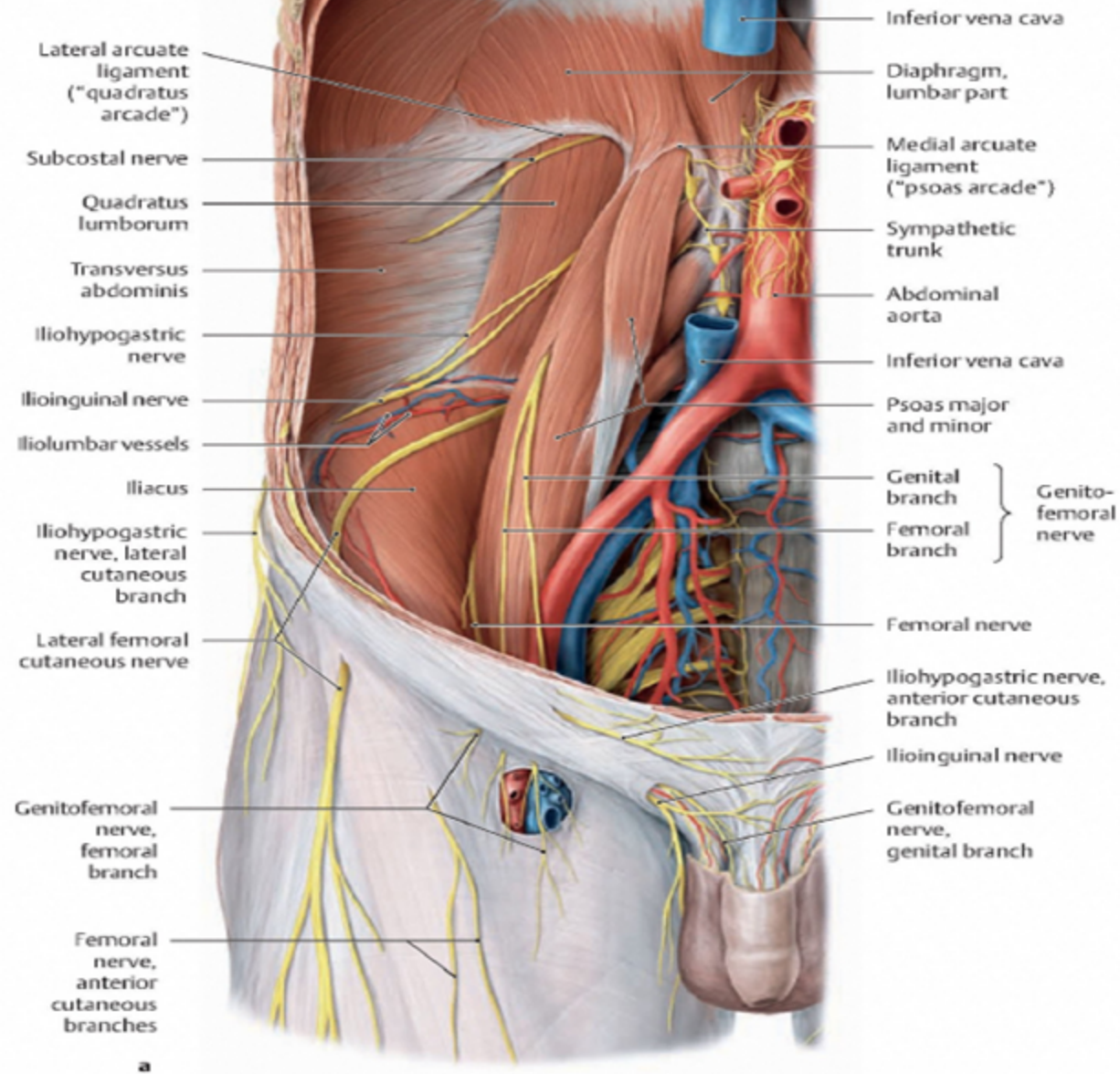
Impaired Calcium Pump/Inability to relax a part of a contracted muscle (Trigger Points)

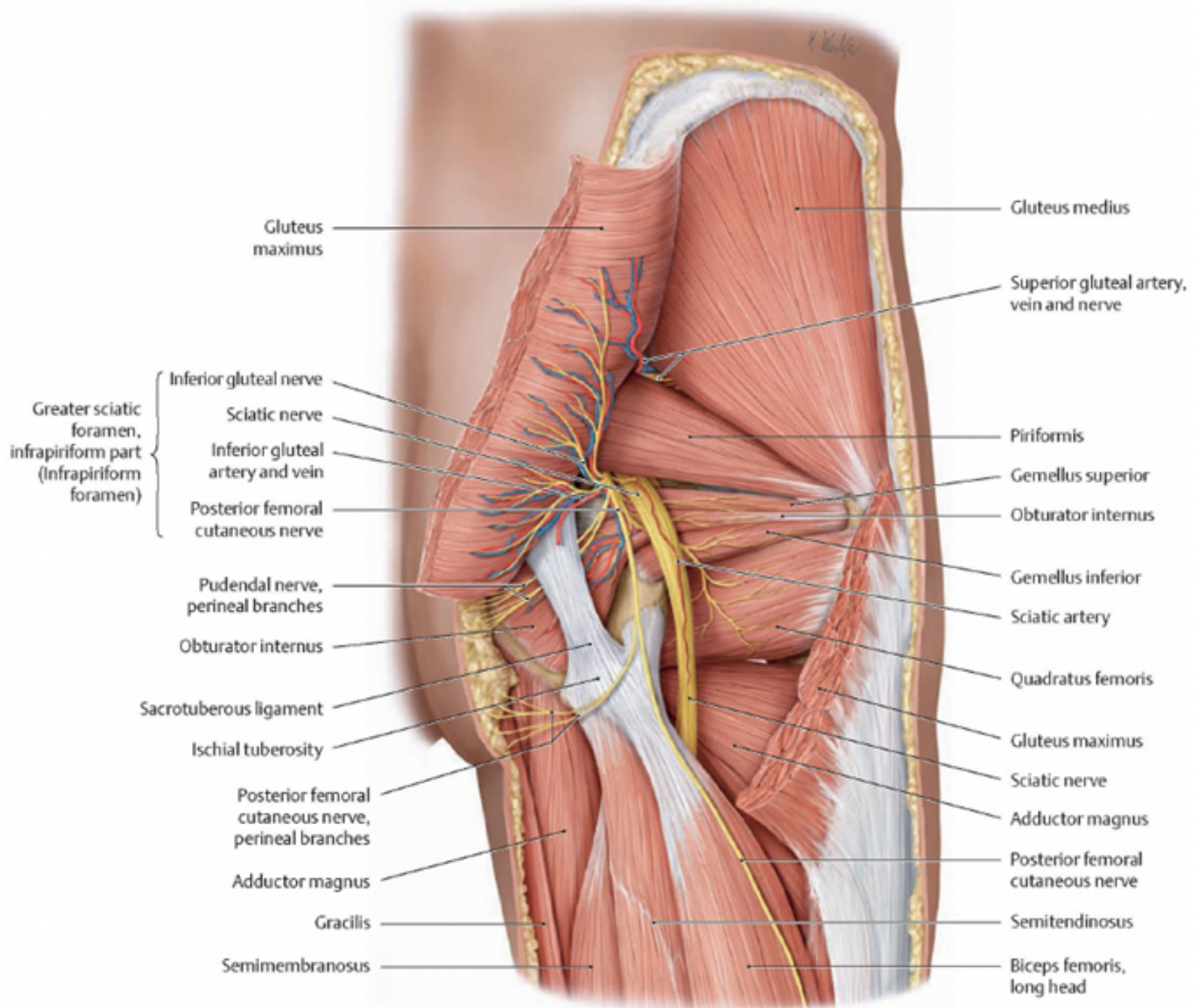
Areas of lower oxygen cause **Pain** with activity





Nerve entrapment often  
mistaken for pain from the  
spine





If muscles can be a common source of  
pain...

Why are they ignored?

Pathophysiology rarely studied

No discipline owns muscle



# Properties of Muscle Nociceptors

## Mechano-nociceptors, Chemo-nociceptors, Polymodal

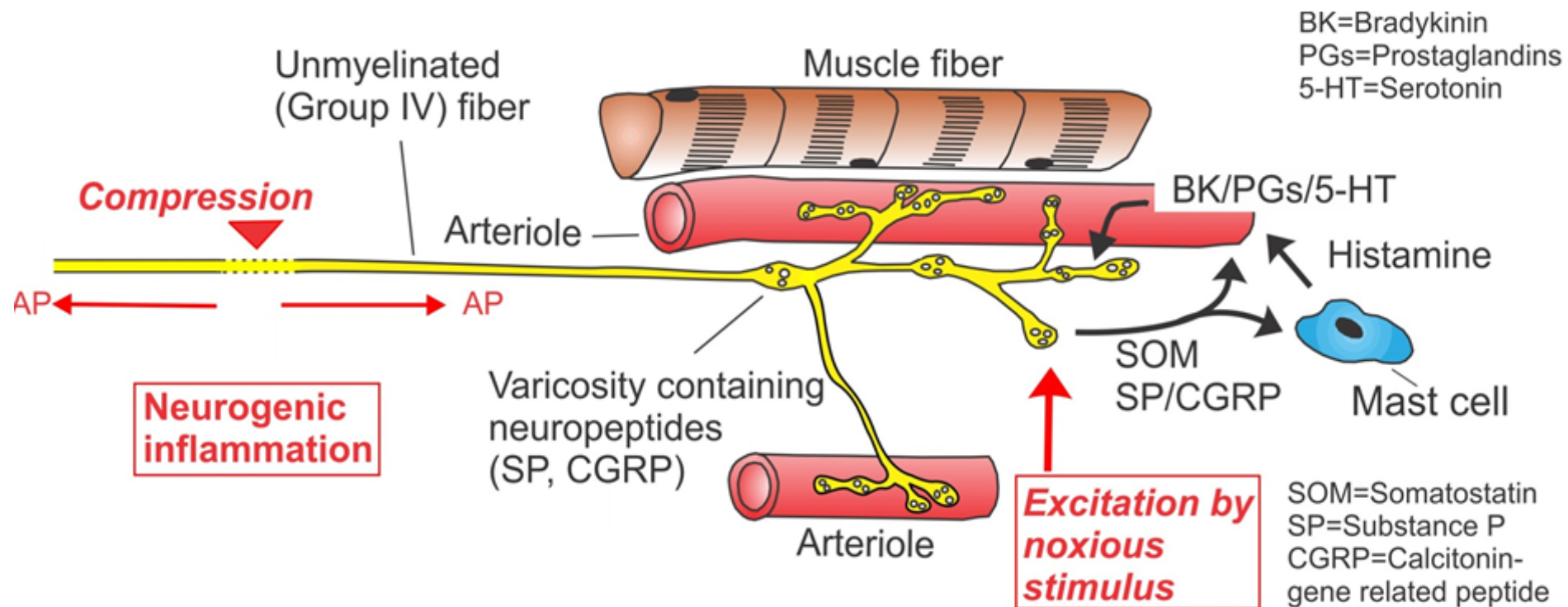
- Group III (A-delta) and IV (C) fibers
- Receptive free nerve ending activated by noxious (tissue-threatening, subjectively painful) stimuli. Useful in preventing as well as detecting tissue damage.
- High stimulation threshold

Mense, S and Gerwin, R. Muscle Pain: Understanding the Mechanisms. Springer: 2010.

# How Muscles Hurt

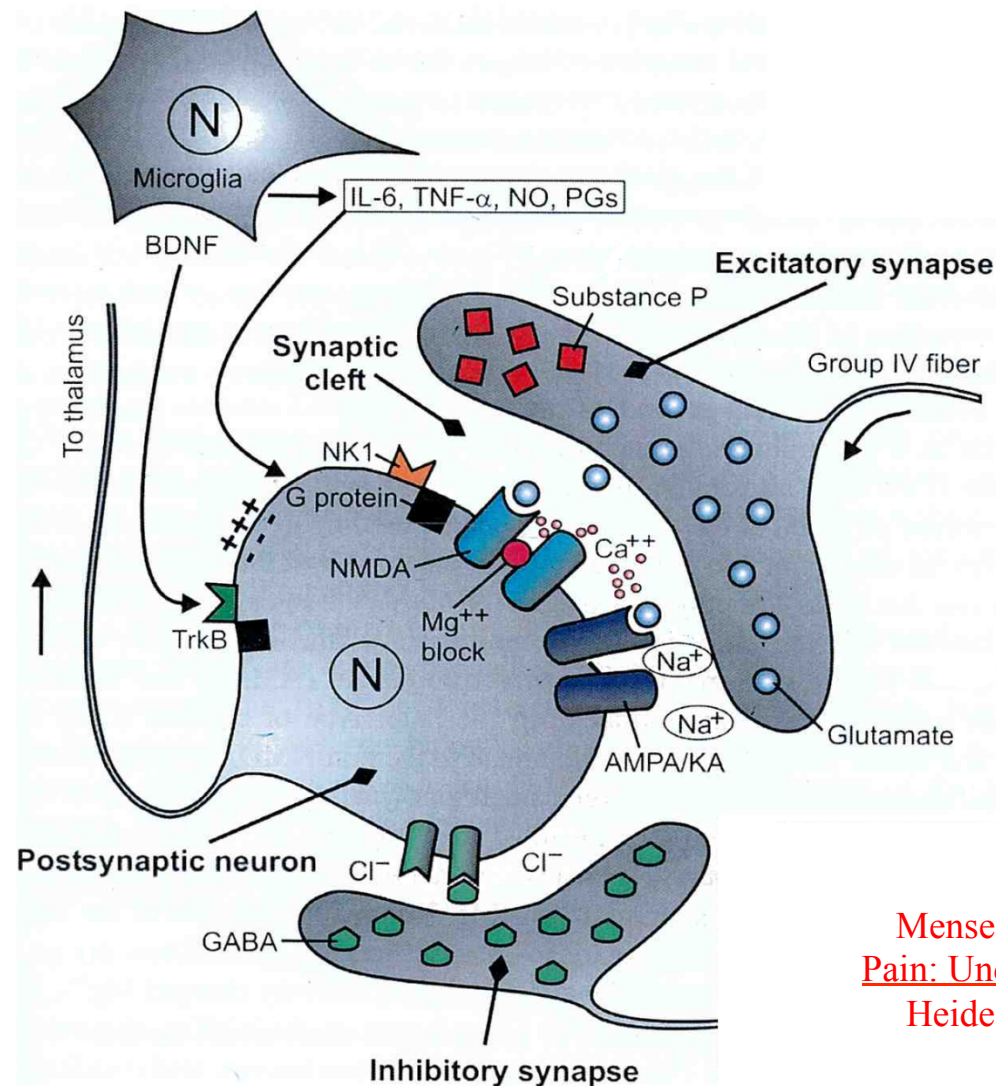
- Specialized muscle nerves carry information telling us damage has, or is about to occur.
- Chemical or Mechanical = Polymodal  
Nociceptors
- Normally - High threshold to stimulate





Marcus, N. & Mense, S. :Muscle Pain: Pathophysiology, Evaluation, and Treatment." *Principles and Practice of Pain Medicine*. Ed. Bajwa, Z, Wooton, J., Warfield, C. McGraw-Hill, In press.

# Transmission of Peripheral Impulses into Dorsal Horn Neurons



Mense S, Gerwin RD (eds.) Muscle Pain: Understanding the Mechanisms. Heidelberg: Springer, 2010. pp111.

# Peripheral Sensitization

increased excitatory response to all stimuli

Lowered mechanical threshold

tenderness and

painful movement/allodynia

Increased response magnitude to noxious stimuli

hyperalgesia

Resting activity discharges

spontaneous pain

# Sensitization

- What is it?
  - Picture of nerve with action potential

# Peripheral Sensitization

increased response to all stimuli

Lowered mechanical threshold  
tenderness and painful movement

Resting activity discharges  
spontaneous pain



# Central Sensitization (CS)

- Glutamate alone released affecting non-NMDA channels
- Following minutes of lasting or strong input from muscle nociceptors, SP also released (1<sup>st</sup> step in CS):
  - Opening of NMDA channels → persistent depolarization
  - Reduction of threshold to depolarize.

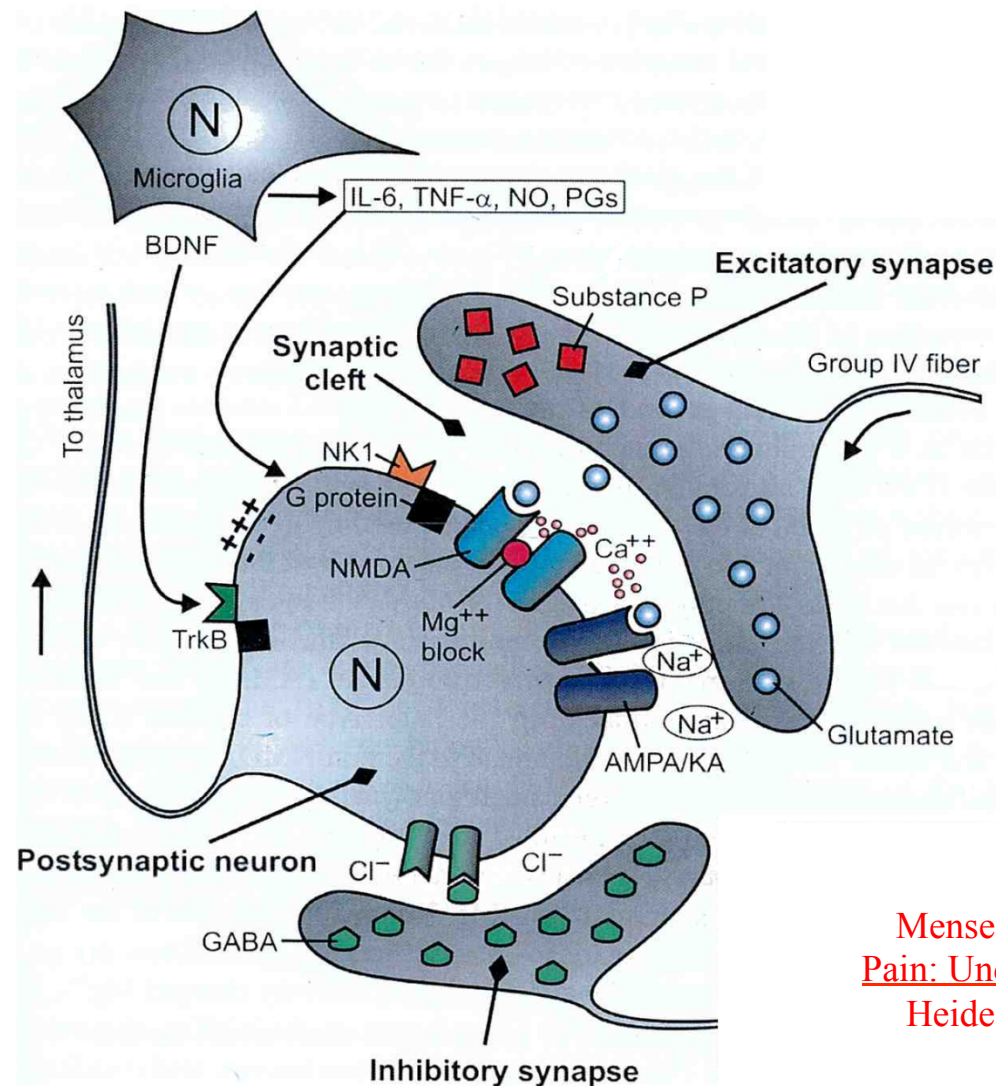
\*Wall PD, and Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *The Journal of Physiology*. 1984; 356: 443-458



# Central Sensitization (Pain causes more pain)

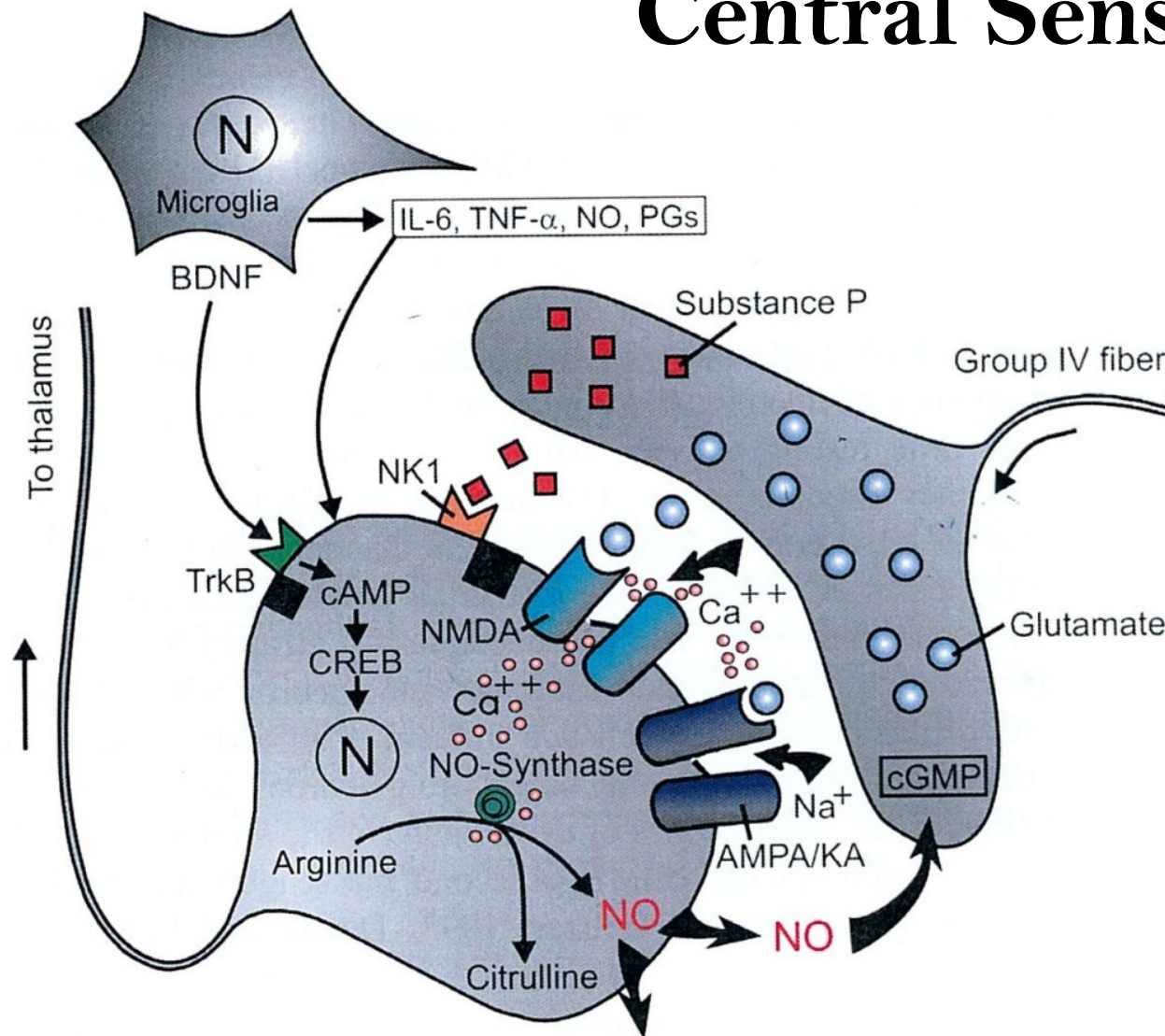
Persistent peripheral nerve stimulation causes  
nerves in the spinal cord to be altered  
producing  
muscle pain referral patterns

# Transmission of Peripheral Impulses into Dorsal Horn Neurons



Mense S, Gerwin RD (eds.) Muscle Pain: Understanding the Mechanisms. Heidelberg: Springer, 2010. pp111.

# Central Sensitization



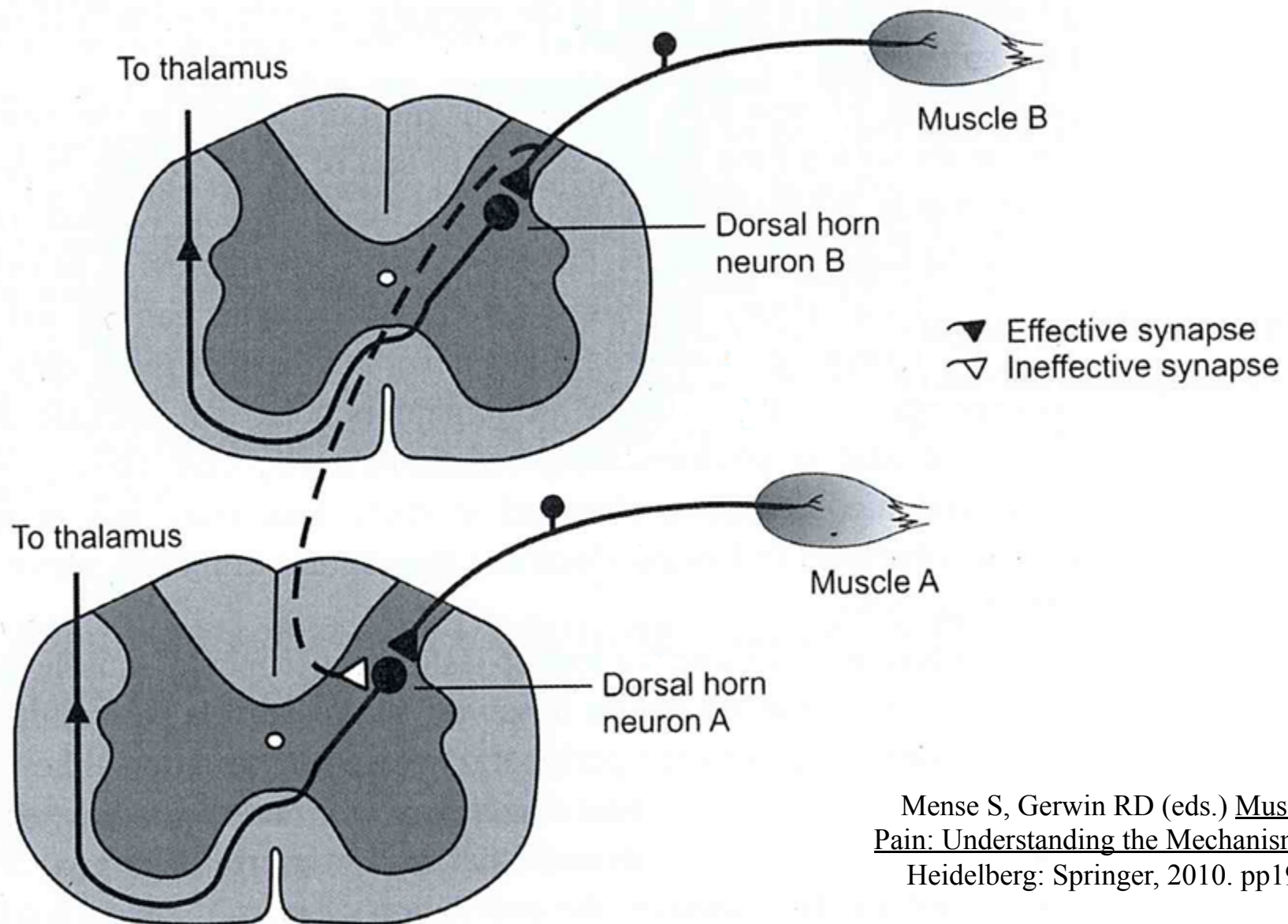
Mense, S and Gerwin, RD. Muscle Pain: Understanding the Mechanisms. Springer: 2010. pp142.

# Mechanisms of Muscle Pain Referral

- Opening of ineffective connections  
--> Existing closed pathways open up
- Convergence
- Heterosynaptic potentiation/Facilitation



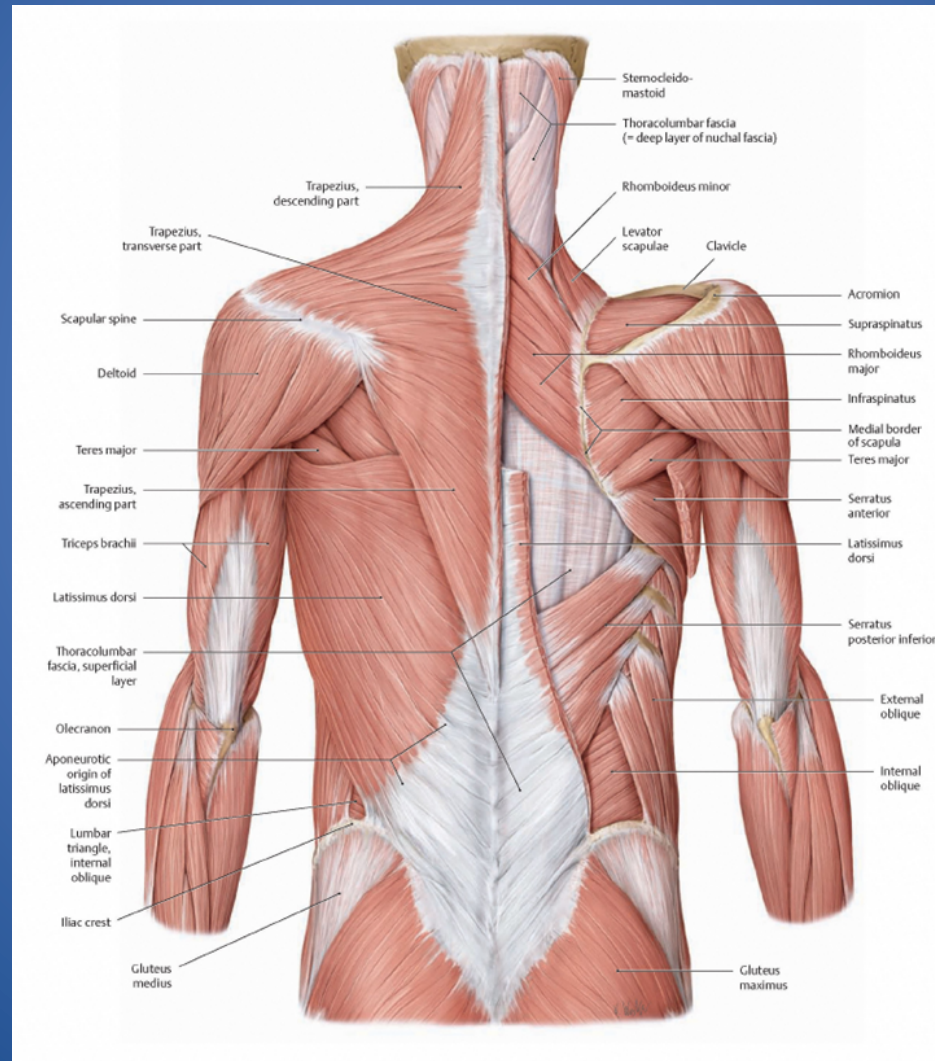
# Opening ineffective connections



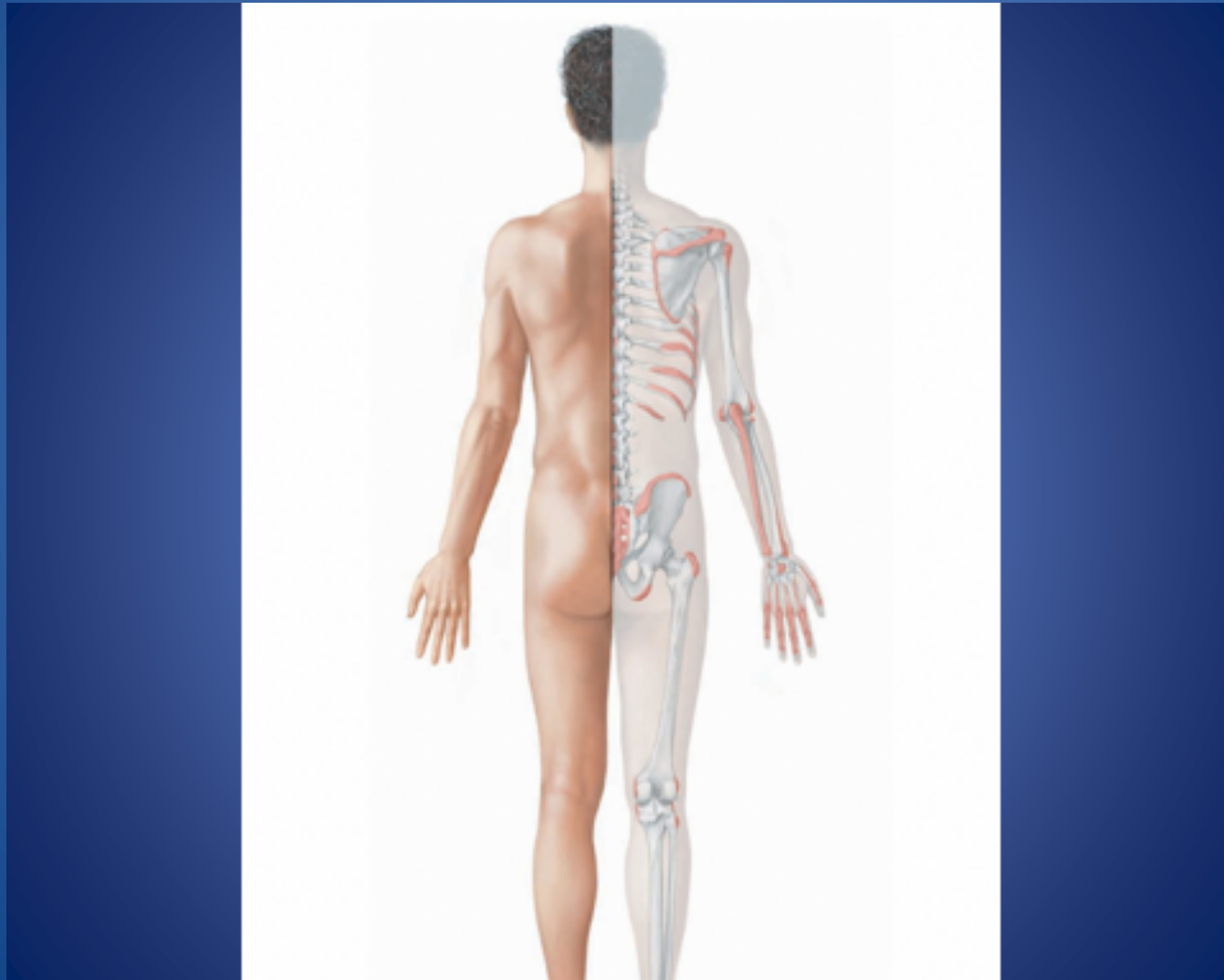
Mense S, Gerwin RD (eds.) Muscle Pain: Understanding the Mechanisms.  
Heidelberg: Springer, 2010. pp195.



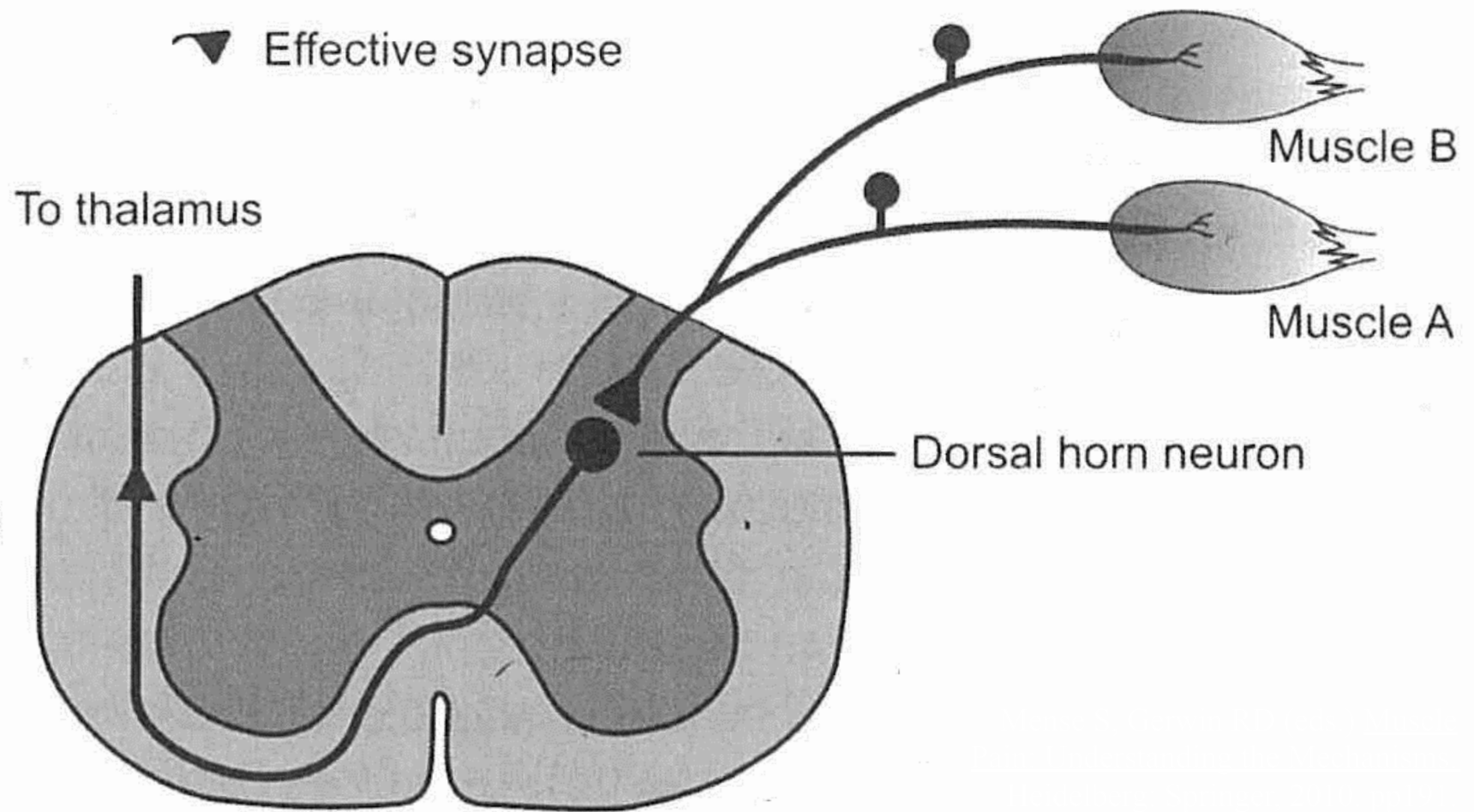
# Muscle Pain Referral



# Heterosynaptic Facilitation

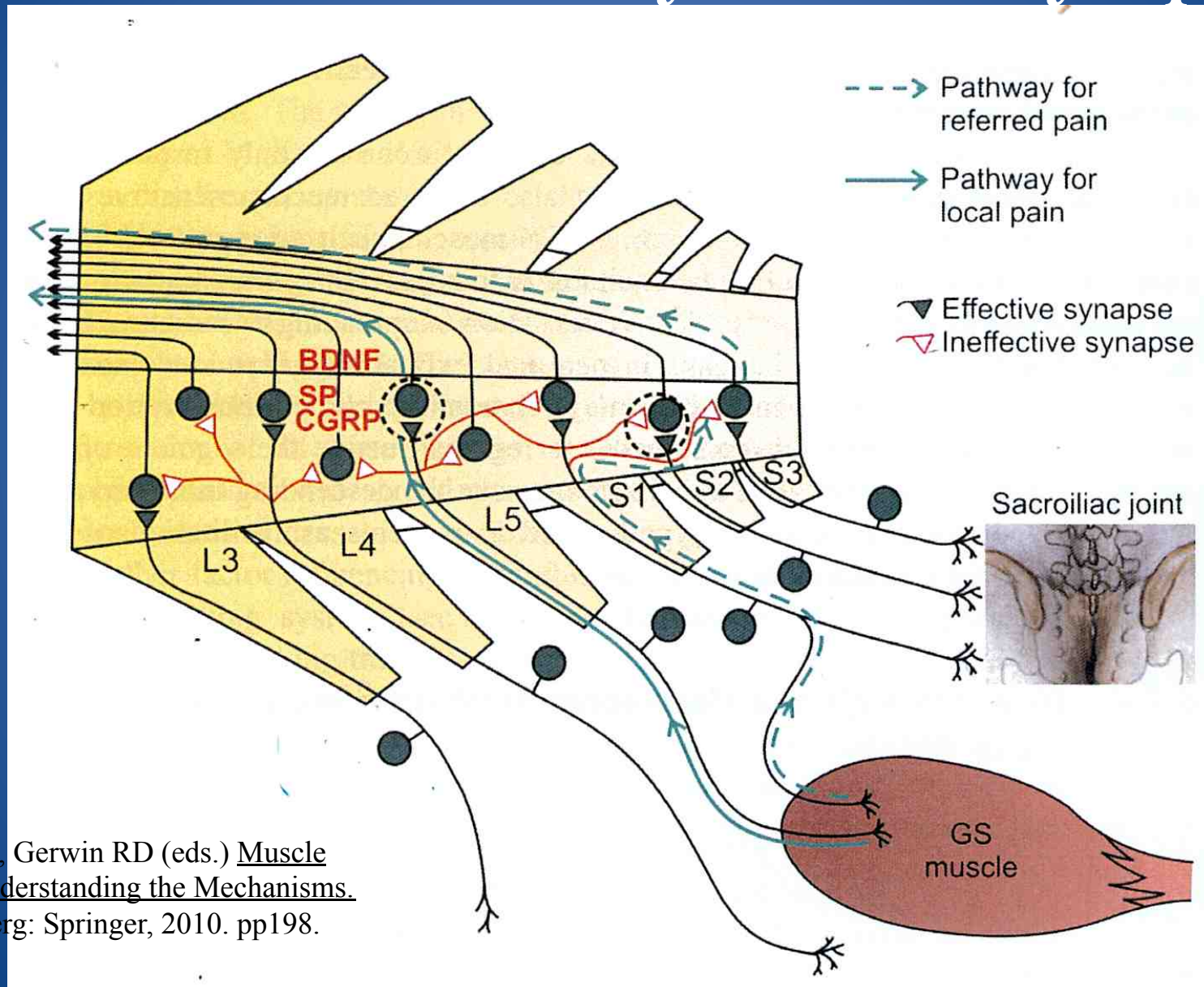


# Convergence





# Referred Pain Pathways- Heterosynaptic



Mense S, Gerwin RD (eds.) Muscle Pain: Understanding the Mechanisms.  
Heidelberg: Springer, 2010. pp198.

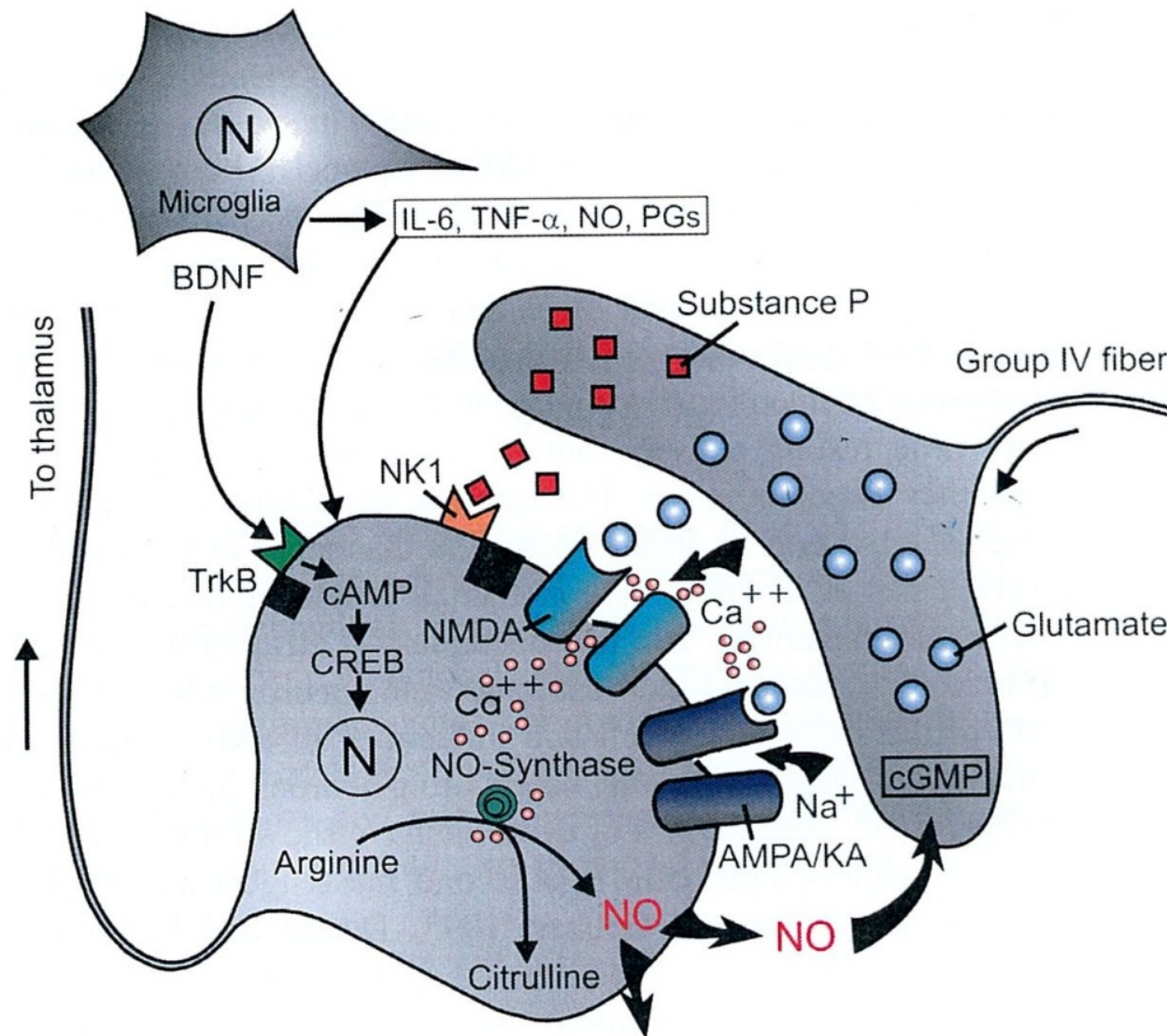
# Glial Cells and Central Sensitization

Astrocytes and microglia produce pro-inflammatory cytokines when activated by peripheral pathological changes such as inflammation

Marchand, F, et al. Role of the immune system in chronic pain. *Nat Rev Neuroscience* 6:521-532 (2005)



# ation: Glia



Mense, S and Gerwin, RD. Muscle Pain: Understanding the Mechanisms. Springer: 2010.

# Peripheral mechanism of referred pain in a sciatic nerve injury model

- Mirror Pain @ Day 1
- Dorsal spinal cord Astrocyte activation @ Day 7 but no microglia activation
- ? Rx targets: rheumatoid arthritis, complex regional pain syndrome and neuropathic pain

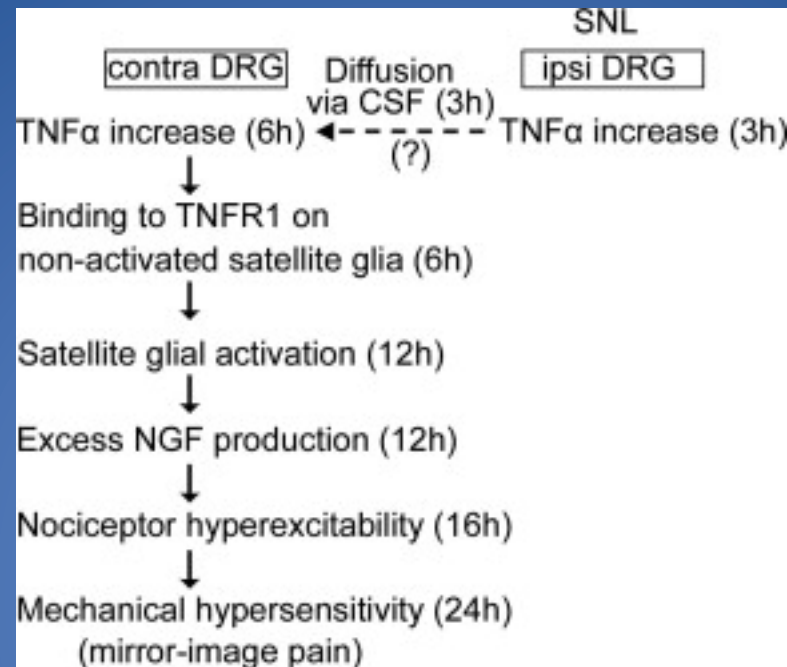


Fig. 12 Possible mechanism underlying peripheral nerve injury-evoked mirror pain. Following spinal nerve ligation (SNL) on the right side, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is increased greatly in the ipsilateral (ipsi) dorsal root ganglion (DRG), diffuses t...

Chau-Fu Cheng , Jen-Kun Cheng , Chih-Yang Chen , Cheng-Chang Lien , Dachen Chu , Szu-Yi Wang , Meei-Ling Tsaur

**Mirror-image pain is mediated by nerve growth factor produced from tumor necrosis factor alpha-activated satellite glia after peripheral nerve injury**

PAIN®, Volume 155, Issue 5, 2014, 906 - 920

<http://dx.doi.org/10.1016/j.pain.2014.01.010>

# Diffuse Noxious Inhibitory Control (DNIC) Conditioned Pain Modulation (CPM)

Pain inhibits pain

Stronger pains conceal weaker pains

Yarnitsky D. Conditioned Pain Modulation (DNIC) : its relevance for acute and chronic pain states. *Current Opinion in Anaesthesiology*. 2010; 23(5): 611–615.

# Review

- Muscle tissue is a *source of pain*:
- *Acute*
- *Chronic*
- *Referred*



# **Hans Kraus, M.D.**

## **Functional Muscle Pain**

- Tension
- Deficiency: Weakness and/or Stiffness
- Spasm
- Trigger Points

# Muscle Tension

**VOLUNTARY, SUSTAINED  
CONTRACTION OF STRIATED MUSCLE.**

Examples:

- LBP
- TMJ Dysfunction
- Non-specific Neck and Shoulder Pain

# Diagnosis of Tension

**HISTORY** of sustained overuse of muscle groups

**PHYSICAL EXAM** which reveals a failure to *voluntarily relax*

Can sustained feeling states produce prolonged contraction of specific muscle groups and subsequent pain patterns?





# Hans Kraus, M.D.

## Functional Muscle Pain

- Tension
- Deficiency: Weakness and/or Stiffness
- Spasm
- Trigger Points

# The Y's Way to a Healthy Back

- Taught to 300,000 patients – twice a week for six weeks
- 12K patients studied: 80% of patients experienced reduction and/or elimination in back pain
- Patients with previous back surgery had an 82% success rate

Kraus H, Nagler W, Melleby A. Evaluation of an exercise program for back pain. *Am Fam Physician*. 1983;28(3):153-8.

# Kraus/Marcus Lower Body Exercises (Level 1)



**Diaphragmatic Breathing**



**Shoulder Shrugs**



**Leg Slides**



**Head Rotations**



**Single Knee to Chest**



**Side Lying Knee to Chest**



**Buttocks Squeeze**

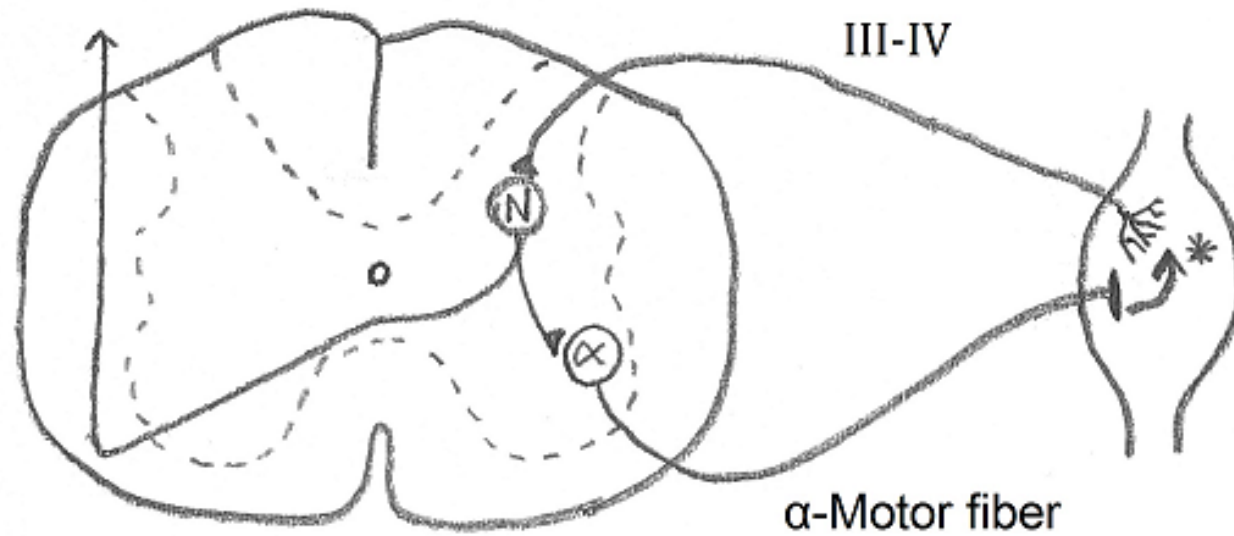
# Hans Kraus, M.D.

## Functional Muscle Pain

- Tension
- Deficiency: Weakness and/or Stiffness
- Spasm
- Trigger Points

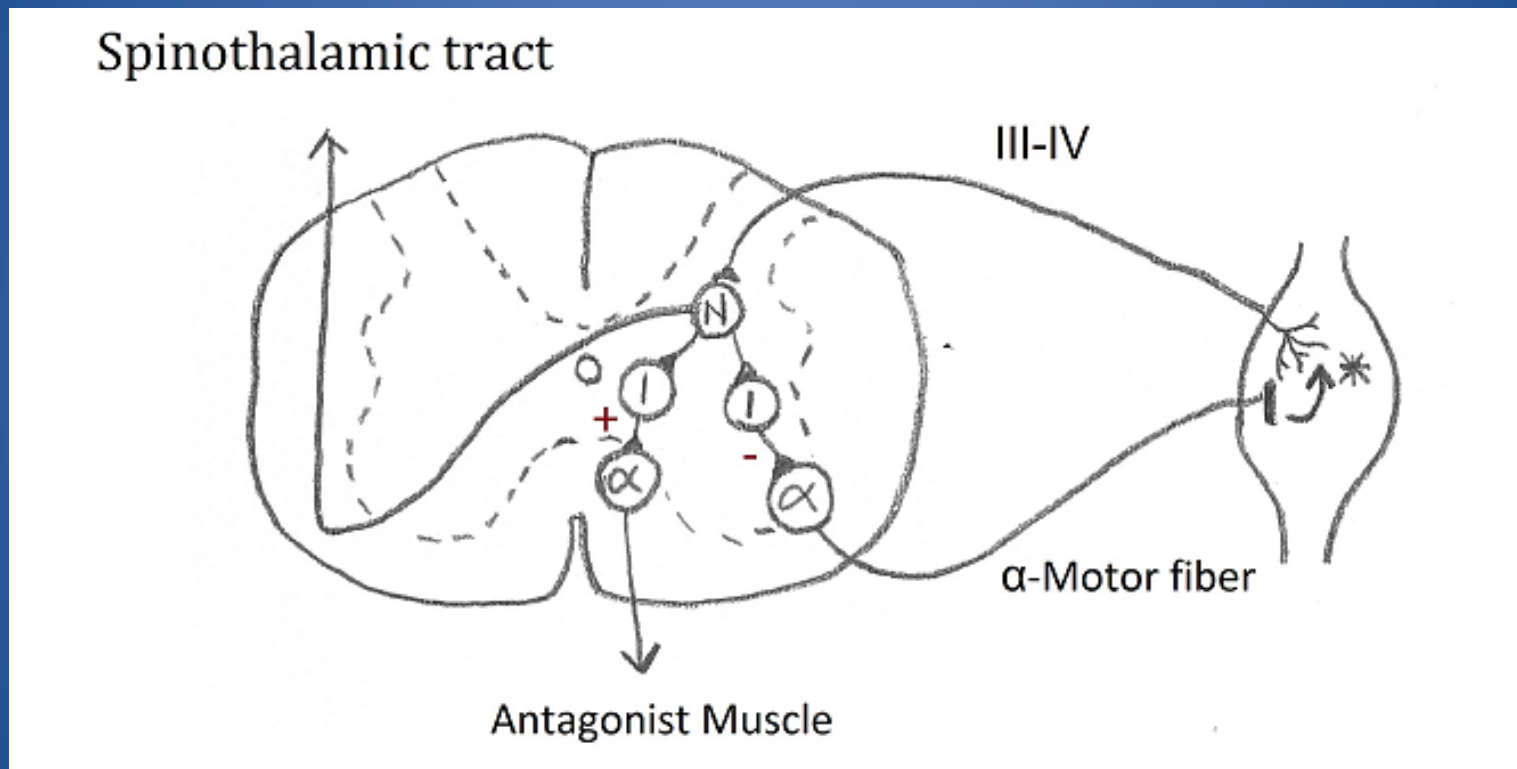
# Pain-Spasm-Pain Concept

Spinothalamic tract





# Lund Hypothesis



Lund J, Donga R, Widmer C, Stohler C. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Canadian Journal of Physiology and Pharmacology*. 1991;69(5):683-694.

# Pain and Spasm

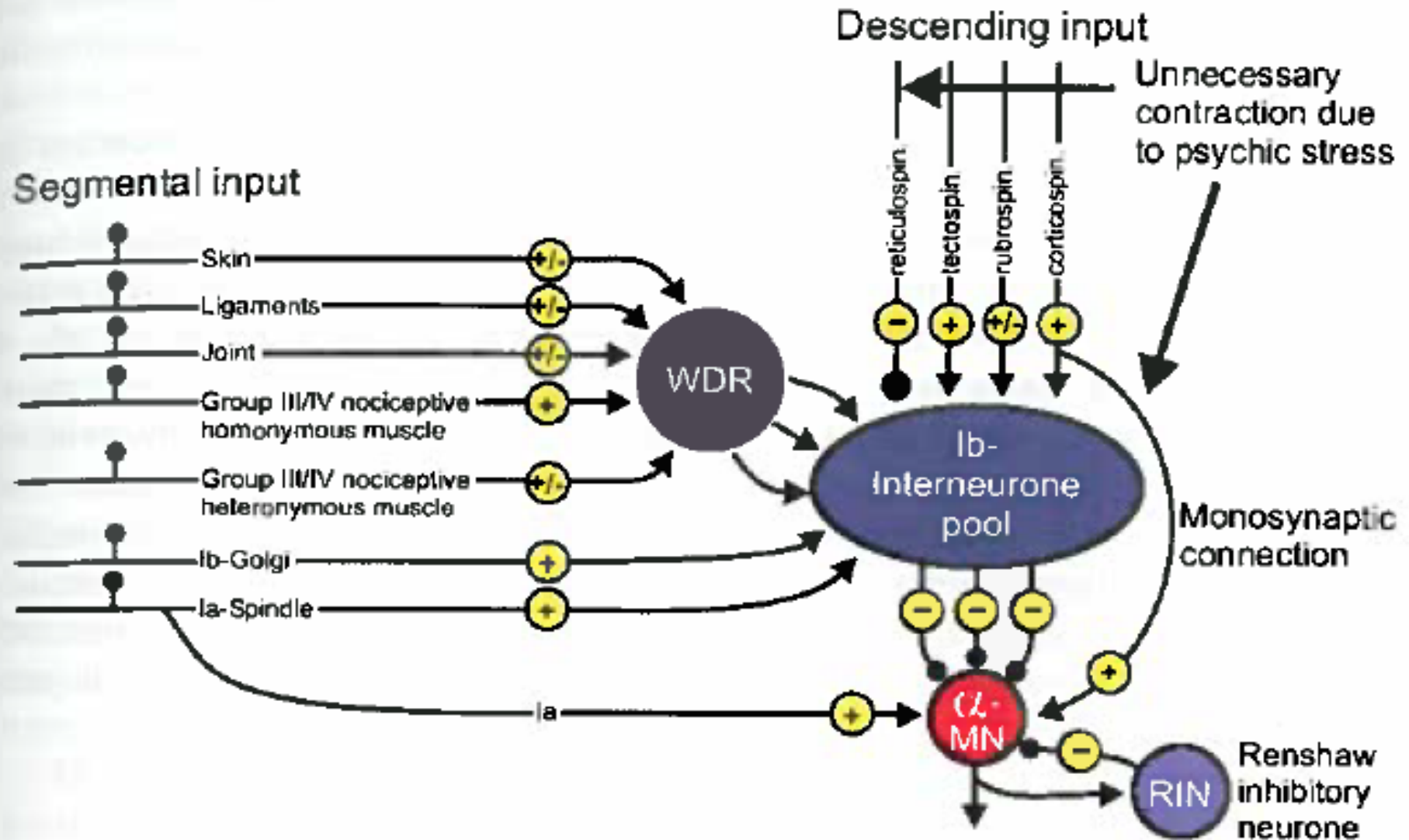
- The muscle in spasm is frequently not the muscle causing your pain.
- Lund hypothesis - The injured or painful muscle has less activity. The antagonist (muscle opposing the injured muscle) has more activity and often spasm.



**Agonist/Antagonist**



# Summary of Neuronal Input to Dorsal and Ventral Horn



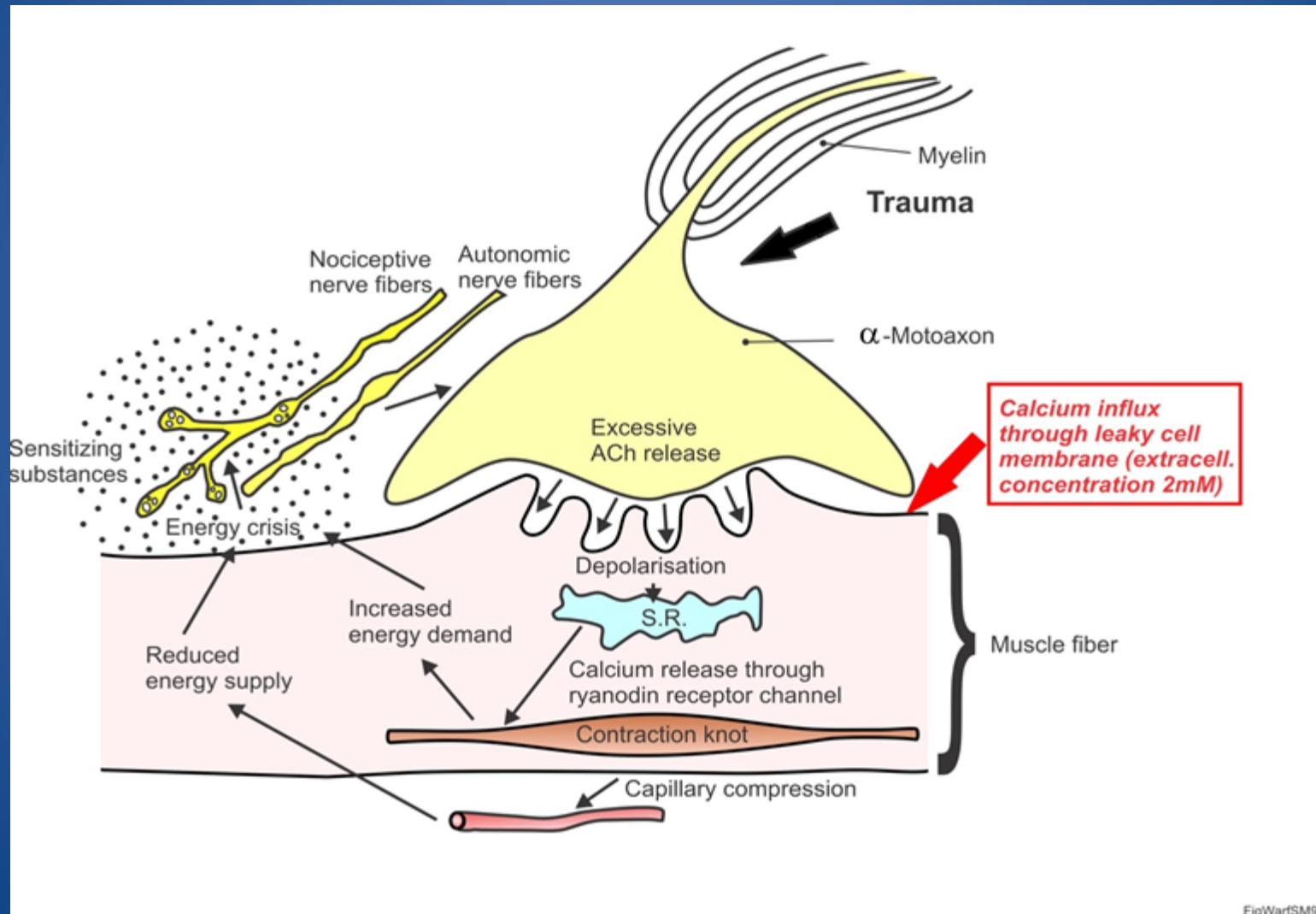


# Hans Kraus, M.D.

## Functional Muscle Pain

- Tension
- Deficiency: Weakness and/or Stiffness
- Spasm
- Trigger Points

# MTrPs Theoretical Model



# Myofascial Trigger Points

- Tender nodular area in muscle
- Taut band
- May refer to proximal and distal muscle
- SP, CGRP, BKN, 5-HT, Cytokines (Shah, J)
- Hypoxia and acid pH
- *Diagnosis made by pain to palpation*

# Validity of MTrP Protocols?

- Scott NA, et al. Trigger Point Injections for Chronic Non-Malignant Musculoskeletal Pain: A Systematic Review. *Pain Medicine*. 2009; 10(1): 54-69.
- Tough, EA, et al. Variability of Criteria Used to Diagnose Myofascial Trigger Point Pain Syndrome – Evidence From a Review of Literature. *Clinical Journal of Pain*. 2007; 23(3): 278-286.

# Palpation/Pressure

- Unreliable
- Sedentary muscle vs. Active muscle
- Misses nociceptors in the muscle attachment sites
- Primary Muscle/Referred Pain?



# Muscle Stimulation Hypothesis

## Postulate:

Externally induced contraction



Stimulates nociceptors in  
the attachments  
(entheses)

Deforms sensitized  
muscle tissue (trigger  
points)

# Painful Muscle Detection Instrument



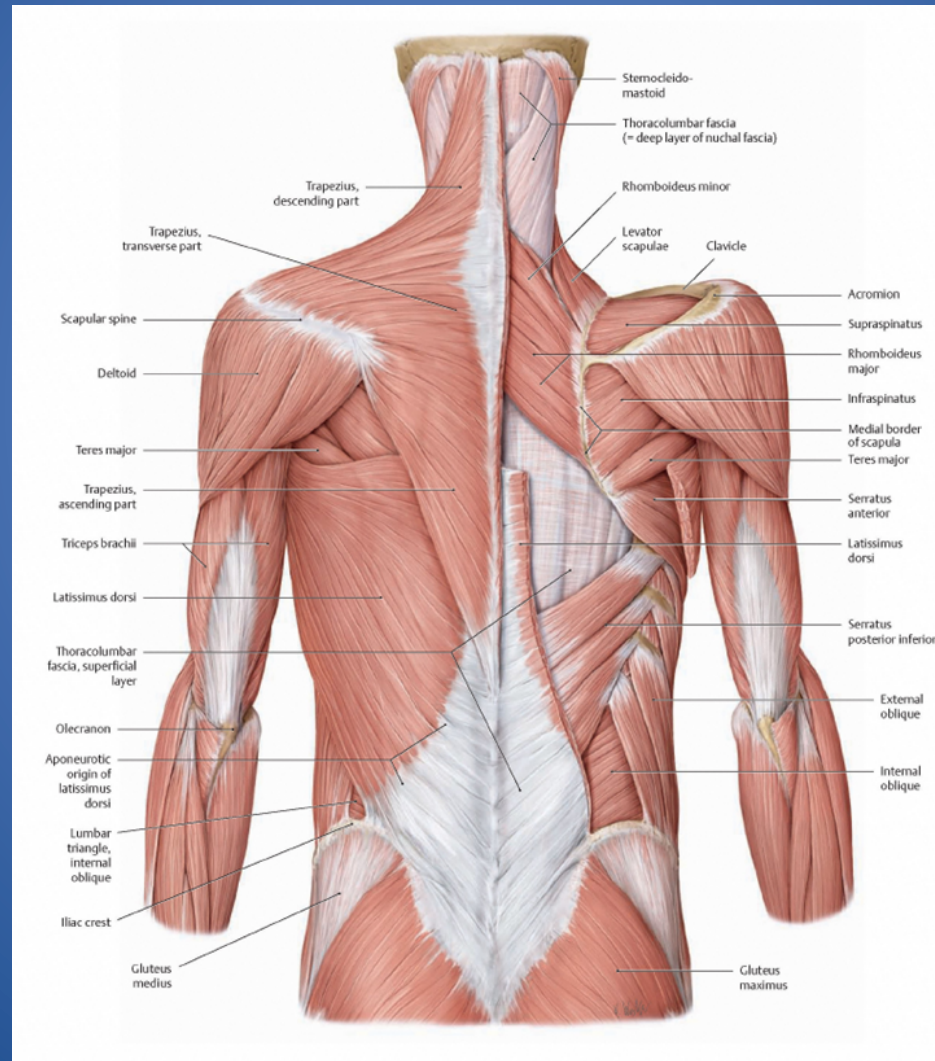




**25 year old man  
with 5 year  
history of Low  
Back Pain, Neck  
Pain, Headaches**



# Muscle Pain Referral





**Post-MTI to  
Right  
Infraspinatus**





Before



8/16/02

After



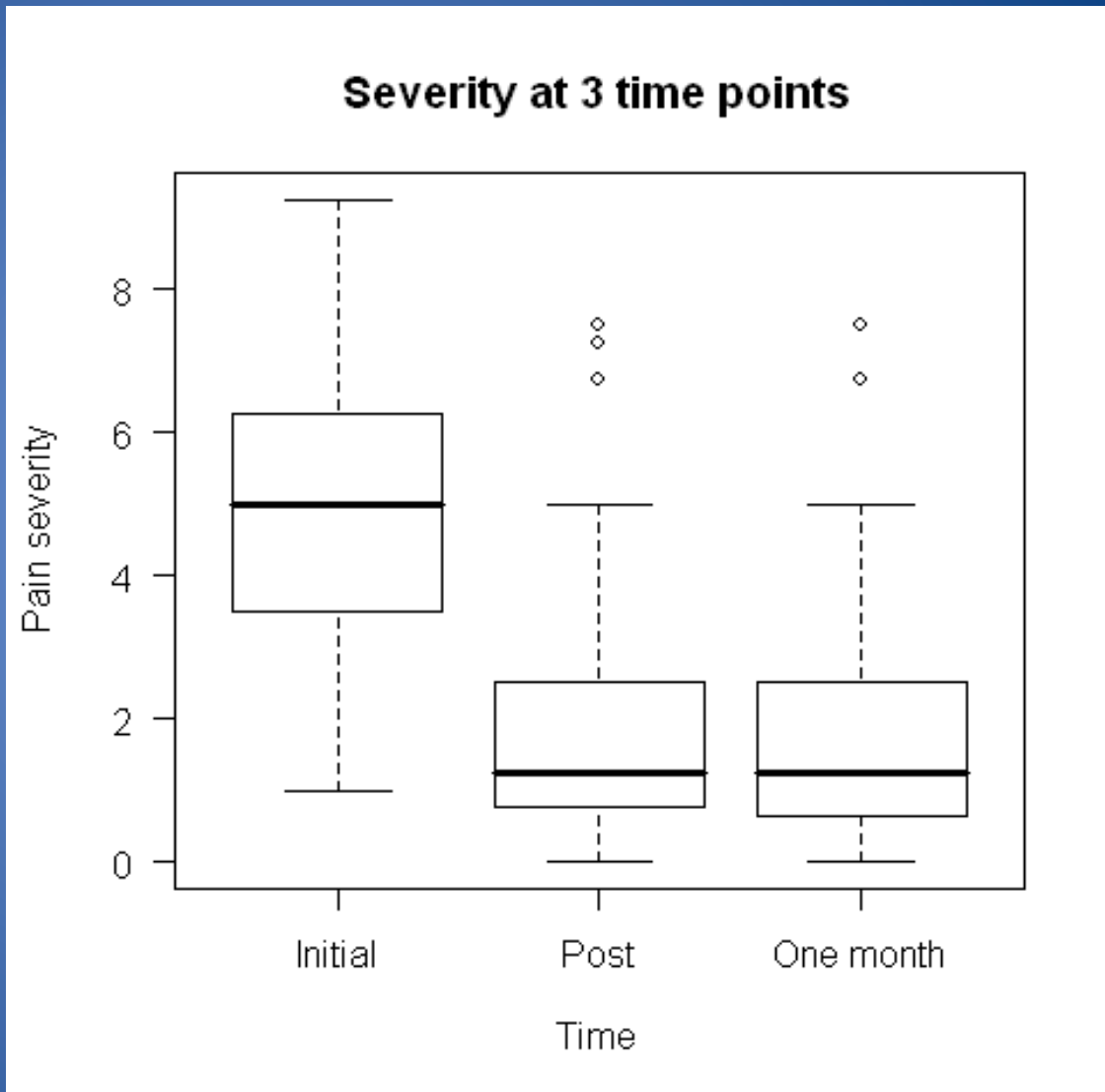
# **A Novel Structured Muscle Algorithm to Diagnose and Treat Pain of Muscular Origin May Successfully and Reliably Decrease or Eliminate Pain in a Chronic Pain Population**

- **176 patients**
  - **133 (76%) identified with muscle pain**
  - **70 patients eligible for treatment**
  - **45 started and finished treatment**

**Initial 4.95/5.00**  
**Post 2.02/1.25**  
**p<.001**

**1month 1.87/1.13**  
**p=1.0**

**Avg decrease 62%**  
**Med decrease 70%**





**Initial 5.28/5.67**

**Post 1.32/0.71**

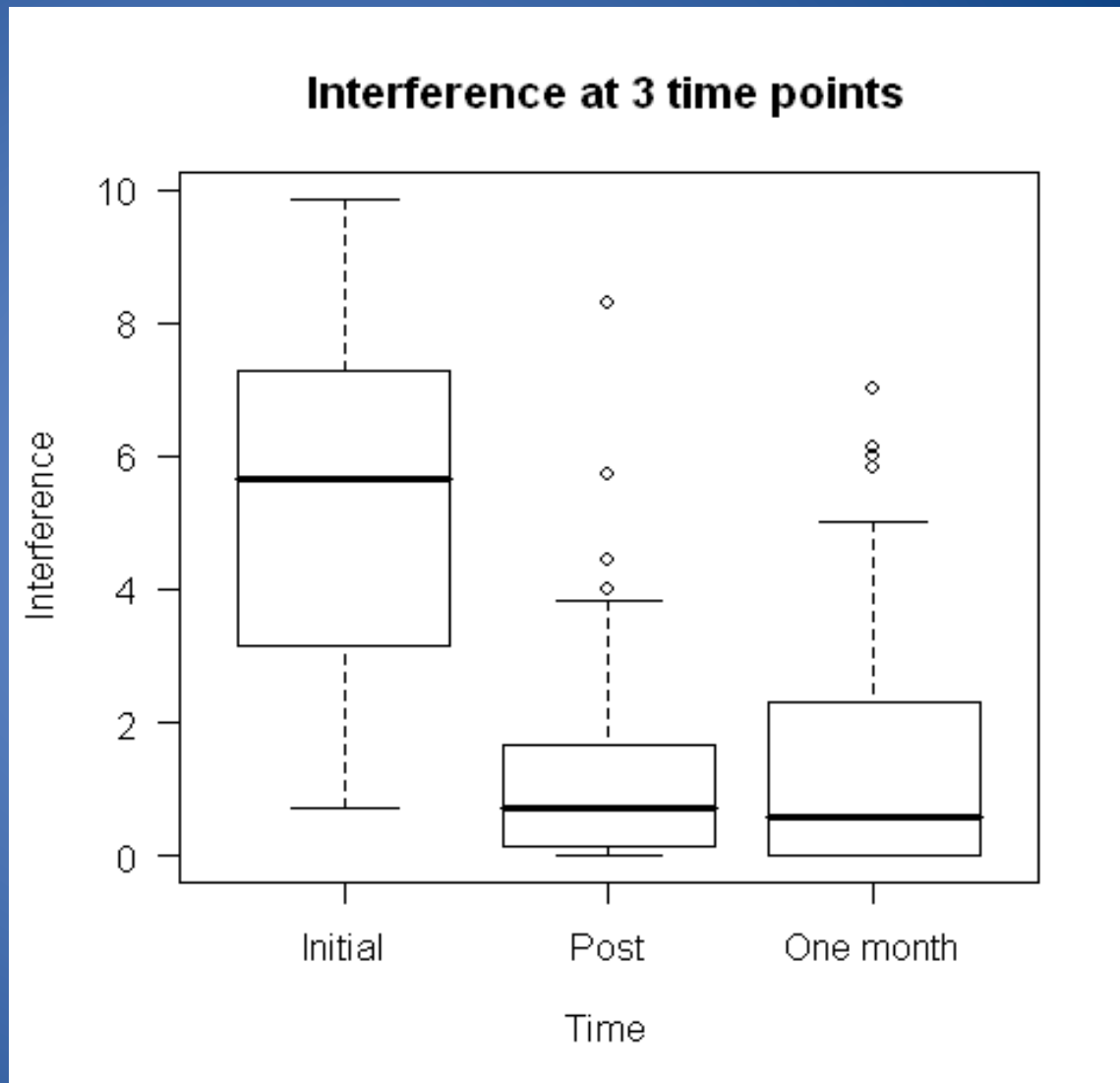
**p<.001**

**1 month 1.57/0.57**

**p=0.49**

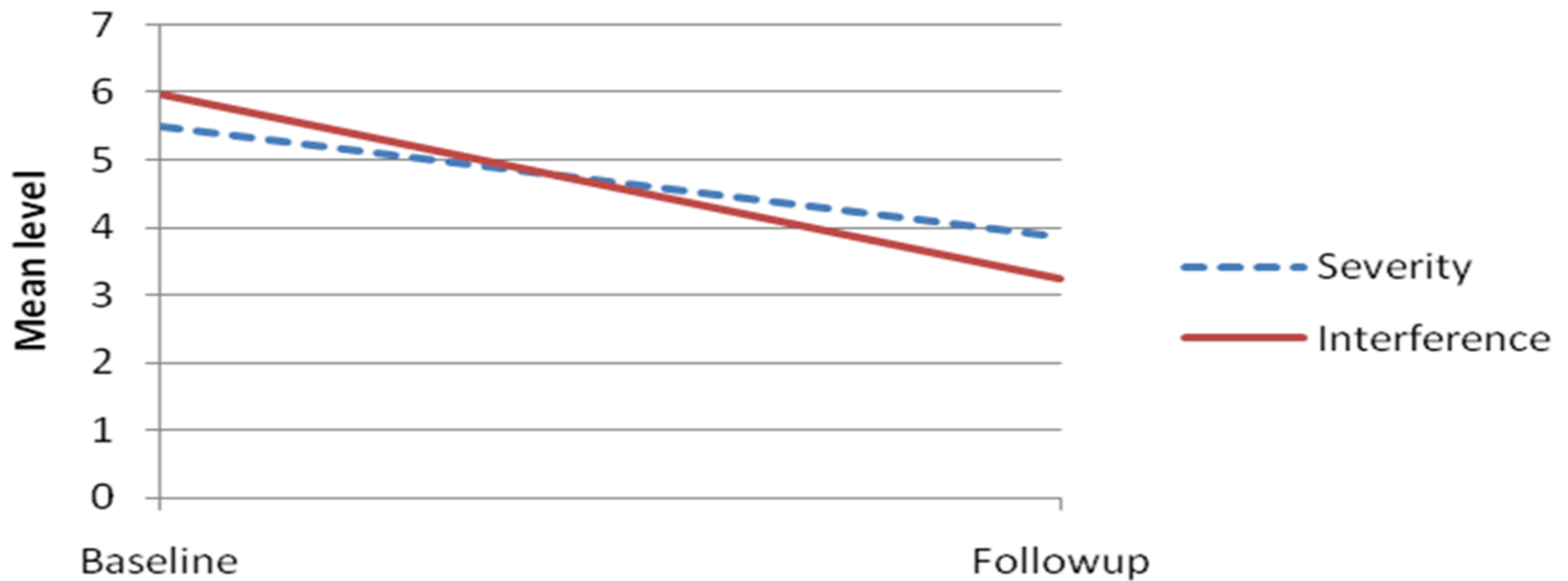
**Avg decrease 68%**

**Med decrease 85%**



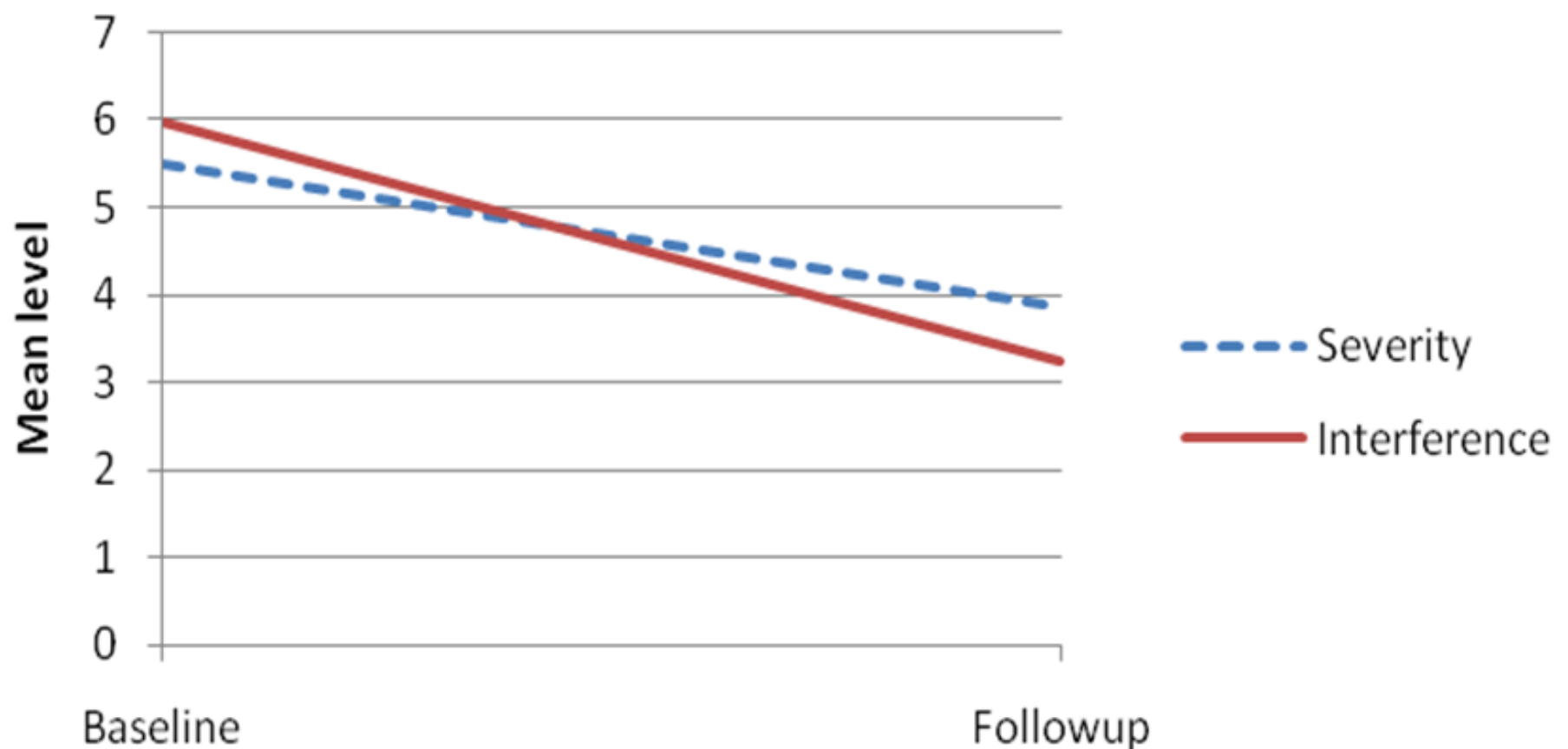


# 67/95 patients S/P FBSS, RFA, ESIs, TPI/Prolotherapy Pre/Post MTIs (77 weeks F/U)



Marcus NJ, Shrikhande AA, McCarberg B, Gracely E. (2013) *A Preliminary Study to Determine if a Muscle Pain Protocol Can Produce Long-Term Relief in Chronic Back Pain Patients*. Pain Medicine, 14(8).

# Mean Severity and Interference Over Time (at $\overline{77}$ weeks)



# Step-care pain treatment

- Most likely contributing diagnoses
- Least harmful interventions
- Most cost-effective

# Outside the Box

- FBSS
- HNP
- DDD
- FMS
- Spinal Stenosis
- Facet disease
- RSD
- Sacroiliac dysfunction
- Rotator cuff tear/Impingement syndrome
- Pelvic pain
- Headaches
- EDS

# Case 1/ Pain onset age 20

Joint hypermobility  
9/9 Beighton Scale

## Diagnoses:

- Facet arthropathy/RFA's
- Low Back Pain
- Migraine Headaches
- Headaches of unknown origin
- Shoulder Pain
- Thigh Pain
- Shin Splints
- IBS



## Case 2

- FBS – onset age 10, initially pain in legs
- Total body pain, wheelchair x 2 years
- Elevated CSF pressure
- Autonomic dysfunction (hypertension)
- Began Treatment for Muscle Pain age 23

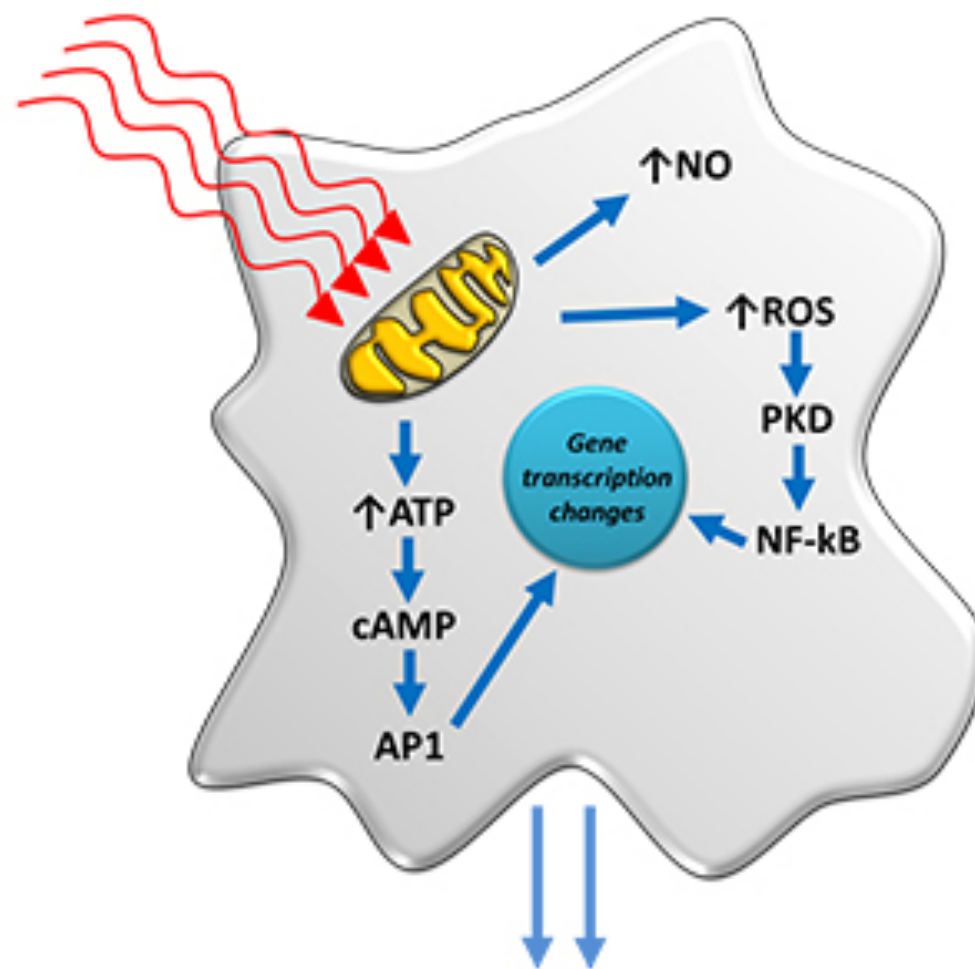
## Case 3

- Multiple Joint Replacements  
(Severe pain post op caused CHF)
- Recurrent Dislocations
- Severe pain and spasm around unstable joints
- Injections relieved pain but caused increased dislocations

# Low Level Laser Therapy

Non-visible spectrum with sufficient energy to penetrate deep tissue.





- Growth Factor production
- Cell proliferation
- Extracellular Matrix Deposition
- Cell mobility / adhesion
- Inhibition of apoptosis



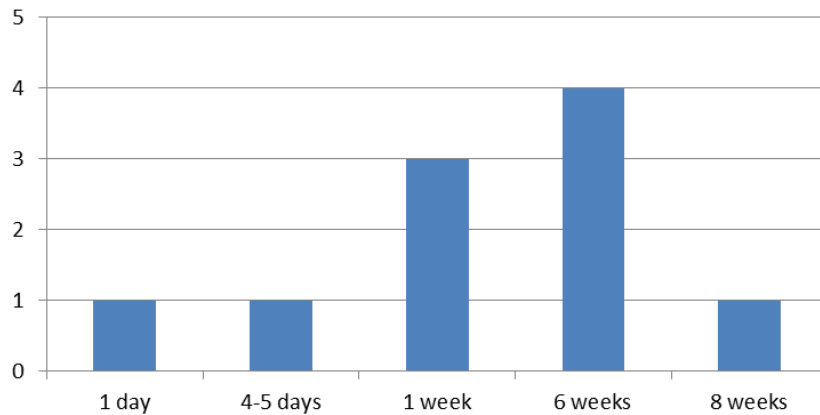


# Foundation for Research and Advocacy for Muscle Pain Evaluation and Treatment (FRAME)

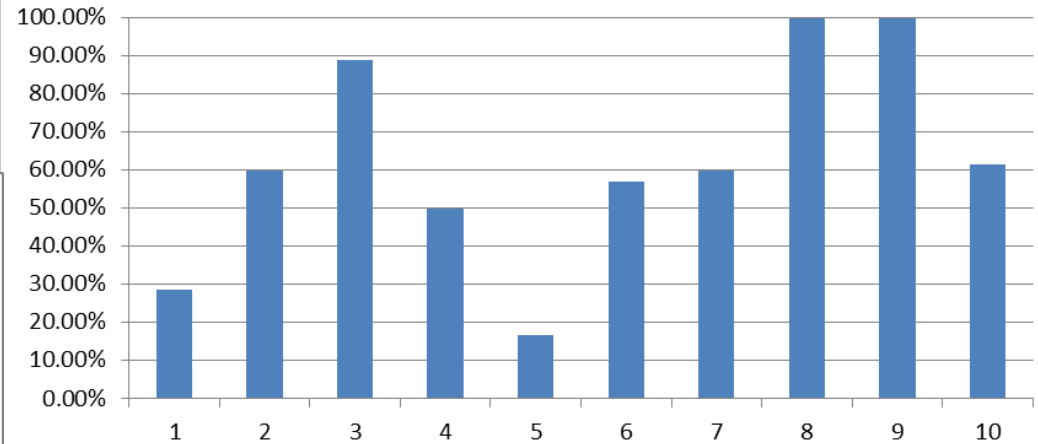
- Laser treatments in EDS Type III (jt. hypermobility type)
- 10 patients (1 male, 9 female)
- 5 sessions

# Results

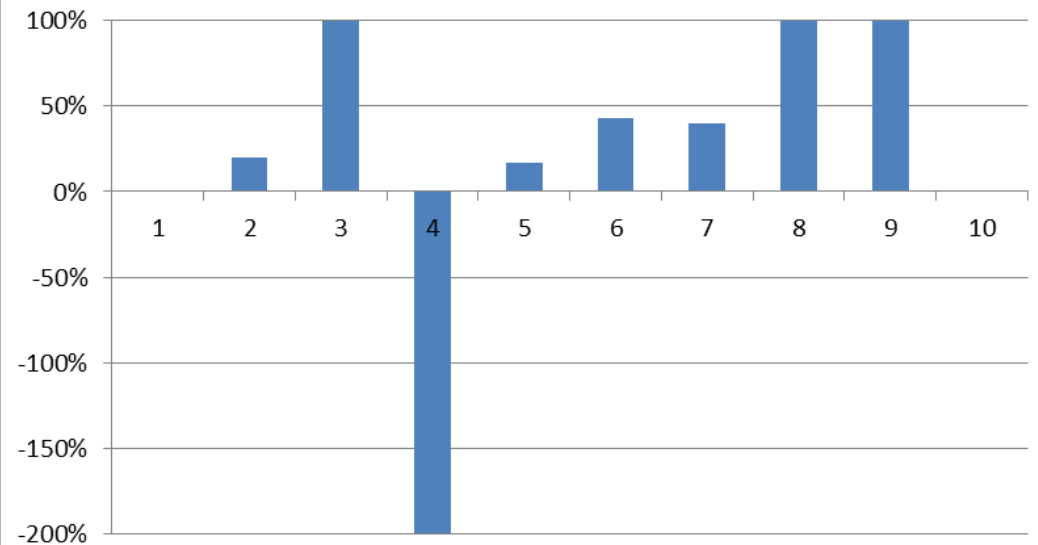
## Length of Pain Relief



## Pain Relief at End of Rx



## Pain Relief S/P 1 Month



For more information please visit:

[www.nmpi.com](http://www.nmpi.com)

# Chronic Painful Work-Related Muscle Syndromes

- Repetitive muscle use
- Sustained uncoordinated contraction
- Time pressure\*
- Psychic Stress\*
- Cinderella syndrome\*\*

\*Hughes L et al, Effects of psychosocial and individual factors on physiological risk factors for upper extremity musculoskeletal disorders Ergonomics 2007, V50, 2:261-274

\*\*Kadefors R et al, Recruitment of low threshold motor units in the trapezius muscle in different static arm positions Ergonomics 1999, V42, 2:359-375