

# Pathophysiology of Pain

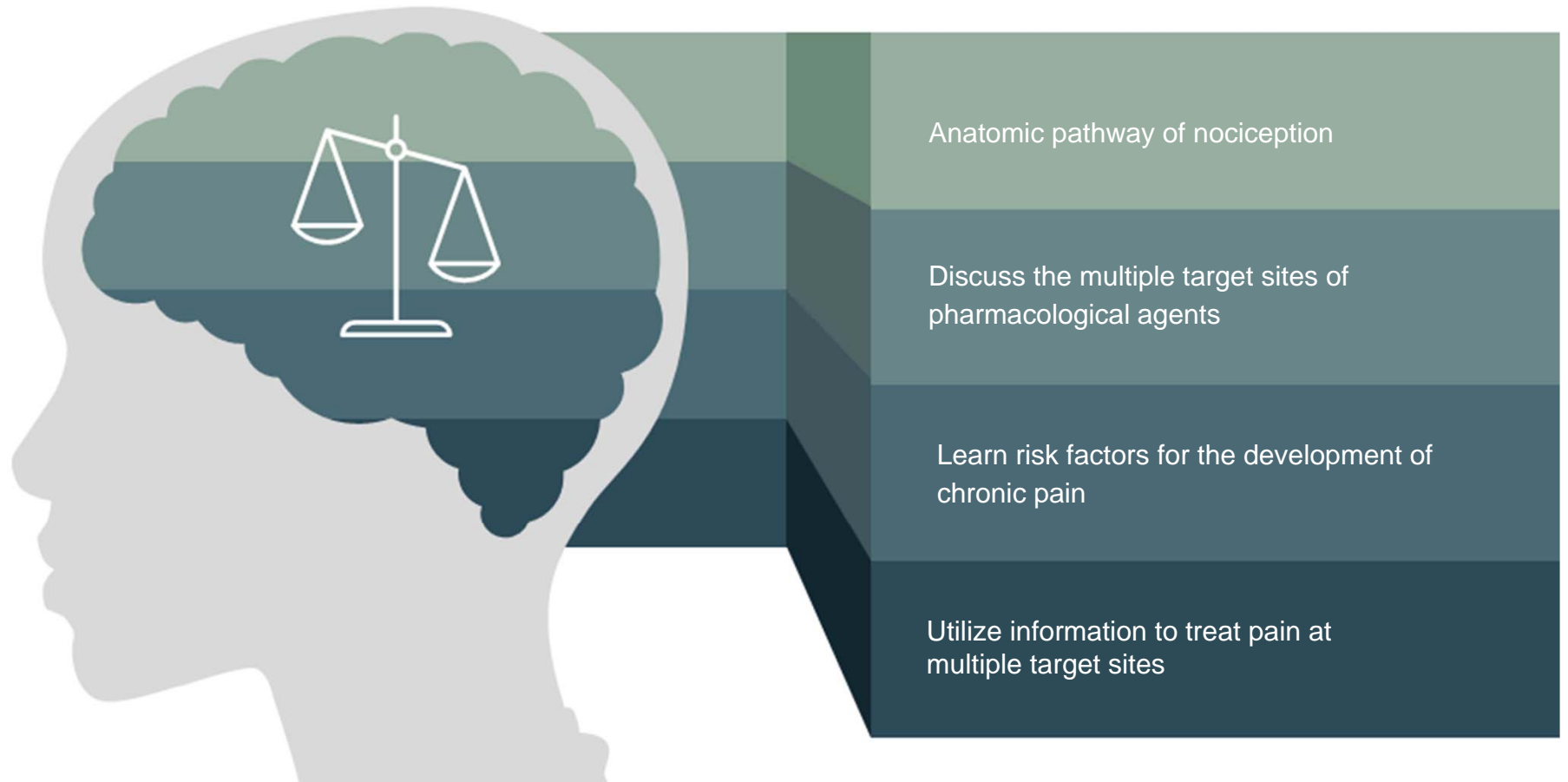
**Ramon Go MD**

Assistant Professor Anesthesiology and Pain medicine  
NYP-CUMC



COLUMBIA UNIVERSITY  
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# Learning Objectives



## What is pain?

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage"



**IASP**<sup>®</sup>

International Association for the Study of Pain

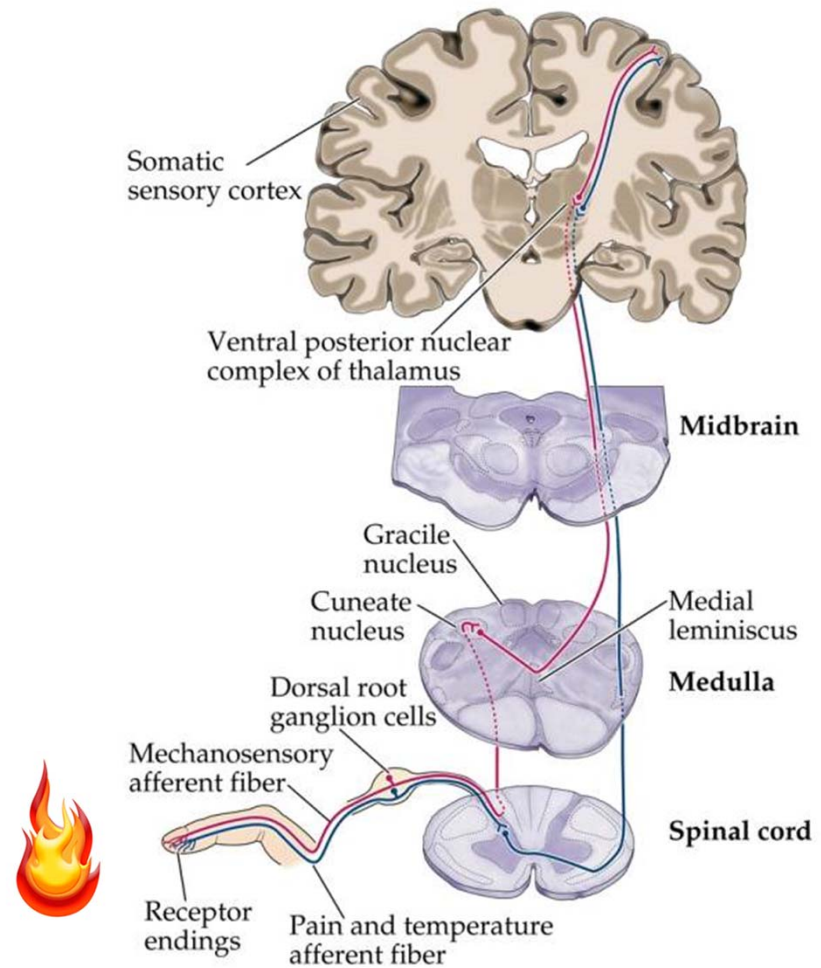
# Anatomy of the Pain Pathway

**Transduction:** Conversion of a noxious stimuli (chemical, mechanical, or thermal) into electrical energy

**Transmission:** Electrical stimulus is sent to the dorsal horn of the spinal cord and synapse at the 2nd order neuron

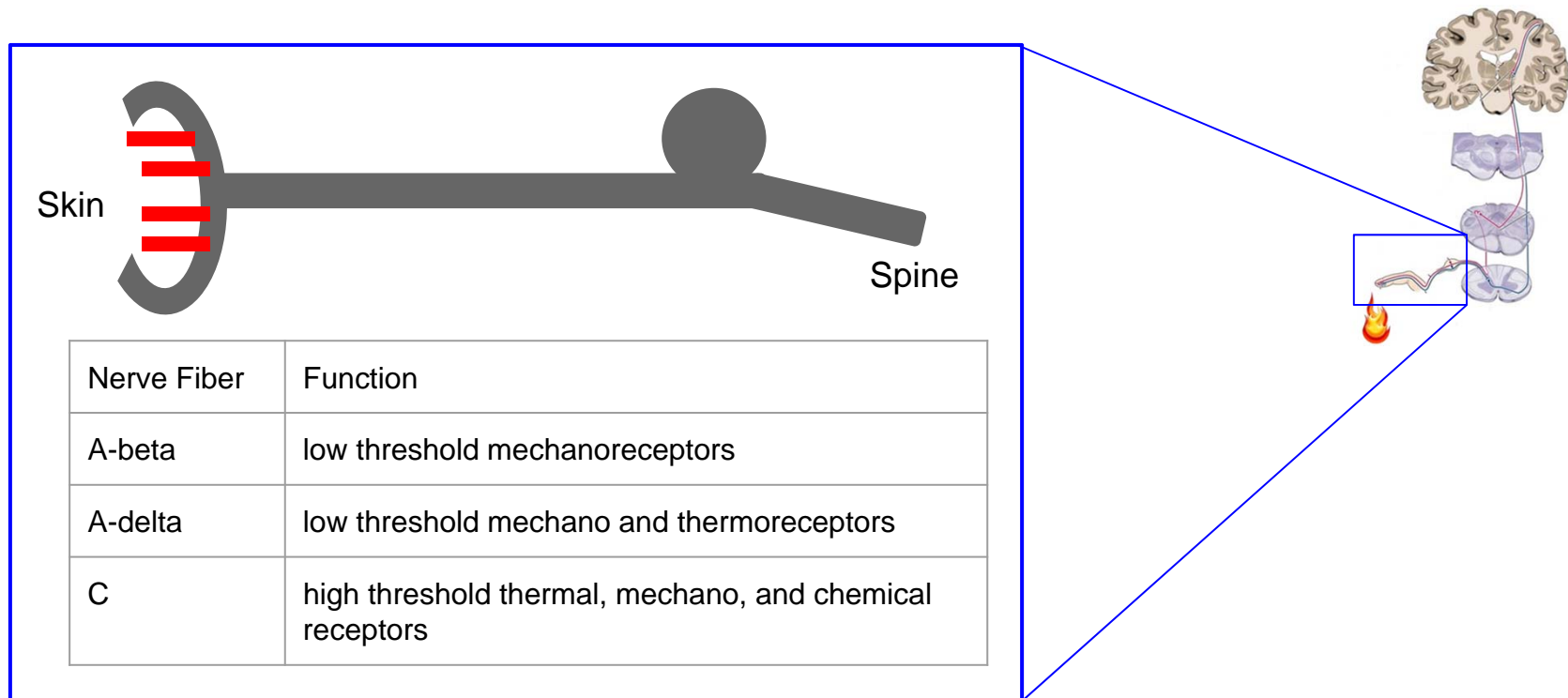
**Modulation:** Inhibition vs amplification of signal (facilitated by EAA)

**Perception:** Conscious awareness of pain as a culmination of previous processes in the context of the individuals experiences.

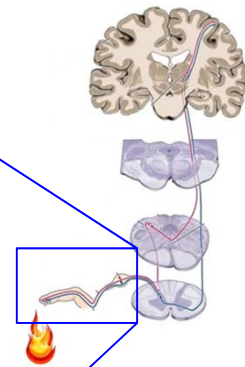
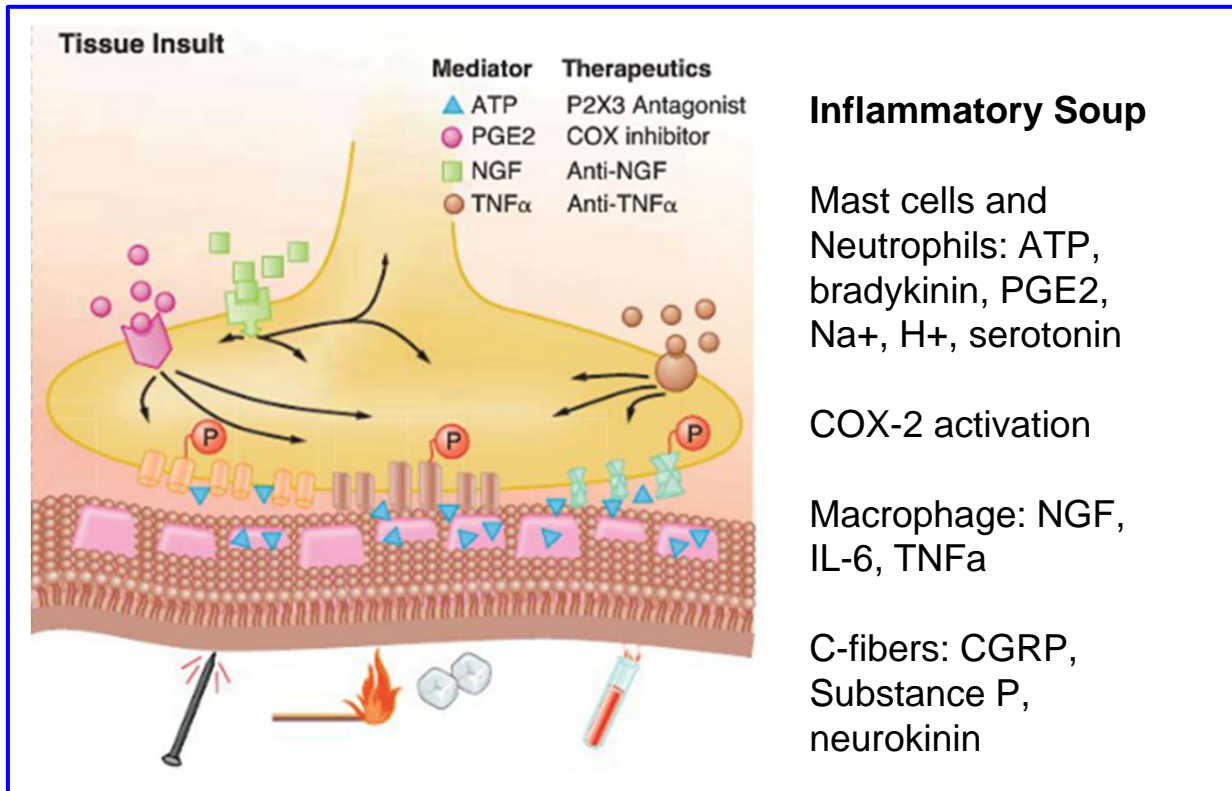


# A closer look

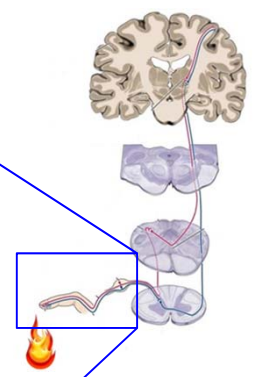
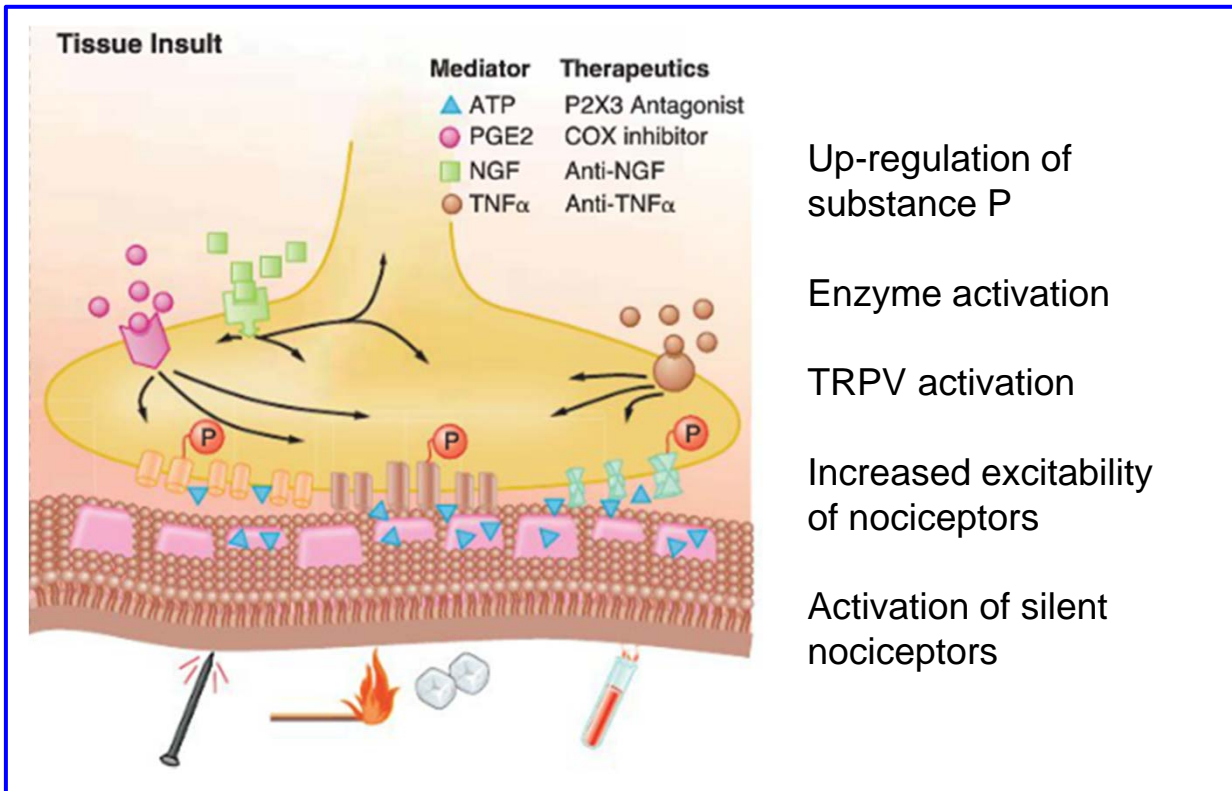
Transduction: Primary afferents



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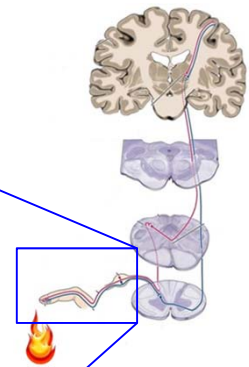


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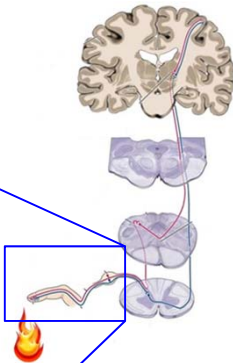
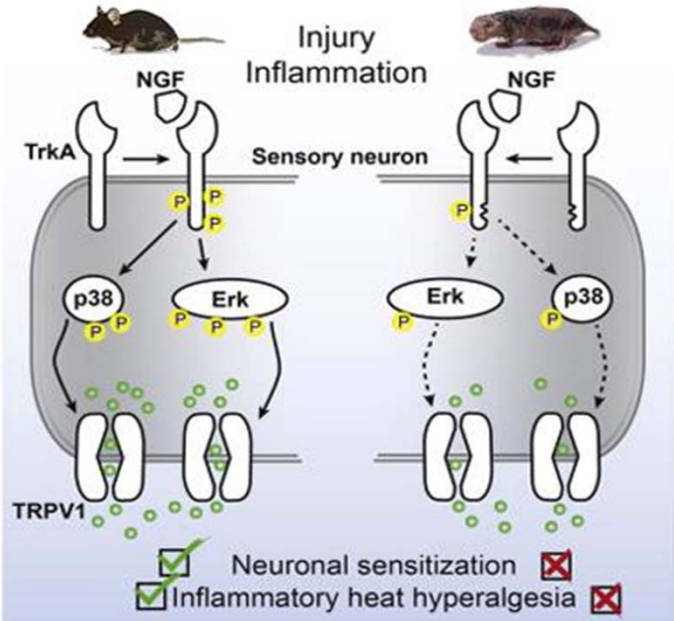
Naked mole rat: Inability to convert capsaicin and acid stimulus to electrical signal



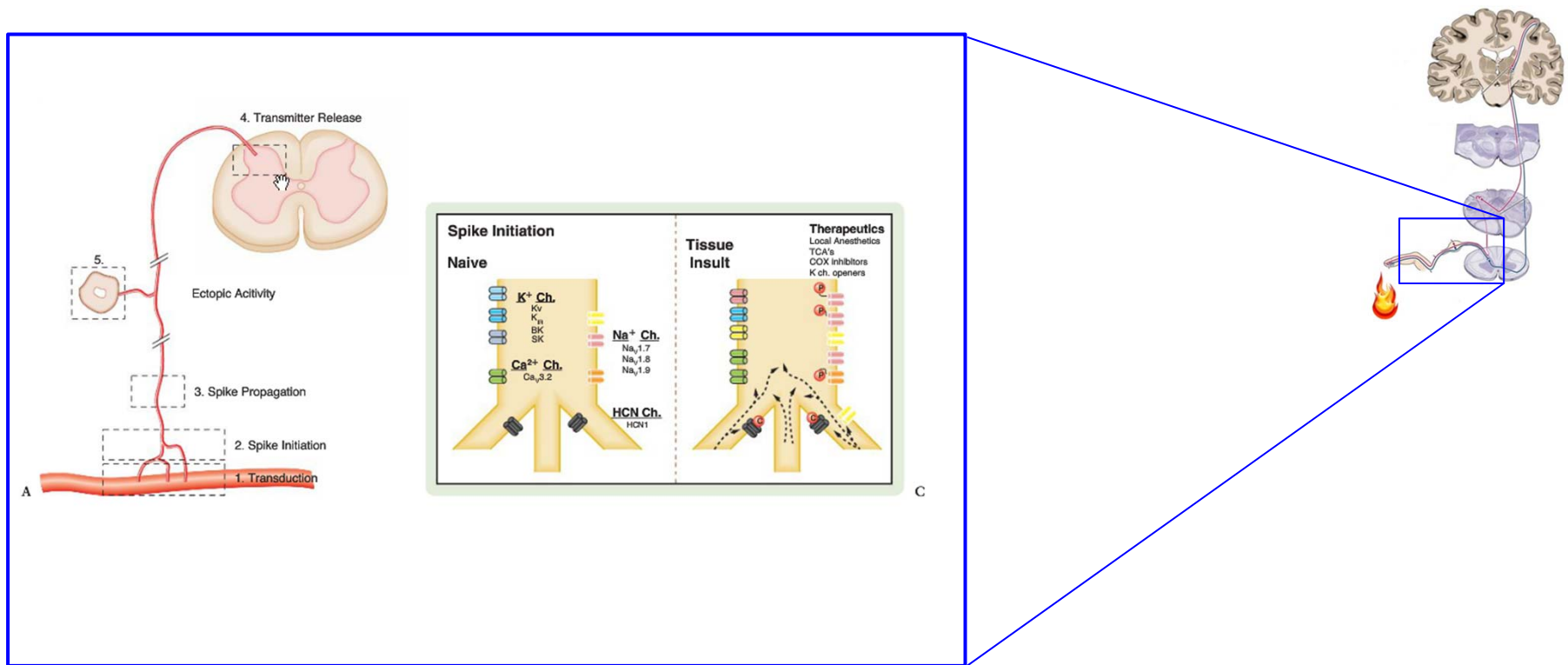


# Transduction: Primary afferents

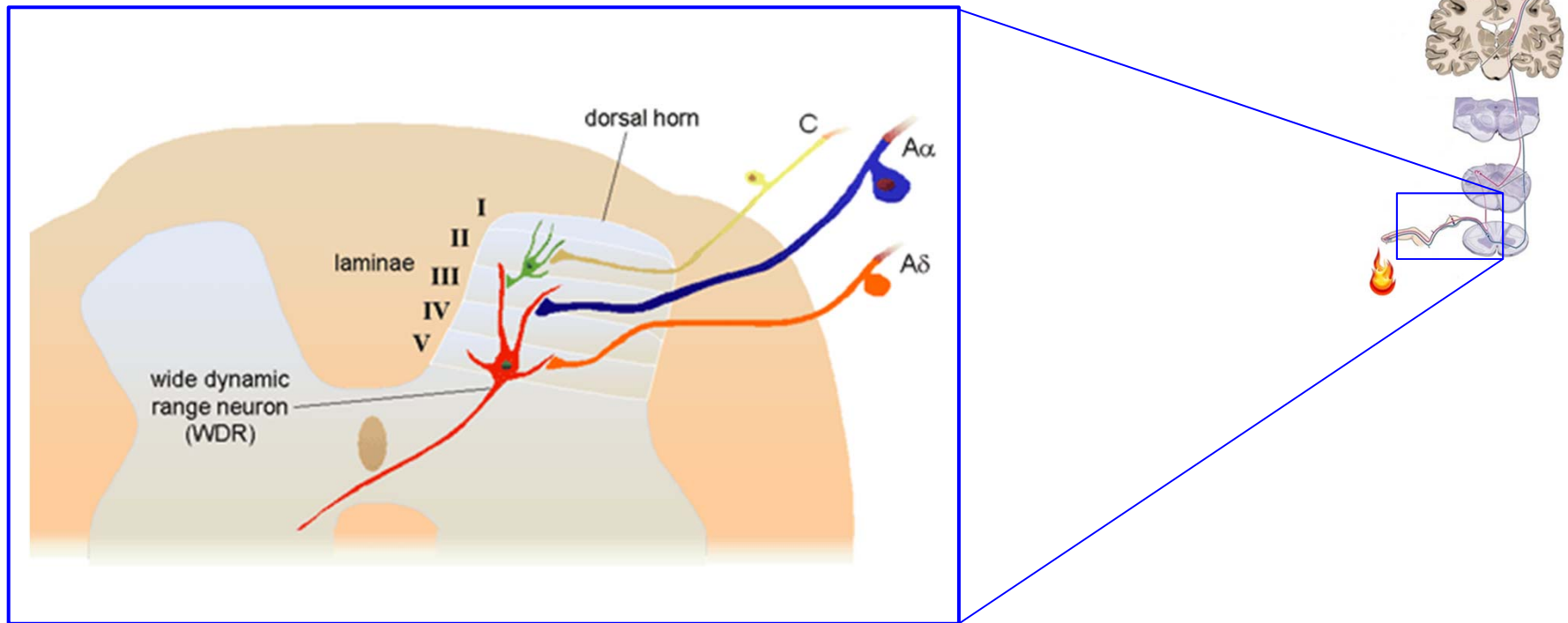
NGF/TRKA Pathway: Activates TRPV1 ion channel allows depolarization and activation of voltage gated Na<sup>+</sup> channels



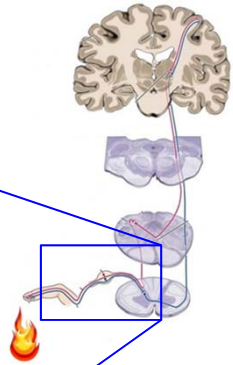
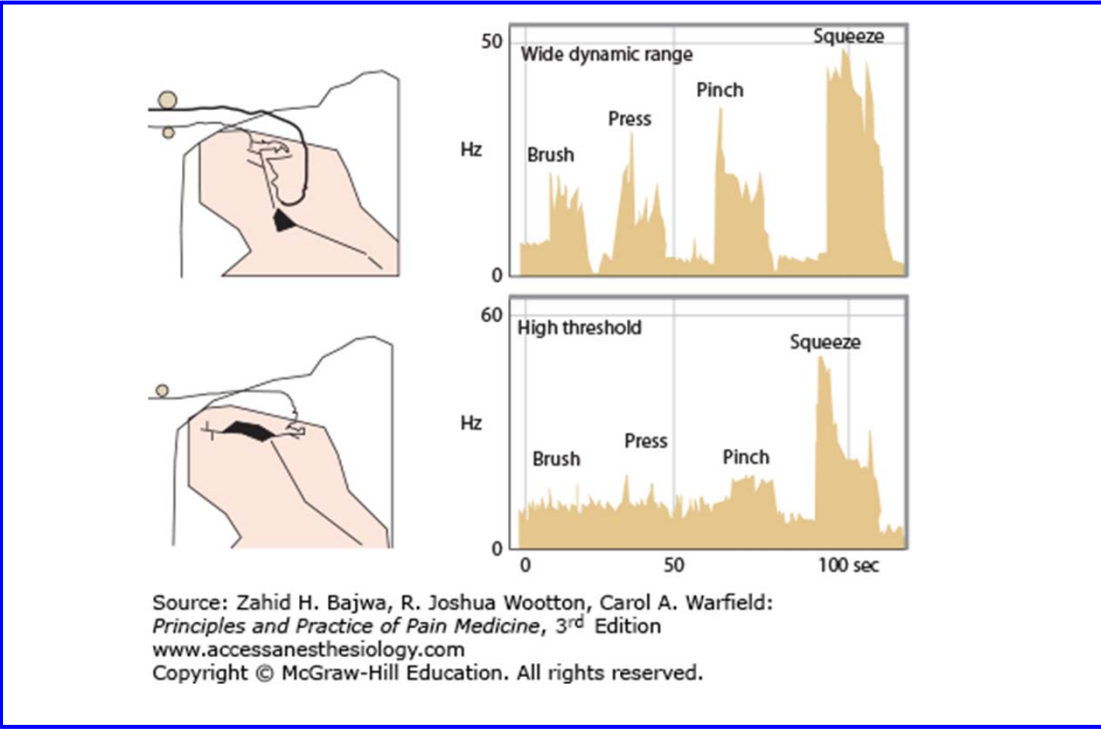
**Transmission:** Electrical stimulus is sent to the dorsal horn of the spinal cord and synapse at the 2nd order neuron



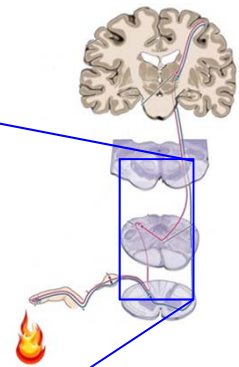
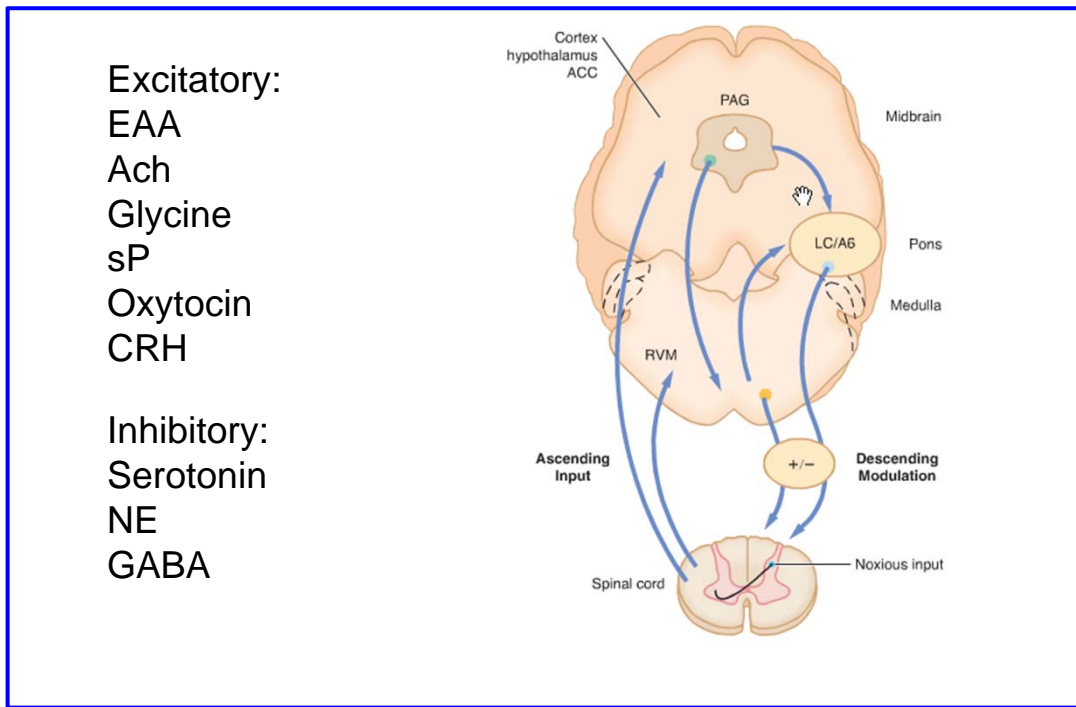
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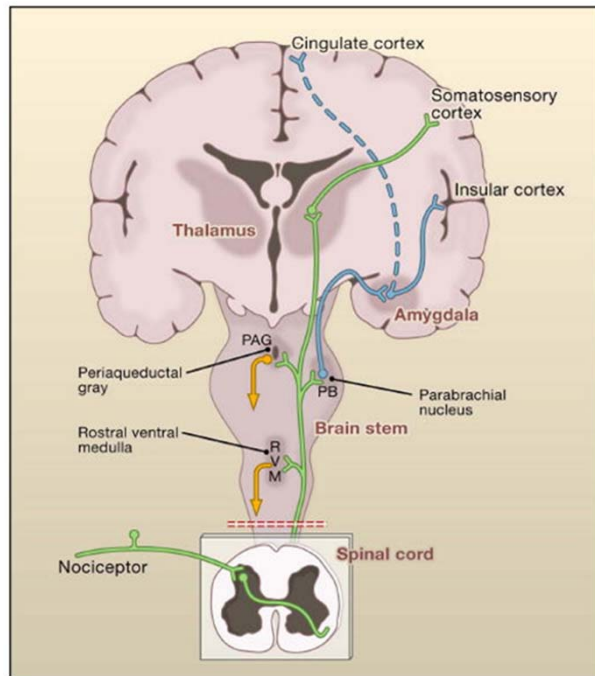
# Transmission: C fiber activity increases Wide Dynamic Range Neurons firing



# Modulation: Inhibition vs amplification of signal.

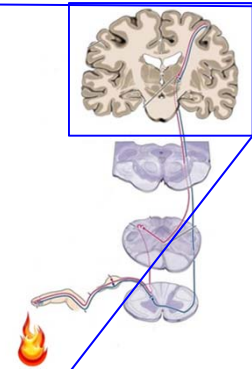


# Perception: Conscious Awareness of Pain

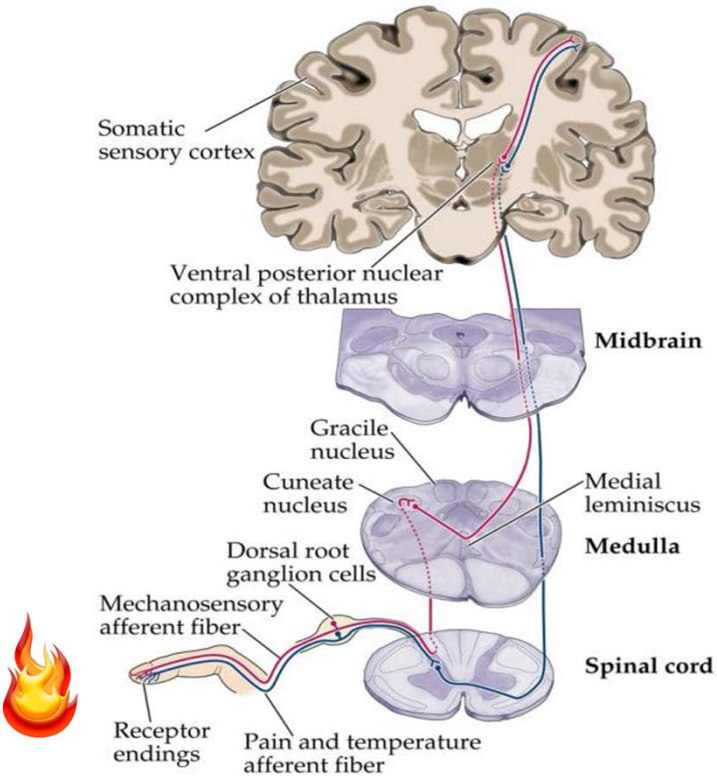


**Cortical:**  
Somatosensory cortex, insula, and anterior cingulate cortex

**Subcortical:**  
hypothalamus, Thalamus, amygdala, hippocampus



# When the norm diverges...



# When acute pain turns to chronic...





## Surgical procedures and prevalence rates of developing postsurgical pain syndrome

<b>Procedure</b>	<b>Prevalence</b>
Breast Surgery	22-35%
Thoracotomy	11-52%
Cholecystectomy	21%
Limb Amputation	5-50%
Hip	7-13%
Laparoscopic Hernia Repair	15% at nine months

**From: Severing the Link between Acute and Chronic Pain: The Anesthesiologist's Role in Preventive Medicine**  
**Anesthes. 2004;101(5):1063-1065.**

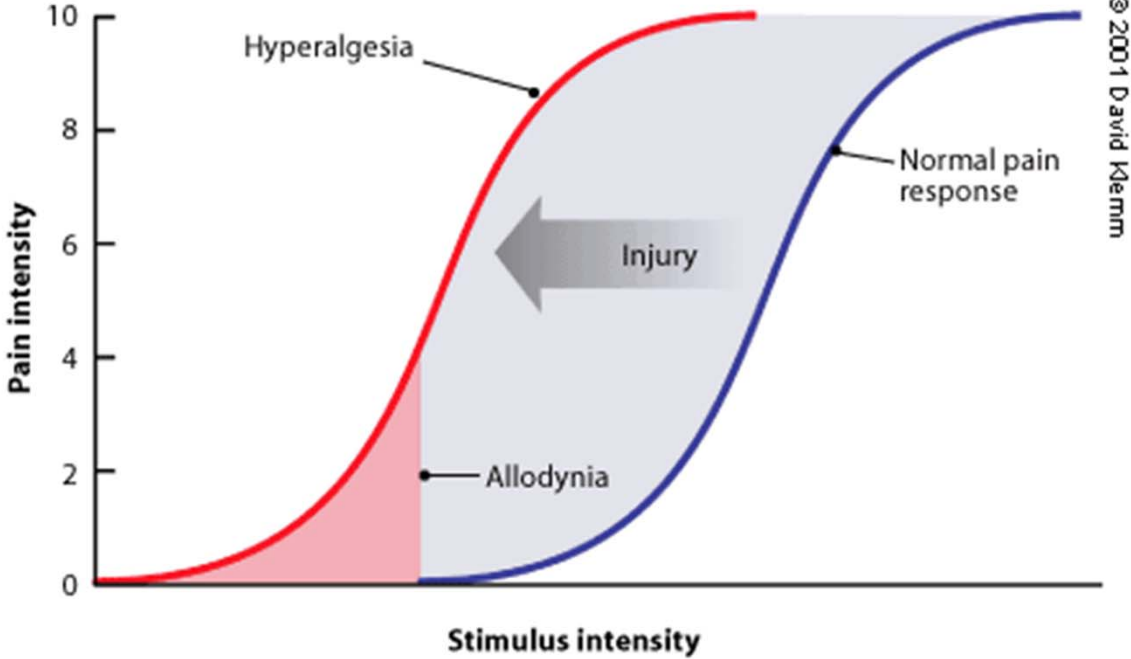
**Table 1. Numbers of Procedures for Specific International Disease Classification (ICD-9) Procedure Codes, Rate of Complex Regional Pain Syndrome (CRPS) for Specific Procedures, and Corresponding Numbers of Cases of CRPS Associated with Common Orthopedic Surgical Procedures**

Procedure (ICD-9 Code)	N† (in thousands/yr)	Rate‡ (%)	CRPS (in thousands/yr)
Arthroscopic knee surgery (80.26)	657	2.3–4.0	15.1–26.3
Carpal tunnel surgery (04.43)	366	2.1–5.0	7.7–18.3
Ankle fractures (79.*6 and 79.*7)	257	13.6	35.0
Total knee arthroplasty (81.54)	247	0.8–13.0	2.0–32.1
Wrist fractures (79.*2 and 79.*3)	194	7.0–37.0	13.6–71.8
Fasciectomy for Dupuytren's Contracture (82.35)	20	4.5–40	0.9–8.0
Total	1741	4.3–11.0	74.3–191.5

\* Refers to any number 0–9. † See reference <sup>7</sup>. ‡ See reference <sup>4</sup>.

[Allan Gottschalk, M.D., Ph.D.](#); [Srinivasa N. Raja, M.D.](#)

# Abnormal Transmission of Pain



Gottschalk et al 2001

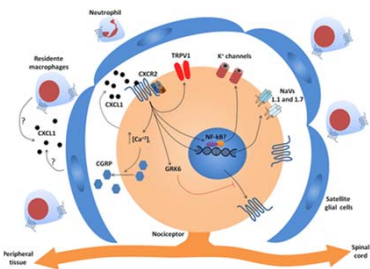
## Changes to the pain pathway in chronic pain

### Transduction

Sustained increase in nociceptors.

Activation of TRPV1-R

Increase in sP and CGRP



### Transmission

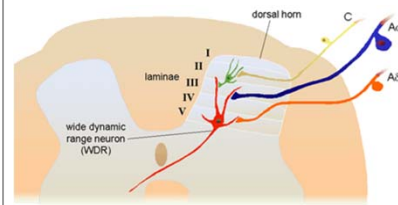
NMDA-R activation

Wind-up

WDR-Neurons sprout abnormal connections

Activation of glial cells

Central sensitization



### Modulation

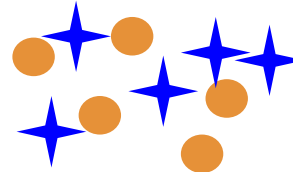
Decreased inhibition

vs

Increased amplification

Loss of pain filtering

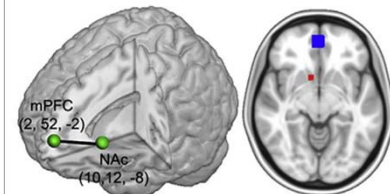
Increased release of pain transmitters



### Perception

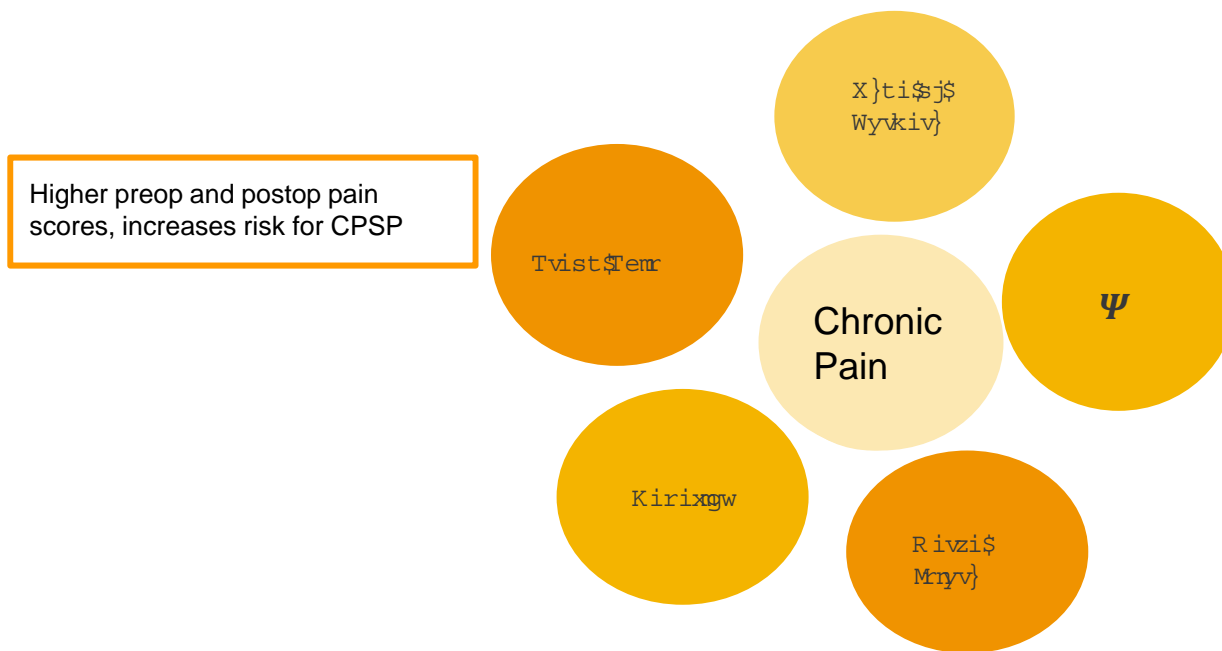
Gray matter decrease (reversible)

Increased connections:  
Medial Prefrontal Cortex (mPFC) and Nucleus Accumbens

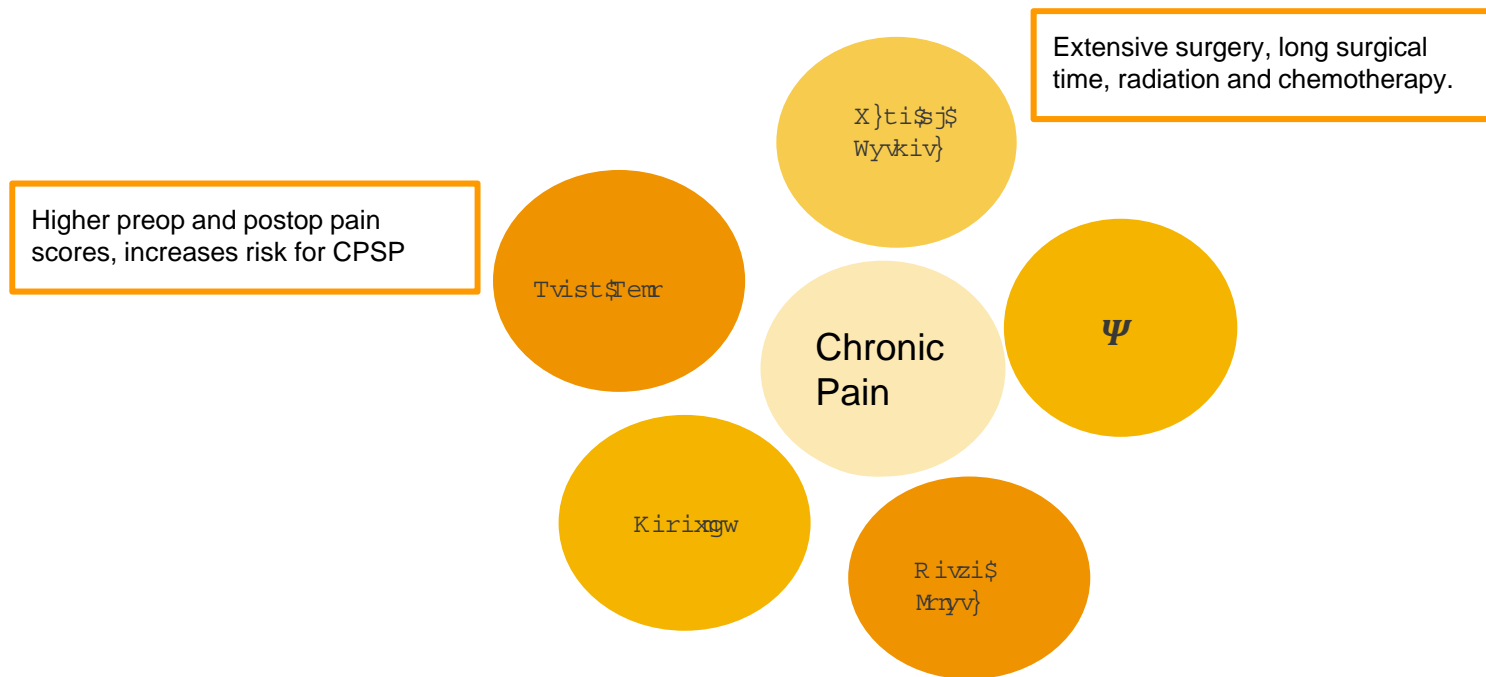


Pain. 2013 Oct;154(10):2160-8. Brain white matter structural properties predict transition to chronic pain. Mansour AR et al

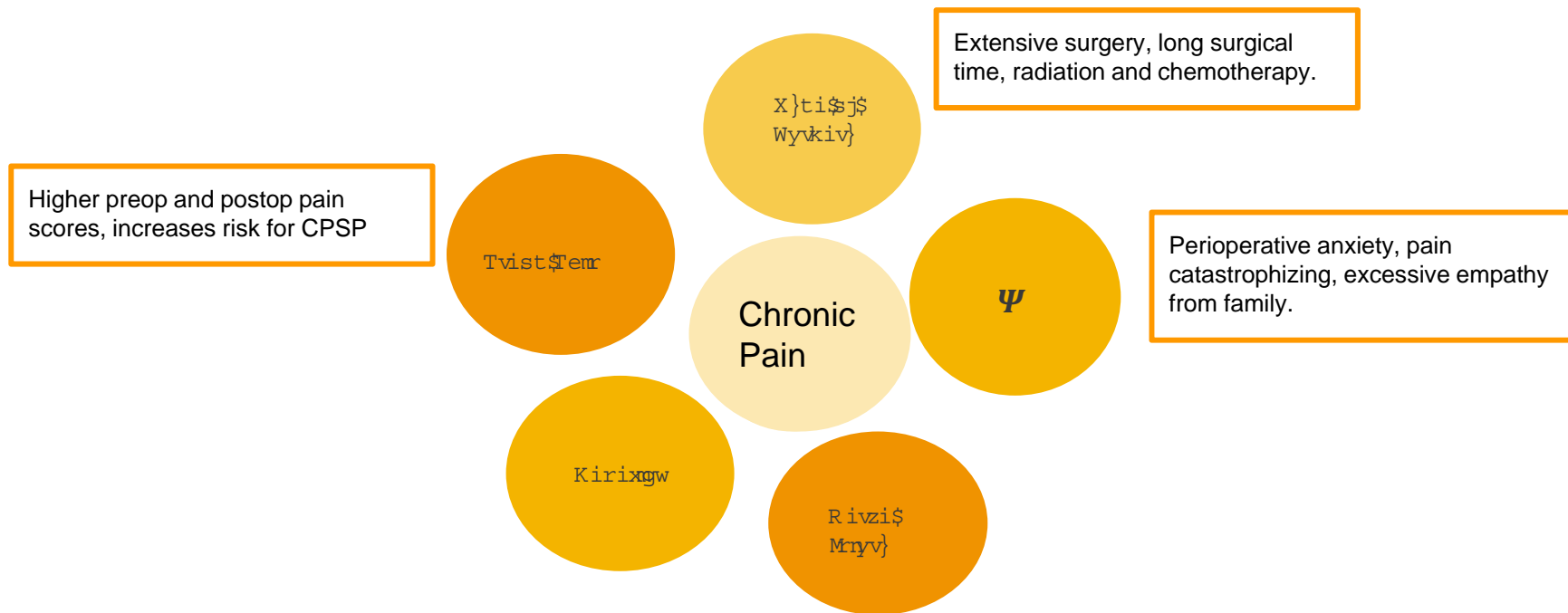
# Risk Factors for acute pain to become chronic...



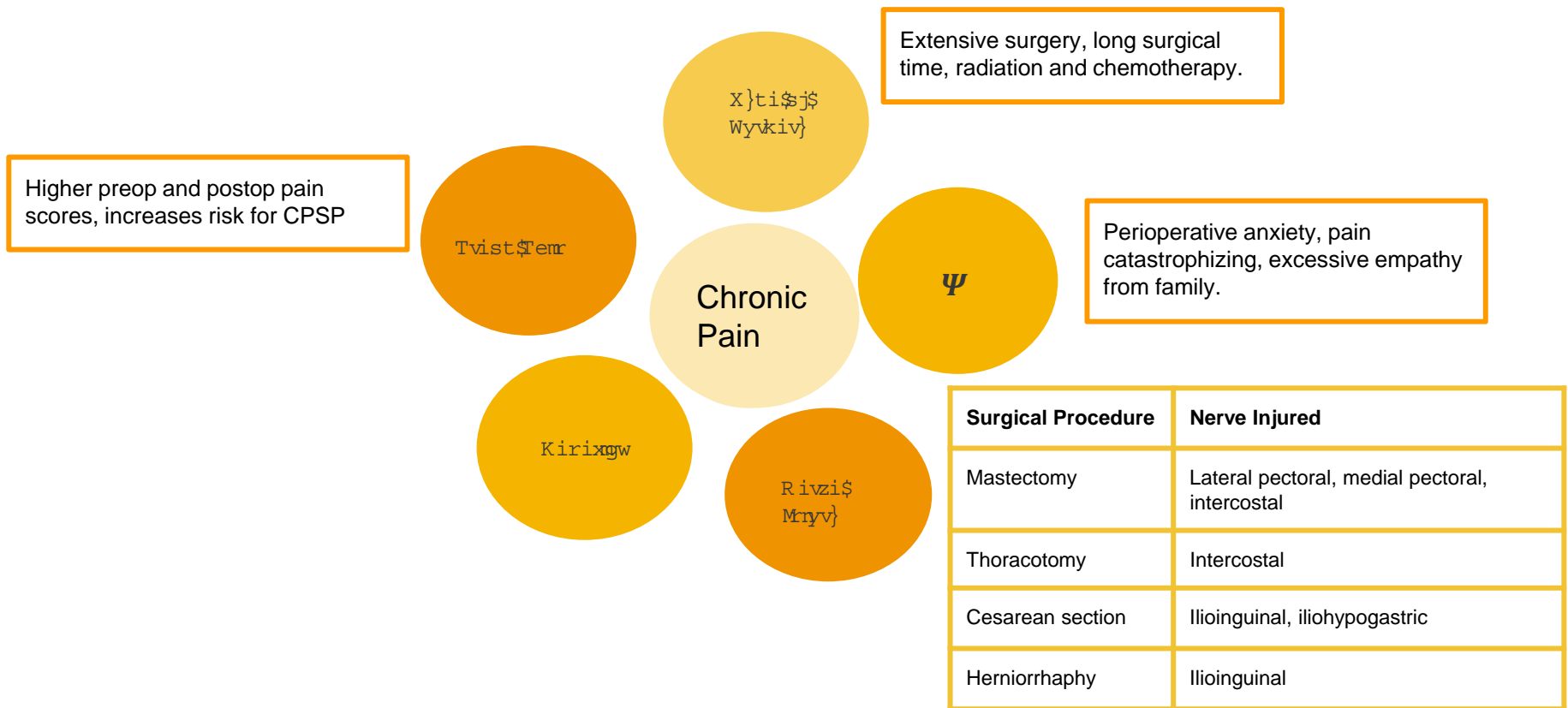
# Risk Factors for acute pain to become chronic...



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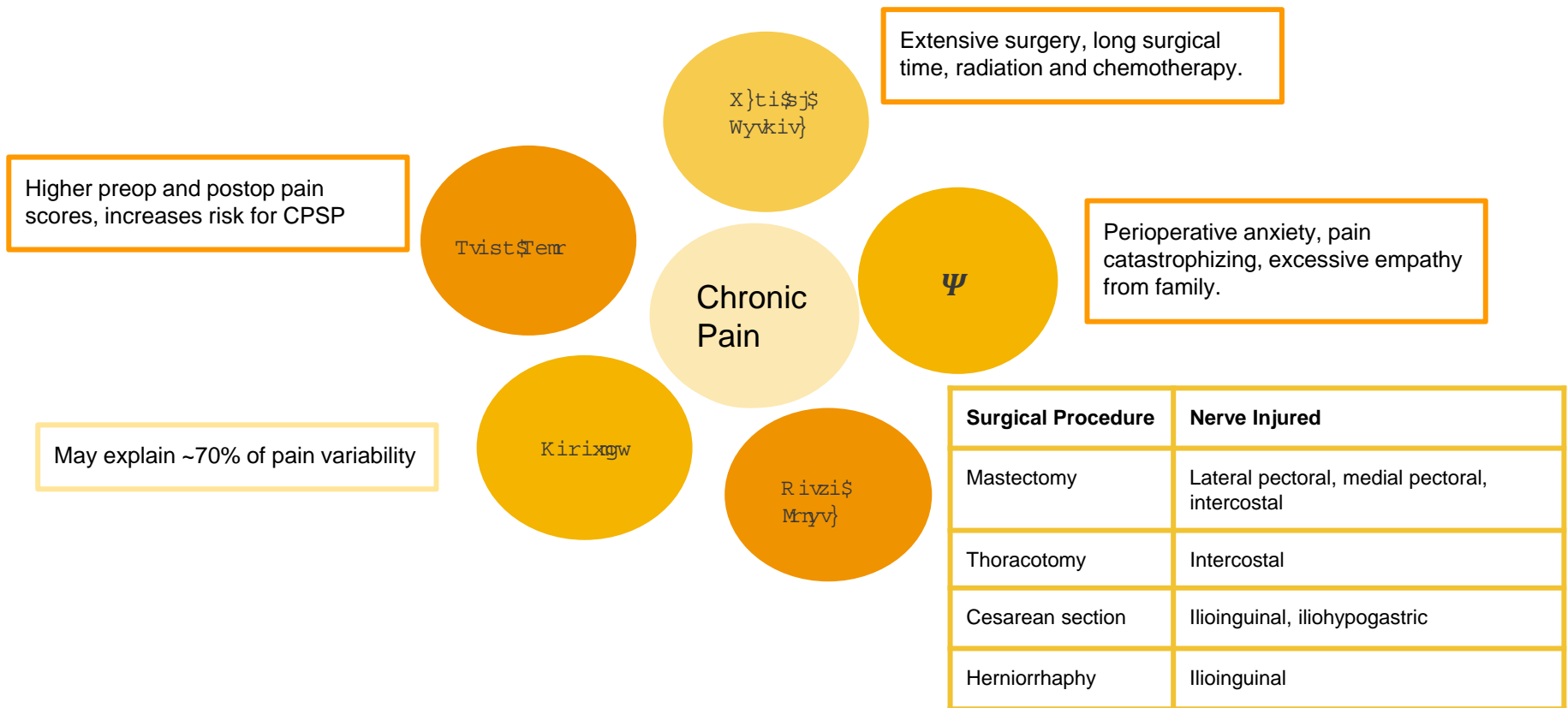


# Risk Factors for acute pain to become chronic...





# Risk Factors for acute pain to become chronic...



Genetic polymorphisms result in altered nociception

Genetics may explain 70% of variability in experiencing pain



SCN9A Gene: Nav1.7



“No pain”

Normal  
Pain  
Perception

“Man on Fire Syndrome”

<b>Increased Pain Sensitivity</b>		
<b>Gene</b>	<b>Protein affected</b>	<b>Phenotype</b>
<i>KCNS1</i>	Voltage gated potassium ion channel	Increase sciatica pain and phantom limb pain
<i>SCN9A</i>	Voltage gated sodium ion channel	Chronic burning pain, phantom limb pain
<i>ADRB2</i>	Beta-2-adrenergic receptor	Risk for widespread body pain
<i>IL6</i>	Interleukin 6	Pain from endometriosis
<i>CACNG2</i>	Voltage-gated calcium ion channel	Post mastectomy pain
<i>HTR2A</i>	Serotonin receptor	Increased post-surgical pain
<b>Decreased Pain Sensitivity</b>		
<b>Gene</b>	<b>Protein affected</b>	<b>Phenotype</b>
<i>COMT</i>	Catechol-O-methyltransferase	Decreased or increased pain perception
<i>OPRM1</i>	<i>OPRM1</i> : opioid receptor mu 1	Decreased pain perception
<i>TRPV1</i>	Transient receptor potential vanilloid 1	Decreased thermal pain sensitivity
<i>MC1R</i>	Melanocortin 1 receptor	Decreased pain perception
<i>GCH1</i>	GTP cyclohydrolase	Decreased post-surgical pain
<i>CACNA2D3</i>	Voltage-gated calcium ion channel	Decreased thermal pain sensitivity

# Summary

## **Normal Pain Signaling**

**Transduction**  
**Transmission**  
**Modulation**  
**Perception**

## **When acute becomes chronic pain**

**Rates of chronic pain**  
**Abnormal changes in the pain  
pathway**  
**RF for acute to chronic pain**  
**Genetics in pain pathway**

Thank you for you attention!



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