

# Fisiopatologia del dolore muscolare e articolare

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# Dolore miogeno

Dolore che origina dalla stimolazione dei nocicettori muscolari

- Mal localizzato
- Spesso riferito con dolore secondario
- Spesso associato ad affaticabilità

## Box 45-1 Characteristics of Muscle Pain

### Objective

No flexor reflexes when the muscle is painfully stimulated  
Autonomic symptoms such as a drop in blood pressure, sweating  
Convergent input from muscle and other sources to central neurons  
Supraspinal processing in centers different from those for cutaneous pain

### Subjective

No first and second pain on sudden stimulation  
Difficult to localize  
Cramping, aching, tearing nature  
Pain referral  
Strong affective component  
Nausea

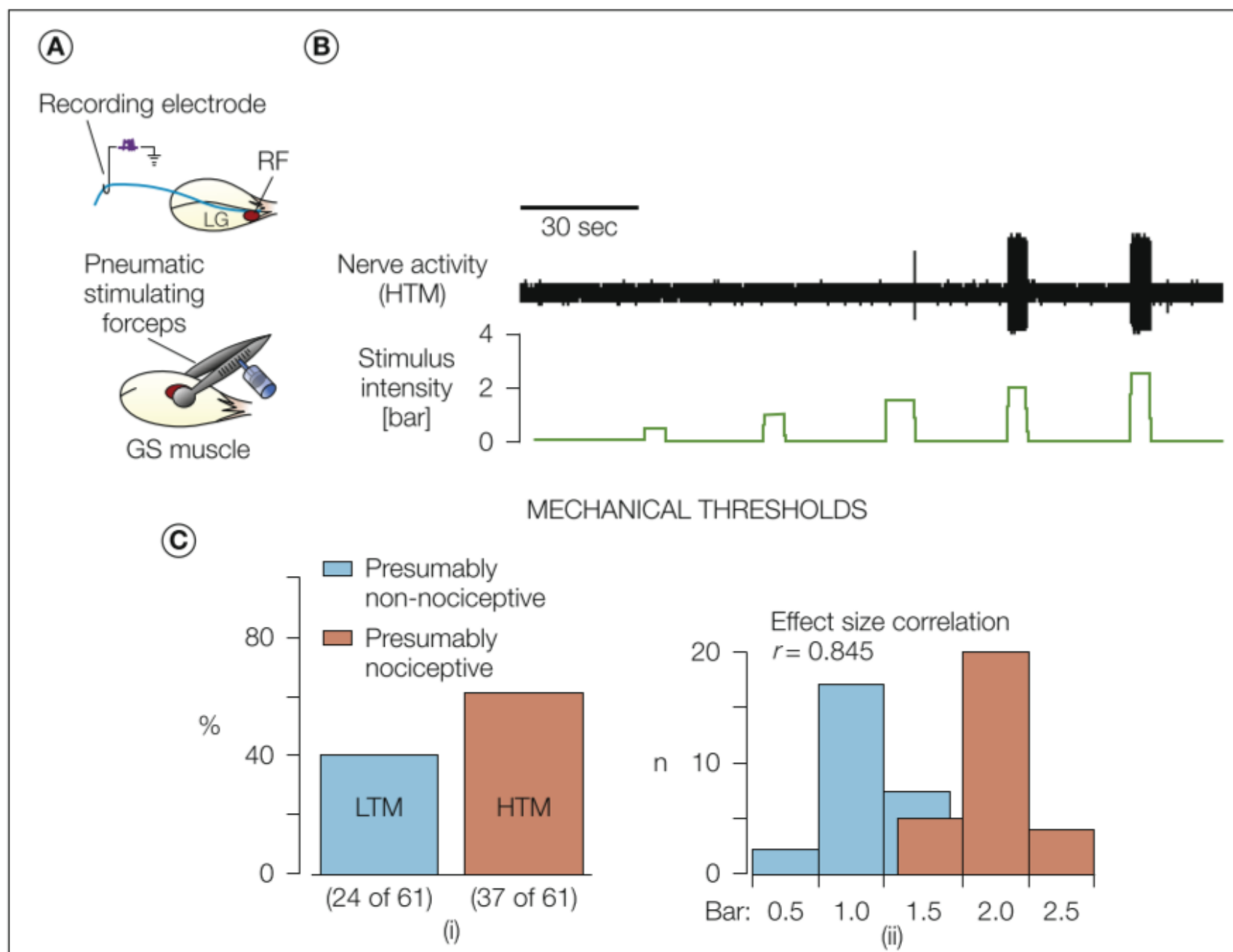
# Innervazione del muscolo

Fibre lievemente mielinizzate (III) e non mielinizzate (IV)

- 20% stato contrazione muscolare
- 10% termocettori
- 30% meccanocettori a bassa soglia (pressione)
- 40% nocicettori

Nel gruppo IV

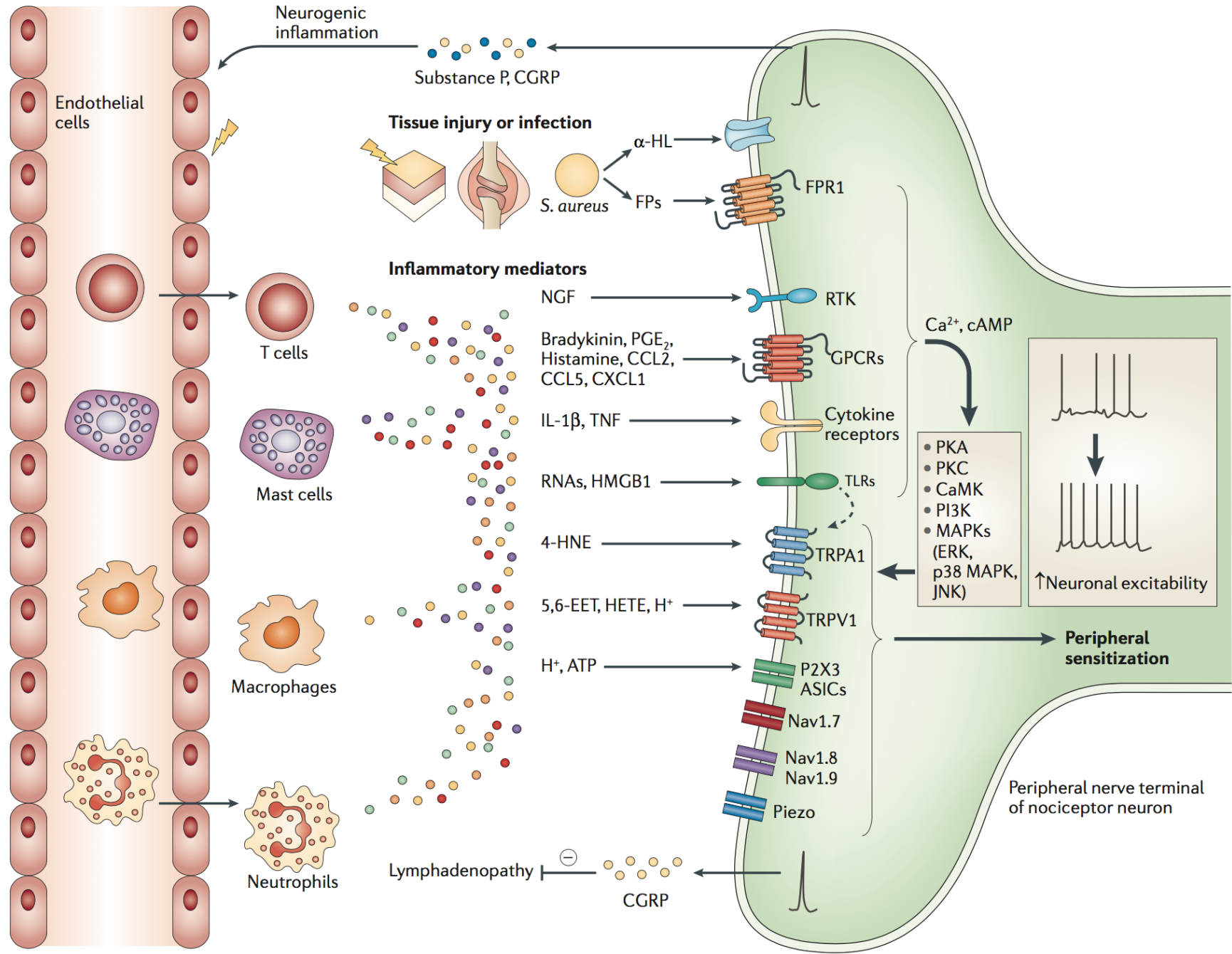
- 60% risponde a stimoli meccanici ad alta soglia HTM→ potenziali nocicettori
- 40% meccanocettori a bassa soglia LTM/ergocettori



# Sensibilizzazione da mediatori chimici

La maggioranza delle fibre III e IV risponde sia a stimoli meccanici sia chimici:

- ATP → recettore  $P2X_3$
- $H^+$  → ASIC 1, ASIC2, TRVP1
- Bradichinina → B1
- Serotonina →  $5HT_3$ ,  $5HT_6$
- $PGE_2$  →  $EP_2$
- NaCl 5-6% → meccanismo sconosciuto (depolarizzazione aspecifica? Osmocettori?)
- NGF → tyrosine kinase receptor A (TrkA, solo su HTM )
- IL-6 → solo su LTM



# Afferenza al midollo spinale

Dal muscolo le fibre:

- Lamina I → Tratto spinotalamico
  - Lamina IV-VI
  - La maggioranza dei neuroni secondari NON sono specifici per il tessuto muscolare ma ricevono afferenze da tendini, fascia, articolazioni
- Imprecisa localizzazione del dolore

# Nocicezione e alterazioni neuroplastiche

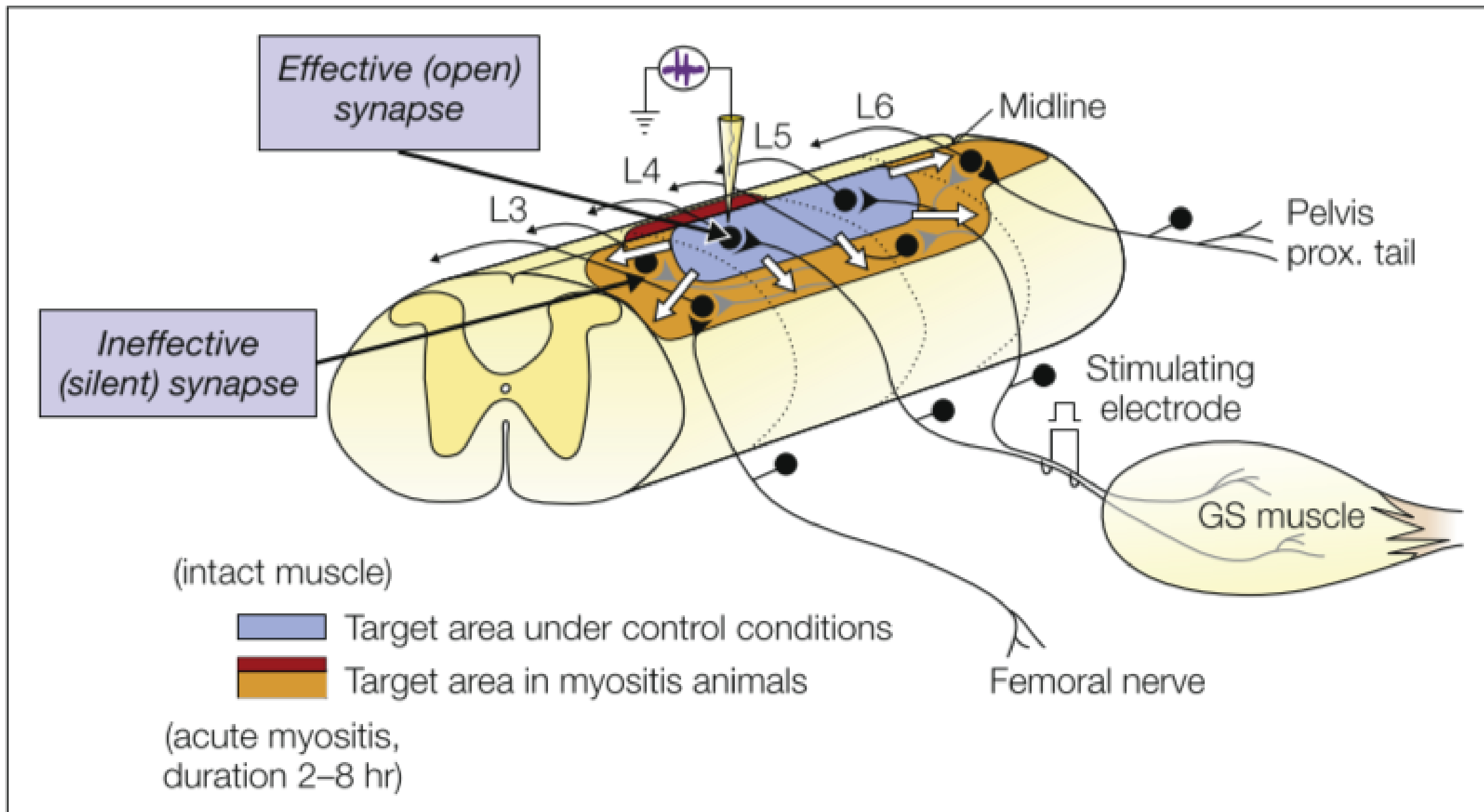
Miosite/iniezione di sostanze algogene

→ ***unmasking* di sinapsi «silenti» con mielomeri rostrali e caudali**

→ Estensione della target area dello specifico muscolo

→ Dolore riferito





# Spasmo muscolare

Sembra che la nocicezione inibisca gli  $\alpha$ -motoneuroni omonimi

L'attività dei  $\gamma$ -motoneuroni dei fusi non sembra facilitata dalla nocicezione

**Lo spasmo muscolare deriverebbe dalla nocicezione in un sito remoto come un altro muscolo, un'articolazione, un viscere**

# Attivazione delle strutture sovracorticali

Tratto SpinoMesencefalico

→ Grigio periacqueduttale

Tratto SpinoReticolare

→ Nucleo Parabrachiale (Ponte)

Tratto SpinoTalamico →

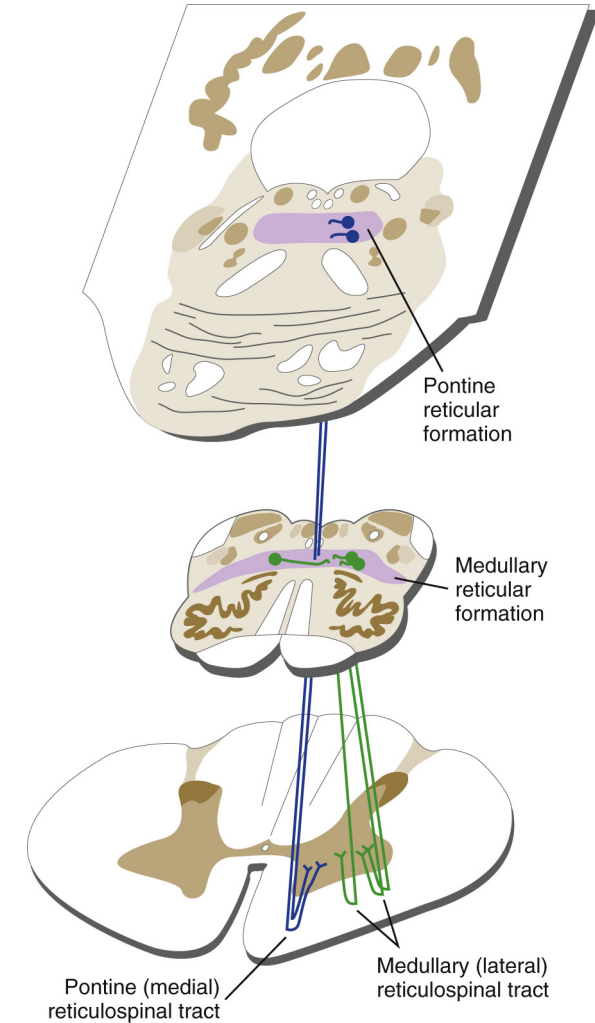
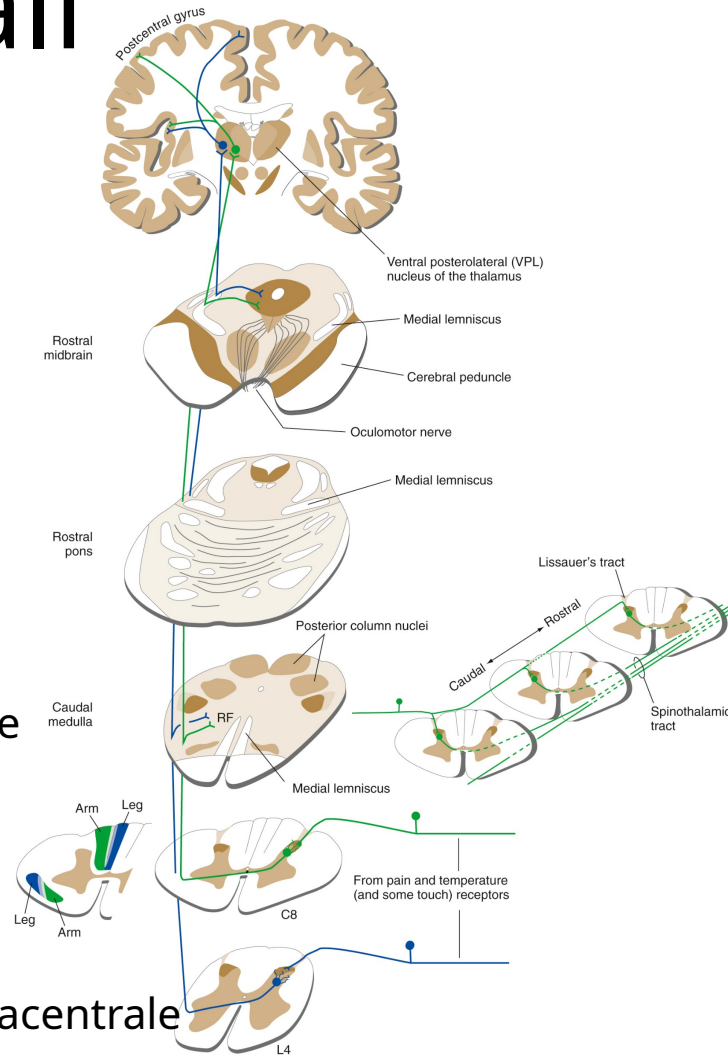
- Talamo Nucleo Ventrale Laterale
- Confine con Nucleo Laterale
- Parte posteriore del Nucleo Mediale

Corteccia

→ Insula anteriore

→ Parte Dorsoventrale del lobulo paracentrale

→ Cingolata posteriore



# Dolore articolare

In condizioni fisiologiche la nocicezione artrogena insorge da

- Pressione sovrasoglia
- Movimento oltre normale ROM

Infiammazione / Osteoartrosi

→ Sensibilizzazione

→ Dolore evocato da movimenti e pressioni normali

→ Dolore a riposo

# Innervazione dell'articolazione

L'articolazione riceve fibre da rami nervosi principali o branche cutanee, muscolari, periostee

Fibre A $\beta$  (II) → corpuscoli Ruffini, Golgi, Pacini  
→ capsula, legamenti, menischi, periostio

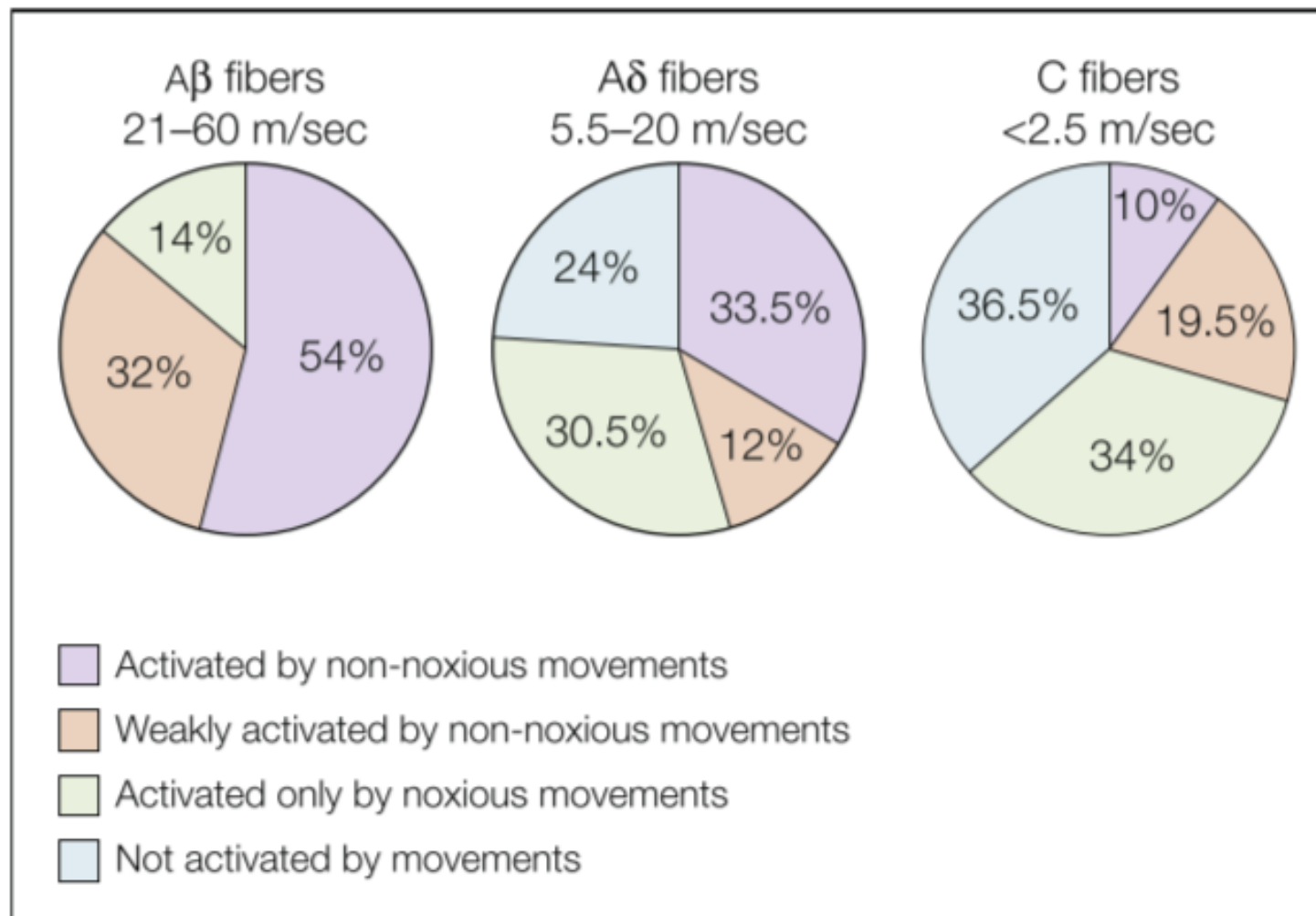
Fibre A $\delta$  (III) → terminazioni libere→

**Fibre C nocicettive (IV) 40%** → terminazioni libere→



Capsula, tessuto adiposo, legamenti, menischi, sinovia, periostio

**La cartilagine non è innervata**



**Figure 44-2. Mechanosensitivity of primary afferent neurons supplying the normal knee joint of a cat.** The graph shows the proportions of Aβ, Aδ, and C fibers in the different sensitivity classes. (From Schaible HG, Grubb BD 1993 *Afferent and spinal mechanisms of joint pain*. Pain 55:5–54. Copyright 1993, from the International Association for the Study of Pain.)

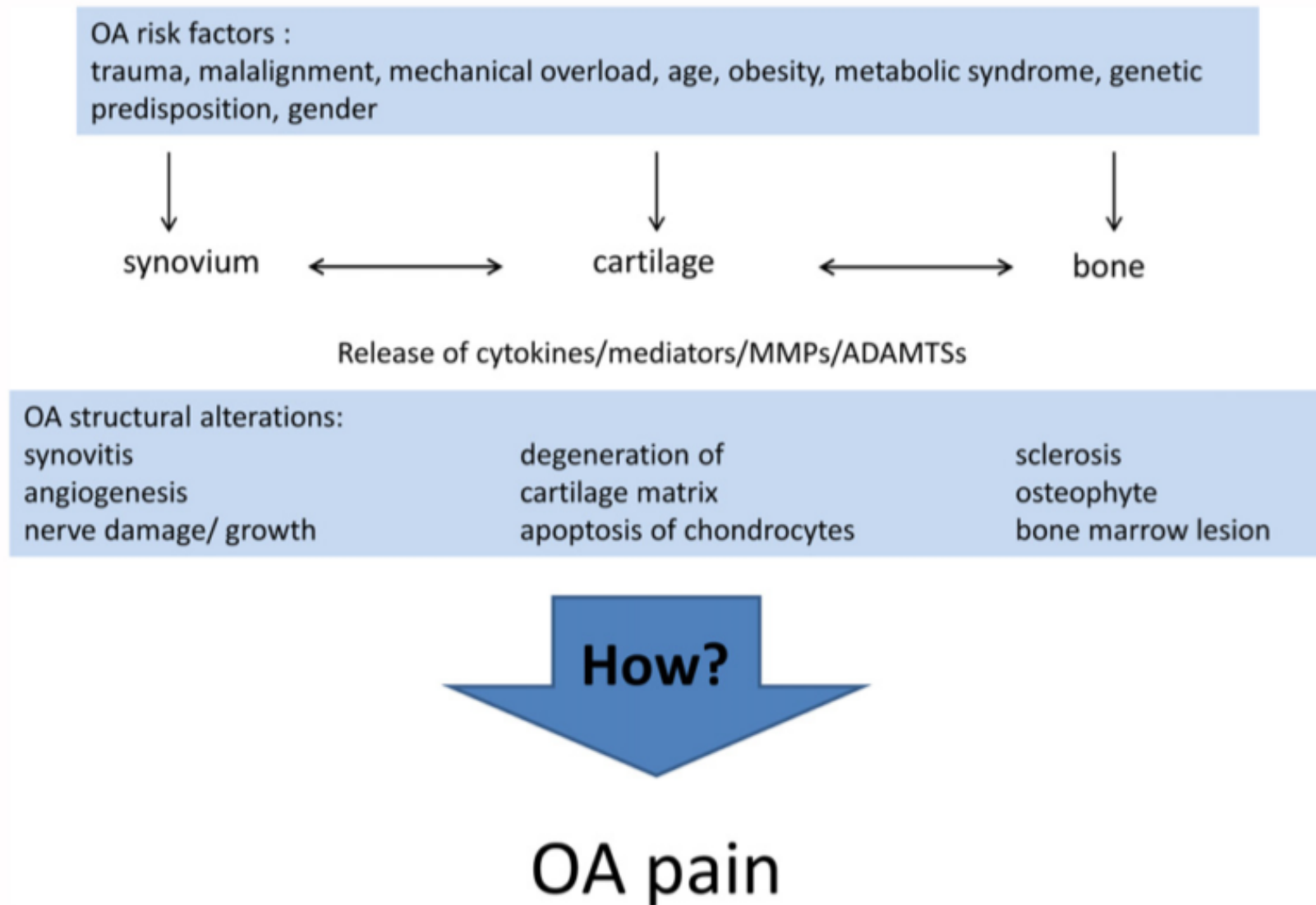
# Sensibilizzazione da stimoli chimici

Table 44-1 Chemosensitivity of A $\delta$ and C Fibers in Normal Joints		
MEDIATOR	RESTING ACTIVITY	MECHANOSENSITIVITY
Bradykinin	↑	↑
Prostaglandin E <sub>2</sub>	↑	↑
Prostaglandin I <sub>2</sub>	↑	↑
Serotonin	↑	↑
Capsaicin/anandamide	↑	
Nitric oxide	↓	
Adenosine triphosphate	↑	
Adenosine	↑	
CB1 agonist		↓
CB2 agonist		↓
Substance P	(↑)	↑
Vasoactive intestinal polypeptide		↑
Somatostatin		↓
Endomorphin 1		↓
Galanin		↑↓
Neuropeptide Y	↑	↑↓
Nociceptin		↑↓
Tumor necrosis factor- $\alpha$		↑
Interleukin-6		↑

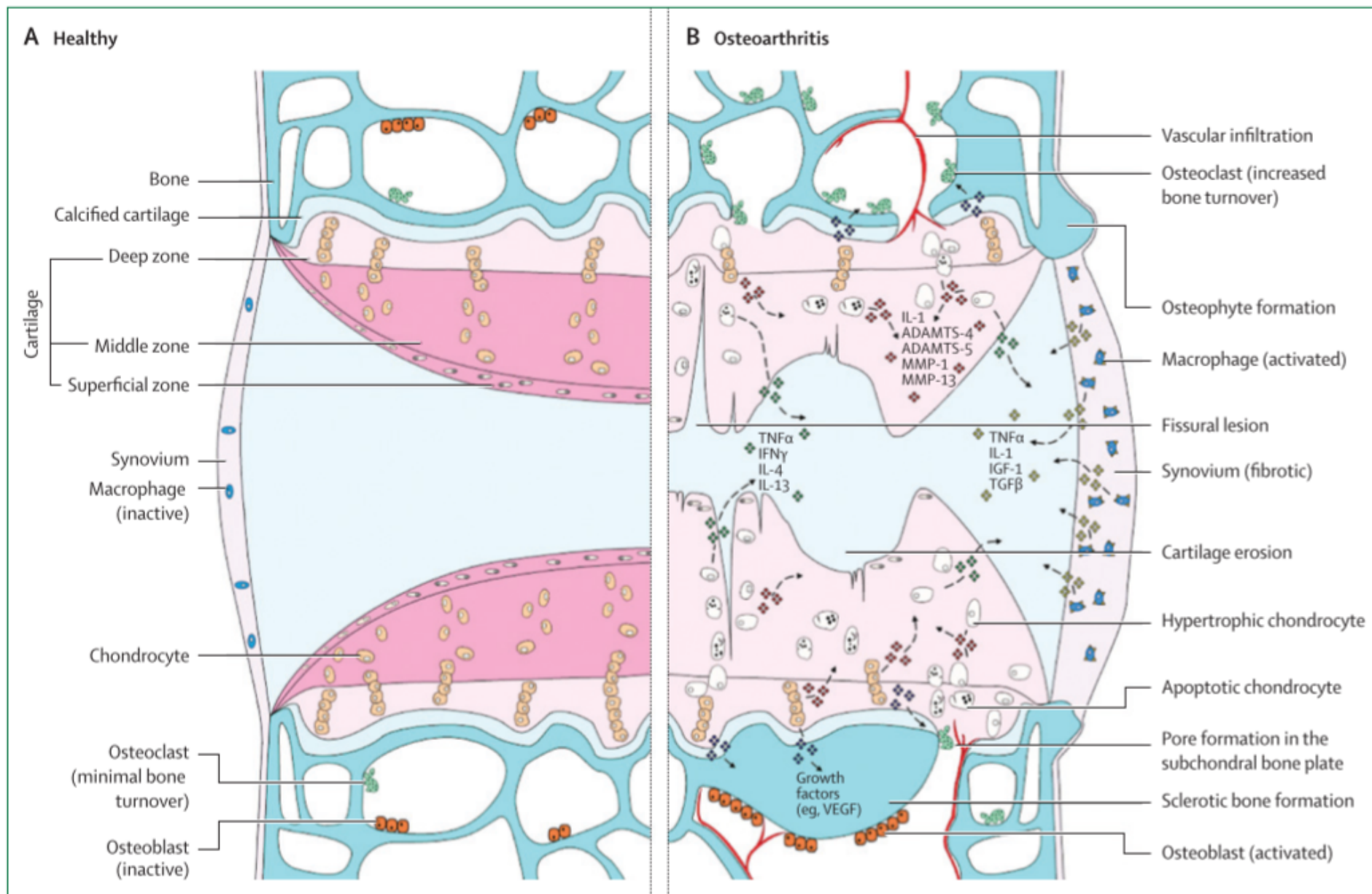
# Osteoartrosi

- Patologia infiammatoria, progressiva, degenerativa con vari fenotipi caratterizzata dal sovvertimento della cartilagine articolare e dal coinvolgimento di tutte le componenti dell'articolazione
- Principale causa di dolore persistente muscoloscheletrico nella popolazione generale
- Prevalenza dal 6-8% al 13-26% (popolazione anziana)





**FIGURE 1 |** Risk factors and pathological events leading to osteoarthritis (OA).



**Figure 3: Signalling pathways and structural changes in the development of osteoarthritis**

ADAMTS=a disintegrin and metalloproteinase with thrombospondin-like motifs. IL=interleukin. MMP=matrix metalloproteinase. TNF=tumour necrosis factor.

IFN=interferon. IGF=insulin-like growth factor. TGF=transforming growth factor. VEGF=vascular endothelial growth factor.

# Driver-based classification

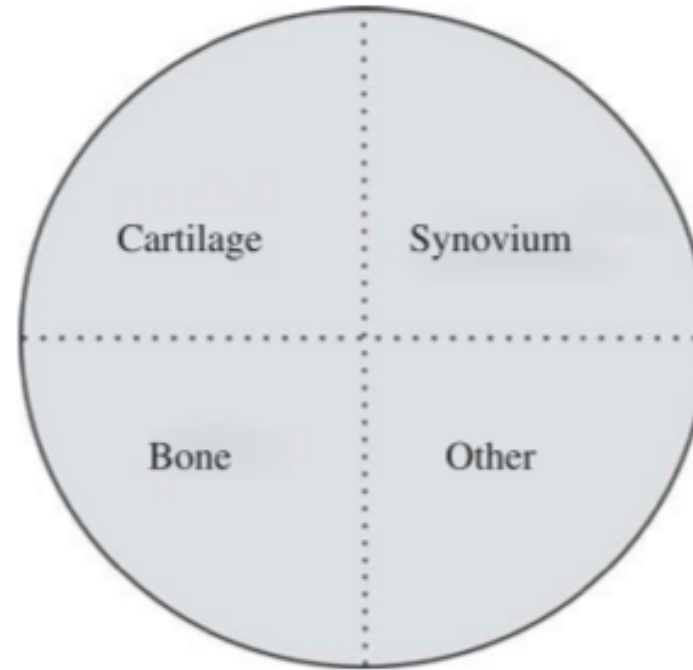
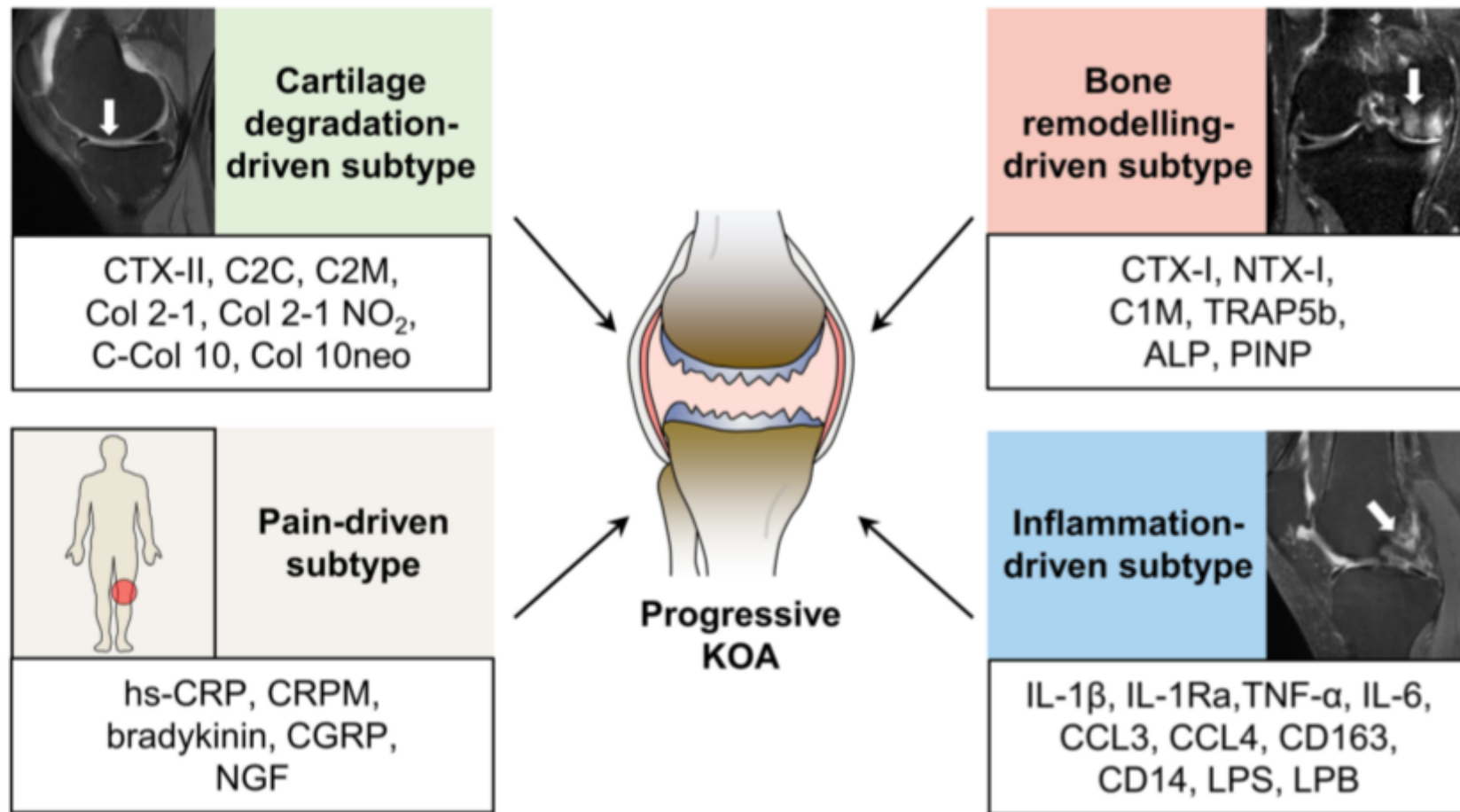


Figure 2. A proposed division of patients with osteoarthritis (OA) into four groups, depending on the driver of the disease. The three main tissues within the joint (cartilage, bone, and synovium) each comprise a driver of OA disease (cartilage, bone, and inflammation). The last proposed group comprises the remainder of the patients who do not fit into any of the categories, that is patients with trauma-driven OA, meniscus-driven OA, or other OA. There might also be subgroups with both bone- and synovium-driven OA or cartilage- and bone-driven OA or other combinations, hence the division of patients in this figure is not definitive and is shown by dotted and not full lines.

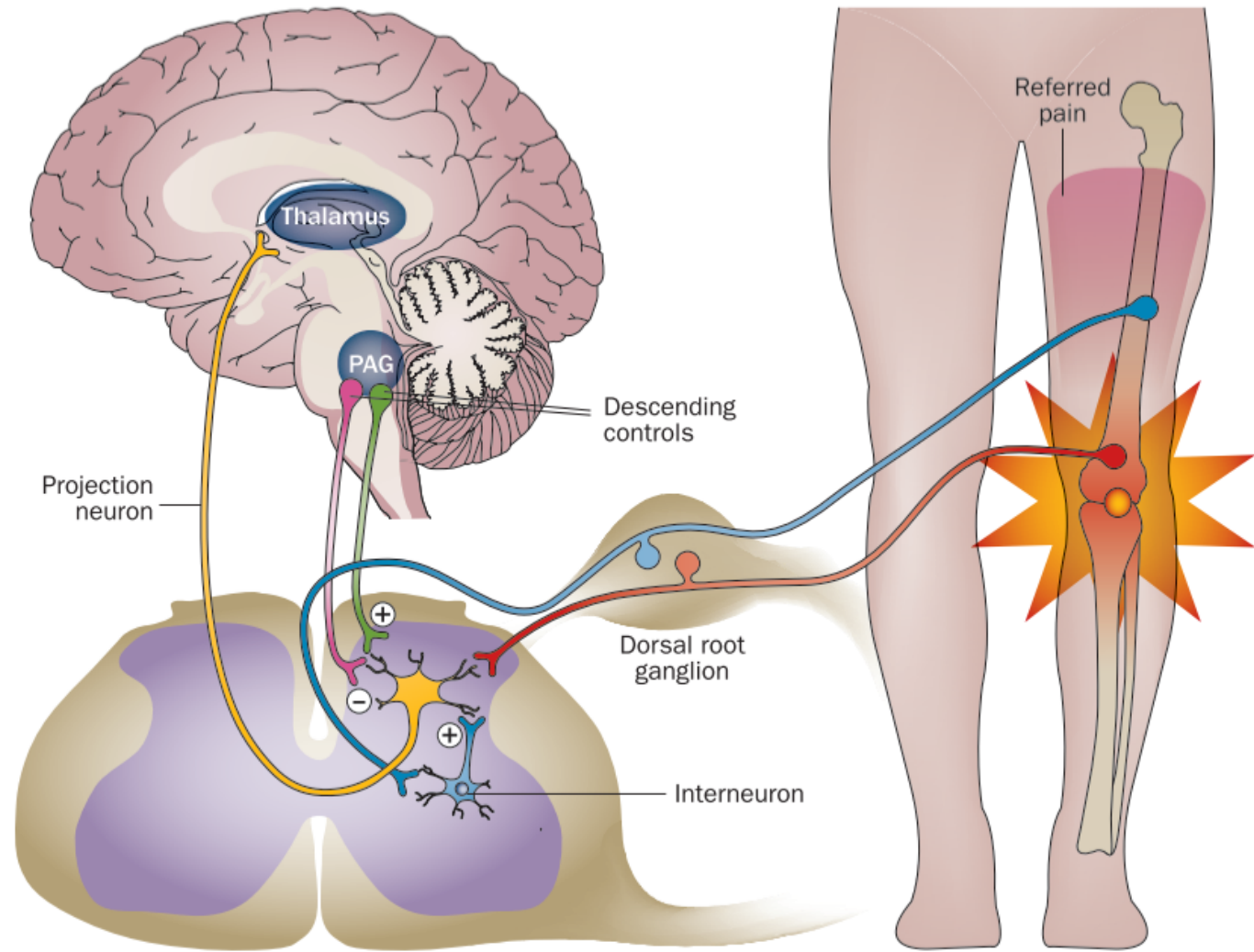


**FIGURE 2 |** Molecular subtypes of progressive KOA. Increasing evidence suggests that progressive KOA patients fall into several subtypes based on the identified molecular profiles, including cartilage degradation-driven subtype, bone remodeling-driven subtype, inflammation-driven subtype, and pain-driven subtype. Representative molecules are listed in the box below the MRI manifestation of each subtype. ALP, alkaline phosphatase; CCL3, CC-chemokine ligand 3; CCL4, CC-chemokine ligand 4; Col 2-1 NO<sub>2</sub>, the nitrated form of Col 2-1; C-Col 10, C-terminus of collagen X; Col 10neo, a neoepitope of collagen 10; CGRP, calcitonin gene-related peptide; CRPM, the fragment of C-reactive protein; CTX-I, C-telopeptide of Col-I; CTX-II, C-telopeptide fragments of Col-II; C2C, the cleavage neoepitope of collagen II; C1M, the product of collagen I degraded by matrix metalloproteinases; C2M, the fragments of collagen II degraded by matrix metalloproteinases; hs-CRP, high sensitive C-reactive protein; IL-1 $\beta$ , interleukin 1 $\beta$ ; IL-1Ra, IL-1 receptor antagonist; IL-6, interleukin 6; KOA, knee osteoarthritis; LPS, lipopolysaccharide; LPB, LPS binding protein; MRI, magnetic resonance imaging; NGF, nerve growth factor; NTX-I, N-telopeptide of Collagen I; PINP, N-terminal collagen type I extension propeptide; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; TRAP5b, tartrate resistant acid phosphatase 5b.



Progressive KOA subtypes		Treatment principle	Main altered molecules	Potential beneficial drugs
Cartilage degradation-driven subtype		Cartilage extra-cellular matrix components supplement	CTX-II, C2M, C2C, Coll 2-1, C-Col 10	Hyaluronic acid (Bannuru et al., 2011), Glucosamine (Fransen et al., 2015), Chondroitin (Fransen et al., 2015), Undenatured collagen II (Lugo et al., 2016)
Bone remodeling-driven subtype	Bone resorption	Anti-resorption	CTX-I, NTX-I, C1M, TRAP5b,	Bisphosphonate (Aitken et al., 2018), Osteoprotegerin (Sagar et al., 2014), Calcitonin (Karsdal et al., 2015), MIV-711 (Conaghan et al., 2019)
	Bone formation	N/A	ALP, PINP	N/A
Inflammation-driven subtype		Anti-inflammation	IL-1 $\beta$ , IL-1Ra, TNF $\alpha$ , IL-6, CCL3, CCL4	IL-1 inhibitor (Jotanovic et al., 2012), TNF $\alpha$ inhibitor (Grunke and Schulze-Koops, 2006), COX2 inhibitor (Hochberg et al., 2016), NSAIDs (Bannuru et al., 2019)
Pain-driven subtype		Analgesia, Anti-inflammation	hs-CRP, CRPM, bradykinin, CGRP, NGF	! Opioids (Kolasinski et al., 2020), NSAIDs (Bannuru et al., 2019), NGF inhibitor (Berenbaum et al., 2020), CGRP inhibitor (Jin et al., 2018), Capsaicin (Kolasinski et al., 2020)

ALP, alkaline phosphatase; C1M, Collagen I degraded by matrix metalloproteinases; C2C, the cleavage neoepitope of collagen II; C2M, the fragments of collagen II degraded by matrix metalloproteinases; C-Col 10, C-terminus of collagen X; CCL3, CC-chemokine ligand 3; CCL4, CC-chemokine ligand 4; CGRP, calcitonin gene-related peptide; Coll 2-1 NO<sub>2</sub>, nitrated form of Coll 2-1; COX2, cyclooxygenase 2; CRPM, the fragment of CRP; CTX-I, C-telopeptide of Col-I; CTX-II, C-telopeptide fragments of Col-II; hs-CRP, high sensitive CRP; IL-1 $\beta$ , interleukin 1 $\beta$ ; IL-1Ra, IL-1 receptor antagonist; IL-6, interleukin 6; KOA, knee osteoarthritis; N/A, not available; NGF, nerve growth factor; NTX-I, N-telopeptide of Collagen I; NSAIDs, non-steroidal anti-inflammatory drugs; PINP, N-terminal collagen type I extension propeptide; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; TRAP5b, tartrate resistant acid phosphatase 5b.



**Figure 2** | Referred pain. Schematic showing how persistent activation of peripheral inputs from one site (red) can lead to the establishment of a referred pain area at a distant site (blue) when central sensitization occurs in second-order processes in the spinal cord (yellow). Ascending sensory messages pass onwards to the thalamus. This process is modulated by excitatory (green) and inhibitory (pink) descending controls projecting to the spinal cord from the periaqueductal grey.

# Caratteristiche

- Dolore nocicettivo
  - Nelle fasi iniziali **meccanico**
  - Sensibilizzazione periferica
  - Aggravato dalla sollecitazione dell'articolazione
- Nelle fasi più avanzate
  - Dolore a **riposo**
  - Sensibilizzazione centrale
  - Estensione dell'area
- In un subset limitato di pazienti
  - Dolore neuropatico**
  - Gain of function+loss of function

