
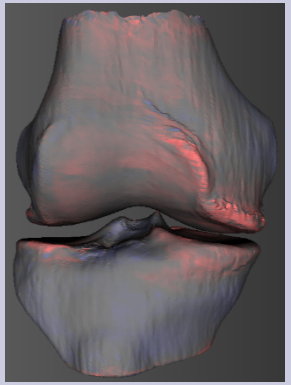
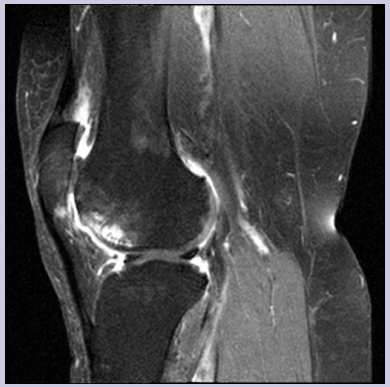
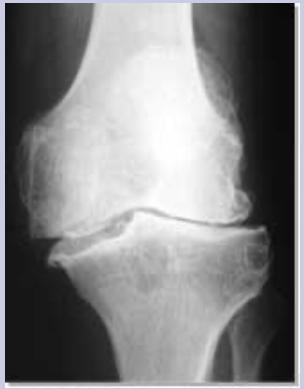


Mechanisms of Pain in OA & Recognizing Pain Phenotypes

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EXCEPTIONAL CARE. WITHOUT EXCEPTION.

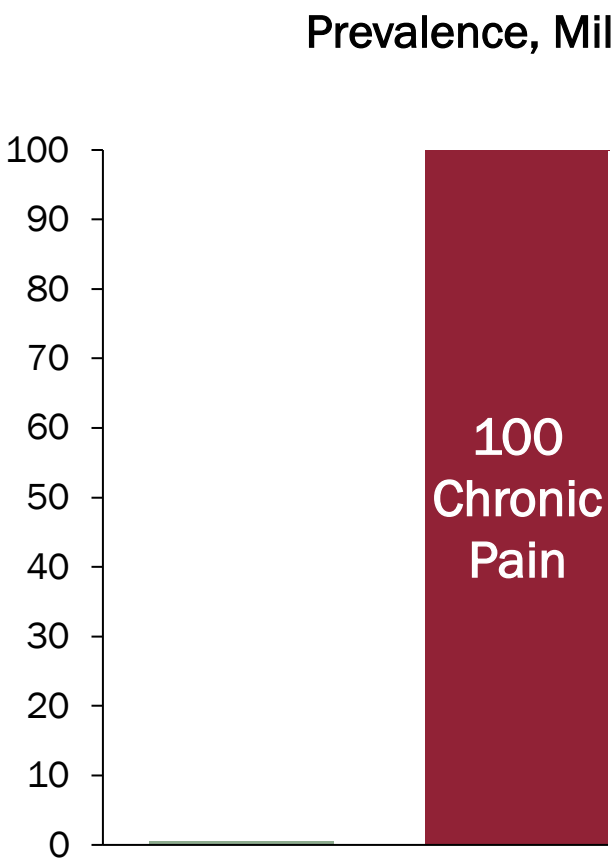
Disclosures

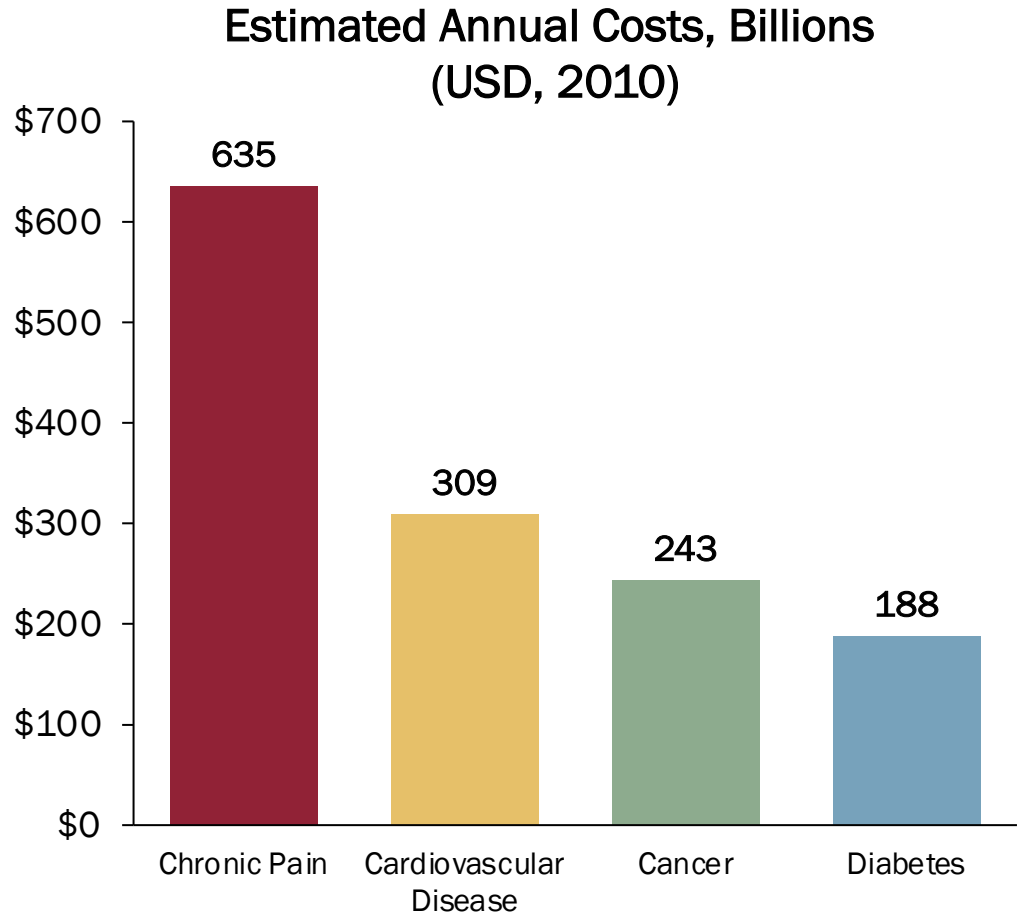
- Consultant/Independent Contractor: EMD Merck-Serono, Novartis, Pfizer/Lilly, Regeneron
- Core Team for 2019 American College of Rheumatology – Arthritis Foundation OA Treatment Guideline
- NIH grants focused on OA, pain

Learning Objectives

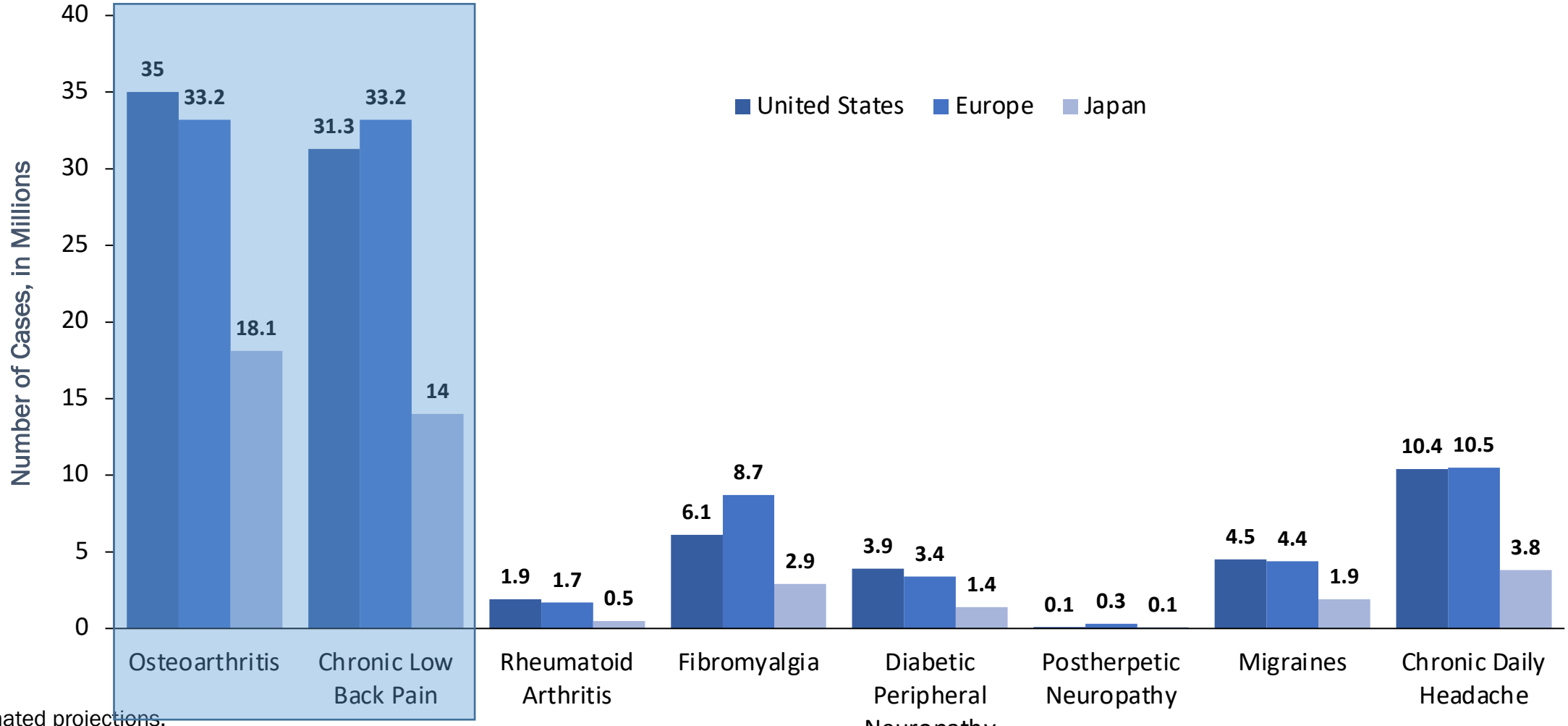
- Review pain patterns in osteoarthritis (OA)
- Recognize the role of pain sensitization in OA
- Identify pain phenotypes that differentiate patients with OA and their outcomes

Chronic Pain is More Prevalent and Costly than other Common Diseases





Chronic Pain: Most of it is OA and Back Pain



*Estimated projections.

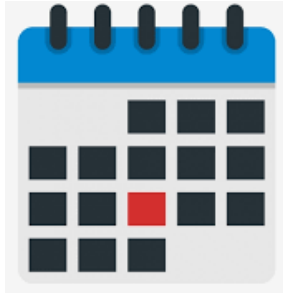
Decision Resources. *Chronic Pain*. November 2011.

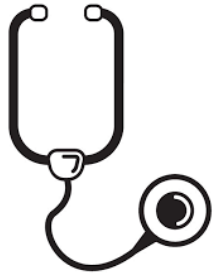
Osteoarthritis Epidemiology

>300-500 million

~10-15%

30%





#1

#1

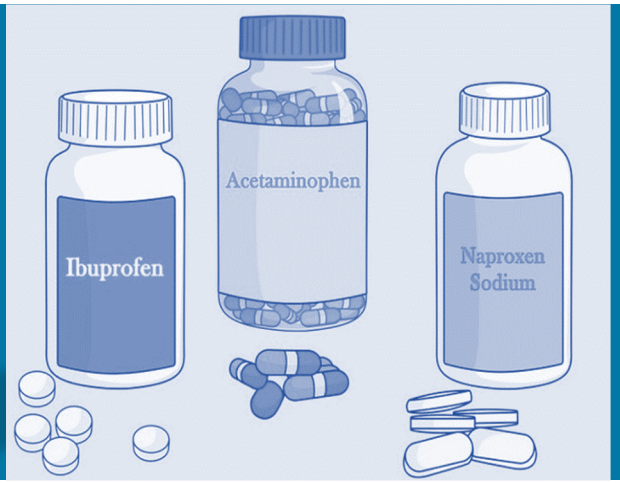
#3

Clinical Knee Osteoarthritis

Pain is primary clinical symptom

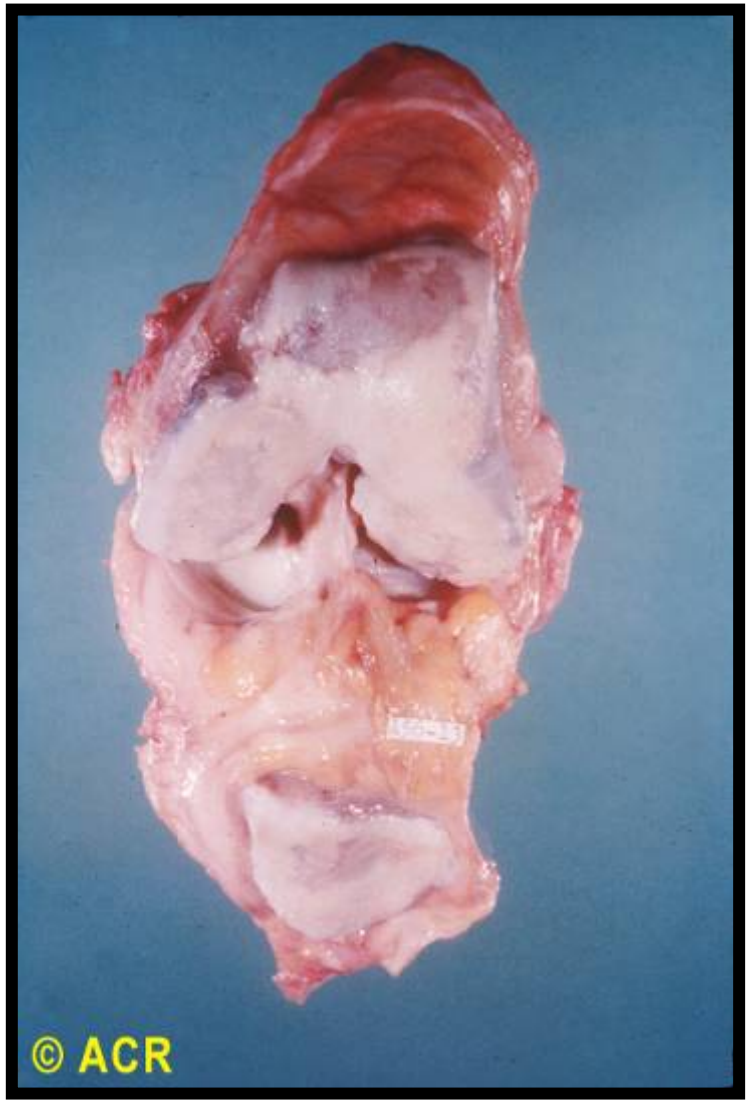
People are living longer with knee OA

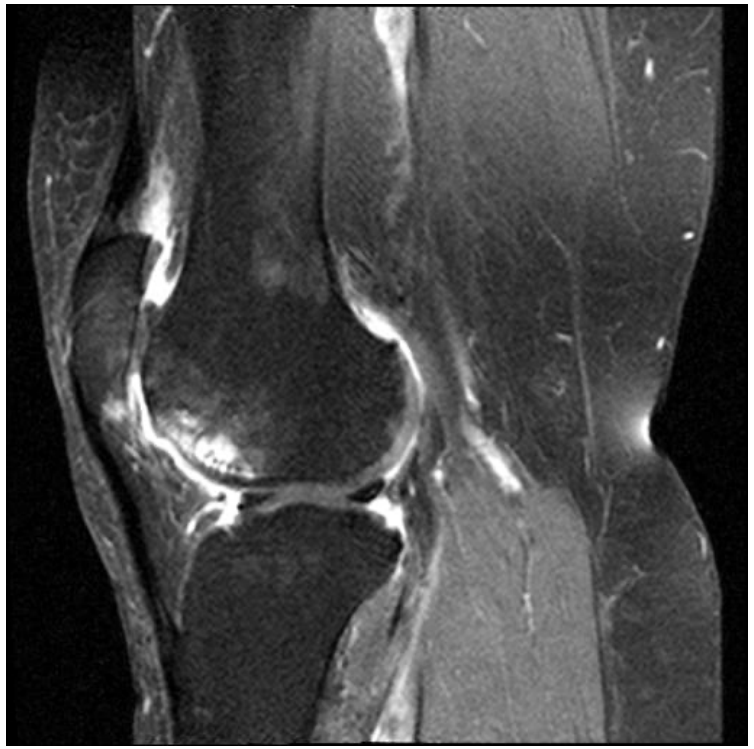
Limited management options

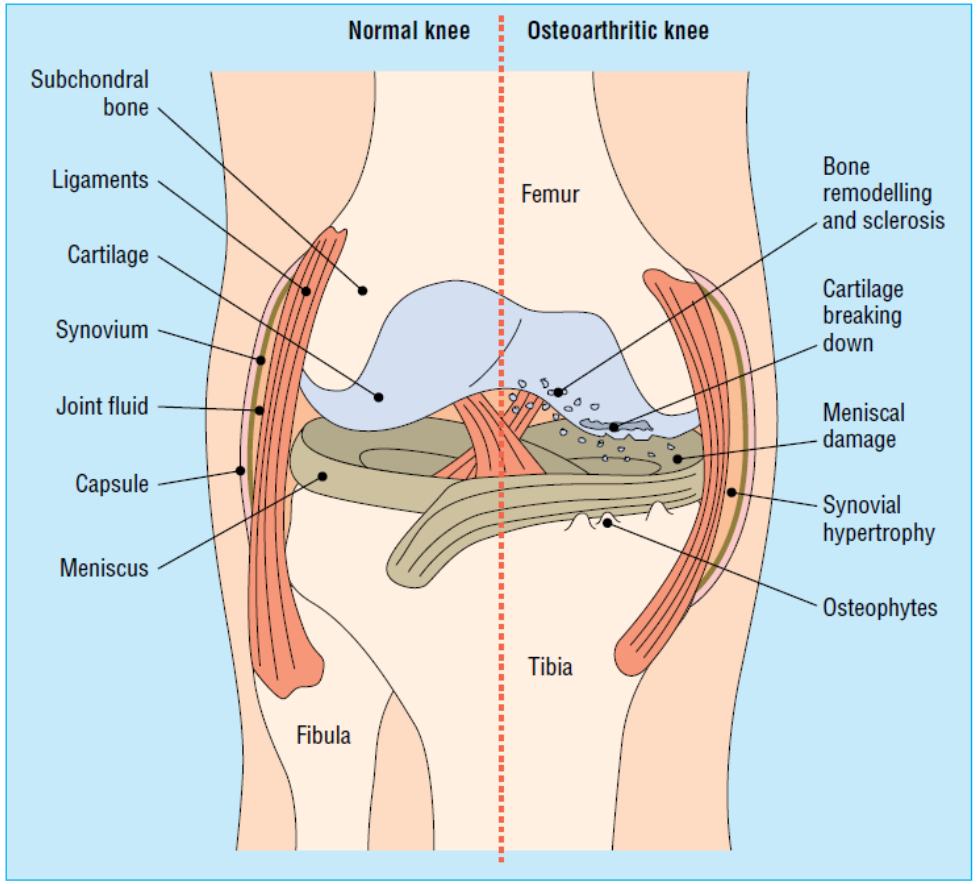


Joint replacement: “definitive treatment”

Do Structures Contribute to Pain?







Hunter and Felson. *BMJ* 2006

Sources of Pain in Knee OA?
Pain Emanates from Structures in the Knee

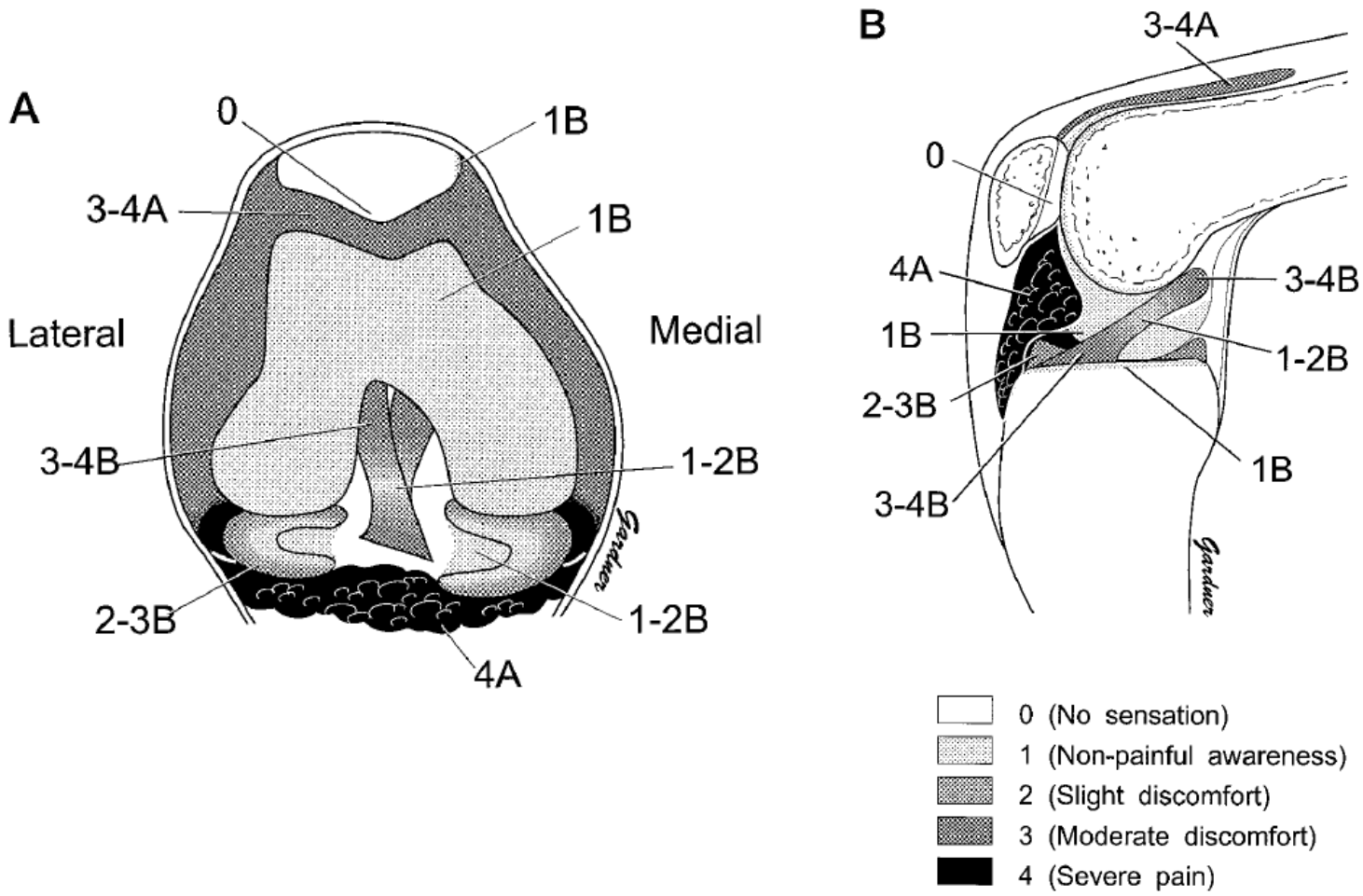
Table 1. VAS scores for rest pain: median (interquartile range).

Time	Intervention Knee: LA	Intervention Knee: Placebo
Baseline	61.5 (20.8–90.0)	36.0 (28.0–64.5)
1 h	0.0 (0.0–28.2)*	38.0 (16.5–63.0)
24 h	27.0 (2.2–65.0)	49.0 (6.7–72.0)
7 days	30.0 (1.5–72.5)	41.5 (17.5–72.7)

* VAS (baseline) vs VAS (1 h) for intervention knees (LA); p = 0.007.
** VAS (baseline) vs VAS (1 h) for nonintervention knees (LA); p = 0.

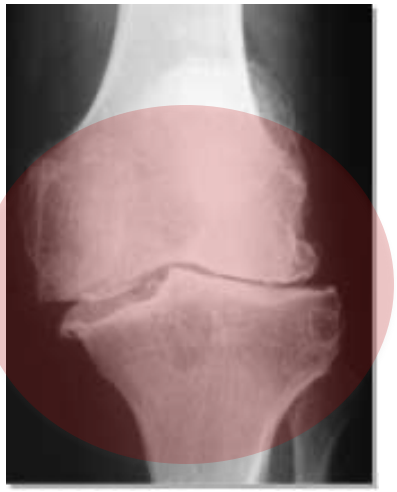
Creamer, et al. *J Rheumatol* 2006

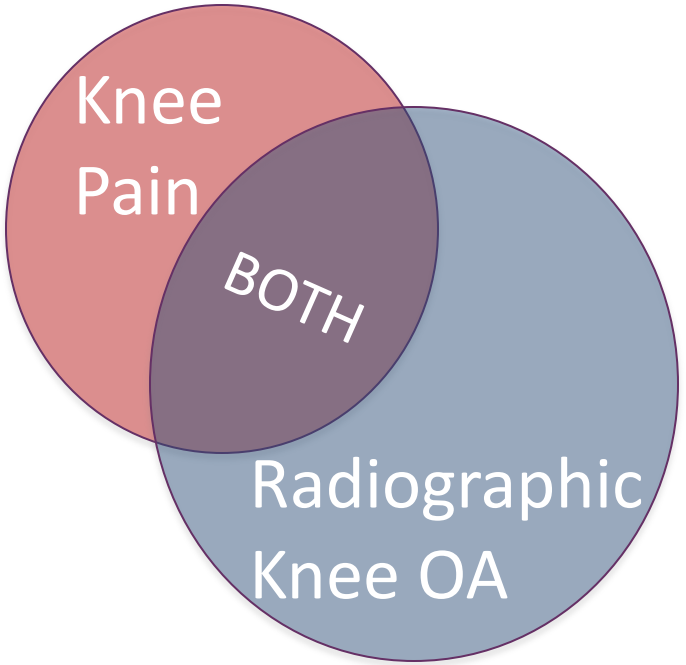
Structural Correlates of Knee Pain



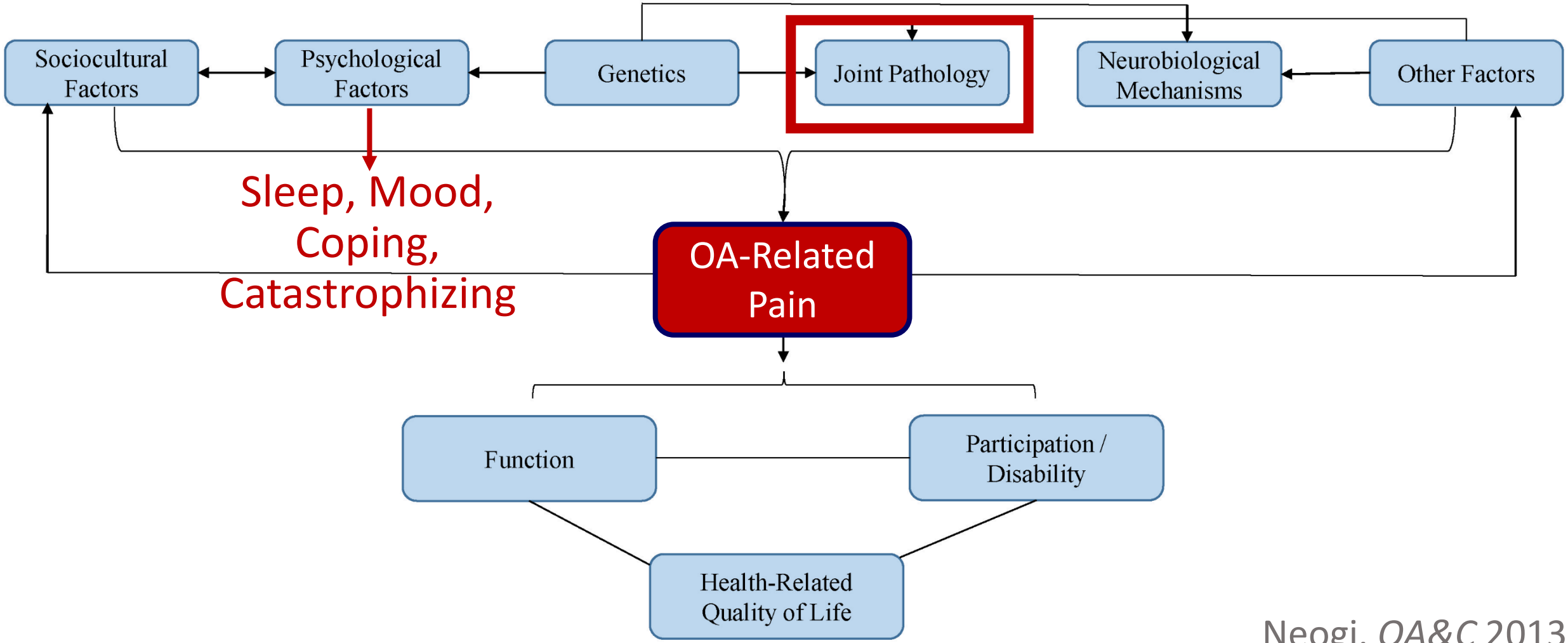
Dye, et al. *Am J Sports Med*. 1998

Structure-Symptom Discordance



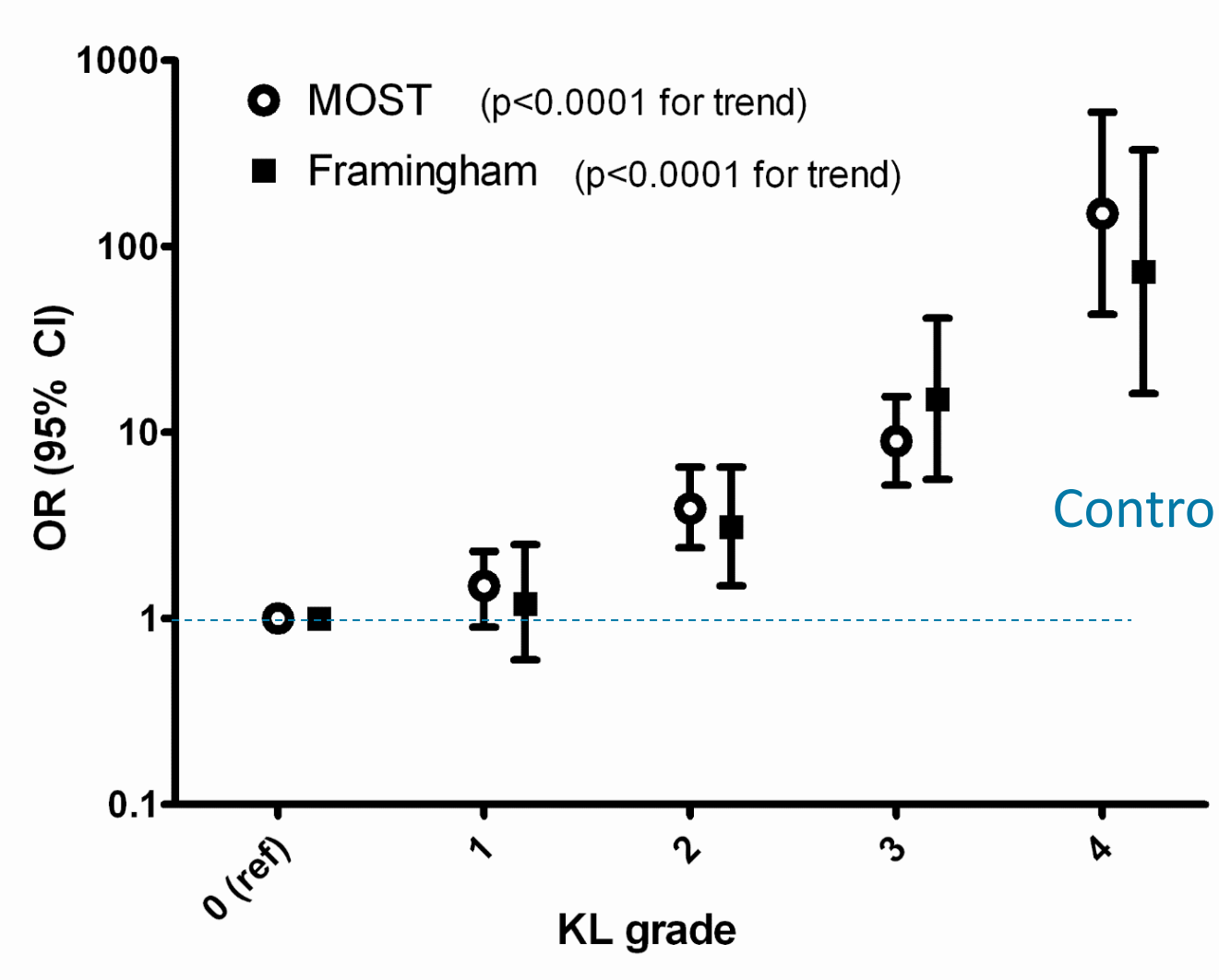


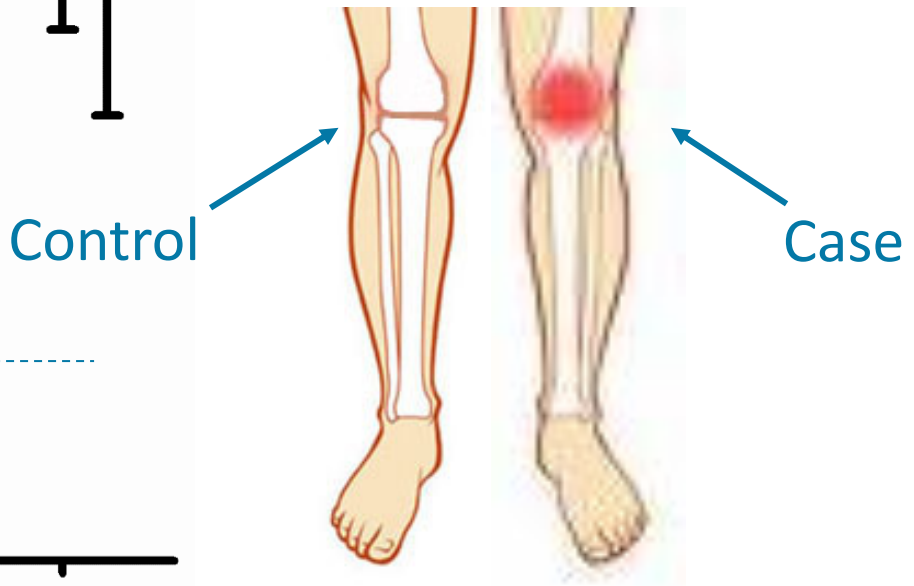
Multiple Contributors to Pain



Neogi. *OA&C* 2013

Structure-Symptom Association





Neogi, et al. *BMJ*, 2009

Structural Lesions are Common

Meniscal Tears	Frequent Knee Symptoms	
	Yes	No
	no. (%)	
Radiographic evidence of osteoarthritis		
One or more meniscal tears	57 (63)	46 (60)
No meniscal tear	33 (37)	31 (40)

Englund, et al. *NEJM* 2008

MRI features	Overall (n=710)	Knee pain		
		Pain (n=206)	No pain (n=489)	P value
Any abnormality	631 (89)	188 (91)	430 (88)	0.20
Osteophytes	524 (74)	158 (77)	353 (72)	0.22
Cartilage damage	492 (69)	149 (72)	333 (68)	0.27
Bone marrow lesions	371 (52)	121 (59)	242 (50)	0.03
Synovitis	259 (37)	78 (38)	175 (36)	0.60
Attrition	228 (32)	78 (38)	147 (30)	0.04
Subchondral cysts	179 (25)	63 (31)	114 (23)	0.04
Meniscal lesions	167 (24)	42 (20)	120 (25)	0.24
Ligamentous lesions	66 (9)	22 (11)	43 (9)	0.44

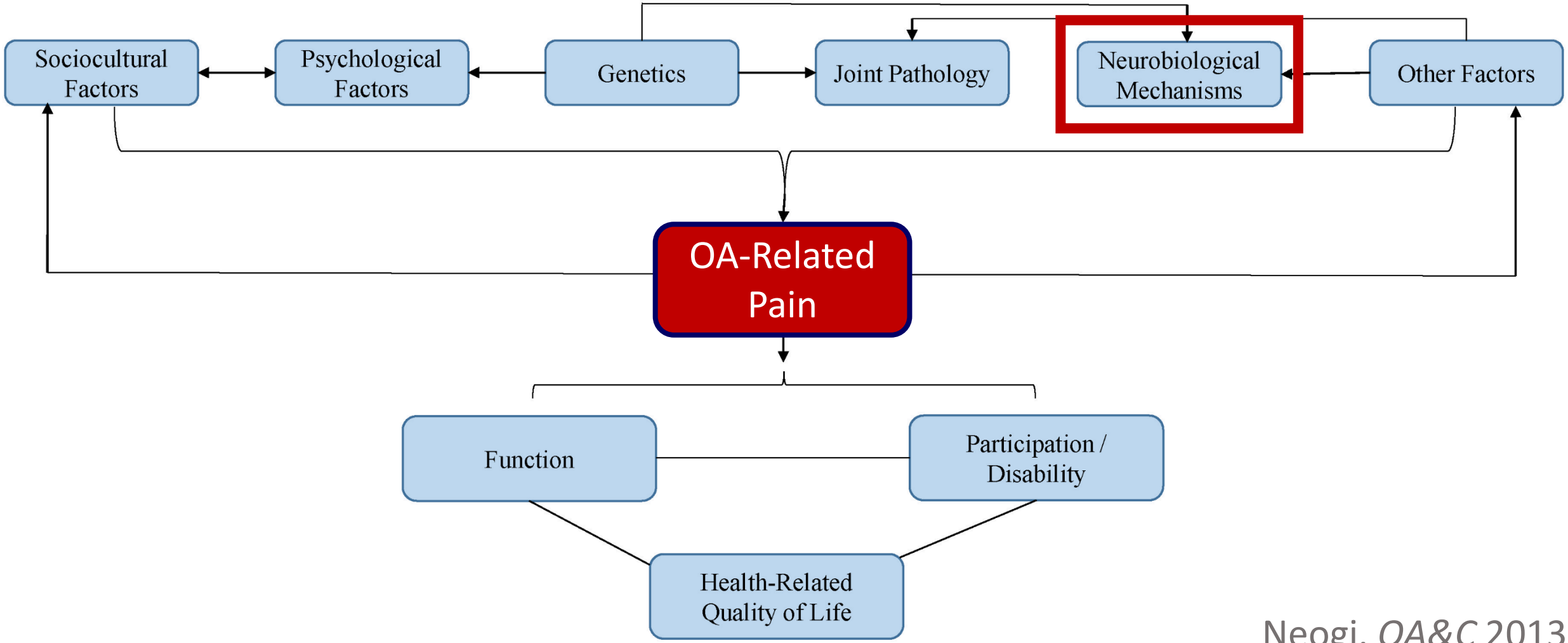
Guermazi, et al. *BMJ* 2012

Therapies Tested for “Structure”

- Cartilage
- Bone marrow lesions
- Synovitis/inflammation
- Meniscus
  - Degenerative tears: feature of OA

➢ Arthroscopic partial meniscectomies are most common orthopedic procedure (700K/year)

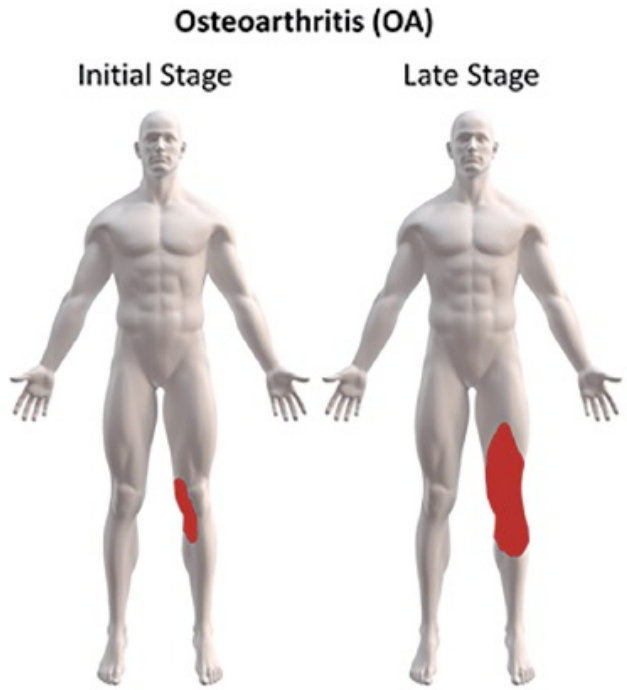
Multiple Contributors to Pain



Neogi. *OA&C* 2013

Nociception in OA

- Nociceptors in joint tissues
  - ➢Appropriate response to initial
- Chronic, persistent pain
  - ➢No longer reflecting pure nociception

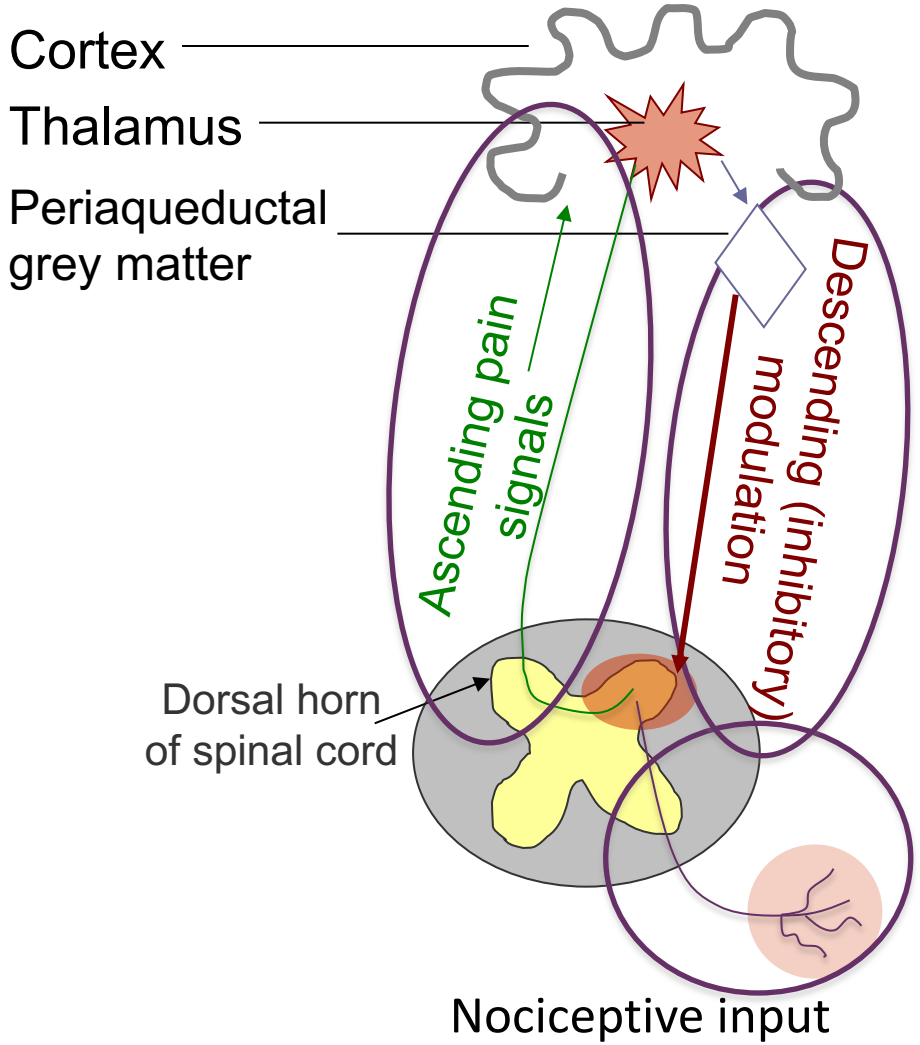


- Altered neurobiological pathways may play a role in OA pain

~~"Neuropathic"~~ Pain in OA?

- <3.5% had objective sensory testing abnormalities
  - Irrespective of OA or pain

Neurobiological Mechanisms



- Peripheral sensitization
  - Alterations in peripheral nociceptors
- Central sensitization
  - Alterations in neurons within CNS
  - ➢Increased sensitivity to stimuli
- Inadequate descending inhibition

→ ***Heightened Pain Sensitivity***

Evidence for Central Pain Mechanisms?

Table 1. VAS scores for rest pain: median (interquartile range).

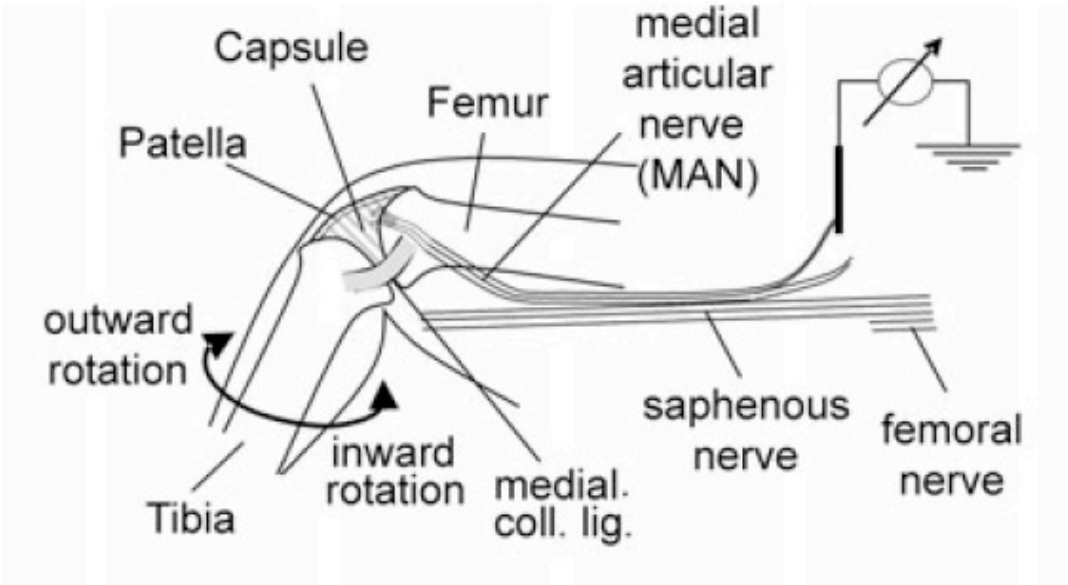
Time	Intervention Knee: LA	Intervention Knee: Placebo	Nonintervention Knee: LA	Nonintervention Knee: Placebo
Baseline	61.5 (20.8–90.0)	36.0 (28.0–64.5)	28.0 (13.0–40.7)	43.5 (12.5–68.0)
1 h	0.0 (0.0–28.2)*	38.0 (16.5–63.0)	1.0 (0.0–30.0)**	38.0 (1.5–47.5)
24 h	27.0 (2.2–65.0)	49.0 (6.7–72.0)	4.0 (0.0–35.5)	28.5 (4.5–52.5)
7 days	30.0 (1.5–72.5)	41.5 (17.5–72.7)	9.5 (0.0–33.5)	34.0 (0.0–46.5)

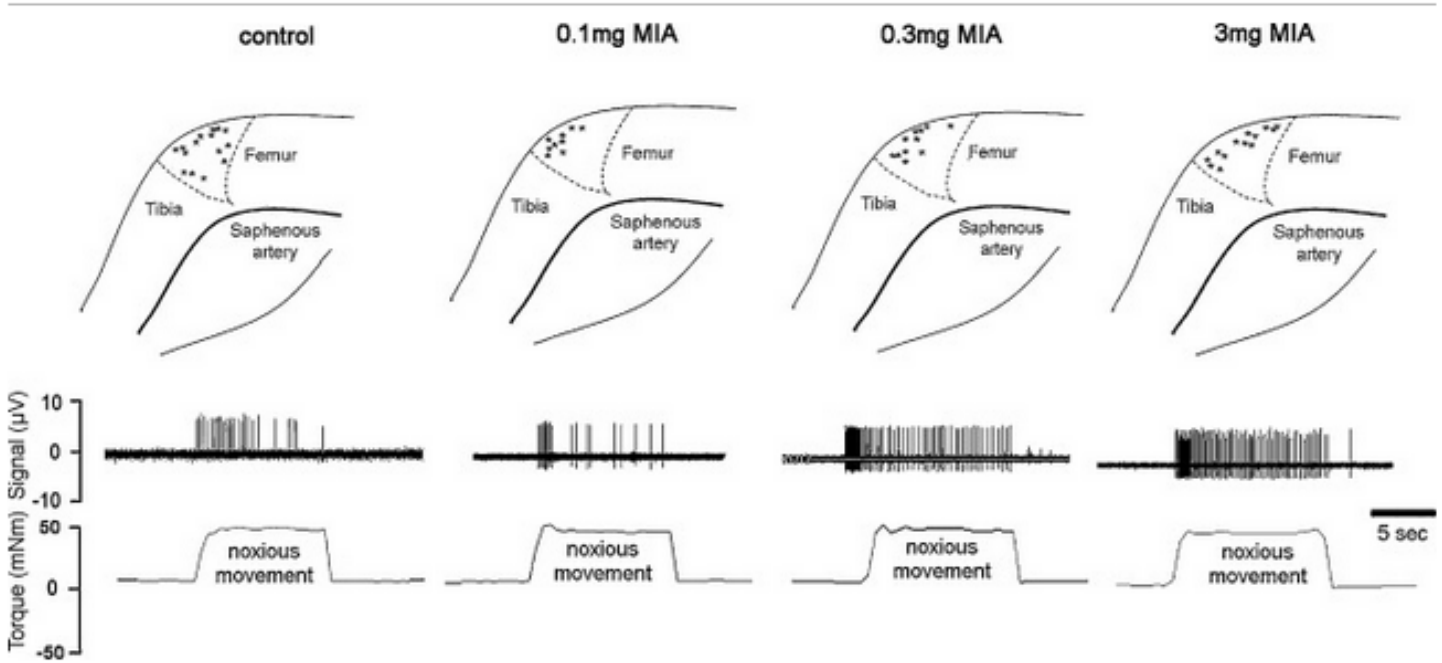
* VAS (baseline) vs VAS (1 h) for intervention knees (LA); p = 0.007.
** VAS (baseline) vs VAS (1 h) for nonintervention knees (LA); p = 0.08.

Creamer, et al. *J Rheumatol* 2006

Assessment of Neurobiologic Mechanisms?

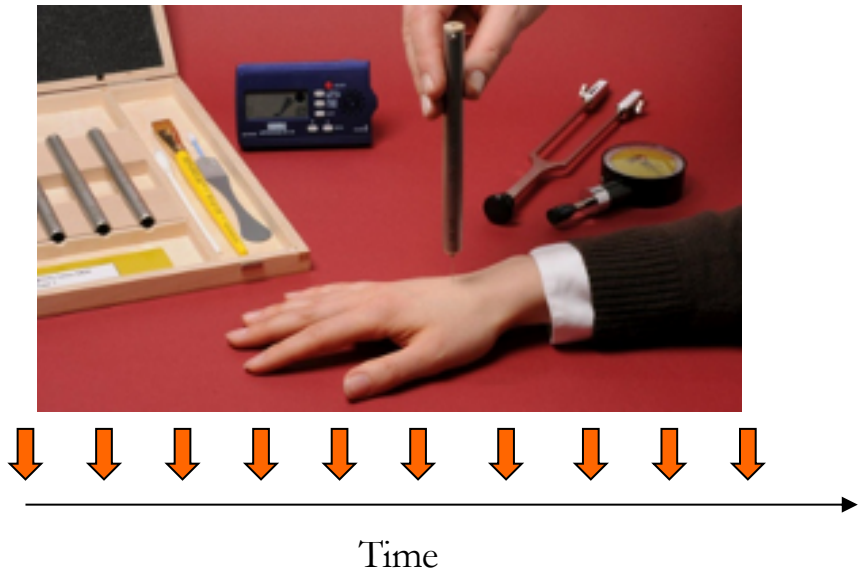
- Mechanisms primarily assessed in animal models

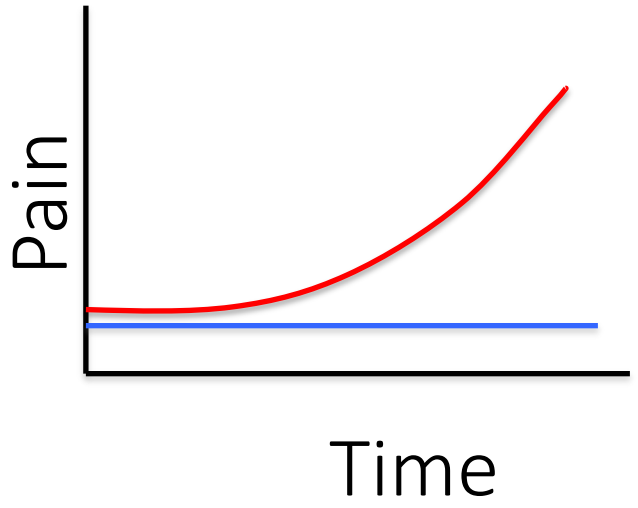




Quantitative Sensory Testing

- Pressure pain threshold
- Temporal summation (wind-up)
- Conditioned pain modulation



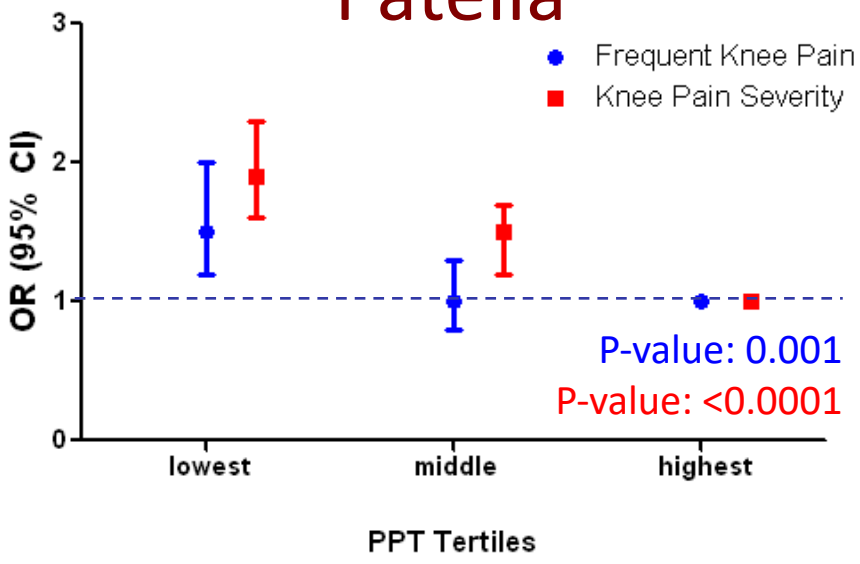


"Normal response": Pain Threshold #1 < Pain Threshold #2

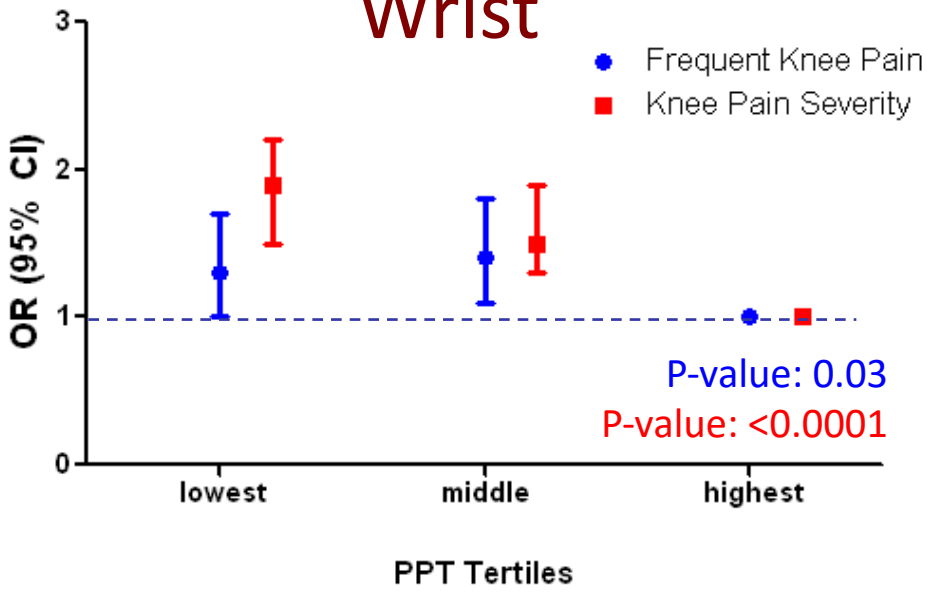
Pressure Pain Threshold (PPT)

- Cohort of ~3000 older adults with/at risk for knee OA

Patella



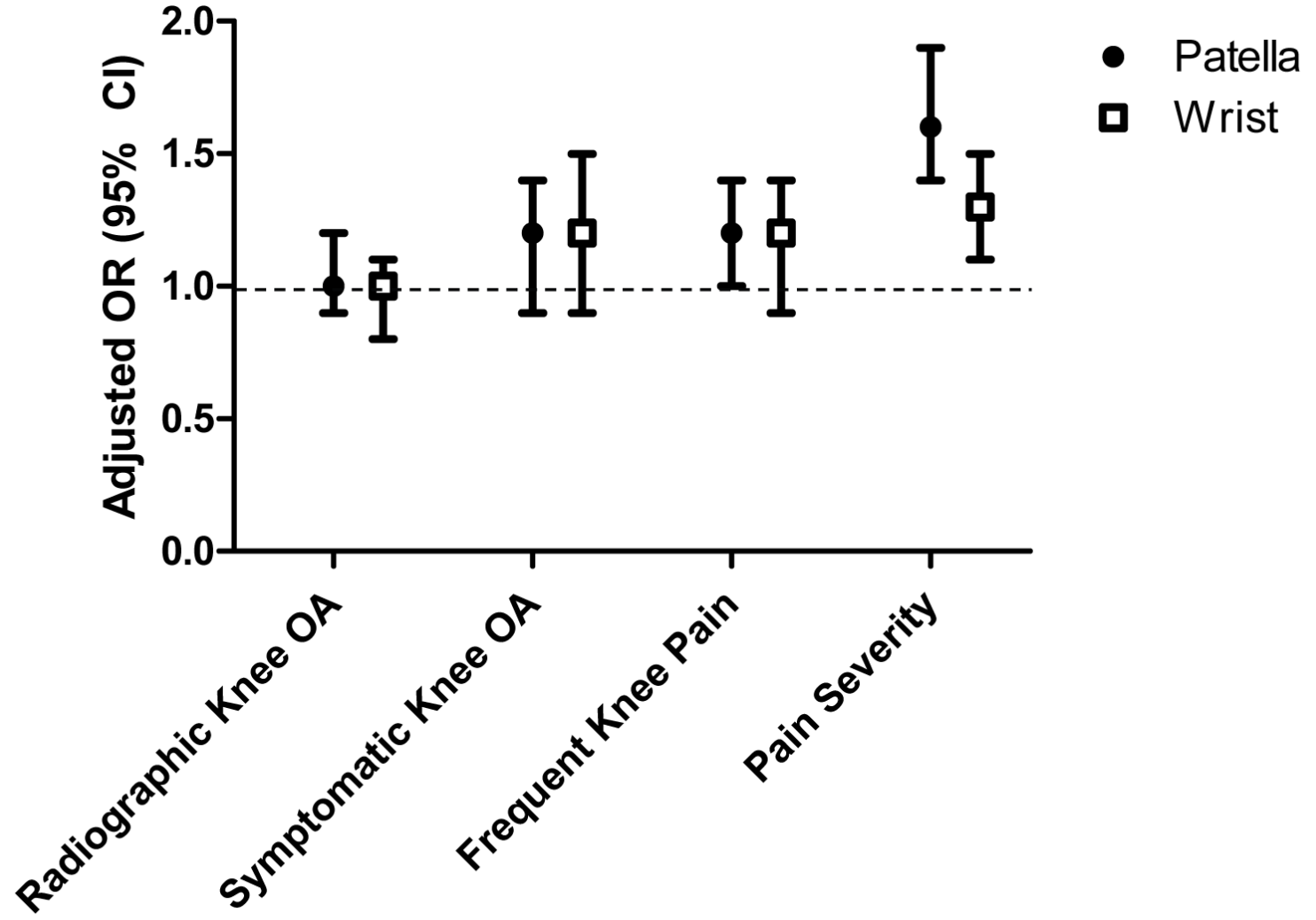
Wrist



- PPT associated with pain severity at site of & distant to pathology

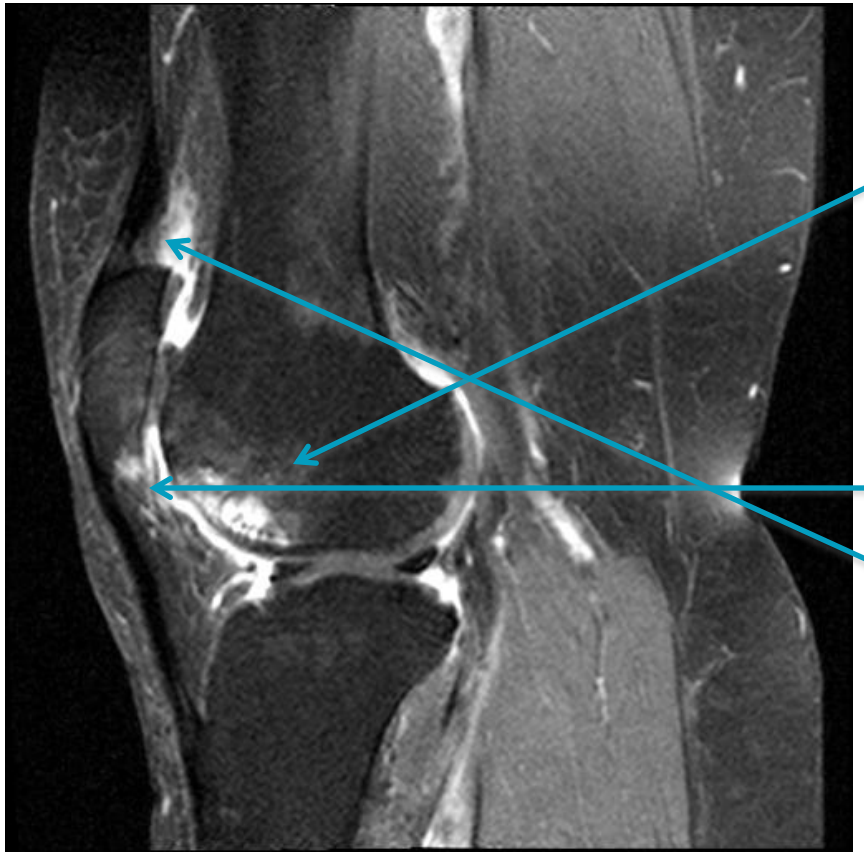
Neogi, et al. *ARD* 2015

Temporal Summation



Neogi, et al. *ARD* 2015

Does specific pathology contribute to sensitization?



Mechanical ✗

- Bone marrow lesions (BMLs)

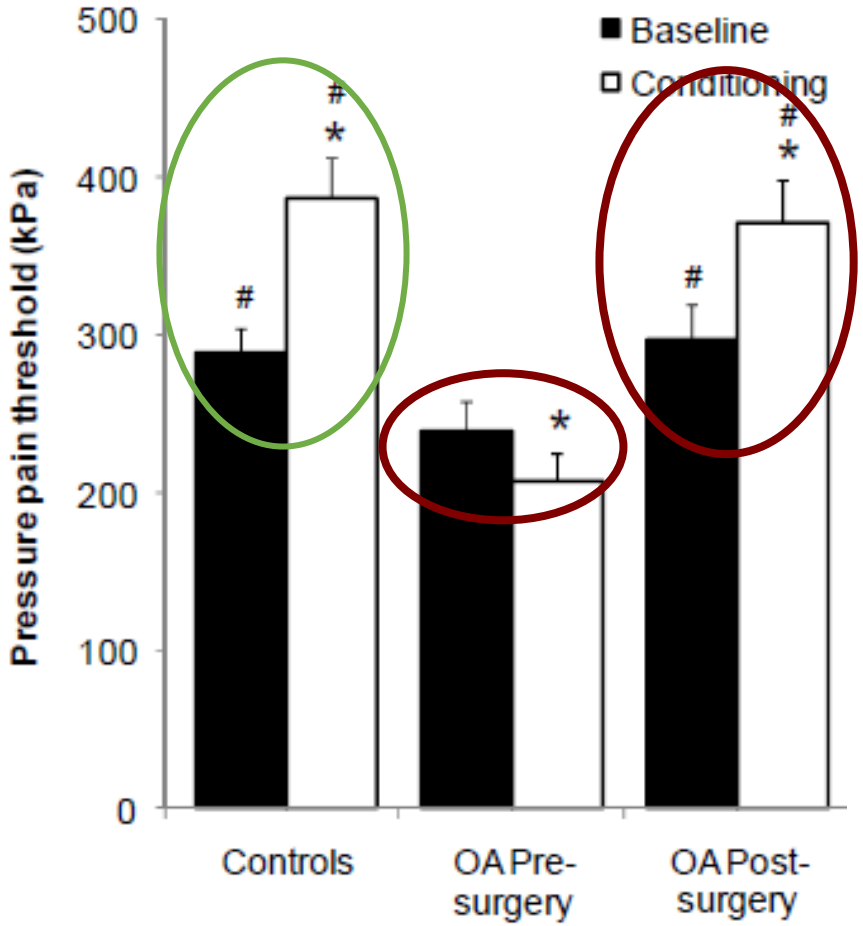
Inflammatory ✓

- Synovitis (Hoffa-synovitis)
- Effusion (effusion-synovitis)

Neogi, et al. *A&R* 2016

Evidence of Normalization in Descending Modulatory Inhibition Post-Knee Replacement

Lower pressure pain threshold reflects more pain sensitivity



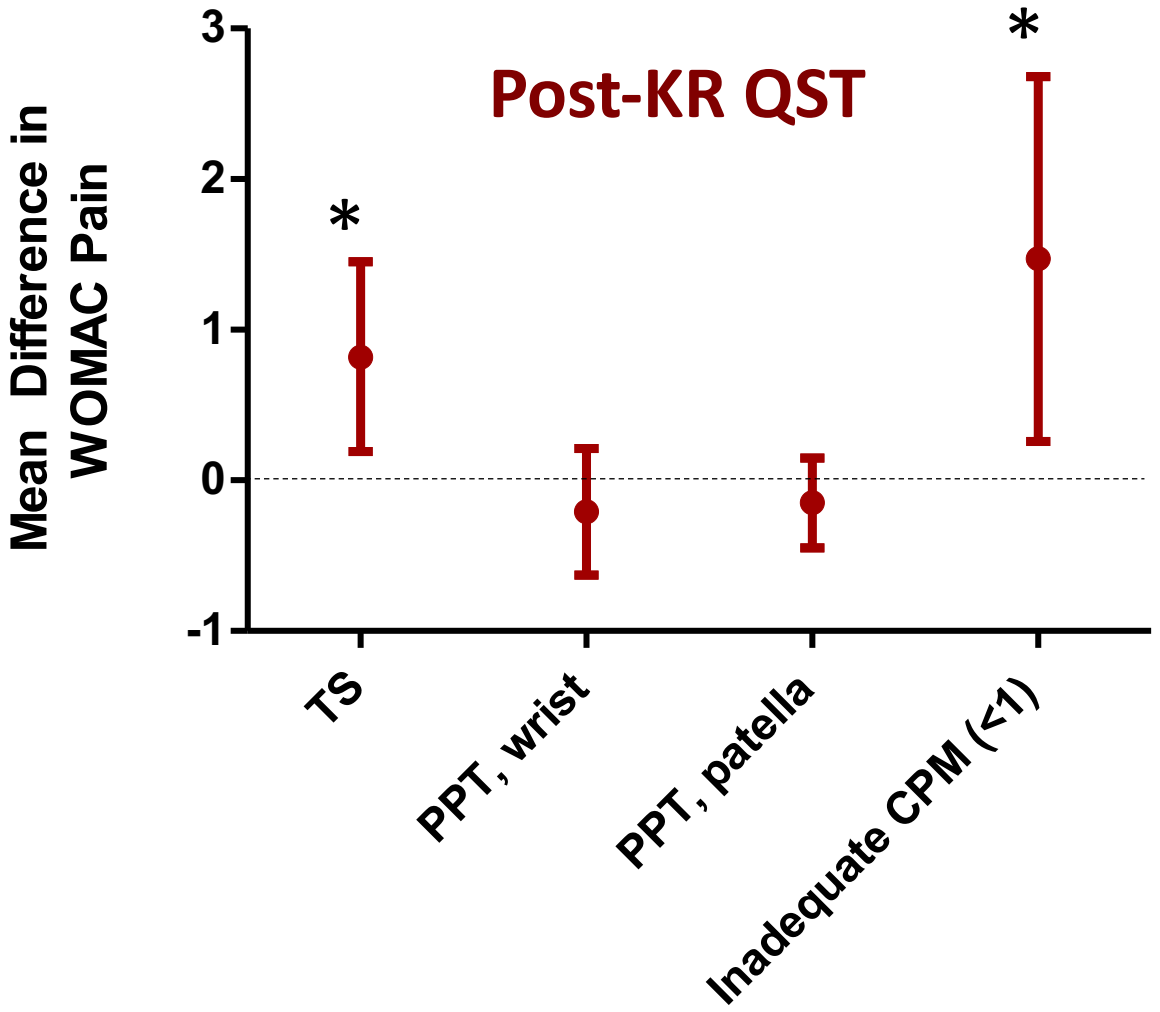
N=20 OA Subjects

N=20 'Healthy' controls

Reversibility of neurobiological mechanisms?

Graven-Nielsen, et al. *A&R* 2012

Relation of ***Post-KR*** QST measures to Post-KR Pain



Post-KR temporal summation and inadequate CPM were associated with worse WOMAC pain post-KR

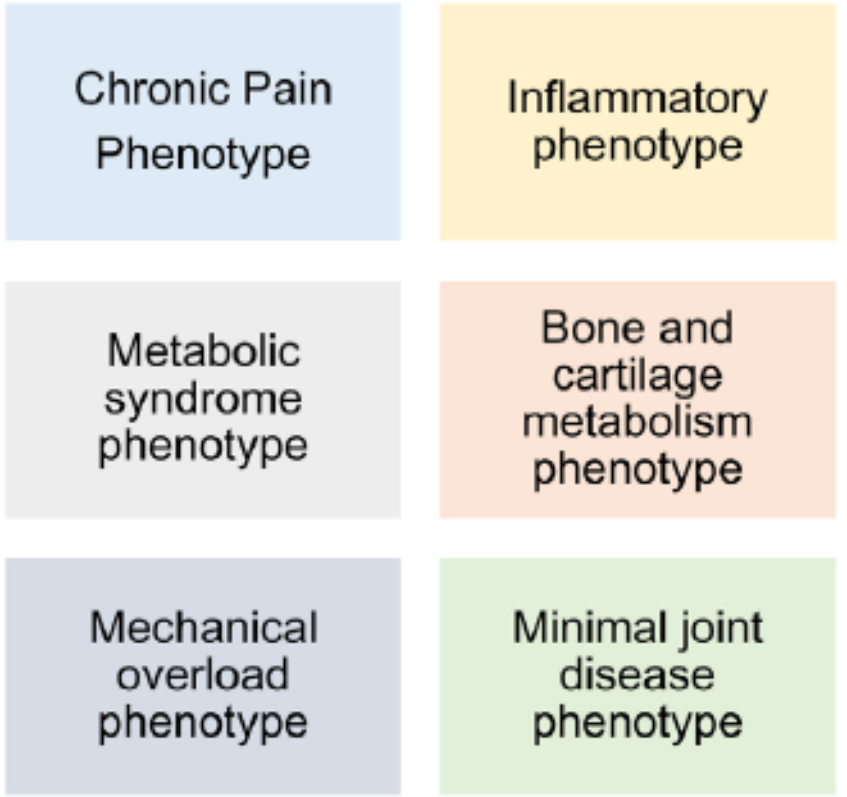
Implications for Pain Phenotyping in OA

Approaches to Pain Phenotyping

- Various agnostic data-driven approaches (e.g., cluster analysis)
  - Statistical tests for model fit
  - Clinical judgement

Phenotyping Studies in OA

- Variables assessed:
  - Psychological comorbidities
  - Pain
  - Comorbidities
  - Biomarkers
  - Quantitative sensory testing
- Relation to other factors (e.g., function) and demographics (e.g., age, sex)

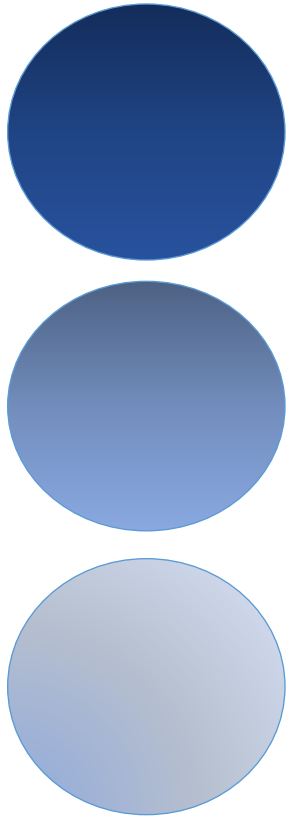


Deveza, et al. *OA&C.* 2017

Dell'Isola, et al. *BMC MSK Dis.* 2016

Examples of Pain Phenotype Studies

- Symptomatic knee/hip OA, N=129



Cluster 1: “FM”-like (pain, fatigue, sleep, depression, high illness burden)

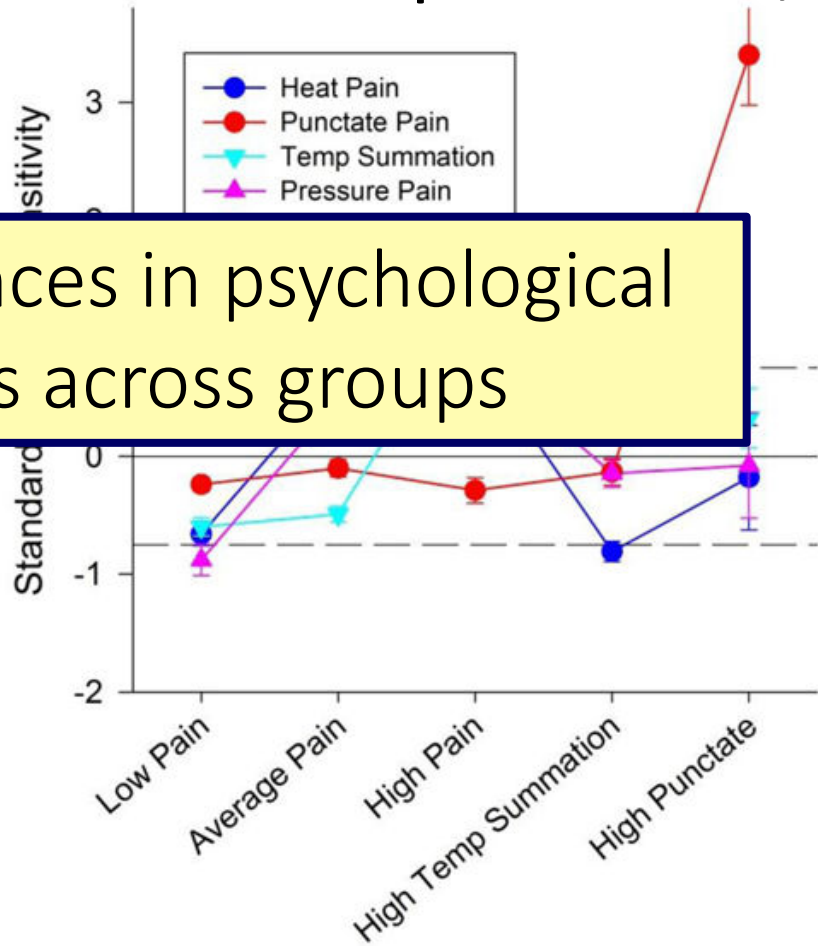
Cluster 2: intermediate

Cluster 3: lowest scores, but sleep issues

Murphy, et al. *AR&T.* 2011

Example using QST

- Knee OA prior to knee replacement, N=218



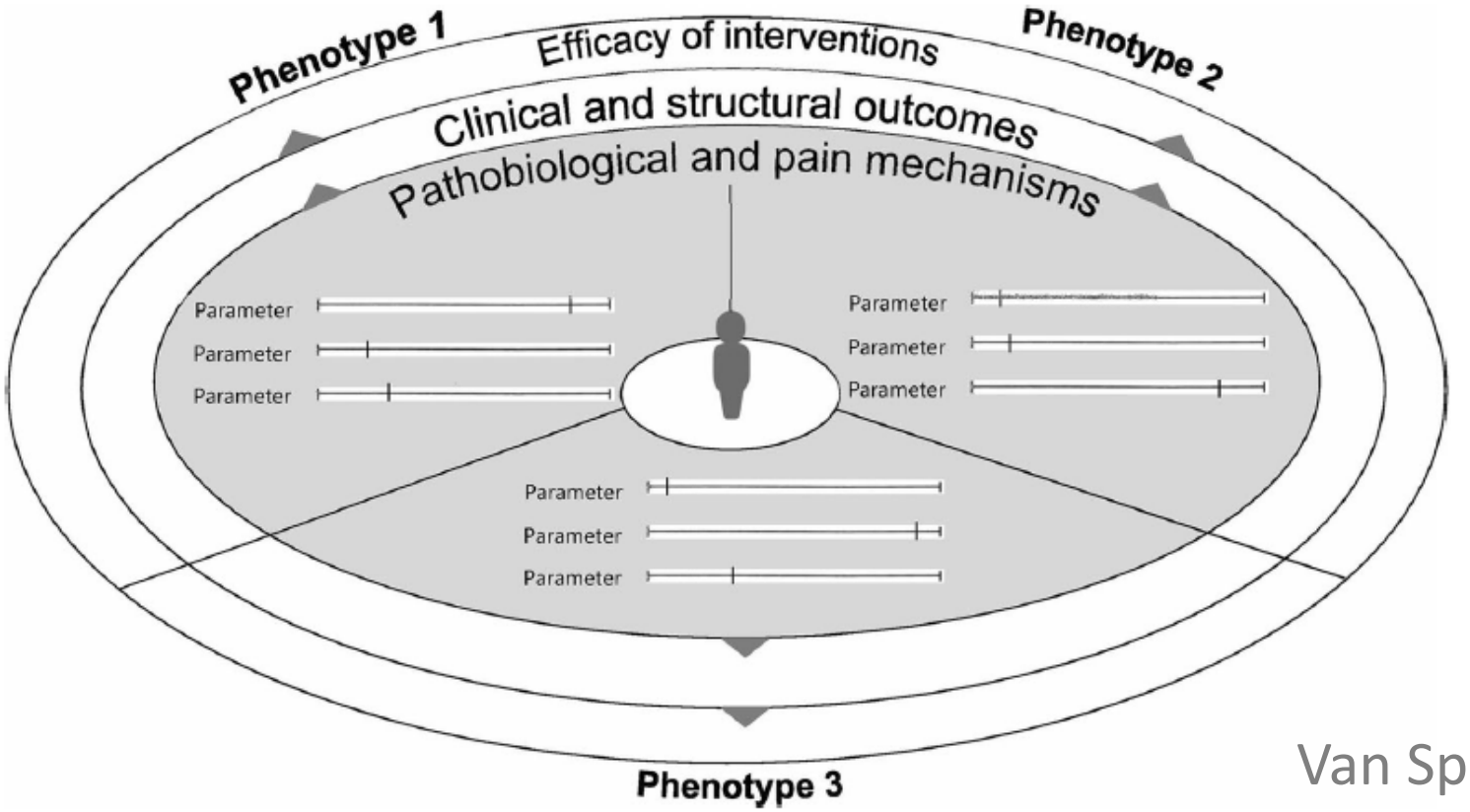
No differences in psychological factors across groups

1. Low Pain
2. Average Pain
3. High Pain
4. High Temp Summation
5. High Punctate

Frey-Law, et al. *Pain.* 2016

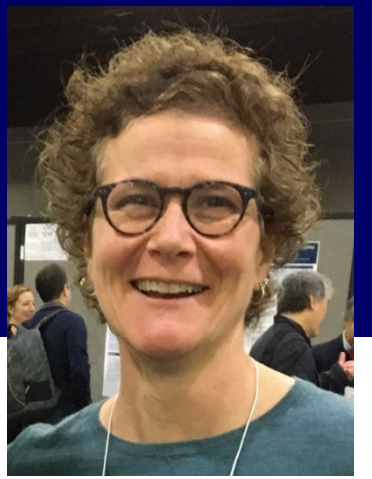
Challenge to Interpreting Prior Studies

- Cross-sectional (and small)
  - Cause or consequence? Relevant outcomes?



Van Spil, et al. *AR&T.* 2020

Pain *Susceptibility* Phenotypes

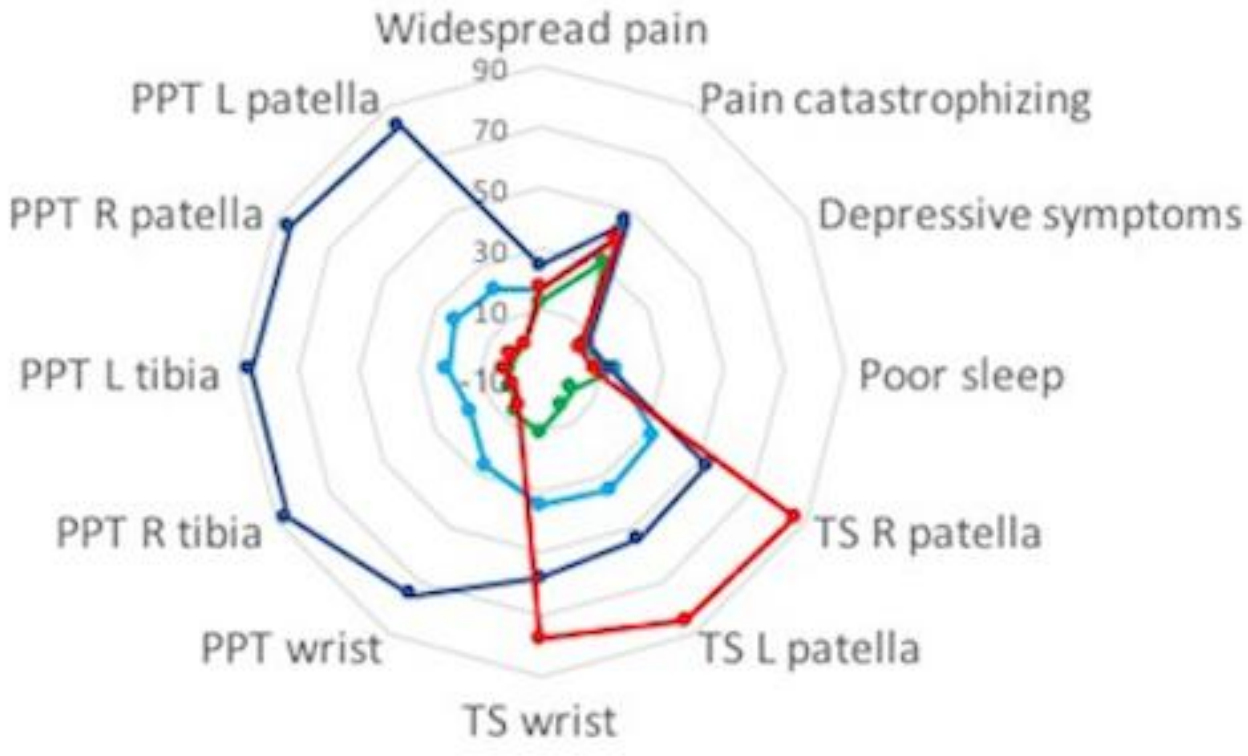


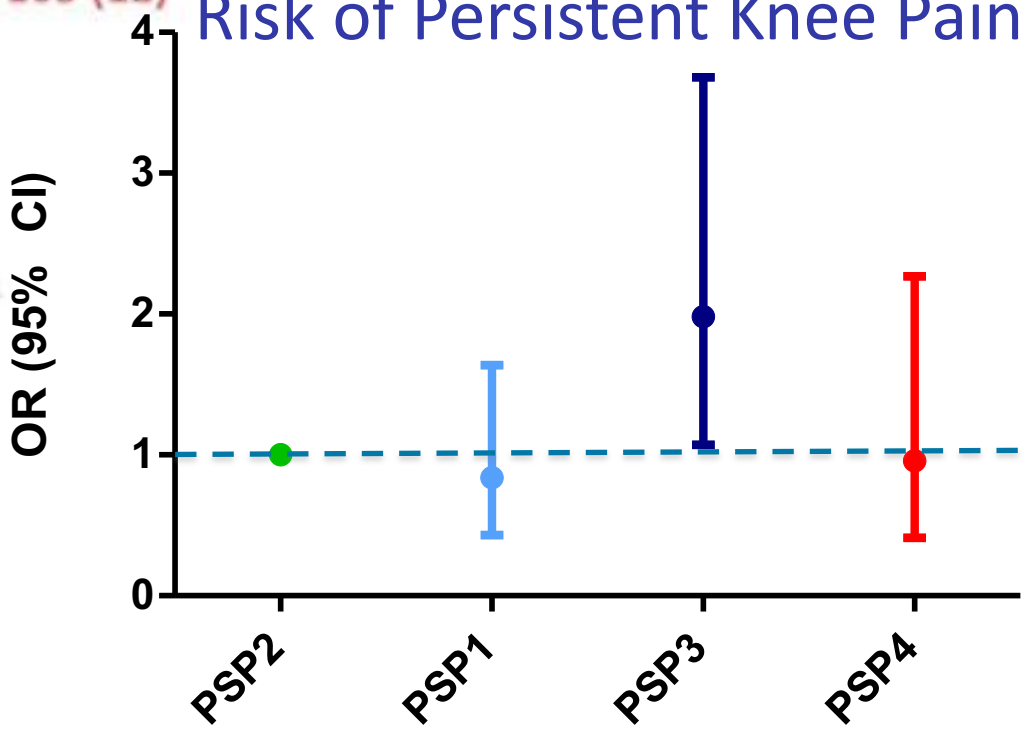
- Factors other than structural pathology:
  - Psychological factors (catastrophizing, depressive symptoms)
  - Sleep
  - Widespread pain
  - Quantitative Sensory Testing (QST)

- Longitudinal study: two year follow-up
  - Among people free of persistent knee pain at baseline (n=852)

Symptom Development: Pain *Susceptibility* Phenotypes (PSPs)

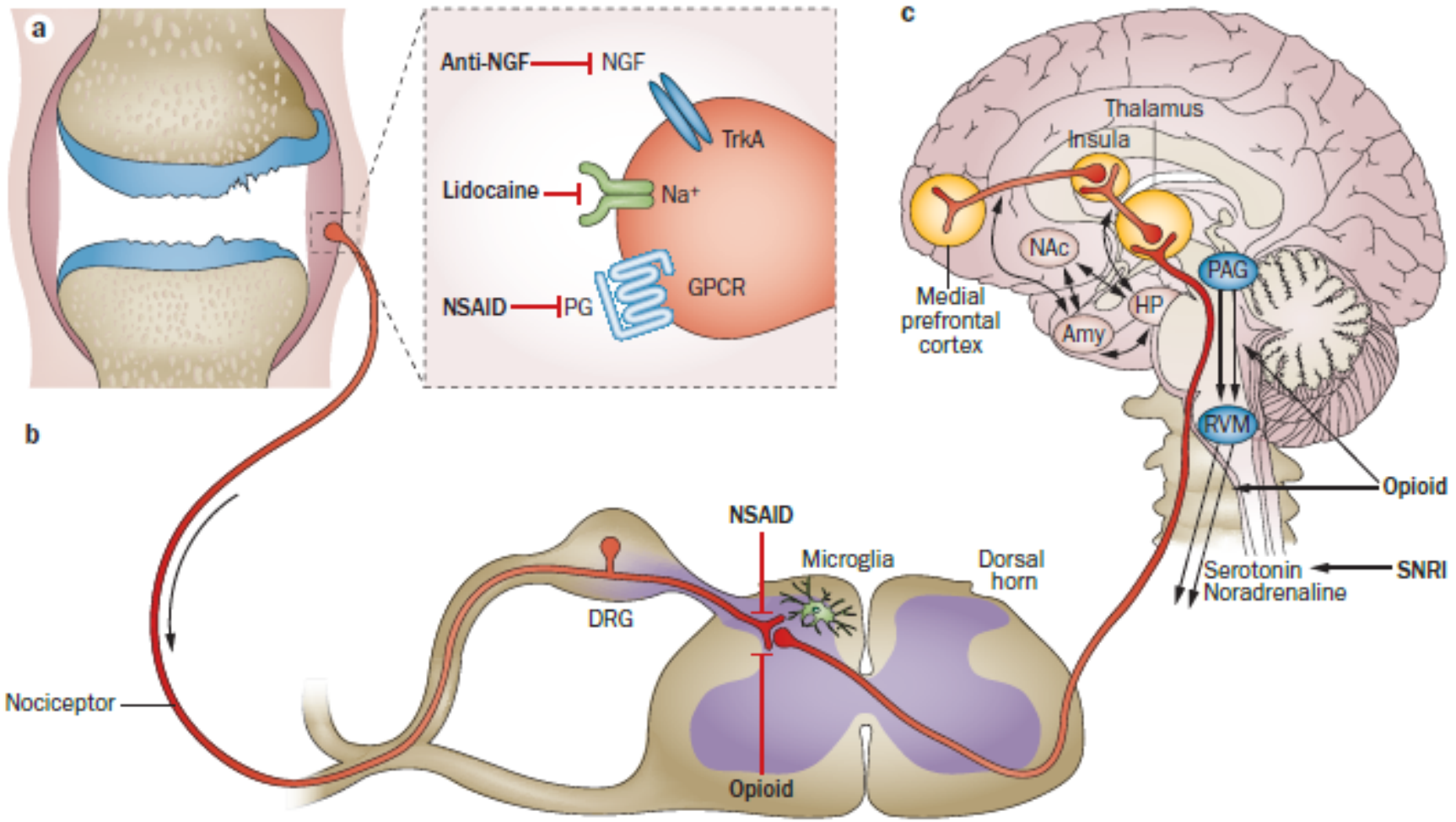
1- Moderate proportion of PP sensitivity + facilitated TS n=285 (34)
2- Low/Absent proportion of both PP sensitivity + facilitated TS n=265 (31)
3- High proportion of PP sensitivity + moderate proportion of facilitated TS n=199 (23)
4- Low proportion of PP sensitivity + high proportion of facilitated TS n=103 (12)





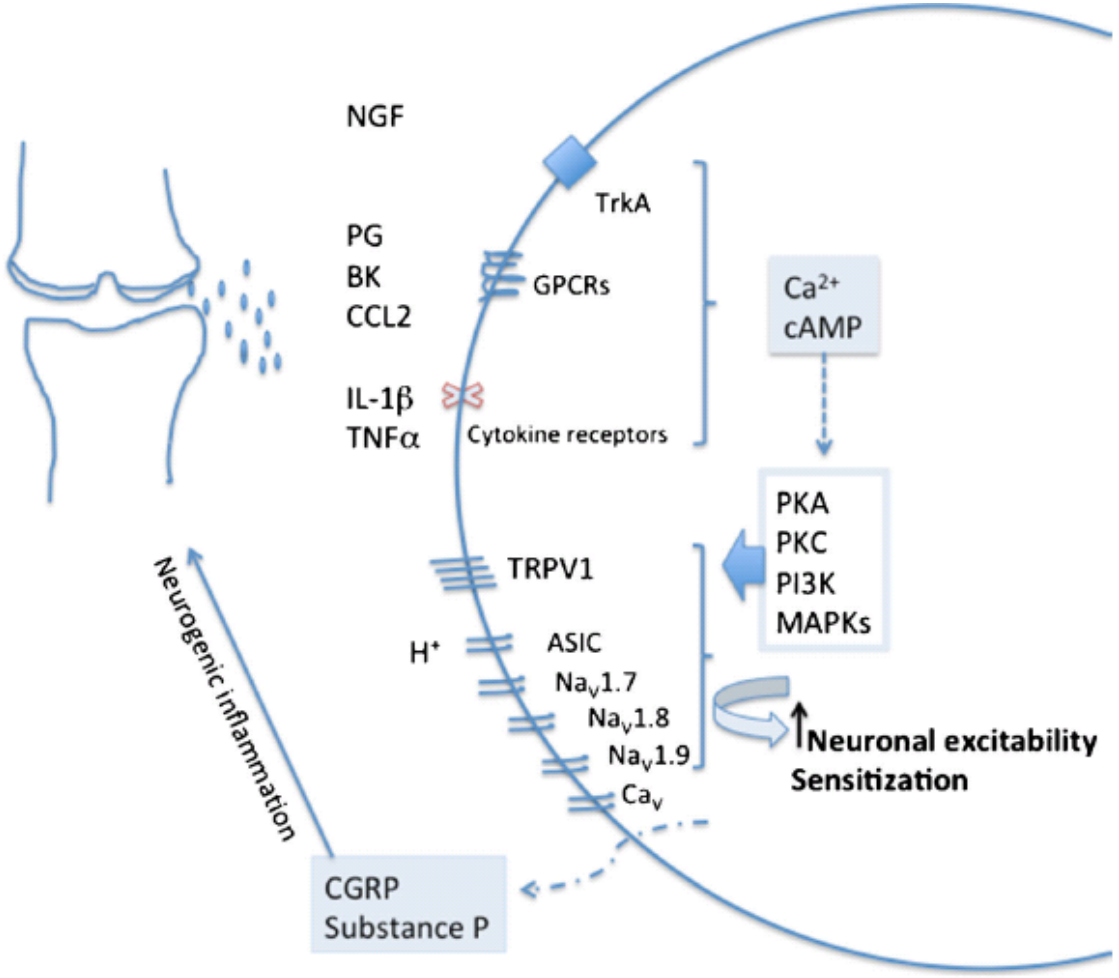
Carlesso, et al. *A&R.* 2019

Future of OA Pain Management?



Malfait & Schnitzer. *Nat Reviews Rheum.* 2013

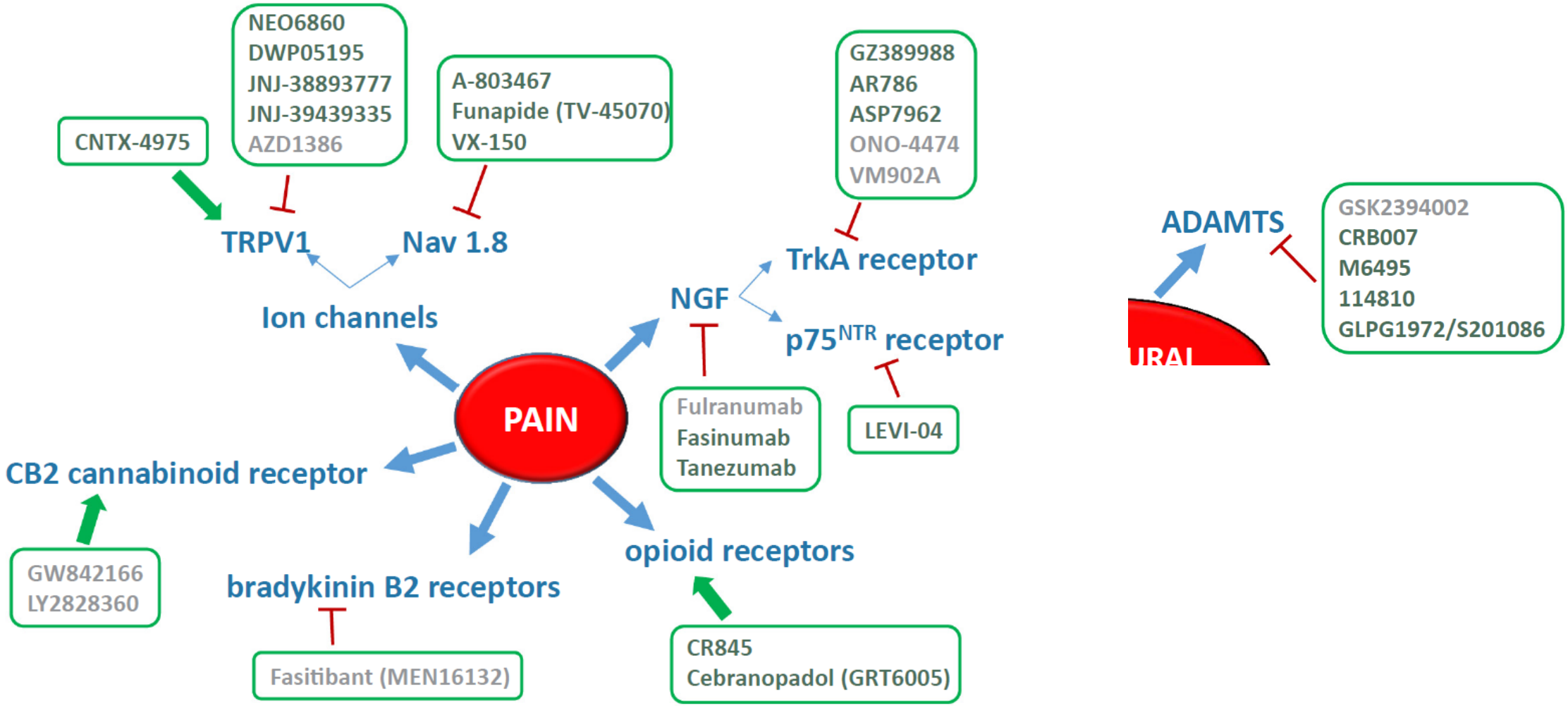
Emerging Pain Targets



- NGF
  - TrkA inhibitors
- TRPV1 (capsaicin)
- CGRP, Subs P
- MCP-1 – CCL2
- Acid-sensing ion channels
- Voltage-gated Na+ & Ca++ channels

Malfait & Miller. *Curr Osteop Rep.* 2016

Therapeutic agents being tested in OA



Alcaraz, et al. *Biochem Pharm.* 2019

Should we completely ablate nociceptive pain?

- Nociceptive pain is needed to a certain extent to prevent harming one's self
  - OA pain pathologi
    - Char sic hip"

- Maintain certain degree of necessary nociception

Summary

- Need better objective tools to identify actual mechanisms operating in a given patient to tailor therapy
  →Mechanism-based approach to treatment

- Pressure pain sensitivity may be important driver of developing persistent knee pain
  →Implications for understanding transition from acute to chronic pain

- Consider stage of pain

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