The Brain or the Body: What is the Target for Pain Treatment?

Roger B. Fillingim, PhD

Disclosure

- Nothing to disclose

Learning Objectives

- List available pain treatments target the body, brain or both
- Describe simple methods that are available to identify centralized pain
- Explain why matching treatments to the patient’s pain mechanisms will improve outcomes

APS Track 2016: Mind-Body Therapies for Pain

- **The Brain or the Body: What is the Target for Pain Treatment? (Fillingim)**
- Noninvasive Neuromodulatory Approaches to the Treatment of Chronic Pain (Dr. Vitaly Napadow)
- Acupuncture Analgesia: Therapy or Sham? (Dr. Rick Harris)
- Neurochemical Imaging as a Probe of Chronic Pain and its Treatment (Dr. Rick Harris)
- Hands On or Hands Off: A Tour of Current Issues Impacting Spinal Manipulative Therapy for Spinal Pain (Dr. Steven George)

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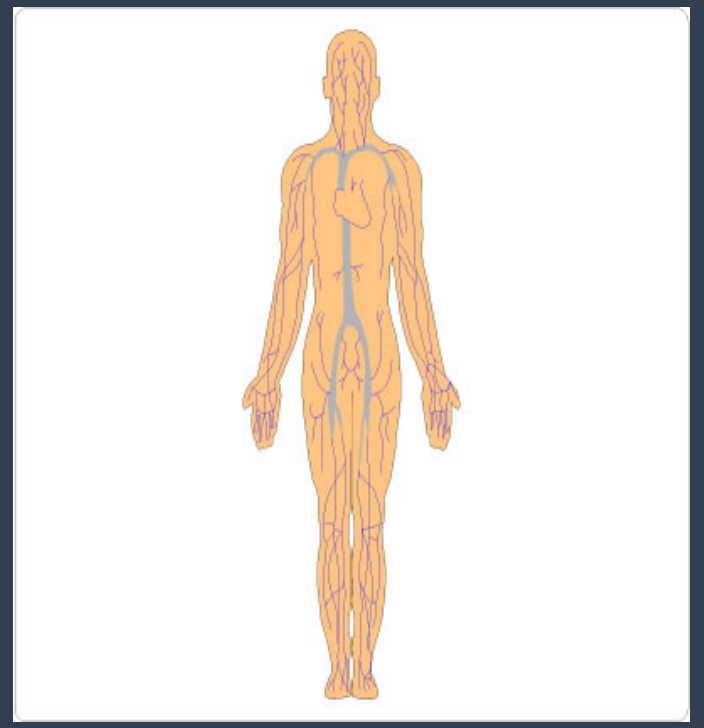
Overview

- **Conceptual Models of Pain**
- Peripheral vs. central pain mechanisms
- Body vs. brain based treatments
- Conclusions & Recommendations

VS



Biomedical Model of Pain

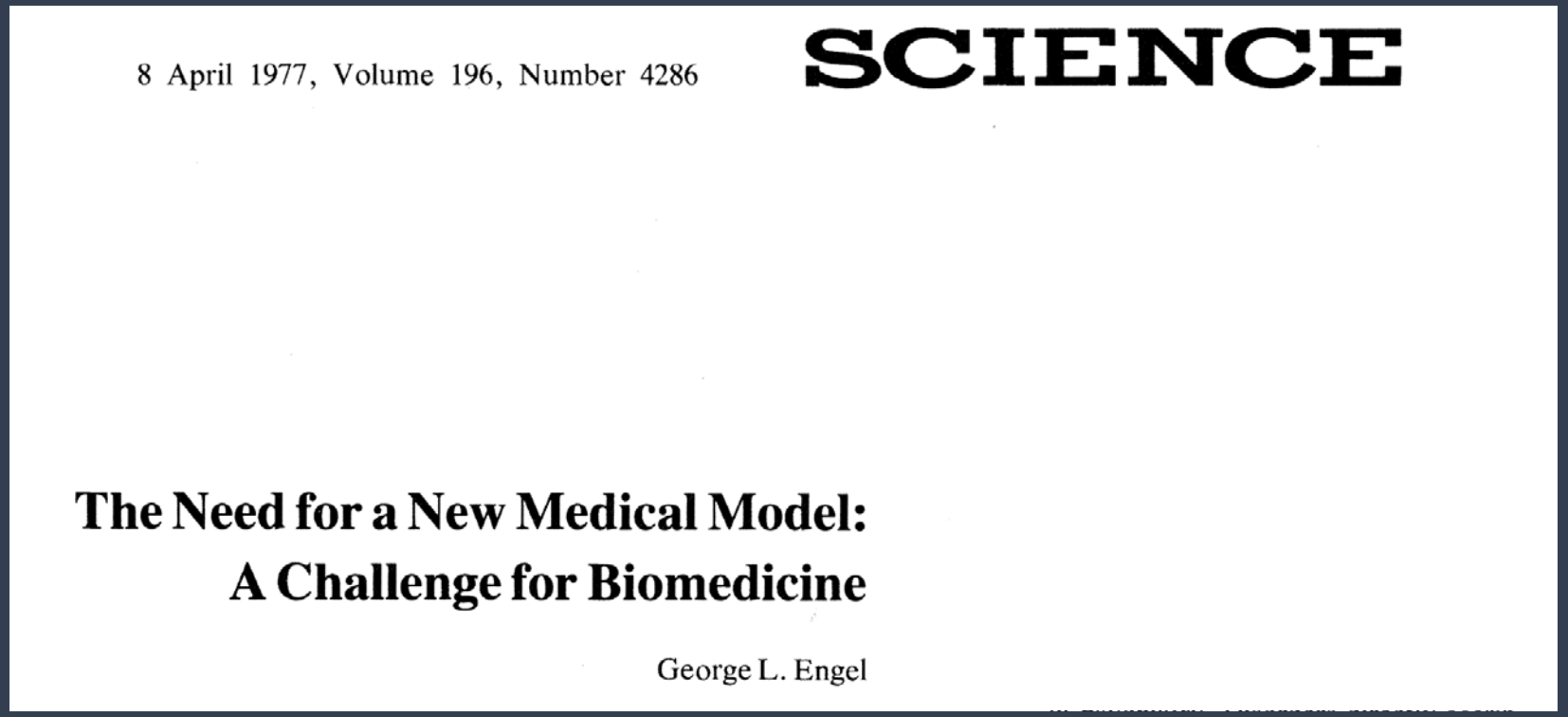
- Pain is a sensory experience arising from peripheral nociception
- Pain is a symptom of disease or tissue damage
- Pain is proportional to tissue damage or observable pathology
- Correcting the disease or tissue damage will ameliorate the pain

Biomedical Model of Pain: Clinical Corollaries

- Extensive testing to identify peripheral drivers of pain is needed
- Peripheral abnormalities that are identified need to be corrected in order to reduce the pain
- Lack of physical findings calls into question the validity of the pain

Important Themes in Pain Research

- Gate Control Theory (Melzack & Wall, 1965)
- Descending Pain Inhibition (Kosterlitz, 1975; Hughes, 1975; Basbaum & Fields, 1978)
- Central Sensitization (Woolf, 1983)
- Centralized Pain (Phillips & Clauw, 2011)



8 April 1977, Volume 196, Number 4286

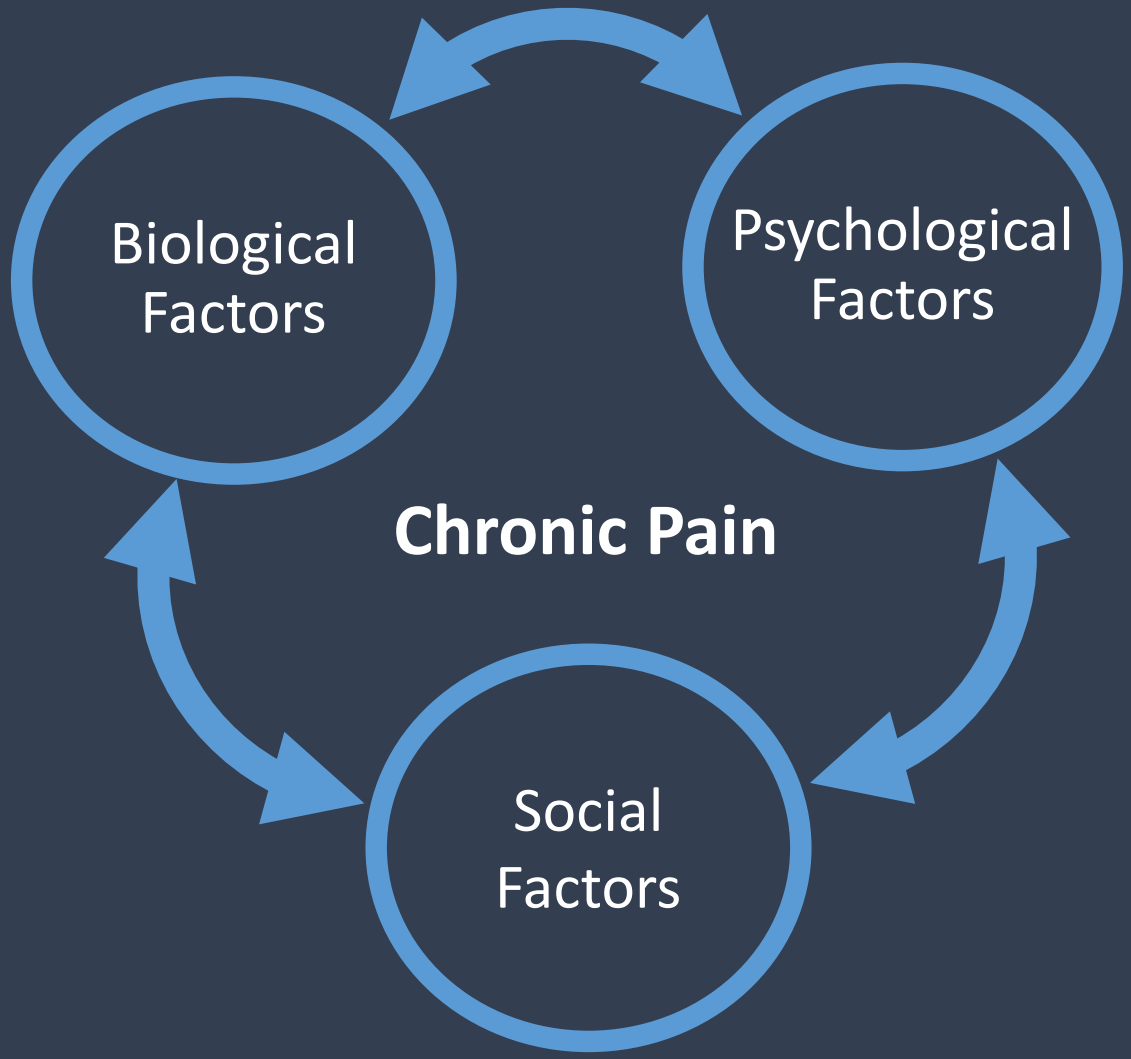
SCIENCE

The Need for a New Medical Model: A Challenge for Biomedicine

George L. Engel

The biomedical model embraces both reductionism, the philosophic view that complex phenomena are derived from a single primary principle, and mind-body dualism, the doctrine that separates the mental from the somatic.

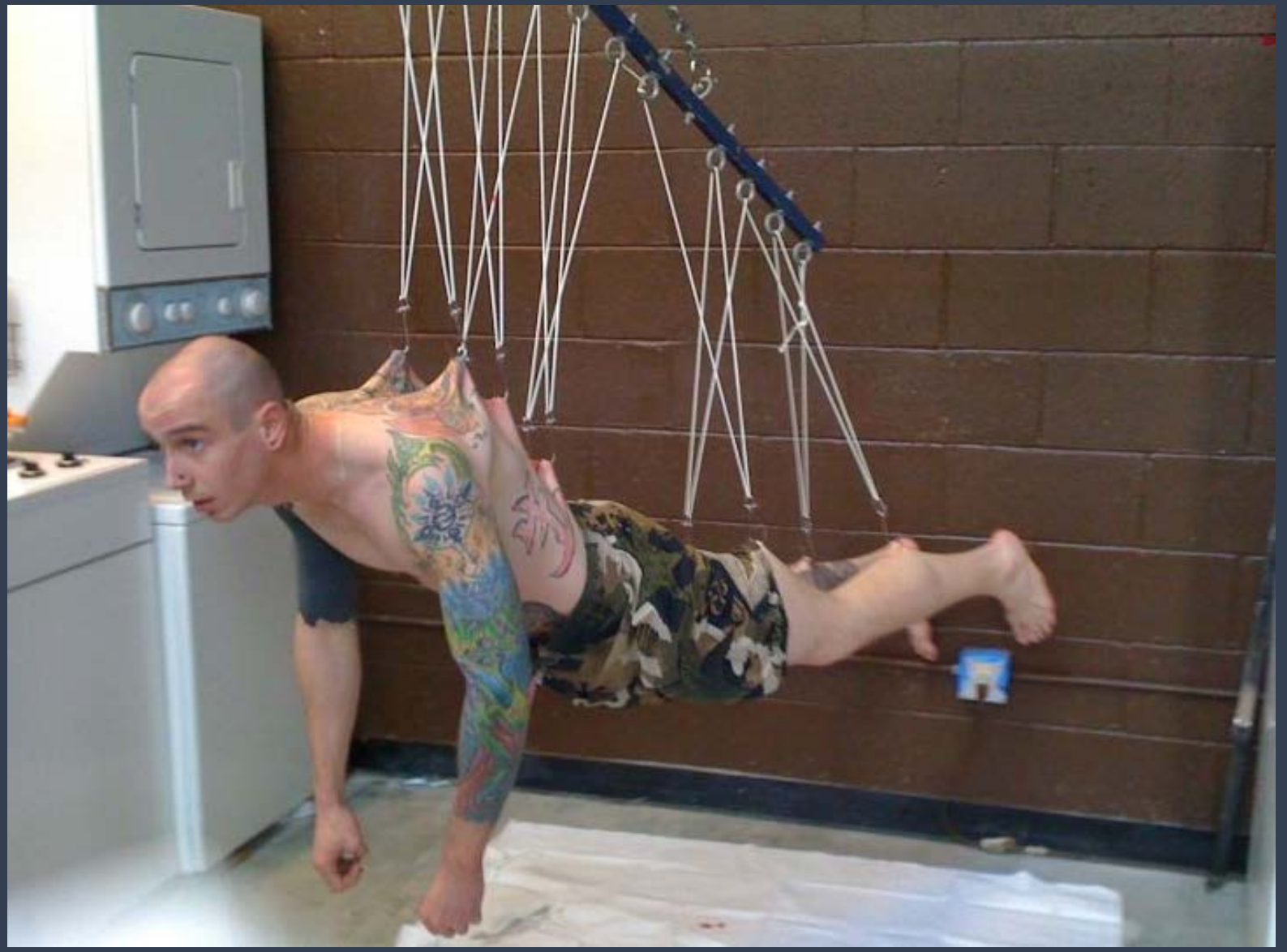
The Biopsychosocial Model of Pain



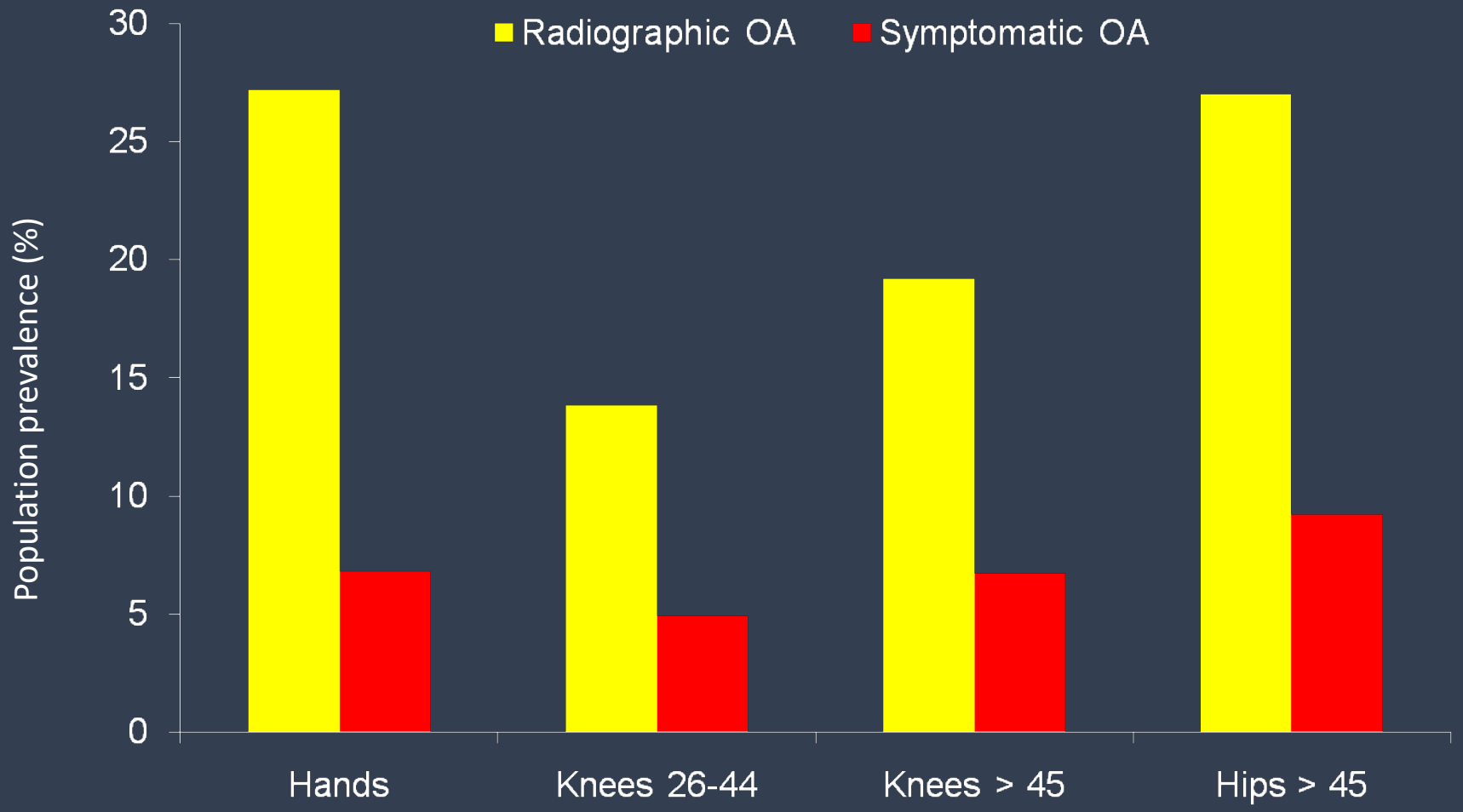
The Biopsychosocial Model Explains…

- **The poor correspondence between tissue damage and pain**
- The difficulty in identifying people at risk for chronic pain
- The limited efficacy of unimodal treatment of chronic pain
- The robust individual differences that characterize pain
- Common factors that contribute to different kinds of pain

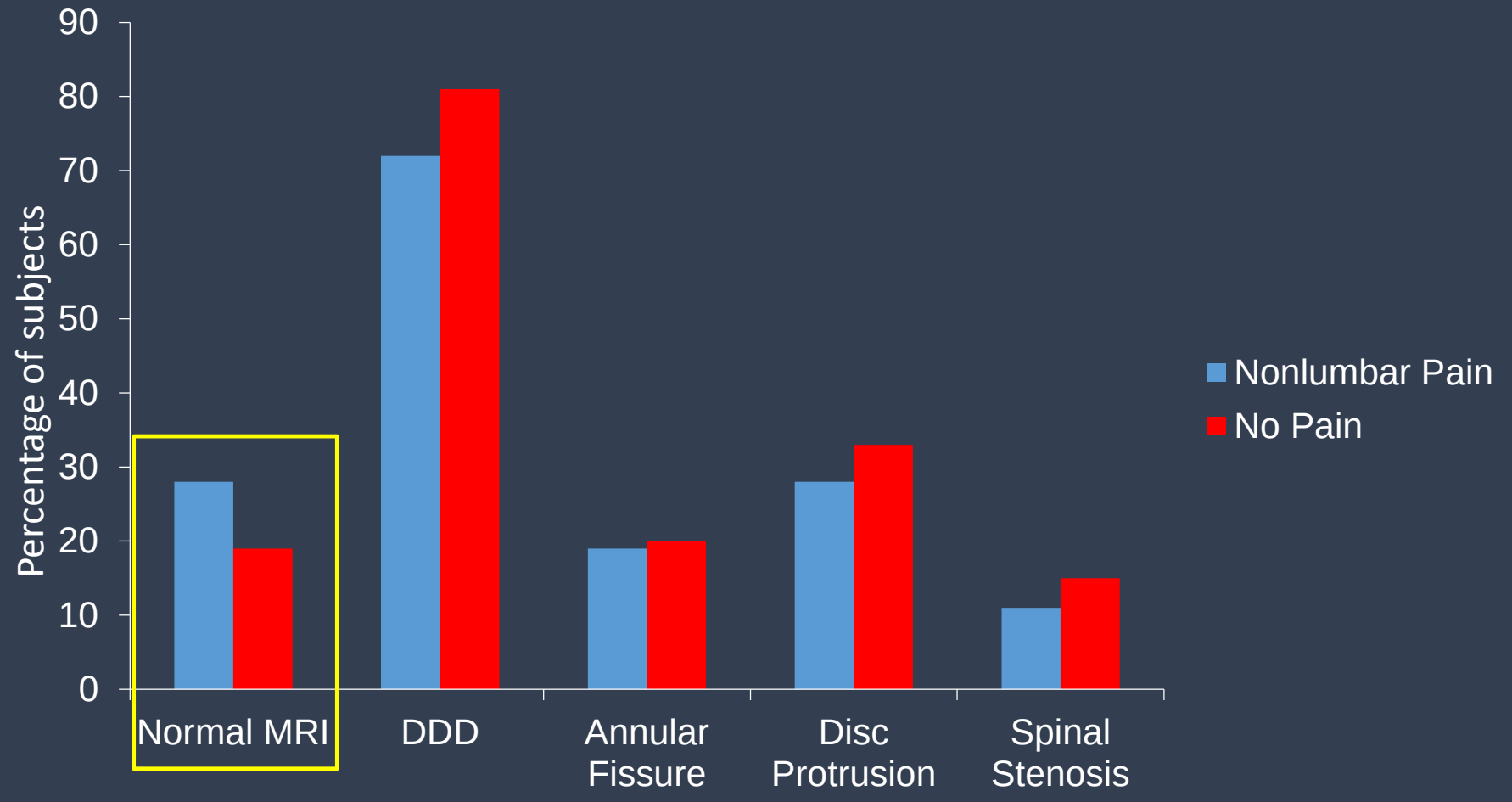
Just Hanging Around



Radiographic vs. Symptomatic Osteoarthritis (Lawrence, et al, 2008)



Abnormal Lumbar MR Findings in Subjects with no Low Back Pain (Carragee, et al, 2006)



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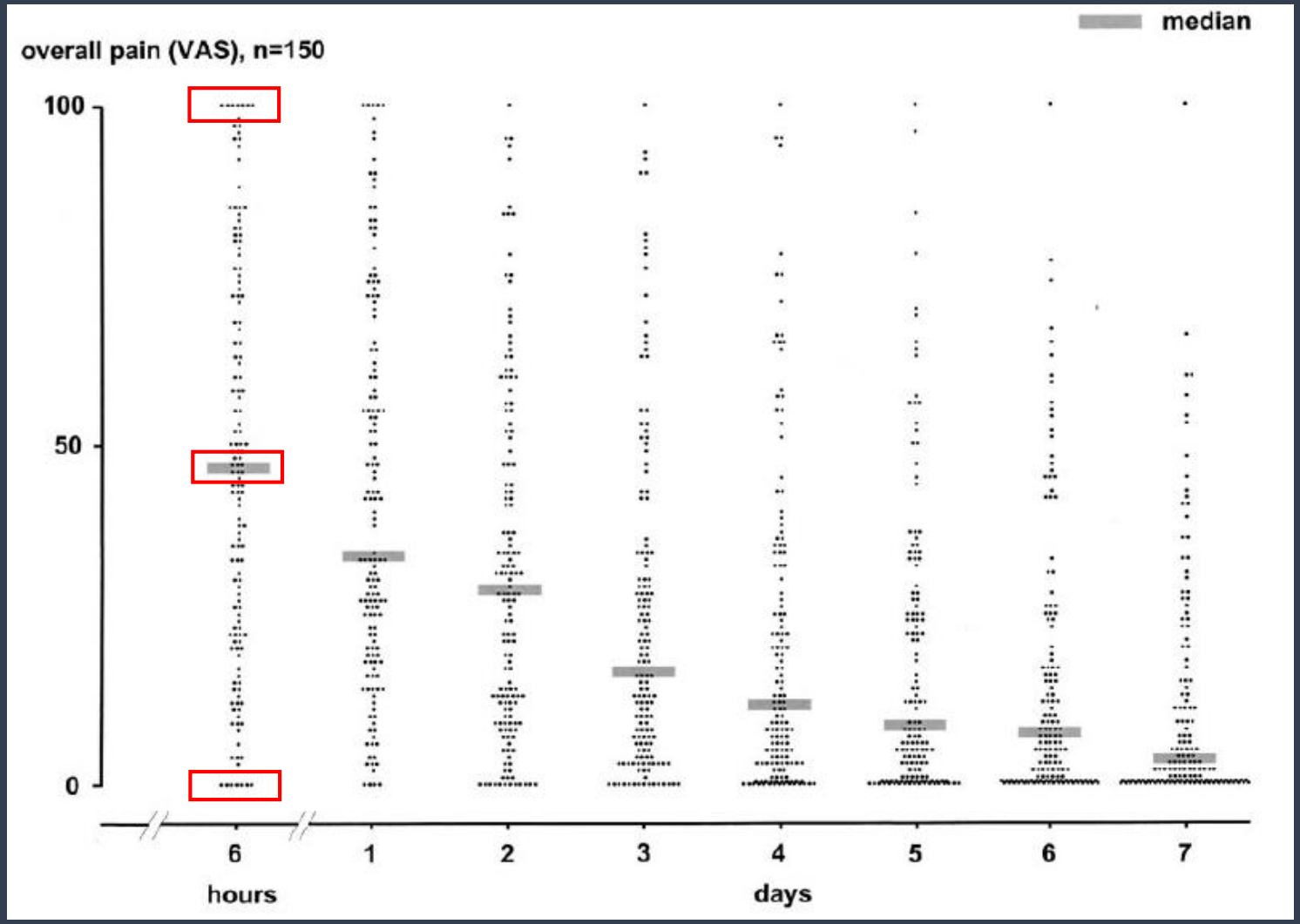
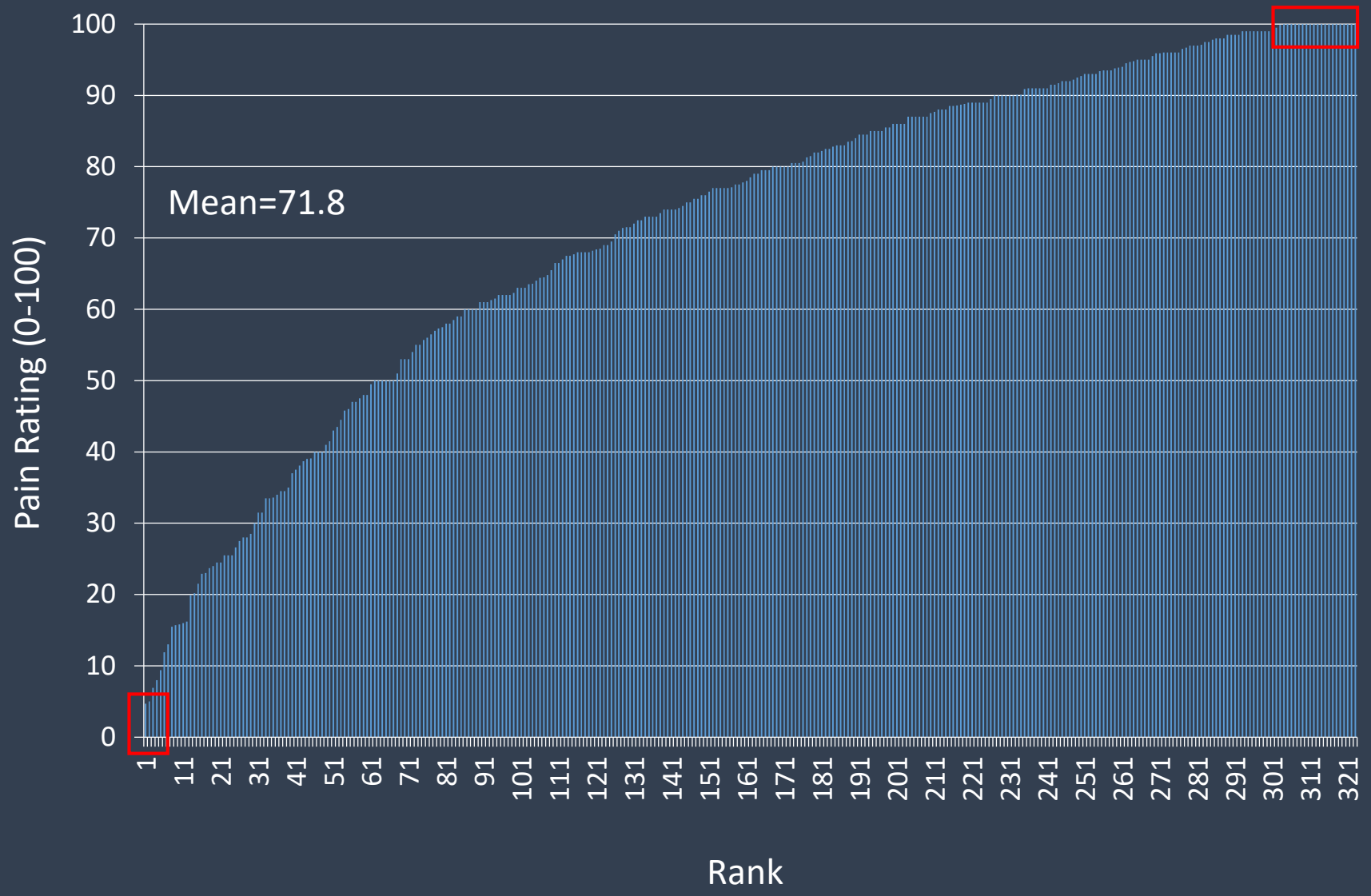
Pain After Laparascopic Cholecystectomy (Bisgaard, et al, 2001)



Ratings of a 48 Degree Thermal Stimulus



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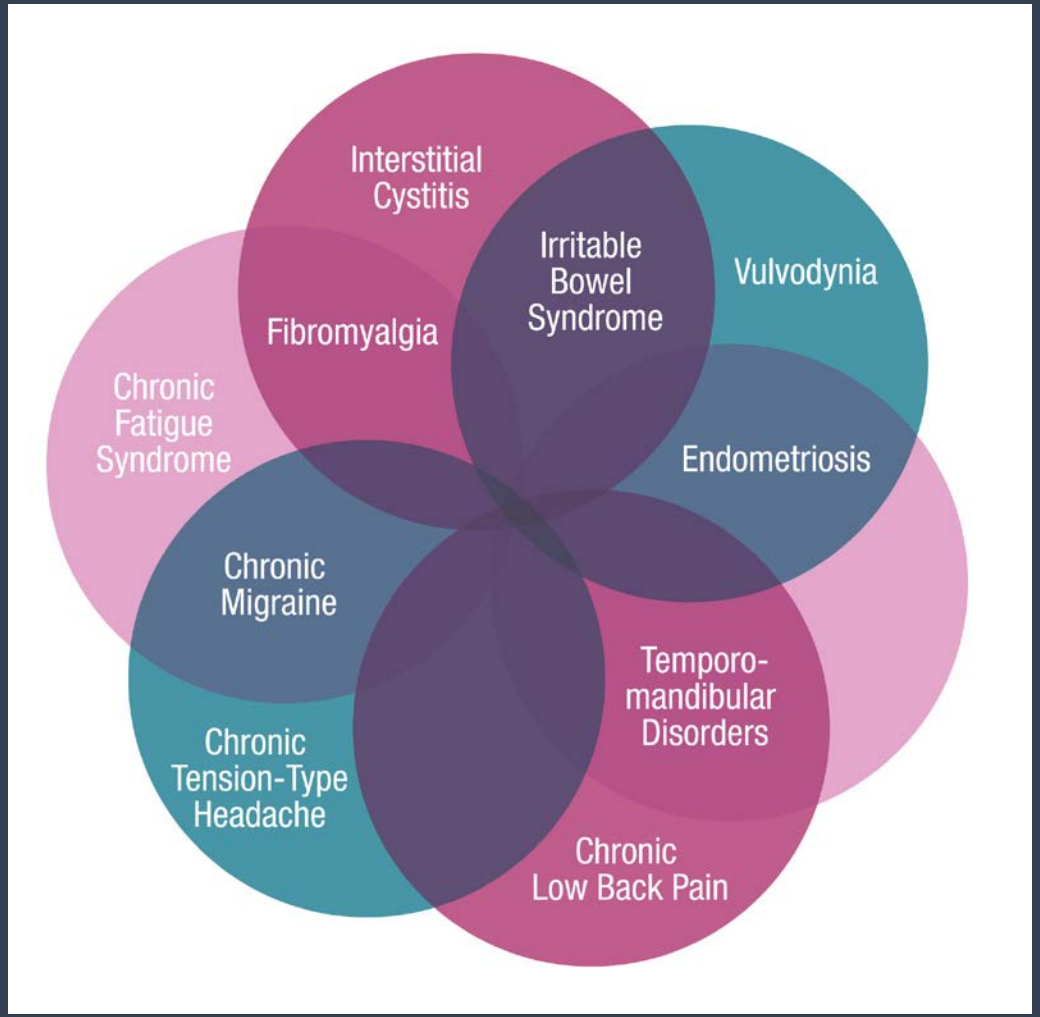
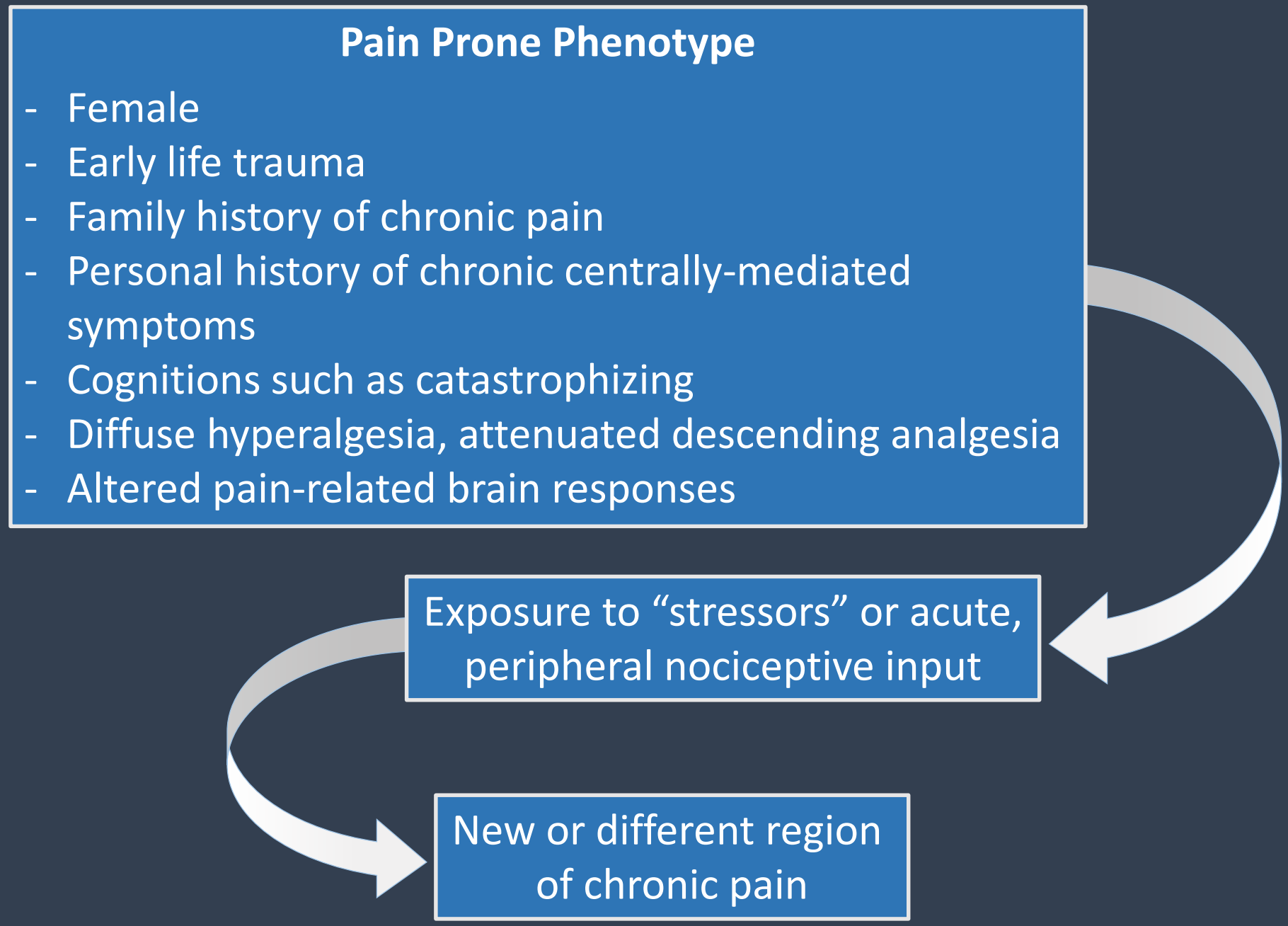
Chronic Overlapping Pain Conditions (COPCs)





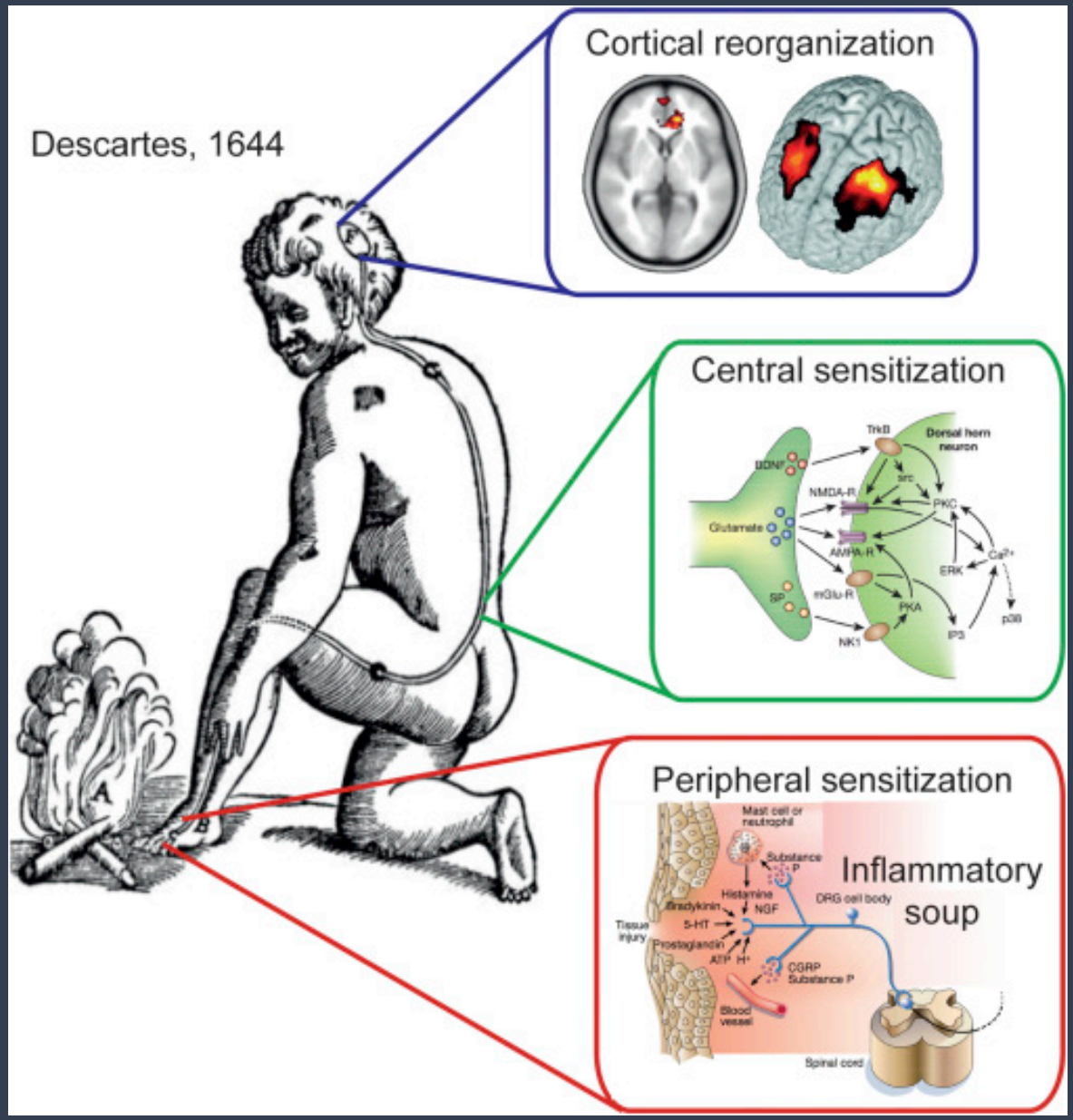
Adapted from Phillips & Clauw, 2013 Arth Rheum 65: 291-302

Overview

- Conceptual Models of Pain
- **Peripheral vs. central pain mechanisms**
- Body vs. brain based treatments
- Conclusions & Recommendations

Nociception, Pain, Negative Moods, and Behavior Selection

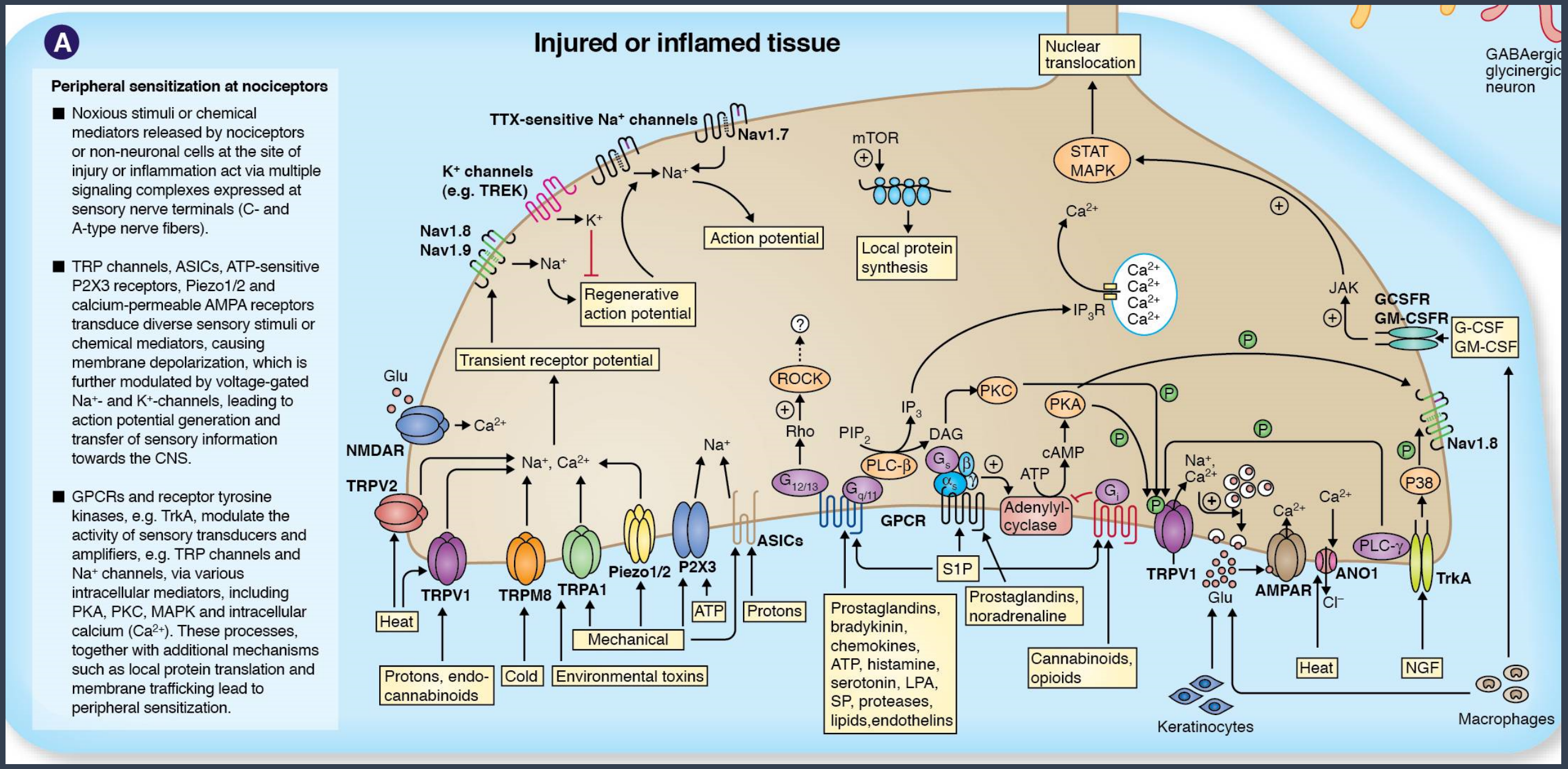
Marwan N. Baliki[1,*] and A. Vania Apkarian[1,2,3,*]
[1]Department of Physiology
[2]Department of Anesthesia
[3]Department of Physical Medicine and Rehabilitation
Feinberg School of Medicine, 303 East Chicago Avenue, Chicago, IL 60610, USA
*Correspondence: m-baliki@northwestern.edu (M.N.B.), a-apkarian@northwestern.edu (A.V.A.)
http://dx.doi.org/10.1016/j.neuron.2015.06.005



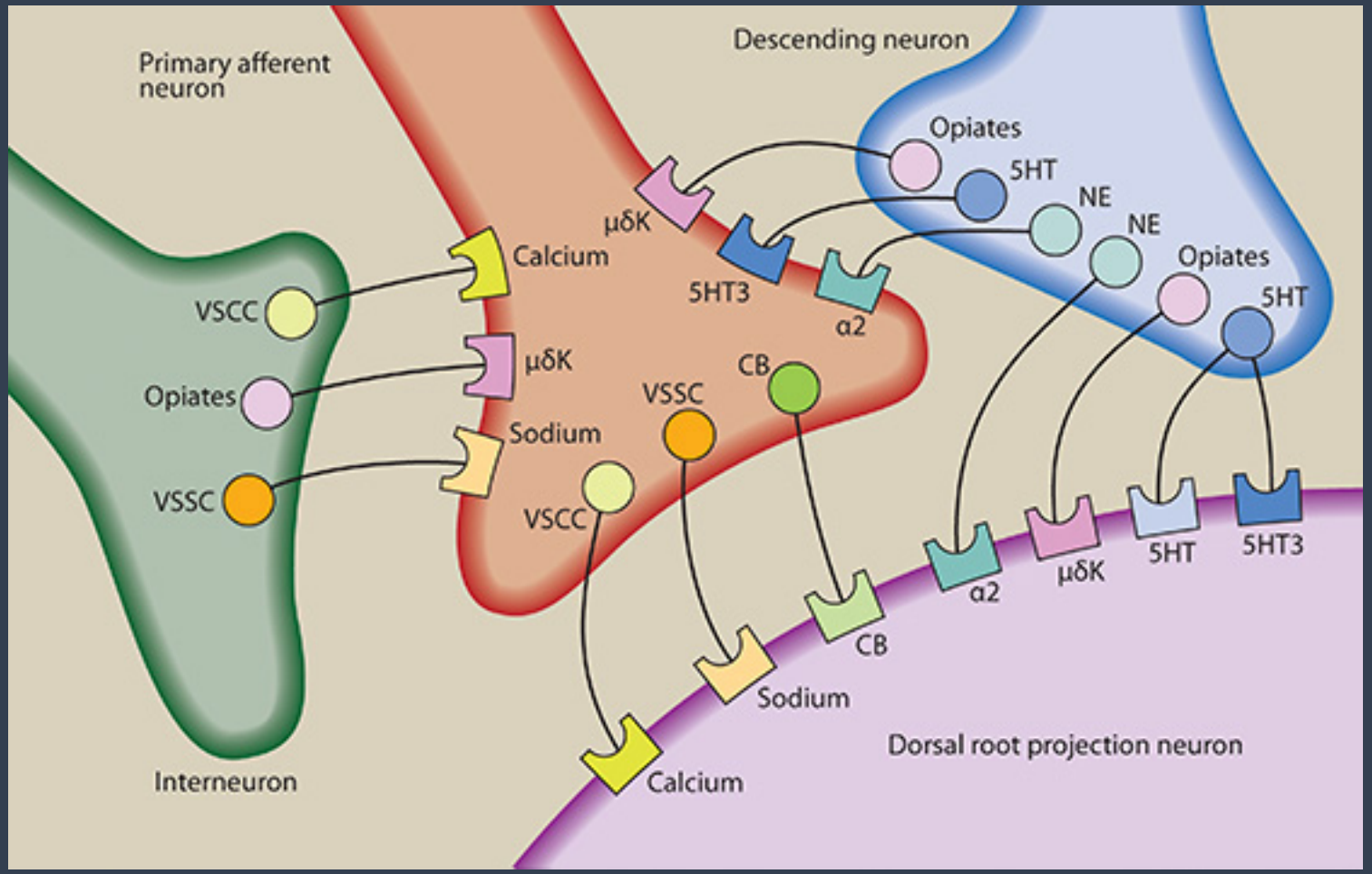
Peripheral Pain Triggers

- Injury
  - Trauma
  - Surgery
  - Overuse
- Disease processes
  - Arthritis
  - Ischemia
  - Neuropathies

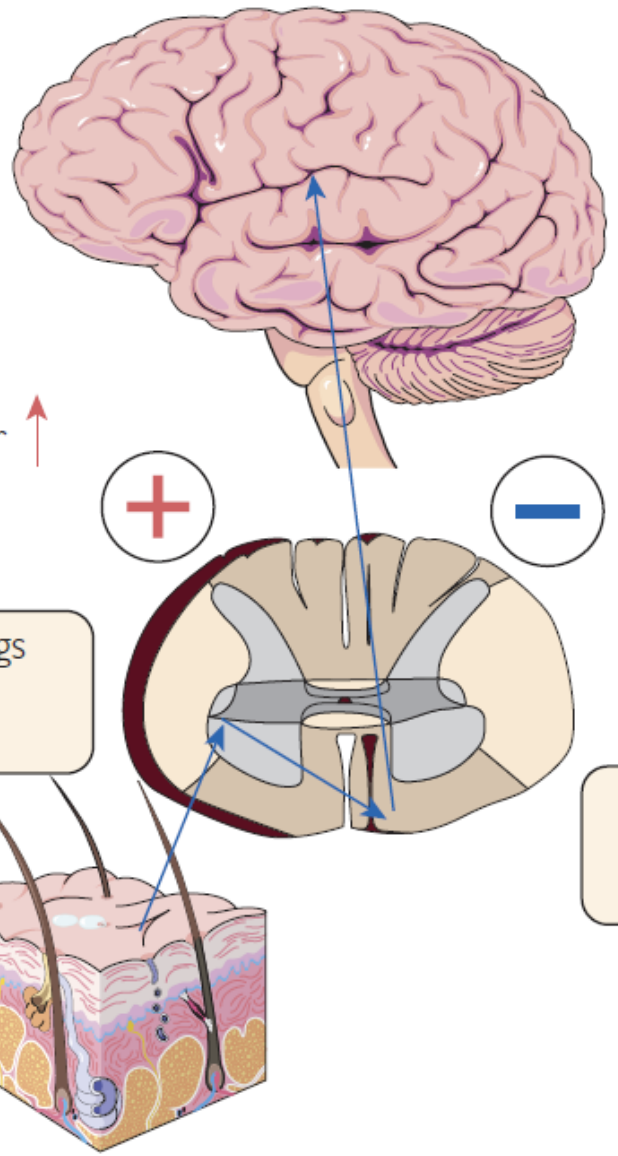
Peripheral Pain Mechanisms (Gangadharan & Khuner, 2013)



Spinal Pain Mechanisms



Central Pain Mechanisms



Generally facilitate pain transmission

Gabapentinoids, ketamine, memantine

- Glutamate
- Substance P
- Nerve growth factor
- Serotonin ($5HT_{2a, 3a}$)

Antimigraine drugs (–triptans), cyclobenzaprine

Generally inhibit pain transmission

- Descending antinociceptive pathways
  - Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine — Tricyclics, SNRIs. tramadol
  - Opioids — Low-dose naltrexone
- Cannabinoids — No knowledge of endocannabinoid activity, but this class of drugs is effective
- GABA — γ-Hydroxybutyrate, moderate alcohol consumption

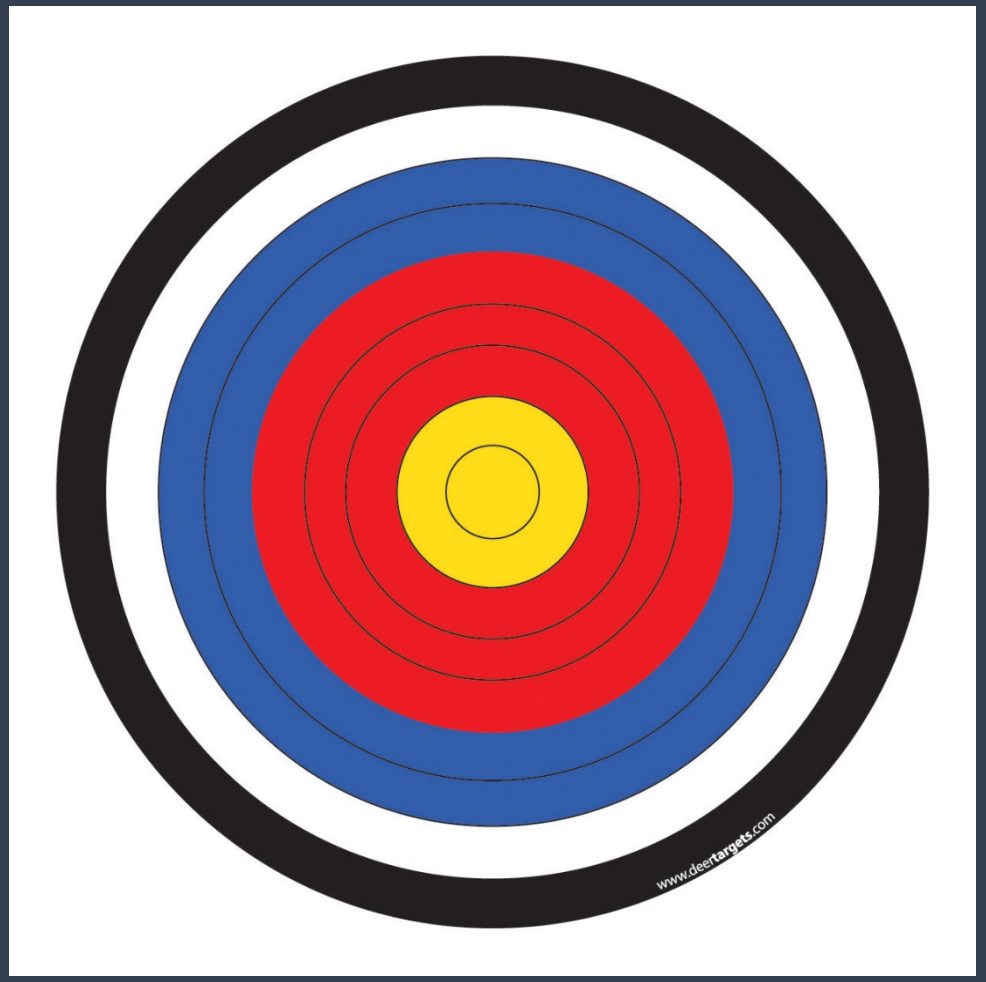
Clauw (2015) Mayo Clin Proc 90:680-92

Overview

- Conceptual Models of Pain
- Peripheral vs. central pain mechanisms
- **Body vs. brain based treatments**
- Conclusions & Recommendations

So, if peripheral (body) and central (brain) mechanisms are both potentially important…

Which do you target?



Available Pain Treatments

Medications (537 on Drug.com)	Surgeries/Procedures	Physical Modalities	Psychological Treatments	Alternative Therapies
NSAIDS	Epidurals	Ice/Heat	Self-management	Acupuncture
Local Anesthetics	Radiofrequency Nerve Lesioning	Electrical stimulation & TENS	Cognitive Behavioral Therapy	Therapeutic touch and Reiki
Opioids	Trigger Pt Injections	Traction	Relaxation	Tai Chi
Antidepressants	Facet joint injections	Ultrasound & Iontophoresis	Motivational interviewing	Herbal Remedies
Antiepileptics	SI joint injections	Laser/Light Therapy	Biofeedback	Aromatherapy
Capsaicin	Sympatholysis	Joint Mobilization	Mindfulness meditation	Nutritional therapy
Ketamine	Intrathecal pump implants	Manual Therapy & Chiropractic	Acceptance & Commitment Therapy	Dietary Supplements
Ziconotide	Spinal Cord Stimulation	Massage	Hypnosis	
Cannabinoids	Vertebral augmentation	Exercise	Resilience Training	
	Intradiscal denervation	Brain stimulation	Interpersonal psychotherapy	

Underlying Mechanisms in Chronic Pain States

Peripheral (nociceptive)
Pain due to inflammation or mechanical damage in tissues
Responsive to NSAIDS and opioids
Responds to procedures
Classic examples - Acute pain due to injury - Osteoarthritis - Rheumatoid arthritis

Underlying Mechanisms in Chronic Pain States

Peripheral (nociceptive)	Neuropathic
Pain due to inflammation or mechanical damage in tissues	Damage or entrapment of peripheral nerves
Responsive to NSAIDS and opioids	Responds to both peripheral and centrally acting pain therapies
Responds to procedures	Entrapment responds to surgery or injection
Classic examples - Acute pain due to injury - Osteoarthritis - Rheumatoid arthritis	Classic examples - Diabetic neuropathic pain - Postherpetic neuralgia

Adapted from Clauw (2015) Mayo Clin Proc 90:680-92

Underlying Mechanisms in Chronic Pain States

Peripheral (nociceptive)	Neuropathic	Centralized
Pain due to inflammation or mechanical damage in tissues	Damage or entrapment of peripheral nerves	Central disturbance in pain processing (diffuse hyperalgesia/ allodynia)
Responsive to NSAIDS and opioids	Responds to both peripheral and centrally acting pain therapies	Responsive to CNS-acting drugs altering neurotransmitters involved in pain, sleep, & mood disturbance
Responds to procedures	Entrapment responds to surgery or injection	Often characterized by presence of multiple pain conditions
Classic examples - Acute pain due to injury - Osteoarthritis - Rheumatoid arthritis	Classic examples - Diabetic neuropathic pain - Postherpetic neuralgia	Classic examples - Fibromyalgia - Irritable bowel syndrome - Temporomandibular disorder - Tension headache

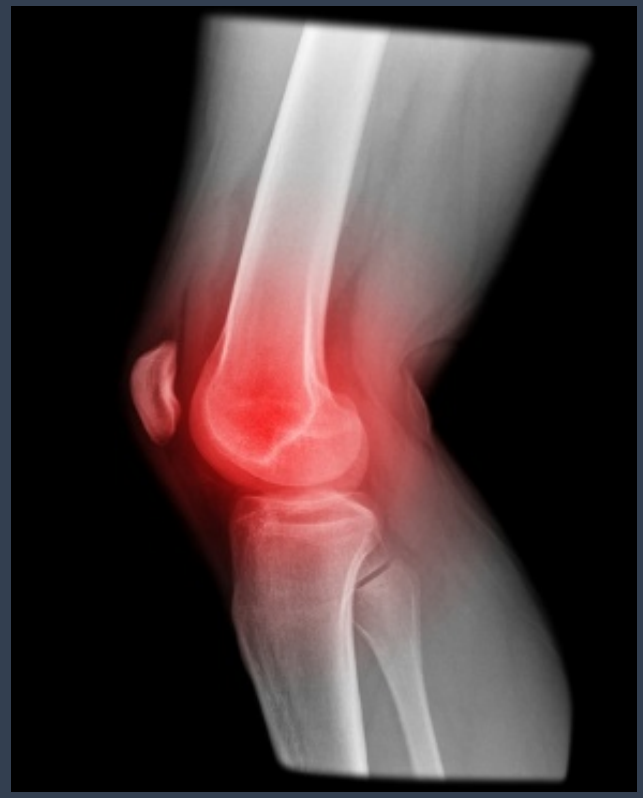
Adapted from Clauw (2015) Mayo Clin Proc 90:680-92

Case Scenario

- Dolores is 57 years old and reports bilateral knee pain, left worse than right. Pain has been present for more than a year but increasingly interferes with activities in the last few months.
- Dolores is generally healthy but has a BMI of 31.5 and has well-controlled hypertension.
- Radiographs reveal moderate knee OA in both joints

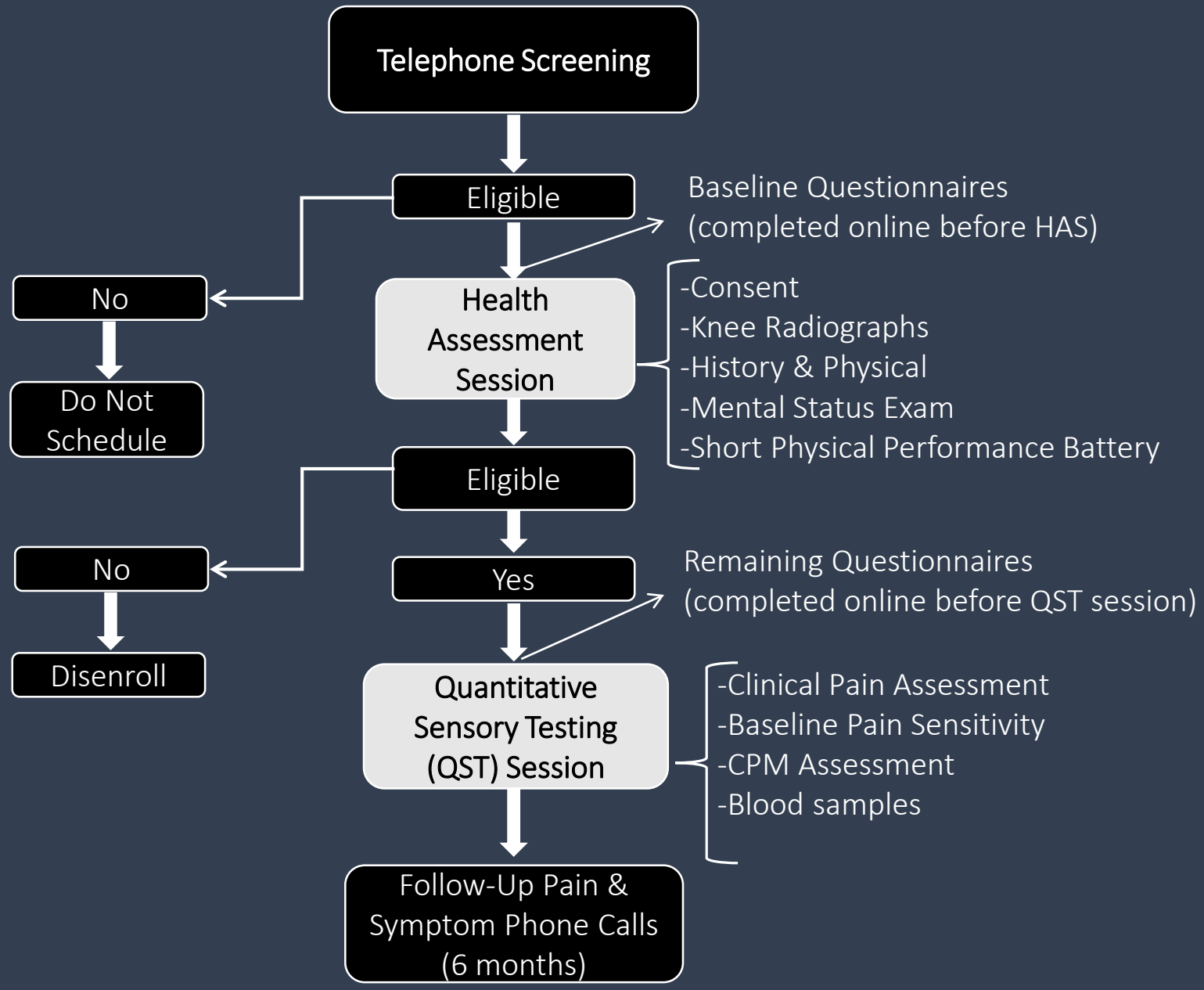
The Example of Knee Osteoarthritis (OA)

- Leading cause of disability in older adults
- Classically viewed as peripherally-based
- Treatments are often been body-based
  - NSAIDS
  - Injections
  - Joint replacement



Understanding Pain and Limitations in OsteoArthritic Disease (UPLOAD) Study

- Two-site study designed to assess biopsychosocial factors contributing to ethnic group differences in knee OA-related pain and disability.


Telephone Screening
Eligible
Baseline Questionnaires
(completed online before HAS)
No
Do Not Schedule
Health Assessment Session
-Consent
-Knee Radiographs
-History & Physical
-Mental Status Exam
-Short Physical Performance Battery
Eligible
No
Disenroll
Yes
Remaining Questionnaires
(completed online before QST session)
Quantitative Sensory Testing (QST) Session
-Clinical Pain Assessment
-Baseline Pain Sensitivity
-CPM Assessment
-Blood samples
Follow-Up Pain & Symptom Phone Calls (6 months)

QST Session

Thermal Pain Testing*	• Heat pain threshold & tolerance • Temporal summation (TS) at three temperatures
Mechanical Pain Testing*	• Pressure pain thresholds • Punctate mechanical pain & TS
Cold Pressor Pain	• Cold pressor pain at 8, 12, 16 deg C • Ratings obtained at 30 sec & 1-minute
Conditioned Pain Modulation	• Heat TS (left hand) before & after 1-minute immersion in cold water (right hand)

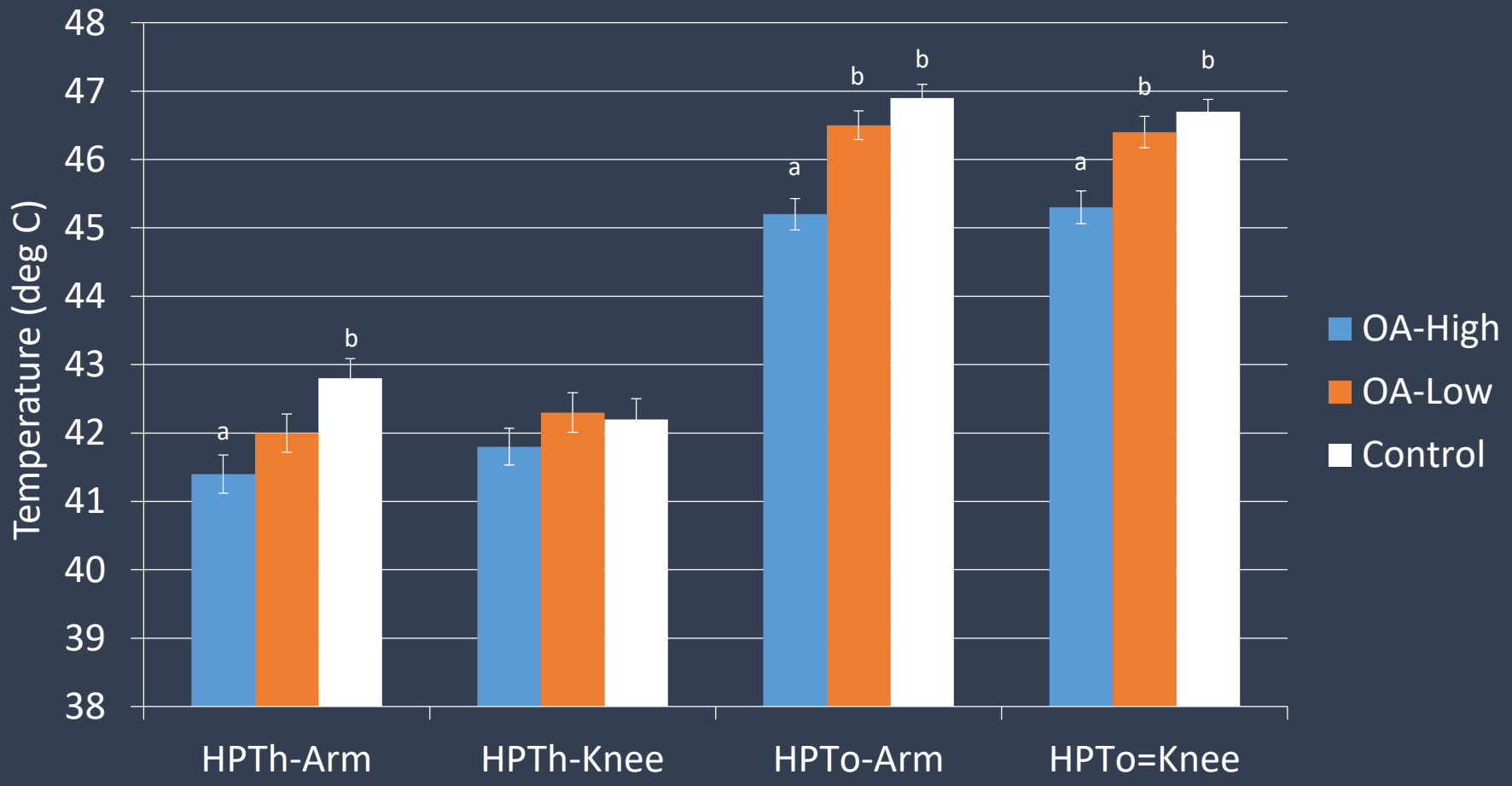
*Thermal and mechanical testing performed on most affected knee and unaffected body sites

Descriptive Statistics

Variable	OA High Pain* (n=155)	OA Low Pain* (n=129)	Controls (n=119)
Demographic Variables			
Age (Years)	55.4 (7.1)	58.4 (7.9)	57.4 (8.0)
Sex (% Female)	65.3	64.8	63.9
Race (% White)*	27.3	39.2	70.6
Clinical Variables			
GCPS-Characteristic Pain (0-100)	67.7 (14.1)	30.6 (12.7)	10.2 (16.8)
GCPS-Disability (0-100)	59.7 (24.5)	24.6 (21.7)	2.1 (7.0)
WOMAC-Pain (0-20)	9.8 (4.1)	4.5 (2.8)	0.6 (1.7)
WOMAC-Physical Function (0-)	31.8 (13.7)	13.9 (10.2)	1.8 (4.8)
SPPB Total Score	9.2 (2.1)	10.5 (1.5)	10.9 (1.4)
CES-D Scores	11.8 (8.3)	7.6 (6.4)	6.5 (6.7)

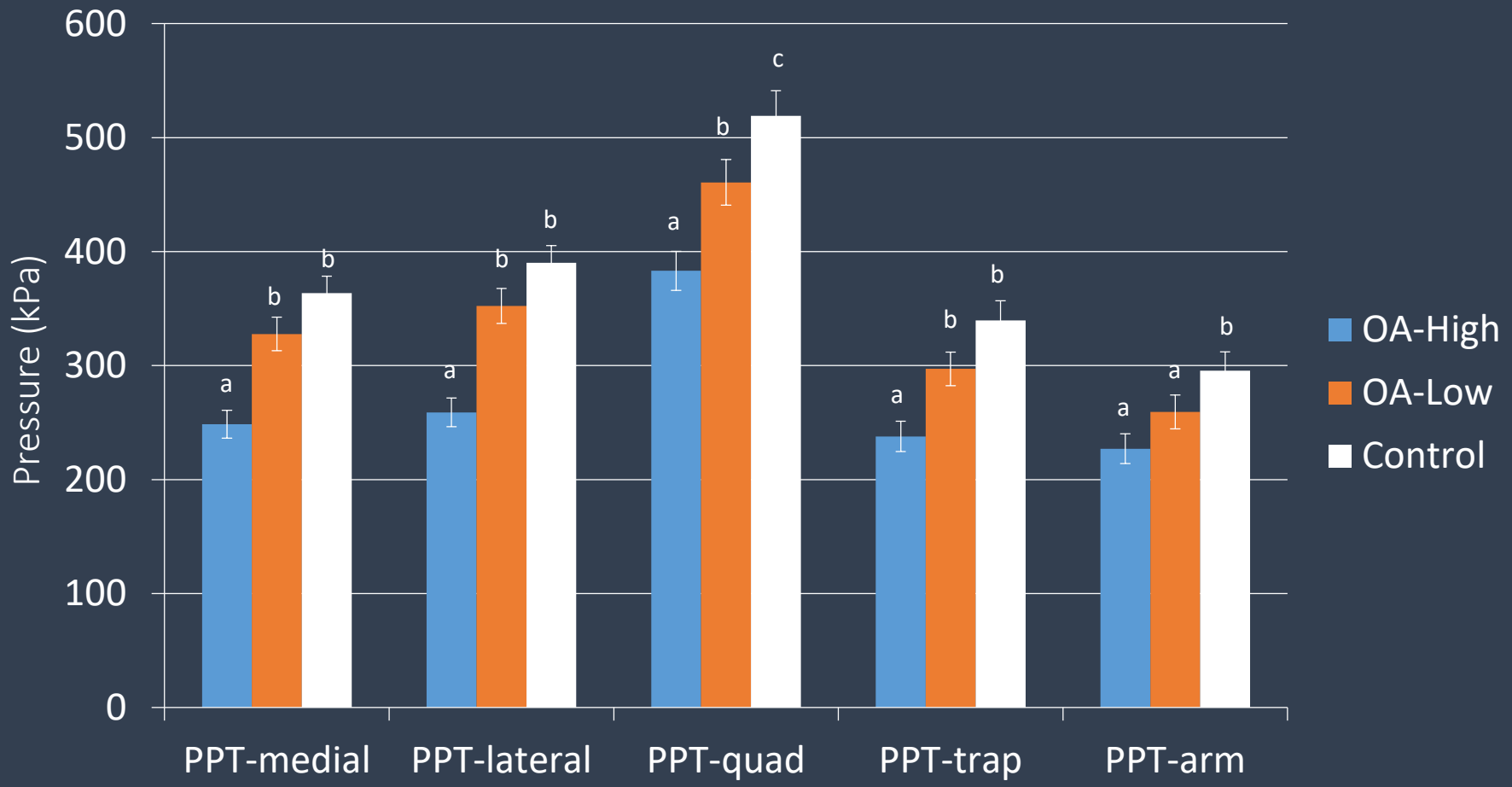
* High vs. low OA pain based on median split of GCPS-Characteristic Pain Score (median=50)

Heat Pain Thresholds and Tolerances for OA Patients and Controls



Groups with unlike letters differ from each other, $p < 0.05$

Pressure Pain Thresholds for OA Patients and Controls



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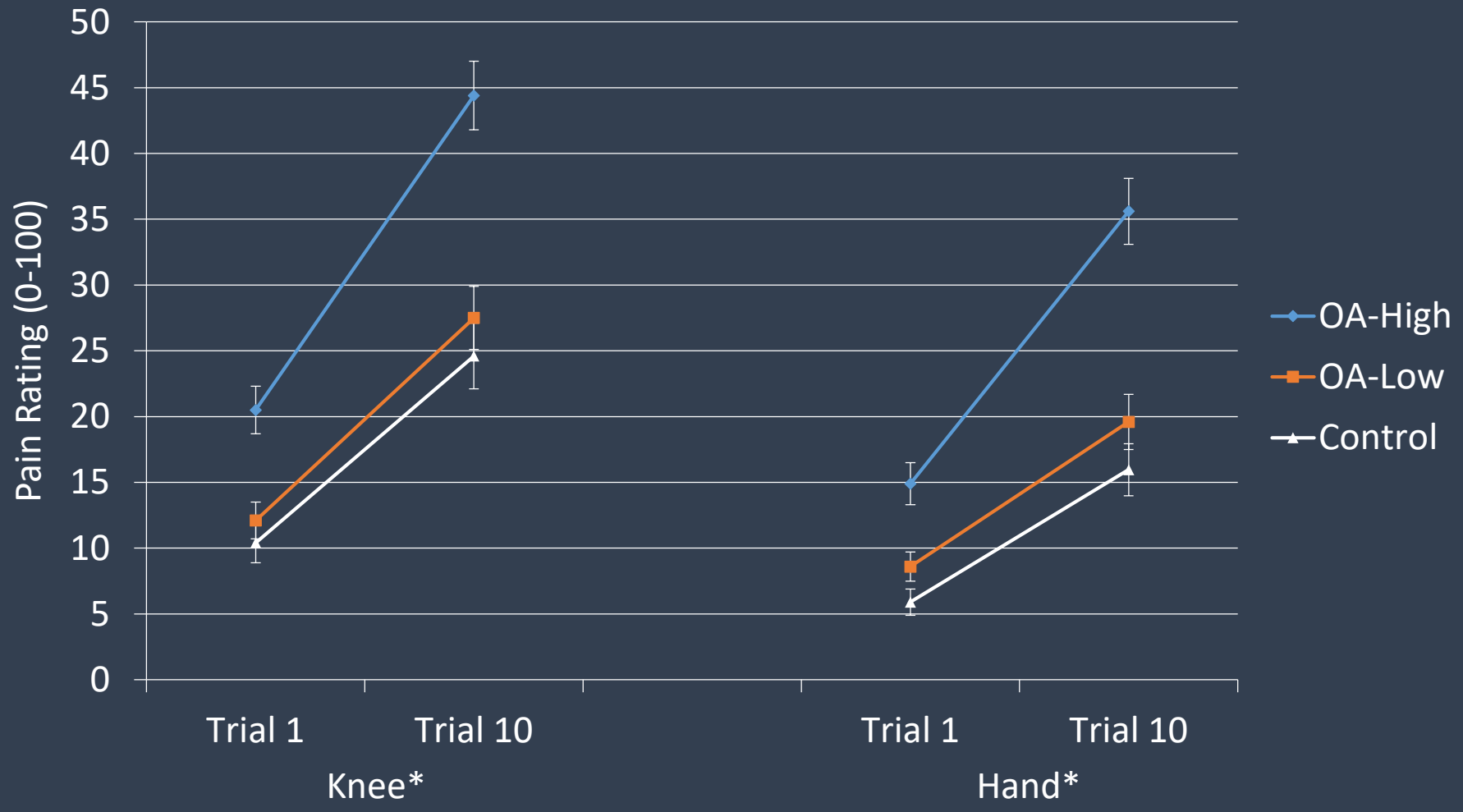
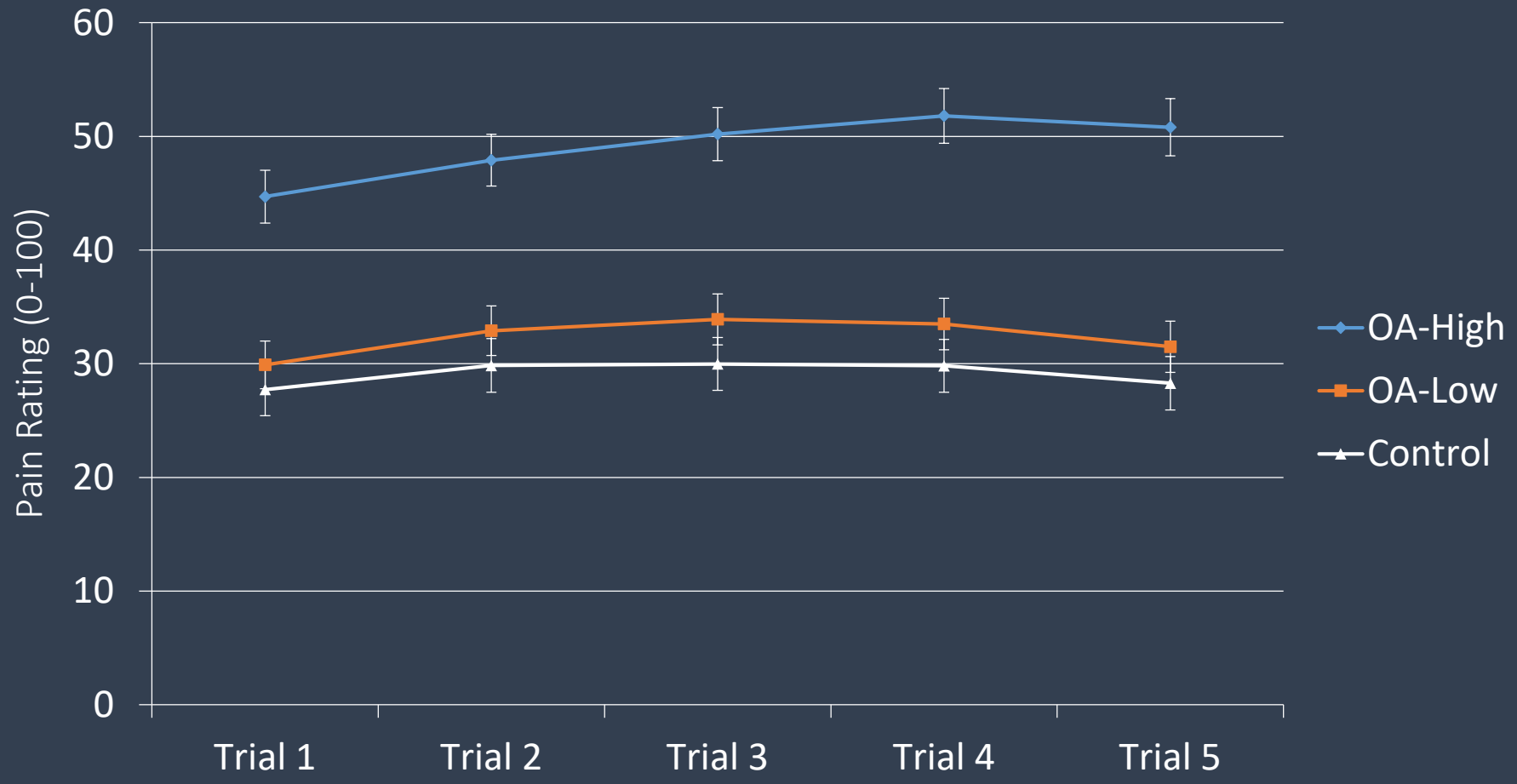
Punctate Mechanical Pain for OA Patients and Controls



*OA-High differs from the other two groups in both average rating and slope ($p < 0.05$)

Temporal Summation of Heat Pain for OA Patients and Controls



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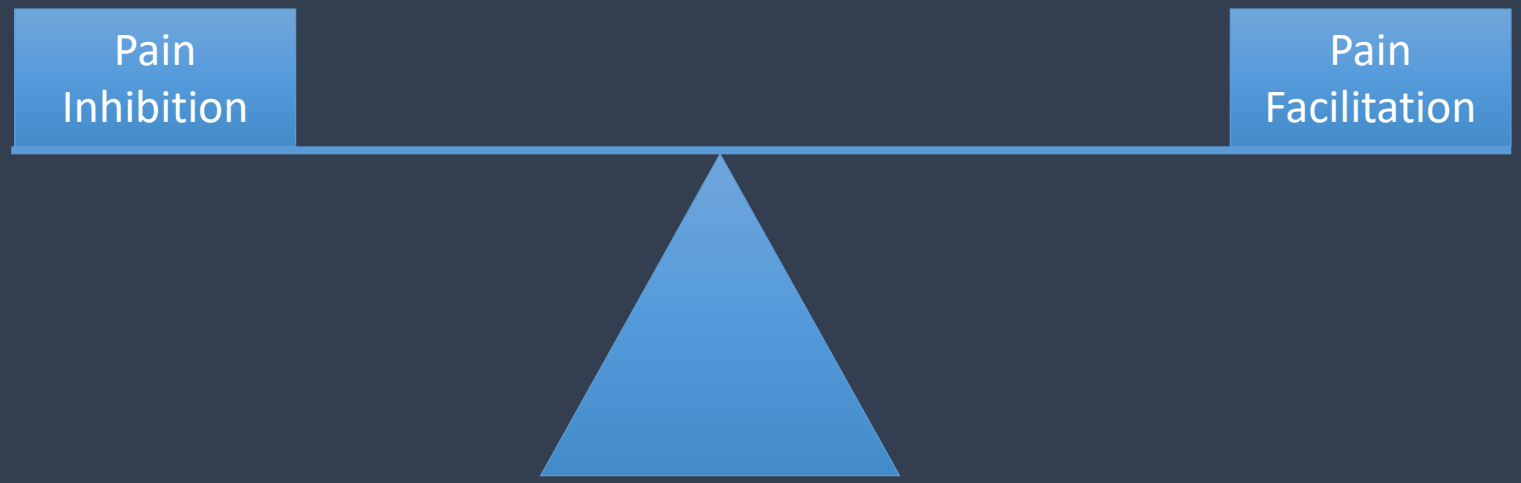
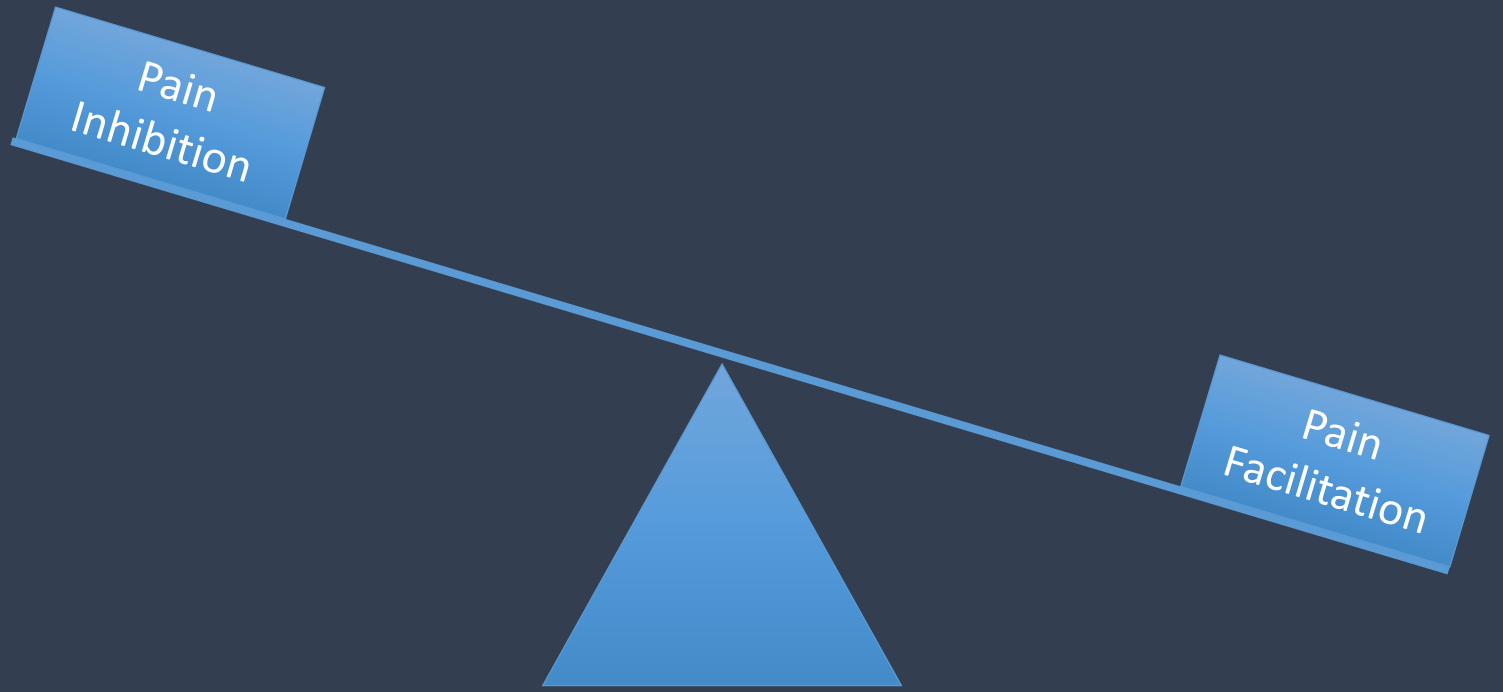
Pain Modulatory Balance



Pain Modulatory Imbalance



Arthritis Care & Research
Vol. 65, No. 11, November 2013, pp 1786–1794
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ORIGINAL ARTICLE

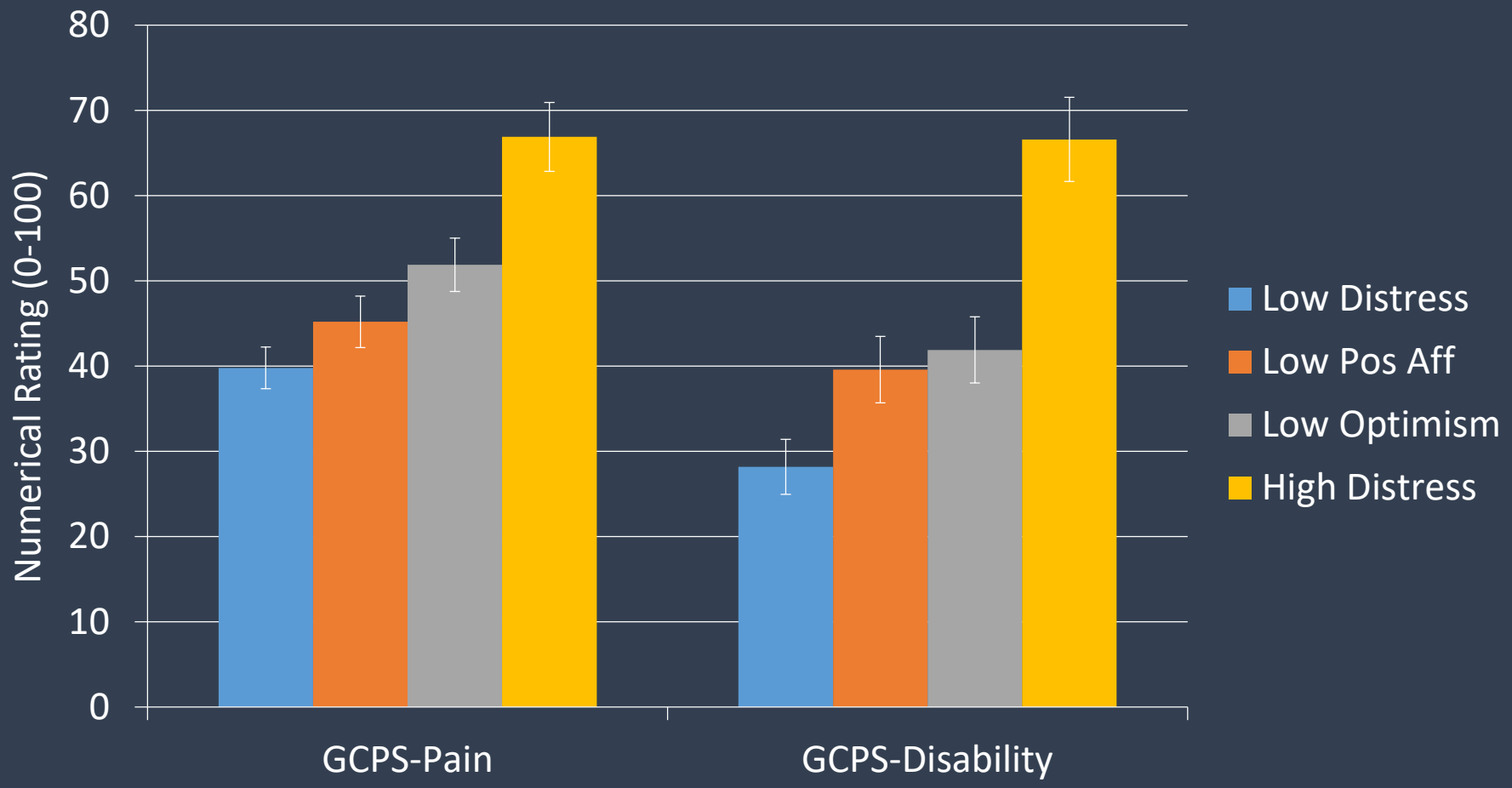
Psychological Profiles and Pain Characteristics of Older Adults With Knee Osteoarthritis

YENISEL CRUZ-ALMEIDA,[1] CHRISTOPHER D. KING,[1] BUREL R. GOODIN,[2] KIMBERLY T. SIBILLE,[1] TONI L. GLOVER,[1] JOSEPH L. RILEY,[1] ADRIANA SOTOLONGO,[2] MATTHEW S. HERBERT,[2] JESSICA SCHMIDT,[2] BARRI J. FESSLER,[2] DAVID T. REDDEN,[2] ROLAND STAUD,[1] LAURENCE A. BRADLEY,[2] AND ROGER B. FILLINGIM[1]

Psychological Profiles Among OA Patients

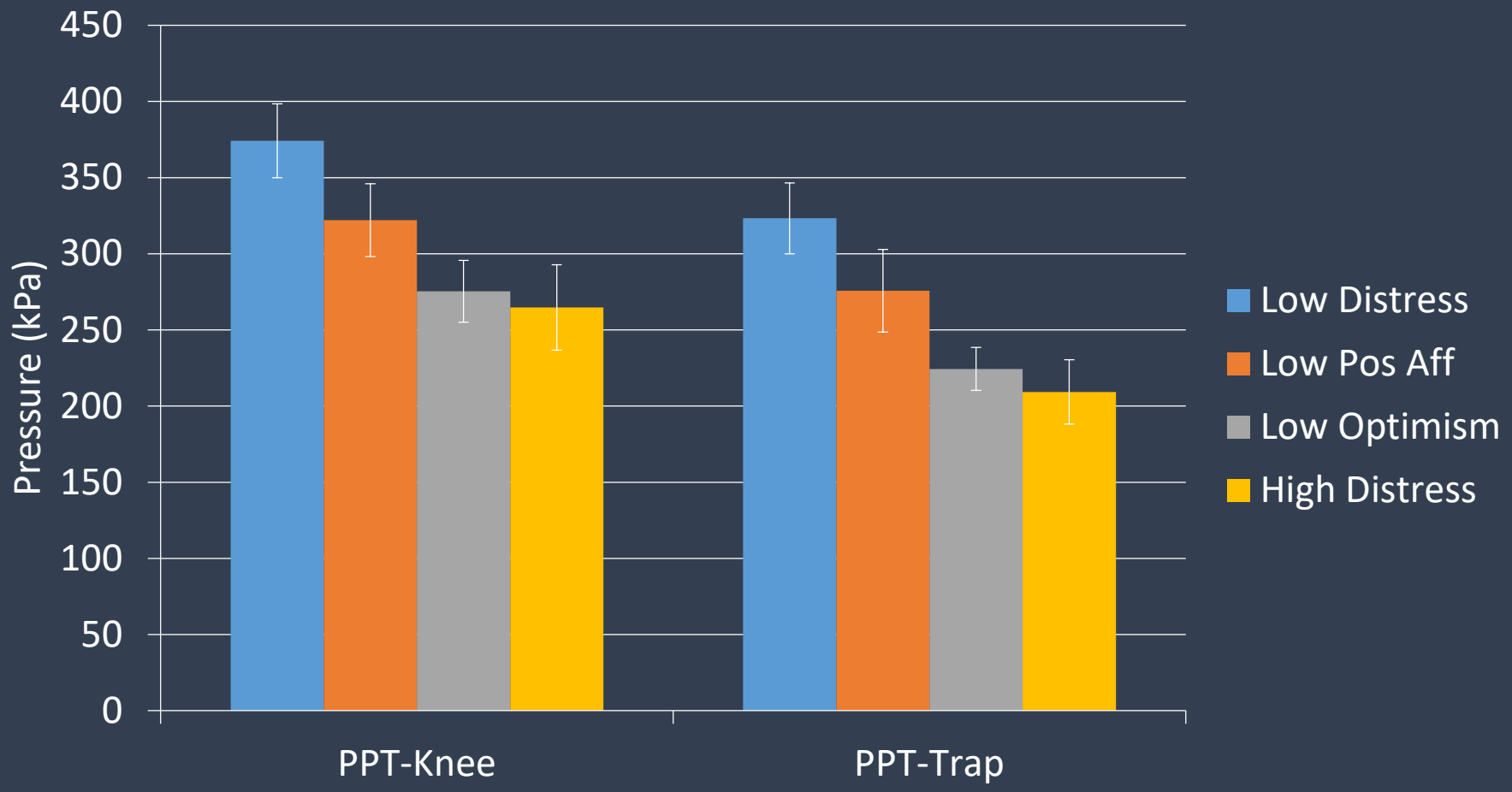
Measures	Cluster 1 Low Distress (*n*=54)	Cluster 2 Low Pos Aff (*n*=45)	Cluster 3 Low Optim (*n*=63)	Cluster 4 High Distress (*n*=32)	p-value
CSQ-R: Active	3.0 (0.9)	2.7 (1.0)	3.1 (1.0)	2.9 (1.0)	0.297
CSQ-R: Passive	1.9 (1.2) [a,b]	2.5 (1.0) [d,e]	3.3 (1.3)	3.7 (1.1)	**0.001**
KRS-18	66.8 (7.5) [a,b,c]	85.3 (7.0) [d,e]	75.4 (7.8) [f]	91.5 (10.8)	**0.001**
PVAQ	30.7 (9.1) [a,b]	34.0 (8.9) [d,e]	54.9 (7.5) [f]	63.0 (8.4)	**0.001**
CES-D	6.4 (5.5) [a,c]	10.6 (7.6)	9.3 (5.9)	12.4 (10.2)	**0.001**
PANAS: Positive	39.2 (7.0) [c]	35.0 (6.8) [d,e]	39.6 (7.3)	39.1 (6.2)	**0.001**
PANAS: Negative	13.4 (4.2) [a,b]	15.8 (3.9)	16.0 (6.9)	16.2 (4.9)	**0.001**
STAXI Trait	15.7 (2.2) [a]	16.3 (2.3)	16.3 (2.9)	18.1 (6.8)	**0.024**
LOT-R	19.1 (4.7) [b]	17.4 (4.2)	16.4 (3.7)	17.8 (4.1)	**0.001**

Clinical Pain and Disability across Clusters



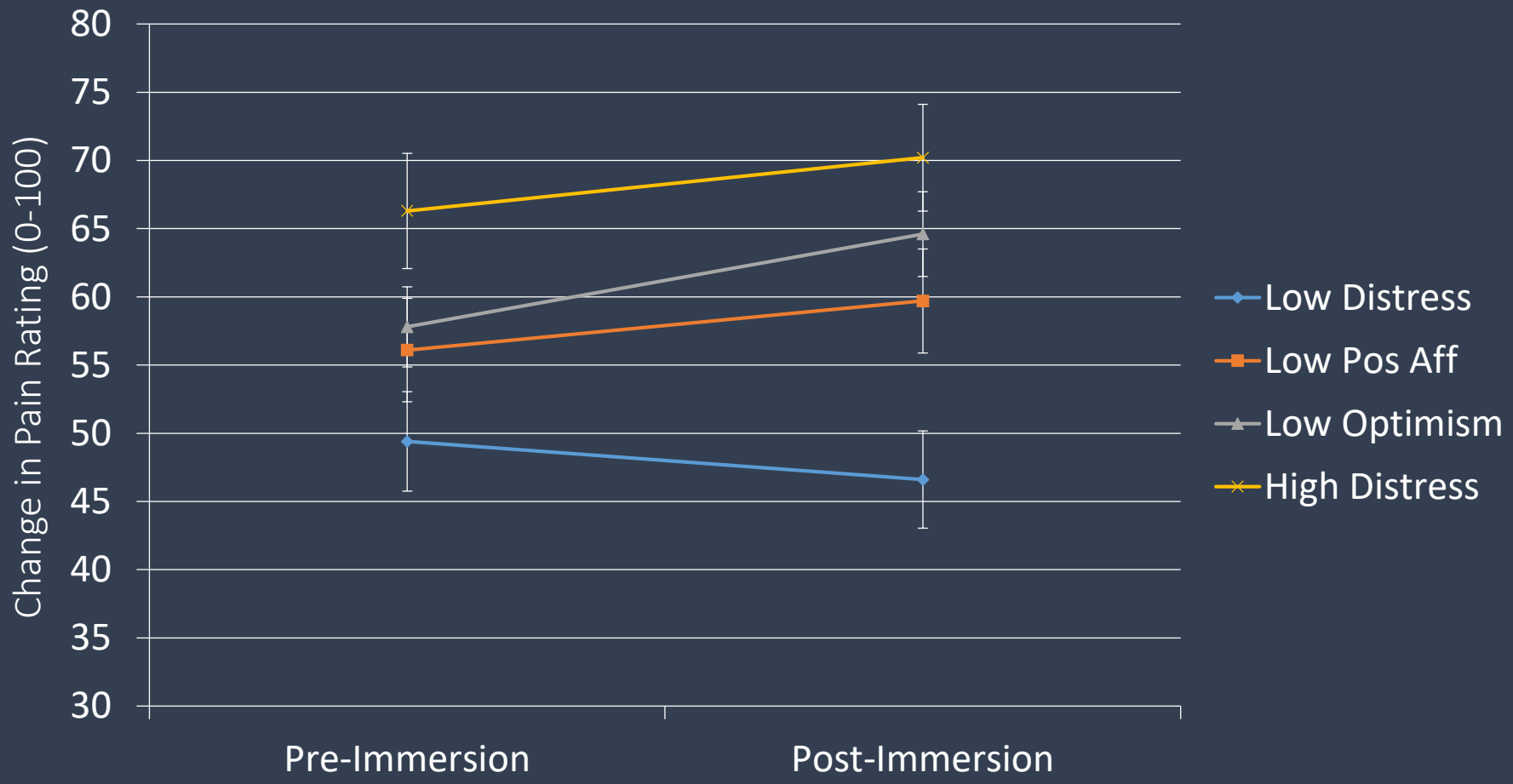
Low Distress and High Distress differ from all other clusters, p's < 0.05

Pressure Pain Thresholds Across Clusters



Low Distress differs from High Distress for both sites, p's < 0.05

Conditioned Pain Modulation Across Clusters



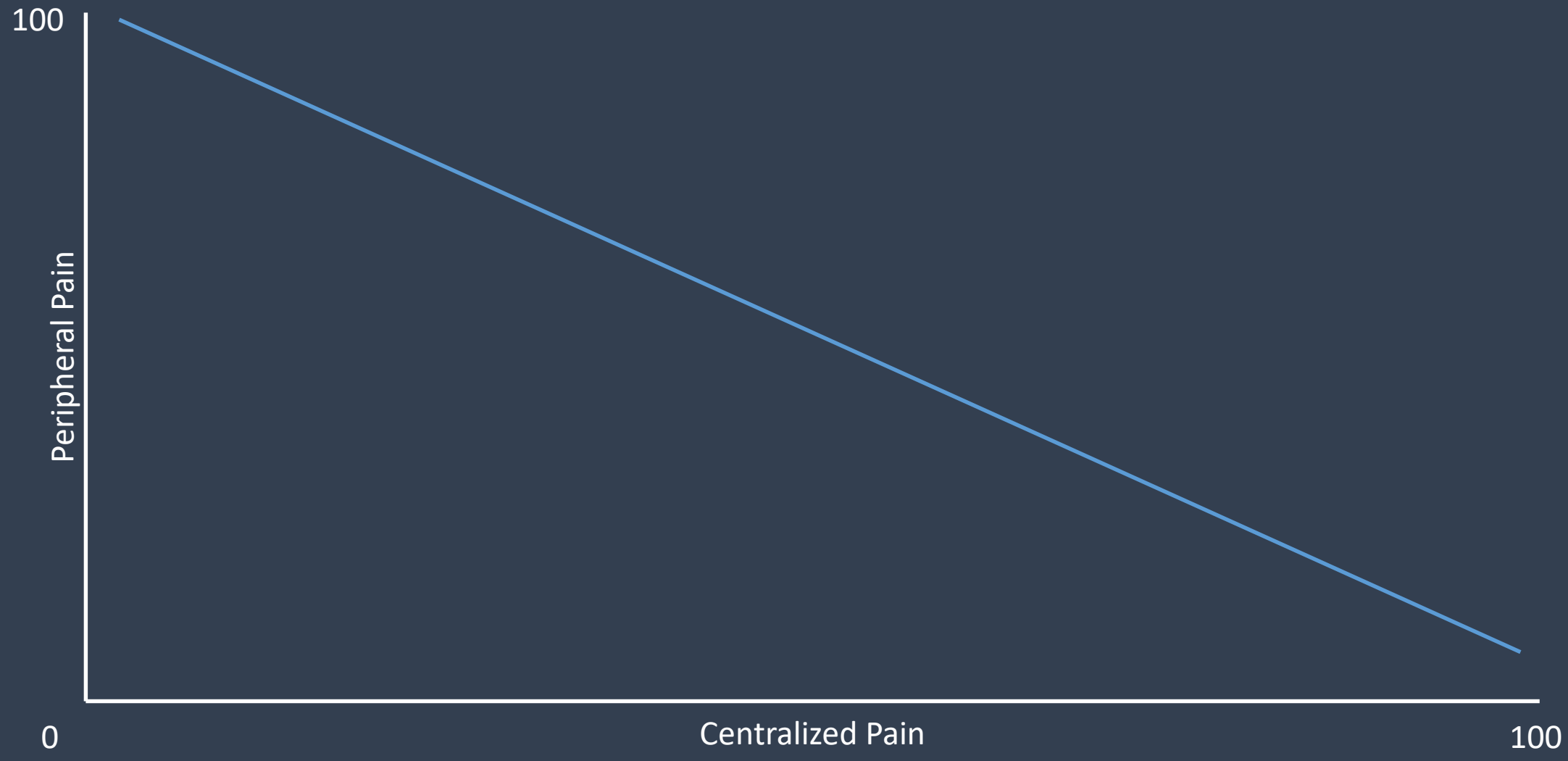
Low Distress differs from High Distress, $p < 0.05$

Case Scenario

- Dolores is 57 years old and reports bilateral knee pain, left worse than right. Pain has been present for more than a year but increasingly interferes with activities in the last few months
- Dolores is generally healthy but has a BMI of 31.5 and has well-controlled hypertension
- Radiographs reveal moderate knee OA in both joints

What else do you need to know?

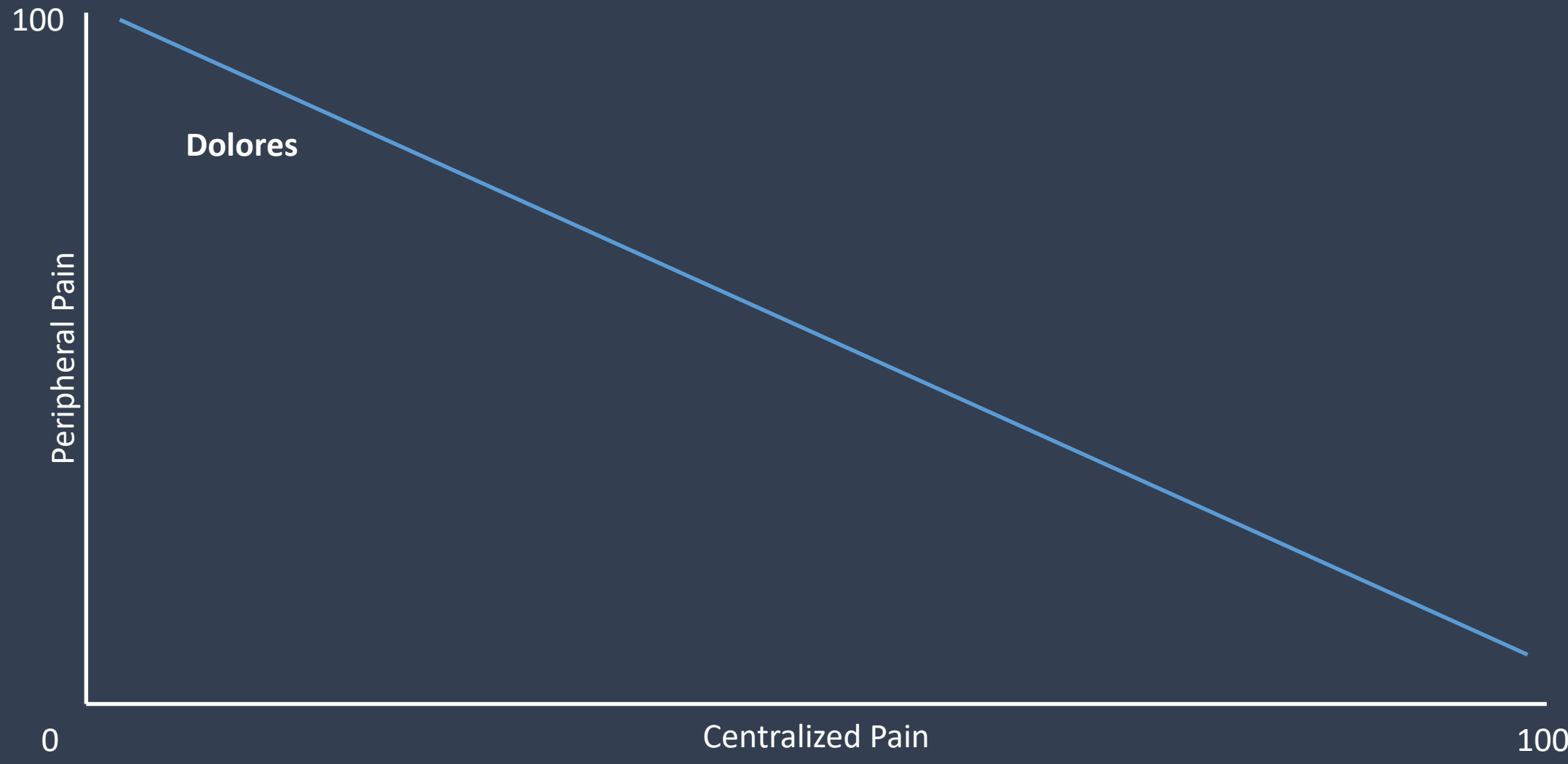
Where on the Continuum Does Dolores Fall?



How Do You Assess for Centralized Pain?

- Pain body map
- Somatic symptoms
- Psychological function
- Quantitative sensory testing
  - Manual palpation

Where on the Continuum Does Dolores Fall?



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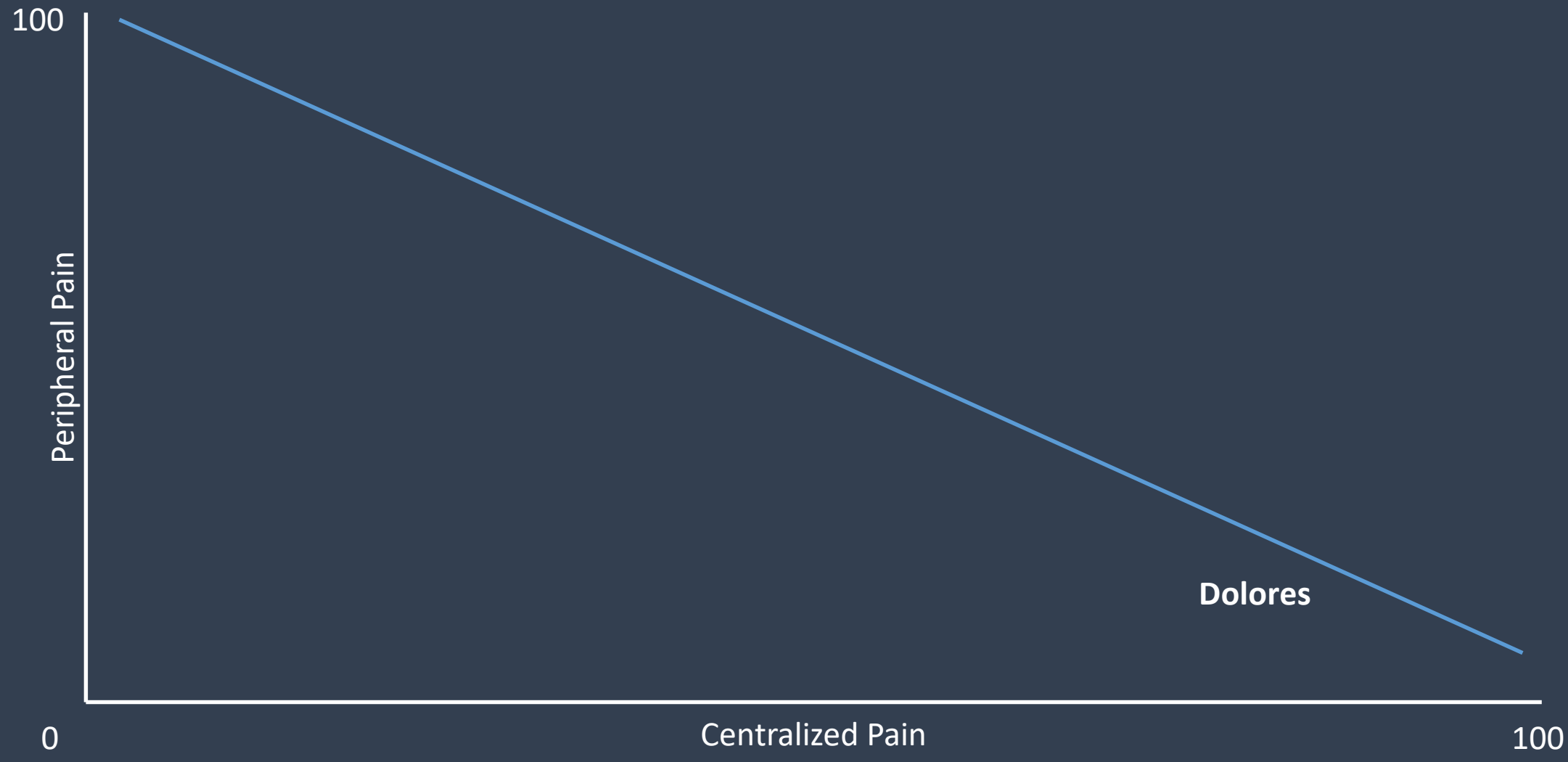
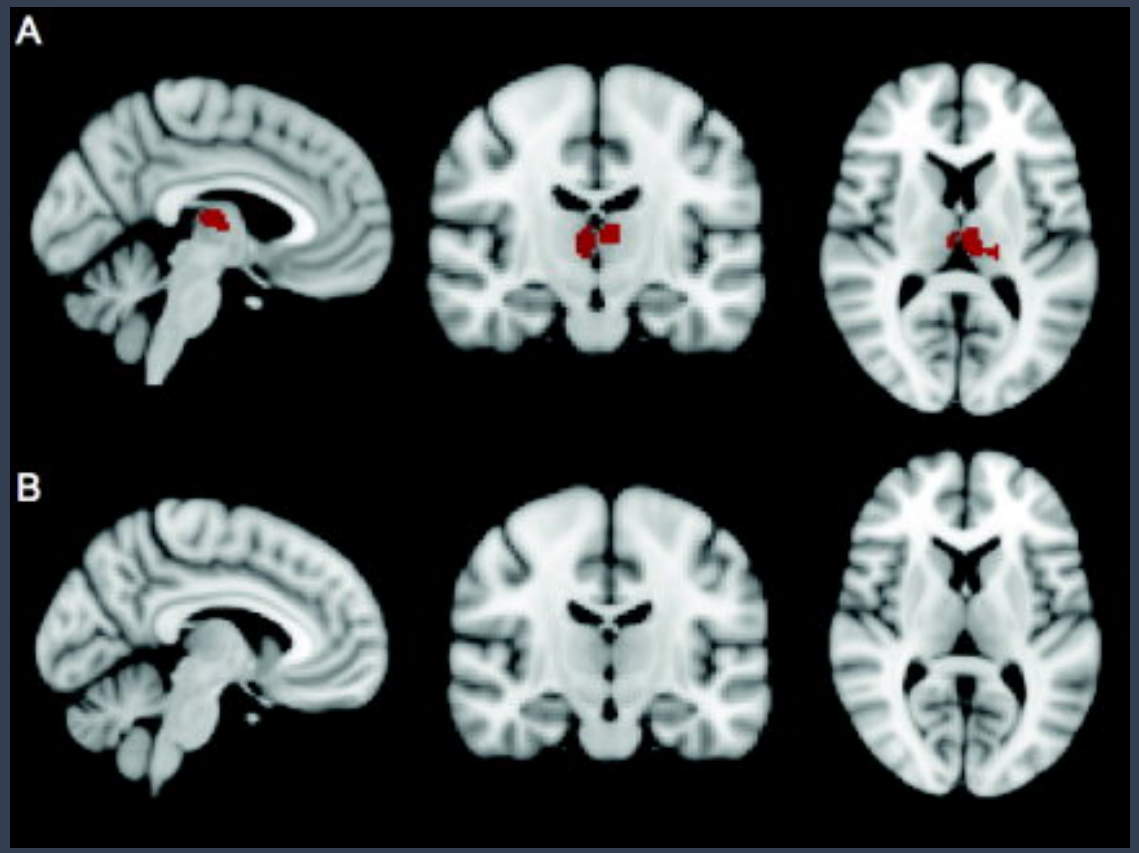


Body vs. Brain Based Treatments?



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Thalamic Atrophy Associated With Painful Osteoarthritis of the Hip Is Reversible After Arthroplasty

A Longitudinal Voxel-Based Morphometric Study

Stephen E. Gwilym, Nicola Filippini, Gwenaelle Douaud, Andrew J. Carr, and Irene Tracey

A. Thalamic gray matter volume in hip OA patients before and after arthroplasty. Results show a significant increase in thalamic gray matter volume after surgery ($P < 0.05$, with correction for multiple comparisons)

B. Contrast of patients vs. controls in the thalamus demonstrates that the atrophy identified preoperatively was no longer present 9 months after surgery

Do These Treatments Target the Body or the Brain?

- NSAIDS
- Weight loss
- Exercise
- Meditation
- Arthroplasty

Summary

- Available pain treatments target the body, brain or (more commonly) both
- Matching treatments to the patient's pain mechanisms will improve outcomes
- While pain conditions are often thought of as peripheral vs. central, phenotyping each patient is necessary
- Simple methods are available to identify centralized pain

Thank You