The Development of Treatments for Pain

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Disclosures

- Consulting
  - Pfizer, Forest, Eli Lilly, Pierre Fabre, Cypress Biosciences, Wyeth, UCB, Astra Zeneca, Merck, J & J, Nuvo, Jazz, Abbott, Cerephex, Iroko, Tonix, Theravance, IMC, Zynerba, Sammumed, Astellas, Aptinyx
- Research support
  - Pfizer, Cypress Biosciences, Forest, Merck, Nuvo, Cerephex
- One-time licensing fee paid to University of Michigan by Eli Lilly

The Development of Treatments for Pain

- Analgesic drug development
- Contemporary view of pain
- Opioid addiction has become a significant public health problem but is a small part of the overall problem in treating chronic pain patients
  - Used far too early and often because providers do not feel comfortable diagnosing and treating pain
  - Patients who feel that they are deriving a benefit but an objective appraisal of benefit:harm suggests otherwise
  - Tolerance/opioid induced hyperalgesia
- Summary

The Development of Treatments for Pain

- **Analgesic drug development**
- Contemporary view of pain
- Opioid addiction has become a significant public health problem but is a small part of the overall problem in treating chronic pain patients
  - Tolerance
  - Misuse
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- Summary

Analgesic Drug Development

- Widely acknowledged to be abject failure
  - Not for a lack of trying
  - Many companies have left this space because of lack of success
- Most commonly used analgesics in 2016 are derivatives of drug classes known to be analgesics for centuries or decades
  - NSAIDs, opioids, cannabinoids, tricyclics
- Why is this?

Reasons for Unsuccessful Analgesic Development

- Animal models are still largely unchanged despite tremendous advances in our understanding of pain
- Most models are models of nociception rather than pain and as such focus on peripheral mechanisms
- Newer operant models will likely be more predictive of analgesic efficacy but these are rarely used at present and are not as amenable to high-throughput screening
- Most companies have not yet integrated modern pain clinical research techniques (e.g. neuroimaging) into their development programs

The Development of Treatments for Pain

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  - Tolerance
  - Misuse
  - Patients who feel that are deriving a benefit but an objective appraisal of benefit:harm suggests otherwise
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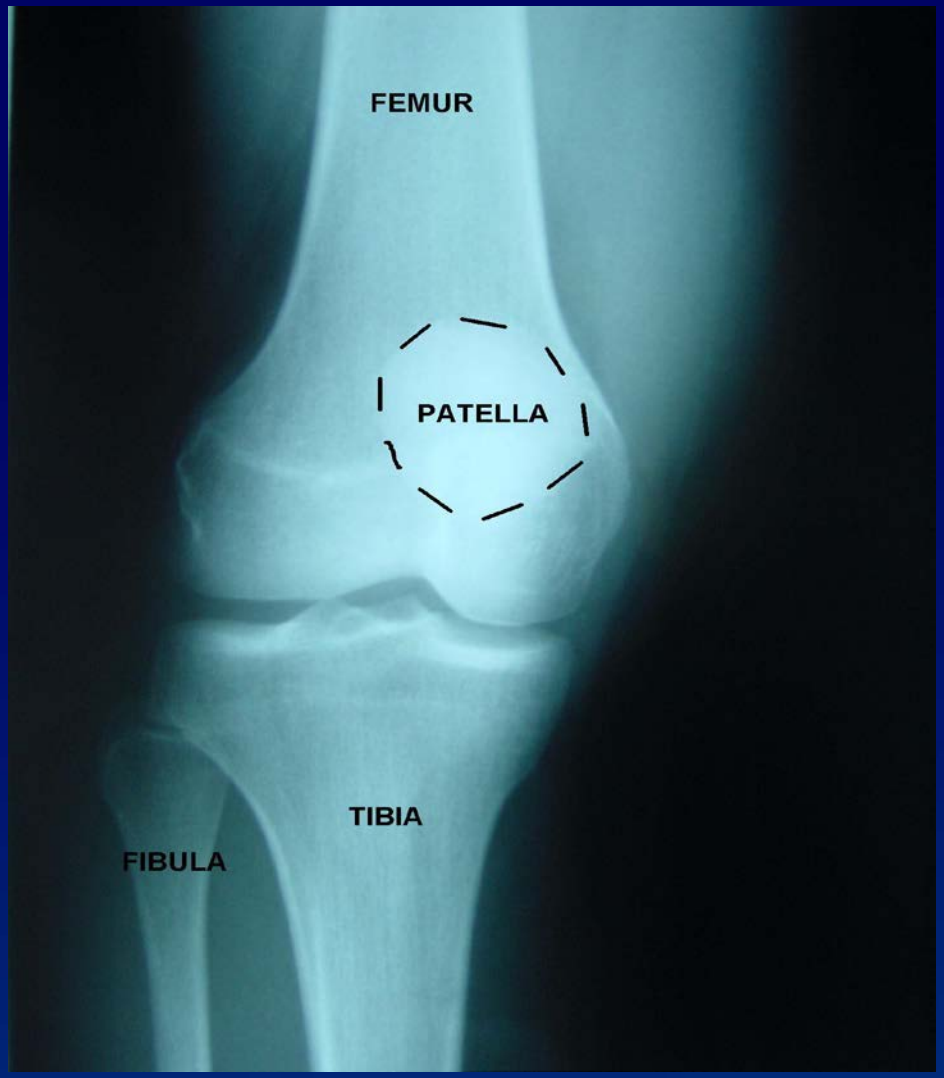
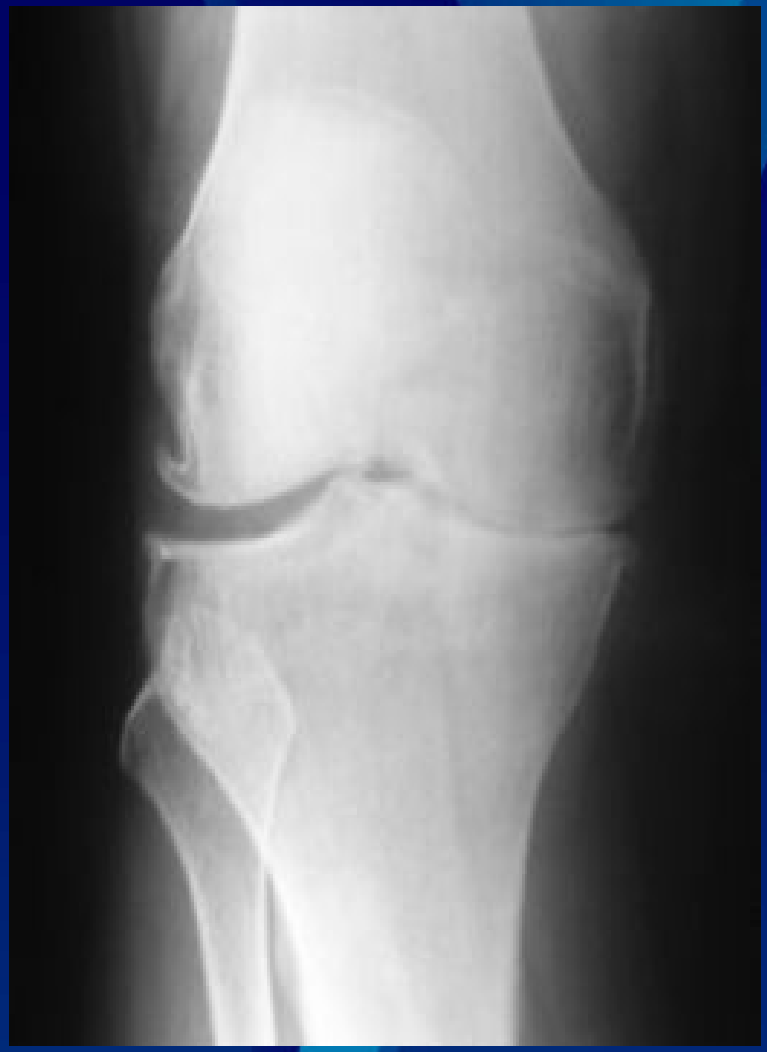
Which person has pain?





Osteoarthritis of the knee - I

- Classic “peripheral” pain syndrome
- Poor relationship between structural abnormalities and symptoms[1]. In population-based studies:
  - 30 – 40% of individuals who have grade 3/4 K/L radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure[2]
- We sometimes delude ourselves into thinking that our current therapies are adequate
  - NSAIDs, acetaminophen, and even opioids have small effect sizes[3,4]
  - Arthroplasty does not predictably relieve pain

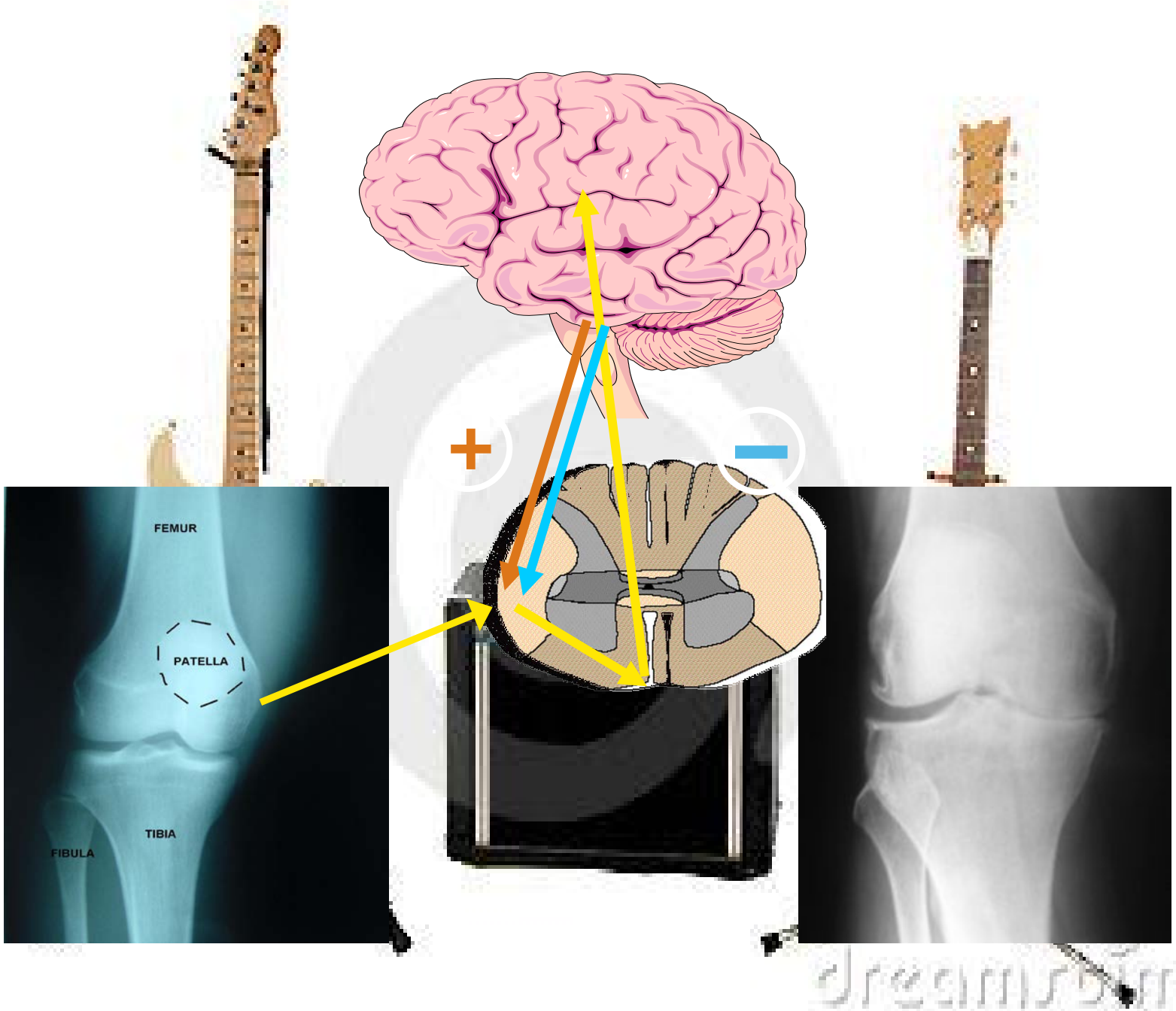
(1) Creamer P, et. al. Br J Rheumatol 1997; 36(7):726-8. (2) Creamer P, et. al. Arthritis Care Res 1998; 11(1):60-5. (3) Bjordal JM, et. al. Eur J Pain 2007; 11(2):125-38. (4) Zhang W, et. al. Ann Rheum Dis 2004; 63(8):901-7.

Mechanistic Characterization of Pain

Any combination may be present in a given individual

Peripheral (nociceptive)	Peripheral Neuropathic	Centralized Pain
▪ Inflammation or mechanical damage in tissues ▪ NSAID, opioid responsive ▪ Responds to procedures	▪ Damage or dysfunction of peripheral nerves ▪ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy	▪ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia) ▪ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission
▪ Classic examples ▪ Acute pain due to injury ▪ Osteoarthritis ▪ Rheumatoid arthritis ▪ Cancer pain	▪ Classic examples ▪ Diabetic neuropathic pain ▪ Post-herpetic neuralgia	▪ Classic examples ▪ Fibromyalgia ▪ Irritable bowel syndrome ▪ TMJD ▪ Tension headache

Mixed Pain States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Centralized pain states - I

- This is an acknowledged misnomer
- In aggregate this may be the most common and costly illness in humans
- It is a chronic multi-symptom illness that typically begins in childhood or young adulthood
- Characterized by:
  - Chronic pain or irritation in various body regions (headache, irritable bowel, temporomandibular joint disorder, interstitial cystitis, etc.) that moves throughout the body over the life of the individual
  - Multiple other somatic symptoms of CNS origin (fatigue, sleep, mood, memory)
  - Sensitivity to sensory stimuli a common symptom

Centralized pain states - II

- This goes by many names and in aggregate is extremely common:
  - **Chronic Overlapping Conditions** – FM, IBS, HA, TMJD, interstitial cystitis, dry eye disease (NIH PA 14-244)
  - **By the stressful trigger**
    - Post-deployment this is called Gulf War Syndrome (first Gulf War) or mild TBI (current conflicts)
    - Post-infection by the name of the triggering infection (post-Lyme disease, chronic EBV)
  - As "**centralized pain**" or "**central sensitization**" in existing chronic pain conditions where there is known nociceptive input
  - As **somatization** by some in psychiatry, although this term is (appropriately) falling into disuse as we understand the biology of these illnesses

The F-Word

Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

- Final common pathway (i.e. centralization)
- Chronic widespread pain
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals

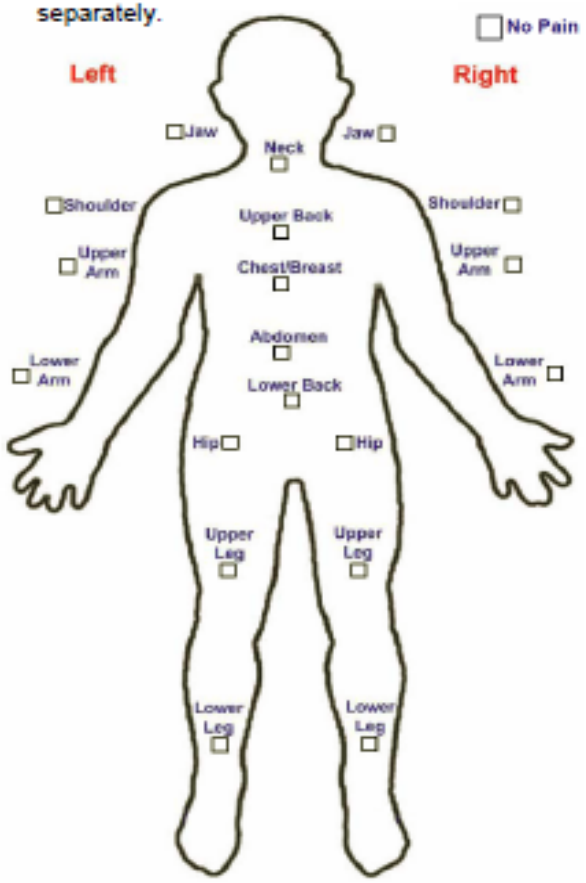
~~Part of a larger continuum~~

~~Tenderness in ≥11 of 18 tender points~~

Concept of “Fibromyalgia-ness”

Fibromyalgia Symptoms (Modified ACR 2010 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.



2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.

No problem
Slight or mild problems: generally mild or intermittent
Moderate: considerable problems; often present and/or at a moderate level
Severe: continuous, life-disturbing problems

	No problem	Slight or mild	Moderate	Severe
a. Fatigue	☐	☐	☐	☐
b. Trouble thinking or remembering	☐	☐	☐	☐
c. Waking up tired (unrefreshed)	☐	☐	☐	☐

3. During the past 6 months have you had any of the following symptoms?

	No	Yes
a. Pain or cramps in lower abdomen	☐	☐
b. Depression	☐	☐
c. Headache	☐	☐

4. Have the symptoms in questions 2-3 and pain been present at a similar level for at least 3 months? **No** ☐ **Yes** ☐

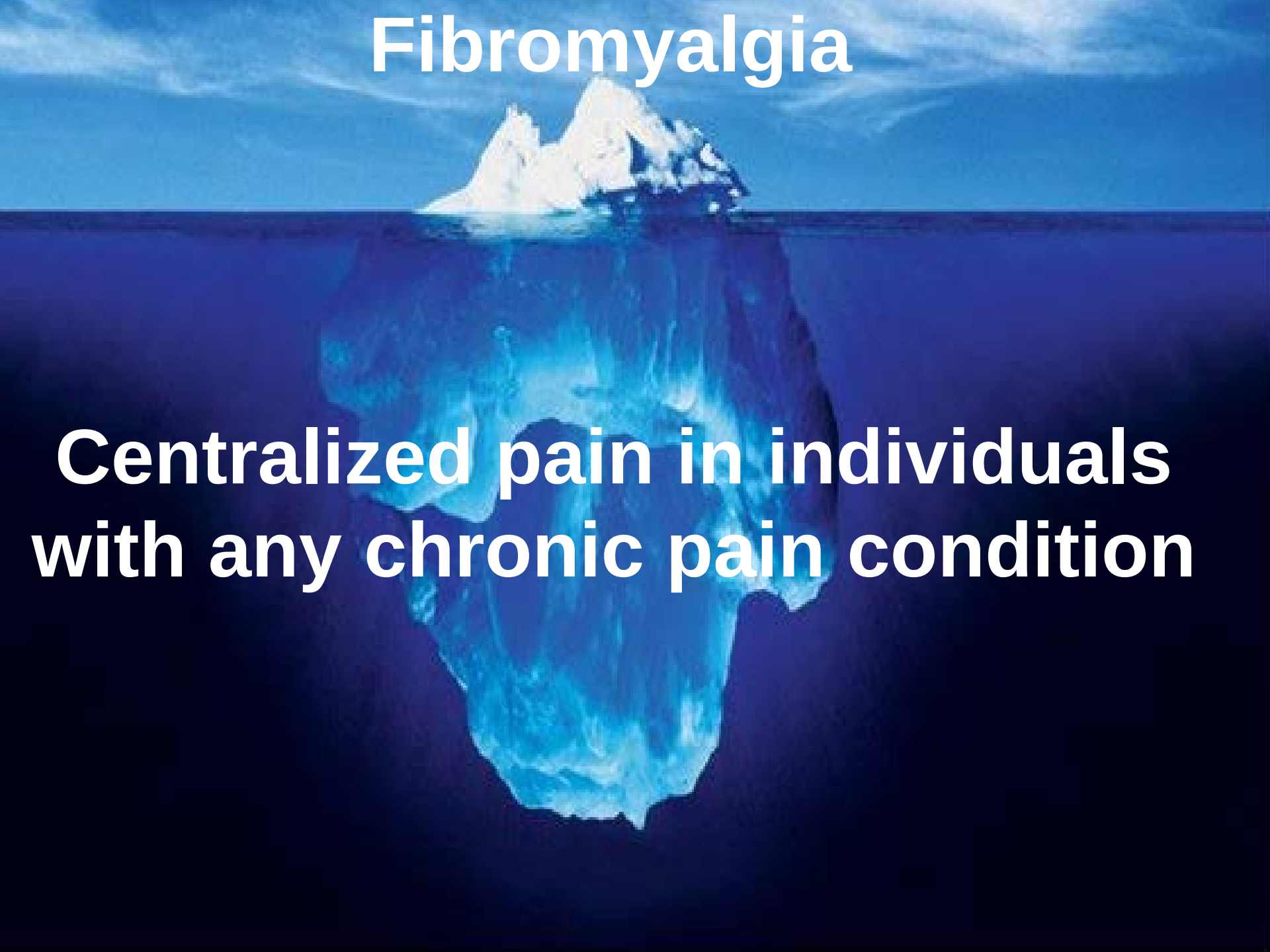
5. Do you have a disorder that would otherwise explain the pain? **No** ☐ **Yes** ☐

1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Fibromyalgia-ness

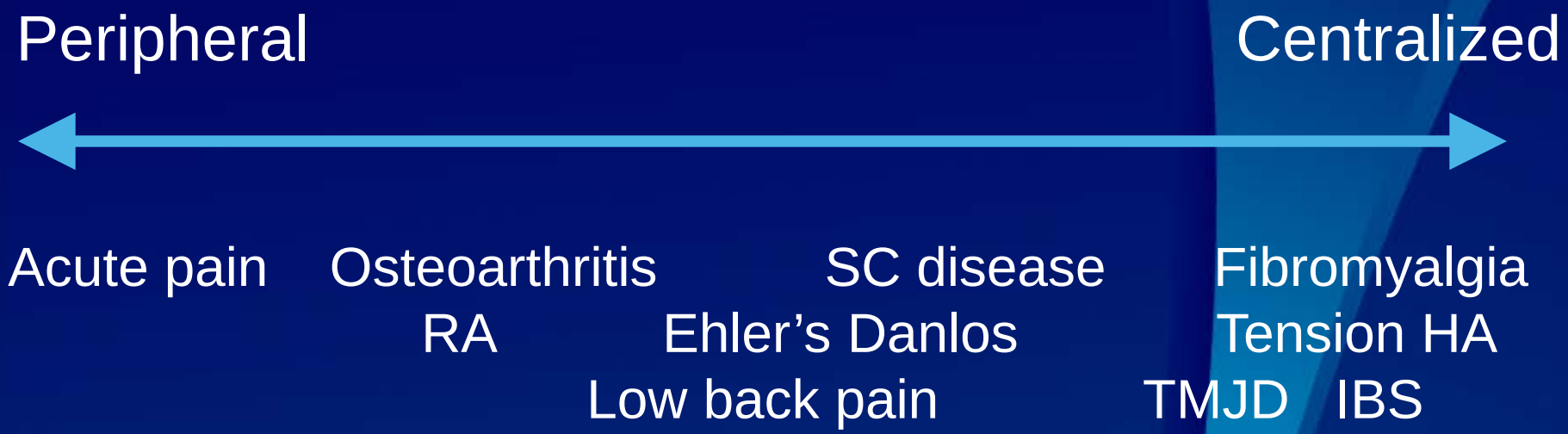
- Term coined by Wolfe to indicate that the symptoms of FM occur as a continuum in the population rather than being present or absent [1]
- In rheumatic disorders such as osteoarthritis, rheumatoid arthritis, lupus, low back pain, etc. this score is more predictive of pain levels and disability than more objective measures of disease [2,3]
- Domain overlaps with somatization in many regards, and there are many questionnaires that collect somatic symptom counts as a surrogate for this construct

1.Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al. *2.J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.


Fibromyalgia
Centralized pain in individuals with any chronic pain condition

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain



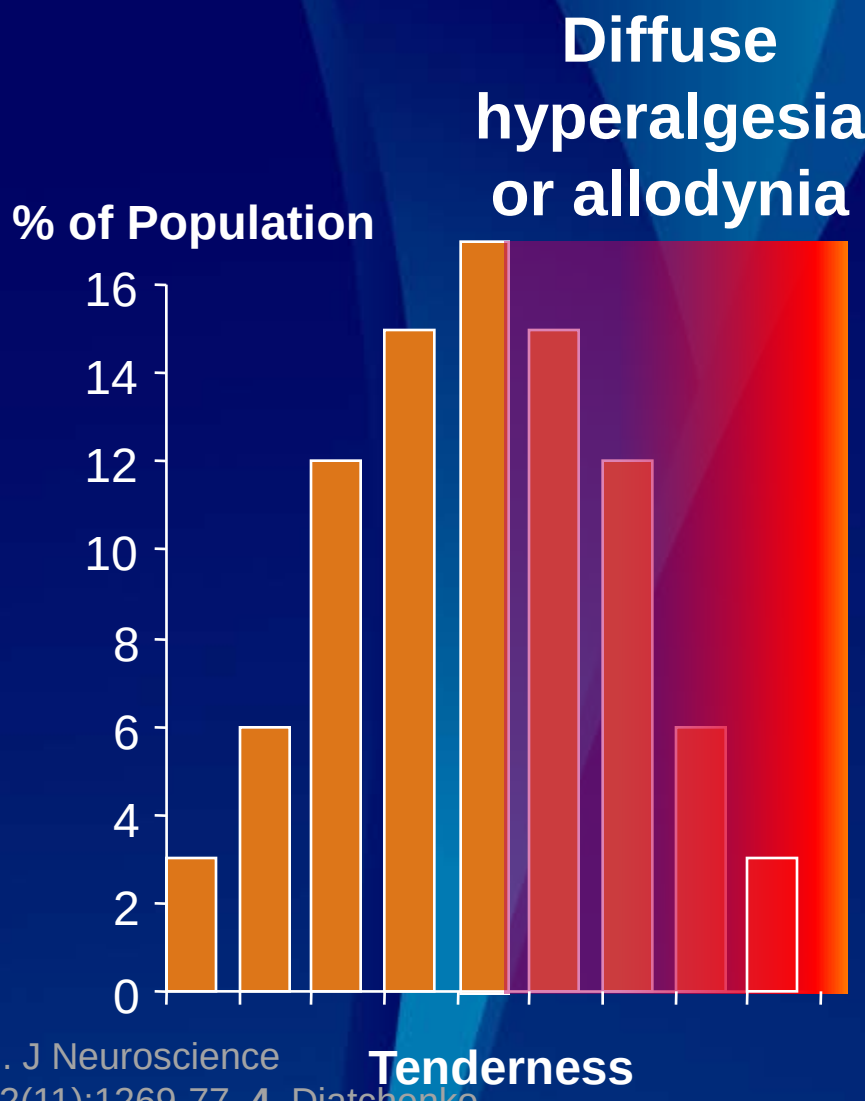
Pathophysiology of centralized pain states

- Augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances in concentrations of CNS neurotransmitters that control sensory processing, sleep, alertness, affect, memory[3,4]
- Autonomic, HPA, and peripheral abnormalities may play some role

1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4.Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9): p. 518-27.

Pain and sensory sensitivity in the population

- Like most other physiological processes, we have a “volume control” setting for how our brain and spinal cord processes pain[1]
- This is likely *set* by the genes that we are born with[2-4], and *modified* by neurohormonal factors and neural plasticity
- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input



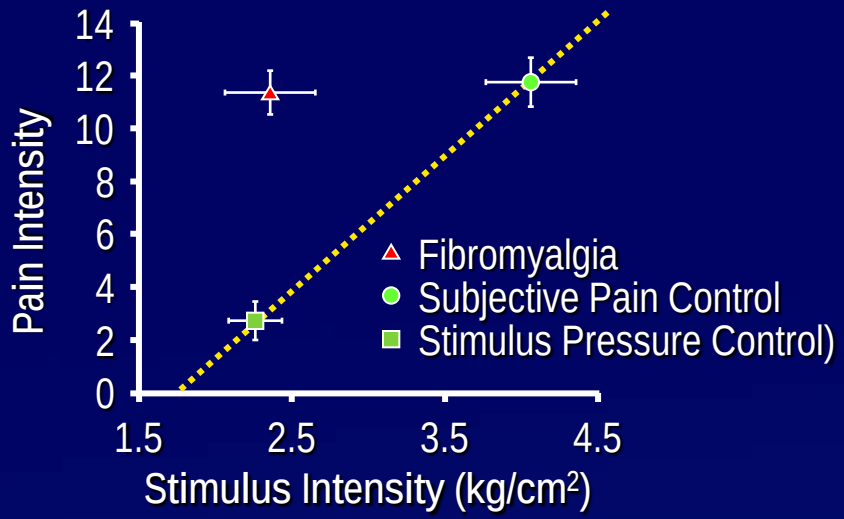
1. Mogil JS. PNAS, 1999;96(14):7744-51. **2.** Amaya et. al. J Neuroscience 2006;26(50):12852-60. **3.** Tegeder et.al., NatMed. 2006;12(11):1269-77. **4.** Diatchenko et. al. HumMolGenet. 2005;14(1):135-43.

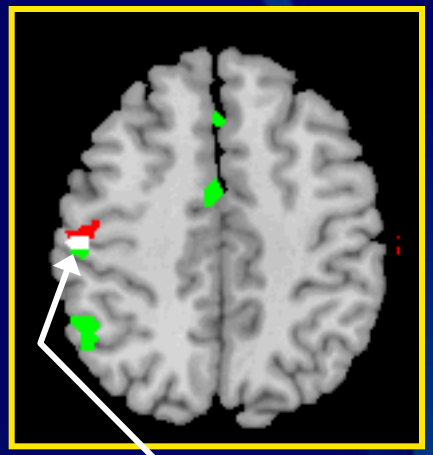
fMRI in Chronic Pain States

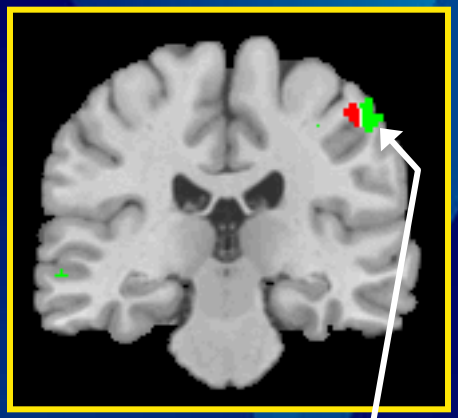
- There is objective evidence of augmented pain processing in a broad range of hyperalgesic pain states[1-4]
- Depression and pain are overlapping neurobiological proccesses[5]
- How individuals think about their pain can affect both the sensory and affective processing of pain[6]

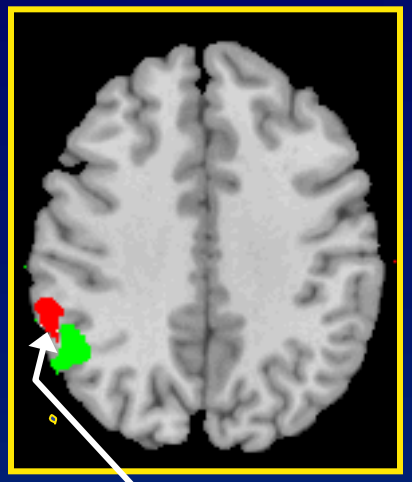
1. Gracely et al. *Arthritis Rheum*. 2002;46:1333-43. 2. Mayer et. Al. Gatstroenterology 2006:: (131):1925-31. 3. Giesecke et al. *Arthritis Rheum*. 2004;50:613-23 4. Giesecke et al. *Arthritis Rheum*. 2003;48:2916-22. 5. Gracely et al. *Brain*. 2004;127:835-43..

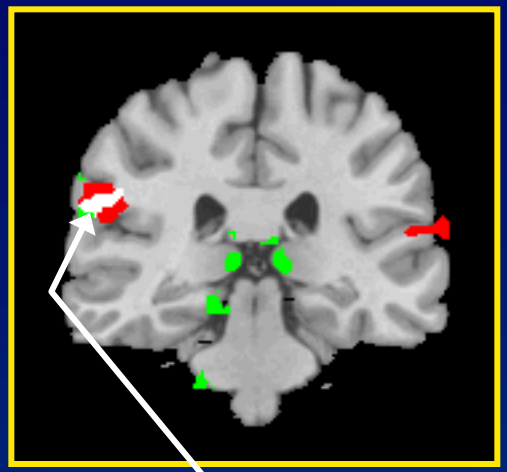
fMRI in Fibromyalgia

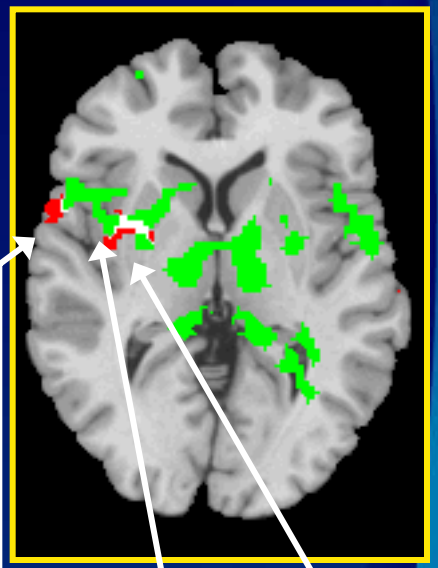


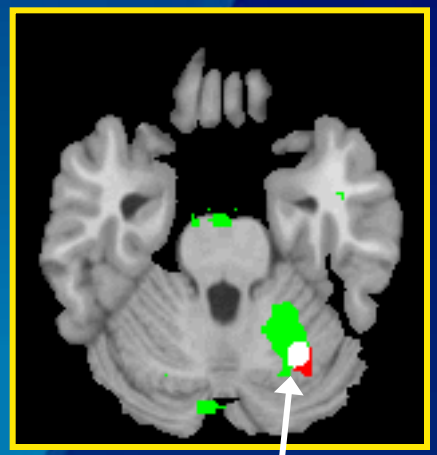








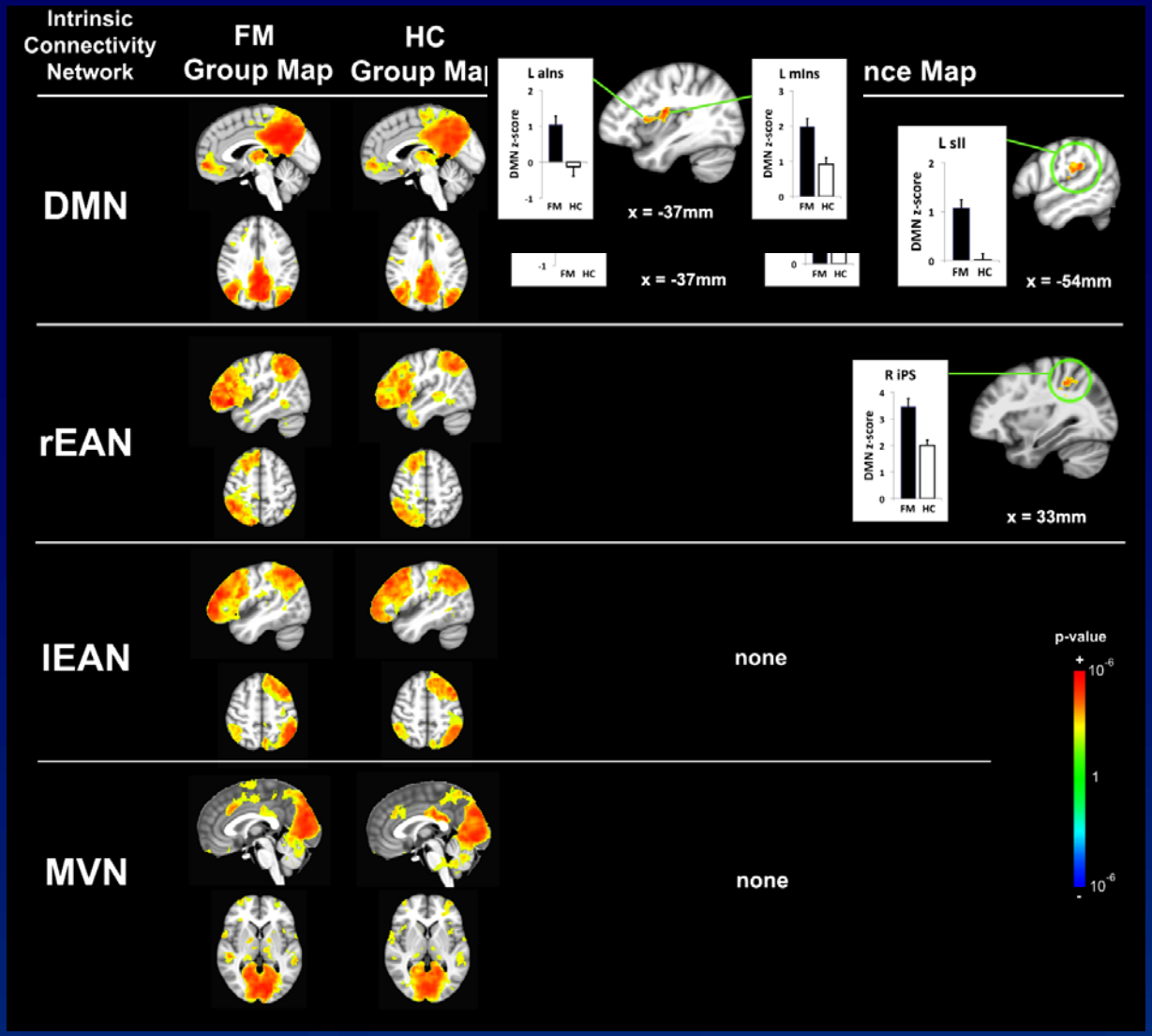




STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

Gracely. *Arthritis Rheum*. 2002;46:1333-1343.

Intrinsic Brain Connectivity is Altered in FM patients



Napadow et al, *Arthritis Rheumatism* 2010

- In FM, DMN and rEAN show greater intrinsic connectivity within component DMN (PCC), and rEAN (iPS) as well as limbic (insula), and sensorimotor (SII) regions outside conventional network boundaries.

- All FM vs. HC differences driven by greater connectivity for FM patients.

Structural Brain Changes in Chronic Pain

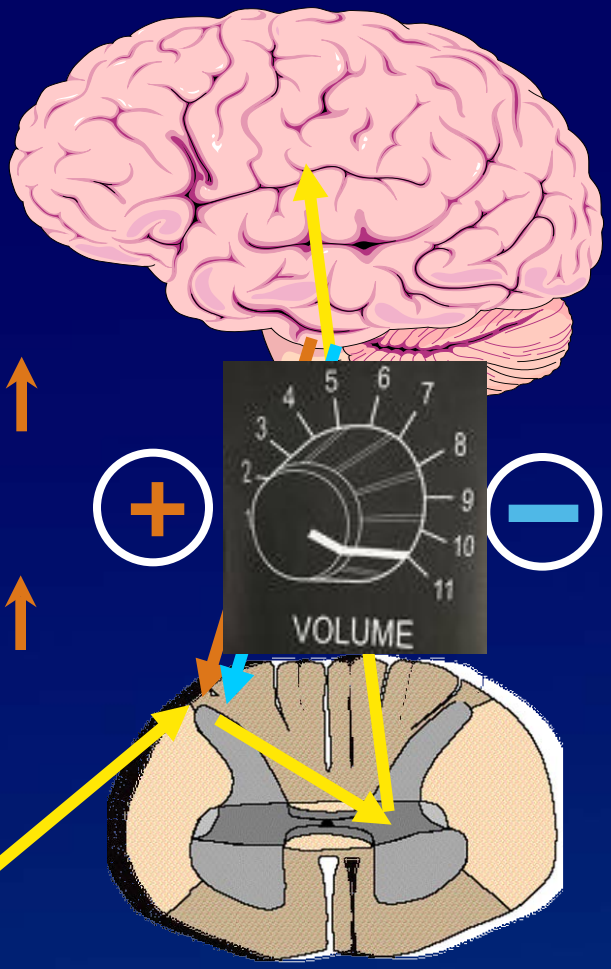
- Apkarian[1] was first to show that chronic pain may be associated with decrease of size of brain areas involved in pain processing
- More recently seen in other pain states including
  - Headache (insula and ACC)[2]
  - IBS (insula and ACC)[3]
  - Fibromyalgia[4] (multiple regions)
  - PTSD[5] (insula)
- A note of caution
  - After carefully controlling for co-morbid mood disturbances much of this went away[6]

1. Apkarian et al. *J Neurosci*. 2004;24:10410-5. 2. Schmidt-Wilcke et al. *Pain*. 2007;132 Suppl 1:S109-16.
3. Davis et al. *Neurology*. 2008;70:153-4. 4. Kuchinad et al. *J Neurosci*. 2007;27:4004-7.
5. Chen et al. *Psychiatry Res*. 2006;146:65-72. 6. Hsu et. al. *Pain*. Jun 2009;143(3):262-267.

Neural Influences on Pain and Sensory Processing

Facilitation

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



Inhibition

- Descending anti-nociceptive pathways
  - ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
  - ↑ Opioids
  - ↓ GABA
  - Cannabanoids

1. Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
2. Clauw DJ. JAMA. 2014.

Pharmacological Therapies for Fibromyalgia (i.e. Centralized Pain)

Strong Evidence	▪ Dual reuptake inhibitors such as
	  ▪ Tricyclic compounds (amitriptyline, cyclobenzaprine)
	  ▪ SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)
	▪ Anticonvulsants (e.g., pregabalin, gabapentin)

Modest Evidence	▪ Tramadol ▪ Older less selective SSRIs ▪ Gamma hydroxybutyrate ▪ Low dose naltrexone ▪ Cannabinoids
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

Modified from Goldenberg et al. *JAMA*. 2004;292:2388-95.

CNS Neurotransmitters Influencing Pain

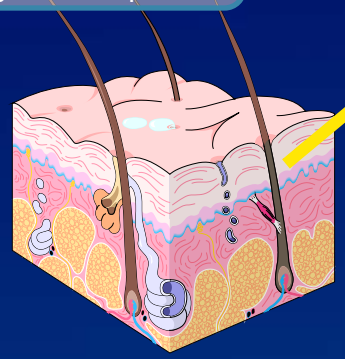
Arrows indicate direction in Fibromyalgia

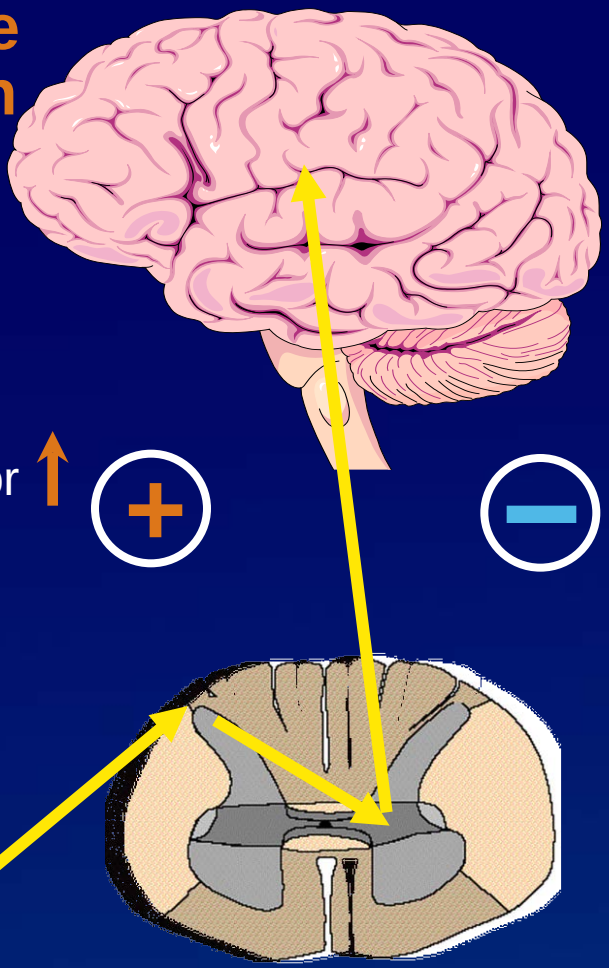
Generally facilitate pain transmission

Gabapentinoids, ketamine, memantine

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

Anti-migraine drugs (–triptans), cyclobenzaprine





Generally inhibit pain transmission

- Descending anti-nociceptive pathways
- ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine

Tricyclics, SNRIs. tramadol

- ↑ Opioids

Low dose naltrexone

- Cannabanoids
- ↓ GABA

Gammahydroxybutyrate, moderate alcohol consumption

No knowledge of endocannabinoid activity but this class of drugs is effective

1. Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
2. Clauw DJ. JAMA. 2014.

Mechanistic Characterization of Pain

Any combination may be present in a given individual

Peripheral (nociceptive)	Peripheral Neuropathic	Central Neuropathic or Centralized Pain
▪ Inflammation or mechanical damage in tissues ▪ NSAID, opioid responsive ▪ Responds to procedures	▪ Damage or dysfunction of peripheral nerves ▪ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy	▪ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia) ▪ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission
▪ Classic examples ▪ Acute pain due to injury ▪ Osteoarthritis ▪ Rheumatoid arthritis ▪ Cancer pain	▪ Classic examples ▪ Diabetic neuropathic pain ▪ Post-herpetic neuralgia	▪ Classic examples ▪ Fibromyalgia ▪ Irritable bowel syndrome ▪ TMJD ▪ Tension headache

Mixed Pain States

Treating Based on Mechanisms

Any combination may be present

	Peripheral (nociceptive)	Neuropathic	Centralized Pain
NSAIDs	+	-	-
Opioids	+	+	-
Surgery/ Injections	+	+	-
Tricyclics	+	+	+
SNRIs	+	+	+
Gabapentinoid	-	+	+
Cannabinoid	-	+	+

Osteoarthritis of the Knee – II

- Subsets of patients with OA of the knee display hyperalgesia and attenuated DNIC.[1]
- In past years, 2 classes of neuroactive drugs likely acting on volume control of pain processing have been shown to be effective:
  - Duloxetine (formerly tricyclic drugs had shown this same effect but have not gained wide usage)[2]
  - Tanezumab, a nerve growth factor inhibitor[3]
- Functional and structural neuroimaging results from Tracey group
  - Identify hyperalgesia/central sensitization in OA
  - Show that thalamic atrophy on VBM at baselone in knee OA normalizes following arthroplasty

1. Kosek E, Ordeberg G. *Pain*. 2000;88:69-78. 2-4. Clauw DJ, et al. Presented at: 2008 American College of Rheumatology Annual Meeting; October 24, 2008; San Francisco, CA; and 2008 International Association for the Study of Pain meeting; August 17, 2008; Glasgow, Scotland. 5. Gwilym et. al. . Arthritis Rheum. 2009 Sep 15;61(9):1226-34. 6. Gwilym et .al. Arthritis Rheum Vol. 62, No. 10, October 2010, pp 2930–2940

Ongoing Study of Predictors of Outcomes in OA Patients Undergoing Arthroplasty and Hysterectomy

- Primary hypothesis of studies is that a simple self report measures of centralized pain (2011 FM Criteria) predicts failure to respond to surgery meant to improve pain, and to perioperative opioids
- Extensive preoperative phenotype using validated self-report measures of pain, mood, and function
- Two outcomes of interest:
  - Postoperative opioid consumption
  - Pain relief from procedure at 6 months

1. Brummett CM, et. al. Anesthesiology. 2013;119(6):1434-1443. **2.** Janda AM, et. al. Anesthesiology. 2015;122(5):1103-1111. **3.** Brummett CM, et. al. **3.** Arthritis & Rheumatology. 2015;67(5):1386-1394. **4.** Bruehl S. Anesthesiology. 2015. **5.** Brummett CM, Clauw DJ. Anesthesiology. 2015;122(4):731-733.

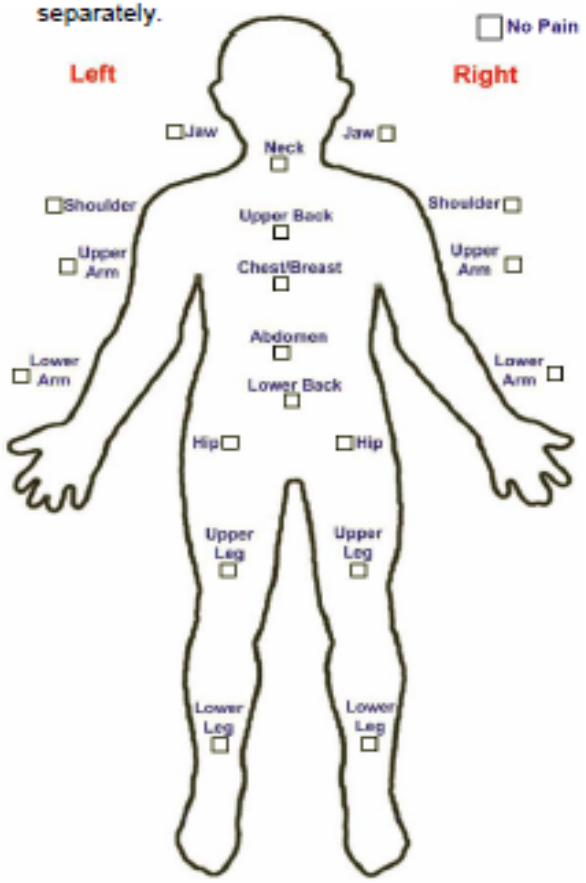
Variables Analyzed

- Age
- Sex
- Surgery (Knee vs Hip)
- Primary anesthetic (GA vs neuraxial)
- Home opioids (IVME)
- Pain severity (BPI)
  - Overall
  - Surgical site
- Neuropathic pain score (PainDETECT)
- Depression (HADS)
- Anxiety (HADS)
- Catastrophizing
- Physical function-WOMAC

Concept of “Fibromyalgia-ness”

Fibromyalgia Symptoms (Modified ACR 2010 Fibromyalgia Diagnostic Criteria)

1. Please indicate below if you have had pain or tenderness over the past 7 days in each of the areas listed below. Check the boxes in the diagram below for each area in which you have had pain or tenderness. Be sure to mark right and left sides separately.



2. Using the following scale, indicate for each item your severity over the past week by checking the appropriate box.

No problem
Slight or mild problems: generally mild or intermittent
Moderate: considerable problems; often present and/or at a moderate level
Severe: continuous, life-disturbing problems

	No problem	Slight or mild	Moderate	Severe
a. Fatigue	☐	☐	☐	☐
b. Trouble thinking or remembering	☐	☐	☐	☐
c. Waking up tired (unrefreshed)	☐	☐	☐	☐

3. During the past 6 months have you had any of the following symptoms?

	No	Yes
a. Pain or cramps in lower abdomen	☐	☐
b. Depression	☐	☐
c. Headache	☐	☐

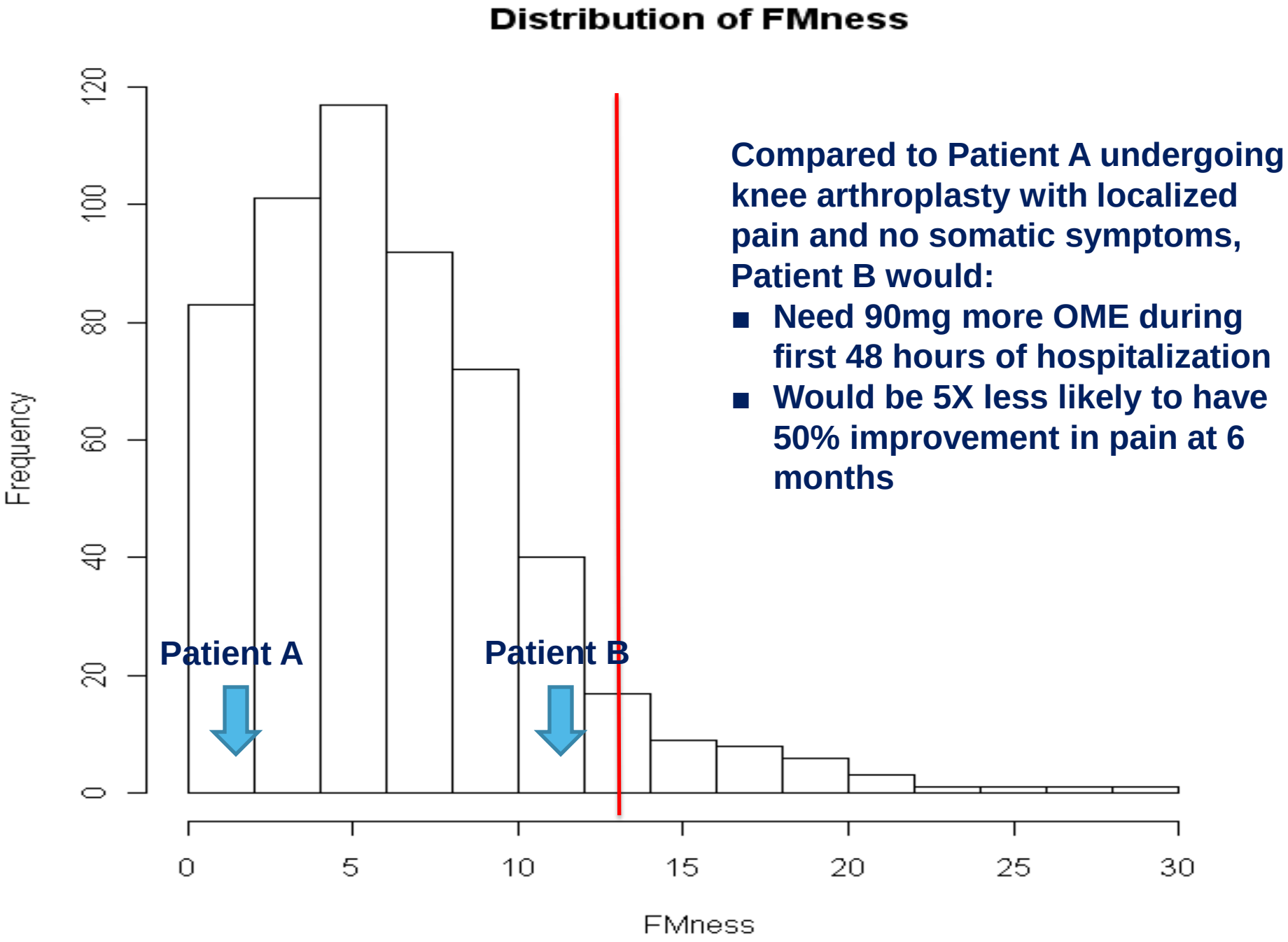
4. Have the symptoms in questions 2-3 and pain been present at a similar level for at least 3 months? **No** ☐ **Yes** ☐

5. Do you have a disorder that would otherwise explain the pain? **No** ☐ **Yes** ☐

1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Each one point increase in fibromyalgianess from 0-31 led to:

- 7- 9 mg greater oral morphine requirements during acute hospitalization (8mg greater when all individuals taking opioids as outpatients excluded)
- 20 – 25% greater likelihood of failing to respond to knee or hip arthroplasty (judged by either 50% improvement in pain or much better or very much better on patient global)
- These phenomenon were linear across entire scale and equally strong after individuals who met criteria for FM were excluded
- This was independent of classic psychological factors (anxiety, depression, catastrophizing)



Compared to Patient A undergoing knee arthroplasty with localized pain and no somatic symptoms, Patient B would:

- **Need 90mg more OME during first 48 hours of hospitalization**
- **Would be 5X less likely to have 50% improvement in pain at 6 months**

Yet Another Problem . . . .

Opioids Originally Given for Acute Pain are Being Used for Chronic Pain

- Very few US physicians are willing to newly prescribe an opioid for chronic pain
- Then why are 30 – 40% of individuals with chronic pain conditions where opioids are strongly discouraged (fibromyalgia, headache) using opioids?
- These “new starts” are commonly occurring when individuals with chronic pain are prescribed an opioid for acute pain (surgical procedure, ED visit) and feel it is helping their chronic pain so they continue it
- This puts treating physicians in position of being empathetic and continuing to prescribe a drug they would not have started - or discontinuing the drug

New Opioid Starts Following Arthroplasty

- 574 TKA and THA patients were longitudinally assessed pre-op and then for 6-months post-surgery
- Among patients who were opioid naïve the day of surgery, **8.2% of TKA and 4.3% of THA patients were newly using opioids at 6 months**
- In comparison, 53.3% of TKA and 34.7% of THA patients who reported opioid use the day of surgery continued to use opioids at 6 months
  - Patients taking >60 mg oral morphine equivalents preoperatively had an 80% likelihood of persistent use postoperatively.

Goesling et. al. Trends and Predictors of Opioid Use Following Total Knee and Total Hip Arthroplasty. Pain. 2016 Feb 11. [Epub].

New Opioid Starts Following Arthroplasty

- Day of surgery predictors for 6-month opioid use by opioid naïve patients included greater overall body pain (p=0.002), greater affected joint pain (knee/hip) (p=0.034), and greater catastrophizing (p=0.010).
- For both opioid naïve and opioid users on day of surgery, decreases in overall body pain from baseline to 6 months were associated with decreased odds of being on opioids at 6 months (aOR=0.72, p=0.001); however, change in affected joint pain (knee/hip) was not predictive of opioid use (aOR=0.99, p=0.963).

Goesling et. al. Trends and Predictors of Opioid Use Following Total Knee and Total Hip Arthroplasty. Pain. 2016 Feb 11. [Epub].

The Development of Treatments for Pain

- Analgesic drug development
- Contemporary view of pain
- **Opioid addiction has become a significant public health problem but is a small part of the overall problem in treating chronic pain patients**
  - **Used far too early and often because providers do not feel comfortable diagnosing and treating pain**
  - **Patients who feel that they are deriving a benefit but an objective appraisal of benefit:harm suggests otherwise**
  - **Tolerance/opioid induced hyperalgesia**
- Summary

The Development of Treatments for Pain

- Analgesic drug development
- Contemporary view of pain
- Opioid addiction has become a significant public health problem but is a small part of the overall problem in treating chronic pain patients
  - Tolerance
  - Misuse
  - Patients who feel that are deriving a benefit but an objective appraisal of benefit:harm suggests otherwise
- **Summary**

Summary

- Our ability to develop new analgesic drugs his been disappointing
  - It is less risky, and equally remunerative, to develop *me too* drugs (especially opioids) than drugs with novel MOAs
  - Pharma needs to move to:
    - operant animal models
    - integrate use of new methodologies (e.g. neuroimaging) into drug development
    - trials enriched for individuals who have the mechanism of pain that best matches that drug
  - CNS-acting drugs need to be tried earlier in pain
- Our current taxonomy for chronic pain conditions is inappropriate
  - assumes that chronic pain in one region of the body or due to one underlying disease all has the same underlying mechanism

Summary

- Regulatory precedent has caused significant problems with respect to opioids and chronic pain
  - Opioids likely work well for some individuals with chronic pain, but . . .
    - Opioids get a broad label for acute and chronic pain even though almost all registration trials are performed in just a few chronic pain states ... so we simply don't know what types of pain conditions or mechanisms opioids work best for
    - The widespread use and acceptance of randomized withdrawal designs distorts the overall efficacy of opioids in chronic pain
- Some of our approaches to the opioid problem are misguided
  - REMS programs are in the wrong place (new starts for chronic pain) and focus on the wrong risk factors (addiction)
  - Focusing on developing tamper-resistant opioids is akin to playing Whack-a-Mole