Pain, Disability and Biomarkers: An Emphasis on Fibromyalgia

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Disclosures

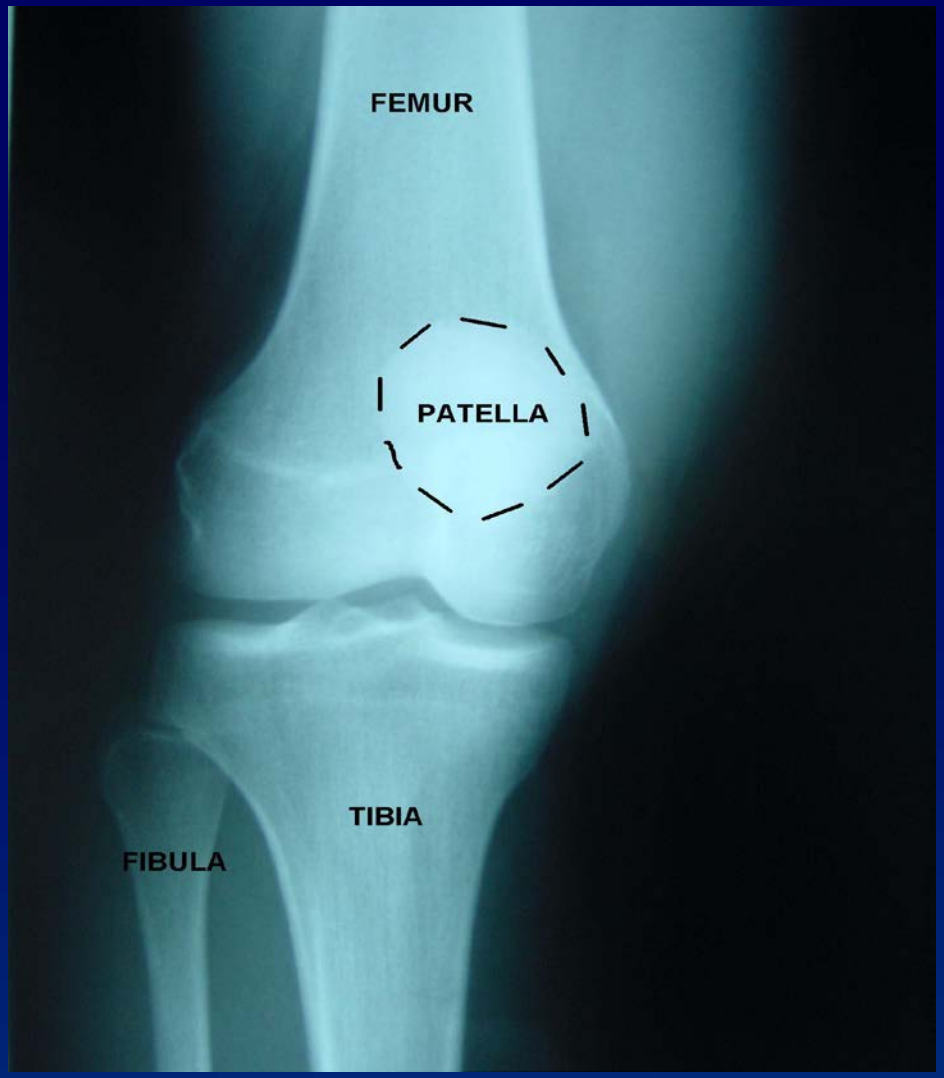
- Consulting
  - Pfizer, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo, Intec, Regeneron, Teva
- Research support
  - NIH, Pfizer, Cerephex, Aptinyx
- Litigation
  - Testified against opioid manufacturers in State of Oklahoma

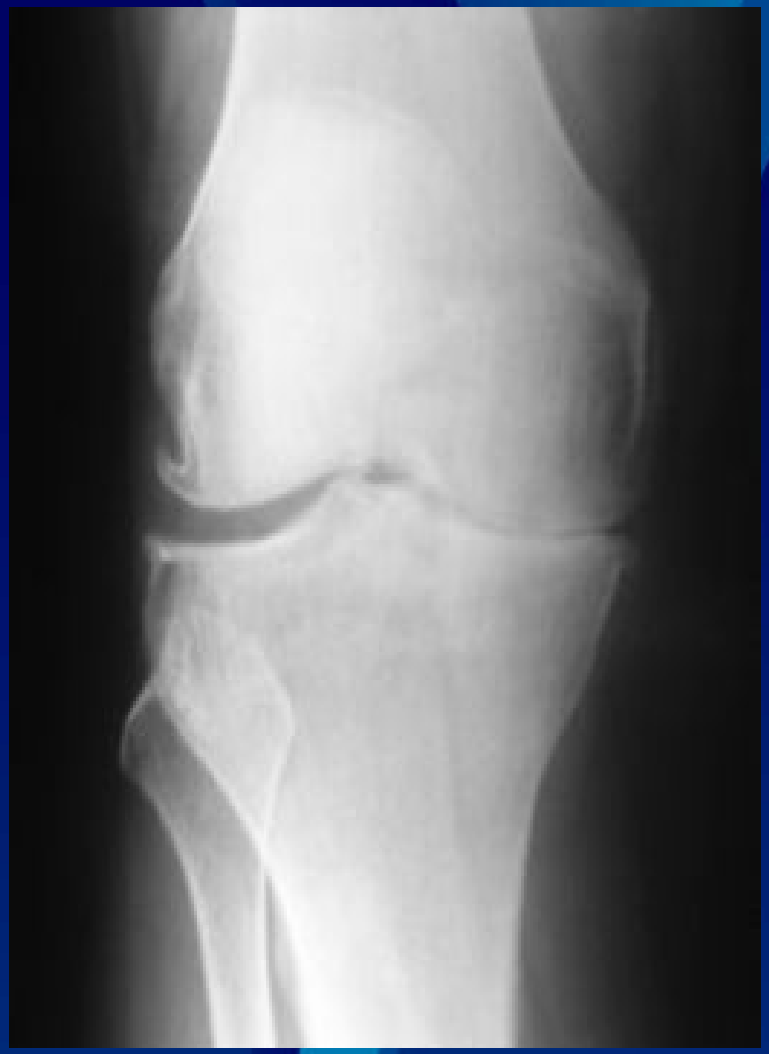
I've been wanting to give this talk to this audience my entire academic career because I've never thought our ways of assessing disability made any sense – but biomarkers are not the answer

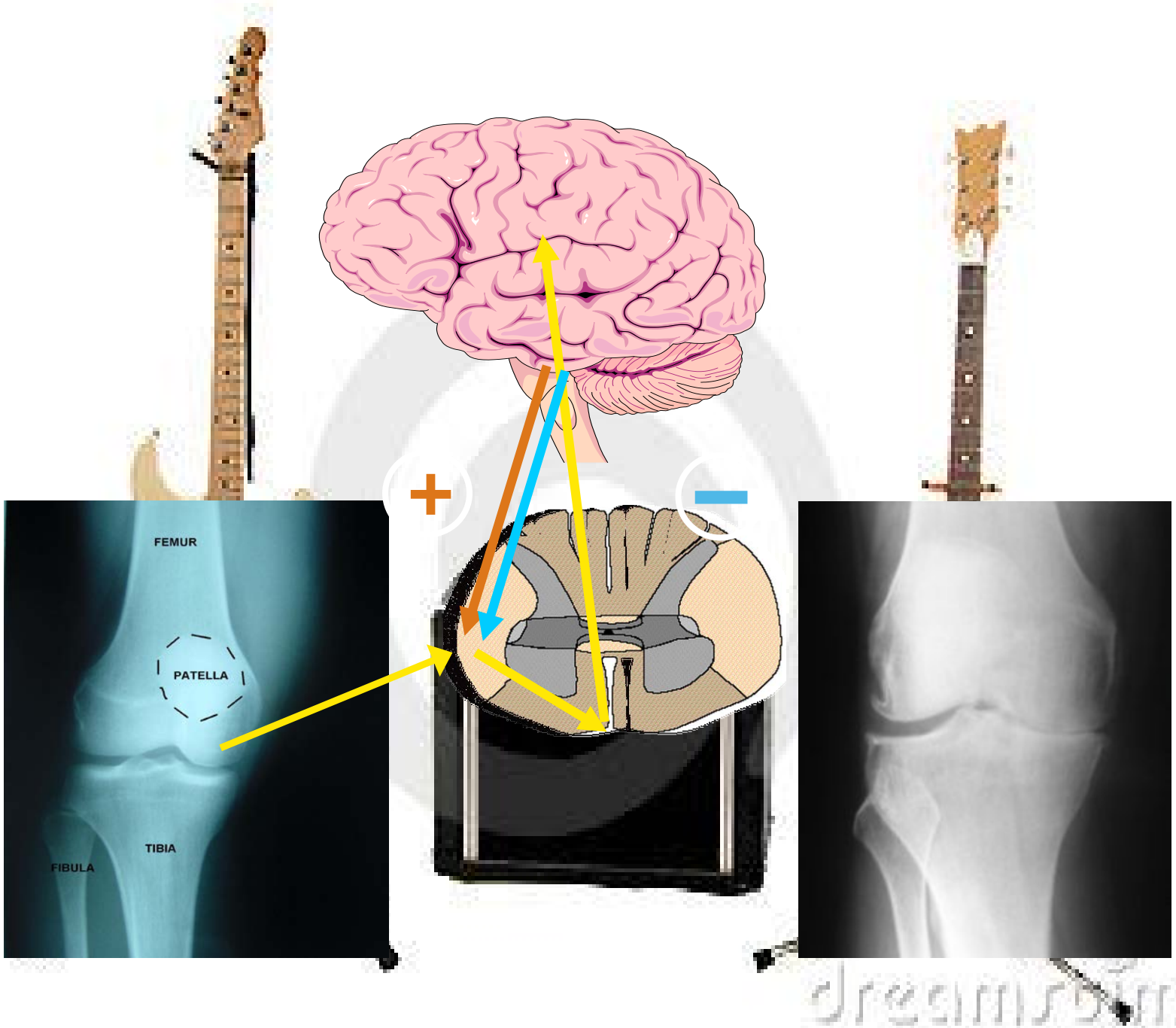
Pain, Disability and Biomarkers

- There is no chronic pain condition where there is a good relationship between any type of peripheral damage or inflammation - and the presence or severity of pain
- The primary reason for this is that pain occurs because of a combination of biopsychosocial factors that are not typically assessed or treated in clinical practice , especially central nervous system (CNS) factors that are playing prominent roles in most individuals with severe chronic pain and or disability
- We do have biomarkers that can measure these CNS factors – but should we – or are we simply perpetuating a misguided approach?

Which person has pain?



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Evolution of Thinking Regarding Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Pathophysiology poorly understood and thought to be psychological in nature

- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points

- Final common pathway (i.e. pain centralization)
- Poster child for nociplastic pain
- Not just pain
- Pathophysiology fairly well understood and is a CNS process that is independent from classic psychological factors

Mechanistic Characterization of Pain

Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized/Nociplastic
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain

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Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

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Abstract: There is increasing recognition that many if not most common chronic pain conditions are heterogeneous with a high degree of overlap or coprevalence of other common pain conditions along with influences from biopsychosocial factors. At present, very little attention is given to the high degree of overlap of many common pain conditions when recruiting for clinical trials. As such, many if not most patients enrolled into clinical studies are not representative of most chronic pain patients. The failure to account for the heterogeneous and overlapping nature of most common pain conditions

Chronic Overlapping Pain Conditions

- Most highly prevalent pain conditions in individuals under age 50
  - Headache
  - Fibromyalgia
  - Irritable bowel
  - TMJ Disorder
  - Interstitial cystitis
  - Low back pain
  - Endometriosis
  - Vulvodynia
  - Chronic fatigue syndrome
- Same central mechanisms play significant roles in all pain conditions, even those with known peripheral contributions

Fibromyalgia-ness

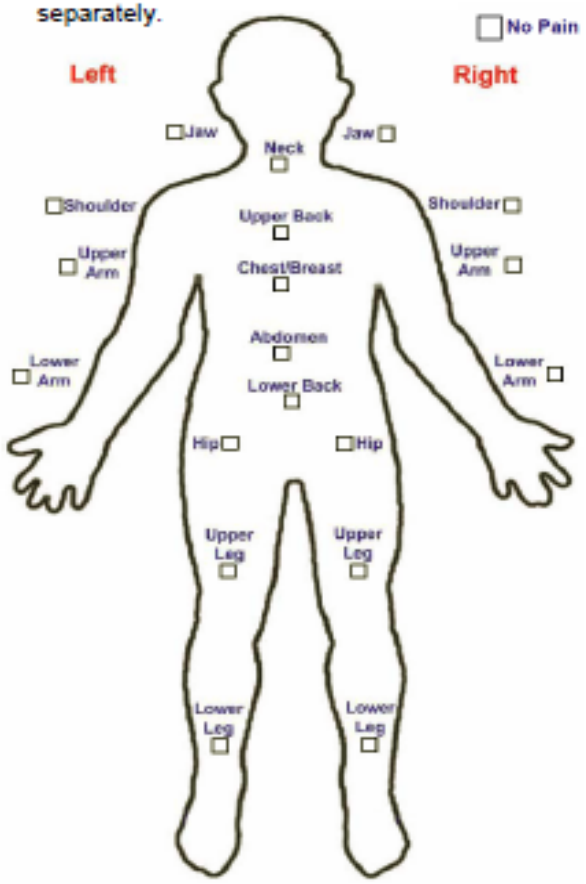
- Term coined by Wolfe to indicate that the symptoms of FM occur as a continuum in the population rather than being present or absent [1]
- In rheumatic disorders such as osteoarthritis, rheumatoid arthritis, lupus, low back pain, etc. this score is more predictive of pain levels and disability than 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.

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.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.


Fibromyalgia
Centralized pain in individuals with any chronic pain condition

Sub-threshold FM is Highly Predictive of Surgery and Opioid Non-responsiveness in Patients Undergoing Arthroplasty and Hysterectomy

- Primary hypothesis of studies is the measures of centralized pain in OA (FMness) will predict failure to respond to arthroplasty and hysterectomy
- 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, C.M., et al., Anesthesiology, 2013. **119**(6): p. 1434-43.
2. Brummett, C.M., et al., Arthritis Rheumatol, 2015. 67(5):1386-94.
3. Janda, A.M., et al., Anesthesiology, 2015. **122**(5): p. 1103-11.

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

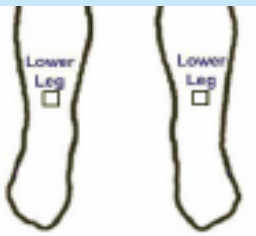
“Fibromyalgia-ness” can be scored 0-31

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.

☐ No Pain

Left Right



19/31 potential FM score derived from how widespread pain is

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

Severe

a. Fatigu ☐
b. Troub reme ☐
c. Wakir (unre ☐

3. During th symptoms?

a. Pain
b. Depre
c. Head

4. Have the at a similar level for

5. Do you h n?

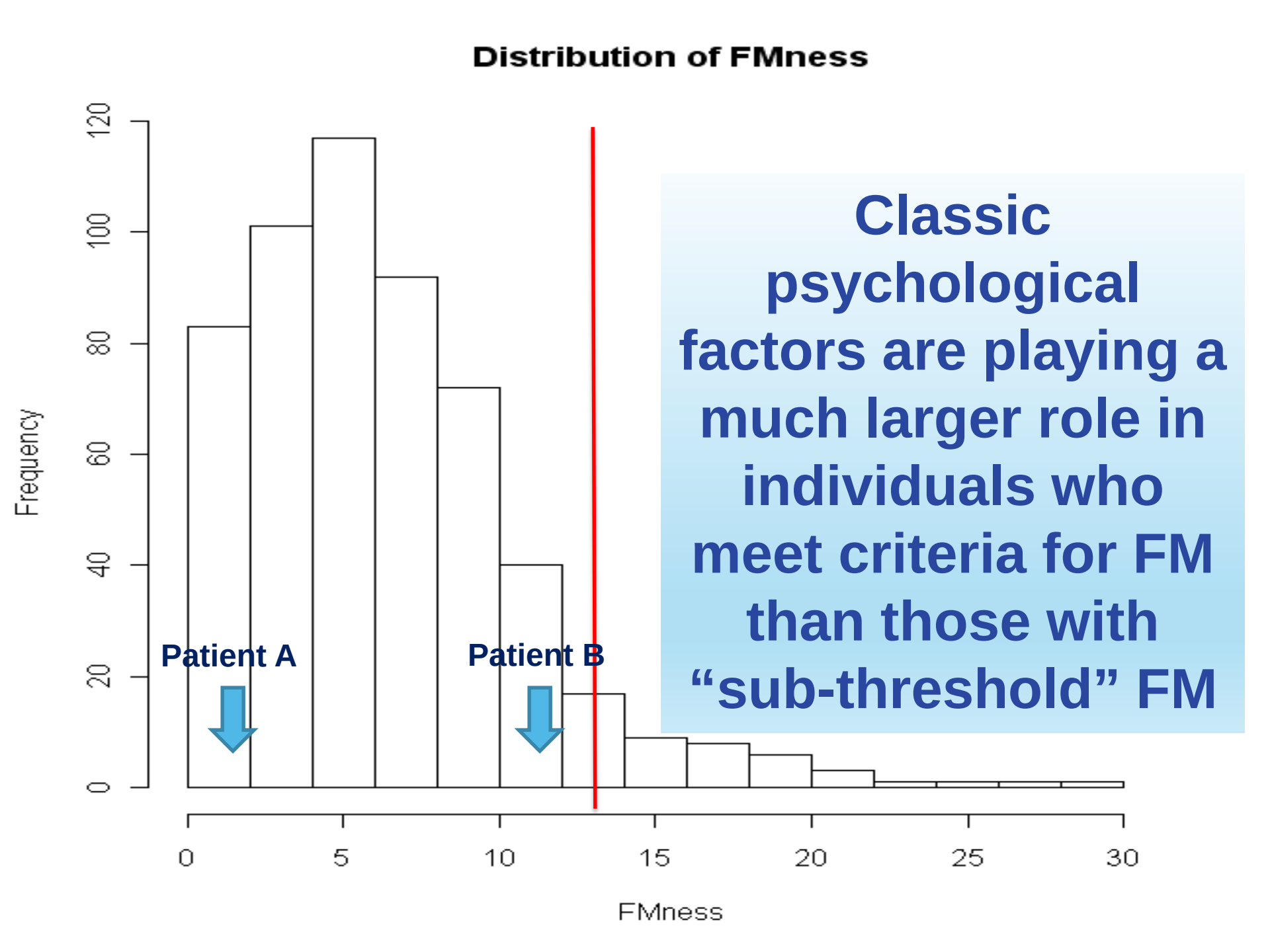
No ☐ Yes ☐

12/31 potential FM score derived from co-morbid CNS-derived symptoms that accompany CNS pain

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.

Each one point increase in fibromyalgianess led to:

- 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 up to a score of approximately 18 - and equally strong after individuals who met criteria for FM were excluded
- This phenomenon was much stronger than and largely independent of classic psychological factors



Classic psychological factors are playing a much larger role in individuals who meet criteria for FM than those with "sub-threshold" FM

Mechanistic Characterization of Pain

Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
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Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain

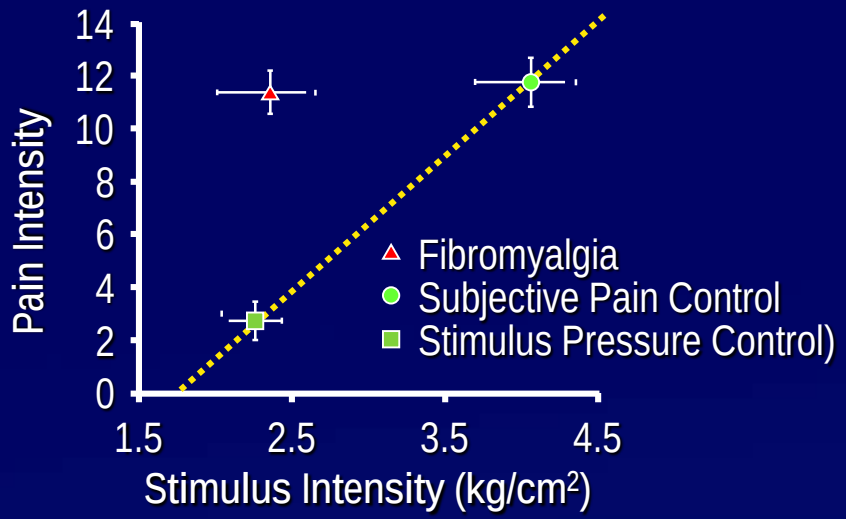
Mixed Pain States

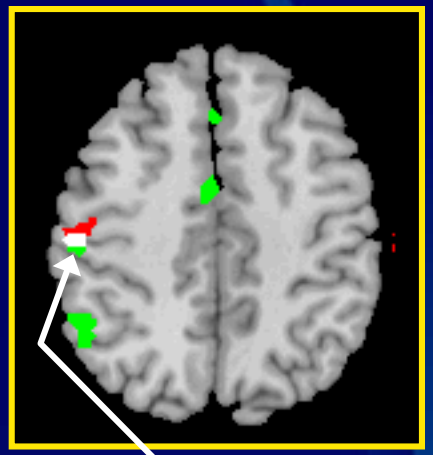
Pathophysiology of centralized pain states

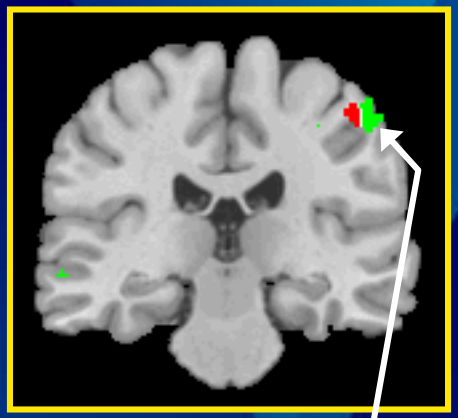
- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances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

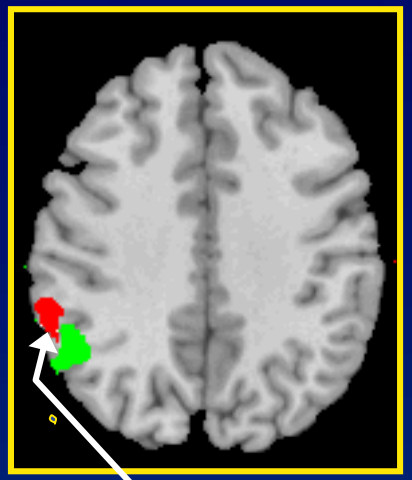
1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4.Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9):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

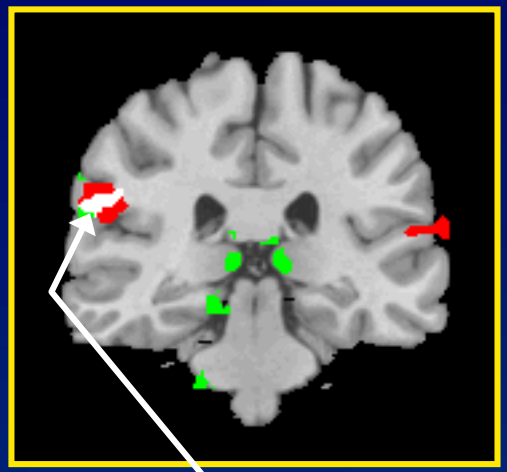
fMRI in Fibromyalgia

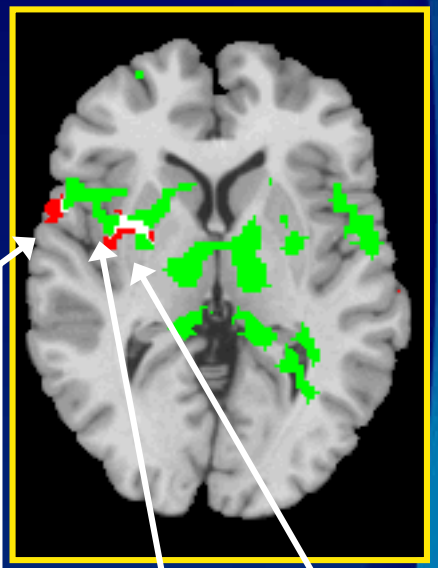


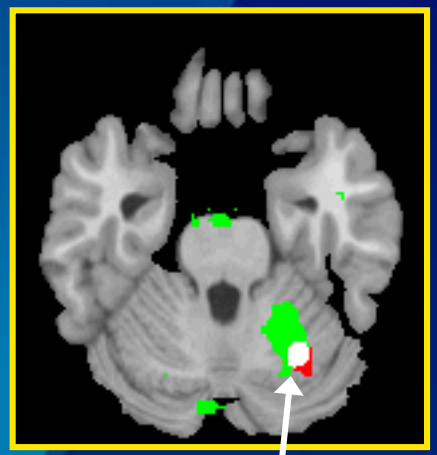








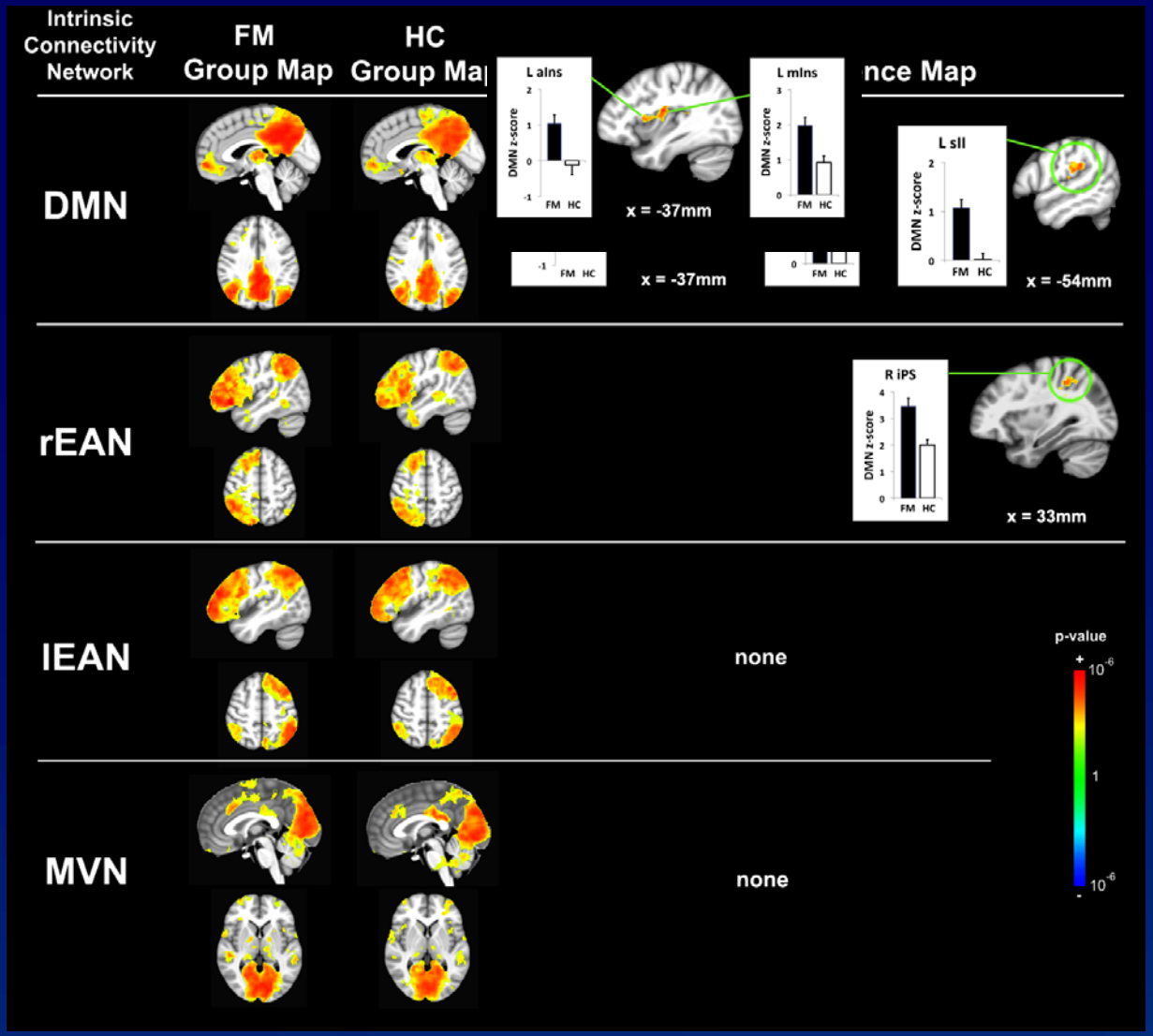




STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

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

Intrinsic Brain Connectivity is Altered in FM patients



- 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.

Napadow et al, *Arthritis Rheumatism* 2010

CNS Neurotransmitters Influencing Pain

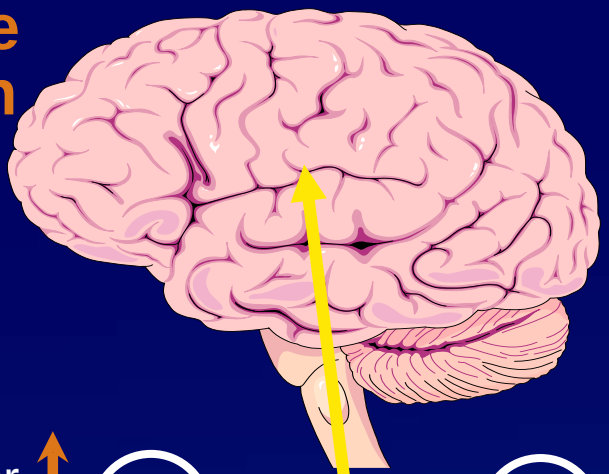
Arrows indicate direction in Fibromyalgia

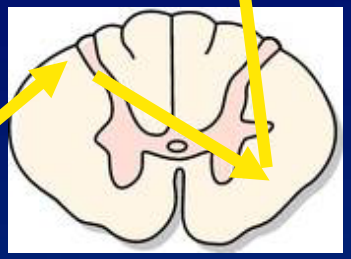
Generally facilitate pain transmission

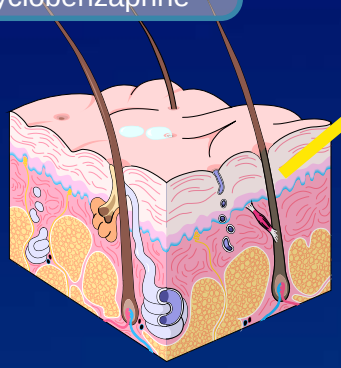
Gabapentinoids, ketamine, memantine

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

Anti-migraine drugs (–triptans), cyclobenzaprine







Generally inhibit pain transmission

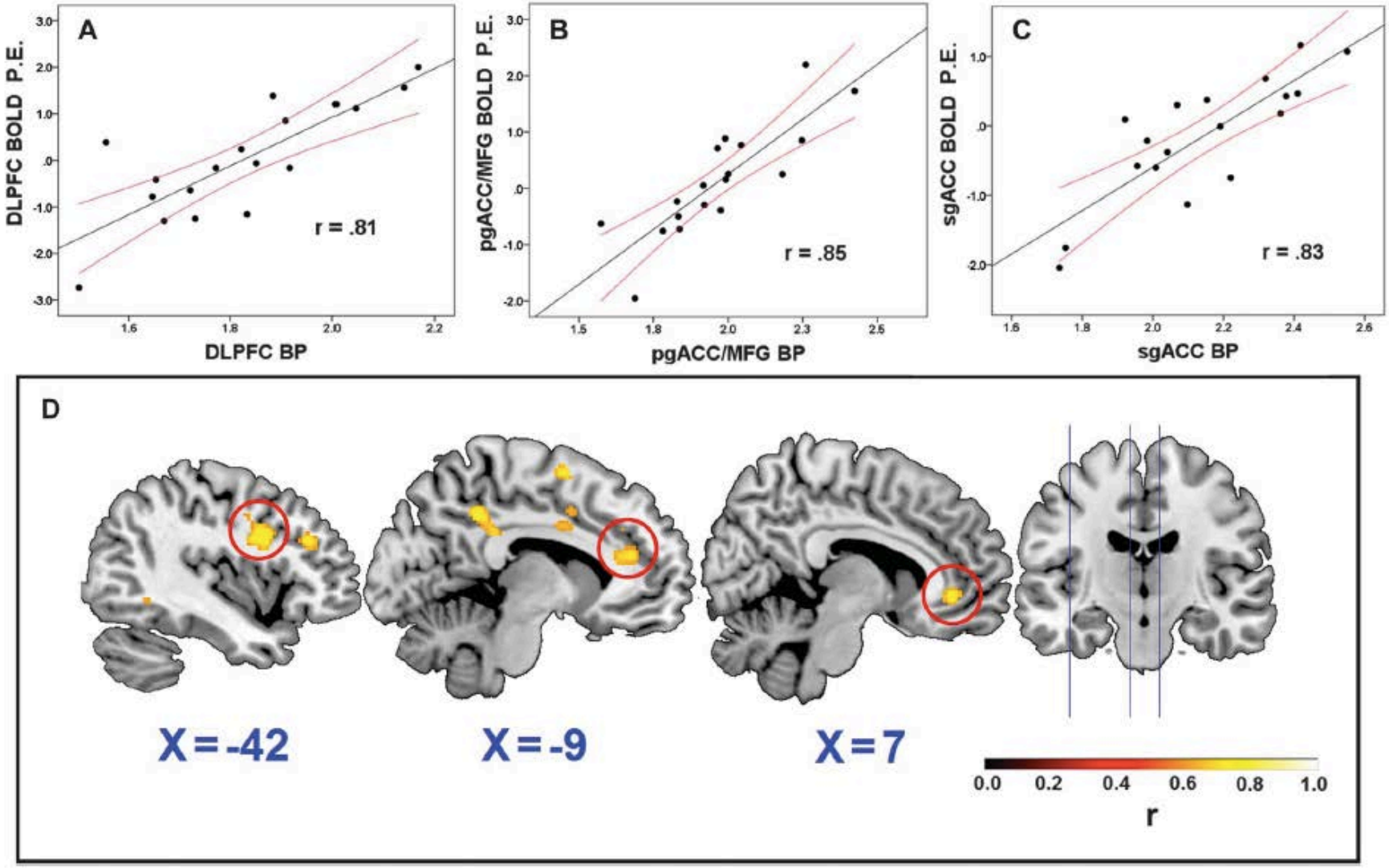
- Descending anti-nociceptive pathways
  - ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
    - Tricyclics, SNRIs. tramadol
  - ↑ Opioids
    - Low dose naltrexone
  - Cannabinoids
  - ↓ GABA
    - Gammahydroxybutyrate moderate alcohol consumption
    - No knowledge of endocannabinoid activity but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

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

PAIN

Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study

Andrew Schrepf[a,*], Daniel E. Harper[a], Steven E. Harte[a], Heng Wang[a], Eric Ichesco[a], Johnson P. Hampson[a], Jon-Kar Zubieta[b], Daniel J. Clauw[a], Richard E. Harris[a]



PAIN®

Towards a neurophysiological signature for fibromyalgia

Marina López-Solà[a,b,*], Choong-Wan Woo[a,b], Jesus Pujol[c], Joan Deus[c,d,e], Ben J. Harrison[f], Jordi Monfort[g], Tor D. Wager[a,b]

Abstract

Patients with fibromyalgia (FM) show characteristically enhanced unpleasantness to painful and nonpainful sensations accompanied by altered neural responses. The diagnostic potential of such neural alterations, including their sensitivity and specificity to FM (vs healthy controls) is unknown. We identify a brain signature that characterizes FM central pathophysiology at the neural systems level. We included 37 patients with FM and 35 matched healthy controls, and analyzed functional magnetic resonance imaging responses to (1) painful pressure and (2) nonpainful multisensory (visual–auditory–tactile) stimulation. We used machine-learning techniques to identify a brain-based FM signature. When exposed to the same painful stimuli, patients with FM showed greater neurologic pain signature (NPS; Wager et al., 2013. An fMRI-based neurologic signature of physical pain. N Engl J Med 2013;368:1388–97) responses. In addition, a new pain-related classifier ("FM-pain") revealed augmented responses in sensory integration (insula/operculum) and self-referential (eg, medial prefrontal) regions in FM and reduced responses in the lateral frontal cortex. A "multisensory" classifier trained on nonpainful sensory stimulation revealed augmented responses in the insula/operculum, posterior cingulate, and medial prefrontal regions and reduced responses in the primary/secondary sensory cortices, basal ganglia, and cerebellum. Combined activity in the NPS, FM pain, and multisensory patterns classified patients vs controls with 92% sensitivity and 94% specificity in out-of-sample individuals. Enhanced NPS responses partly mediated mechanical hypersensitivity and correlated with depression and disability ($P_{uncorrected} < 0.05$); FM-pain and multisensory responses correlated with clinical pain ($P_{uncorrected} < 0.05$). The study provides initial characterization of individual patients with FM based on pathophysiological, symptom-related brain features. If replicated, these brain features may constitute objective neural targets for therapeutic interventions. The results establish a framework for assessing therapeutic mechanisms and predicting treatment response at the individual level.

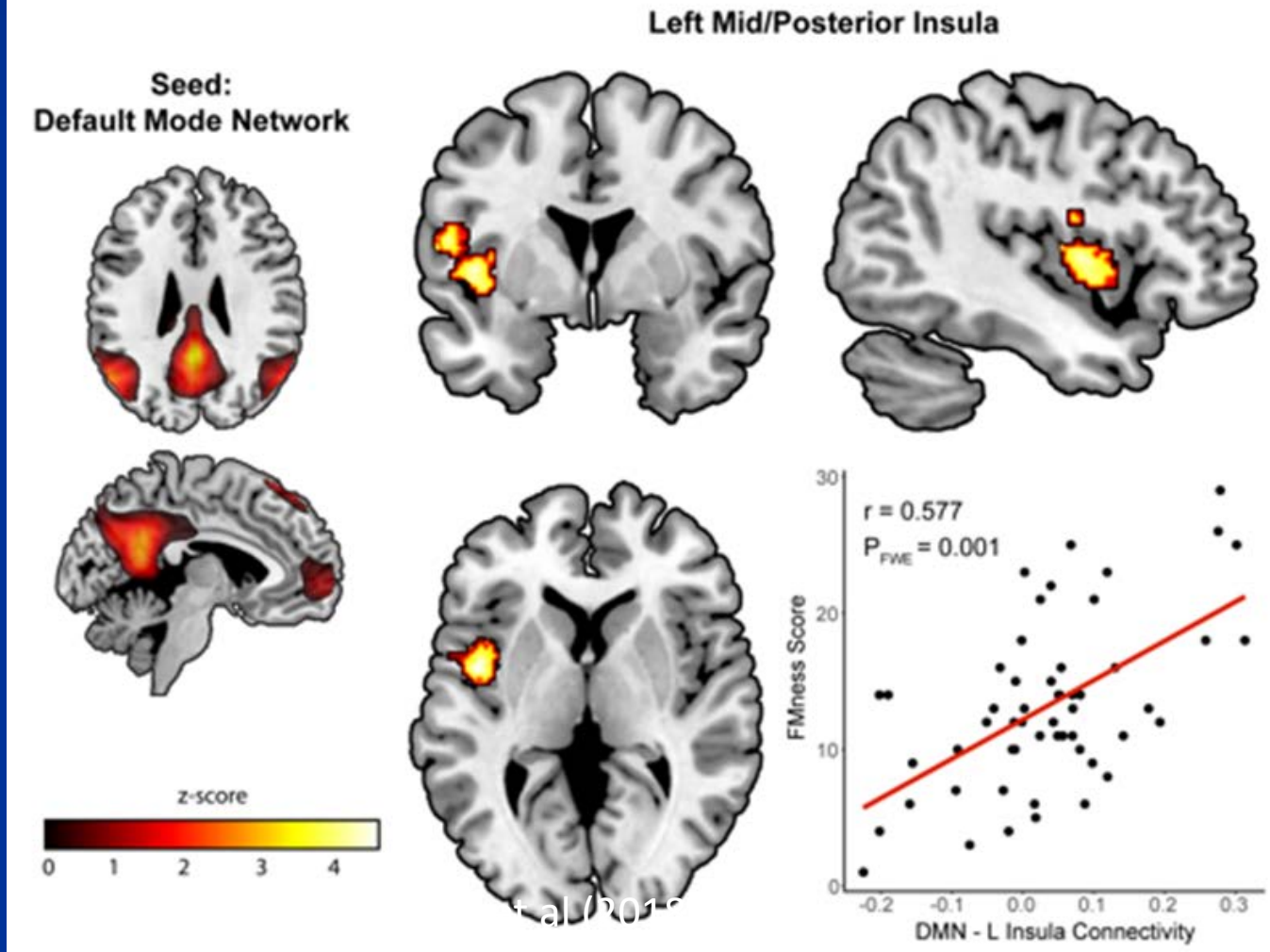
Keywords: Fibromyalgia, fMRI, Brain, Chronic pain, Multisensory, Pressure, Machine learning, Predict

Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
AMERICAN COLLEGE OF RHEUMATOLOGY

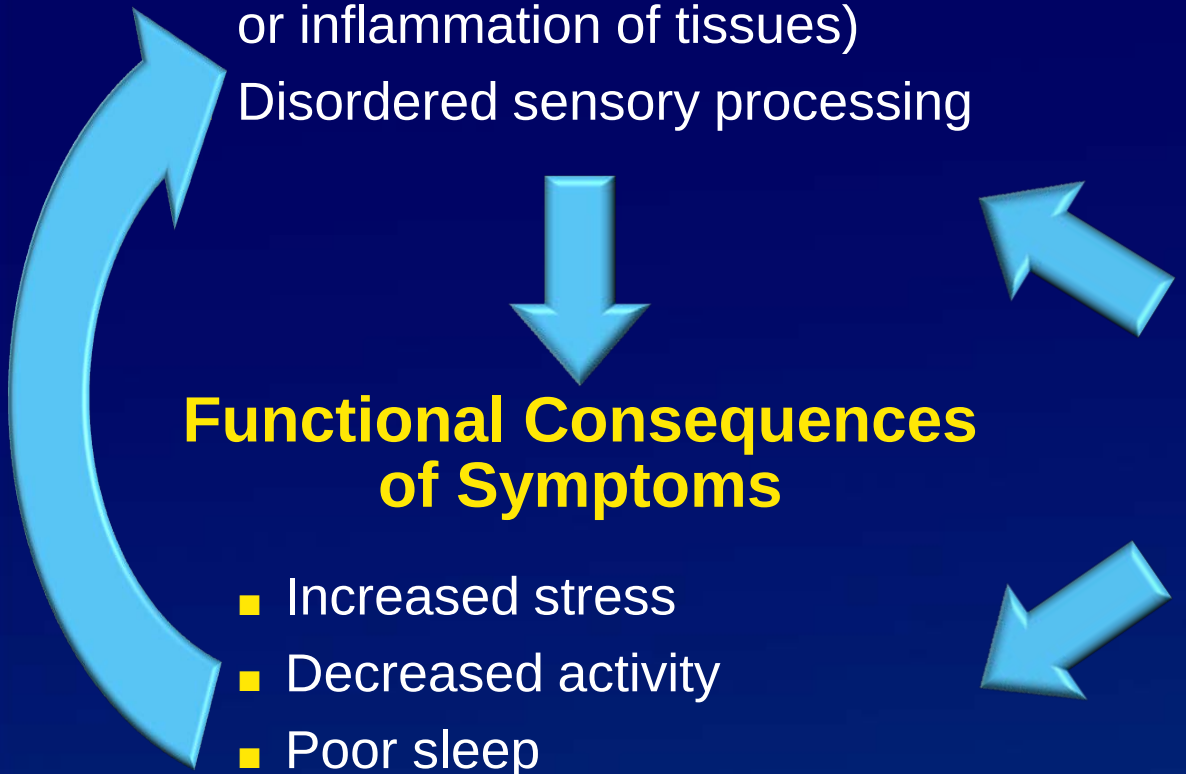
Original Article | Free Access

Neurobiologic Features of Fibromyalgia Are Also Present Among Rheumatoid Arthritis Patients

Neil Basu MD, PhD, Chelsea M. Kaplan PhD, Eric Ichesco BS, Tony Larkin BS, Richard E. Harris PhD, Alison Murray MD, PhD, Gordon Waiter PhD, Daniel J. Clauw MD



Process of Pain Chronification/Centralization



Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased stress
- Decreased activity
- Poor sleep
- Obesity
- Maladaptive illness behaviors

Dually Focused Treatment

- Pharmacological therapies to improve **symptoms**
- Nonpharmacological therapies to address **dysfunction**

Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Nonpharmacological Therapies are similar to those for any Chronic Pain State

Strong Evidence	▪ Education ▪ Aerobic exercise ▪ Cognitive behavior therapy
Modest Evidence	▪ Strength training ▪ Hypnotherapy, biofeedback, balneotherapy, yoga, Tai Chi ▪ Neuromodulation ▪ Acupuncture, chiropractic, manual and massage therapy
Weak Evidence	▪ Trigger point injections
No Evidence	▪ Doing nothing

Modified from Clauw *JAMA*. 2014

VA/DoD Stepped Care Model for Pain Management

Stepped Care Model for Pain Management (SCM-PM)

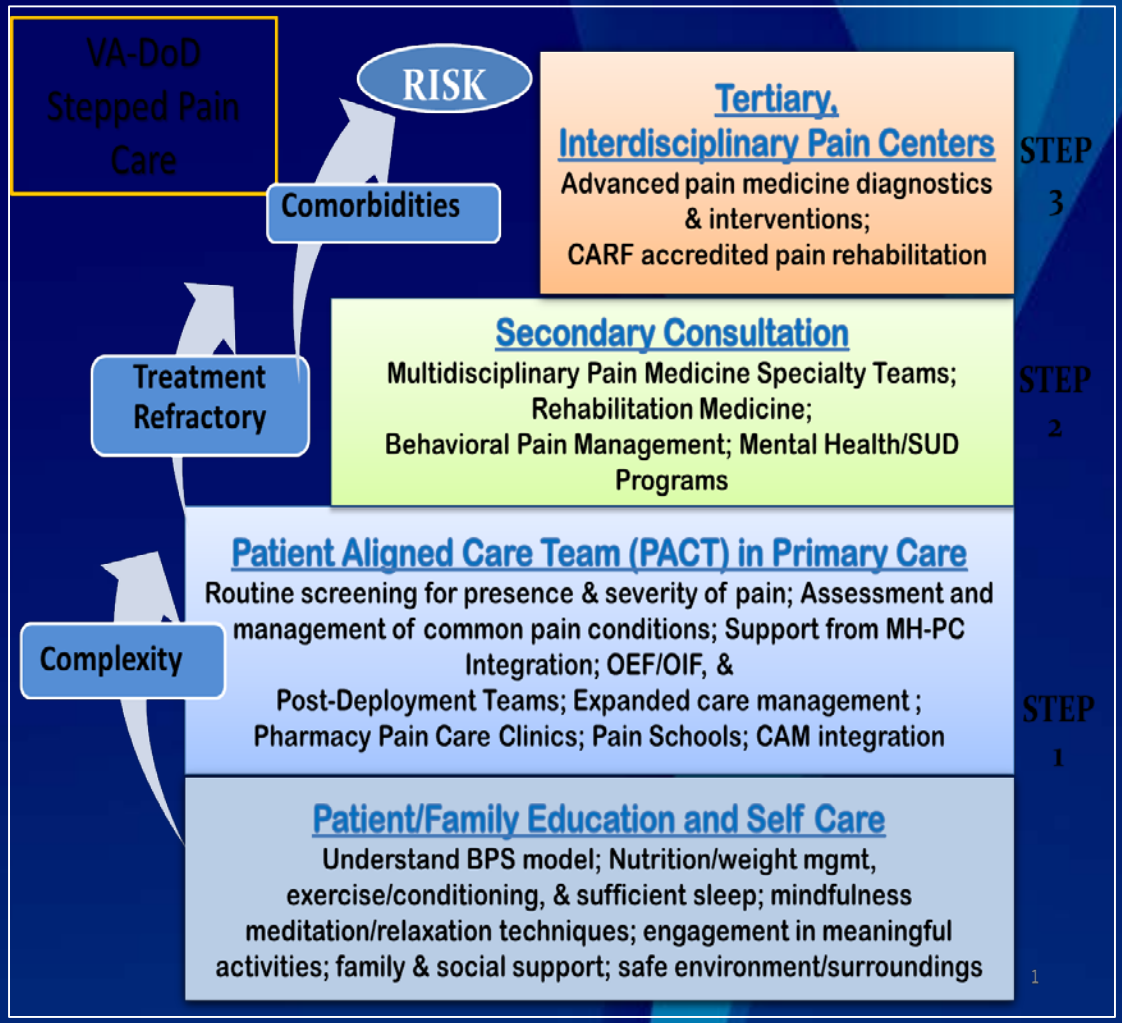
Foundational Step: Self-Care/Self-Management

Primary Care (PACT) = Medical Home

- Coordinated care and a long-term healing relationship, instead of episodic care based on illness
- Primary Care Mental Health Integration (PCMHI) at all facilities

CARA Legislation:

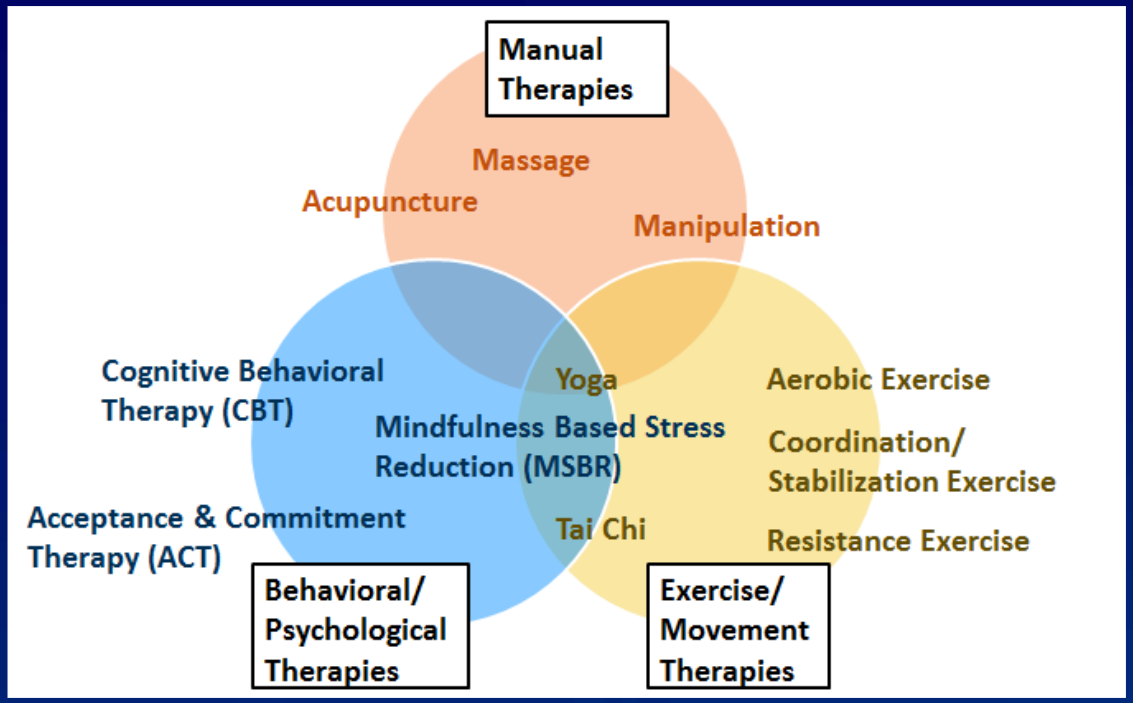
- Full implementation of the SCM-PM at all VHA facilities
- Pain Management Teams at all facilities



Non-Pharmacological Pain Treatments in VHA

VA State of the Art Conference Nov. 2016: Evidence-based non-pharmacological approaches for MSK pain management

- Evidence to support CIH and conventional therapies.
- Provision of multi-modal therapies accessible from Primary Care.



VHA Directive 1137: Advancing Complementary and Integrative Health (May 2017)

- List 1: Approaches with published evidence of promising or potential benefit.
  - Acupuncture
  - Massage Therapy
  - Tai Chi
  - Meditation
  - Yoga
  - Clinical Hypnosis
  - Biofeedback
  - Guided Imagery

Chiropractic Care was approved as a covered benefit in VHA in 2004 and is part of VA whole health care.
To be made available across the system, if recommended by the Veteran's health care team.

Pain, Disability and Biomarkers

- There is no chronic pain condition where there is a good relationship between any type of peripheral damage or inflammation - and the presence or severity of pain
- The primary reason for this is that pain occurs because of a combination of biopsychosocial factors that are not typically assessed or treated in clinical practice , especially central nervous system (CNS) factors that are playing prominent roles in most individuals with severe chronic pain and or disability
- **We do have biomarkers that can measure these CNS factors – but should we – or are we simply perpetuating a misguided approach?**

Chronic Pain – Disability Conundrum

- The overwhelming majority of individuals who go on to get disability for chronic pain have chronic pain
  - Most of us in clinical practice rarely see individuals who are truly faking their pain – so adding expensive measures to determine if someone is really in pain doesn't seem prudent
- When patients with chronic pain are contemplating applying for disability this is a cry for help
  - The patient feels that a combination of social, work, and financial issues preclude them from continuing to do their current job
  - It takes time and money to do the treatments we recommend – they typically have neither

Chronic Pain – Disability Conundrum

- Even though the patient feels that the only way out of their current conundrum is to go on disability, as providers we know that if they do - *they almost always get worse medically and functionally, because they become less active, more depressed, etc.*
- *And if that wasn't bad enough, the process of proving that the patient is disabled*
- For several decades I have been teaching that FM patients are as disabled or more disabled than patients with most any other disease - but that it is a generally a terrible idea for FM patients to go on permanent disability

VA/DoD Stepped Care Model for Pain Management

Stepped Care Model for Pain Management (SCM-PM)

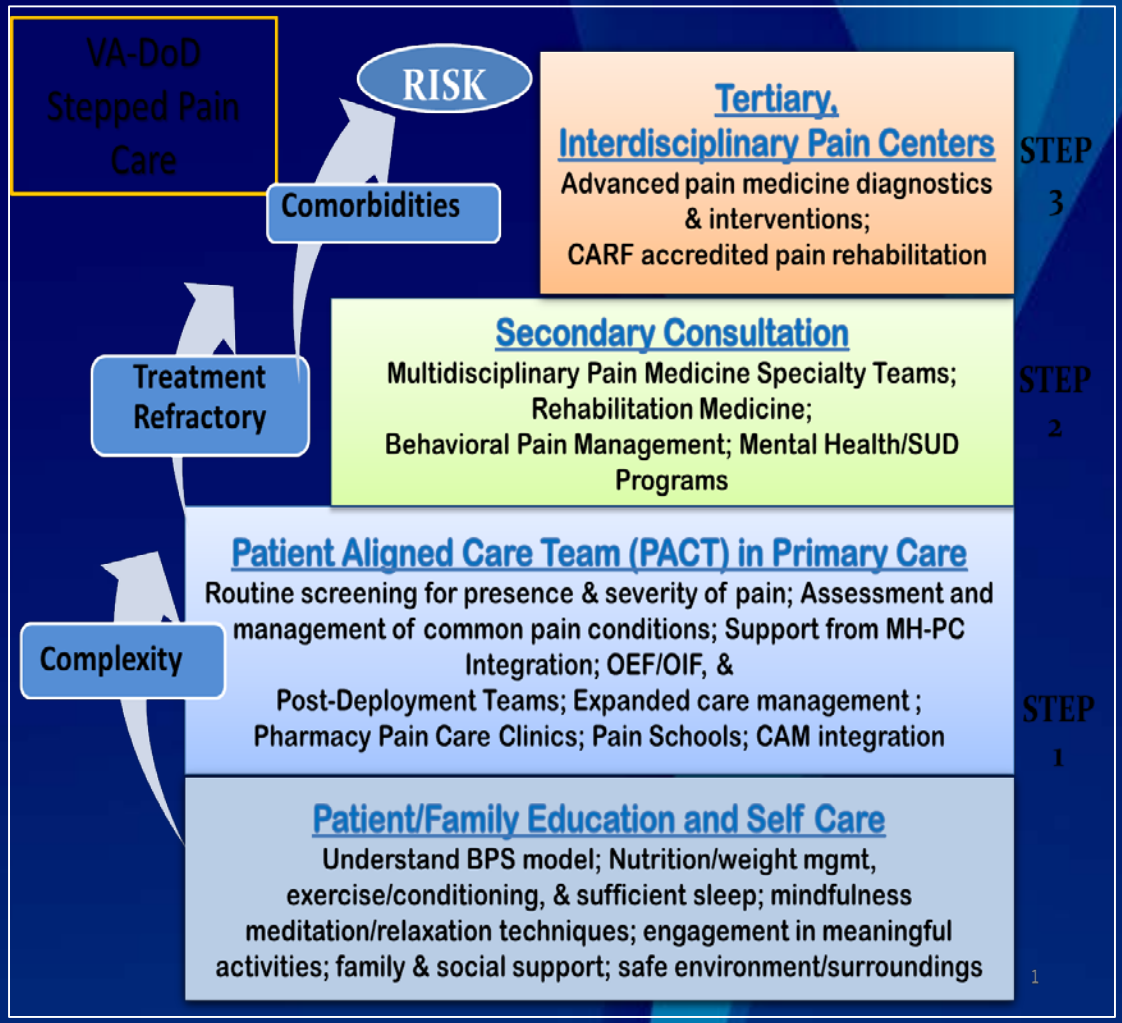
Foundational Step: Self-Care/Self-Management

Primary Care (PACT) = Medical Home

- Coordinated care and a long-term healing relationship, instead of episodic care based on illness
- Primary Care Mental Health Integration (PCMHI) at all facilities

CARA Legislation:

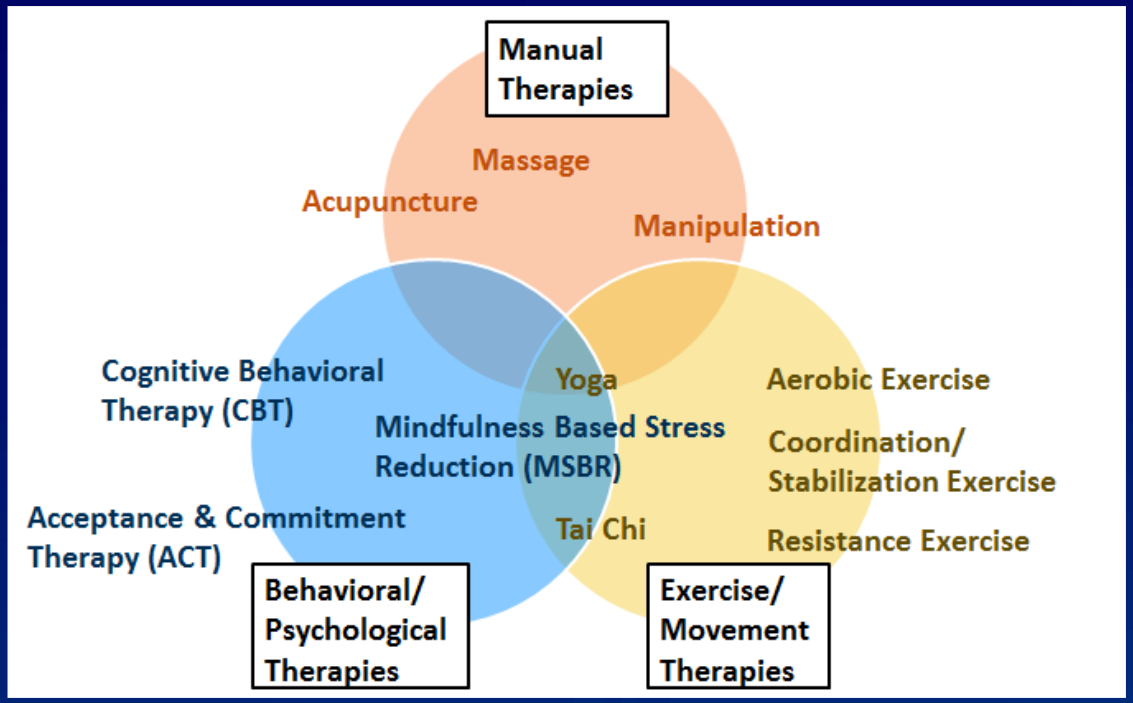
- Full implementation of the SCM-PM at all VHA facilities
- Pain Management Teams at all facilities



Non-Pharmacological Pain Treatments in VHA

VA State of the Art Conference Nov. 2016: Evidence-based non-pharmacological approaches for MSK pain management

- Evidence to support CIH and conventional therapies.
- Provision of multi-modal therapies accessible from Primary Care.



VHA Directive 1137: Advancing Complementary and Integrative Health (May 2017)

- List 1: Approaches with published evidence of promising or potential benefit.
  - Acupuncture
  - Massage Therapy
  - Tai Chi
  - Meditation
  - Yoga
  - Clinical Hypnosis
  - Biofeedback
  - Guided Imagery

Chiropractic Care was approved as a covered benefit in VHA in 2004 and is part of VA whole health care.
To be made available across the system, if recommended by the Veteran's health care team.