Advances in Our Understanding of Diagnosing and Treating Chronic Pain

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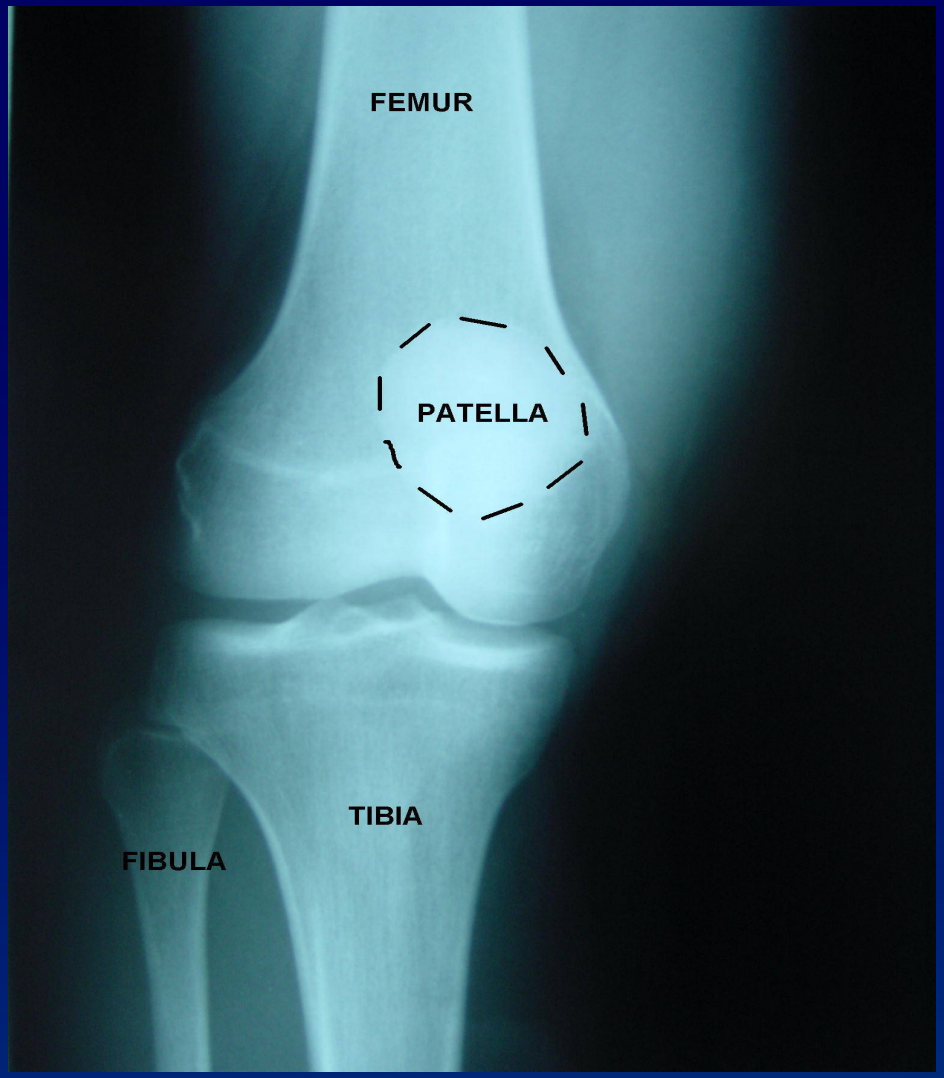
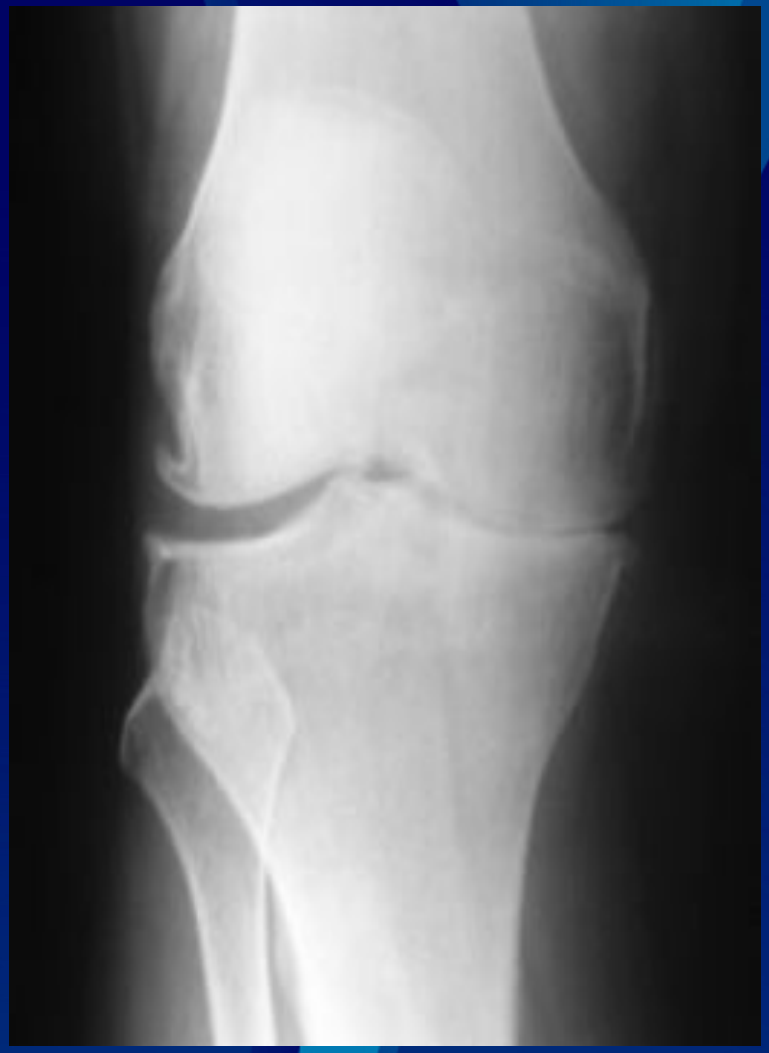
Disclosures

- Consulting
  - Pfizer, Tonix, Theravance, Zynerba, Samumed, Aptinyx, Daiichi Sankyo, Intec, Regeneron, Teva, Lundbeck, Virios
- Research support
  - Pfizer, Cerephex, Aptinyx
- Litigation – testified against opioid manufacturers in State of Oklahoma, Florida

Which person has pain?





Osteoarthritis

- 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

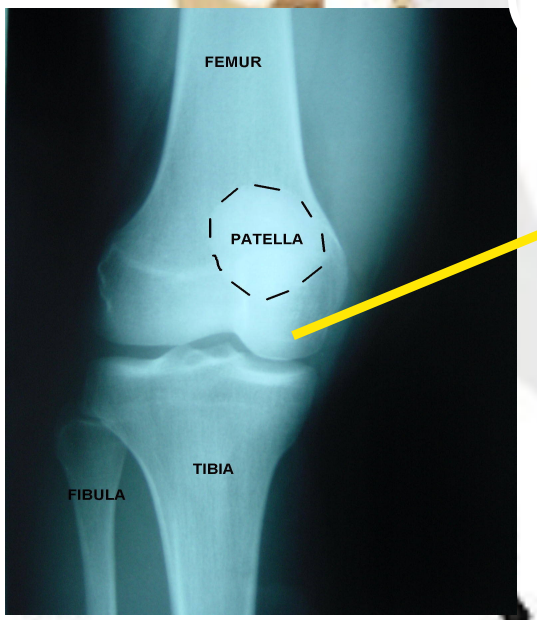
(1) Creamer P, et. al. Br J Rheumatol 1997; 36(7):726-8. (2) Creamer P, et. al. Arthritis Care Res 1998; 11(1):60-5. (3) Bjordal JM, et. al. Eur J Pain 2007; 11(2):125-38. (4) Zhang W, et. al. Ann Rheum Dis 2004; 63(8):901-7.

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

- 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


FEMUR
PATELLA
TIBIA
FIBULA

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

Chronic Pain 2

Nociplastic pain: towards an understanding of prevalent pain conditions

Mary-Ann Fitzcharles, Steven P Cohen*, Daniel J Clauw, Geoffrey Littlejohn, Chie Usui, Winfried Häuser*

Lancet 2021; 397: 2098–110

See **Comment** page 2029

This is the second in a **Series** of three papers about chronic pain

*Contributed equally

Department of Rheumatology and Alan Edwards Pain Management Unit, McGill University, Montreal, QC, Canada (M-A Fitzcharles MBChB); Department of Psychiatry and Behavioral Sciences and Department of Anesthesiology and Critical Care Medicine, Neurology and Physical Medicine and Rehabilitation at

Nociplastic pain is the semantic term suggested by the international community of pain researchers to describe a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented CNS pain and sensory processing and altered pain modulation play prominent roles. The symptoms observed in nociplastic pain include multifocal pain that is more widespread or intense, or both, than would be expected given the amount of identifiable tissue or nerve damage, as well as other CNS-derived symptoms, such as fatigue, sleep, memory, and mood problems. This type of pain can occur in isolation, as often occurs in conditions such as fibromyalgia or tension-type headache, or as part of a mixed-pain state in combination with ongoing nociceptive or neuropathic pain, as might occur in chronic low back pain. It is important to recognise this type of pain, since it will respond to different therapies than nociceptive pain, with a decreased responsiveness to peripherally directed therapies such as anti-inflammatory drugs and opioids, surgery, or injections.

Introduction

occur in isolation or as a comorbidity in individuals with

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Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

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†Center for Translational Pain Medicine, Department of Anesthesiology, Duke University, Durham, North Carolina.
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§Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

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

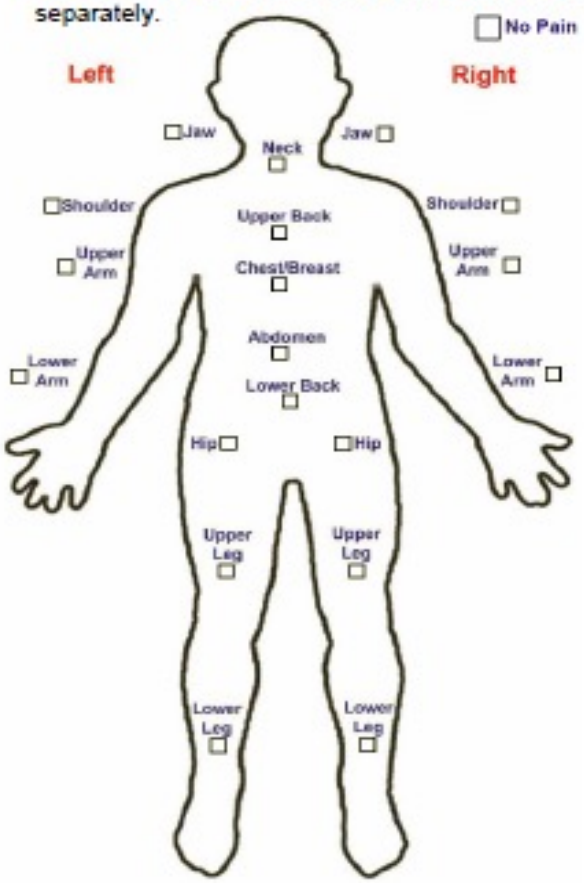
Chronic Overlapping Pain Conditions

- 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

2010/11/16 ACR criteria for FM

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** ☐

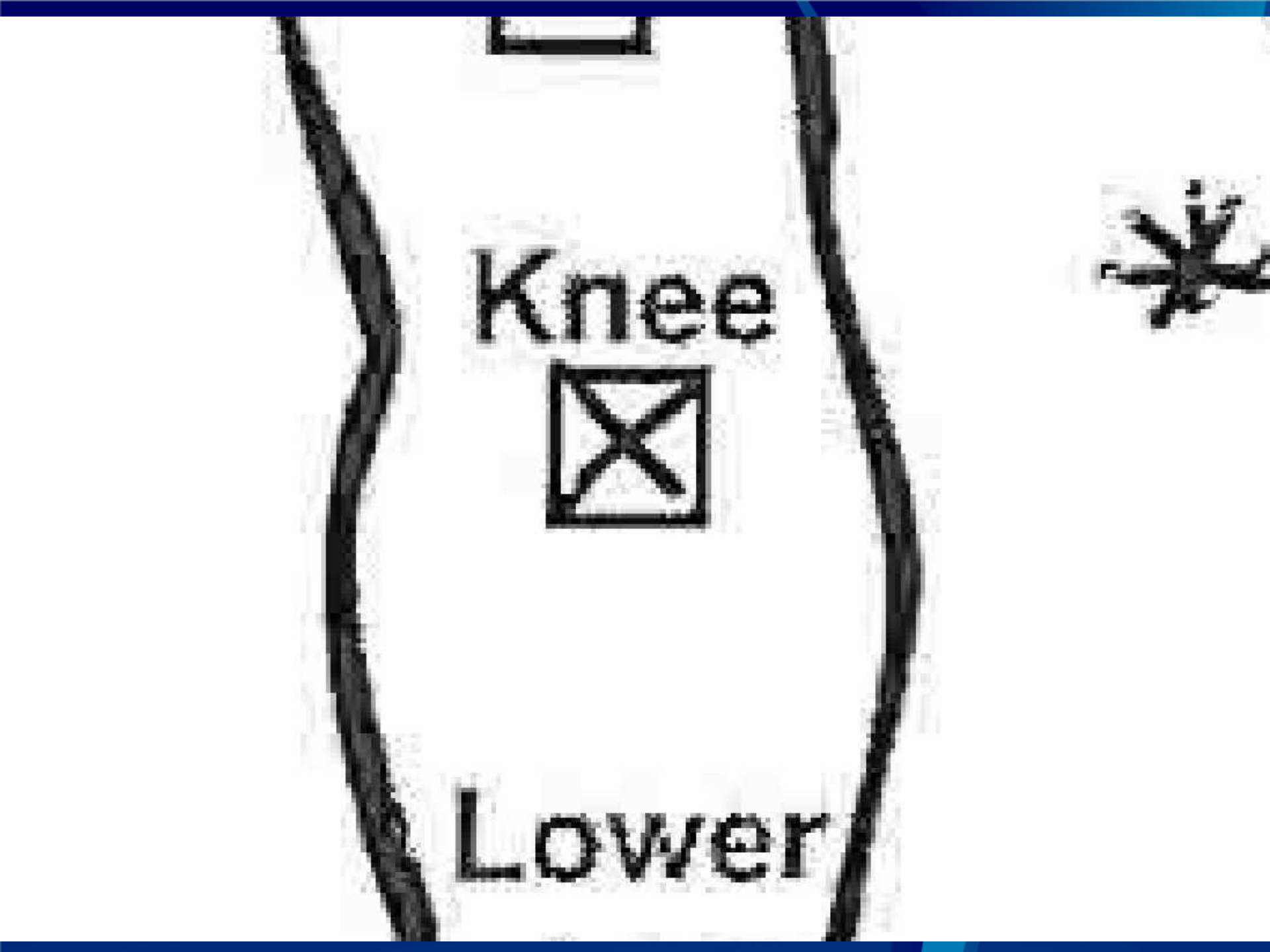
5. Do you have a disorder that would otherwise explain the pain? **No** ☐ **Yes** ☐

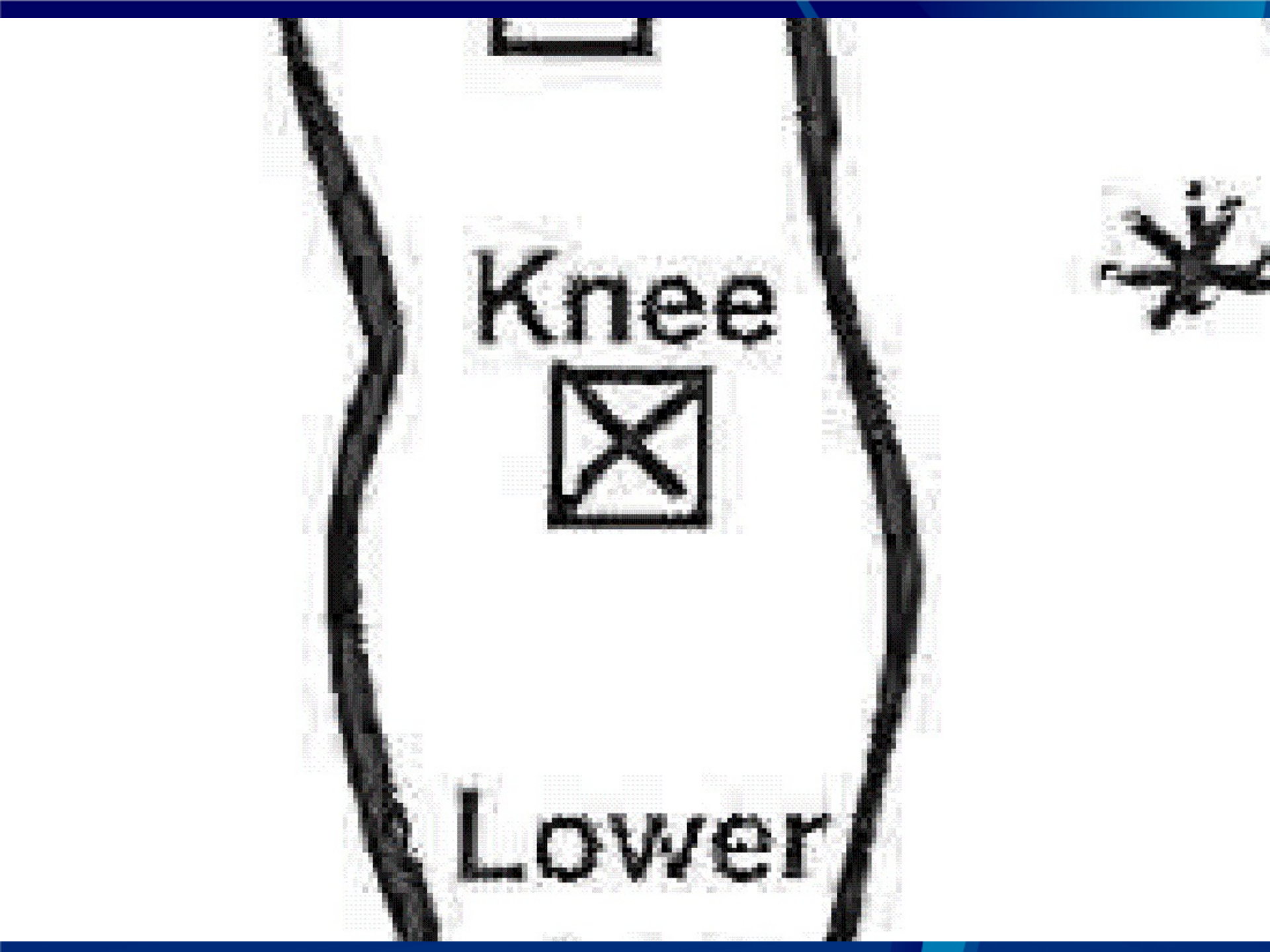
1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Fibromyalgia-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.

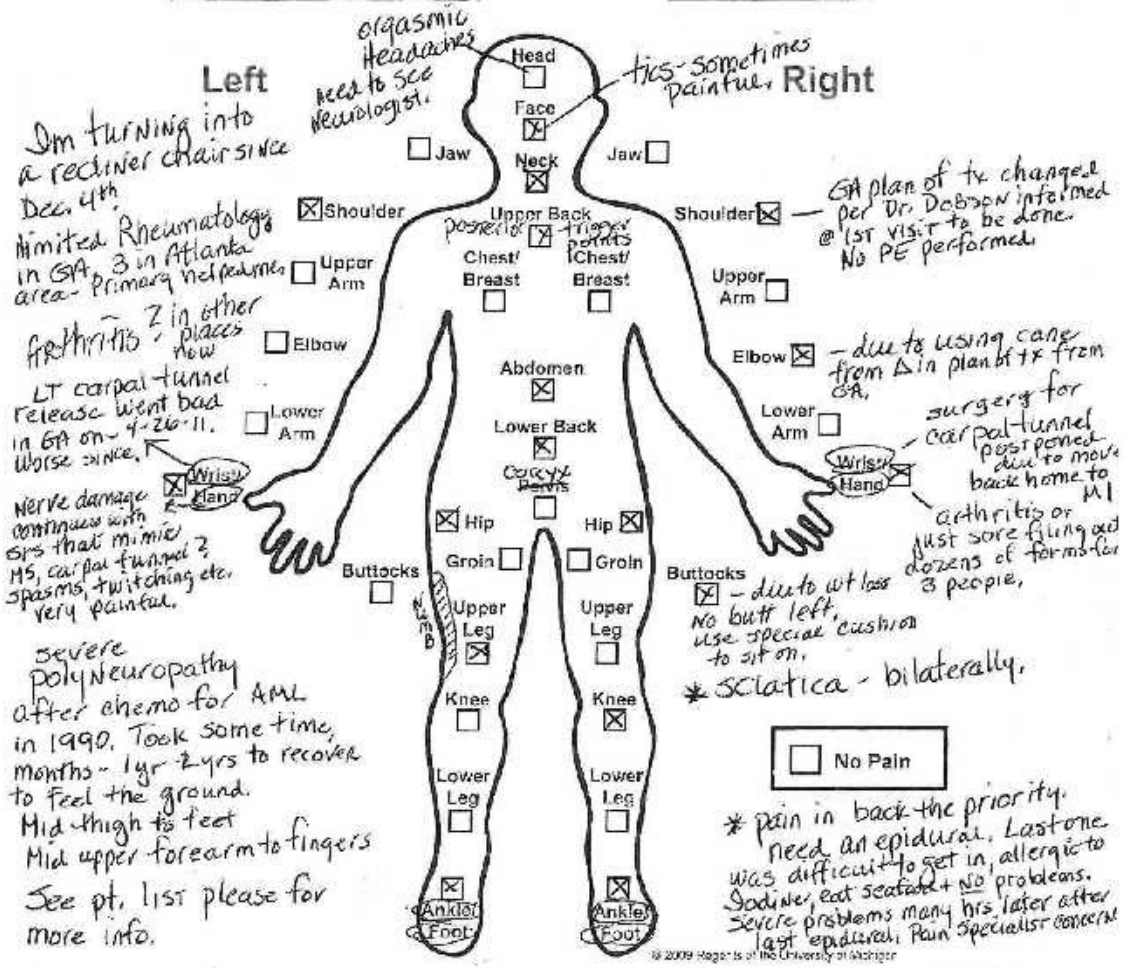

Knee
Lower


Knee
Lower

UNIVERSITY OF MICHIGAN HOSPITALS & HEALTH CENTERS	NAME
Anesthesiology	REG NO.
New Patient Questionnaire - Back and Pain Center	BIRTHDATE

Michigan Body Map

On the image below, identify **all** the areas of your body where you have felt ***persistent or recurrent pain*** present for the last ***3 months or longer***.



Im turning into a recliner chair since Dec. 4th.

limited Rheumatology in GA, 3 in Atlanta area- primary not pain management

Arthritis ? in other places now

LT carpal tunnel release went bad in GA on ~ 4-26-11. Worse since.

Nerve damage continues with sprs that mimic MS, carpal tunnel ?, spasms, twitching etc. very painful.

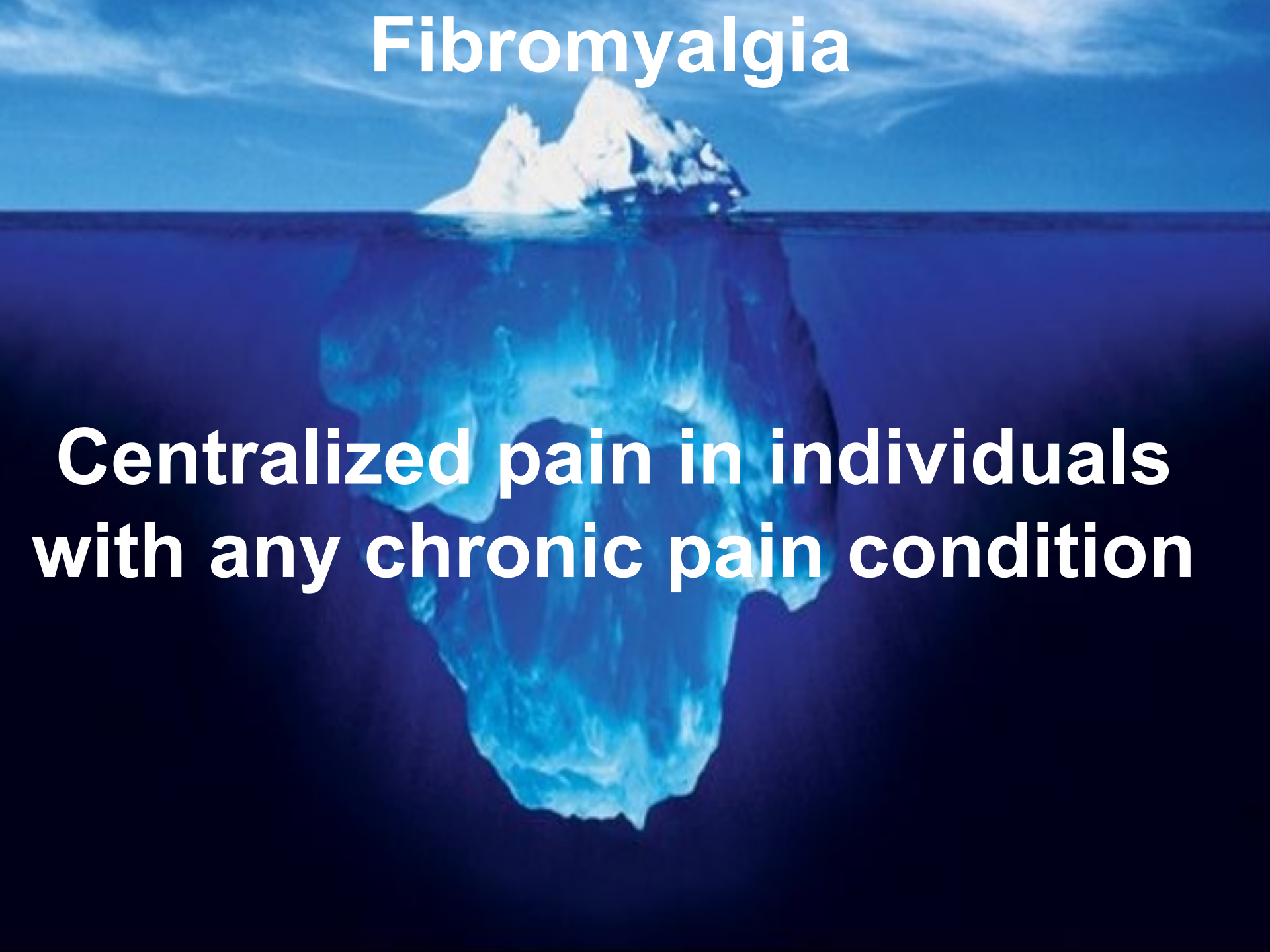
severe PolyNeuropathy after chemo for AML in 1990. Took some time, months ~ 1yr 2yrs to recover to feel the ground.
Mid thigh to feet
Mid upper forearm to fingers
See pt. list please for more info.

arthritis or just sore filing and dozens of forms for 3 people.

* sciatica - bilaterally.

* pain in back the priority. need an epidural. Last one was difficult to get in, allergic to Iodine, eat seafood + No problems. Severe problems many hrs later after last epidural. Pain Specialist concerned

5[illegible]10C04	VER: 8/11 HIM: 07/11	Medical Record	M	New Patient Questionnaire - Back and Pain Center

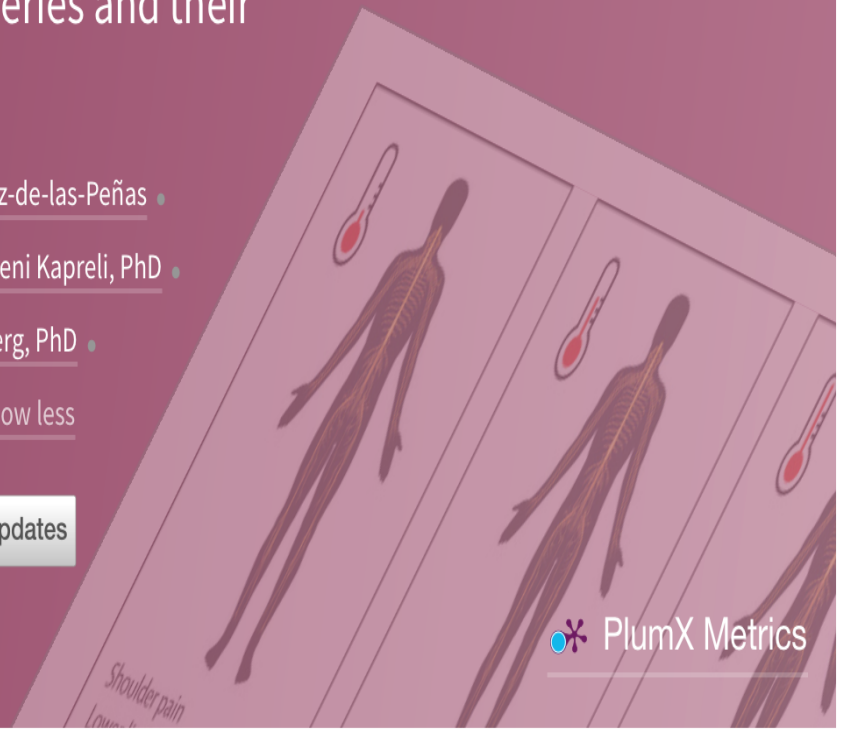

Fibromyalgia
Centralized pain in individuals with any chronic pain condition

THE LANCET
Rheumatology

Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine

Prof Jo Nijs, PhD • Prof Steven Z George, PhD • Prof Daniel J Clauw, MD • Prof César Fernández-de-las-Peñas • Prof Eva Kosek, MD • Kelly Ickmans, PhD • Prof Josué Fernández-Carnero • Andrea Polli, PhD • Prof Eleni Kapreli, PhD • Eva Huysmans, MSc • Prof Antonio I Cuesta-Vargas, PhD • Ramakrishnan Mani, PhD • Prof Mari Lundberg, PhD • Laurence Leysen, PhD • David Rice, PhD • Prof Michele Sterling, PhD • Prof Michele Curatolo, MD • Show less

Published: March 30, 2021 • DOI: https://doi.org/10.1016/S2665-9913(21)00032-1 •



Summary

Chronic pain is a leading cause of disability globally and associated with enormous health-care costs. The discrepancy between the extent of tissue damage and the magnitude of pain,

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

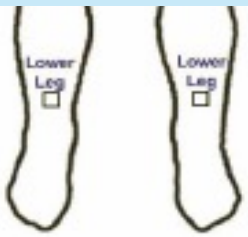
“Fibromyalgia-ness” can be scored 0-31

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?

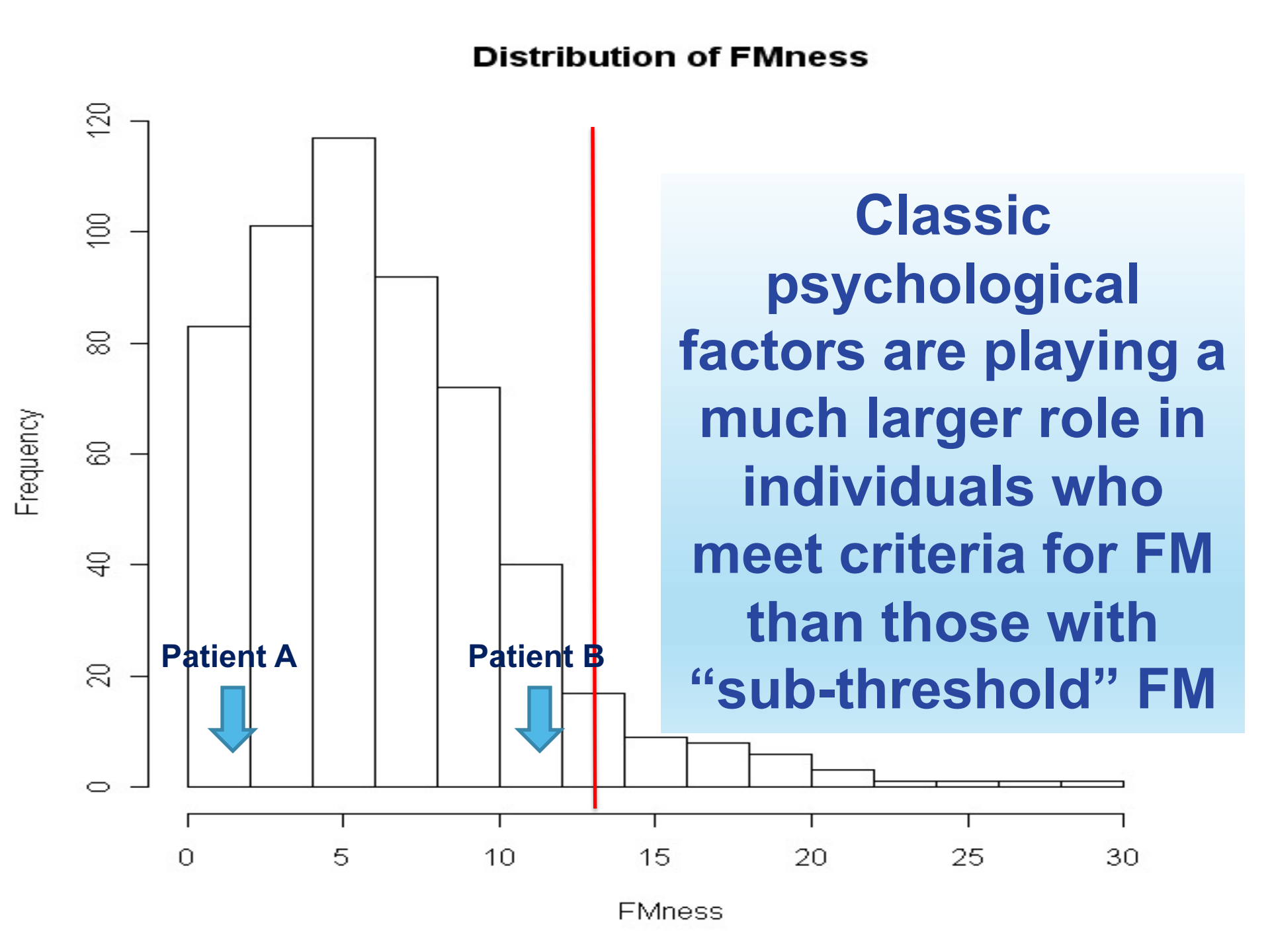
No ☐ Yes ☐

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. *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

Incidence and predictors of persistent pelvic pain following hysterectomy in women with chronic pelvic pain

Sawsan As-Sanie, MD, MPH; Sara R. Till, MD, MPH; Andrew D. Schrepf, PhD; Kendall C. Griffith, MD; Alex Tsodikov, PhD; Stacey A. Missmer, ScD; Daniel J. Clauw, MD; Chad M. Brummett, MD

BACKGROUND: Chronic pelvic pain is a debilitating problem that afflicts 15% to 20% of women in the United States. Although more than 200,000 hysterectomies are performed annually for the treatment of chronic pelvic pain, previous studies indicate that 1 in 4 women undergo the discomfort and morbidity of hysterectomy without the relief of pain. The factors that predict treatment failure remain poorly characterized.

OBJECTIVE: To describe the incidence of persistent pelvic pain 6 months following hysterectomy in women with chronic pelvic pain and determine whether a simple, self-reported measure of central sensitization is associated with a greater risk of persistent pelvic pain following hysterectomy.

STUDY DESIGN: We conducted a prospective, observational cohort study of women undergoing hysterectomy at an academic tertiary care center for a benign indication. Patients with preoperative chronic pelvic pain, defined as average pelvic pain $\geq$3 on a 0 to 10 numeric rating scale for $>$3 months before hysterectomy, were included in this analysis. The patients completed validated assessments of pain, anxiety, depression, and centralized pain (using the 2011 Fibromyalgia Survey Criteria, 0–31 points) preoperatively and 6 months after hysterectomy. The demographic information, surgical history, intraoperative findings, and surgical pathology were abstracted from the

RESULTS: Among 176 participants with pelvic pain before hysterectomy, 126 (71.6%) were retained at 6 months, and 15 (11.9%) reported persistent pelvic pain. There was no difference in age (P=.46), race (P=.55), average pain severity during menses (P=.68), average overall pelvic pain (P=.10), or pain duration (P=.80) in those with and without persistent pelvic pain. Whereas intraoperative findings of endometriosis (P=.05) and uterine fibroids (P=.03) were associated with a higher incidence of persistent pain on univariate analysis, the surgical route (P=.46), pelvic adhesions (0.51), uterine weight (P=.66), and adenomyosis on histopathology (P=.27) were not related to the risk of persistent pain. Higher preoperative centralized pain scores (P=.01) but not depression (P=.64) or anxiety (P=.45) were more common in women with persistent pelvic pain. Multivariate logistic regression adjusting for age, preoperative pain severity, anxiety, depression, and operative findings of endometriosis and fibroids indicated that every 1-point increase in centralized pain before hysterectomy was associated with a 27% increase in the odds of persistent pelvic pain (odds ratio, 1.27; 95% confidence interval, 1.03–1.57) 6 months after surgery.

CONCLUSION: Although the majority of women with chronic pelvic pain report considerable improvement in pain following hysterectomy, higher degrees of centralized pain before hysterectomy is a robust pre-

RHEUMATOLOGY

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Advance Access publication 14 August 2019

Original article

Top down or bottom up? An observational investigation of improvement in fibromyalgia symptoms following hip and knee replacement

Andrew Schrepf[1], Stephanie Moser[1], Steven E. Harte[1], Neil Basu[2], Chelsea Kaplan[1], Ellen Kolarik[1], Alexander Tsodikov[3], Chad M. Brummett[1] and Daniel J. Clauw[1]

Abstract

Objectives. Many patients with osteoarthritis have comorbid symptoms of FM, but it is unknown how these symptoms respond to surgical procedures that address nociceptive input in the periphery, such as total joint replacement. Here we explore differences in clinical characteristics between patients whose FM symptoms do and do not improve following total hip or knee replacement.

Methods. Participants were 150 patients undergoing knee or hip replacement who had a minimum FM survey score of 4 or greater prior to surgery. The top tertile of patients experiencing the most improvement in FM symptoms at month 6

Arthritis & Rheumatology

AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Original Article

Heritability of the Fibromyalgia Phenotype Varies by Age

Diptavo Dutta, Chad M. Brummett, Stephanie E. Moser, Lars G. Fritsche, Alexander Tsodikov, Seunggeun Lee, Daniel J. Clauw, Laura J. Scott ✉, ... See fewer authors

First published: 17 November 2019 | https://doi.org/10.1002/art.41171 | Citations: 3

Results

Overall, the FM score had an estimated heritability of 13.9% (SE 2.9%) ($P = 1.6 \times 10^{-7}$). Estimated FM score heritability was highest in individuals ≤50 years of age (23.5%; SE 7.9%) ($P = 3.0 \times 10^{-4}$) and lowest in individuals >60 years of age (7.5%; SE 8.1%) ($P = 0.41$). These patterns remained the same when we analyzed FM as a case–control phenotype. Even though women had an ~30% higher average FM score than men across age categories, FM score heritability did not differ significantly by sex.

Conclusion

Younger individuals appear to have a much stronger genetic component to the FM score than older individuals. Older individuals may be more likely to have what was previously called "secondary FM." Regardless of the cause, these results have implications for future genetic studies of FM and associated conditions.

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
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

Mixed Pain States

The widespreadedness of pain (half of the 2011 FM criteria) predicts increased responsiveness to duloxetine in Low Back Pain

- In LBP, responsiveness to duloxetine was strongly related to number of sites on the Michigan Body Map.
  - Average number of sites of pain in this LBP study was 3 – 4
  - At 14 weeks, using any measure of pain improvement, individuals with more body sites of pain were significantly more likely to respond
  - Relative response rate for responders (30% improvement in pain)
    - MBM pain sites = 1 RR = **1.07**
    - MBM sites = 2 **1.30**
    - MBM sites = 3 **1.34**
    - MBM sites = 4 **1.47**
    - MBM sites > 5 **1.60**

1. Alev et. al. Clinical Journal of Pain, 2017

ELSEVIER journal homepage: http://www.elsevier.com/locate/jos

Original Article

Efficacy of duloxetine for multisite pain in patients with knee pain due to osteoarthritis: An exploratory post hoc analysis of a Japanese phase 3 randomized study

Naohiro Itoh [a], Toshinaga Tsuji [a, *], Mitsuhiro Ishida [b], Toshimitsu Ochiai [c], Shinichi Konno [d], Yuji Uchio [e]

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[b] *Project Management Development Department, Shionogi & Co., Ltd., Osaka, Japan*
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A R T I C L E I N F O

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A B S T R A C T

Background: Central sensitization, including dysfunction of descending inhibitory pain pathways, may contribute to multisite pain in patients with chronic musculoskeletal conditions. Duloxetine is a centrally acting analgesic that effectively reduces pain in patients with knee osteoarthritis. Here we assessed the efficacy of duloxetine (60 mg/day) in Japanese patients (N = 353) with pain due to knee osteoarthritis based on the number of painful body sites, determined using the Michigan Body Map.

Methods: Post hoc analysis of a phase 3, randomized, placebo-controlled trial (ClinicalTrials.gov; NCT02248480).

Results: At Week 14, the change from baseline in Brief Pain Inventory-Severity average pain score ("pain reduction") was significantly greater with duloxetine compared with placebo in patients with 3, 4, or ≥5 painful sites, but not in patients with 1 or 2 painful sites. In patients with ≥3 painful sites (57% of patients), pain reduction was significantly greater with duloxetine (n = 100) compared with placebo (n = 101) throughout the study (least squares mean change from baseline to Week 14: −2.68 vs −1.68). Greater pain reduction with duloxetine (n = 77) than placebo (n = 75) also occurred in patients with ≤2 painful sites, although the between-group difference was significant only at Week 4.

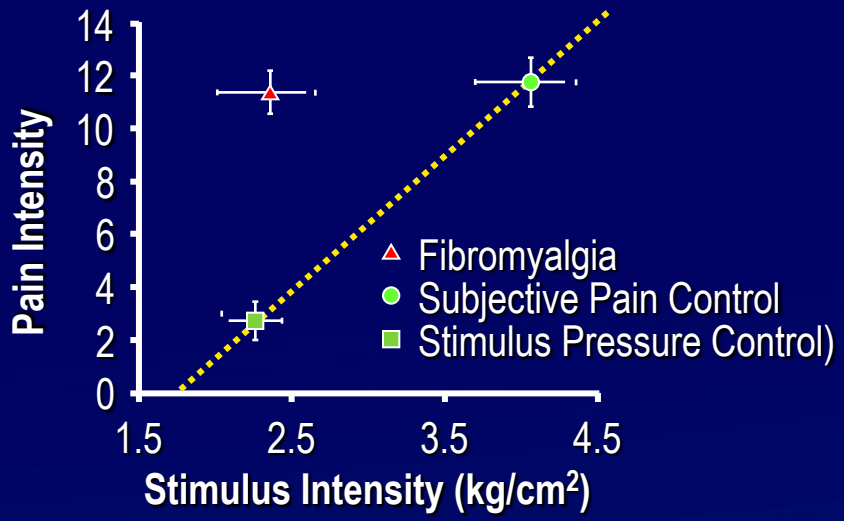
Conclusions: These results are consistent with duloxetine enhancing the activity of descending inhibitory pain pathways that are dysfunctional in patients with central sensitization and multisite pain. In addition, these results suggest that duloxetine may be an effective choice of analgesic for patients with knee osteoarthritis and multisite pain.

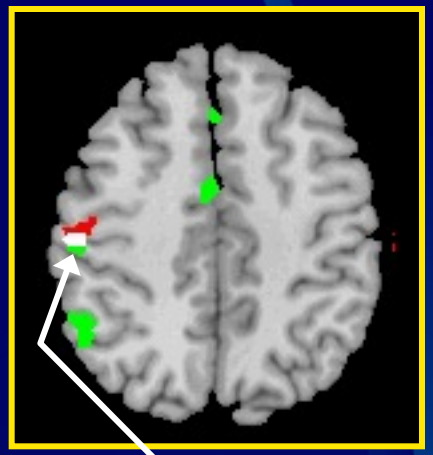
Pathophysiology of centralized pain states

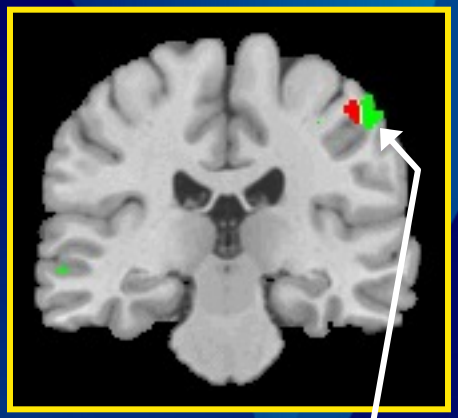
- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances 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

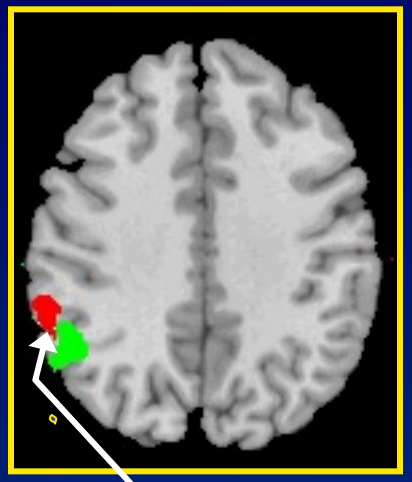
1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4.Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9):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

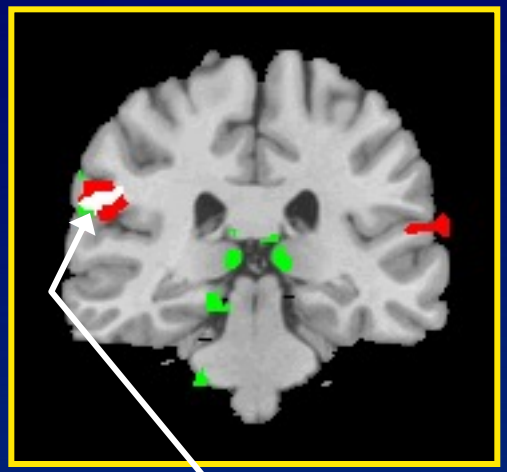
fMRI in Fibromyalgia

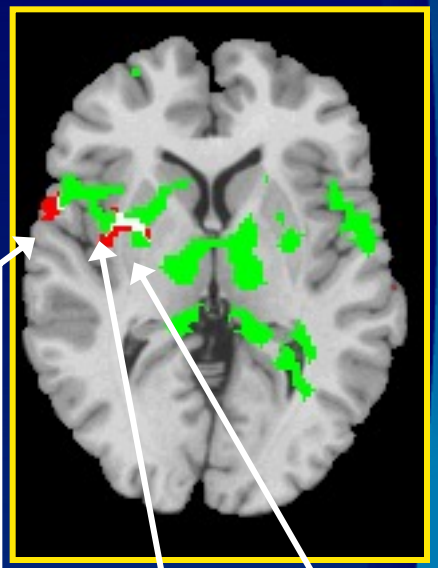


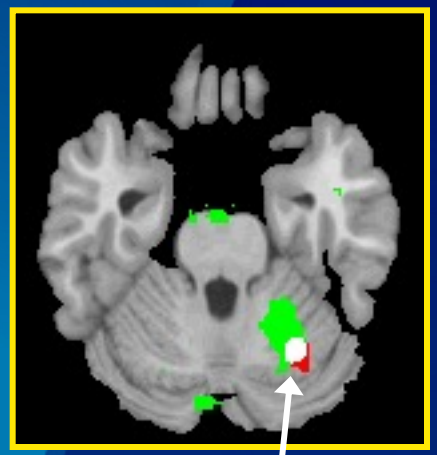








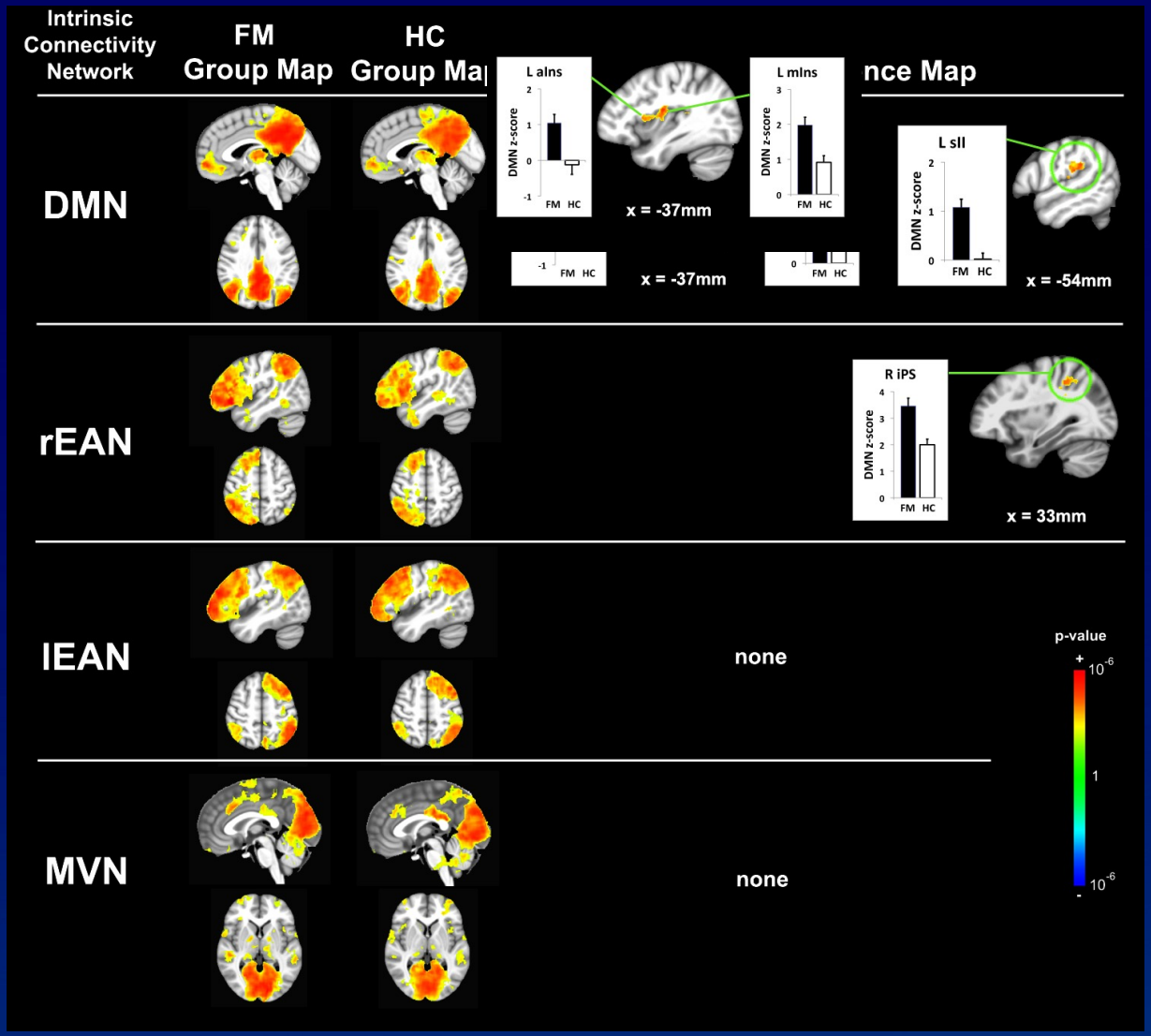




STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

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

Research Paper

PAIN®

Neurobiological antecedents of multisite pain in children

Chelsea M. Kaplan[a,*], Andrew Schrepf[a], Ishtiaq Mawla[b], Eric Ichesco[a], Kevin F. Boehnke[a], Adriene Beltz[c], Emily Foxen-Craft[d], Michael P. Puglia II[a], Alexandre Tsodikov[e], David A. Williams[a,b,f,g], Afton L. Hassett[a], Daniel J. Clauw[a,f,g], Steven E. Harte[a,b,g], Richard E. Harris[a,b,g]

Abstract

Altered brain structure and function is evident in adults with multisite chronic pain. Although many such adults trace their pain back to childhood, it has been difficult to disentangle whether central nervous system alterations precede or are consequences of chronic pain. If the former is true, aberrant brain activity may identify children vulnerable to developing chronic pain later in life. We examined structural and functional brain magnetic resonance imaging metrics in a subset of children from the first 2 assessments of the Adolescent Brain and Cognitive Development Study. Children (aged 9-10) who were pain free at baseline and then developed multisite pain 1 year later (n = 115) were matched to control children who were pain free at both timepoints (n = 230). We analyzed brain structure (cortical thickness and gray matter volume) and function (spontaneous neural activity and functional connectivity). Results were deemed significant at the cluster level $P < 0.05$ false discovery rate corrected for multiple comparisons. At baseline, children who subsequently developed multisite pain had increased neural activity in superior parietal /primary somatosensory and motor cortices and decreased activity in the medial prefrontal cortex. They also exhibited stronger functional connectivity between the salience network, somatosensory, and default mode network regions. No significant differences in the brain structure were observed. Increased neural activity and functional connectivity between brain regions, consistent to that seen in adults with chronic pain, exist in children before developing multisite pain. These findings may represent a neural vulnerability to developing future chronic pain.

Keywords: Multisite pain, Children, fMRI, Functional connectivity, Risk factors

Changes in size and shape of brain regions indicate CNS neuroplasticity 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 virtually all other chronic pain states including headache,[2] IBS,[3] FM[4]
- May be partially due to co-morbid mood disturbances[6]
- Data from NIH MAPP network suggests *increase* in size of and connectivity to S1 may represent neural signature for widespreadedness of pain

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. 7. Kutch et. al. IASP 2016

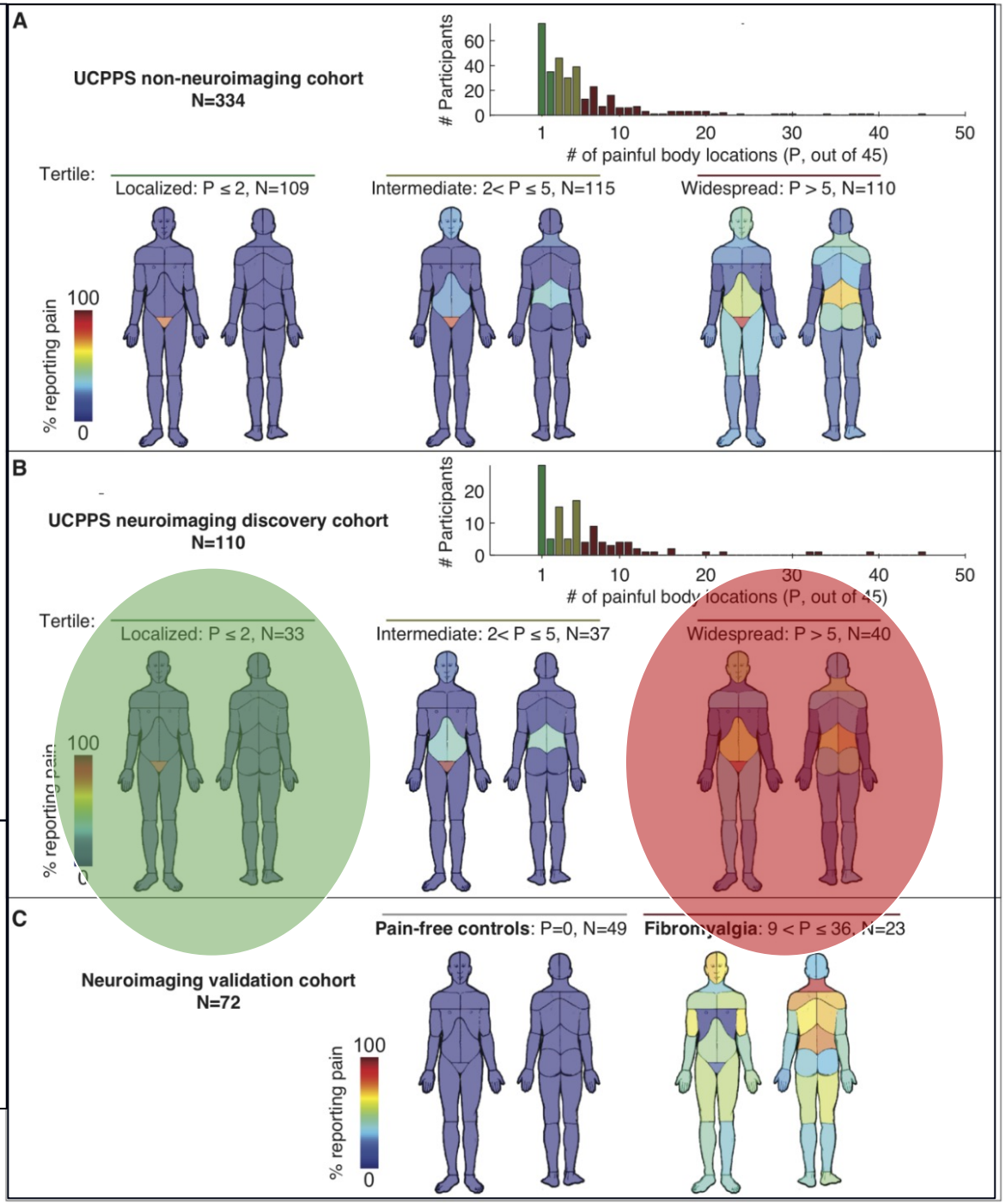
Interstitial Cystitis Tertiles of body pain distribution:

local, intermediate, widespread

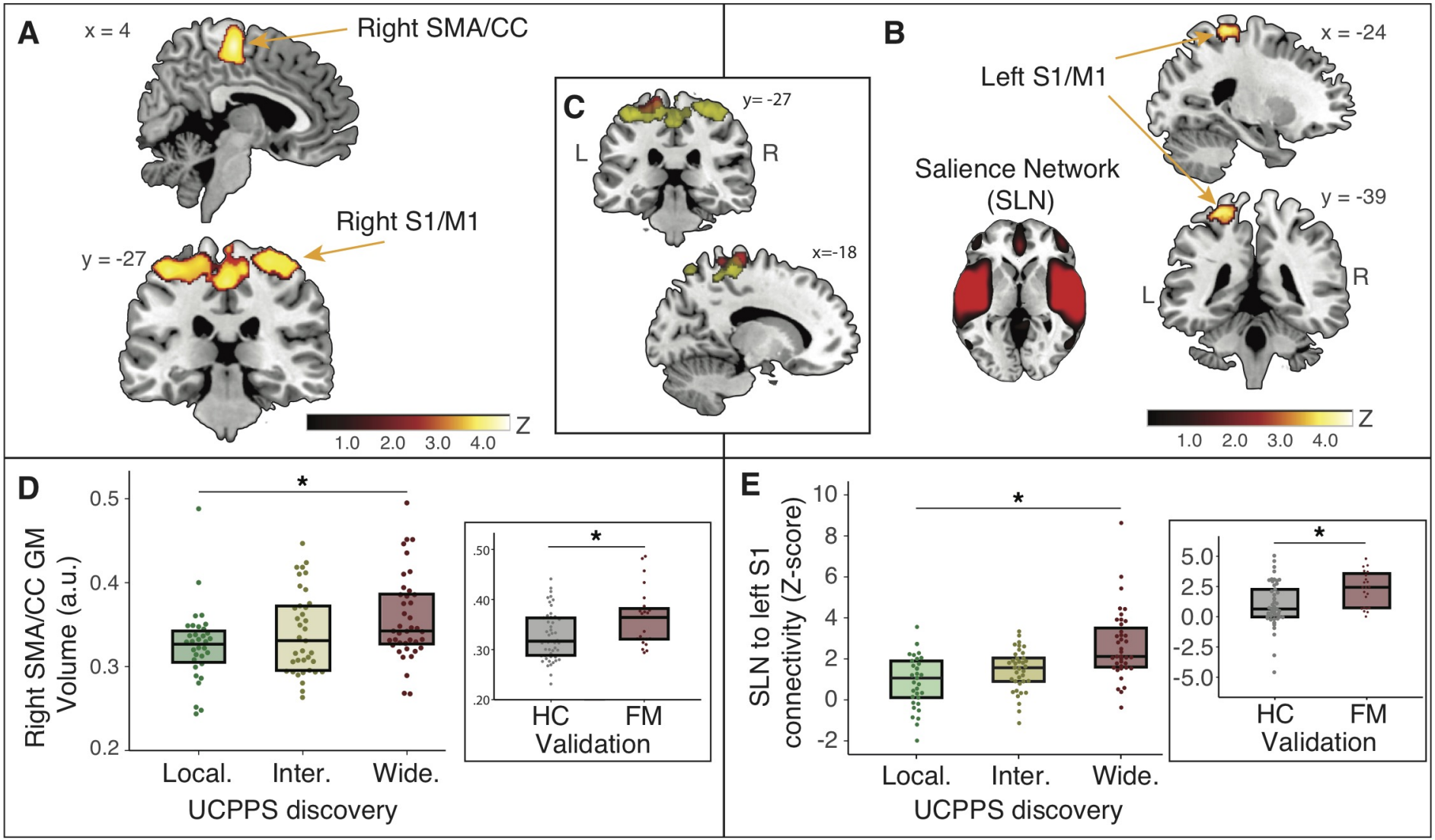
Non-Neuroimaging (N=334)

Neuroimaging (N=110)

Validation
FM (N=23)
HC (N=49)



Increased Gray Matter Volume *in* and Connectivity *to* Sensory Cortex In Widespread Pain



PAIN®

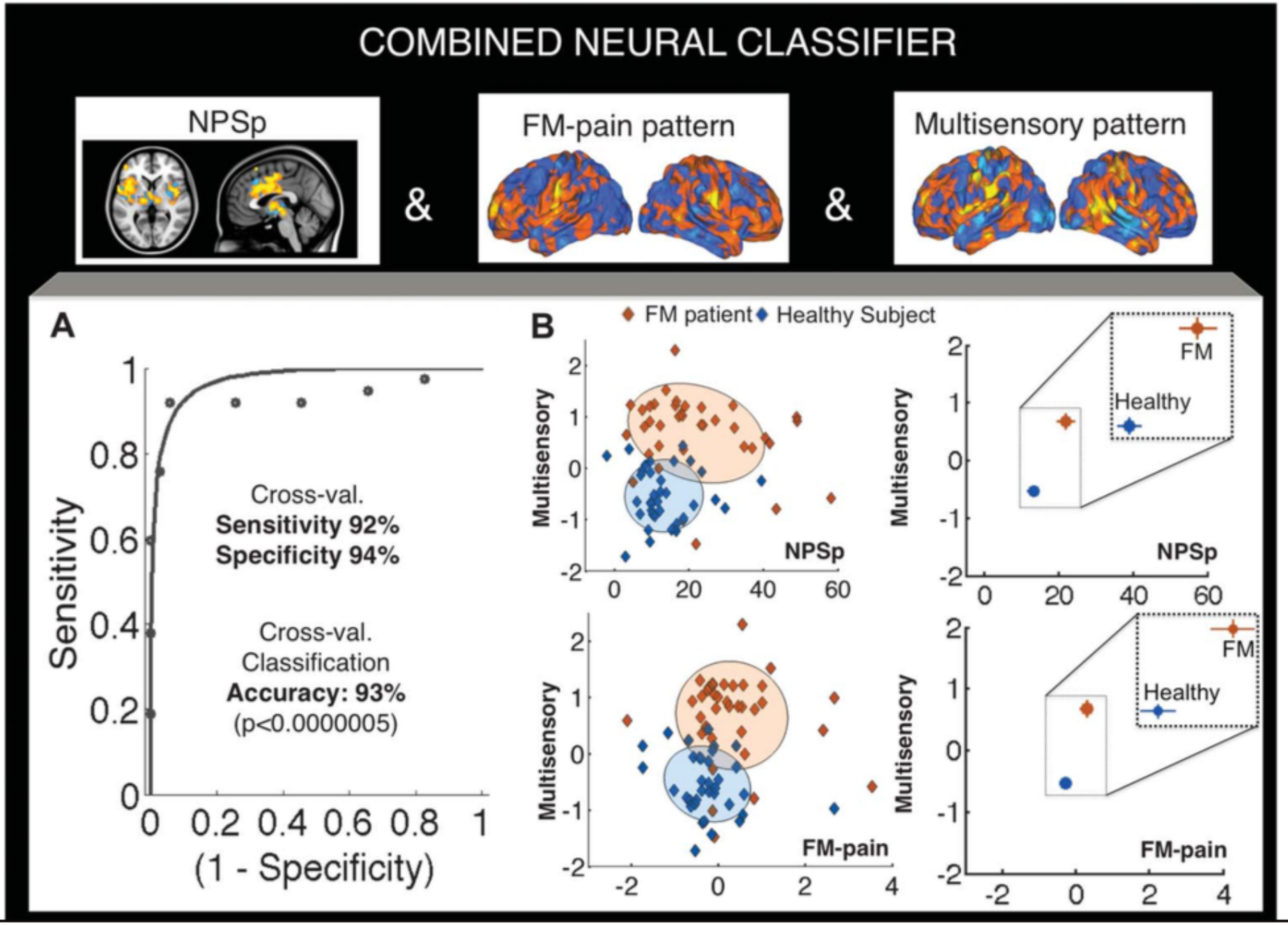
Towards a neurophysiological signature for fibromyalgia

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


COMBINED NEURAL CLASSIFIER
NPSp
&
FM-pain pattern
&
Multisensory pattern
A
Sensitivity
(1 - Specificity)
Cross-val.
Sensitivity 92%
Specificity 94%
Cross-val.
Classification
Accuracy: 93%
(p<0.0000005)
B
FM patient
Healthy Subject
Multisensory
NPSp
FM
Healthy
FM-pain

In RA, the residual pain and fatigue seen despite treatment with biologics can be treated as such

- In a large cohort of RA patients being treated at a US academic medical center, 47.3% continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of FM or Fmness.[1]
- Using quantitative sensory testing, active inflammation was associated with heightened pain sensitivity at joints (peripheral sensitization), whereas poor sleep was associated with diffuse pain sensitivity as noted in FM (central sensitization or centralized pain).[2]
- In a cross-over trial of six weeks of milnacipran in RA patients, in the overall group there was no statistical improvement, but in the subgroup with the least inflammation (swollen joint count </= 1) milnacipran decrease average pain intensity more than placebo (95% CI -2.26 to -0.01, p = 0.04).[3]

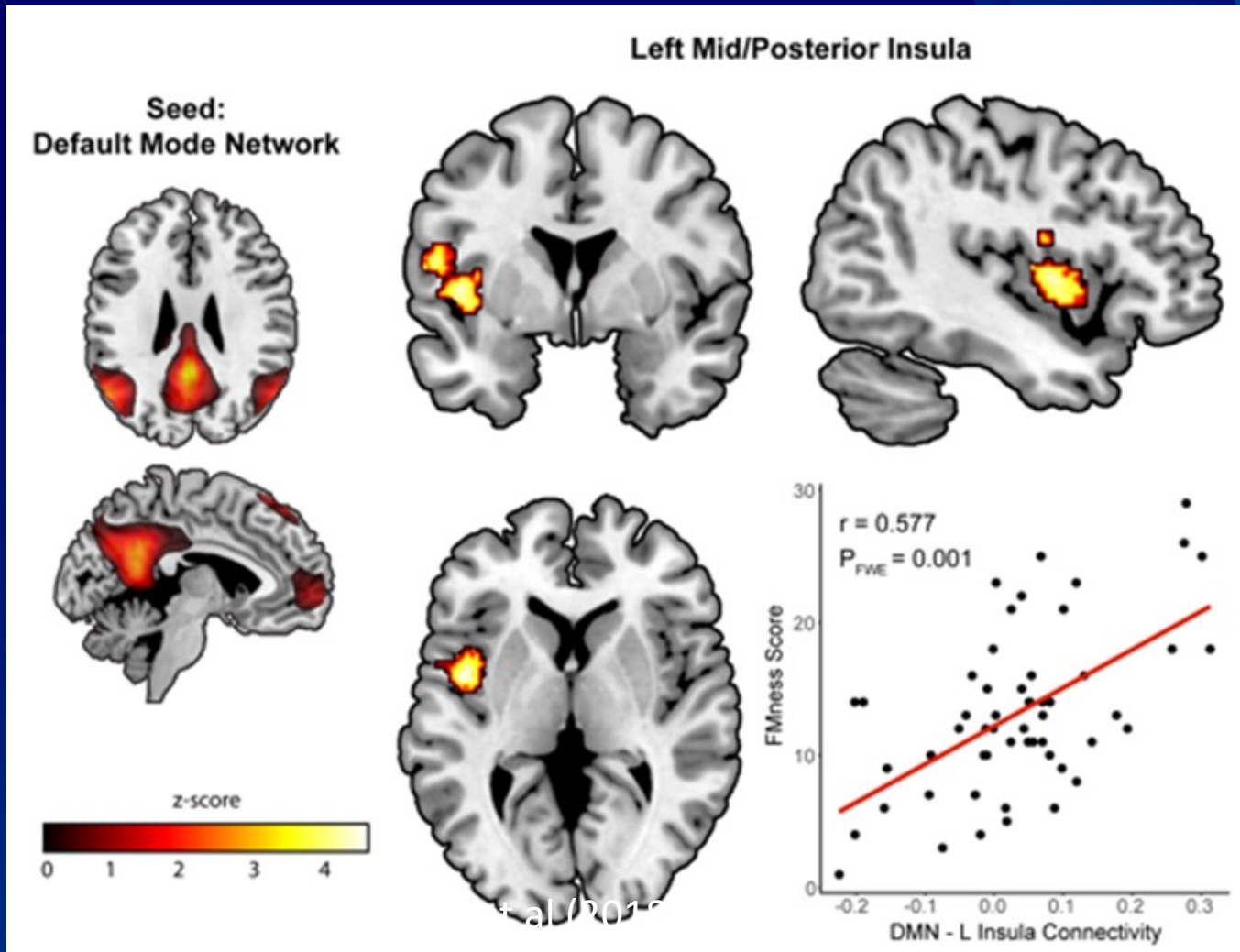
1. Lee YC, et. al. *Arthritis Res Ther.* 2009;11(5):R160. 2. Lee YC, et. al. *Arthritis & rheumatology.* 2014;66(8):2006-2014. 3. Lee YC, et. al. *J Rheumatol.* 2016;43(1):38-45.

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



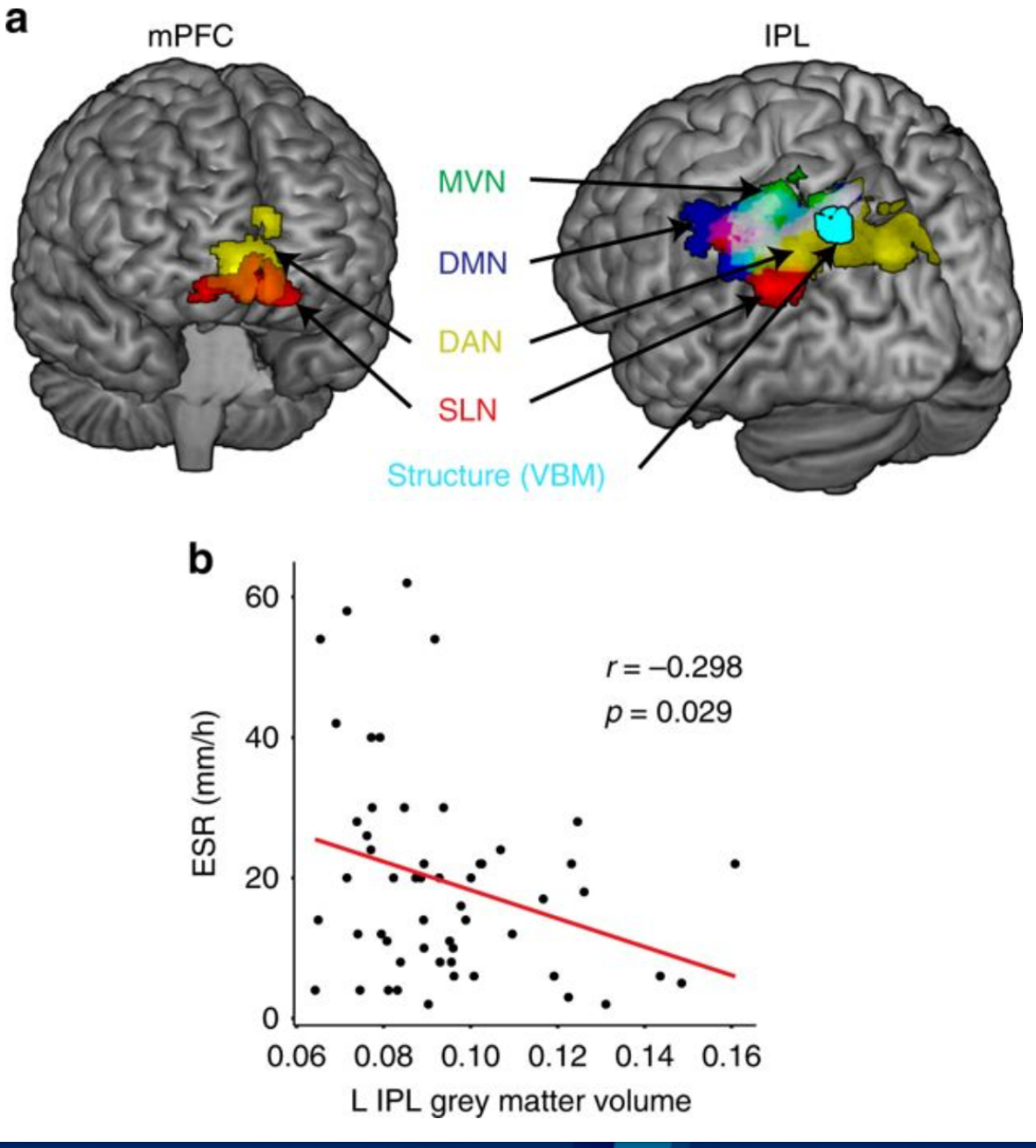
nature COMMUNICATIONS

Article | OPEN | Published: 08 June 2018

A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis

Andrew Schrepf, Chelsea M. Kaplan, Eric Ichesco, Tony Larkin, Steven E. Harte, Richard E. Harris, Alison D. Murray, Gordon D. Waiter, Daniel J. Clauw & Neil Basu

Nature Communications **9**, Article number: 2243 (2018) | Download Citation

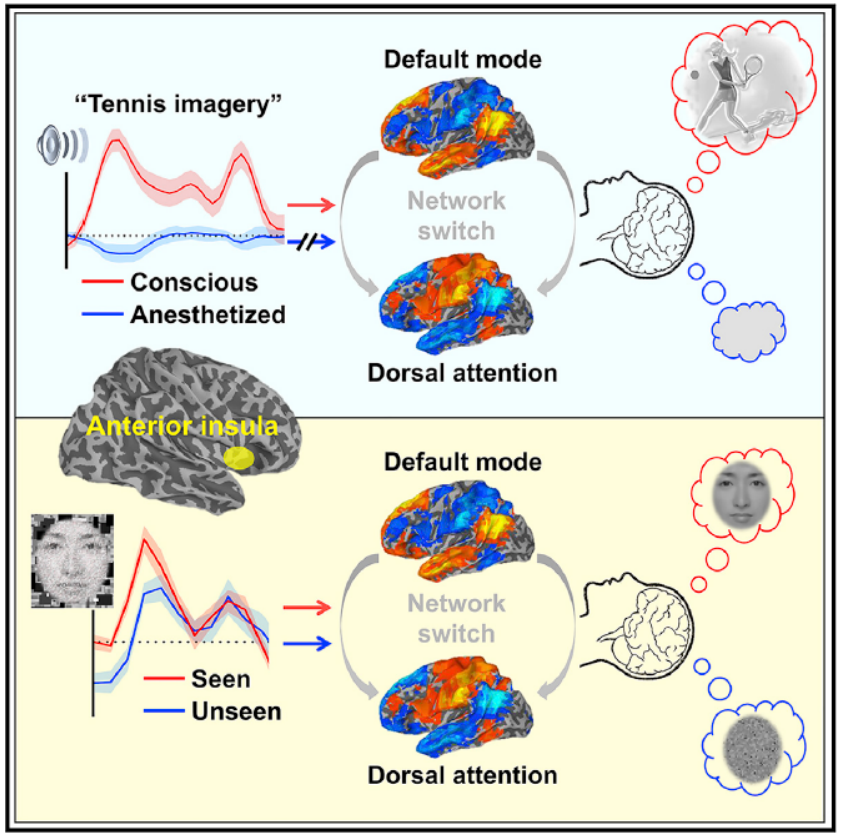


Cell Reports

Article

Anterior insula regulates brain network transitions that gate conscious access

Graphical abstract



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Zirui Huang, Vijay Tarnal, Phillip E. Vlisides, ..., Paul Picton, George A. Mashour, Anthony G. Hudetz

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huangzu@umich.edu (Z.H.), ahudetz@med.umich.edu (A.G.H.)

In brief

In a human neuroimaging study, Huang et al. manipulate the level and content of consciousness using independent experimental protocols to demonstrate that the anterior insula, situated between unimodal and transmodal cortical areas along the brain's functional hierarchy, serves as a gate for conscious access of sensory information.

Highlights

- Dysfunction of anterior insula during anesthesia disables brain network transitions

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?)
	▪ Gabapentinoids (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 Clauw *JAMA*. 2014

CNS Neurotransmitters Influencing Pain

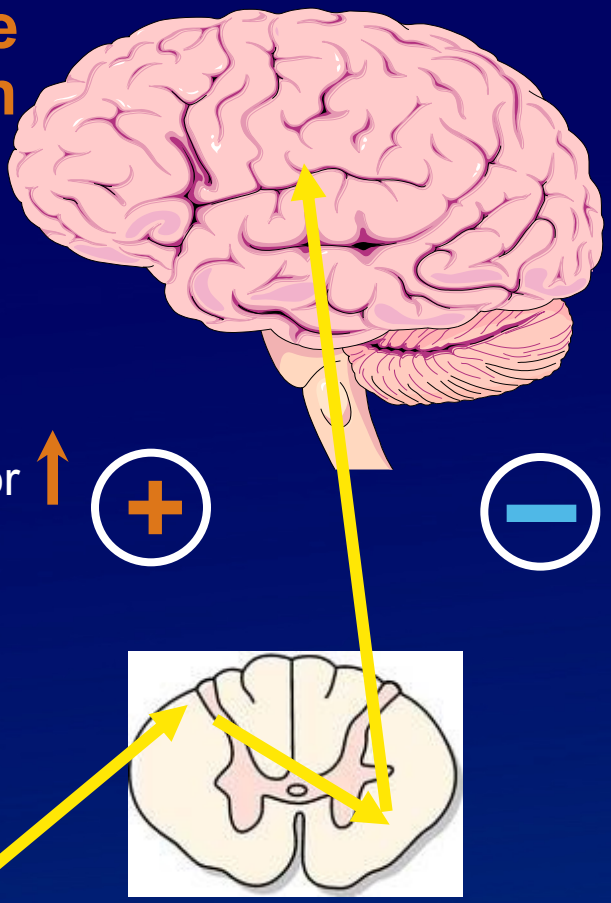
Arrows indicate direction in Fibromyalgia

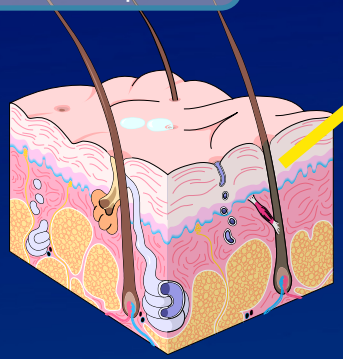
Generally facilitate pain transmission

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.

Commentary

PAIN®

Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

Daniel Clauw

In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, "The discovery of endogenous opioid systems: what it has meant for the clinician's understanding of pain and its treatment".[1] This review adds to these authors' significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can "hijack" this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endoge-

These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy,[3] have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

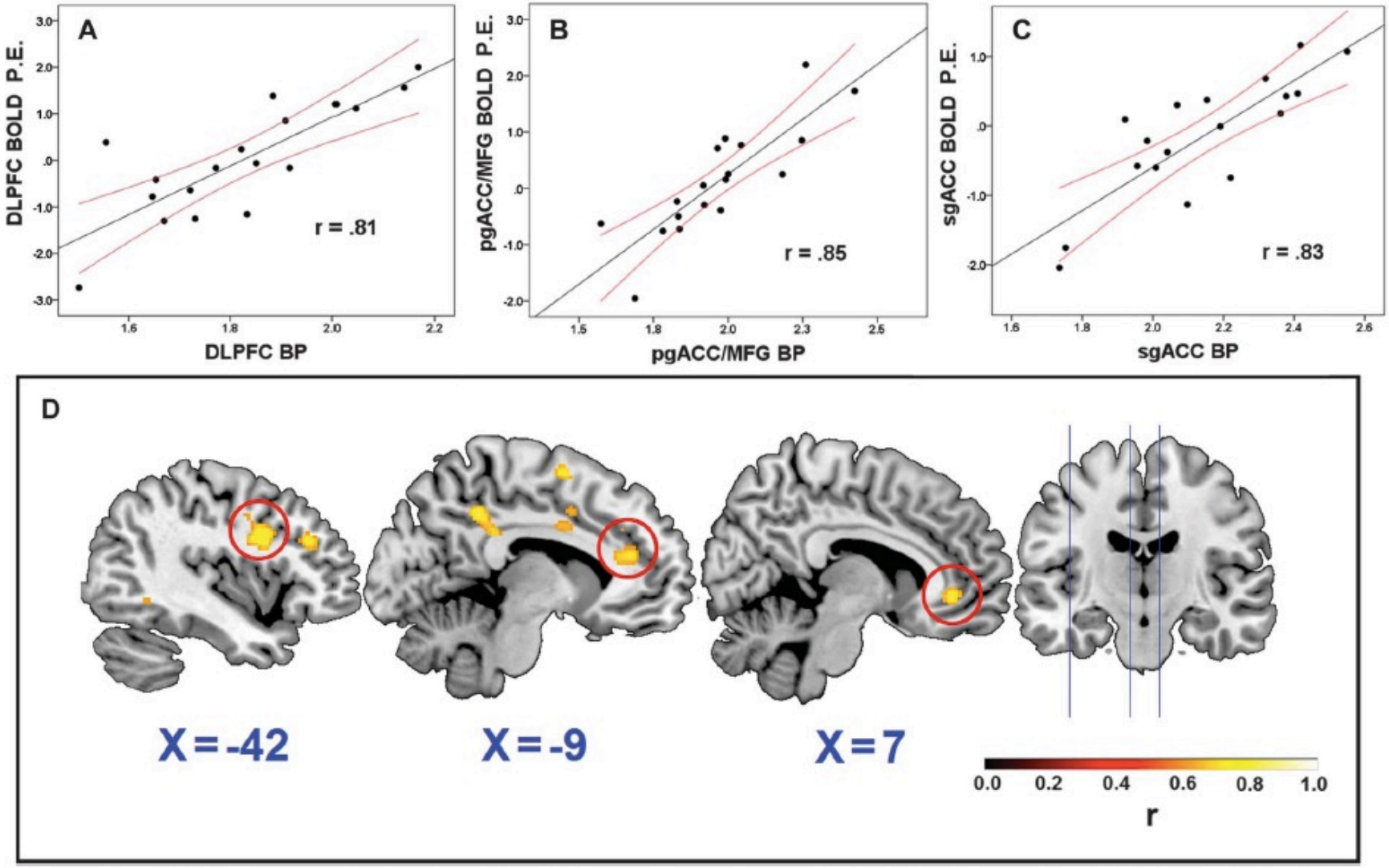
This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to "need" opioids to replicate the functions of endogenous opioids that are no longer being

PAIN

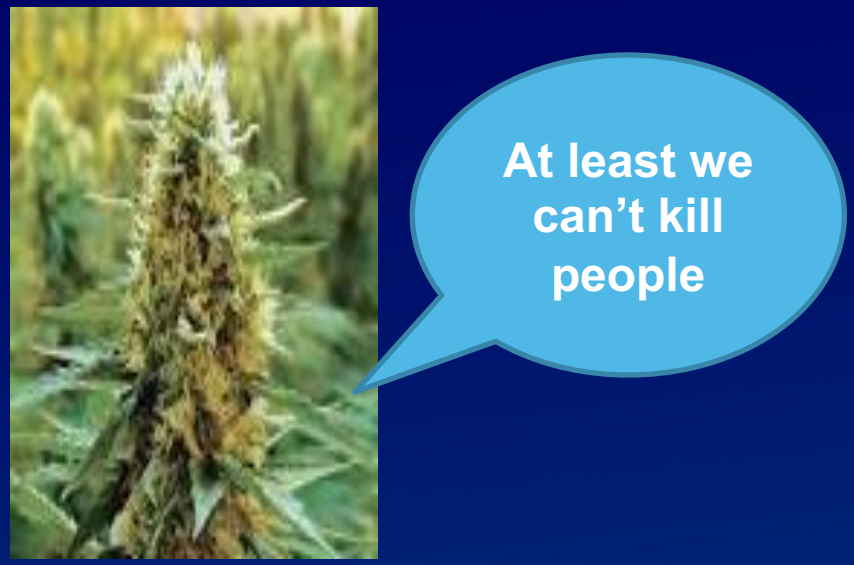
Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study

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]



Proposed marketing program for medical cannabis

Cannabis plant talking to opium producing poppy plant



Pragmatic Advice for Using Cannabinoids in 2021

- Where possible use a cannabinoid or cannabinoid extract of consistent and known potency
- Start with 5 – 10 mg of CBD twice daily and go up to as high as 50 – 100mg twice a day
- If CBD alone ineffective then go to low dose of low THC:high CBD strain and go up slowly
- Emerging evidence of U-shaped curve
- Oral dosing better once stable dose and strain identified
- The strongest recommendation based on current benefit: risk data is for the use of cannabinoids instead of opioids for neuropathic or centralized pain states
  - Data from US suggest that legalizing cannabis in a state leads to fairly dramatic reductions in opioid overdoses[1]

CBD, cannabidiol; THC, tetrahydrocannabinol

1. Bachhuber MA, et. al. JAMA Int Med 2014;174:1668-73.

Treating Based on Mechanisms

Any combination may be present

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

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.

Topical Review

PAIN®

Considering the potential for an increase in chronic pain after the COVID-19 pandemic

AQ:1

Daniel J. Clauw[b], Winfried Häuser[b,c], Steven P. Cohen[d,e], Mary-Ann Fitzcharles[f,g,*]

1. Introduction

The COVID-19 pandemic has impacted the lives and health of persons worldwide, with potential for further effects in the future. The experience of living within this pandemic has disrupted daily life across all sectors, including those living with chronic pain (CP), those infected with the coronavirus Severe Acute Respiratory Syndrome (SARS)-CoV2, healthcare providers and essential workers, as well as those who remained physically healthy. The toll of this pandemic extends beyond physical illness, with important psychosocial stressors that include prolonged periods of limited interpersonal contact, isolation, fear of illness, future uncertainty, and financial strain. Uncertainty is fuelled by the organ-specific biological factors, which may preferentially occur in individuals with a fragile stress response system.[8,10,24,40,47] The COVID-19 pandemic has many characteristics that could potentially increase the prevalence of CP, especially with stressors extending over many months.

The worldwide pain community is invited to consider the possible downstream consequences of COVID-19, not only for patients surviving infection, but also for the wider community that has experienced psychological, social, and economic effects. Although we address these issues from the perspective of physicians practicing in developed countries, many of the consequences discussed will be particularly relevant for people in other countries, with a call for colleagues in Asia, Africa, and

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

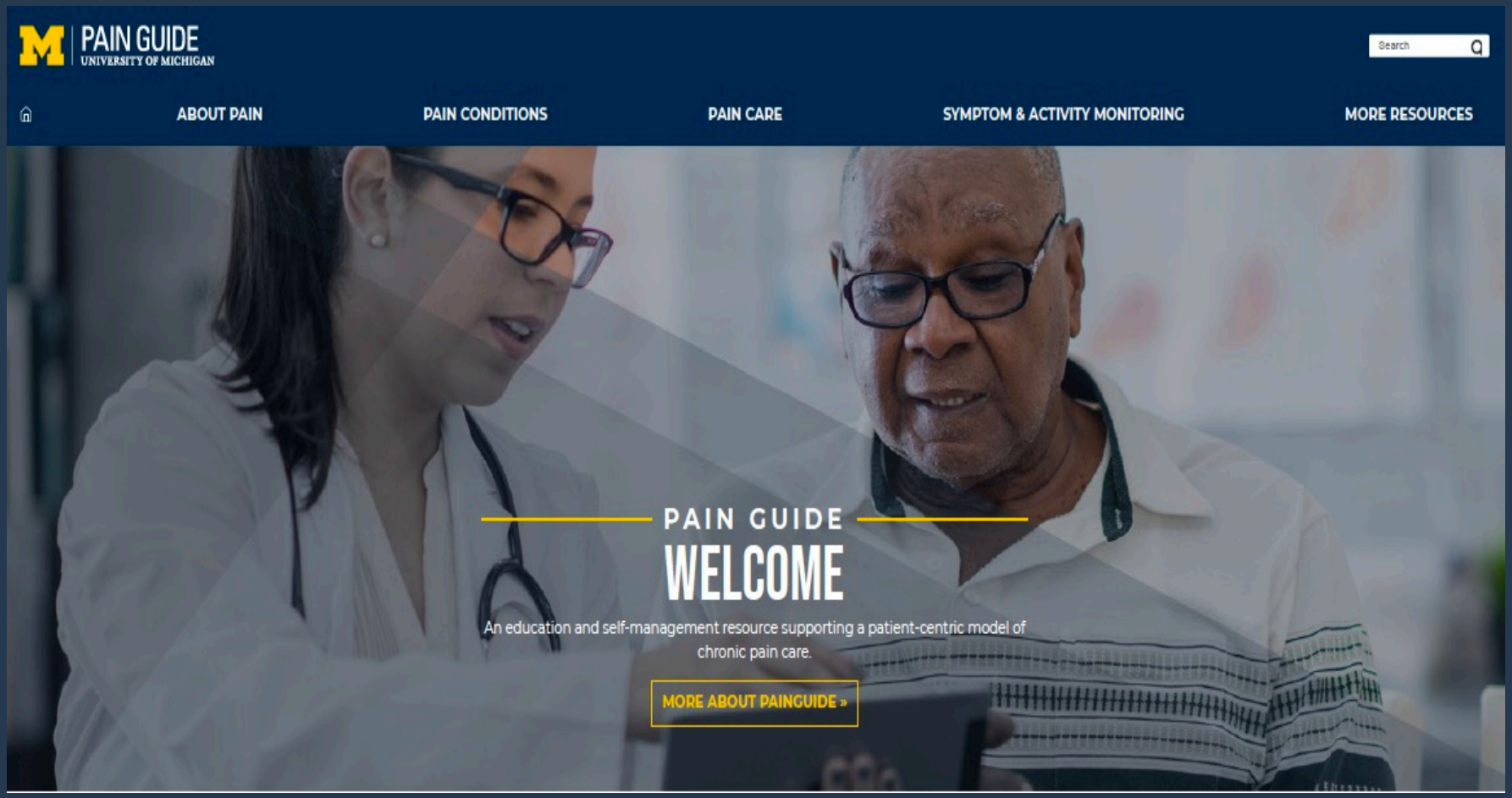
Modified from Clauw *JAMA*. 2014

www.fibroguide.com

- Program features 10 CBT modules:
  - Understanding Fibromyalgia
  - Being Active
  - Sleep
  - Relaxation
  - Time for You
  - Setting Goals
  - Pacing Yourself
  - Thinking Differently
  - Communicating
  - Fibro Fog

- In a RCT of 118 FM patients comparing the earlier version of this website plus usual care, to usual care alone, Williams demonstrated statistically significant improvements in pain (29% in the WEB group had 30% improvement in pain vs 8% in usual care, p=.009) and function (i.e., 31% in WEB-SM had .5 SD improvement in SF-36 PF vs. 6% in standard care, p<.002) Williams et. al. Pain. 2010;151(3):694-702

www.painguide.com



Self Care

Exercise

Exercise, when done safely, can benefit you physically and mentally. It helps prevent deconditioning of muscles which is often associated with more pain. Studies find that exercise is one of the most beneficial approaches to managing pain.

Learn more >

Pacing

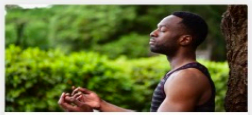
People with pain often "over do" resulting in pain flare ups. Pacing can allow activities to get accomplished safely, without flare-ups, and in a manner that conserves energy (i.e., with less fatigue).

Learn more >

Nutrition & supplements

Eating a healthy diet has many benefits for everyone; however there may be some specific benefits for pain sufferers. The examination of pain and diet is an emerging literature.

Read nutrition & supplements tips >



Relaxation

Teaching the body to relax can both diminish muscle tension and decrease stress. To work properly, regular practice is needed so that the body learns a rhythm of relaxation and can relax on your command. Less tension and less stress can lead to decreased pain intensity.

Learn more >

Reframing

What we think influences how we feel and how much pain we experience. Sometimes negative thoughts become automatic and make us feel worse. Learning to reframe our thinking in realistic terms that challenge negative automatic thinking can help diminish pain intensity.

Learn more >

Managing Emotions

Emotions are integral to the production of pain. You cannot have pain without emotions. Thus anything we can do to alter the emotional content of one's brain will influence pain. Better management of stress can influence pain as well as engaging in pleasant activities. The pleasant activities will help diminish pain intensity.

Learn more >

Communication skills

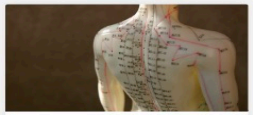
Conflictual social relationships with family, friends, doctors, and employers can make pain worse. Alternatively, these same relationships can be used constructively to make pain better. Communication skills can help make social relationship work in your favor.

Learn more >

Sleep

Pain and Sleep are closely related such that poor sleep can make pain worse. These are a number of behavioral sleep strategies that can be used to get a more refreshing night's sleep.

Learn more >



Acupressure

Like acupuncture, which uses needles, acupressure is an ancient treatment that uses the pressure of one's own finger on the skin so as to help re-balance the flow of energy through the body as a means of reducing symptoms such as pain.

Learn more >

Sprituality

The belief in something "bigger," "more powerful," or "more knowledgeable" than oneself has been key to many individuals being able to successfully deal with pain. Spirituality may refer to a specific religious belief or it can be any belief that provides a source of strength and comfort to the individual with pain.

Learn more >

Ergonomics/Posture

How you sit, stand, transition and lift can either make pain worse or allow you to function even with pain. This section offers help in optimizing how you interact with your environment in ways that don't exacerbate pain.

Learn more >

Resilience

We often focus on fixing what is broken but we can't lose sight of our personal strengths that help us get through challenging times. Finding our sources of resilience can be a valuable tool for reducing pain and living a quality-filled life.

Learn more >

PAIN CARE

- Self Care
- **Professional Care**
  - Medications
  - Therapies
  - Devices
  - Procedures

Emerging Issues in Fibromyalgia and Chronic Pain

- Vitamin D
- Small fiber neuropathy
- Neuroinflammation/Glial activation
- Diet/nutrition

Can we use diet/nutrition to treat chronic pain?

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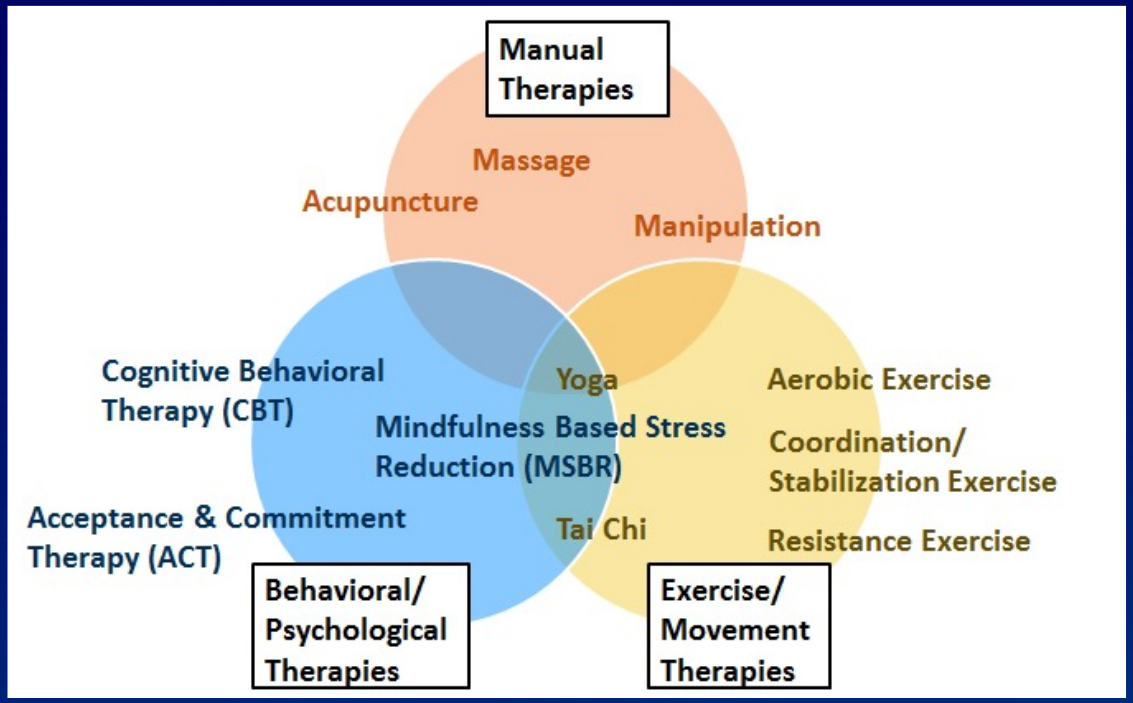
Abstract: **Weight loss is known to improve pain localized to weight-bearing joints but it is not known how weight loss affects the spatial distribution of pain and associated somatic symptoms like fatigue. We sought to determine if weight loss using a low-calorie diet improves pain, affect, and somatic symptoms commonly associated with chronic pain conditions in an observational study. We also documented changes in inflammatory markers in serum before and after weight loss. Participants were 123 obese individuals undergoing a 12- to 16-week calorie restriction weight loss intervention. The spatial distribution of pain, symptom severity (eg, fatigue, sleep difficulties), depression, and total fibromyalgia scale scores were measured before and after weight loss. Pain ($P = .022$), symptom severity ($P = .004$), depression ($P < .001$), and fibromyalgia scores ($P = .004$) improved after weight loss; men showed greater improvement than women on somatic symptoms and fibromyalgia scores (both $P < .01$). Those who lost at least 10% of body weight showed greater improvement than those who lost <10%. Levels of the regulatory cytokine interleukin-10 increased after the intervention ($P = .002$). Weight loss may improve diffuse pain and comorbid symptoms commonly seen in chronic pain participants.**

Perspective: ***This article presents the effect of a weight loss intervention on characteristics of chronic pain, including the spatial distribution of pain and comorbid somatic symptoms. Weight loss appeared to produce larger improvements in somatic symptoms for men.***

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.

Take Home Messages for Managing Chronic Pain

- Have patient complete the FM measure (or a body map) intermittently to help determine whether pain is nociceptive, neuropathic, nociplastic – or some combination – and treat based on that assessment
- Look for and treat common co-morbidities
  - Sleep
  - Mood
  - Fatigue
- Embrace the effectiveness of non-pharm therapies
  - Your patients can tell if you don't think these therapies are as effective as drugs
- Encourage patients try new therapies rather than allowing them to get into rut