Biomedical and Biopsychosocial Aspects of Pain Management

MI-CCSI

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Disclosures

- Consultant to Community Health Focus Inc.
- Consultant to Swing Therapeutics, Inc.
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OpenAI
ChatGPT

Why is Chronic Pain so difficult to treat?

- Multiple underlying causes
- Individual differences
- Neuroplasticity
- Treatment limitations
- Biopsychosocial factors
- A holistic approach is required

Why is Chronic Pain so difficult to treat?

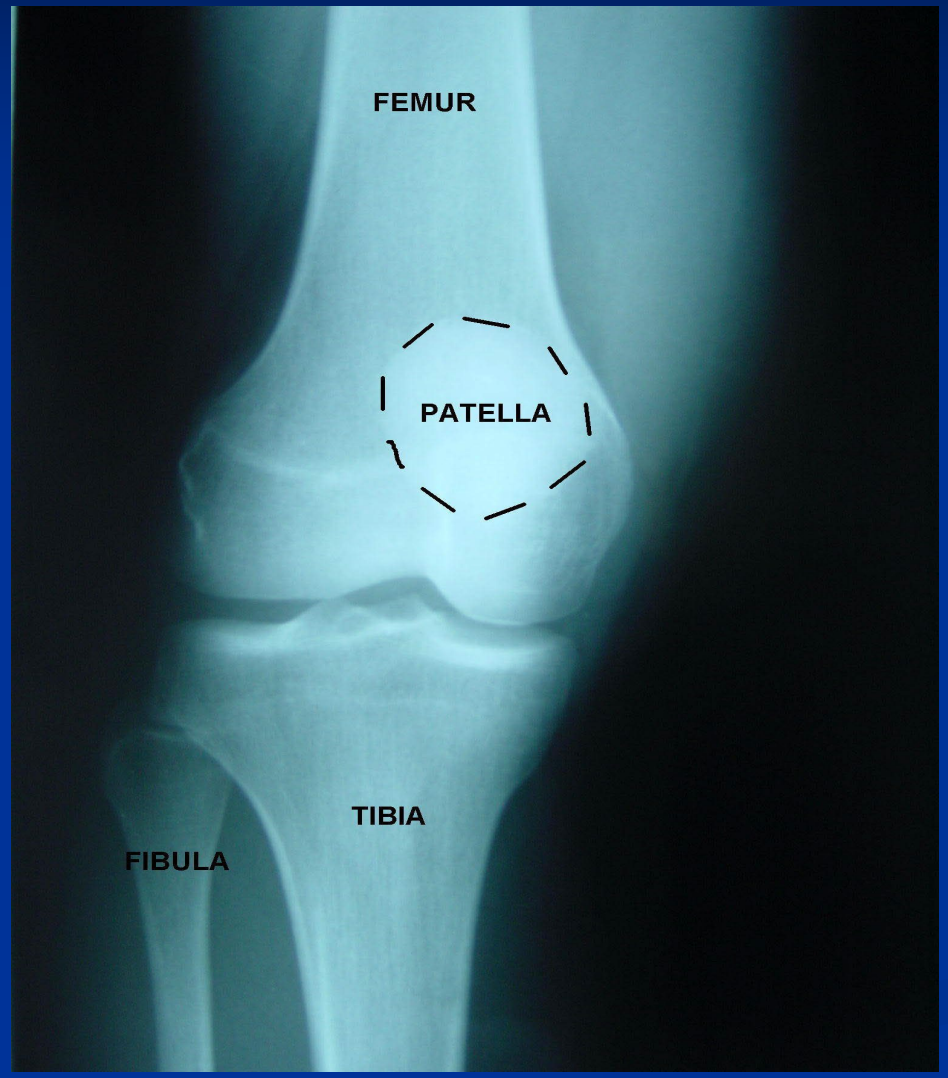
Section 1

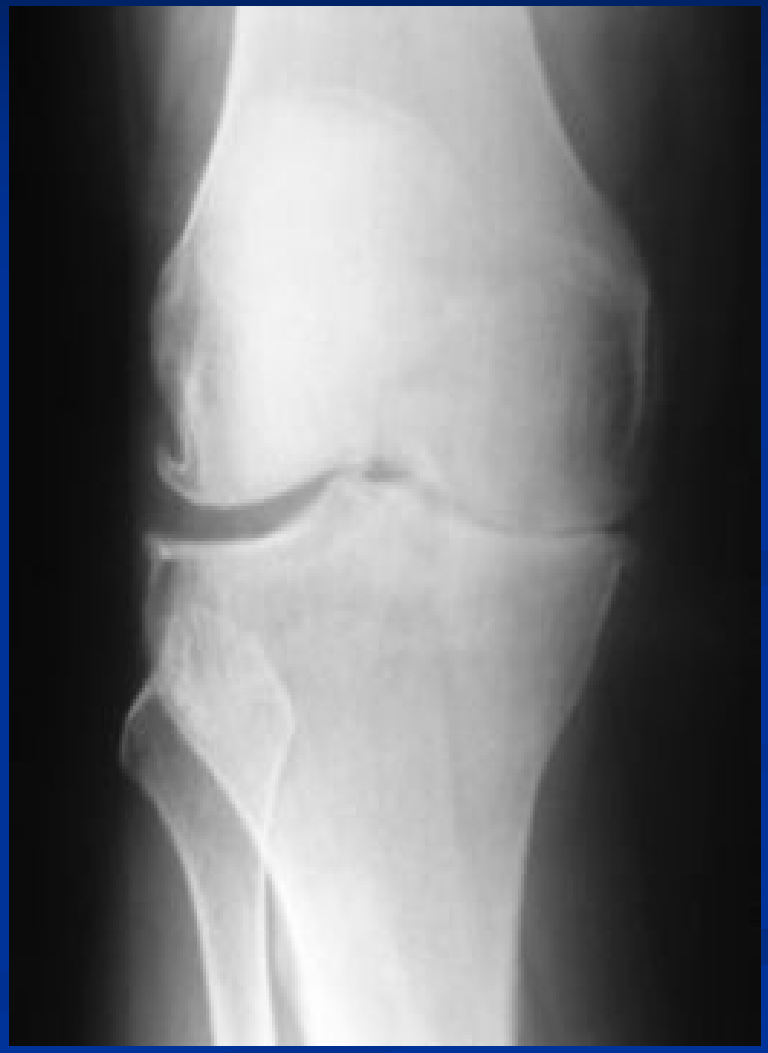
- Multiple underlying causes
- Individual differences
- Neuroplasticity

Section 2

- Treatment limitations
- Biopsychosocial factors
- A holistic approach is required

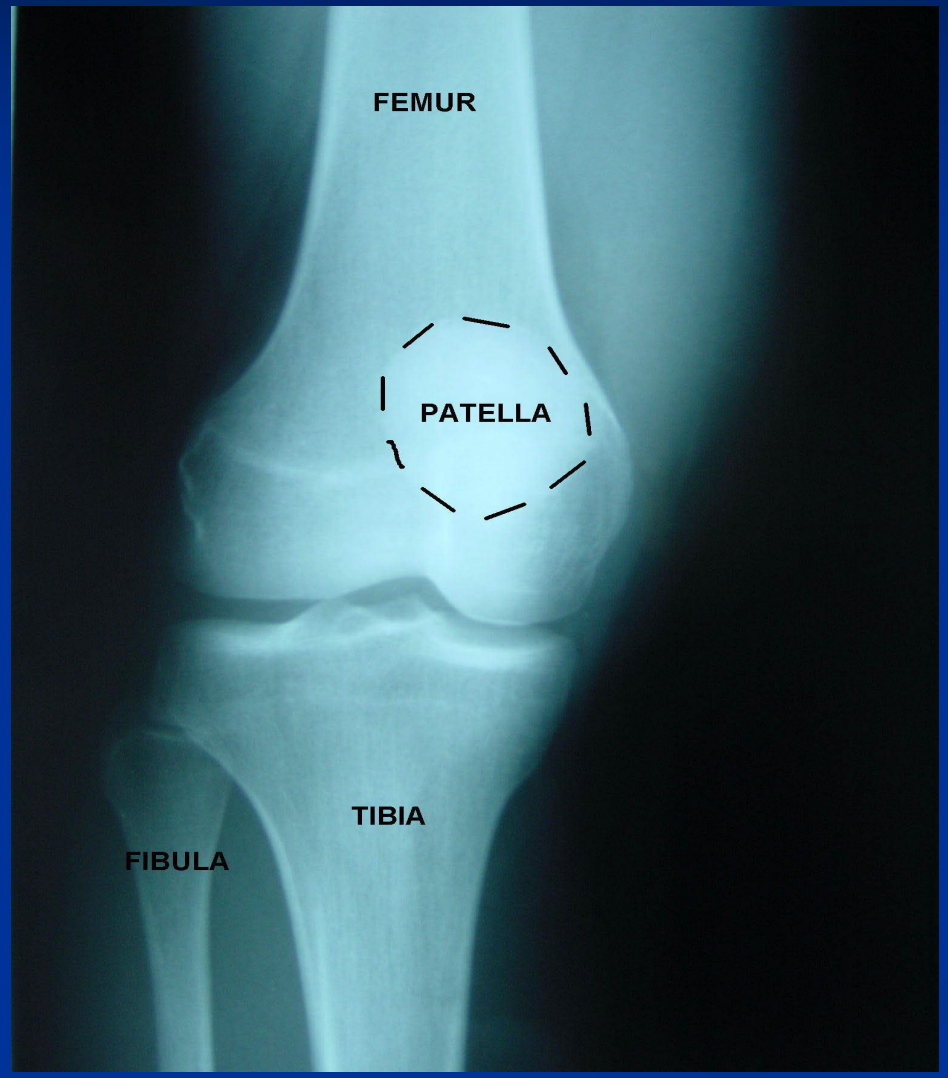
Which person has pain?

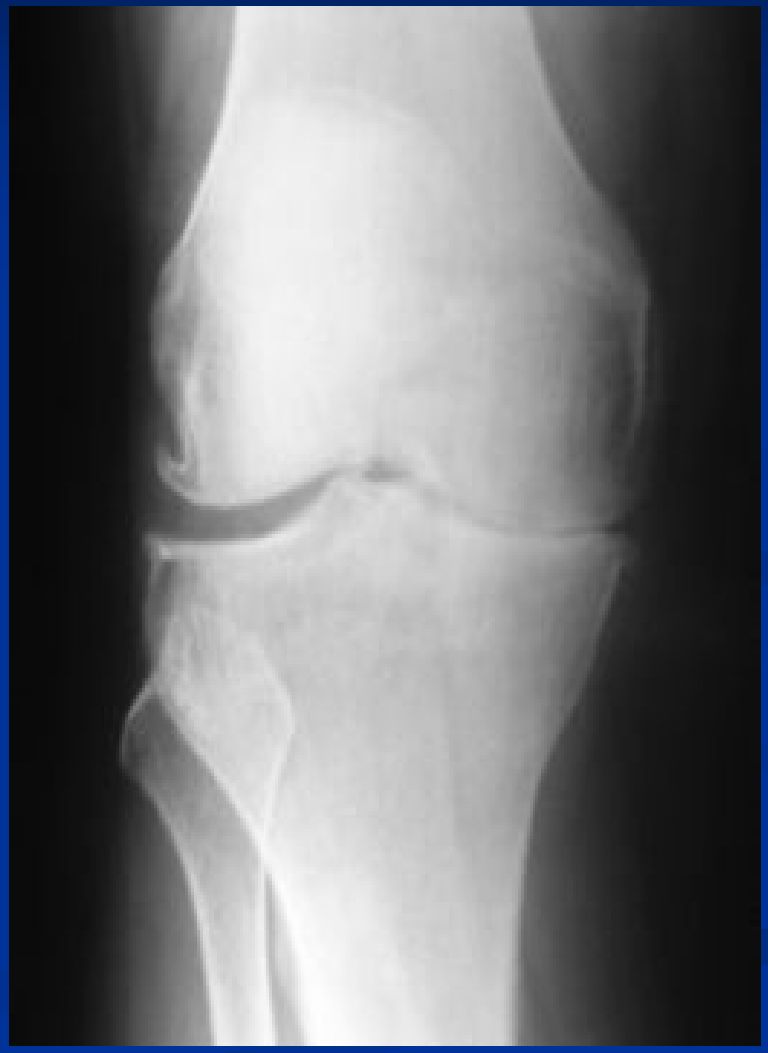




Which person has pain?

"Normal"
10% have pain





Bone on bone
30-40%
Have no pain

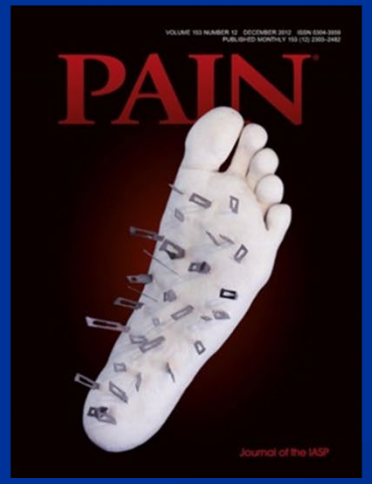
How is Pain Classified?

Time	Body Location	Suspected Etiology
Acute Vs Chronic	Head, Neck, Back, Pelvis	Cancer, Rheumatic, etc.

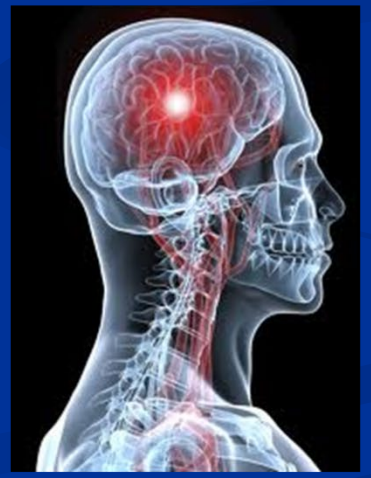
Newest Classification: Pain Mechanisms

Nociceptive
Peripheral damage or inflammation

Neuropathic



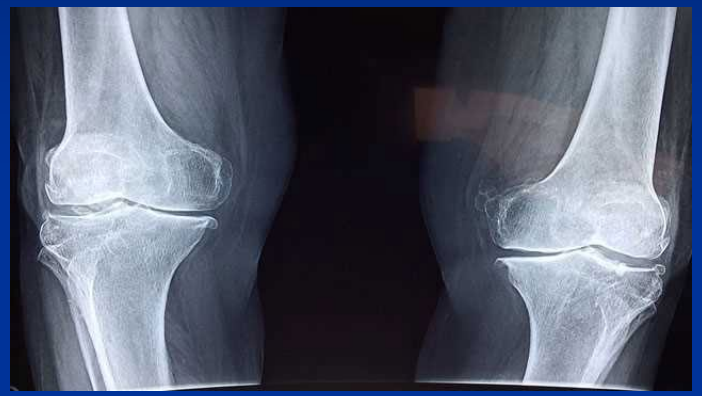
Nociplastic



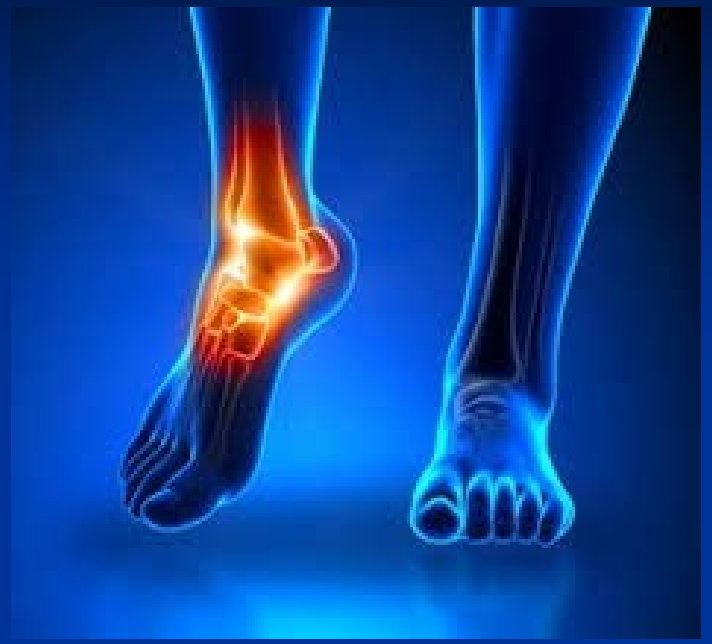
[1]Woolf CJ. *J Clin Invest*. 2010;120(11):3742-3744. [2]Costigan M, et al. *Annu Rev Neurosci*. 2009;32:1-32. [3]Dickinson BD, et al. *Pain Med*. 2010;11:1635-1653. [4]Williams DA, Clauw DJ. *J Pain*. 2009;10(8):777-791.

Nociceptive Pain

(mechanical, thermal, chemical)



Neuropathic Pain

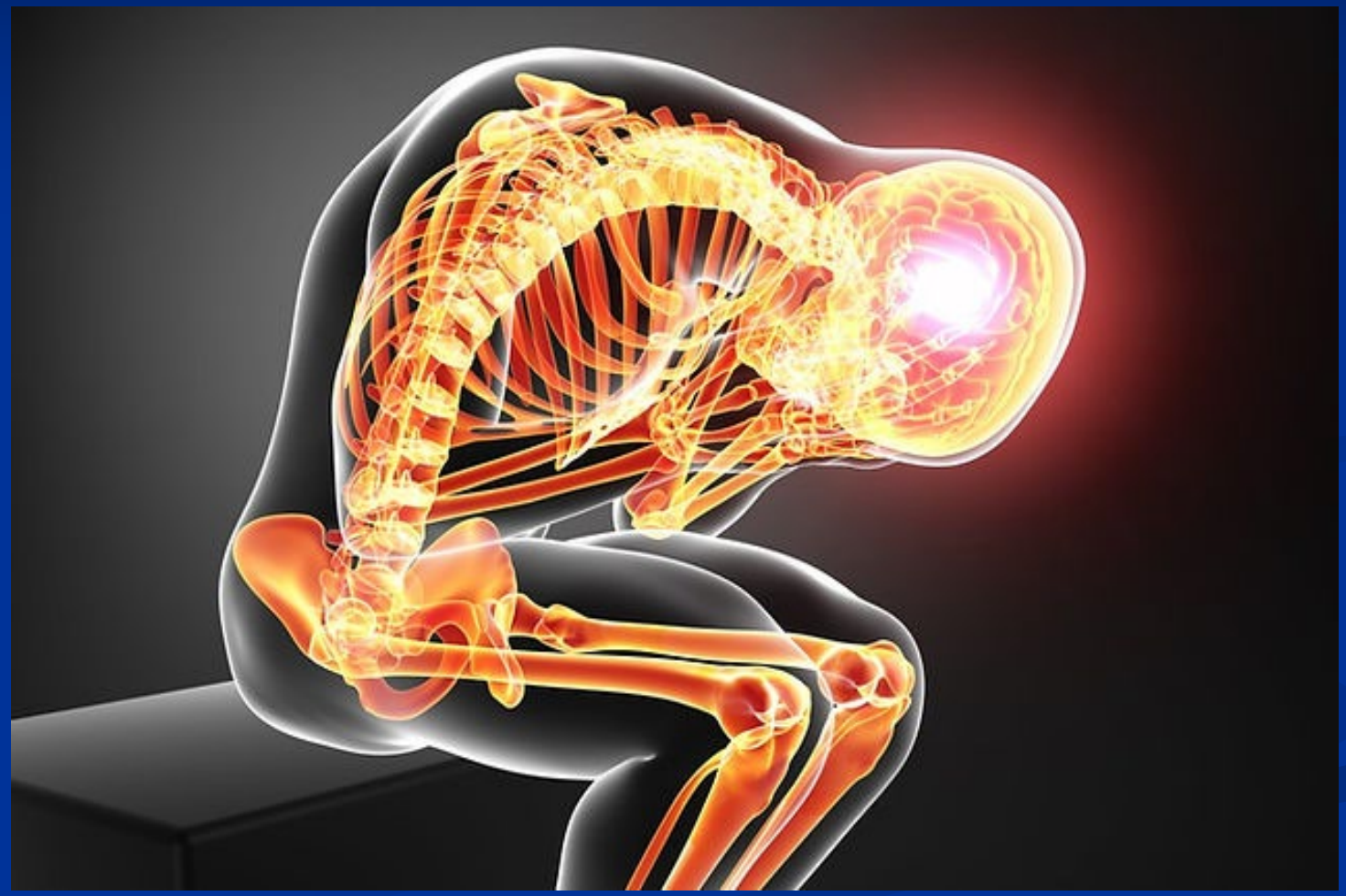


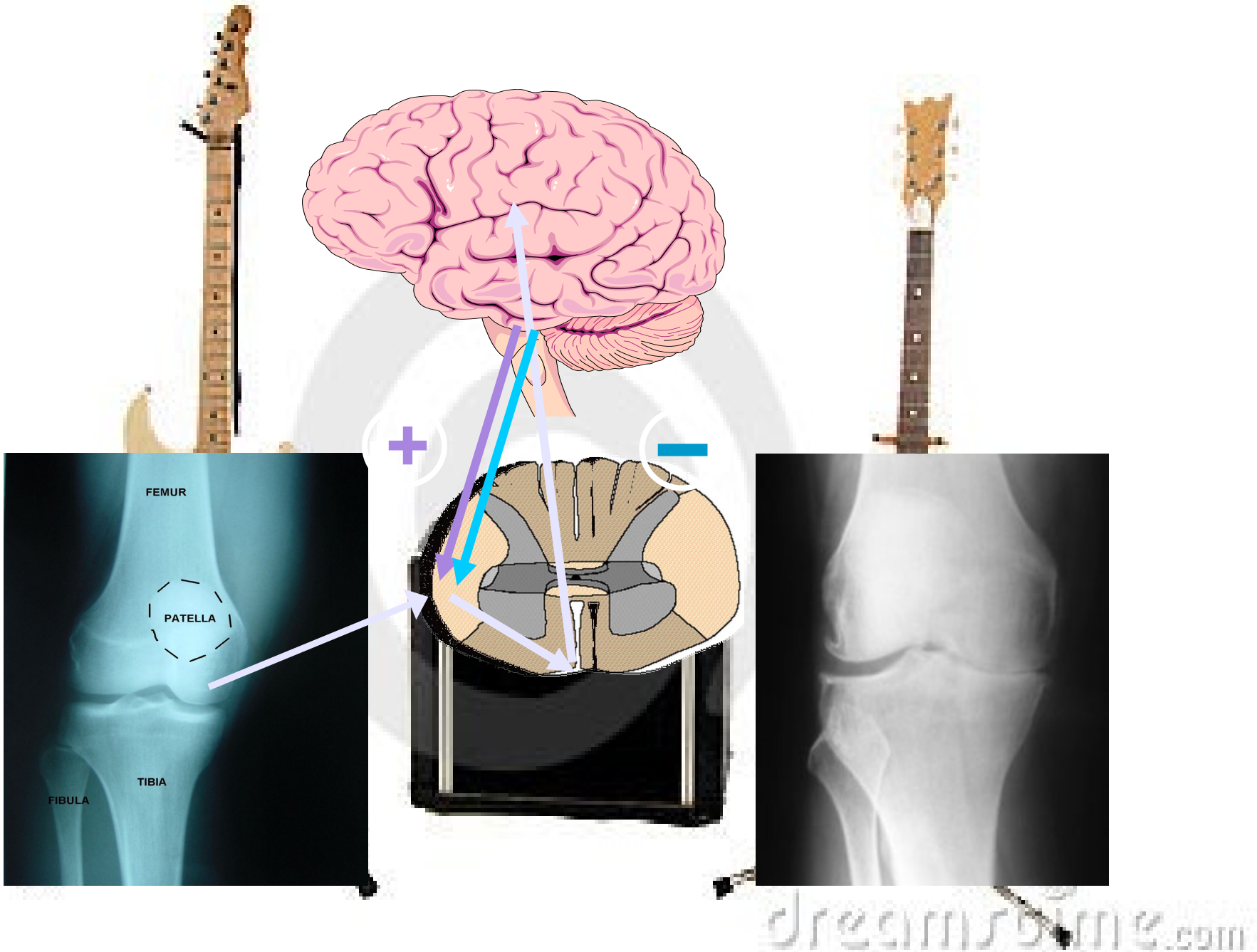
Peripheral

Central

Nociplastic Pain

CNS augmentation of peripheral nociception or CNS generation



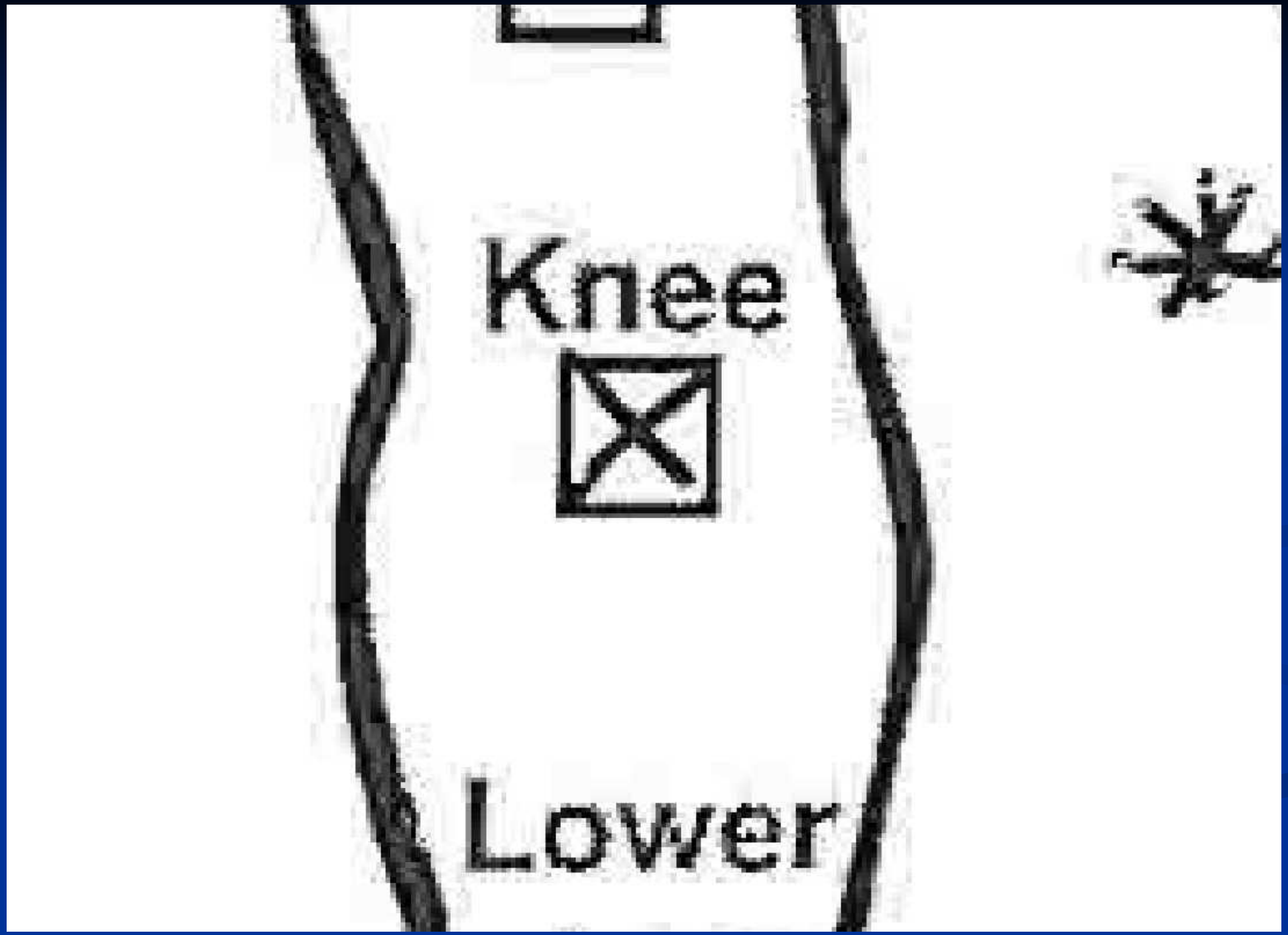

FEMUR
PATELLA
TIBIA
FIBULA
+
−

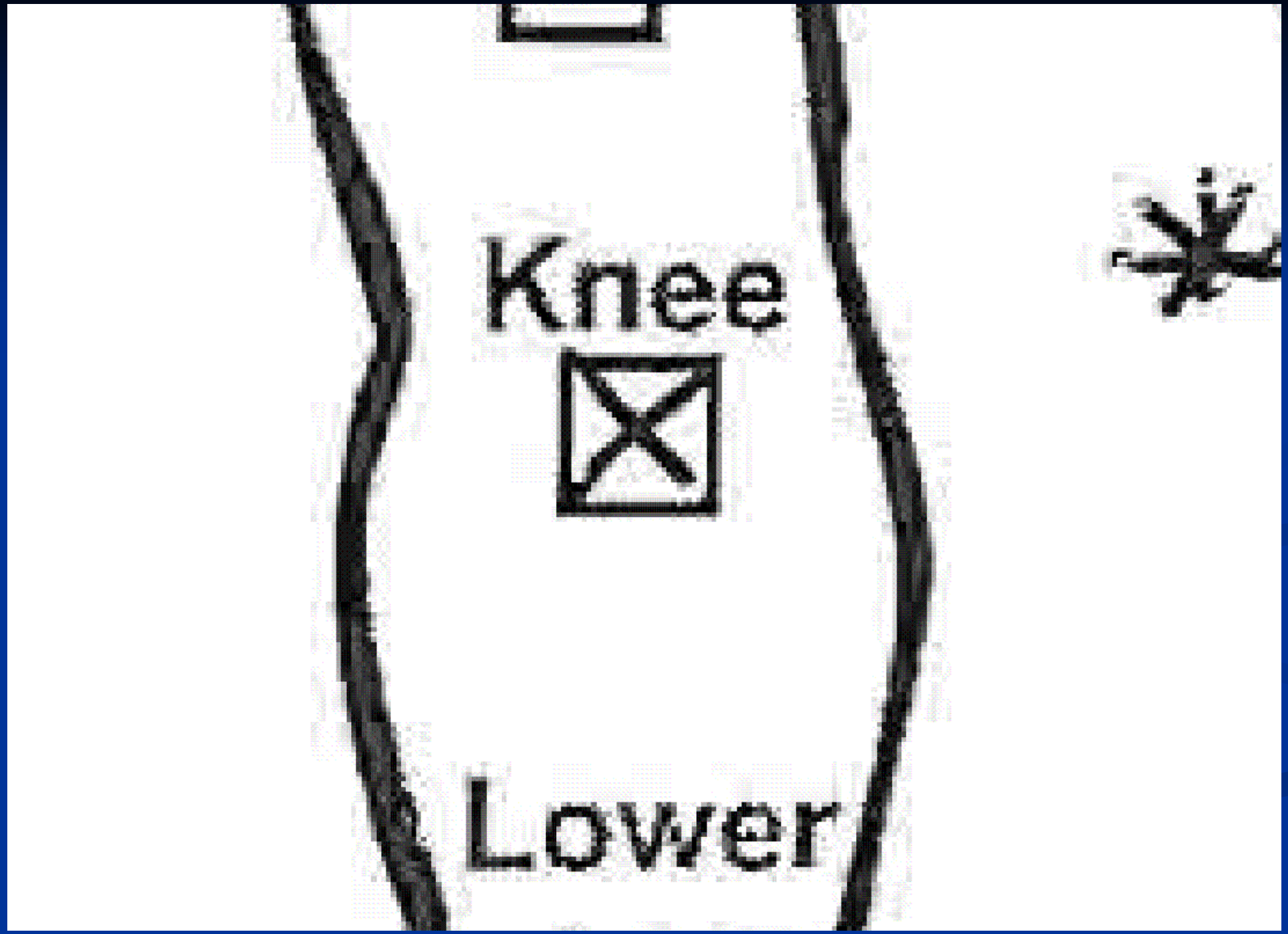
The PainSensations

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
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 syndrome

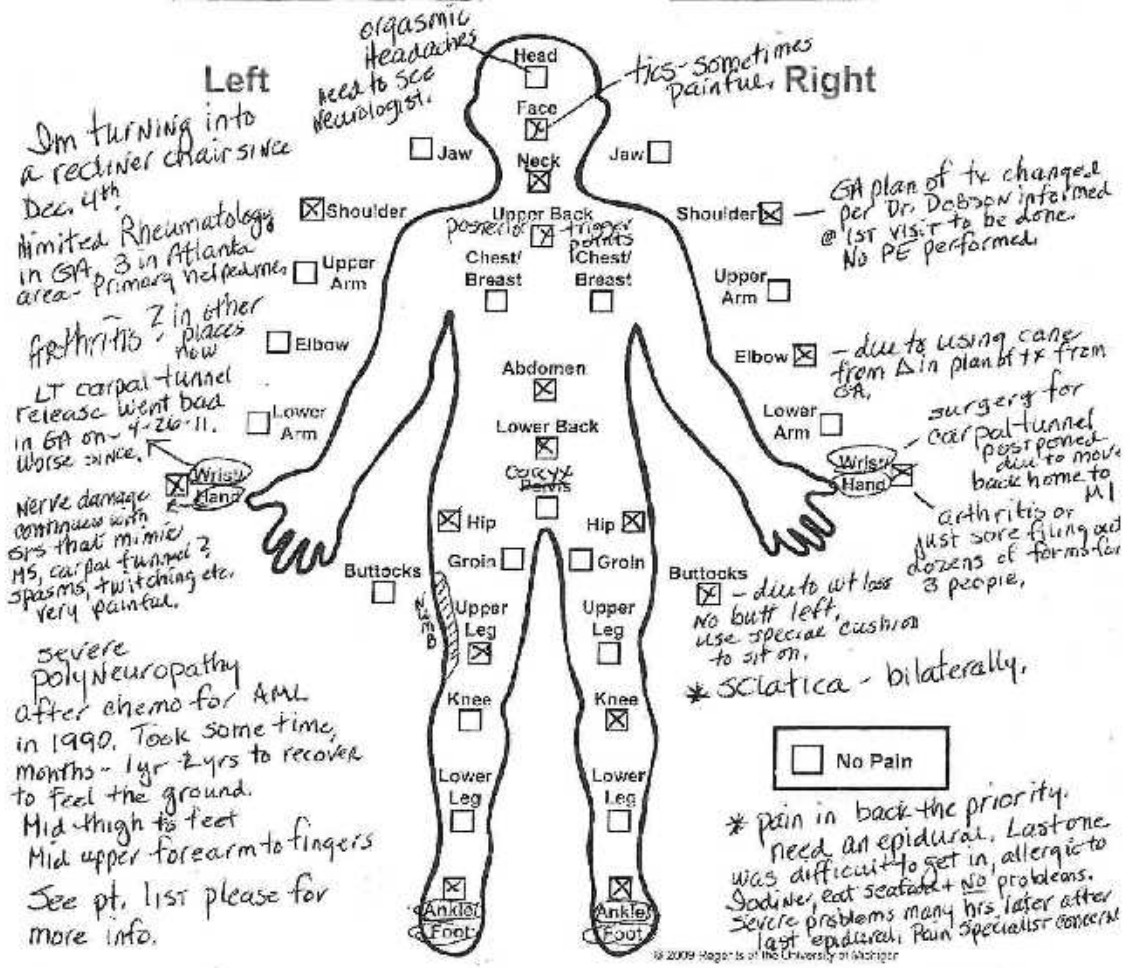

Knee
Lower


Knee
Lower

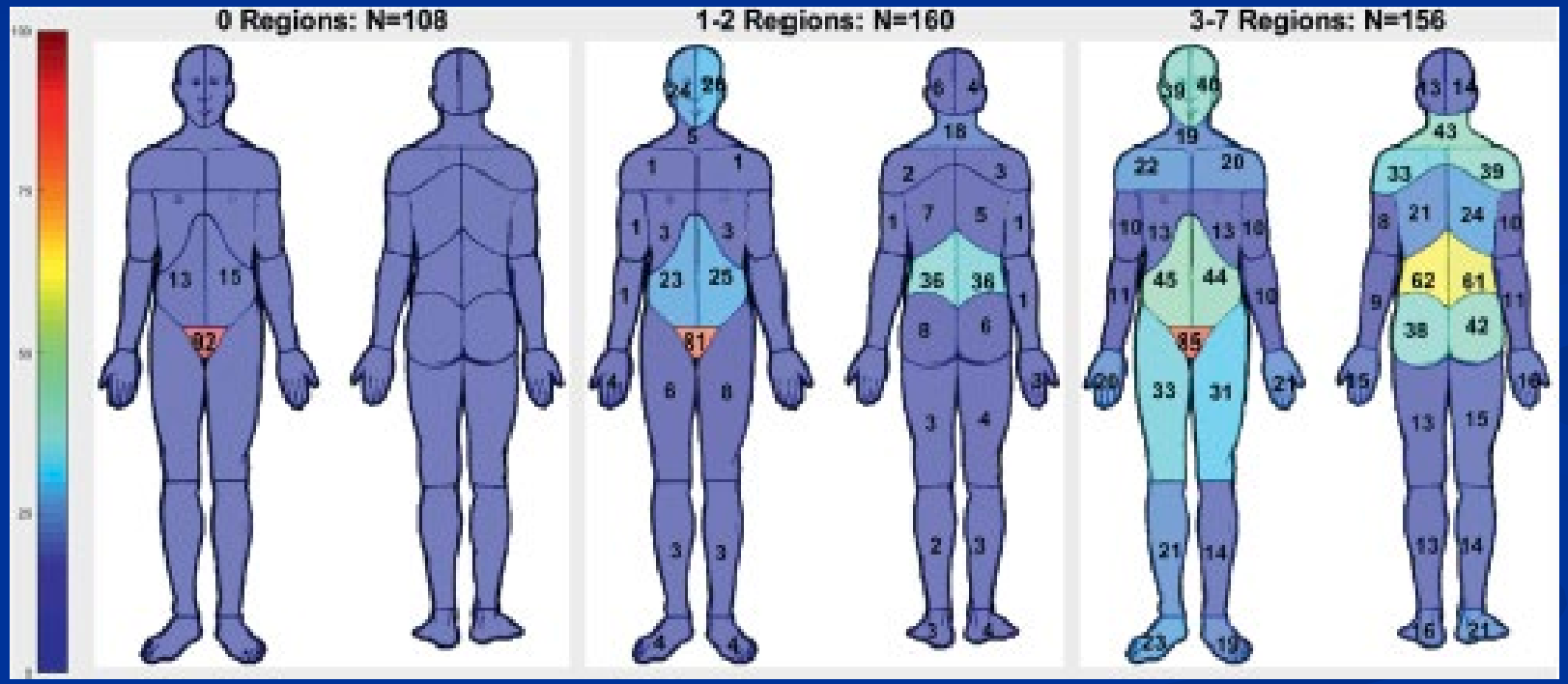
UNIVERSITY OF MICHIGAN HOSPITALS & HEALTH CENTERS	NAME
Anesthesiology	REC NO.
New Patient Questionnaire - Back and Pain Center	BIRTHDATE

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***.



Pain Distribution in IC (MAPP)

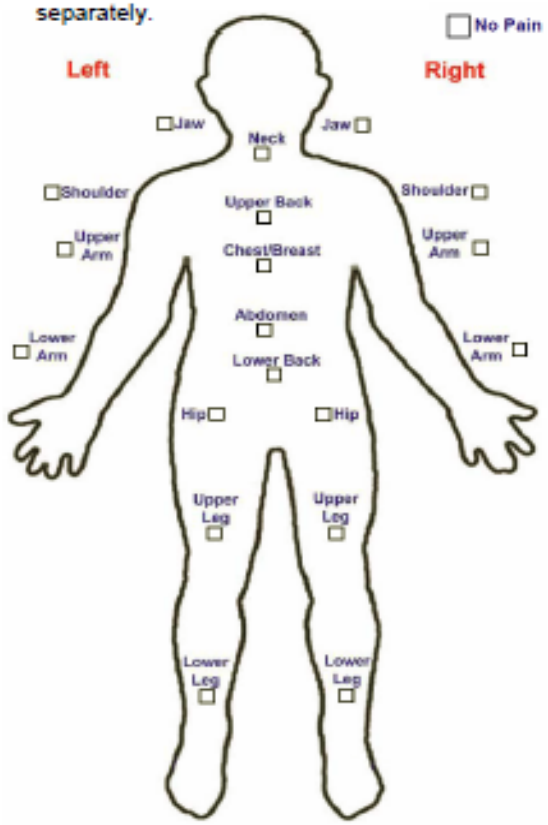


Lai, HH, Jemielita, T, Sutcliffe, S., Bradley CS, Naliboff, B, Williams, DA et al,. J. Urology. (2017), 198(3): 622-631.

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.

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

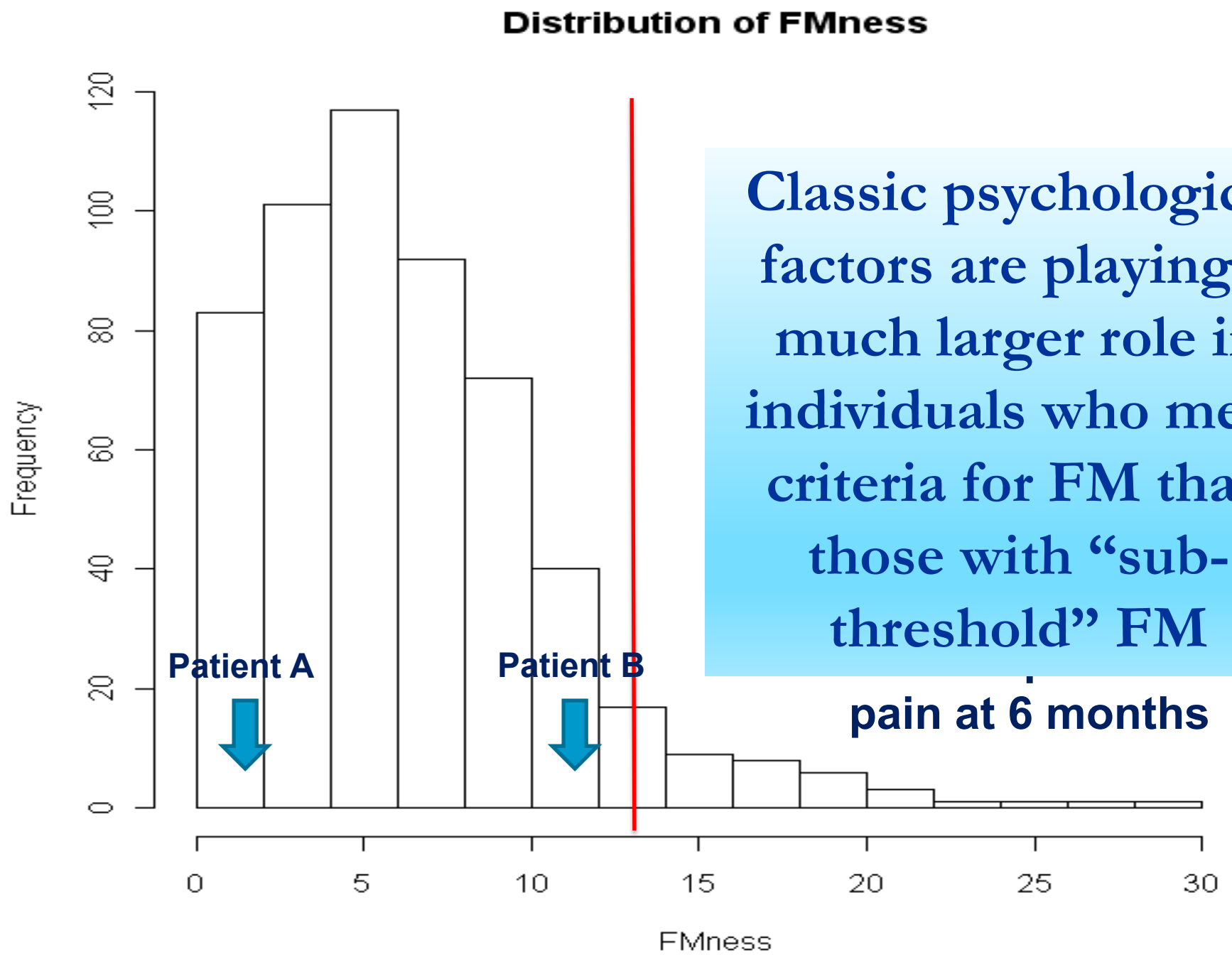
1. Brummett, C.M., et al., Anesthesiology, 2013. **119**(6): p. 1434-43.
2. Brummett, C.M., et al., Arthritis Rheumatol, 2015. 67(5):1386-94.
3. Janda, A.M., et al., Anesthesiology, 2015. **122**(5): p. 1103-11.

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
- FM Survey score

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 psychiatric factors



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

pain at 6 months

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.

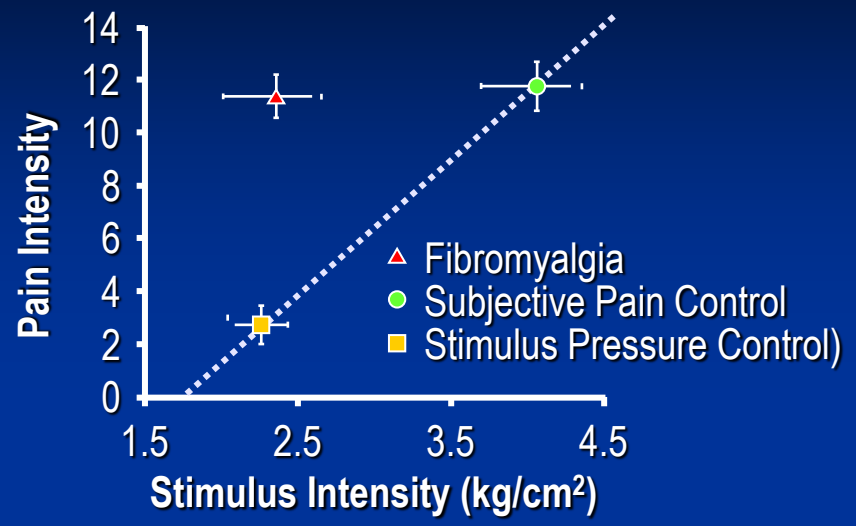
CONCLUSION: Although the majority of women with chronic pelvic pain report considerable improvement in pain following hysterectomy, higher degrees of centralized pain before hysterectomy is a robust pre-

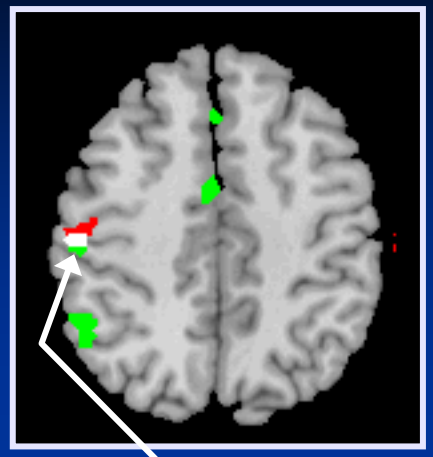
Pathophysiology of centralized pain states– understading the "central amplifier"

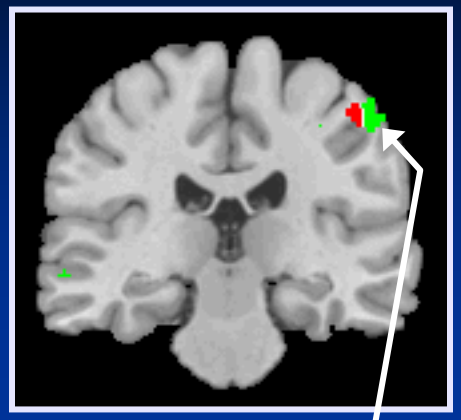
- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances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

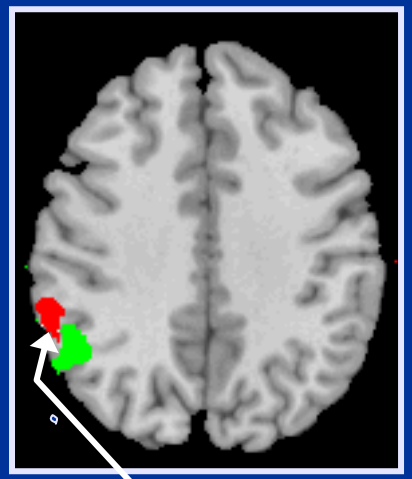
1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4. Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9):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

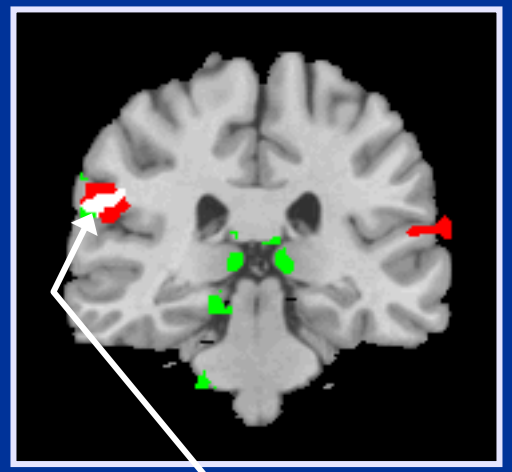
fMRI in Fibromyalgia

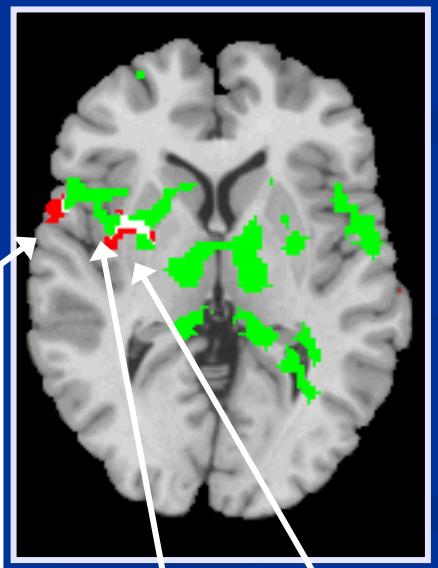


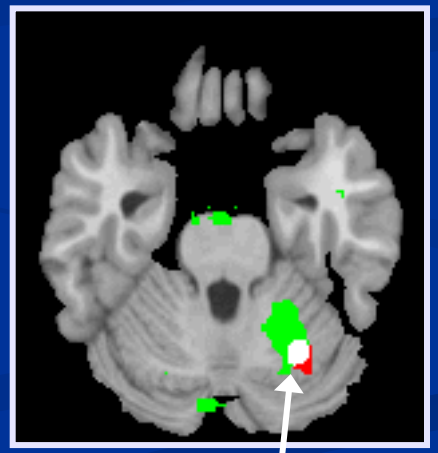








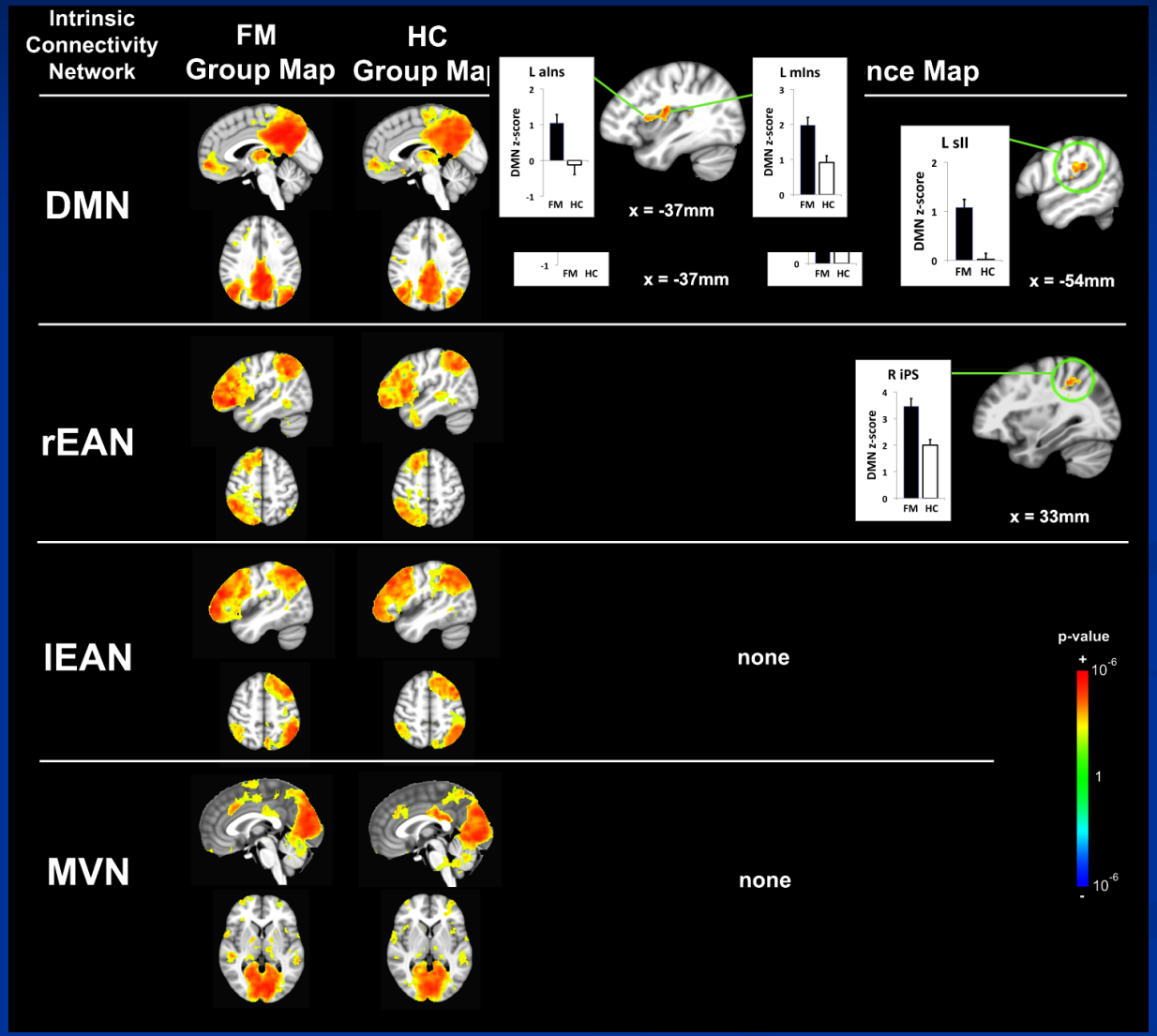




STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

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

PAIN®

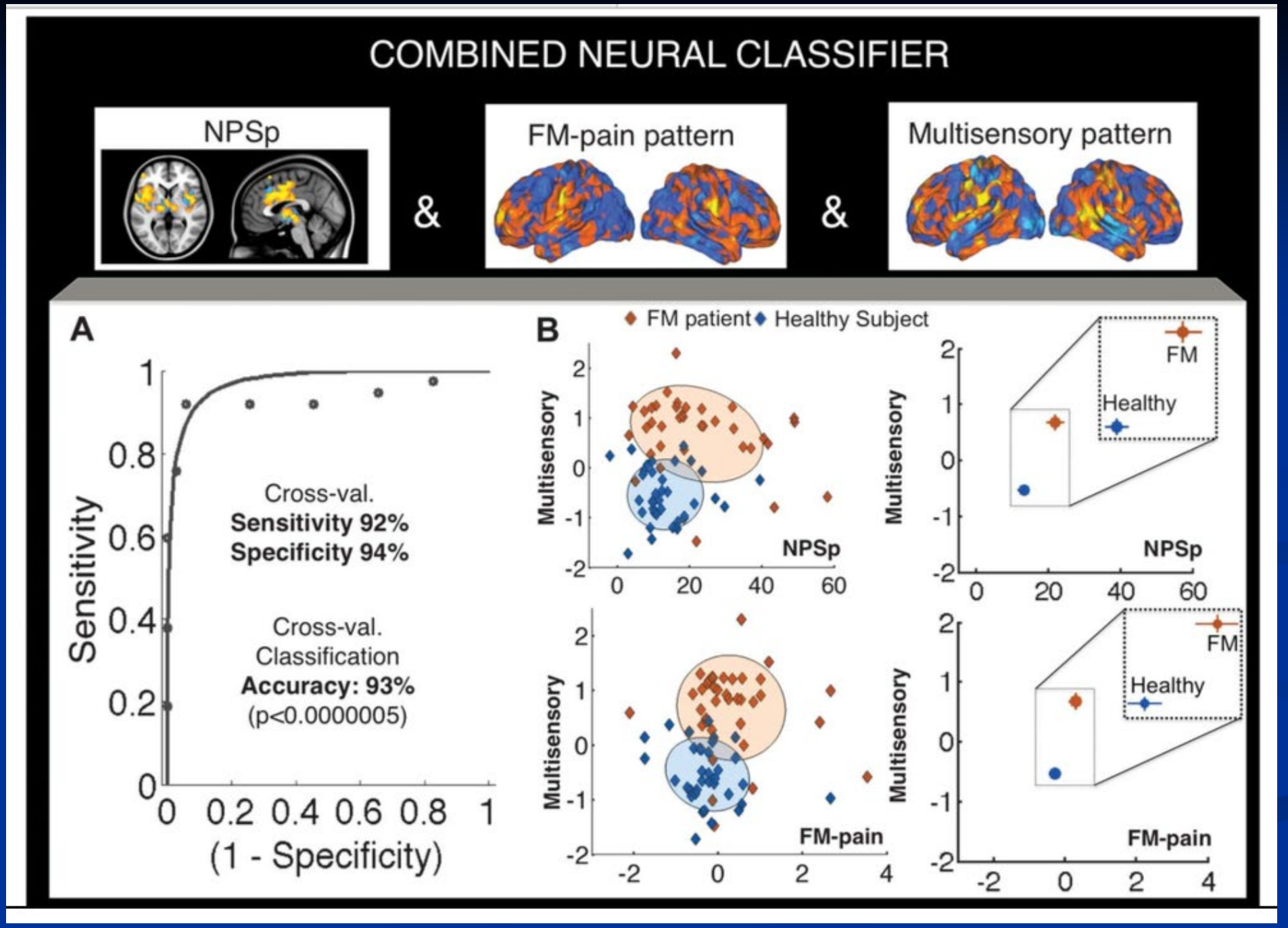
Towards a neurophysiological signature for fibromyalgia

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

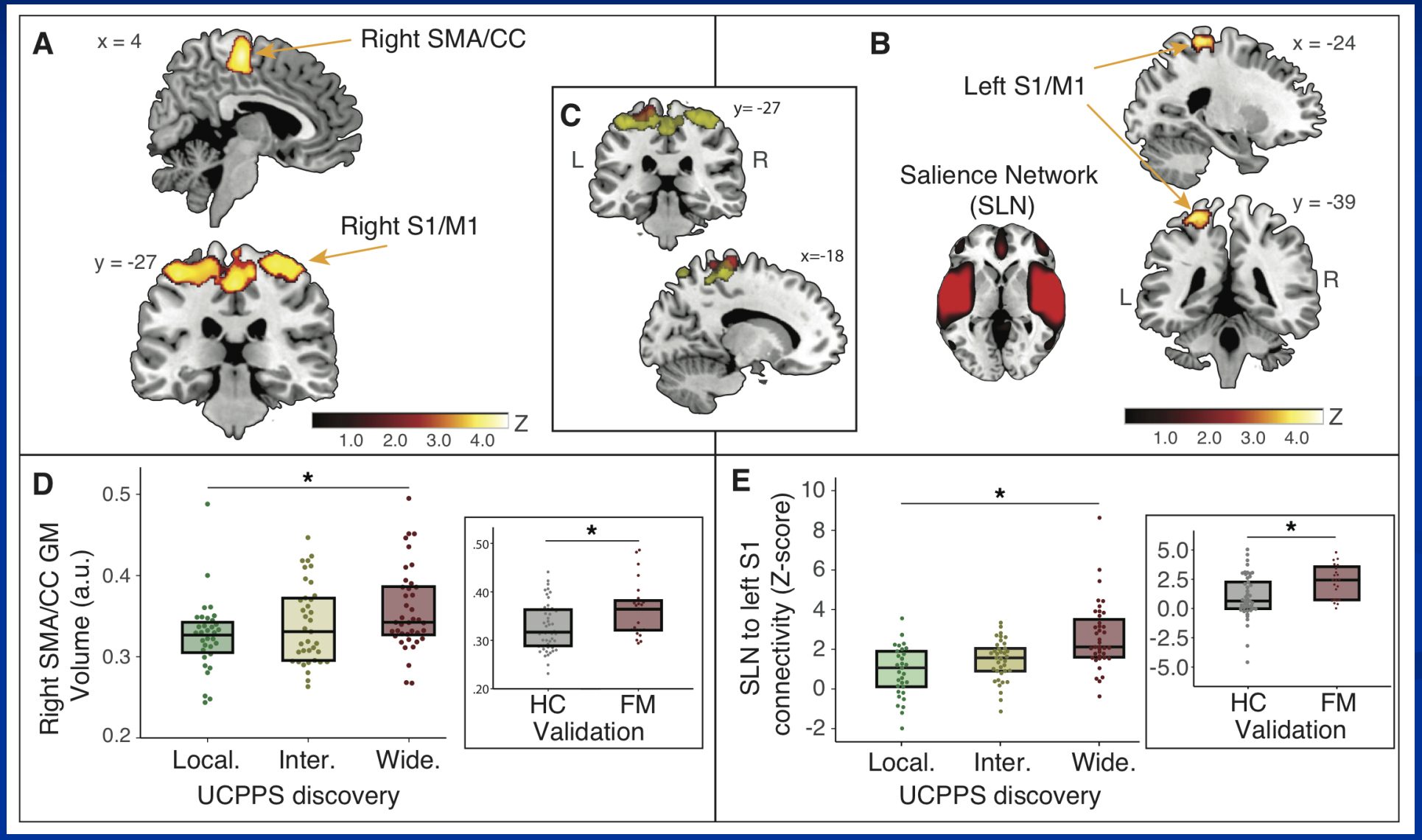

COMBINED NEURAL CLASSIFIER
NPSp
&
FM-pain pattern
&
Multisensory pattern
A
Sensitivity
(1 - Specificity)
Cross-val.
Sensitivity 92%
Specificity 94%
Cross-val.
Classification
Accuracy: 93%
(p<0.0000005)
B
FM patient
Healthy Subject
Multisensory
NPSp
FM
Healthy
FM-pain

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

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



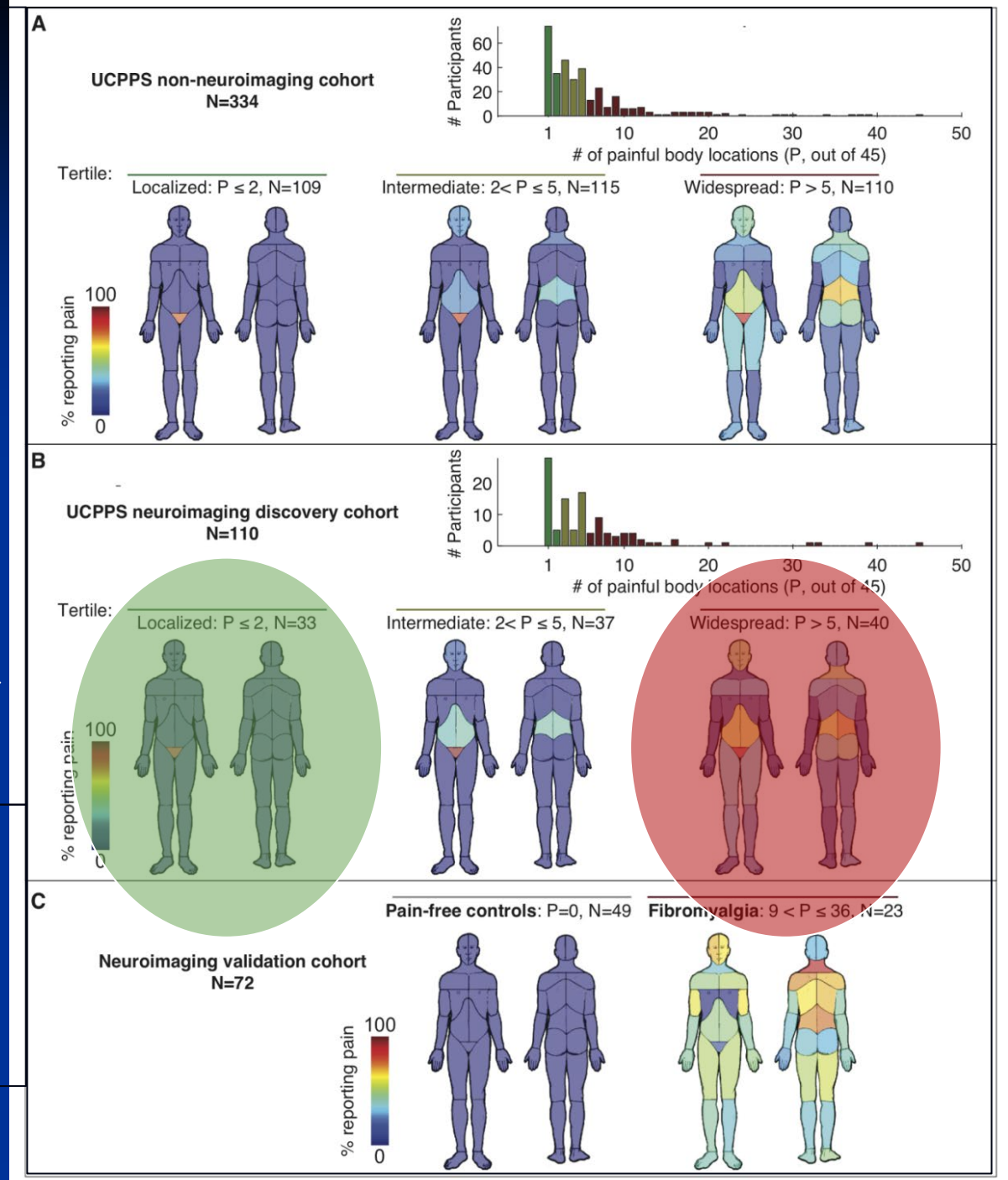
Interstitial Cystitis

Tertiles of body pain distribution:
local, intermediate, widespread

Non-Neuroimaging (N=334)

Neuroimaging (N=110)

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



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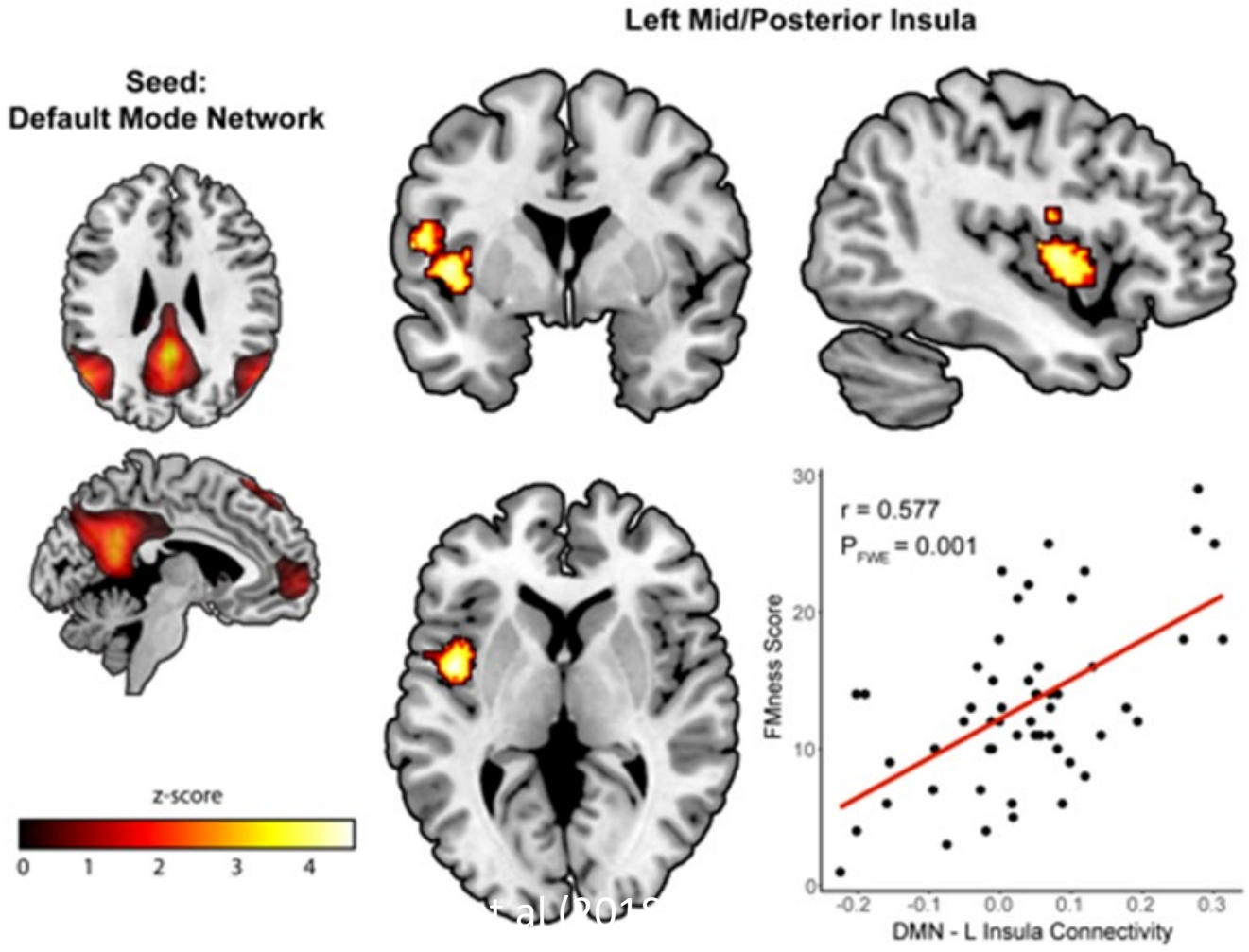
Original Article | Free Access

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



Arthritis & Rheumatology

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American College of Rheumatology

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.

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

CNS Neurotransmitters Influencing Pain

Facilitation

Gabapentinoids, ketamine

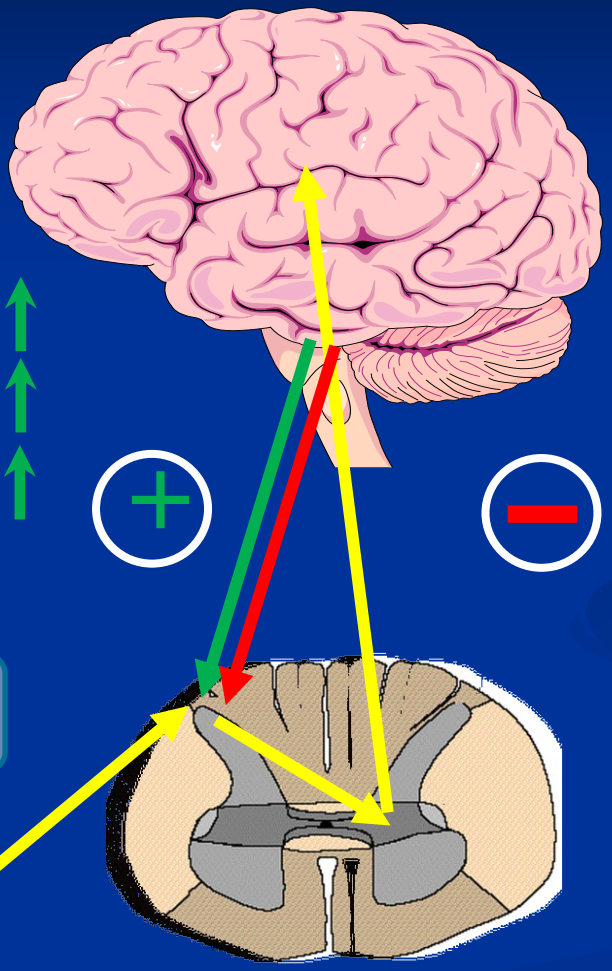
Glutamate and EAA

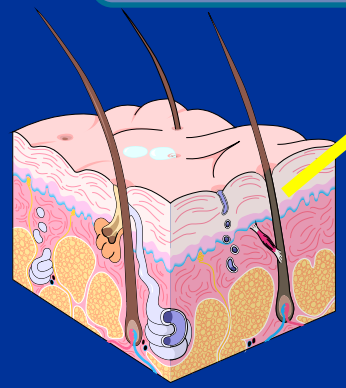
Substance P

Nerve growth factor

Serotonin ($5HT_{2a, 3a}$)

Anti-migraine drugs (–triptans), cyclobenzaprine





Inhibition

Descending anti-nociceptive pathways

Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine

Tricyclics, SNRIs. tramadol

Opioids

Low dose naltrexone

Cannabinoids

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

GABA

Gammahydroxybutyrate, moderate alcohol consumption

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

Neurotransmitters for Pain Processing

Norepinephrine

Concentration

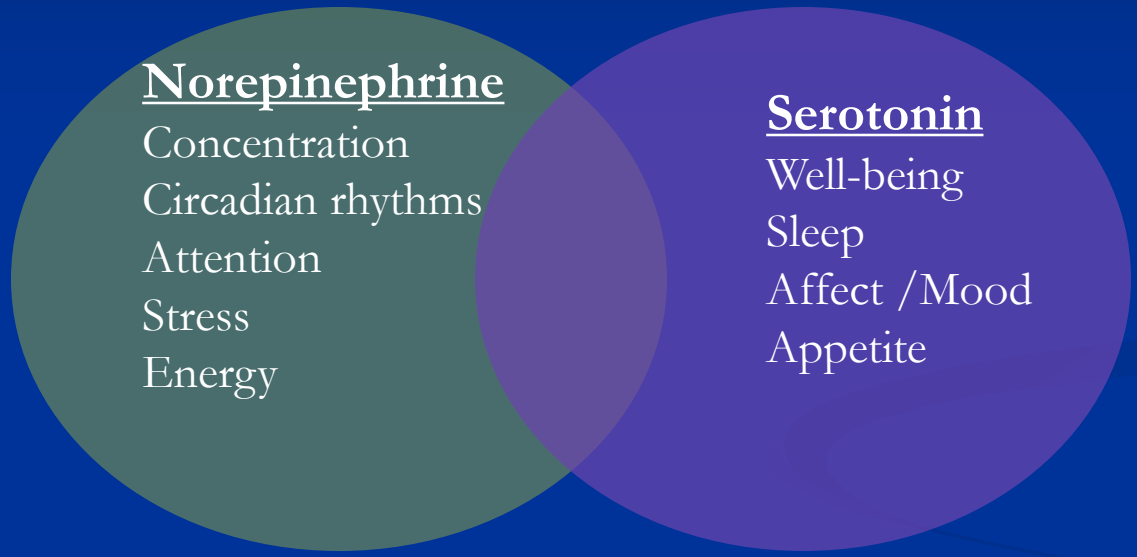
Circadian rhythms

Attention

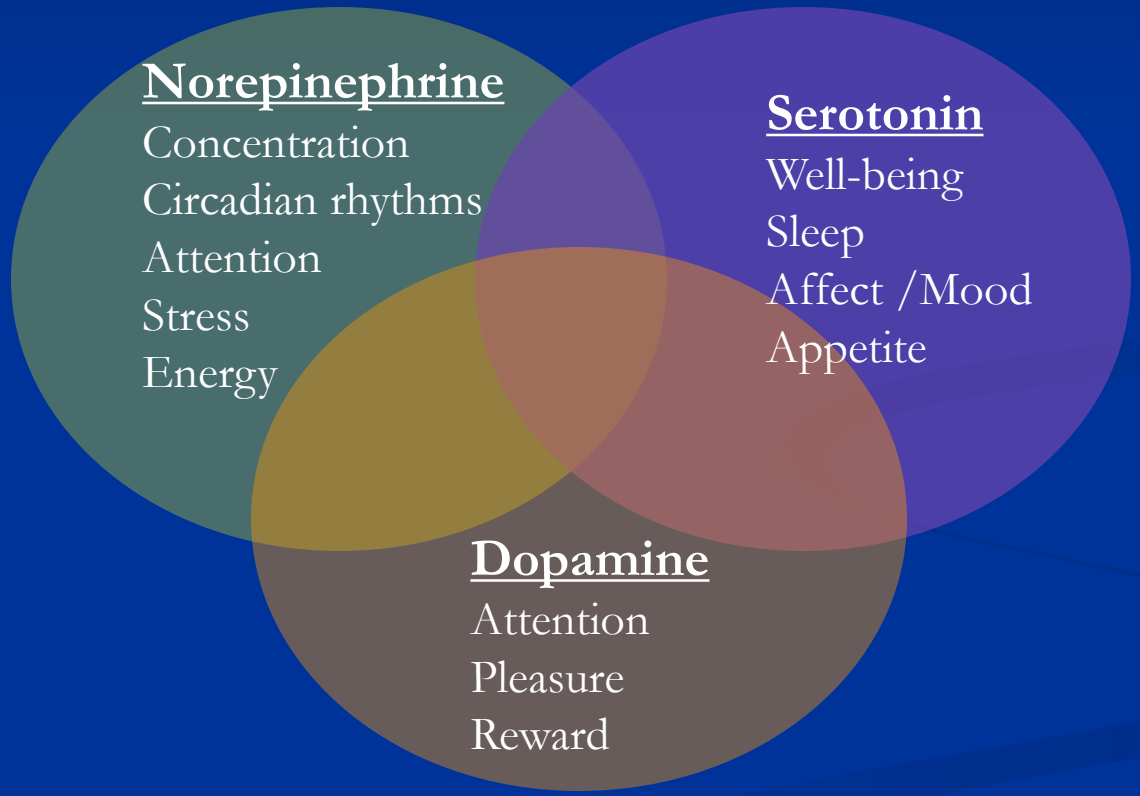
Stress

Energy

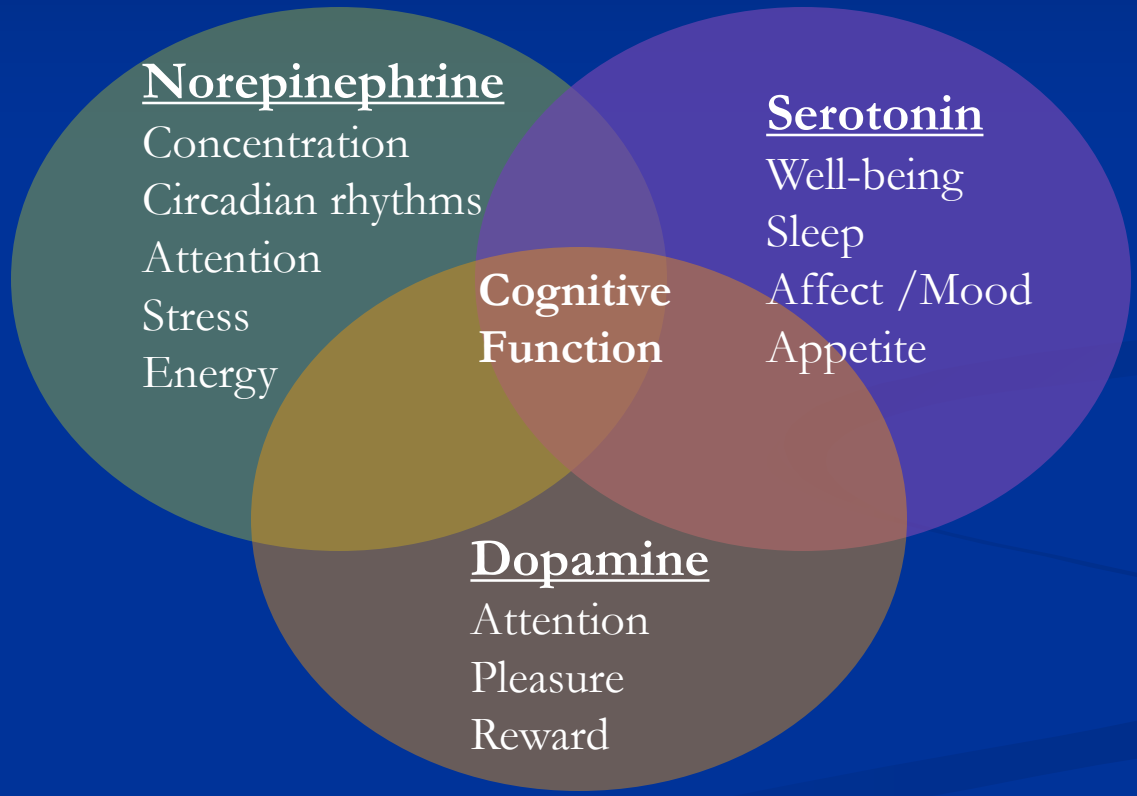
Neurotransmitters for Pain Processing



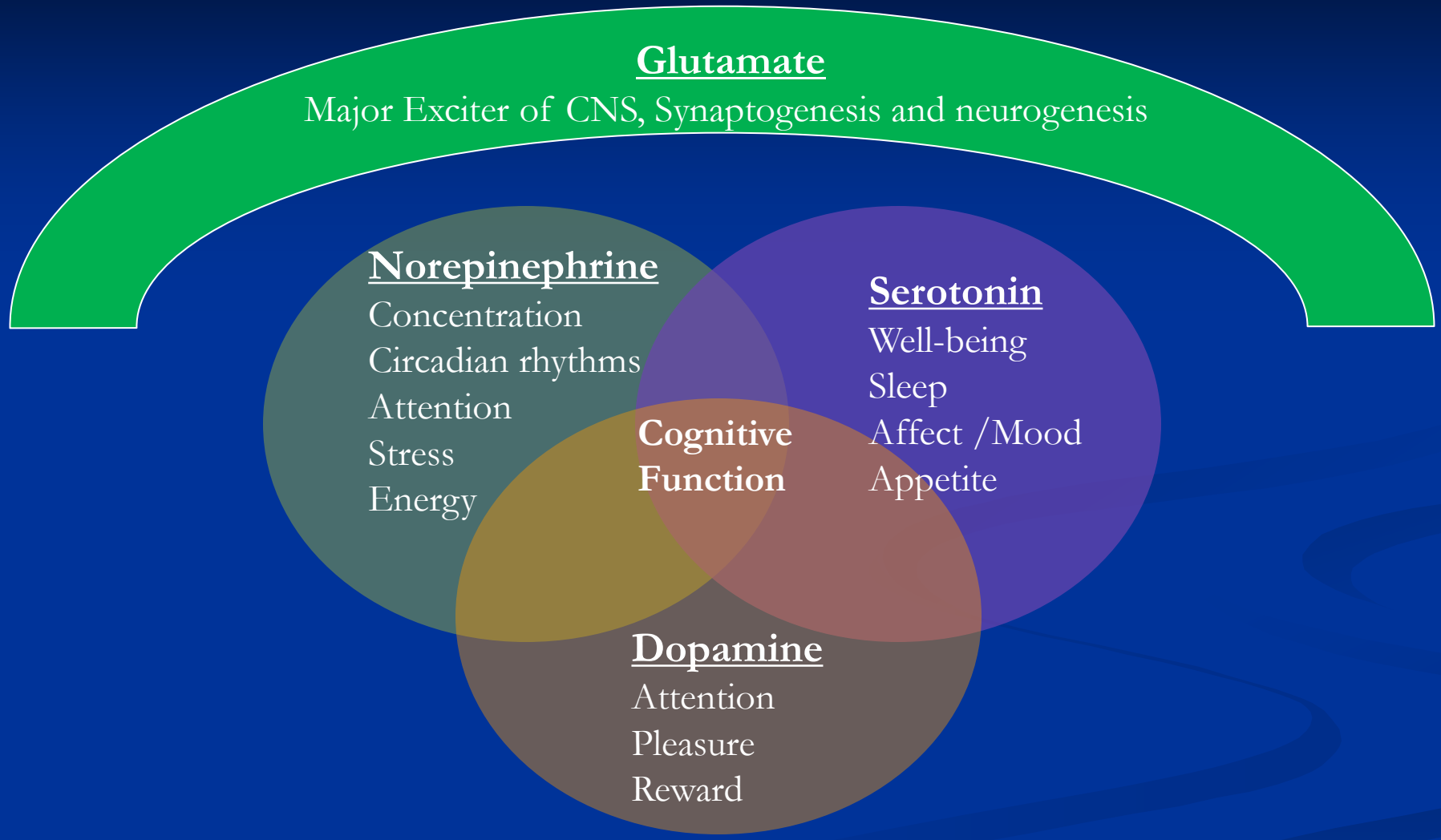
Neurotransmitters for Pain Processing



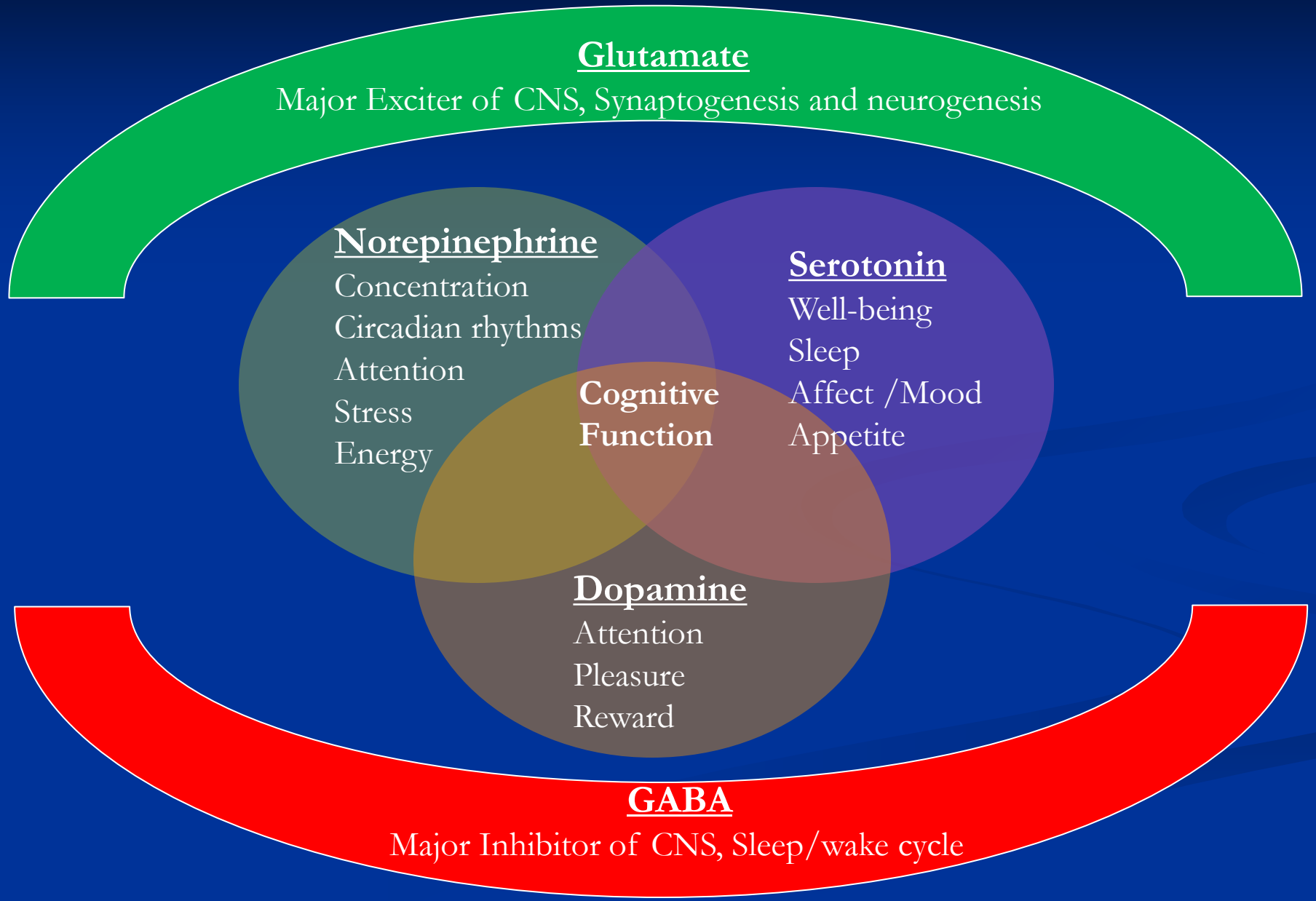
Neurotransmitters for Pain Processing



Neurotransmitters for Pain Processing



Neurotransmitters for Pain Processing



Shared Neurotransmitters Explain

- The complexity of chronic pain presentation

Williams, DA (2018). JABR, 23(2):e12135. Schrepf, A et al., JPain, 2018 (in press).

Shared Neurotransmitters Explain

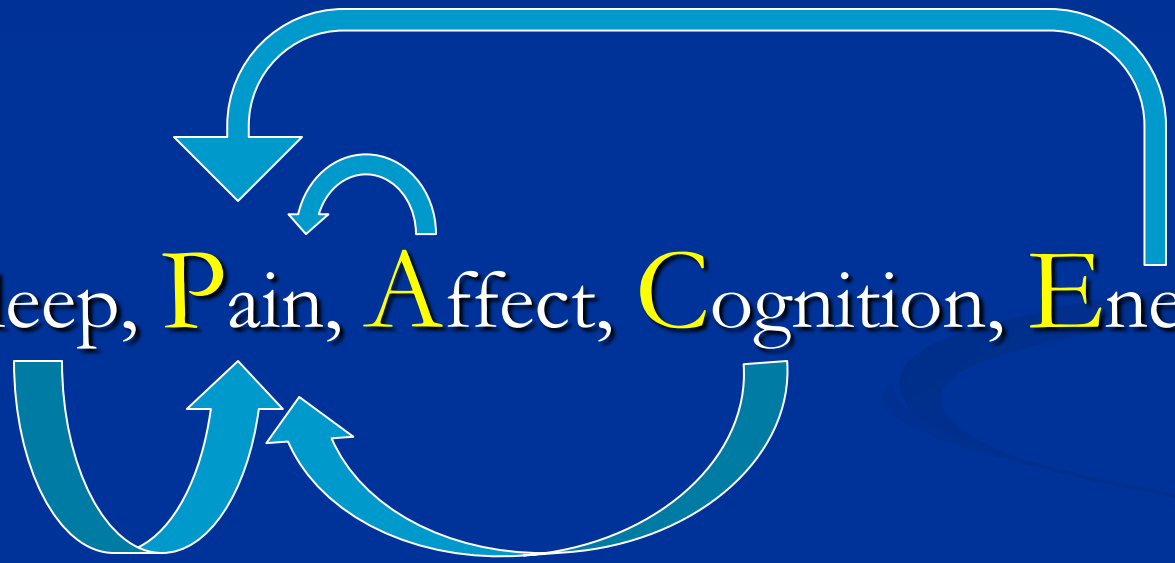
- The complexity of chronic pain presentation

- Sleep, Pain, Affect, Cognition, Energy

Williams, DA (2018). JABR, 23(2):e12135. Schrepf, A et al., JPain, 2018 (in press).

Shared Neurotransmitters Explain

- The complexity of chronic pain presentation



- Sleep, Pain, Affect, Cognition, Energy
- **SPACE** represents new targets for treating pain perception

Williams, DA (2018). JABR, 23(2):e12135. Schrepf, A et al., JPain, 2018 (in press).

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

Trends/terms

- Nociplastic/Primary pain
  - Widespread
  - Co-morbid CNS symptoms sleep, fatigue, memory
  - Sensory sensitivity
  - Low grade (neurogenic) inflammation
- Re-think role of CNS-mediated symptom clusters as shared mechanism and potential treatment targets

Stretch Break

Music about Pain

- Pain – Three Days Grace
- Pain – Tupac Shakur
- Pain – Pusha T
- Pain – Jimmy Eats World
- Pain – War on Drugs
- Pain – Hollywood Undead
- Pain – The Used

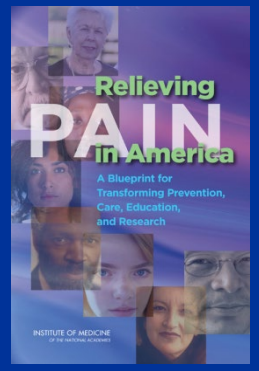
- King of Pain – Police
- No More Pain – 2Pac
- Feel No Pain – Sade
- The Sweetest Pain – Dexter Wansel
- I Feel Pain – A Boogie wit Da Hoodie
- I Can't Stand the Pain - James Brown
- Physical Pain – Future Island

- Hurt – Johnny Cash
- Everybody Hurts – R.E.M.
- Hurt – Nine Inch Nails

- Give Me Novocain – Green Day
- Pain Killer – Judas Priest
- The Drugs Don't Work – The Verve

What's a doctor to do?

Chronic Pain Numbers



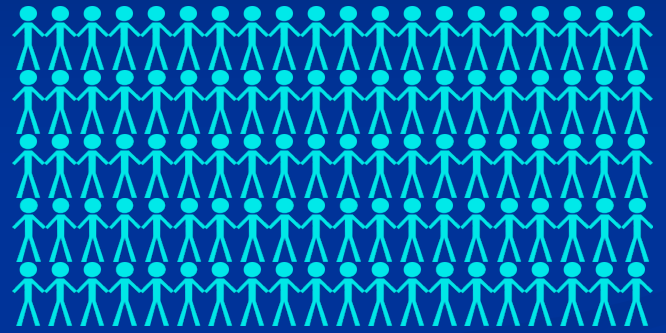
100 Million People
- US

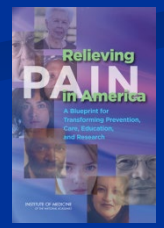
150 Million
- 37 Countries

Eccleston, C., Wells, C. (2017). European Pain Management. Oxford University Press

More people have Chronic Pain than Diabetes, Heart Disease, and Cancer Combined

Chronic Pain	100 Million
Diabetes	29.1 Million
Heart Disease	27.6 Million
Cancer	13.7 Million





= 1 Million individuals

Most Pain Care Visits occur within Primary Care

Peterson K, et al.. VA ESP Project #09-199; 2017.

Primary Care Physicians Receive Little Training in Pain Management

- 80% of American Medical Schools have no formal pain education
- Those that do, report 5 or fewer hours
  - Emphasis of education is often cellular and subcellular rather than interpersonal or social in nature
- Only 34% of physicians reported feeling comfortable treating chronic pain
  - Only 1% found it a satisfying practice

Loeser, JD & Schatman, ME (2017). Chronic pain management in medical education: a disastrous omission. Postgraduate Medicine, 129 (3): 332-335.

Pain Medicine Versus Pain Management: Ethical Dilemmas Created by Contemporary Medicine and Business

John D. Loeser, MD† and Alex Cahana, MD, PhD*†*

Biomedical Model
Interventional
Pain Medicine

- Procedure Driven
- Focus on curing/fixing

Patient is passive recipient

Biopsychosocial model
Interdisciplinary
Pain Management

- Focus on multidisciplinary teams
- Focus on pain management

Patient is active participant

Loeser, J & Cahana, A. (2013). Clinical Journal of Pain, 29 (4): 311-316.

How good is our black bag for treating chronic pain?

Treatment	Impact on Chronic Pain
Long term opioids	32% reduction
Pain drugs generally (across classes)	30% - 40% get 40% - 50% relief
Spinal fusion	75% still have pain
Repair herniated disk	70% still have pain
Repeat Surgery	66% still have pain
Spinal cord stimulators	61% still in pain after 4 yrs. average pain relief 18% across studies

Turk, D. C. (2002). *Clin.J Pain, 18*(6), 355-365; Backonja MM et al. *Curr Pain Headache Rep* 2006;10:34-38

Are Invasive Procedures Effective for Chronic Pain? A Systematic Review

Wayne B. Jonas, MD,* Cindy Crawford,† Luana Colloca, MD, PhD,‡ Levente Kriston, PhD,§ Klaus Linde, MD, PhD,¶ Bruce Moseley, MD,‖ and Karin Meissner‖,**

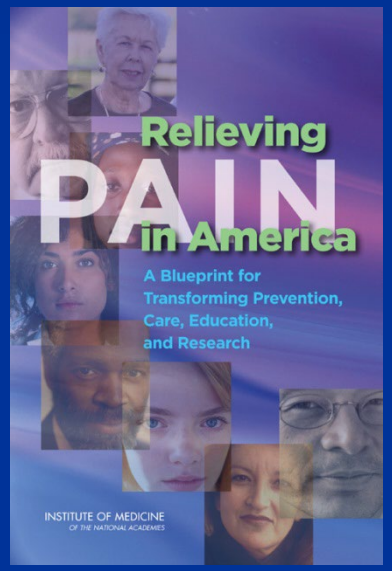
Conclusions. There is little evidence for the specific efficacy beyond sham for invasive procedures in chronic pain

Pain Medicine, 20(7), 2019, 1281–1293
doi: 10.1093/pm/pny154
Advance Access Publication Date: 10 September 2018
Review Article

OXFORD

Recommendations in Multiple Federal Documents

Self-Management, Evidence-Based, Patient-Centric, Multi-Modal Pain Care



National Pain Strategy

A Comprehensive Population Health-Level Strategy for Pain

Healthy People 2030

EFFECTIVELY AND RESPONSIBLY MANAGE CHRONIC PAIN

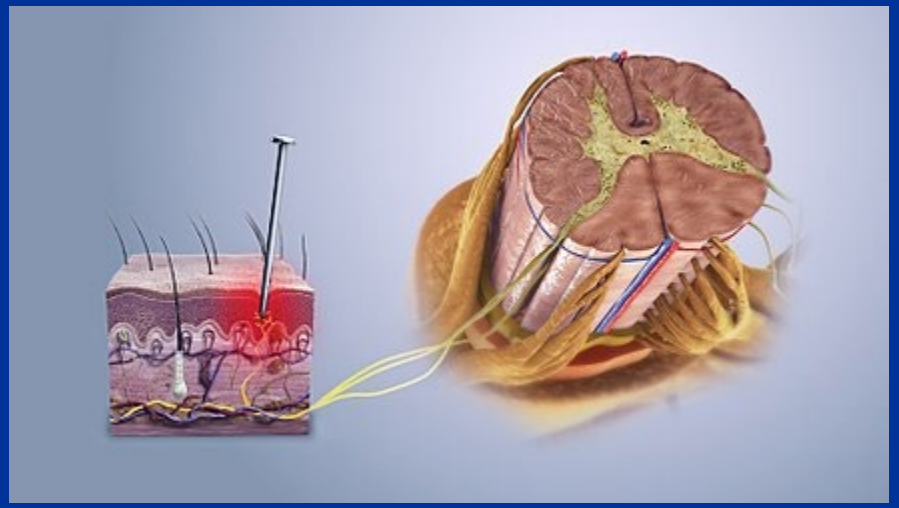
GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

www.cdc.gov

We Need to Approach Chronic Pain Differently

Thinking Differently about Pain

- Damaged tissue and pain are not the same thing
- Sometimes they occur together, so they seem to be the causal
- Nociception provides bodily information that may or may not be interpreted as pain



Nociception

PAIN

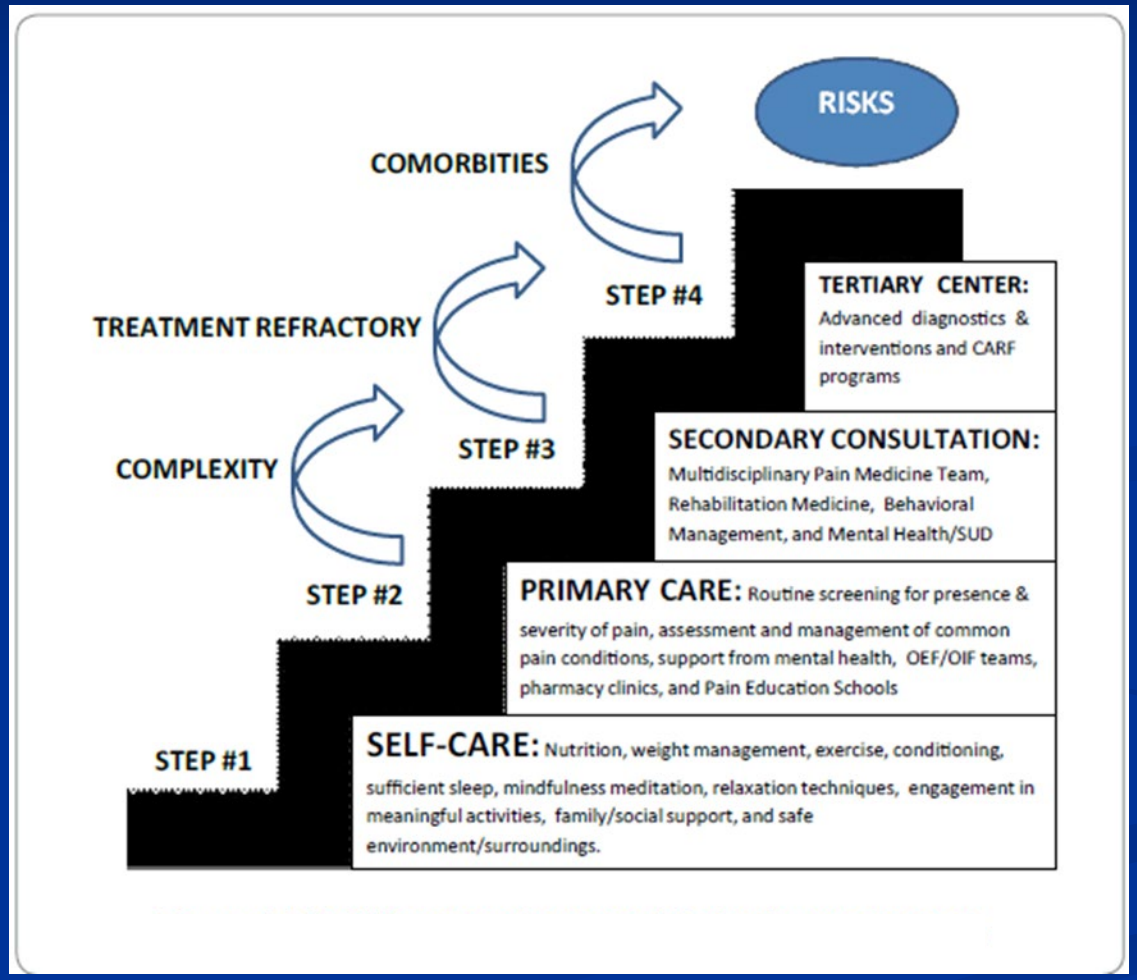
Thinking Differently about Chronic Pain

- Pain is a Perceptual Experience formed in the brain
  - Other perceptual experiences with flexible biological associations include the following:
    - hunger, itch, tickle, urinary urgency, orgasm

Thinking Differently about Chronic Pain

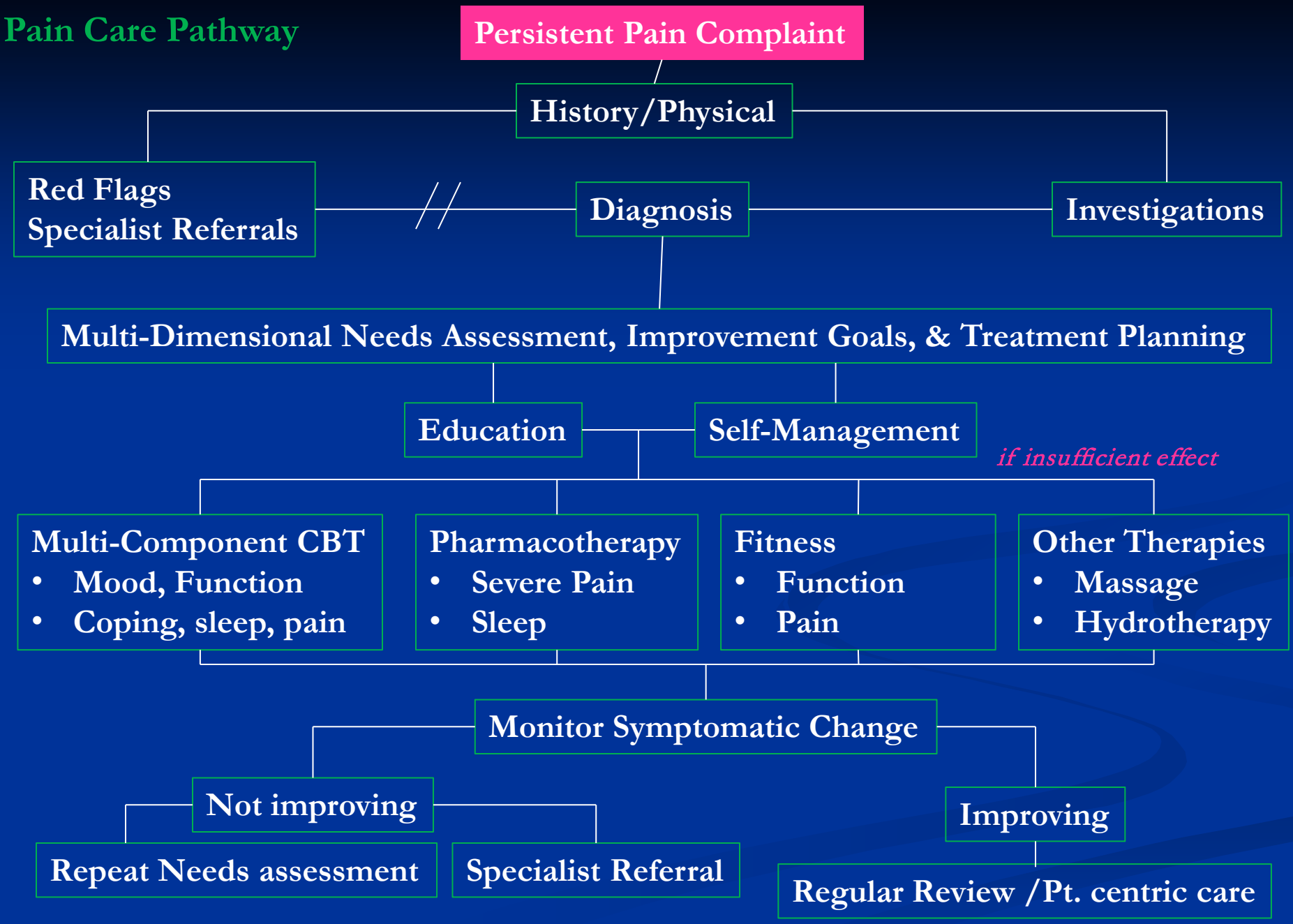
- Treating a perception requires different techniques than fixing damaged tissues

VA's Stepped Care Model of Pain Management



Kerns et al (2011). Transl Behav Med, 1:635-643. Coslo & Swaroop. (2016). J Pain Mgt & Med., 2:2

Pain Care Pathway



Adapted from Macfarlane et al. Ann Rheum Dis, 2017;76:318-328; Lee, et al., BJA 2014; 112:16-24; Peterson et al, VA ESP Project #09-199, 2017

Chronic Overlapping Pain Conditions

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 9 (September), Suppl. 2, 2016: pp T93-T107
Available online at www.jpain.org and www.sciencedirect.com

Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

CrossMark

William Maixner,*,† Roger B. Fillingim,‡ David A. Williams,§ Shad B. Smith,*,† and Gary D. Slade*,¶,‖

*Center for Pain Research and Innovation, ¶Department of Dental Ecology, ‖Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
†Center for Translational Pain Medicine, Department of Anesthesiology, Duke University, Durham, North Carolina.
‡Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, Florida.
§Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

- **Term defined by the National Institutes of Health ~ 2013**
- **Conditions likely to co-exist sharing neurobiological underpinnings**
- **Conditions predominantly (or solely) affecting women**
- **Any number and combination of conditions is possible**
- **Several conditions can develop at once or gradually over years**

COPCs[1]	US Prevalence
Irritable Bowel Syndrome	44 Million
Temporomandibular Disorder	35 Million
Chronic Low Back Pain	20 Million
Interstitial Cystitis / BPS; chronic prostatitis	8 Million
Migraine Headache	7 Million
Tension Headache	7 Million
Endometriosis (Painful)	6 Million
Vulvodynia	6 Million
Fibromyalgia	6 Million
Myalgic Encephalopathy / CFS	4 Million

[1]Veasley, C. et al (2015). White paper from the *Chronic Pain Research Alliance*.

Two methods for assessing COPCS for clinical research

- ICD-10 Computable Phenotype
- The Chronic Overlapping Pain Conditions Screener (COPCS)

US ASP
US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 21, No 1–2 (January/February), 2020: pp 59–70
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

ICD-10 Codes for the Study of Chronic Overlapping Pain Conditions in Administrative Databases

Andrew Schrepf,* Vy Phan,† J. Quentin Clemens,‡ William Maixner,§ David Hanauer,¶ and David A. Williams*

*Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan, †Trinity College-Hartford, Hartford, Connecticut, ‡Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, §Center for Translational Pain Medicine, Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina, ¶Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan

FM	IBS	IC/BPS, CP	VVD	MI
• M79.7	• K58.[0,1,2,8,9]	• N30.[1,3] • N41.1	• N94.8[10,18,19]	• G43.xx
TTH	TMD	cLBP	ME/CFS	ENDO+pain
• G44.[201,209,211,219,221,229]	• M26.*[60,62,63]* • *S03.0xxA*	• M54.[5,40,41,42,89]	• R53.82	• N80.xxx +R10.2, • N80.xxx +N94.[4,5,6,10,11,12,19]

	FM	IBS	TMD	UCPPS	ENDO	VVD	cLBP	cTTH	MI	CFS
FM										
IBS	10.18									
TMD	5.64	3.70								
UCPPS	9.91	9.10	4.75							
ENDO	4.06	5.05	1.87	18.62						
VVD	3.14	3.97	1.85	24.99	15.56					
cLBP	5.29	2.29	1.24	2.34	2.30	1.20				
cTTH	2.43	1.58	2.64	1.94	1.25	N/A	3.36			
MI	5.27	3.30	6.13	3.29	3.21	1.63	1.99	4.27		
CFS	6.07	2.90	1.48	2.78	1.86	1.19	1.75	1.82	2.67	
diab neurop	2.60	1.66	N/A	0.86	N/A	N/A	2.08	0.51	1.06	1.18
COPD	3.14	1.78	0.89	1.05	0.54	0.50	1.92	0.71	1.11	1.29
chronic viral hepatitis	2.20	1.48	0.56	1.19	N/A	N/A	1.22	0.56	0.68	1.01

Odds ratio =

5+

3-5

1-3

Chronic Overlapping Pain Conditions Screener (COPCS)

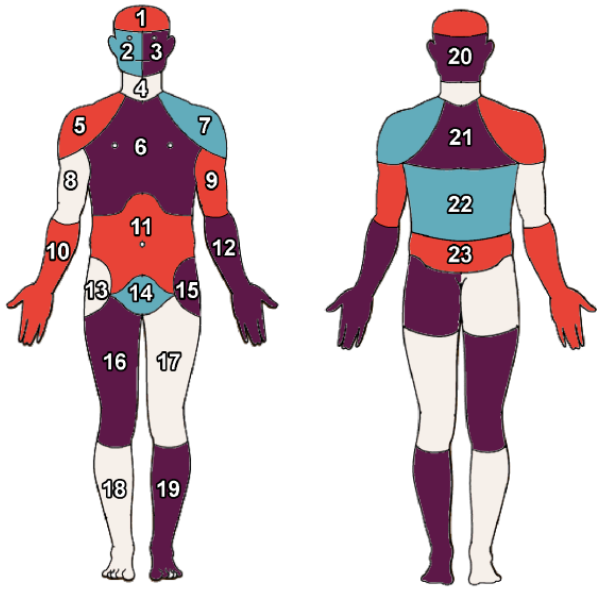
DEMOGRAPHICS

First name: _____

Last name: _____

What is your biological sex? Male| Female

BODY MAP



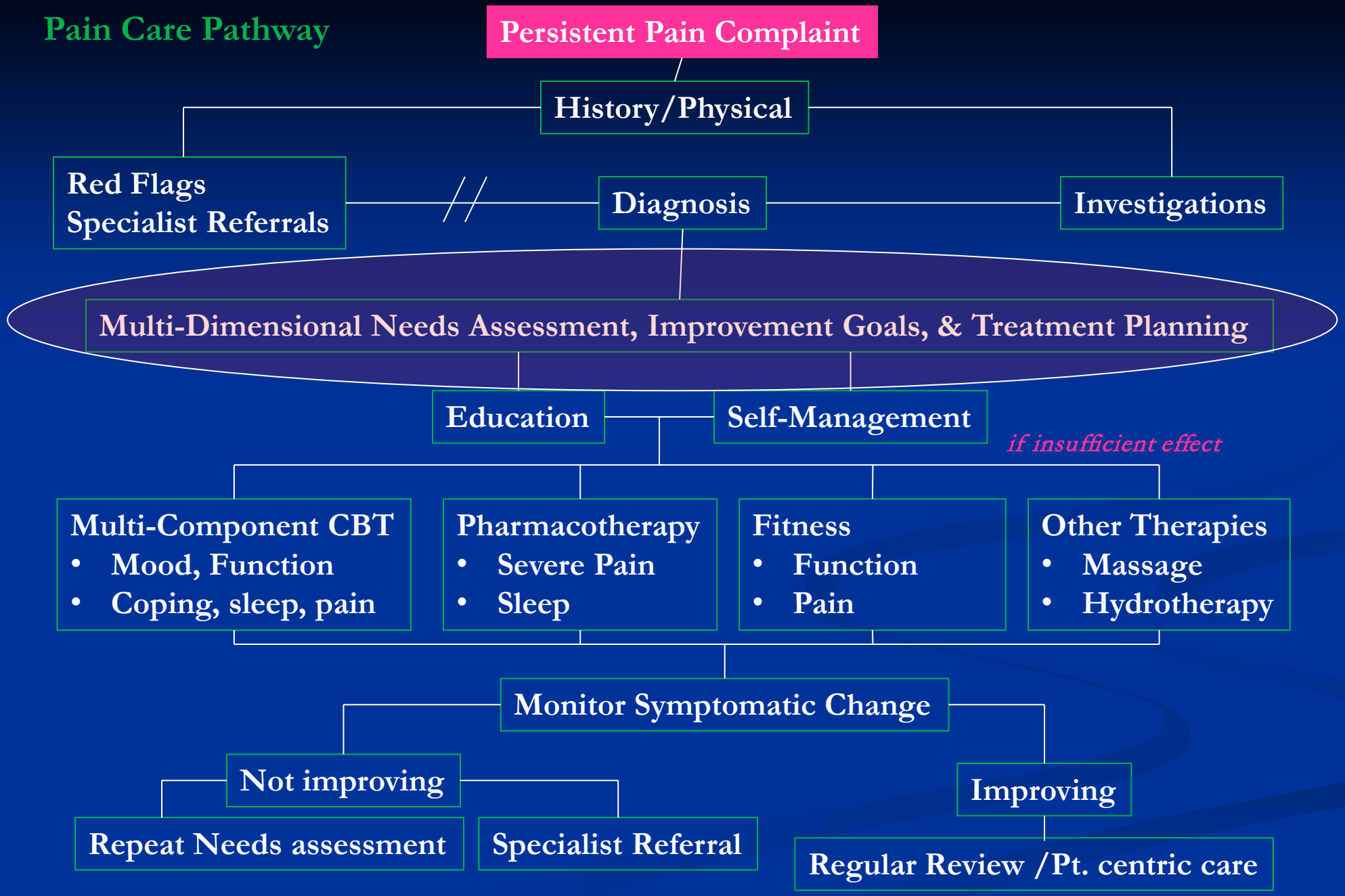
- VULVODYNIA (VVD)
- FIBROMYALGIA (FM)
- ENDOMETRIOSIS (ENDO)
- CHRONIC PROSTATITIS (ICBPS)
- CHRONIC LOW BACK PAIN (CLBP)
- IRRITABLE BOWEL SYNDROME (IBS)
- TEMPOROMANDIBULAR DISORDER (TMD)
- MIGRAINE/ CHRONIC TENSION-TYPE HEADACHE (MITTH)
- MYALGIC ENCEPHALOMYELITIS/ CHRONIC FATIGUE SYNDROME (ME/CFS)

https://copcscreener.com

Report	
Condition	Class
FM	Y/N
IBS	Y/N
TMD	Y/N
MI	Y/N
TTH	Y/N
IC/CP	Y/N
cLBP	Y/N
ME/CFS	Y/N
ENDO-pain	Y/N
VVD	Y/N
Total	x/10

Schrepf A, Williams DA, Maixner W. Chronic Overlapping Pain Conditions Screener - The REDCap Version: Users Guide, Version 11.0. Ann Arbor, MI: University of Michigan; 2022.

Pain Care Pathway



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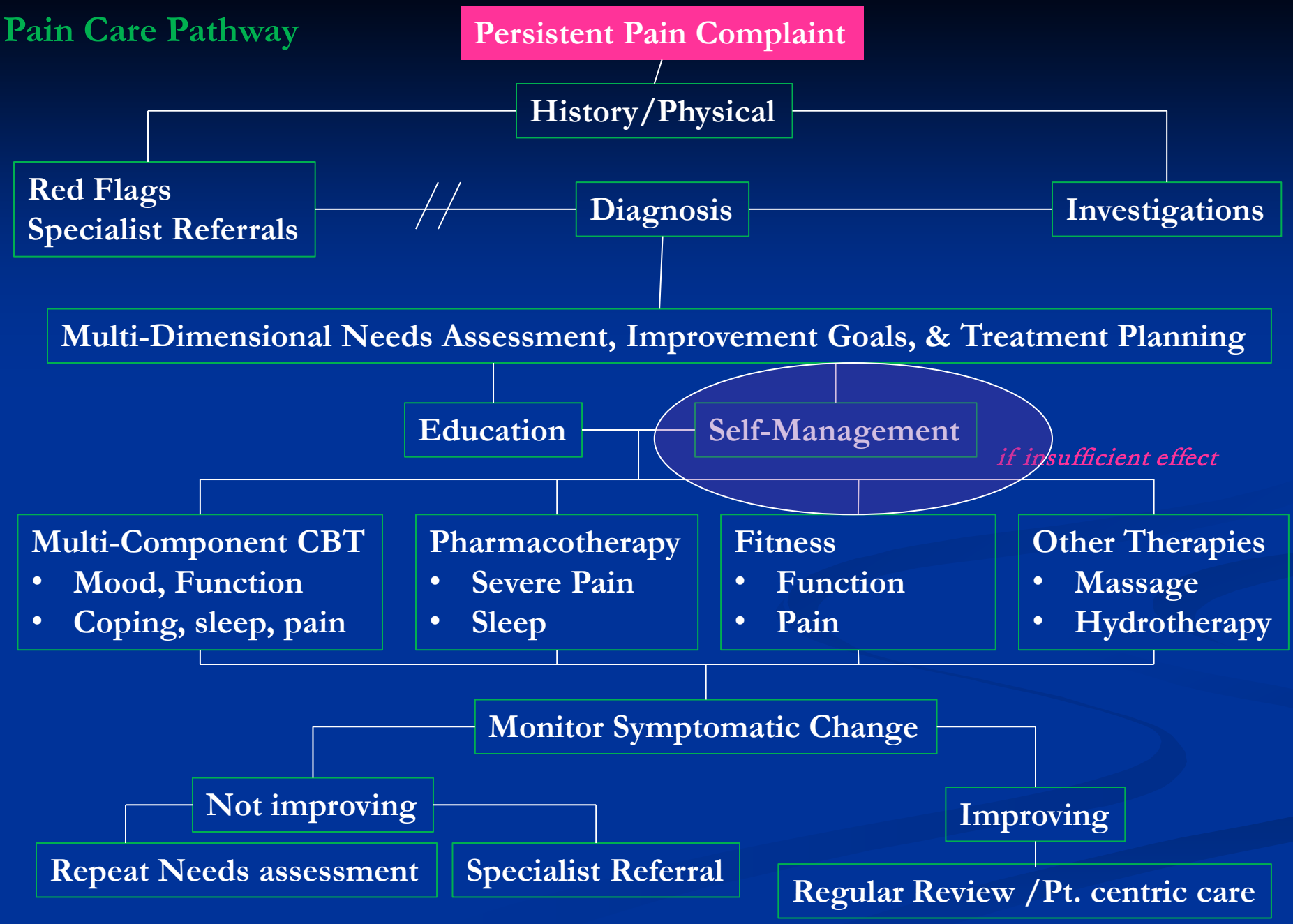
Pain Care Pathway



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How to ERASE S.P.A.C.E.

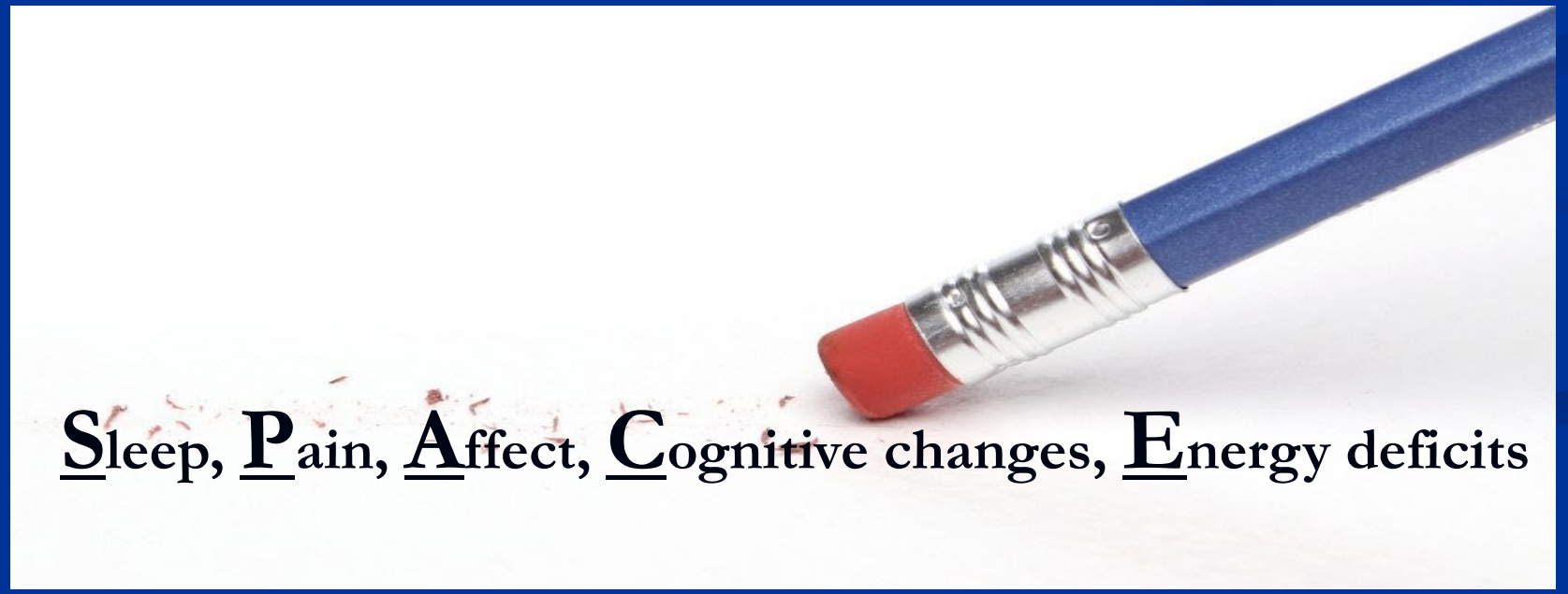
Emotions

Reflections

Actions

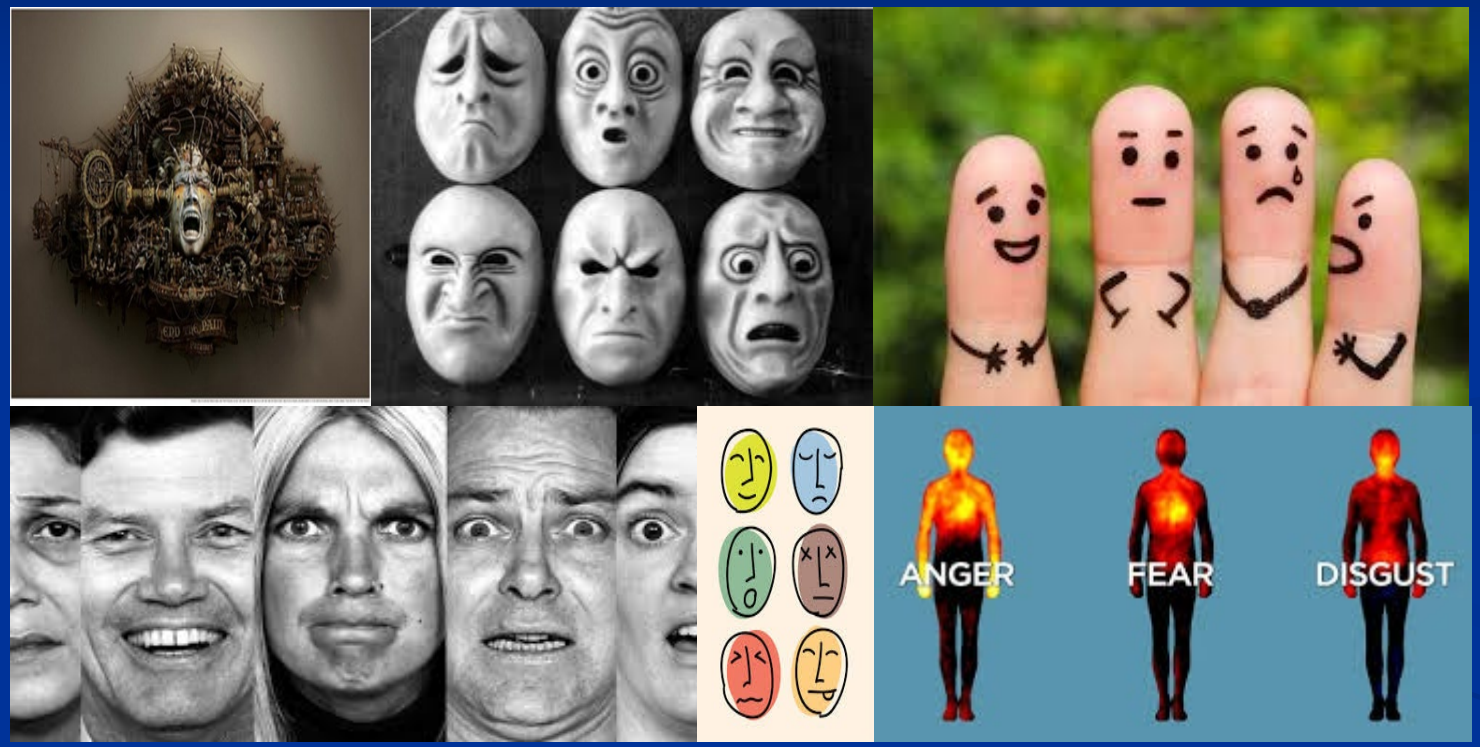
Sleep

Environment



ERASE

Emotions



Altering pain perception through Emotions

Patients do not need to be mentally ill to have chronic pain

Approaches to Resolve Negative Affect Influencing Chronic Pain

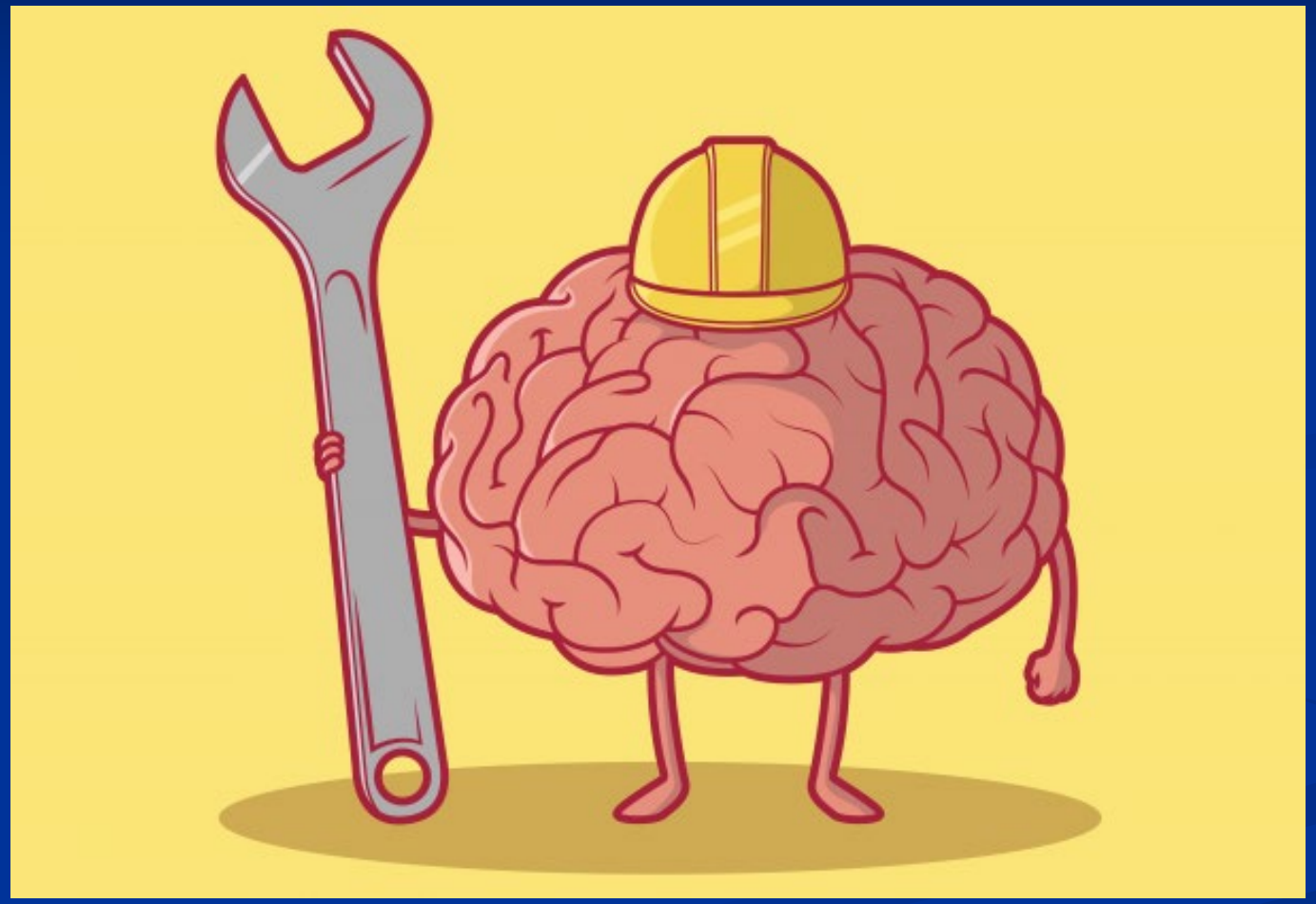
Emotional Awareness and Expression Therapy (EAET)

Pleasant Activity Scheduling

Traditional Psychotherapy

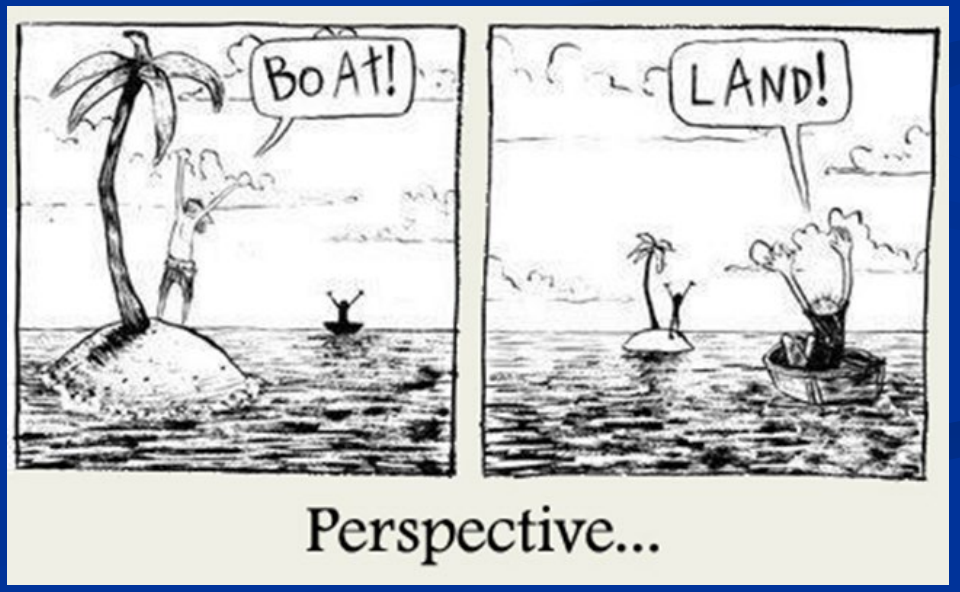
ERASE

Reflections



Using Cognition to alter pain perceptions

Reframing



The Relaxation Response

Visual Imagery

Meditation

Biofeedback

ERASE

Actions

Using Behavior to alter pain perceptions and provide a foundation of wellness

Exercise

- Multiple reviews and meta-analyses, and professional society guidelines recommend exercise and physical activity for the treatment of chronic pain and fatigue
- Increase Fitness
- Increase Function

Hassett & Williams. Best Pract Res Clin Rheumatol 2011;25:299-309

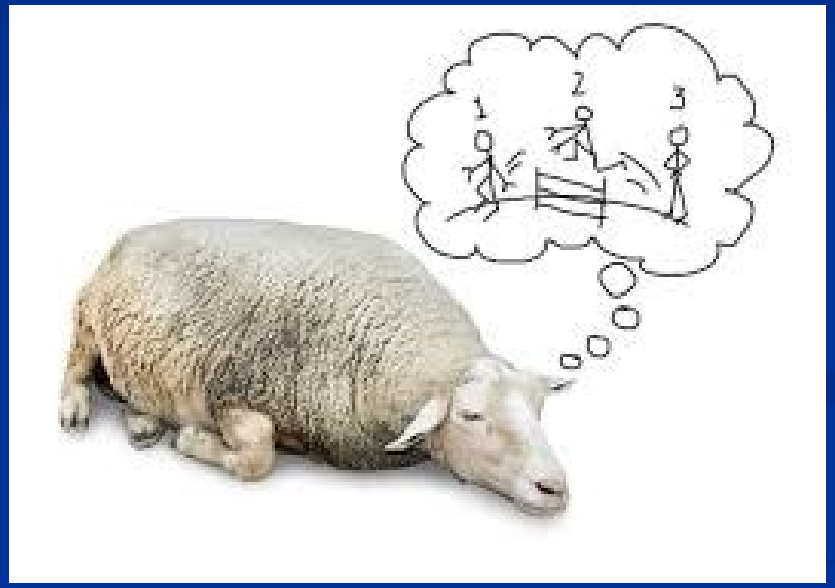
Lifestyle Physical Activity

Pacing for Energy Efficiency

Problem Solving / Goal Setting

ERASE

Sleep



Altering Pain via Sleep

Behavioral and Sleep Hygiene Skills

Timing
Regular bed time/wake time

Sleep Behavior
Get in bed only when sleepy
Use bed for sleep
Get up after 15' if no sleep

Thermal Tips
Decline in core temp signals sleep
Exercise, warm bath before bed

Environment
Steady room temperature
Keep room dark

Ingestion
Decrease nicotine
Decrease Caffeine
Alcohol interferes with sleep
Light snack is recommended

Mental Control
Effort will not produce sleep
Avoid mental stimulation
Seek mental quiescence

Edinger, JD et al. *Arch Intern Med.* 2005;161(21):2527-2535
Morin, CM et al. Am J Psychiatry. 1994;151:1172-1180.

ERASE

Environment

Using the Environment to alter pain perceptions and provide a foundation of wellness

Social Challenges

Dr. -Patient

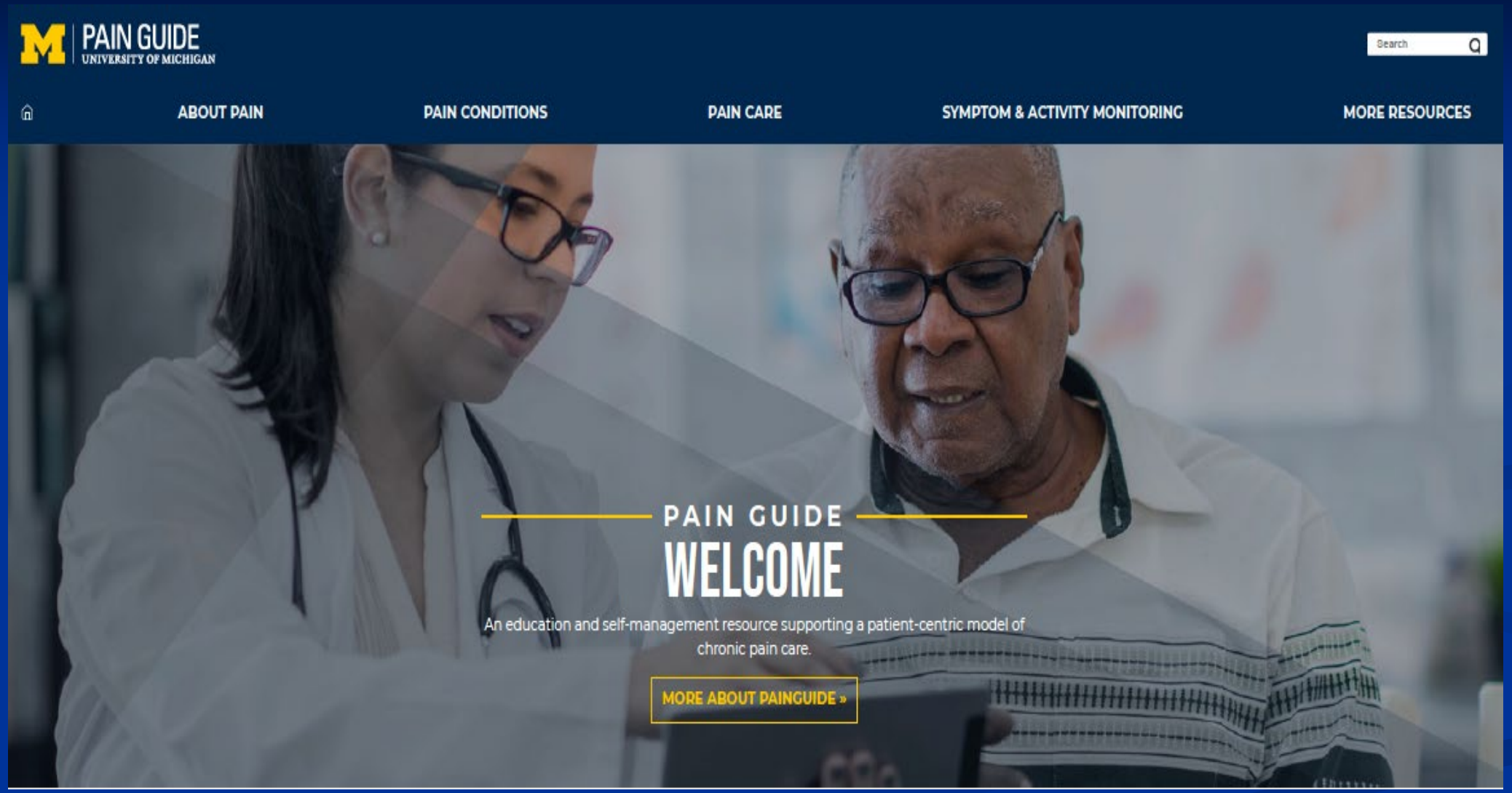
Friends

Family

Employer and co-workers

Physical Challenges

Web-based self-management



http://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

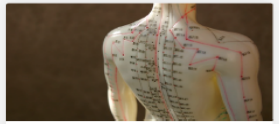
Conflictual social relationships with family, friends, doctors, and employers can make pain worse. Alternatively, these same relationships can be used constructively to make pain better. Communication skills can help make social relationship work in your favor.

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

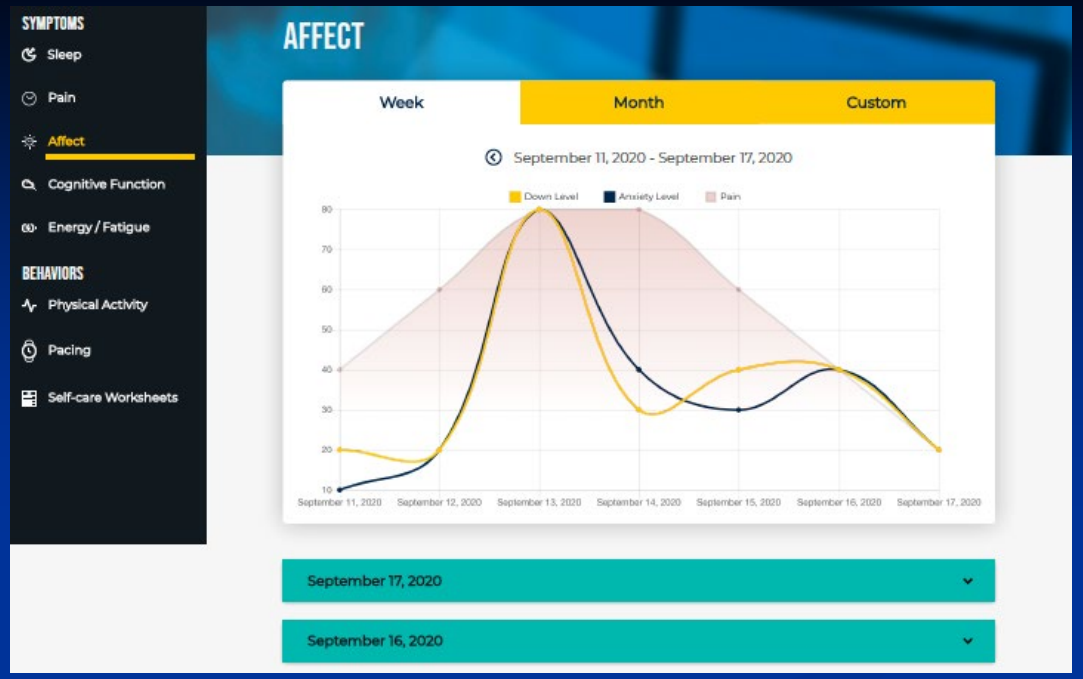
How you sit, stand, transition and lift can either make pain worse or allow you to function even with pain. This section offers help in optimizing how you interact with your environment in ways that don't exacerbate pain.

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.

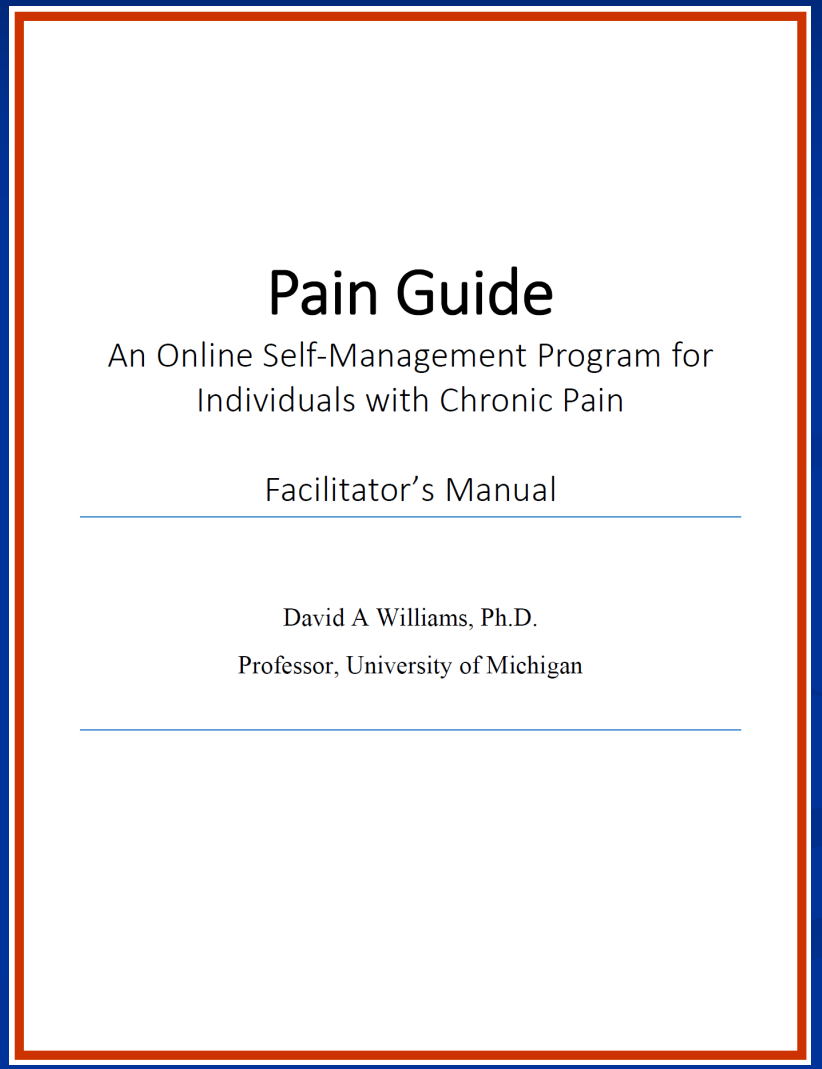
Learn more >



PAIN CARE

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

Pain Guide
can serve as the foundation for CBT



Pain Guide

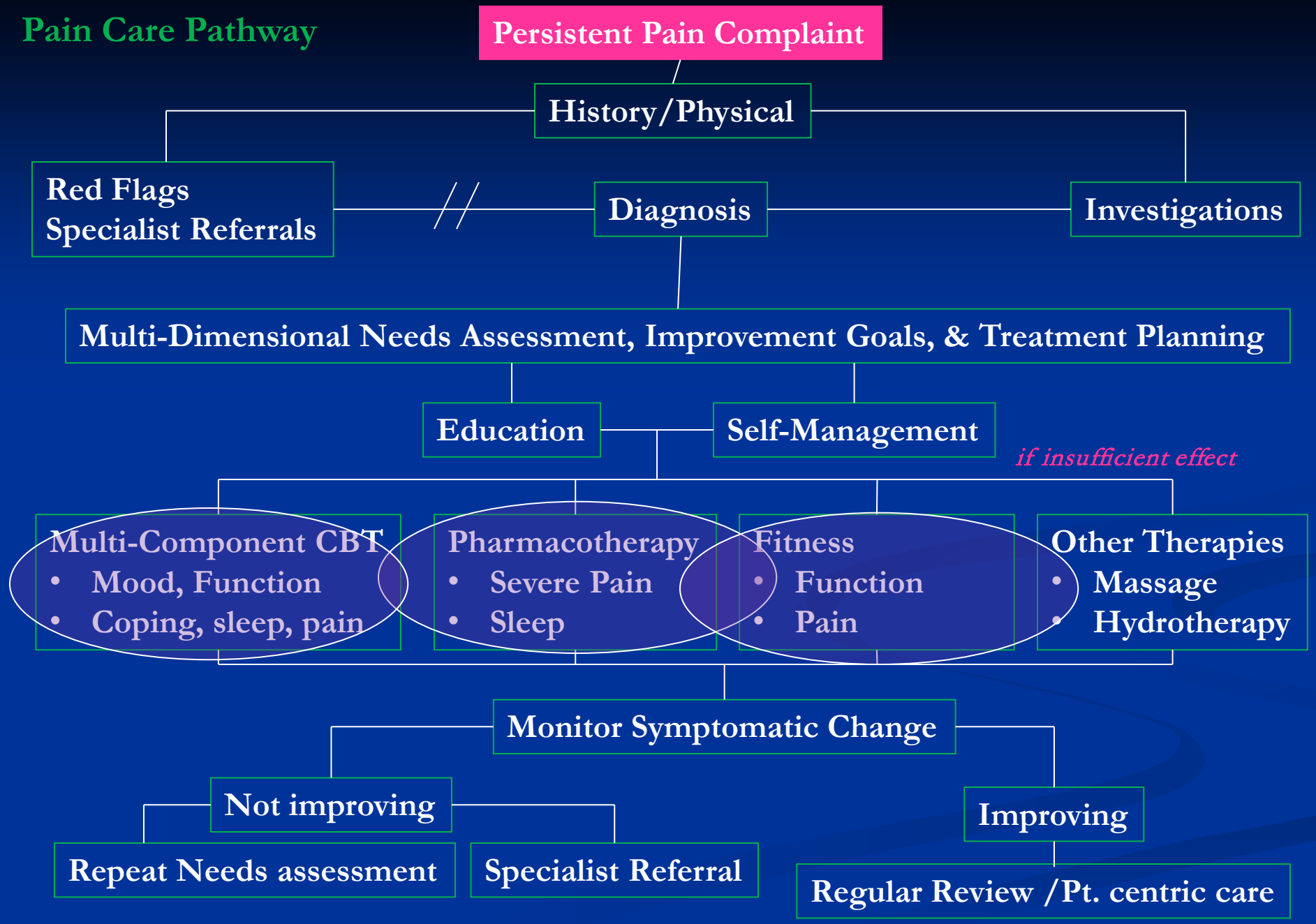
An Online Self-Management Program for Individuals with Chronic Pain

Facilitator's Manual

David A Williams, Ph.D.

Professor, University of Michigan

Pain Care Pathway



Adapted from Macfarlane et al. Ann Rheum Dis, 2017;76:318-328; Lee, et al., BJA 2014; 112:16-24; Peterson et al, VA ESP Project #09-199, 2017

Pharmacological Therapies for Central Pain States

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

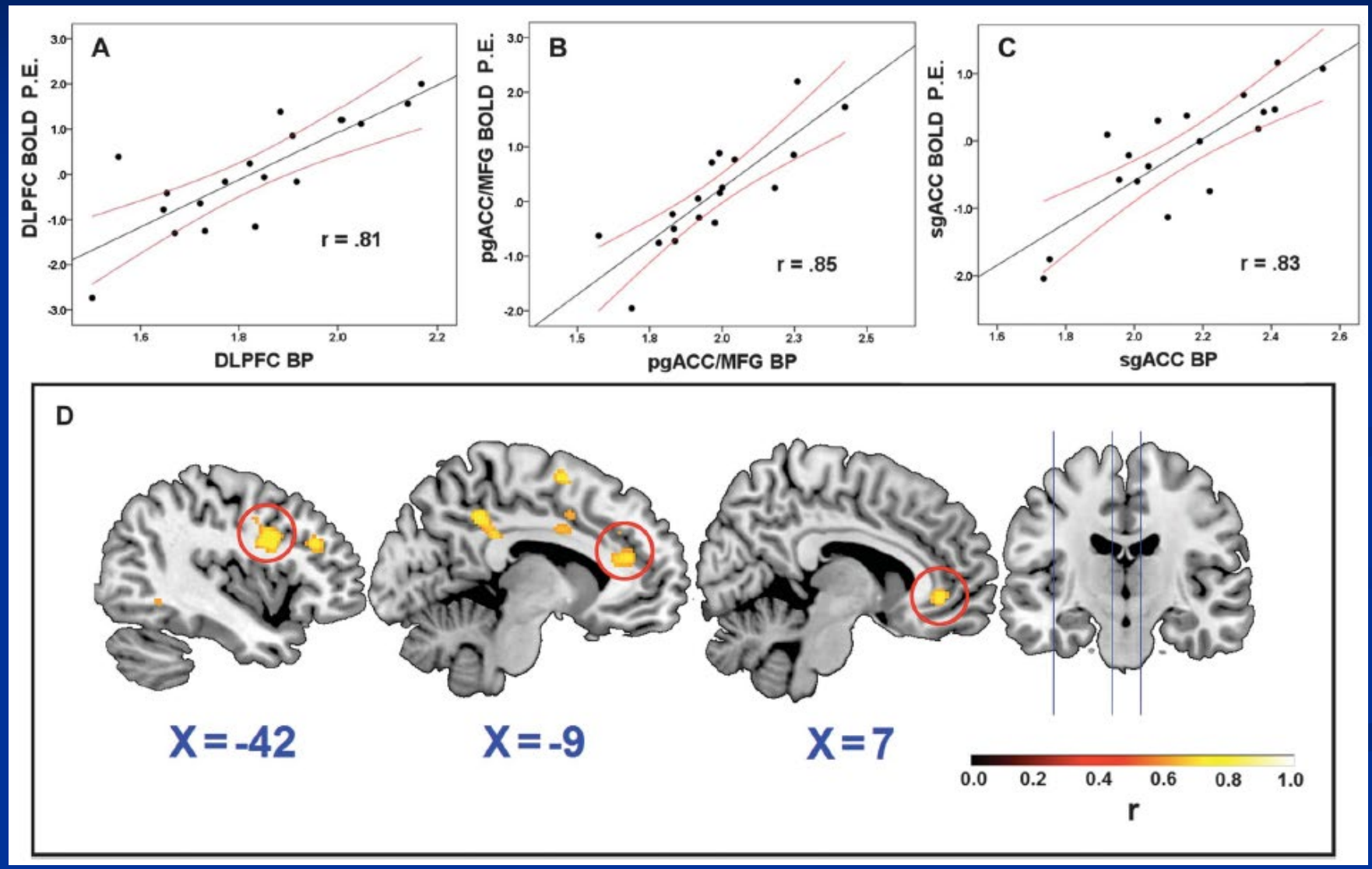
Modest Evidence	▪ Tramadol ▪ Older less selective SSRIs ▪ Gamma hydroxybutyrate ▪ Low dose naltrexone ▪ Cannabinoids
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine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

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

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]



Treating Based on Mechanisms

Any combination may be present

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

Nonpharmacological Therapies are similar to those for any Chronic Pain State - 2023

Strong Evidence	▪ Education ▪ Aerobic exercise ▪ Cognitive behavior therapy (ACT, CBT-i, empowered self-care
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

Can we use diet/nutrition to treat chronic pain?

Andrew Schrepf,* Steven E. Harte,* Nicole Miller,† Christine Fowler,† Catherine Nay,† David A. Williams,* Daniel J. Clauw,* and Amy Rothberg†,‡

*Chronic Pain and Fatigue Research Center, Department of Anesthesiology, †Department of Internal Medicine, ‡School of Public Health, University of Michigan, Ann Arbor, Michigan.

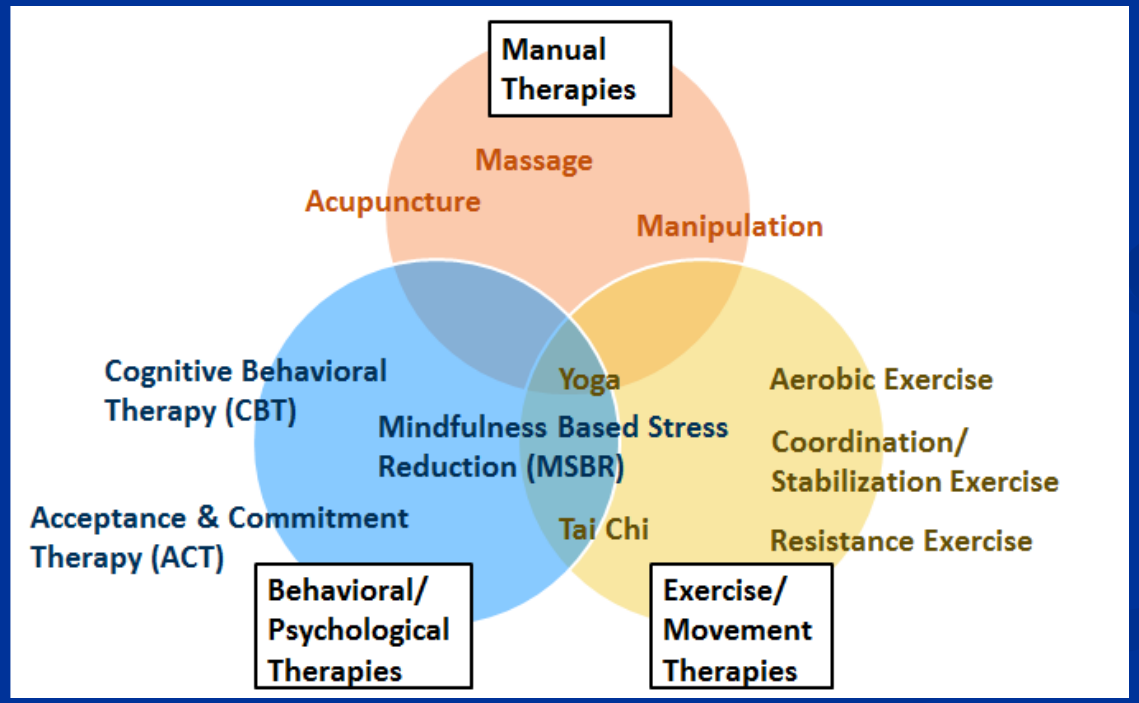
Abstract: **Weight loss is known to improve pain localized to weight-bearing joints but it is not known how weight loss affects the spatial distribution of pain and associated somatic symptoms like fatigue. We sought to determine if weight loss using a low-calorie diet improves pain, affect, and somatic 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.

Bottom Line

- 1. Pain is not located in a body part. It is a perception and needs to be treated as a perception.
- 2. Taking time to just listen to the patient's story is a necessary part of pain treatment. You will be establishing rapport and identifying pain and non-pain treatment targets.
- 3. If you recommend self-management (exercise, relaxation, sleep hygiene etc.), ask about it with the same enthusiasm and regularity that you ask about drugs. Patients learn what you think is <u>really</u> important by what you ask about.