



HARVARD MEDICAL SCHOOL
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Neuropsychiatry of Pain

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Disclosures

I have no relevant disclosures to report.





Outline

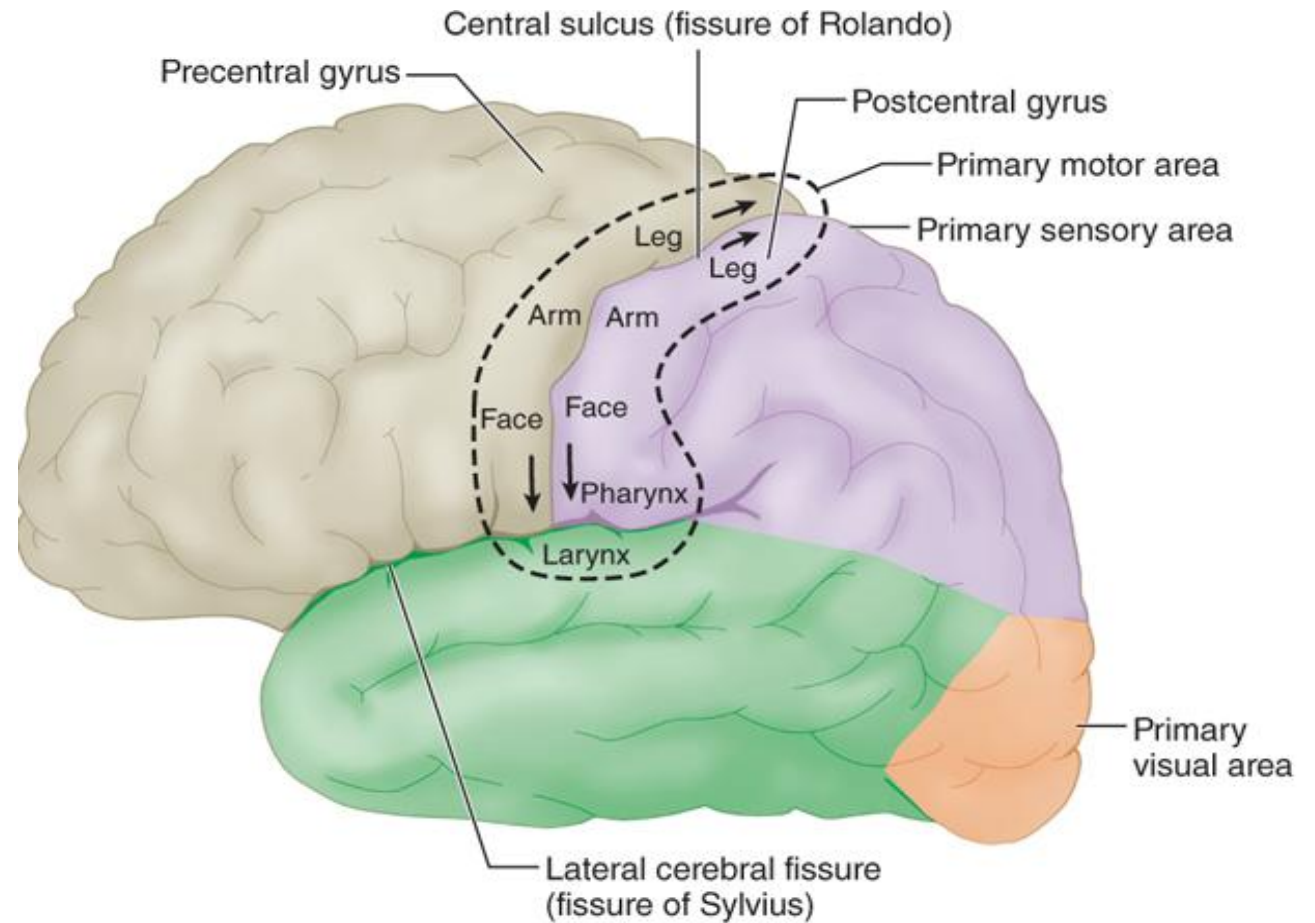
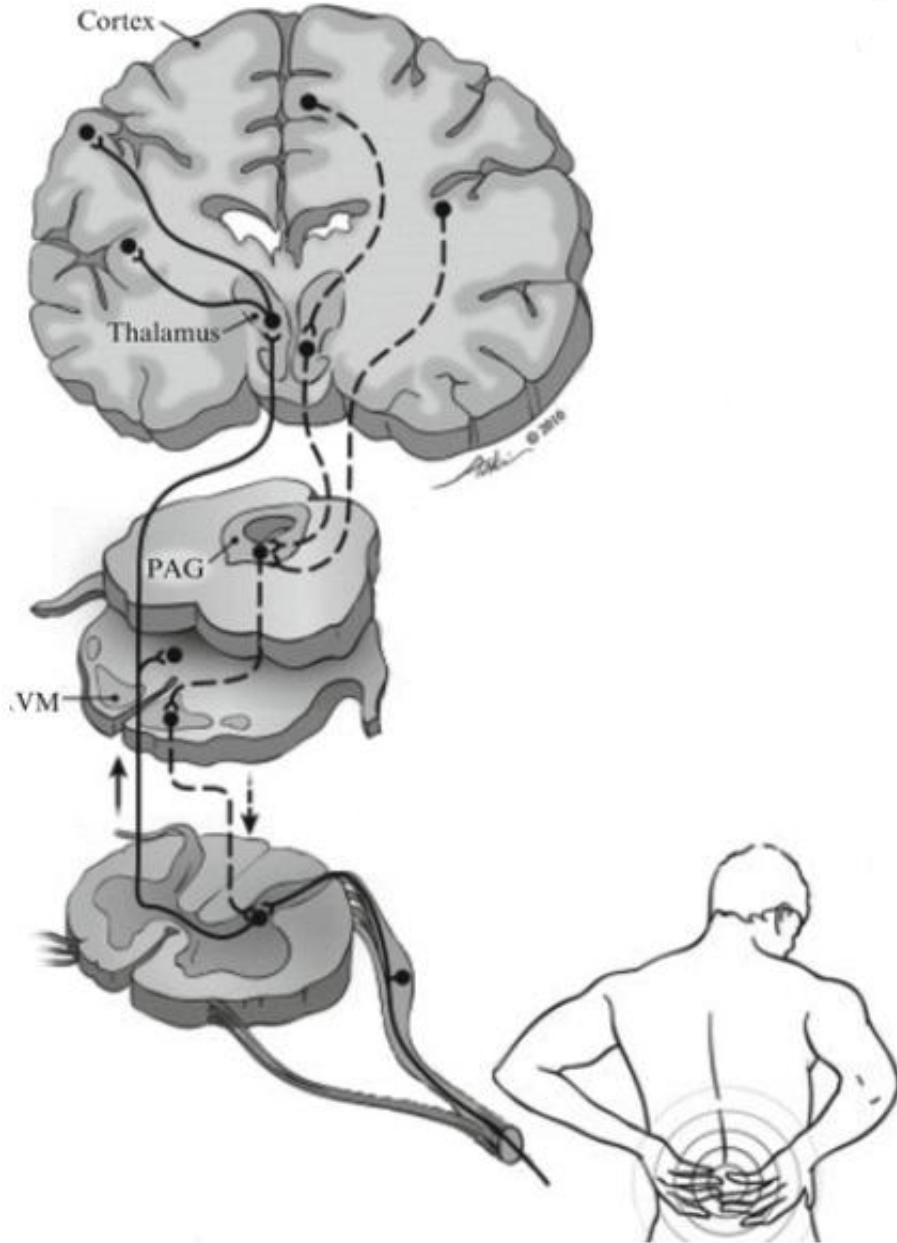
- Pain neurobiology
- Centralization of pain
- Treatment models

Utility of acute pain

- Nociception and pain provide an evolutionary advantage.
- An alarm system to alert the organism of potential tissue damage.
- Afferent signals → efferent signals:
 - Avoid or limit activity in the present



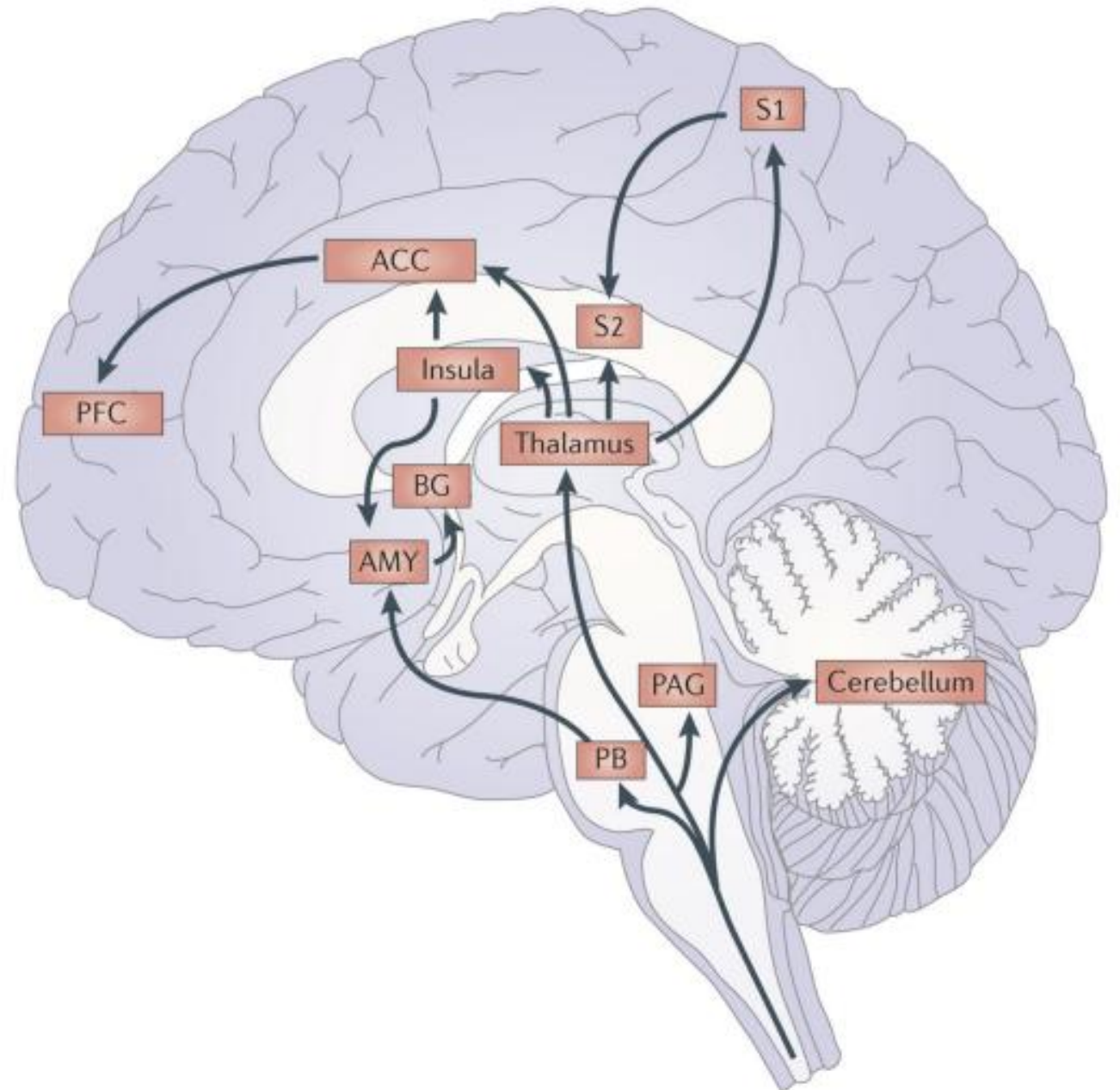
Pathophysiology of Pain



Pathophysiology of Pain

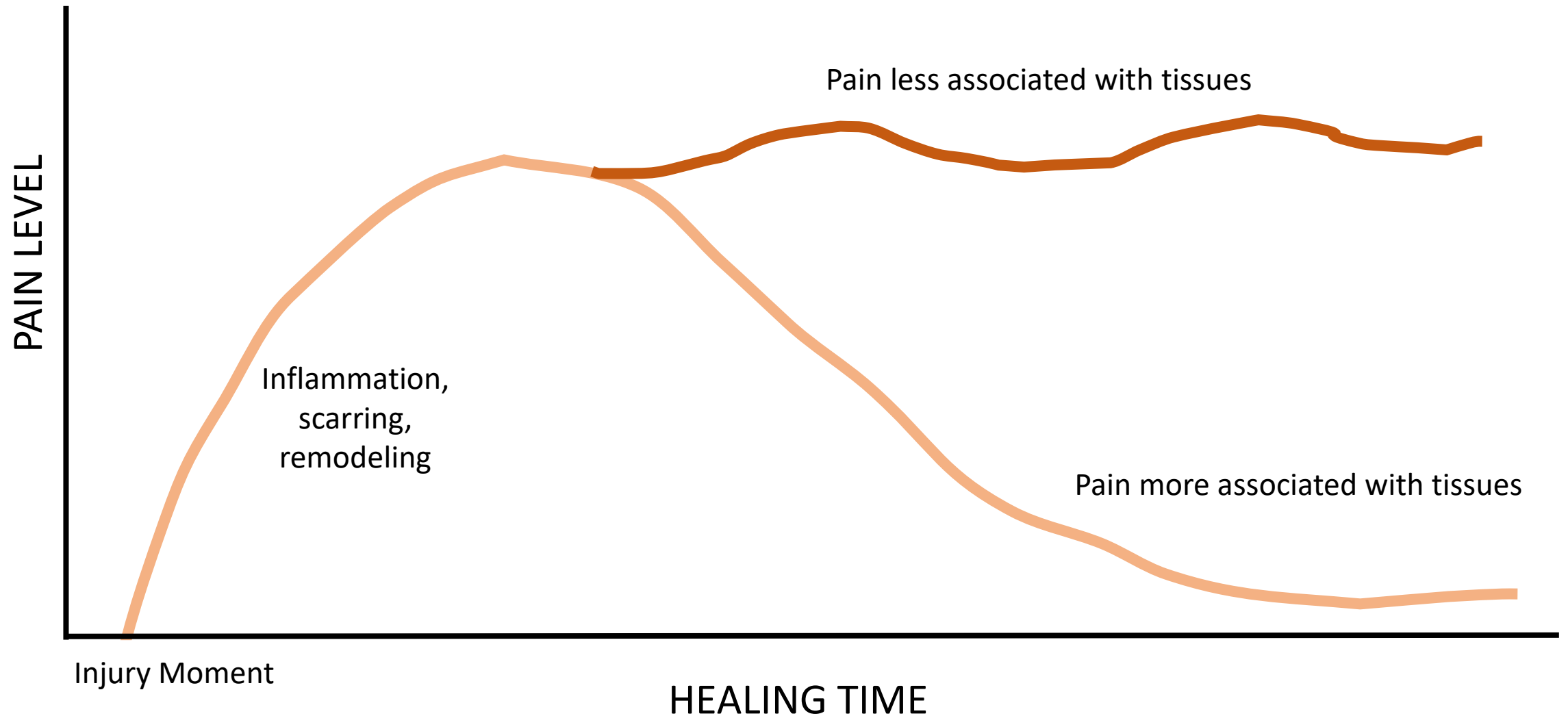


- Sensory signals
- Cognitive-evaluative
- Affective-emotional
- Motivational-motor



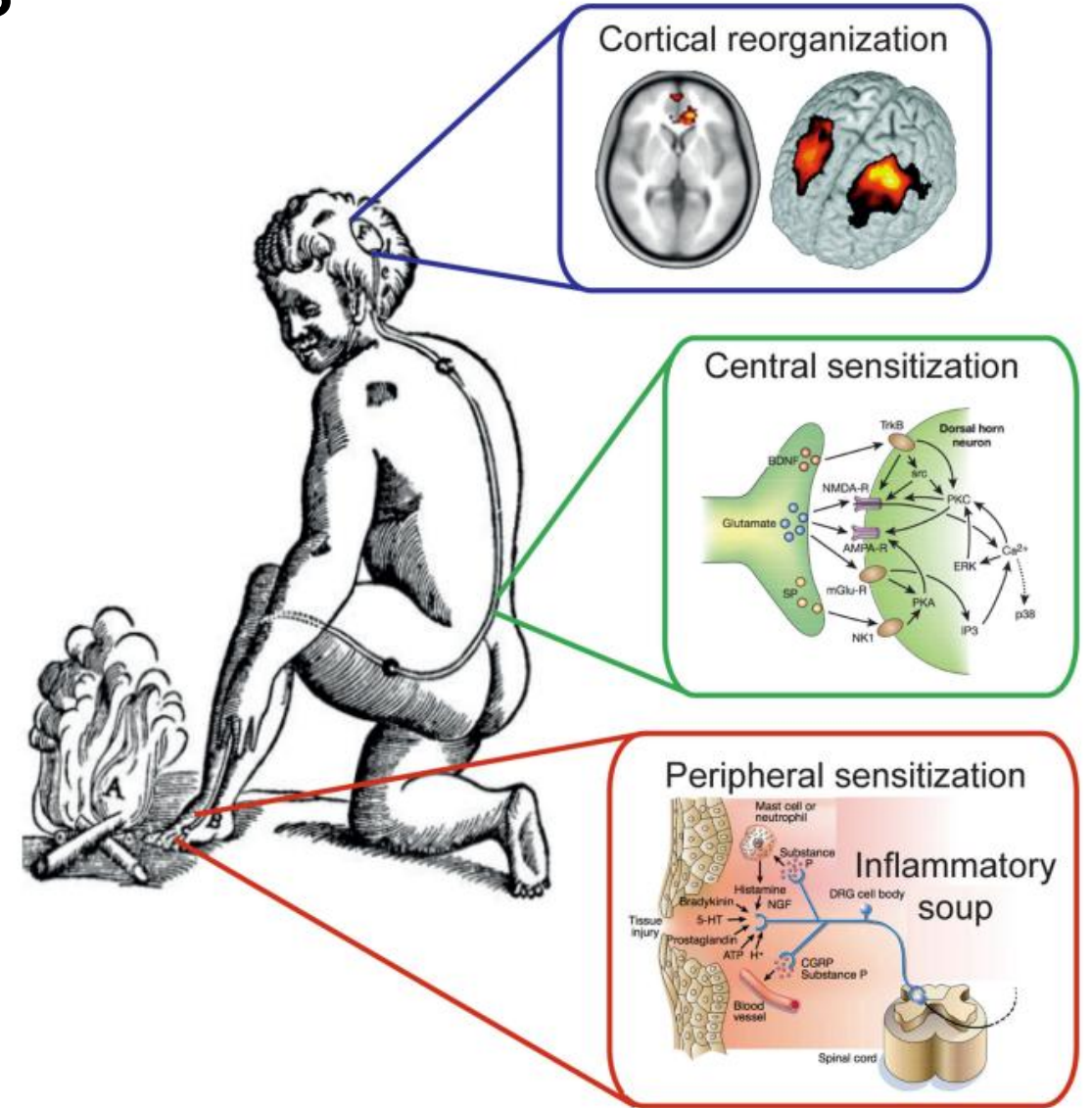
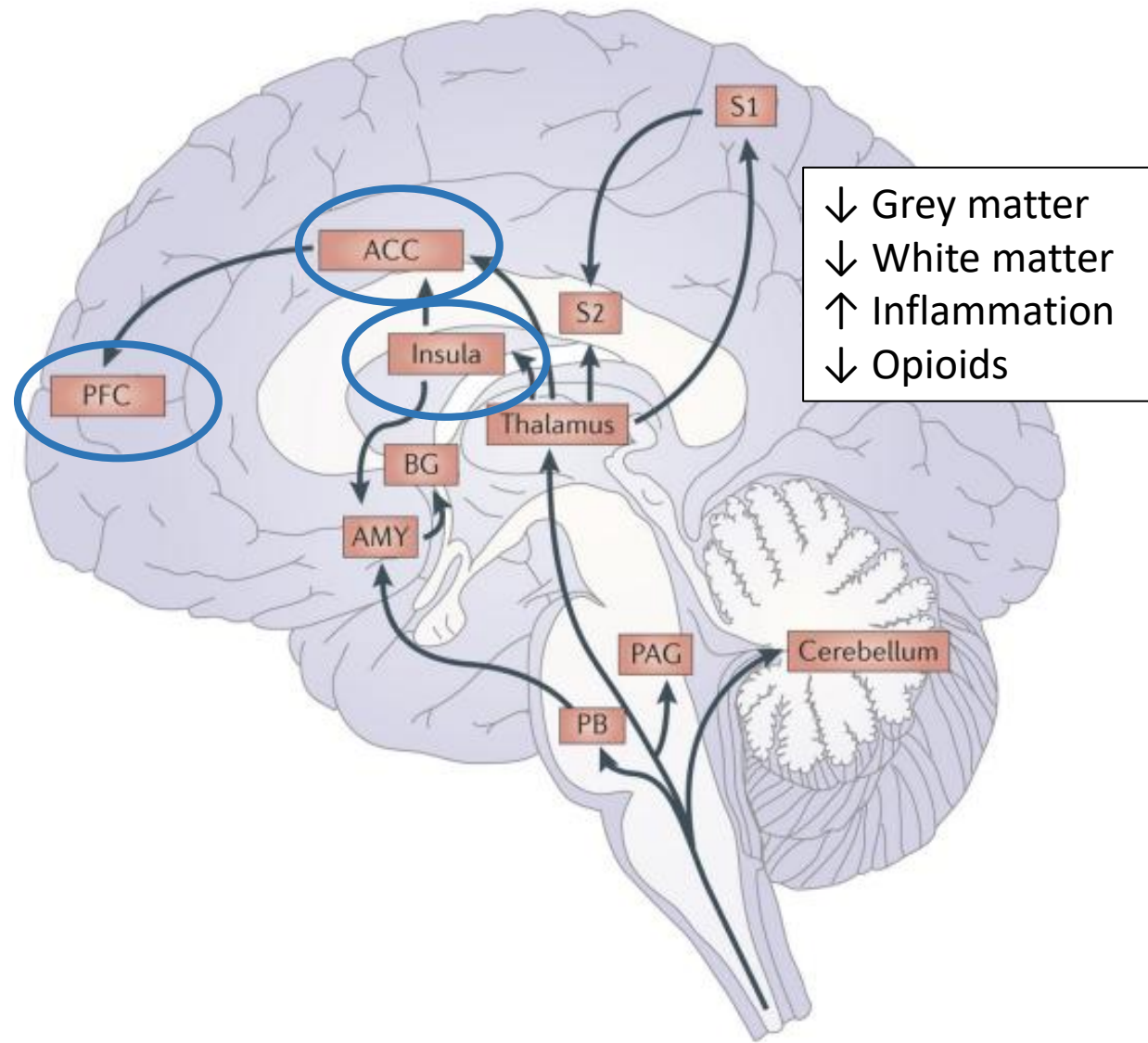
(Bushnell 2013)

Chronic pain is maladaptive



(Adapted from Butler 2013)

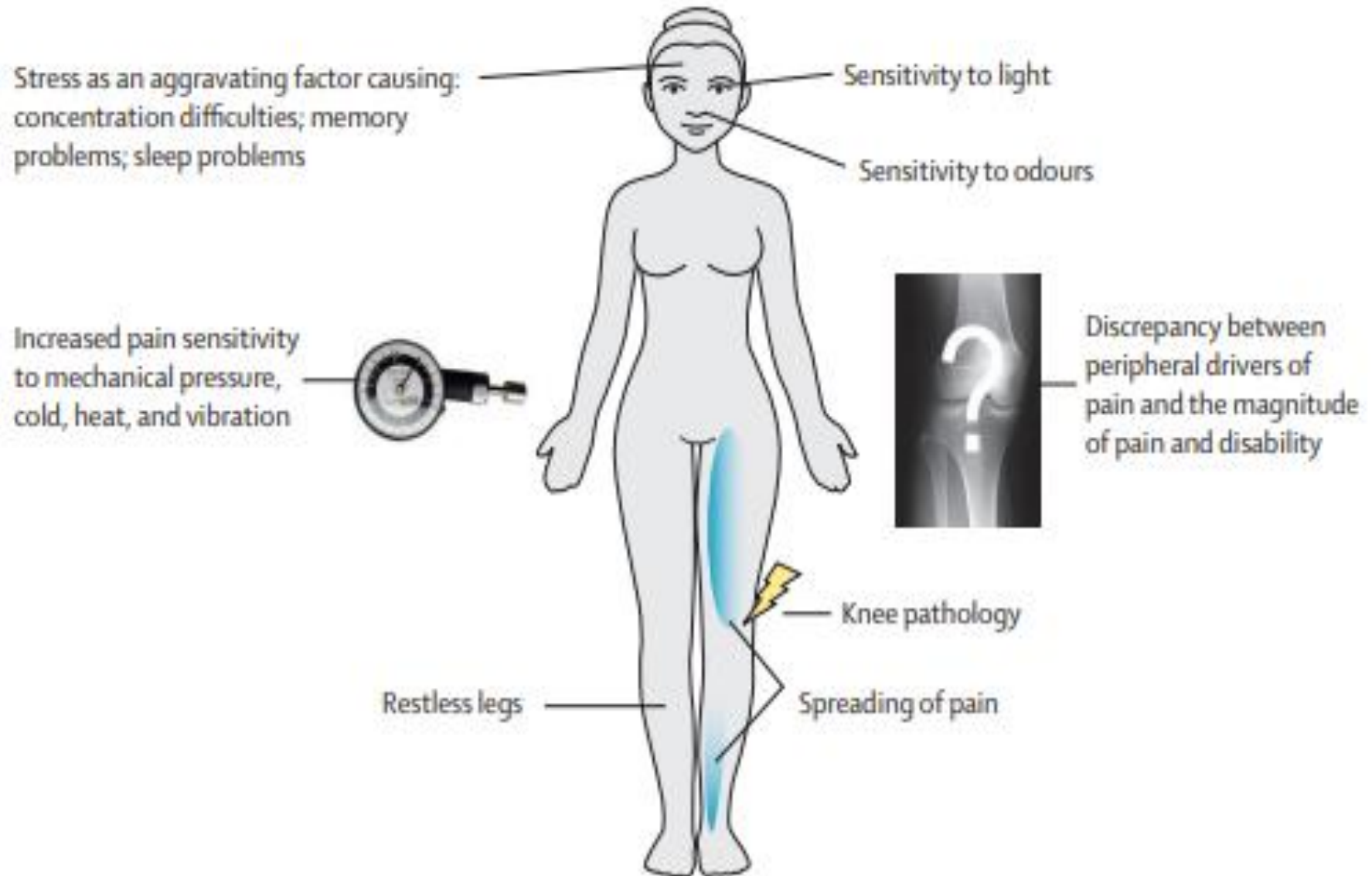
Nervous system remodeling



Types of pain

	Nociceptive	Neuropathic	Centralized/chronic
Cause	Inflammation/damage	Nerve injury	CNS/systemic
Examples	Musculoskeletal injury, OA, cancer	Diabetic neuropathy, sciatica	Muscle pain disorders, fibromyalgia
Clinical features	Localized, activity-dependent	Dermatomal, sharp, numb, tingling	Widespread, accompanying fatigue, mood, sleep, cog
Treatment	NSAIDs, injections, surgery	Surgery, injections, topical, CNS-acting	CNS-acting, non-pharmacologic

Centralization



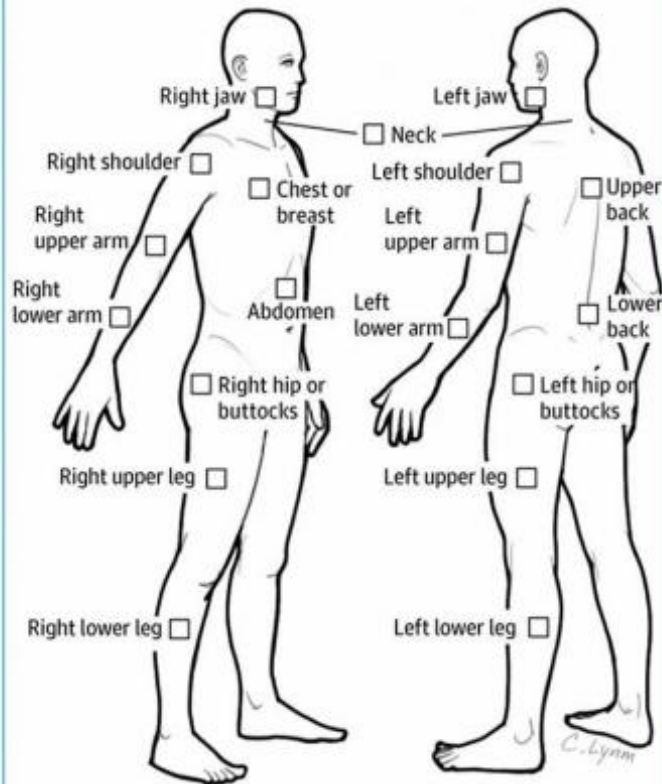
2011 Survey Criteria for Fibromyalgia

Clinically phenotyping centralization

Widespread Pain Index

(1 point per check box; score range: 0-19 points)

- ① Please indicate if you have had pain or tenderness during the past 7 days in the areas shown below. Check the boxes in the diagram for each area in which you have had pain or tenderness.



Symptom Severity

(score range: 0-12 points)

- ② For each symptom listed below, use the following scale to indicate the severity of the symptom during the past 7 days.
- No problem
 - Slight or mild problem: generally mild or intermittent
 - Moderate problem: considerable problems; often present and/or at a moderate level
 - Severe problem: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
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?

Points	0	1
A. Pain or cramps in lower abdomen	☐ No	☐ Yes
B. Depression	☐ No	☐ Yes
C. Headache	☐ No	☐ Yes

Additional criteria (no score)

- ④ Have the symptoms in questions 2 and 3 and widespread 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

The *Widespread Pain Index* and *Symptom Severity Index* are combined for a total FM score of 0–31.

(Wolfe 2011; Brummett 2016)

Centralization impacts peripheral treatment outcomes

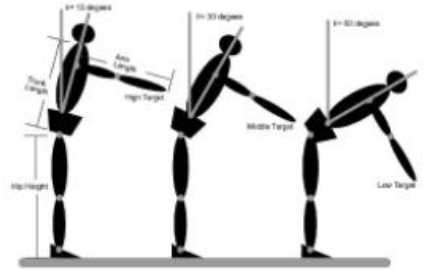
Hysterectomy for chronic pelvic pain and higher centralized pain scores:

- More likely to have persistent pelvic pain 6-months post-surgery.
- Every 1-point of FM was associated with a 27% increase of persistent pelvic pain (As-Sanie 2021).

Knee or hip arthroplasty for chronic pain with variable “FM-ness:”

- Independently associated with higher opioid consumption
- Greater likelihood of poor response to surgery (Brummett 2013; 2015).

Chronic pain models



(Vlaeyen 2016)

Pain catastrophizing

Pain Catastrophizing Scale

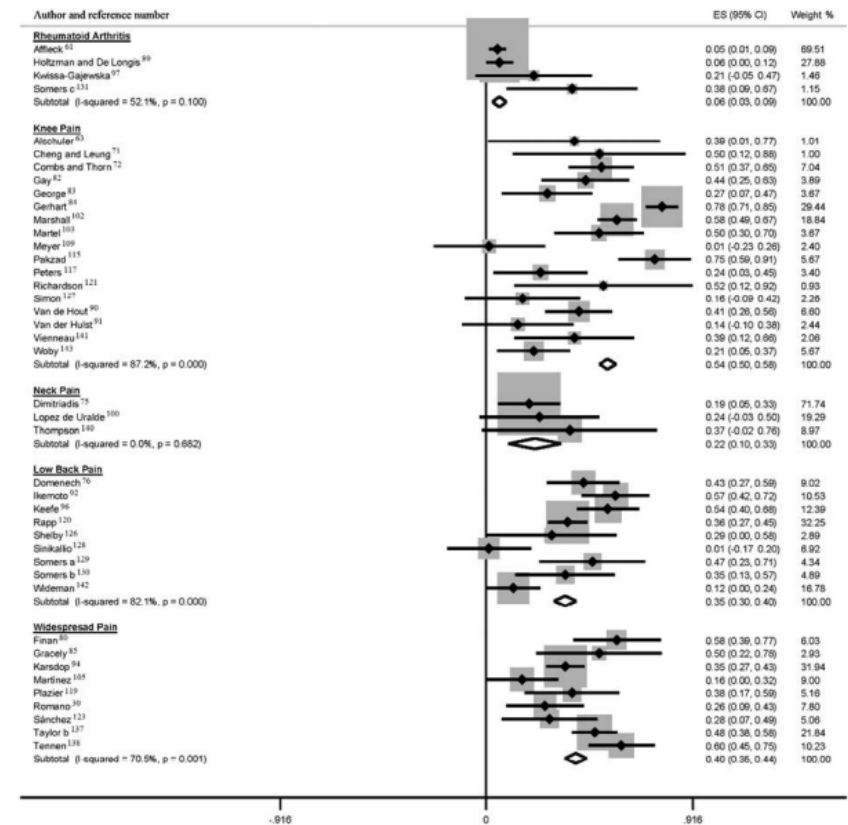
Directions: Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint, or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures, or surgery. We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are 13 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 - not at all 1 - to a slight 2 - to a moderate 3 - to a great 4 - all the time
degree degree degree

1. _____ I worry all the time about whether it will end.
2. _____ I feel I can't go on.
3. _____ It's terrible and I think it's never going to get any better.
4. _____ It's awful and I feel that it overwhelms me.
5. _____ I feel I can't stand it anymore.
6. _____ I become afraid that the pain will get worse.
7. _____ I keep thinking of other painful events.
8. _____ I anxiously want the pain to go away.
9. _____ I can't seem to get it out of my mind.
10. _____ I keep thinking about how much it hurts.
11. _____ I keep thinking about how badly I want the pain to stop.
12. _____ There's nothing I can do to reduce the intensity of the pain.
13. _____ I wonder whether something serious may happen.

Exaggerated negative affect when experiencing/anticipating pain

Meta-analysis of the association between pain catastrophizing and pain intensity by diagnosis/pain site.



(Martinez-Calderon 2019; Marshall 2017; Sullivan 1995)

Kinesiophobia

Tampa Scale for Kinesiophobia

1. I'm afraid that I might injury myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

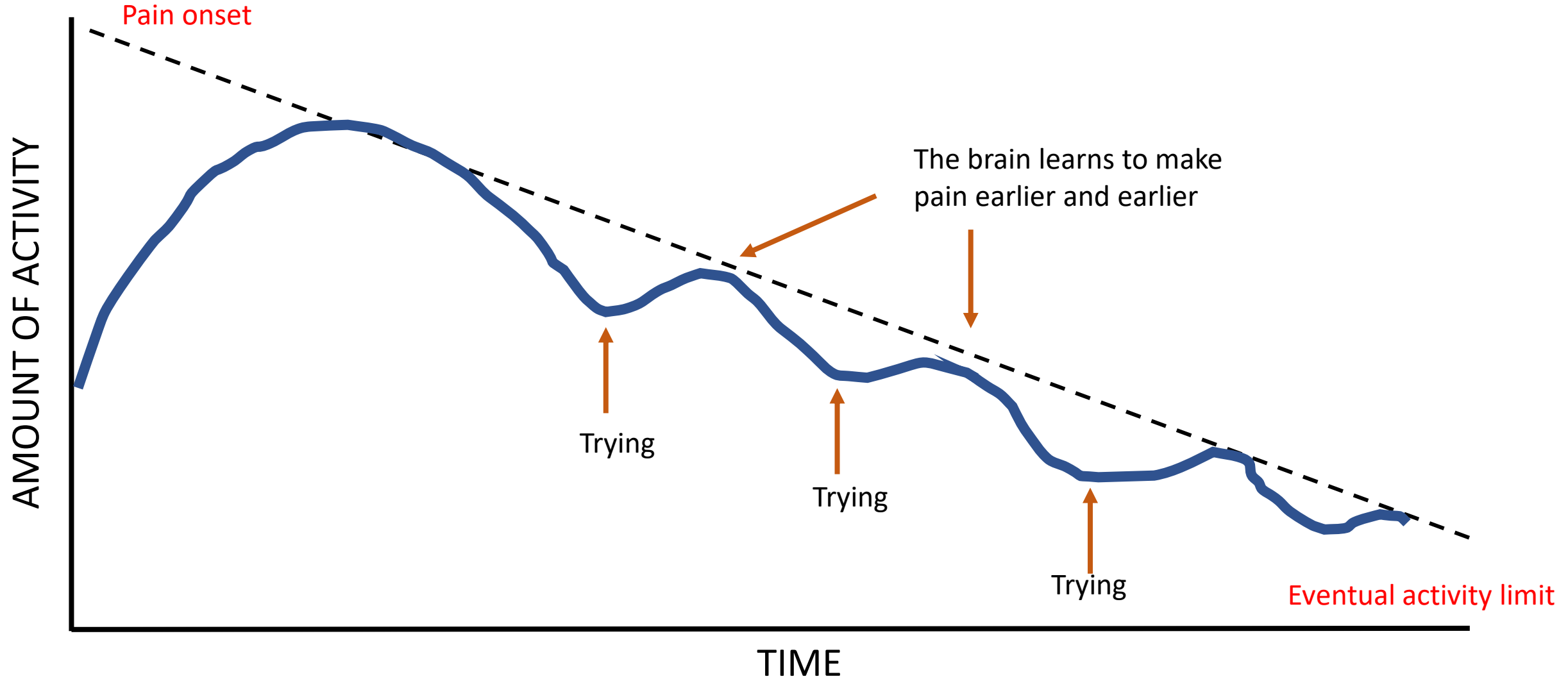
Excessive fear of physical movement or activity, a sense of vulnerability due to injury

Table 1 Modified Cochrane Back and Neck Pain Group criteria for overall level of evidence based on cross-sectional studies

Outcome	No. of studies	No. of participants	Level of evidence
Kinesiophobia (association with)			
Quality of life	8	1426	Moderate (negative association)
Disability	46	9351	Strong (positive association)
Pain intensity	38	6806	Strong (positive association)
Pain severity	4	767	Moderate (positive association)

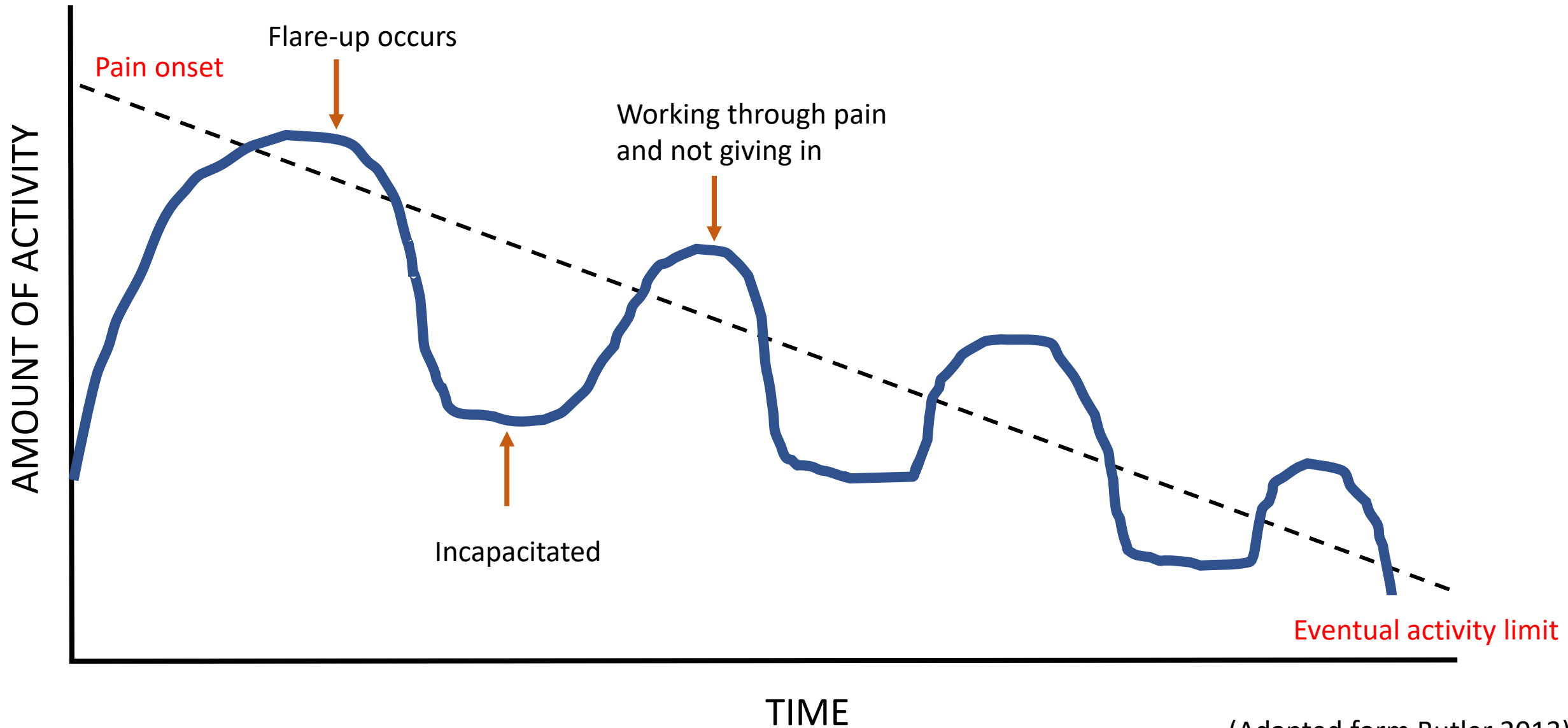
(Kori 1990; Luque-Suarez 1990; Miller 1991; Martinez-Calderon 2019)

Avoiding pain



(Adapted from Butler 2013)

Trying to beat pain



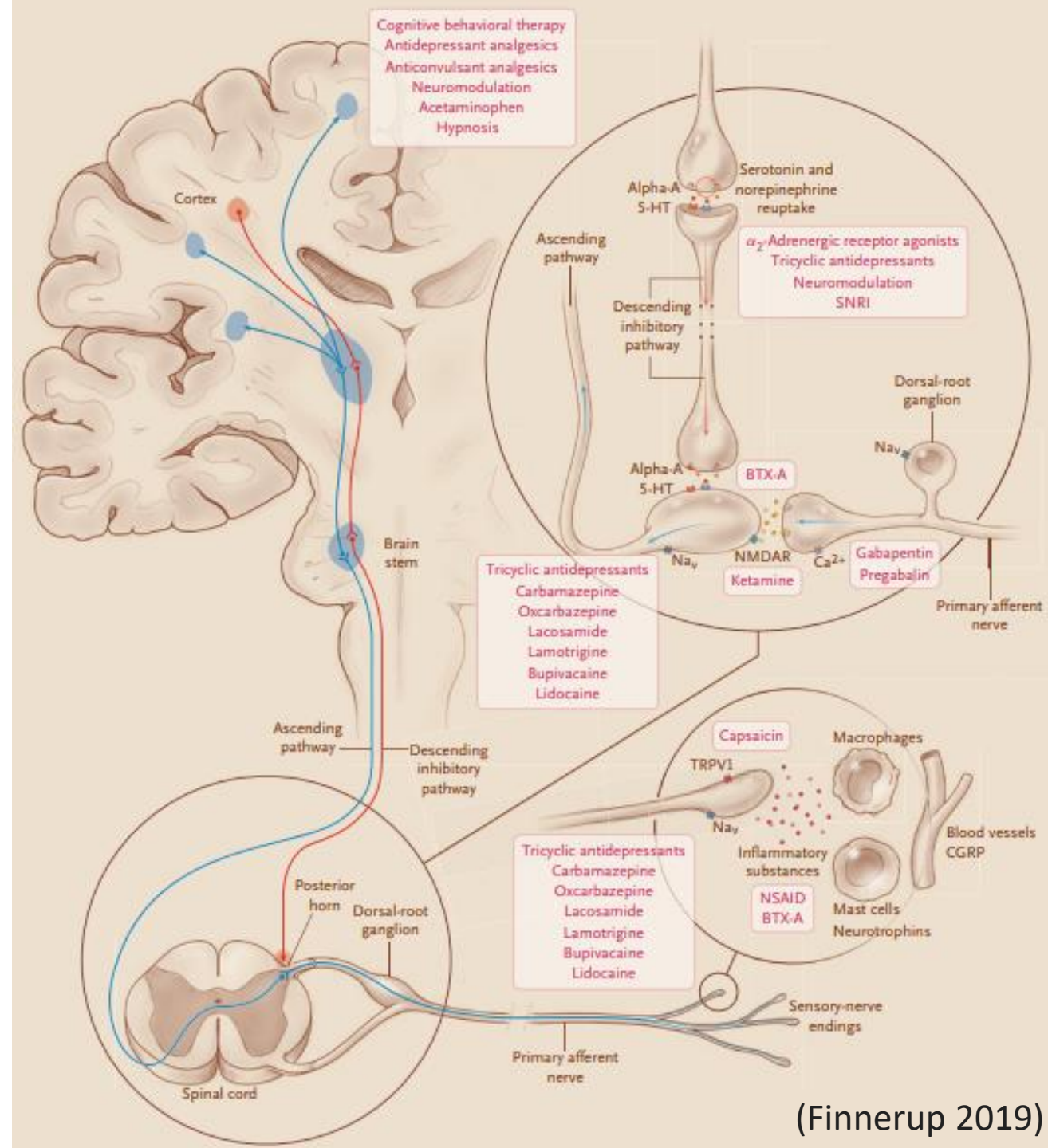
(Adapted form Butler 2013)

Chronic pain therapies

- Pharmacology
- Education
- Exercise
- Psychological Therapies
- Integrative therapies (acupuncture, chiropractic, massage, yoga, tai chi, biofeedback)

Pharmacotherapy for centralized pain

- Tricyclics
- SNRIs
- Gabapentinoids



Accounting for centralized pain in treatment-planning

Duloxetine improved pain levels amongst individuals with FM with or without MDD (Arnold 2009).

Responsive to duloxetine versus placebo in LBP increased with a greater number of body sites of pain on the Michigan Body Map (Alev 2017).

Patients receiving TKA with higher pain catastrophizing scores, received escitalopram versus placebo 1d prior to surgery to POD#6. No difference in ambulation 24h after surgery (Lunn 2015).

Education for chronic LBP

SYSTEMATIC REVIEW

The Effect of Neuroscience Education on Pain, Disability, Anxiety, and Stress in Chronic Musculoskeletal Pain

Adriaan Louw, PT, MAppSc, Ina Diener, PT, PhD, David S. Butler, PT, EdD, Emilio J. Puentedura, PT, DPT

ABSTRACT. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil* 2011;92:2041-56.

Objective: To evaluate the evidence for the effectiveness of neuroscience education (NE) for pain, disability, anxiety, and stress in chronic musculoskeletal (MSK) pain.

Data Sources: Systematic searches were conducted on Biomed Central, BMJ.com, CINAHL, the Cochrane Library, NLM Central Gateway, OVID, ProQuest (Digital Dissertations), PsycInfo, PubMed/Medline, ScienceDirect, and Web of Science. Secondary searching (PEARLing) was undertaken, whereby reference lists of the selected articles were reviewed for additional references not identified in the primary search.

Study Selection: All experimental studies including randomized controlled trials (RCTs), nonrandomized clinical trials, and case series evaluating the effect of NE on pain, disability, anxiety, and stress for chronic MSK pain were considered for inclusion. Additional limitations: studies published in English, published within the last 10 years, and patients older than 18 years. No limitations were set on specific outcome measures of pain, disability, anxiety, and stress.

Data Extraction: Data were extracted using the participants, interventions, comparison, and outcomes (PICO) approach.

Data Synthesis: Methodological quality was assessed by 2 reviewers using the Critical Review Form—Quantitative Studies. This review includes 8 studies comprising 6 high-quality RCTs, 1 pseudo-RCT, and 1 comparative study involving 401 subjects. Most articles were of good quality, with no studies rated as poor or fair. Heterogeneity across the studies with respect to participants, interventions evaluated, and outcome measures used prevented meta-analyses. Narrative synthesis of results, based on effect size, established compelling evidence that NE may be effective in reducing pain ratings, increasing function, addressing catastrophization, and improving movement in chronic MSK pain.

Conclusions: For chronic MSK pain disorders, there is compelling evidence that an educational strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain, disability, catastrophization, and physical performance.

Key Words: Education; Musculoskeletal System; Neurophysiology; Neurosciences; Pain; Rehabilitation.

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PAIN IS A POWERFUL motivating force that guides treatment-seeking behaviors in patients.¹⁻³ Patient education has long been explored in the management of pain, anxiety, and stress associated with low back pain (LBP).⁴⁻⁷ In the orthopedic domain, there are a number of studies on the effect of patient education on pain, with outcomes ranging from “excellent”⁸ to “poor.”^{9,10} The study by Udermann et al⁸ demonstrated that introduction of an individualized educational booklet on back biomechanics can result in decreased pain and frequency of LBP episodes in patients with chronic LBP (CLBP). In contrast to those findings, 2 systematic reviews^{9,10} on the effect of individualized and/or group education for LBP and mechanical neck pain showed little efficacy for such education.

Most education programs for orthopedic patient populations have used anatomic and biomechanical models for addressing pain,^{4,11-14} which not only have shown limited efficacy,^{4,11,12,15,16} but may even have increased patient fears, anxiety, and stress, thus negatively impacting their outcomes.^{11,17-19} Several educational strategies are advocated for patients with LBP, including biomechanical/back school type of education, evidence-based guideline education (ie, *The Back Book*²⁰), cognitive behavioral therapy, and recently, neuroscience education (NE).

NE can be best described as an educational session or sessions describing the neurobiology and neurophysiology of pain, and pain processing by the nervous system. Instead of a

Conclusions: For chronic MSK pain disorders, there is compelling evidence that an educational strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain, disability, catastrophization, and physical performance.

List of Abbreviations

BPPT	brachial plexus provocation test
CFS	chronic fatigue syndrome
CLBP	chronic low back pain
CONSORT	Consolidated Standards of Reporting Trials
LBP	low back pain
MSK	musculoskeletal
NE	neuroscience education
NPRS	numeric pain rating scale
PCI	Pain Coping Inventory
PCS	Pain Catastrophization Scale
PICO	participants, interventions, comparison, outcomes
PPT	pressure pain threshold
PSEQ	Pain Self-Efficacy Questionnaire
RCT	randomized controlled trial
RMDQ	Roland Morris Disability Questionnaire
SLR	straight leg raise
SOPA(R)	Survey of Pain Attitudes (Revised)
TSK	Tampa Scale of Kinesiophobia
VAS	visual analog scale
WAD	whiplash-associated disorders

From the International Spine Pain Institute and Neuro Orthopaedic Institute, Story City, IA (Louw, Puentedura); Department of Physiotherapy, Stellenbosch University, Stellenbosch, South Africa (Diener); Neuro Orthopaedic Institute and University of South Australia, Adelaide, South Australia (Butler); and Department of Physical Therapy, University of Nevada Las Vegas, Las Vegas, NV (Puentedura).

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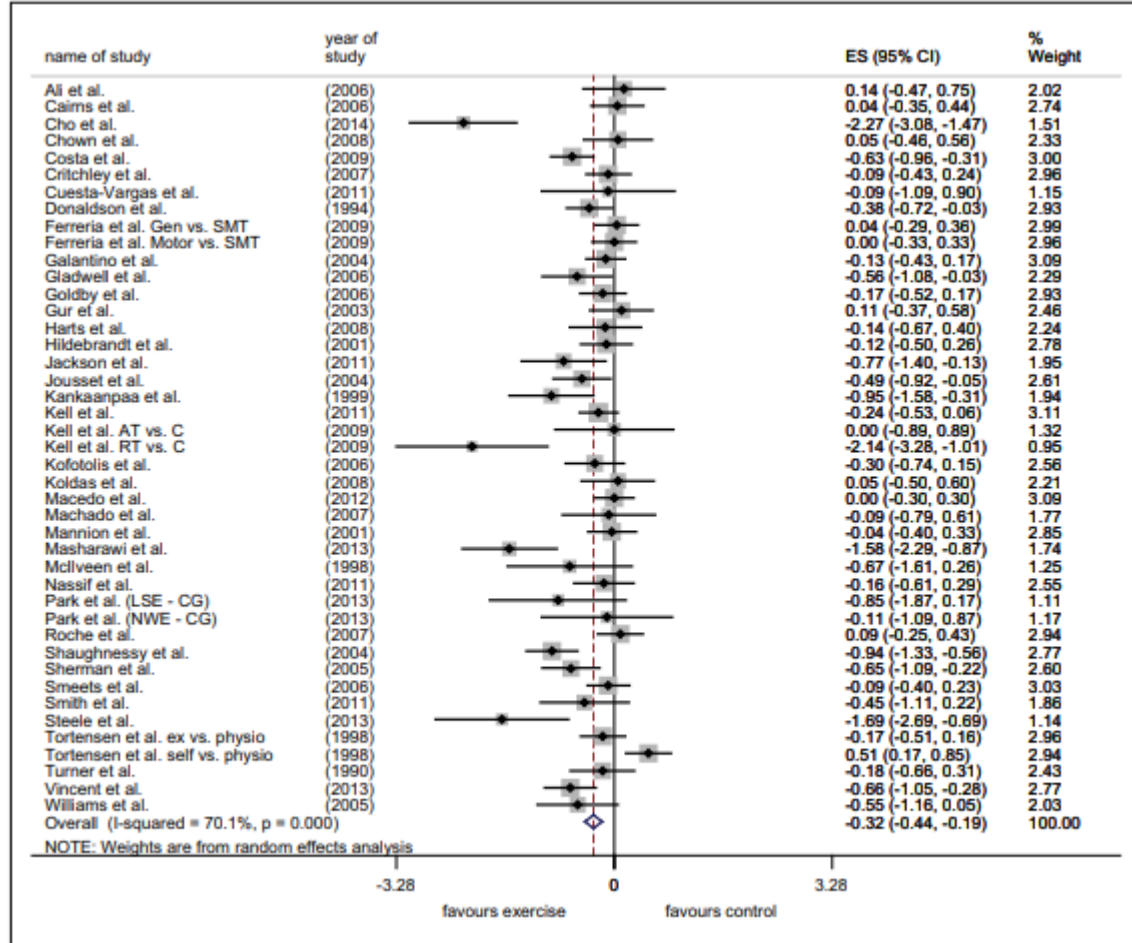
Reprint requests to Emilio J. Puentedura, PT, DPT, Assistant Professor, University of Nevada Las Vegas, School of Allied Health Sciences, Dept of Physical Therapy, 4505 Maryland Pkwy, Box 453029, Las Vegas, NV 89154-3029, e-mail: emilio.puentedura@unlv.edu.

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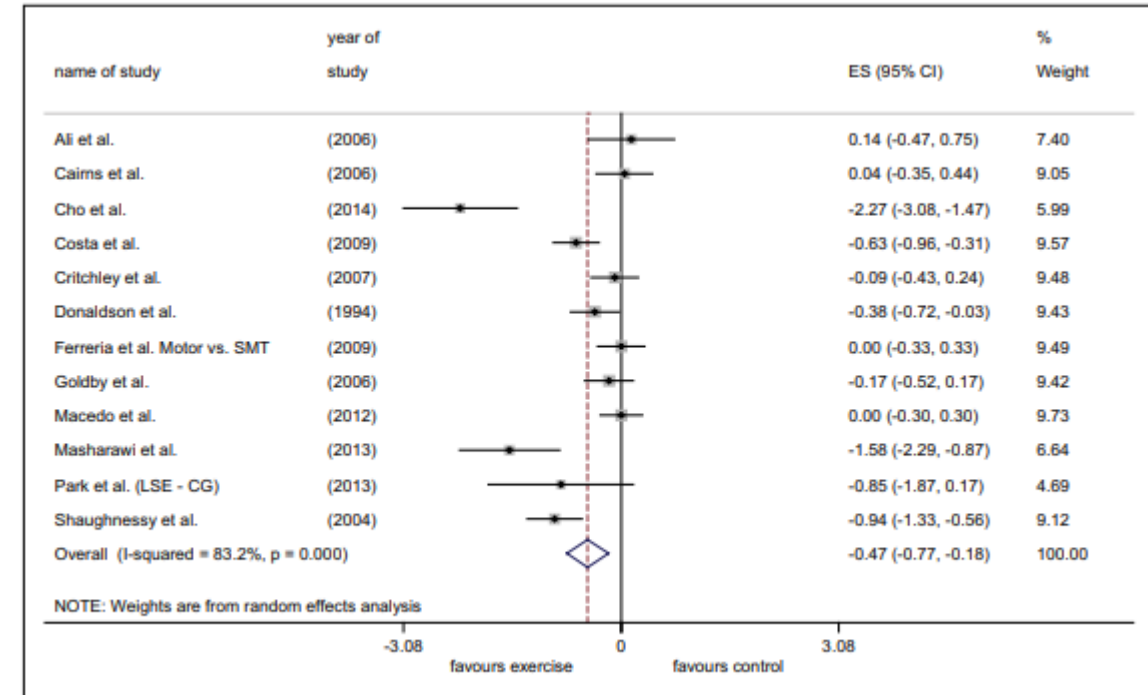
(Louw 2015)

Exercise for chronic LBP

Exercise for LBP versus other intervention



Coordination/stabilization exercise for LBP

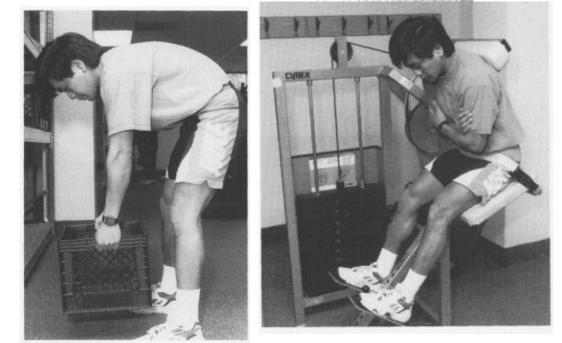


Psychological Therapies

	Reference	Treatment definitions	Study selection	Control treatment	Patients and conditions	Results	Comments or limitations
Psychological treatment							
CBT: a psychosocial intervention focused on challenging and changing maladaptive cognitive distortions and behaviours, improving emotional regulation, and the development of personal coping strategies	Williams et al (2020) ⁶¹	CBT: Methods of cognitive appraisal which assess, test, and revise maladaptive beliefs; involvement of strategies of emotional regulation and exposure; behavioral activation; and skills in problem-solving and motivation	59 RCTs	Active comparator; treatment as usual	5869; with non-malignant pain excluding headache	CBT had a very small benefit for pain, small benefit for disability, and no benefit for distress compared with the active comparator at end of treatment; no benefit for pain or disability at 6 months; compared with treatment as usual, CBT had a small benefit for pain, disability, and distress at end of treatment; at 6 months, a very small benefit for pain and a small benefit for disability and distress were maintained	Treatment results decrease over time after treatment; some evidence based on previous studies for a decrease in health-care use; predominantly moderate quality of evidence
Behavioural therapy: manipulation of external environment and physiological internal environment to effect behavioural change	Williams et al (2020) ⁶¹	Behavioural therapy: identification and reduction of disabling behaviors contingent on pain, or that are strengthened by the short-term benefits of avoidance	8 RCTs	Active comparator; treatment as usual	452; with non-malignant pain excluding headache	No evidence at any time point for benefit compared with active comparator or treatment as usual for any outcome measure	Evidence ranged from very low to moderate quality; results differed from some other reviews
ACT: contextually focused psychotherapy that aims to increase patients' ability to engage in values-based, positive behaviours	Hughes et al (2017) ⁶²	Explicit use of both an acceptance and commitment component	11 RCTs (10 valid for meta-analysis)	Active comparator; wait list or treatment as usual	836; with chronic pain	ACT did not reduce pain intensity compared with active treatment but had a small effect compared with no treatment	Small effects that decline with better study quality and over time; very low quality evidence; concerns with generalisation, treatment heterogeneity, and other sources of bias
Mindfulness therapy: a subtype of CBT defined as moment-to-moment awareness of one's experience without judgment	Hilton et al (2017) ⁶³	Mindfulness meditation either as adjuvant or monotherapy	38 RCTs (30 valid for meta-analysis)	Treatment as usual; passive control education and support groups	3536; with fibromyalgia, musculoskeletal pain, back pain, arthritis, migraine, headache, and irritable bowel syndrome	Mindfulness reduced pain compared with mixed control groups but the higher-quality studies had a smaller effect	Unclear effects on pain but possible short-term effects on anxiety and function; most reviews were of poor or fair quality; similar limitations to CBT

Behaviorally-informed LBP “bootcamp”

- 8-week program for chronic LBP
- Quota-based trunk flexibility, SLR, back extension, lifting, endurance



Approach

- (1) Clinical team holds belief that normal function can exist
- (2) ↓ Chronic pain behaviors: no excuses from exercise, do not redirect treatment toward symptom reduction
- (3) Meet exercise quota at physiologic level regardless of daily pain level
- (4) Encourage and praise exercise and wellness accomplishments

Completion of exercise → decreased fear of pain → greater self-efficacy

Increase wellness behaviors → lessen pain beliefs → reduce disability

Table 1.

Results from rehabilitation of 86 chronic low back pain subjects using aggressive physical therapy to correct impairments in back function, with behavioral support.

	Initial	3 Month Follow-up	12 Month Follow-up
Pain Intensity (0-10)			
Back	5.9	4.2**	4.3**
Leg	4.2	3.2*	3.0*
Oswestry Back Pain Disability (0-100)	42	24**	26**
Trunk Flexion (°)	82	115**	
Straight Leg Raising (°)			
Right	75	91**	
Left	73	91**	
Trunk Strength (%IBW)	50	100**	
PILE (%IBW)			
Lumbar	17	39**	
Cervical	17	31**	
Bicycle (KgM/9 min)	4900	6400**	

PILE = Progressive Isoinertial Lifting Evaluation; %IBW = Percent Ideal Body Weight; *p<0.05; **p<0.01 (p values are for T-test comparison of initial to 3 month, and initial to 12 month measures).

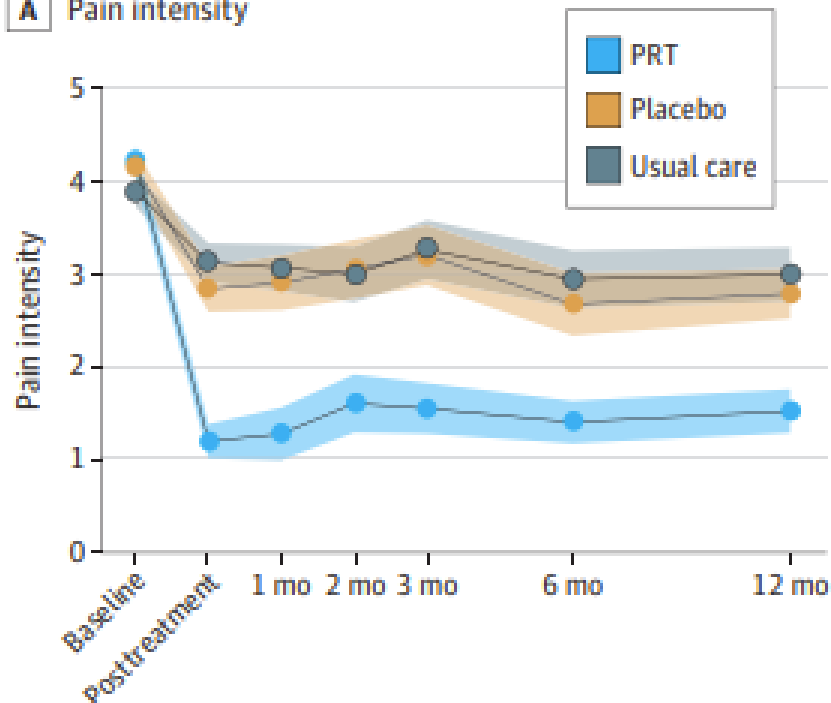
“Pain-Reprocessing Therapy”

- N=151, chronic LBP, mean 10 years
- Randomized to PRT vs saline placebo injection vs usual care
- PRT = MD + 8 psych visits

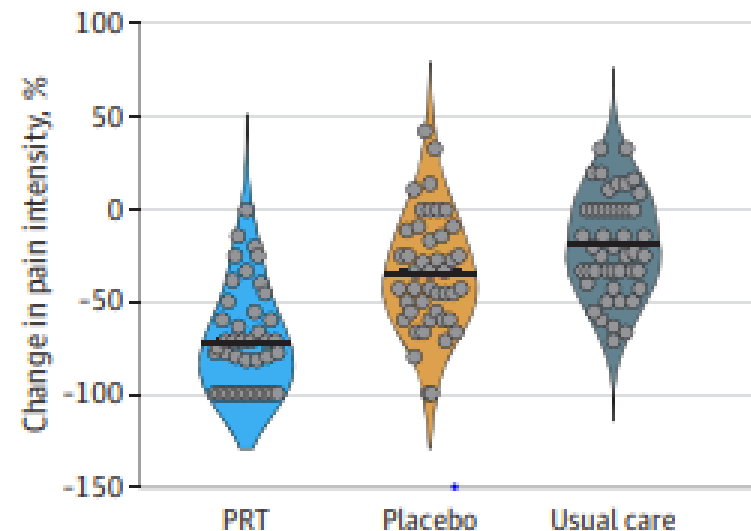
Approach

- (1) personalized evidence for centralized pain
- (2) guided reappraisal of pain sensations while seated and engaging in feared postures or movements
- (3) techniques addressing psychosocial threats (eg, difficult emotions) potentially amplifying pain
- (4) techniques to increase positive emotions and self-compassion

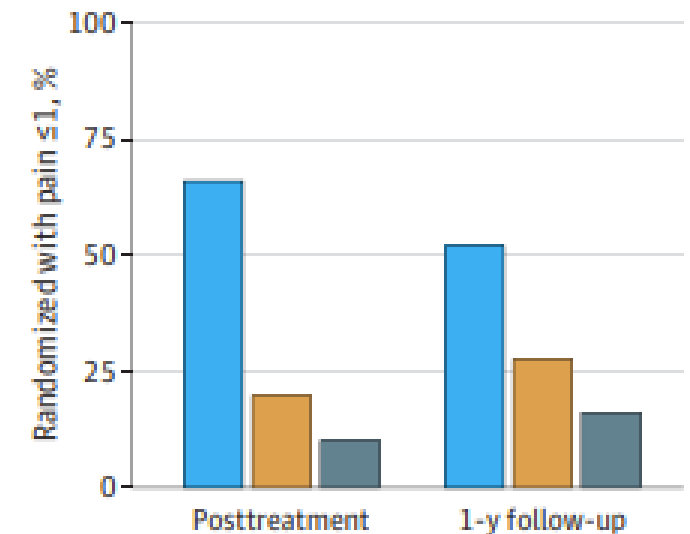
A Pain intensity



B Percent change in pain intensity from baseline to posttreatment



C Patients reporting a pain-free or nearly-pain-free state



Conclusions

Chronic pain is a maladaptive state characterized by diffuse nervous system remodeling

The extent of centralized pain is important to identify as it may warrant a different treatment approach

An individual's cognitive, emotional, and behavioral responses to pain likely affect pain and disability levels

Pharmacologic agents (tricyclics, SNRIs, gabapentoids) show the best evidence for treating centralized pain

Non-pharmacologic strategies include education, exercise, psychological approaches, and integrative approaches

Thank you!

