

A Brief Overview of Current Pain Science

And How This Helps To Explain
What Patients Experience

Daniel Bruns, PsyD



**Opioid
Response
Network**

Disclosures

Commercial Support/Sponsorship:

There is no commercial support for this training.

Conflict of Interest:

In accordance with continuing education guidelines, speakers and planning committee members are asked to disclose relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Faculty: Dr. Bruns is a coauthor of the BHI 2 and BBHI 2 standardized psychological tests for chronic pain.

Planning Committee Members: Have no relevant financial relationship(s) with ineligible companies to disclose. .

Mitigation Steps Implemented:

There were no reported financial relationships to be mitigated.



The Opioid Problem

- ✧ Currently, morphine & oxycodone are regarded as “essential medications” for traumatic injuries, perioperative pain, end of life pain, etc.
 - WHO Model List of Essential Medicines, 2023
- ✧ US Mortality Data
 - In 2022 there were 83,000 deaths associated with opioid overdose (CDC, 2023)
 - (109,000 deaths by overdose all substances)



Numerous Legal Actions Have Found That Poor Pain Treatment is a Primary Cause of Opioid Addiction and Mortality.

As of September 2023, Courts have awarded about \$53 billion dollars in civil damages pertaining to this.



Controlling the Opioid Crisis Requires Better Pain Treatment

What Does Science Say?



Opioid
Response
Network

The Science of Pain

A Brief Review



Opioid
Response
Network

In Medical Settings, Chronic Pain Is a Common Complaint

- Chronic pain is consistently among the most common reasons for seeking medical attention.
- Up to **40% of medical visits** involve chronic pain conditions.



Pain Is An Extremely Costly Condition

The experience of pain is a national public health crisis with physical, emotional, and societal costs.



50 million

adults live with
daily chronic pain



19.6 million

experience high-impact chronic
pain that leads to **disability**



\$560–635 billion

per year is the **cost**
to the nation

Pain Management Inter-Agency Task Force Report

U.S. Department of Health and Human Services • Office of National Drug Control Policy

• U.S. Department of Defense • U.S. Department of Veterans Affairs

• A Panel of Experts



Recent Data on Opioid Prescribing

✦ Opioids are still widely used for pain

- 22.1% of patients with chronic pain reported using prescribed opioid pain Rx. (Dahlhamer, 2021)
- Of 12,500,000 ED visits a year, 8.1% of visits resulted in an opioid prescription (CDC, 2023)
- In 2020, US pharmacies dispensed 143 million prescriptions for opioid pain medication (CDC, 2021)
 - A vast improvement!

✦ While opioids are widely used for acute pain, there is no evidence that opioids work long term for chronic pain (CDC, 2016)



Opioids and Risk

Opioids create a substantial risk of dependence and addiction

21–29%

The number of patients who misuse opioids.

8–12%

The number of patients who become addicted to opioids.

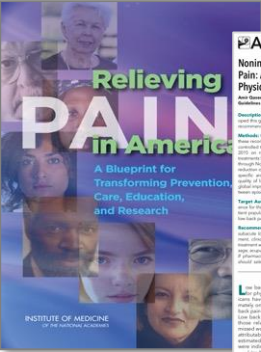
4%

The number of opioid deaths due to suicide. The vast majority of opioid deaths are unintentional. (Vowles, 2015)

CDC & FDA On The Dangers of Discontinuation

- ✦ Rapid discontinuation of opioids associated with withdrawal, uncontrolled pain, transition to illegal opioids and suicide (FDA, 2019)
- ✦ Discontinuation of opioids associated with greater risk when it occurs over shorter periods. (CDC Opioid Guidelines, 2022)
- ✦ **Discontinuation of opioid Rx increased risk of death by overdose or suicide**
 - 6.8X higher risk of death following **discontinuation** in patients prescribed opioids > 400 days (Oliva, 2020)

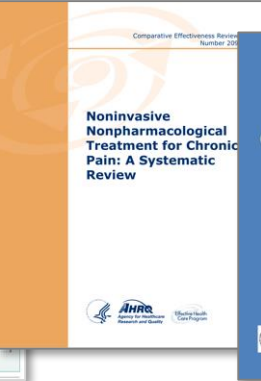




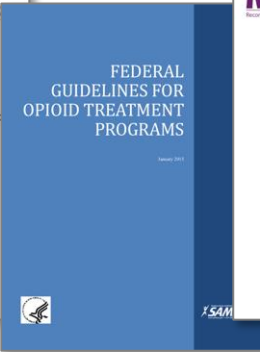
Institute of Medicine



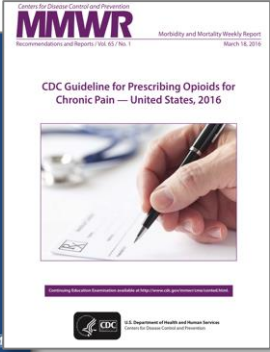
American College of Physicians



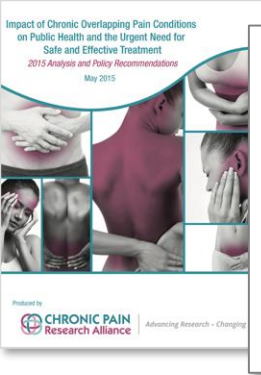
Agency for Healthcare Research and Quality



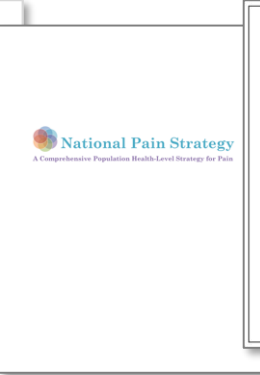
Substance Abuse and Mental Health Services Administration



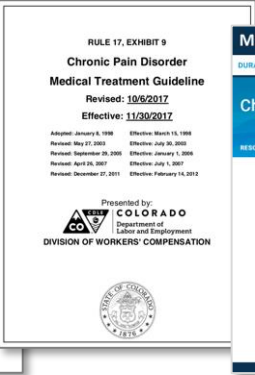
Centers for Disease Control and Prevention



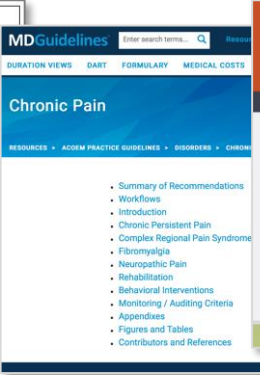
Chronic Pain Research Alliance



Department of Health and Human Services



Colorado Department of Labor and Employment



American College of Occupational and Environmental Medicine



Department of Health and Human Services

Almost Every Pain & Opioid Treatment Guideline Advocates an Interdisciplinary Approach Where Medications and Behavioral Interventions Play a Prominent Role

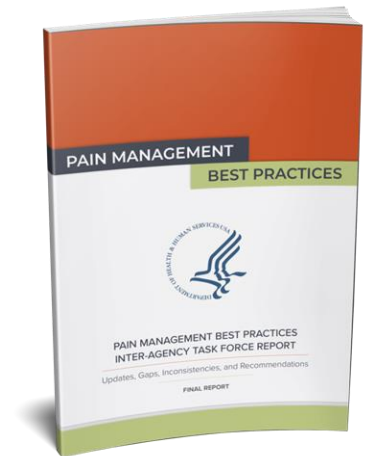


Pain Management Best Practices Inter-Agency Task Force Report, 2019

A joint publication of the
U.S. Department of Health and Human Services
Office of National Drug Control Policy
U.S. Department of Defense
U.S. Department of Veterans Affairs
A Panel of Experts

Conclusions

- Patients with pain in the United States face challenges in obtaining adequate care, with profound physical and emotional costs.
- This report describes the scope of these problems and makes recommendations about what we should do.



Addressing Pain in the Clinical Setting

What would you say if...



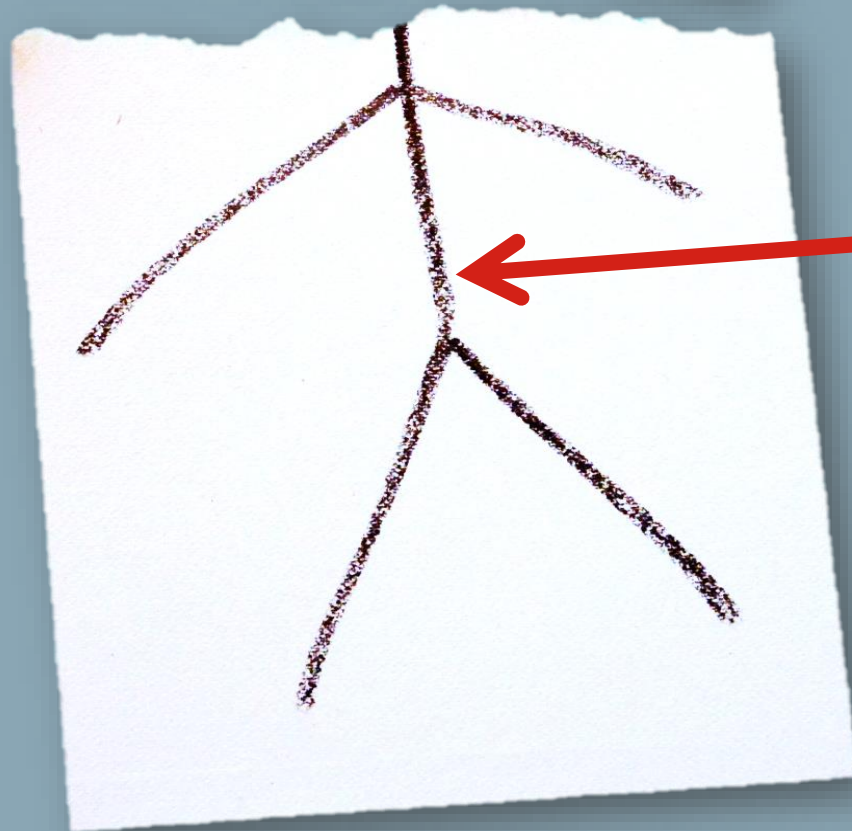
Opioid
Response
Network

**Doctor, do
you think my
pain is in my
head?**

**Or do you
think it is
real?**



*In your
Head*



Real



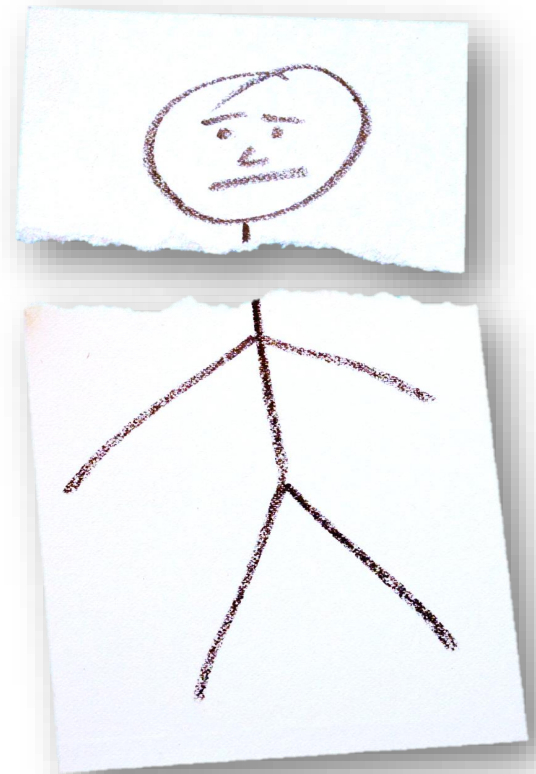
**This discussion is not
based on pain science.**

**This discussion is based on
cultural constructs about pain**



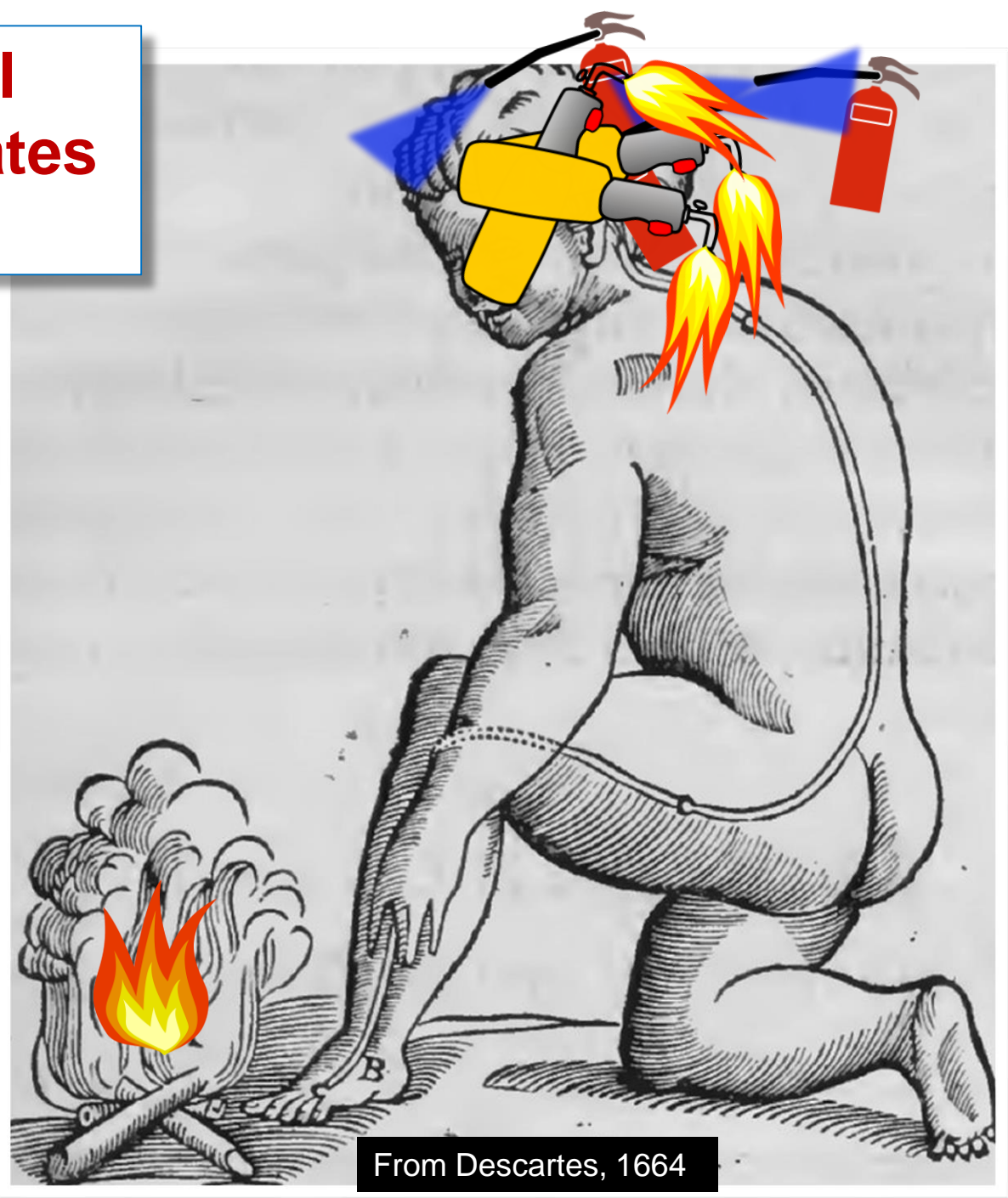
The Discredited Biomedical Model

- ✧ Has promoted the role of objective scientific methods in medical care
- ✧ Downside: Physical health and mental health are regarded as separate and distinct
- ✧ Physical symptoms are either
 - **Real** and biological
 - Or
 - **Not Real** and “In your head”
 - Some people lie about pain (malingering)
 - Others imagine pain (psychopathology)



The Biomedical Theory of Pain Dates Back to 1664

Descartes wrongly thought that mind and body were separate, and that pain was the direct result of injury to the body. **We know now that the sensory system plays an active role in pain perception, dialing the pain up or down in the brain, spine and periphery.** Remarkably, 350 years later this incorrect concept of pain is still commonly used.



There is Strong Evidence That This Mind/Body Distinction Is Wrong



Opioid
Response
Network

Problems with Pain Education

- ✧ Most Physicians and Psychologists Are Not Trained in Pain Treatment
- ✧ In a study of US medical schools
 - Only 3.4% of medical schools offered an *elective* class in pain
 - No medical school required a class in pain
 - 20% of medical schools did not reserve a single hour for pain education (Institute of Medicine, 2011)



Pain Education

- ✦ “Most health care professions’ education programs devote little time to education and training about pain and pain care” (NIH National Pain Strategy, 2016)
- ✦ Evidence points to a major gap between the increasingly sophisticated knowledge of pain and the prevailing inadequacy of its treatment
 - This has been difficult to change, as adding more time spent on pain means decreasing time spent on something else
 - Shipton, 2023



A Brief Overview of Remarkable Findings From Current Pain Science



Opioid
Response
Network

Pain Is Both An Emotion and a Sensation

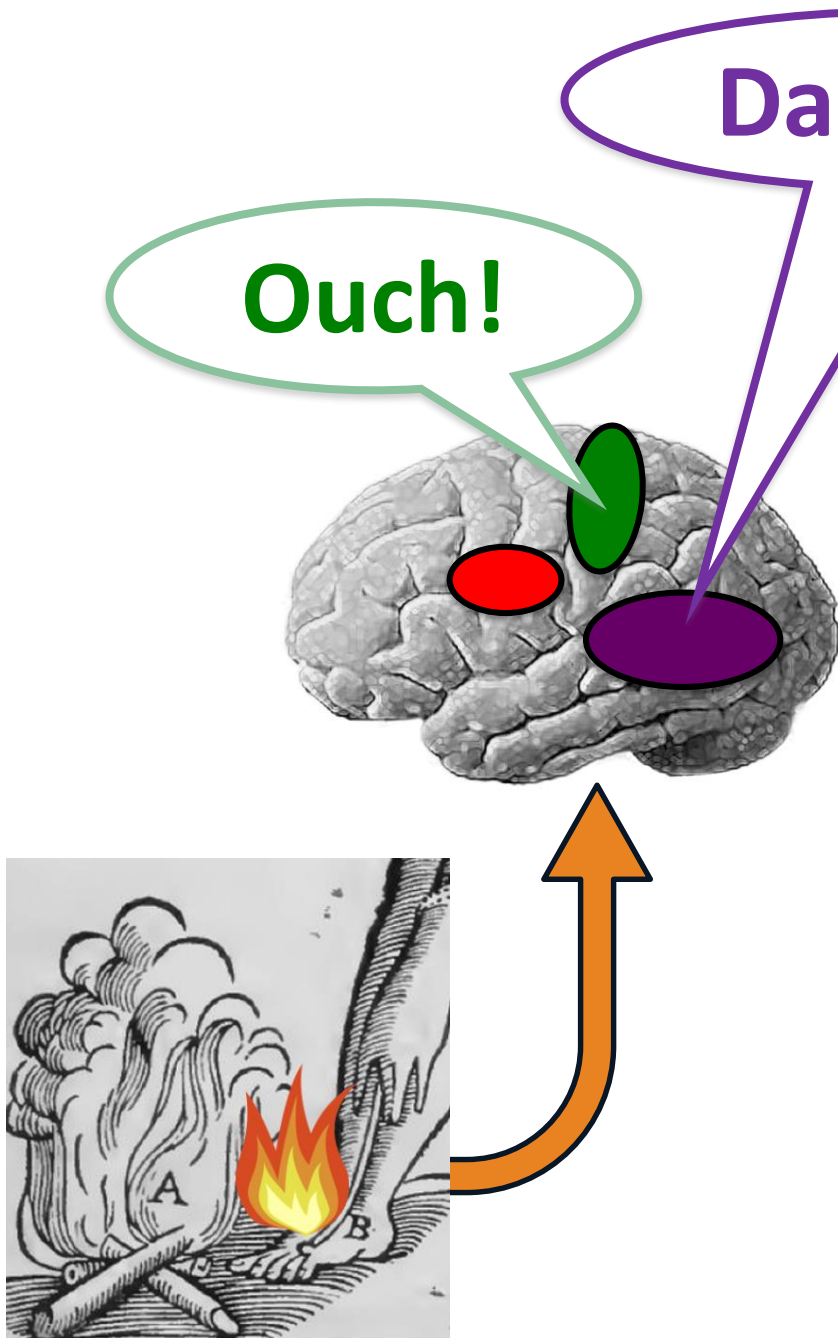
✦ IASP 2018 Definition of Pain:

An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury

— International Association for the Study of Pain, 2020

✦ Pain is part sensation, and part emotion





Ouch!

Dammit!

Ouch! The sensory response to pain is associated with the somatosensory cortex.

Dammit! Swearing is associated with activity in the limbic system.
(Stephens, 2009)

Pain as an emotion: It has been hiding in plain sight

The Nature of Pain

- ✦ Pain and emotion share many of the same neural pathways (Hashmi, 2013)
- ✦ In chronic pain, brain areas related to emotion play a dominant role
 - (Hashmi, 2013; Mansour, 2014)



The Effect of Chronic Pain

✧ **Chronic pain remodels the central nervous system**

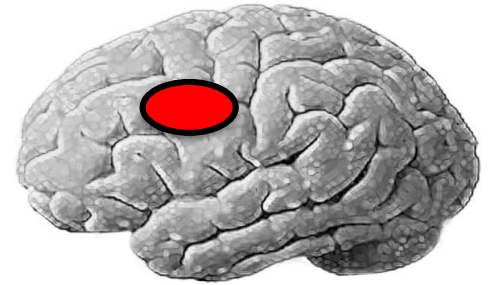
- Windup in spinal cord ganglia (Staud, 2007)
- Central sensitization in the brain (Melzak, 2006; 2007)
- Changed brain connections/structure (Apkarian, 2009; May 2008)

✧ **Chronic pain is associated with**

- Neurodegeneration (Apkarian, 2006)
- Decreased grey matter in prefrontal cortex (Barad, 2014)
- Brains appear 10-20 years older (Apkarian, 2004;2006)
- Memory impairment (Liu, 2014)

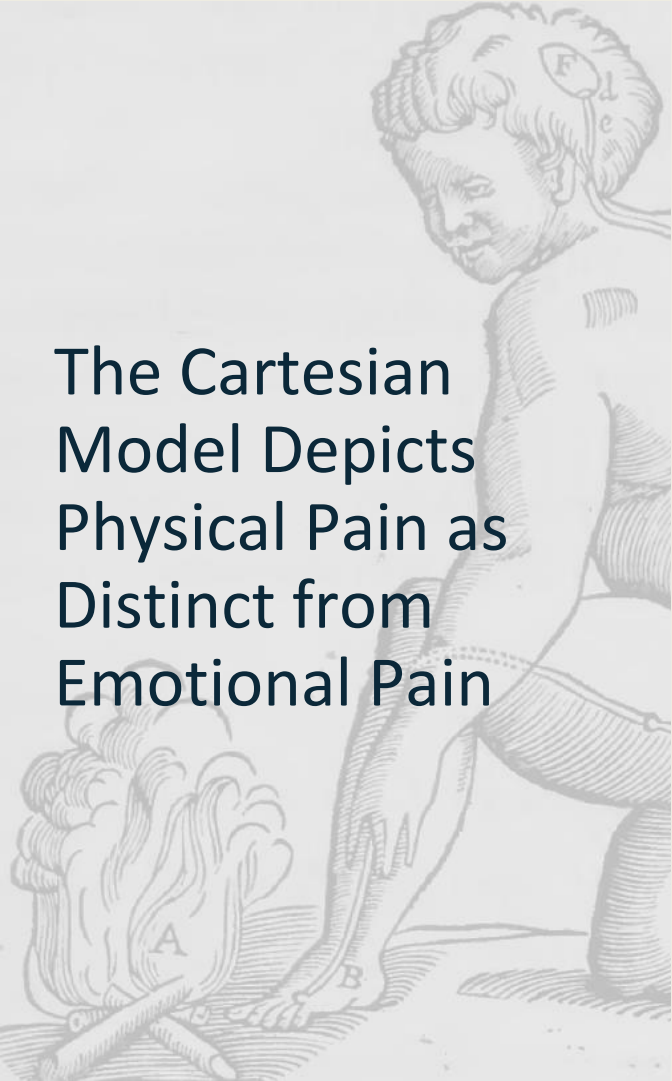


What Activates The Brain's Pain Center?



- ✧ f-MRI studies show that activity in the brain's pain center [the anterior cingulate] can be triggered by:
 - Physical pain/ nociception
 - Social pain/ “hurt feelings” (Eisenberger, et al 2003)
 - Seeing a loved one in pain/ “sympathy pains” (Singer, 2004)
 - Imagined pain (Derbyshire, 2004)
 - Catastrophizing (Gracely, 2004)



An anatomical engraving of a seated female figure, likely representing the Cartesian model of the mind-body dualism. The figure is shown from the waist up, with her head tilted slightly to the left. Her hair is styled in an elaborate, curly fashion. On the right side of her head, a brain is depicted with several letters (A, B, C, D, E, F) marking specific areas. In the foreground, a fire is burning in a brazier, with a stick of wood resting on the ground. The letter 'A' is placed near the fire, and the letter 'B' is placed near the figure's hand, which is resting on her lap. The background is a plain, light color.

The Cartesian Model Depicts Physical Pain as Distinct from Emotional Pain

- Studies of brain functioning demonstrates that physical pain is not distinct from emotional pain.
- Treatment research supports the physical-emotional pain connection.
 - Cognitive therapies and some antidepressants are first line treatments for chronic physical pain.
 - (Slavich, 2019): Acetaminophen reduces social pain / “hurt feelings”
 - (Mischkowski, 2016; 2019): Acetaminophen reduces empathy / “sympathy pains”

How Powerful Are Opioid Analgesics?

- **Benchmarking the power of fentanyl**
 - Fentanyl = Tramadol x 1000
 - Fentanyl = Morphine x 100
 - **Fentanyl = Placebo**
 - (Bingel, 2011)



Efficacy of Remifentanyl vs Placebo At Reducing Thermal Pain

Rx	Experimental Condition	Pain VAS (0-100)	Strength of analgesia
Saline Solution	Baseline	66	None
Remifentanyl	Patient unaware receiving Rx	55 (-11)	Significant analgesia
Remifentanyl + Placebo	Patient told getting Rx Expect relief!	39 (-26)	2.5X analgesia of Remifentanyl alone
Remifentanyl + Nocebo	Patient <u>wrongly</u> told Rx had stopped Expect pain + withdrawal to be worse than ever!	64 (-2)	No analgesia from Remifentanyl
Bingel, 2011			



The Placebo Is A Cognitive Intervention

- ✦ In Bingel's experiment, fMRI demonstrated that **placebo expectations altered brain functioning**
- ✦ **A placebo is a cognitive intervention: A belief that there will be an effect** (e.g. analgesia)
 - Placebo and nocebos changed both patient report & brain activity at a level equal to remifentanyl
 - Bingel, 2011 & 2012; Treede 2016; Lobaov, 2014; Jepma, 2018
- ✦ Bingel carefully created the placebo effect in this experiment



Cognitive Tx Changes Brain Functioning

- ✦ CBT for anxiety decreased blood flow in brain emotion centers (Soravia, 2016)
- ✦ CBT increased blood O₂ level in prefrontal cortex of fibromyalgia patients (Jensen, 2012)
- ✦ 4 days mindfulness Tx reduced pain-related brain activity in the somatosensory cortex
 - Pain sensation down 40%; Pain affect down 57%
 - (Zeidan, 2011)



What Are Cognitions, Anyway?

- ✦ **Cognitions are superordinate neurological processes that can**
 - Organize neurological activity, feelings and behavior
 - Dial pain and inflammation up or down
- ✦ **Cognitions are like software that determines what your computer hardware will do**
 - The purpose of CBT is to upgrade your cognitive software to a more effective version



CBT is a NSAID

Non Steroidal Anti-inflammatory

- ✦ CBT appears to have an anti-inflammatory effect
 - Conclusion of a systematic review of 23 studies
 - (Lopresti, 2017)
 - Presumably due to the fact that stress hormones are pro-inflammatory
- ✦ CBT anti-inflammatory effect is larger if stress level is high (O'Toole, 2018)



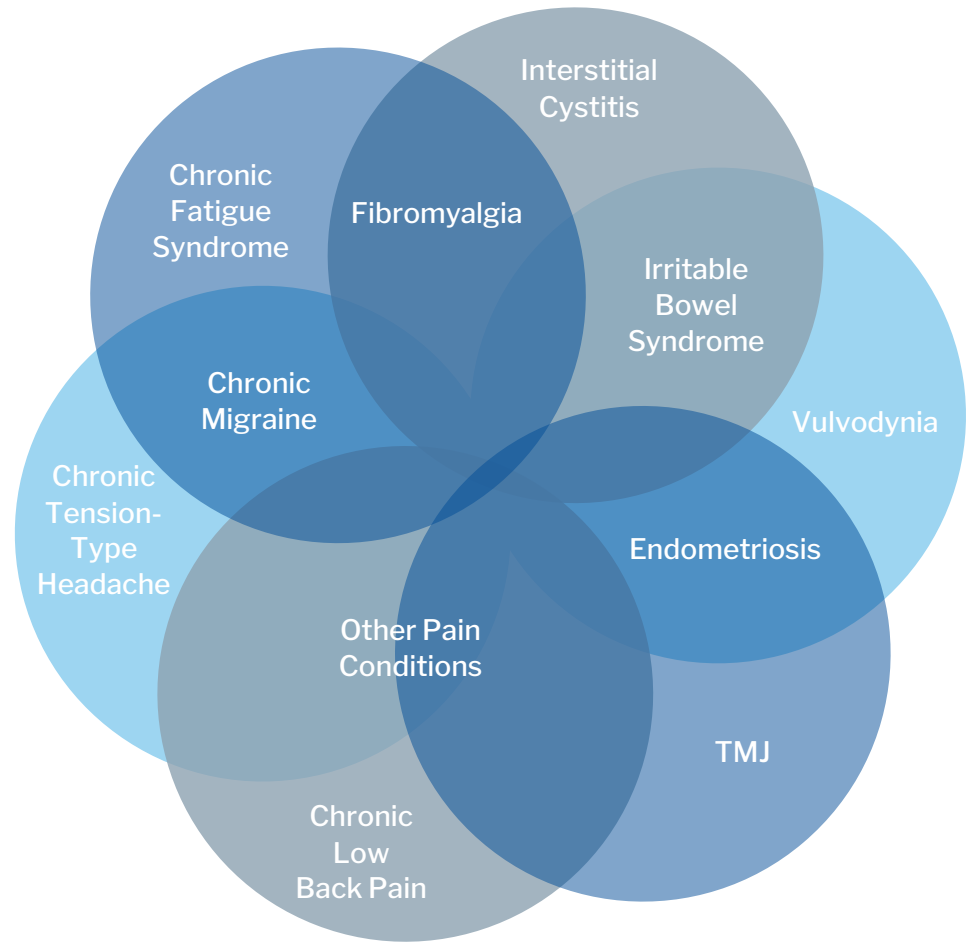
Psychological Tx Can Cause Structural Changes to the Brain

- ✦ **CBT therapy increased prefrontal cortex grey matter in the brains of:**
 - Pain patients (Seminowicz, 2013)
 - Chronic fatigue patients (de Lange, 2008)

- ✦ **Some psychological Tx are exercises for the brain, and can reverse negative neuroplasticity effects (Seminowicz, 2011)**



Dysfunctional Changes in the Pain Sensory System May Underly a Multitude of Conditions



Adapted from Chronic Pain Research Alliance, © 2015.
www.chronicpainresearch.org.

All of these can be diagnosed as

ICD-11: Chronic Primary Pain

Which is believed to be a
Nociplastic Disease



Opioid
Response
Network

IASP Pain Taxonomy

✦ **IASP: There are three mechanisms of pain**

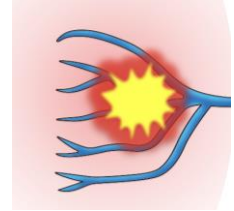
- Nociceptive pain (sensory pain)
- Neuropathic pain (nerve injury pain)
- Nociplastic pain (sensory system disease/
dysregulation)
- International Association for the Study of Pain, 2023



What is Primary Pain?

Understanding Nociceptive Disease

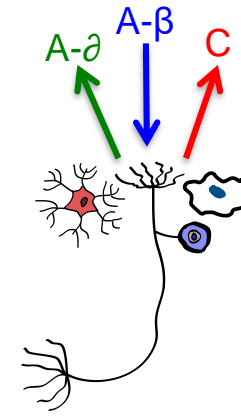
Peripheral Pain Mechanisms



The Pain Sensory System Has Two Main Branches

©2013-2019 Daniel Bruns, PsyD

Peripheral pain nerves connect to CNS nerves in the spine

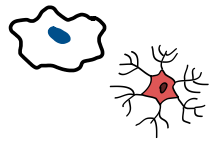


Pain signals to the brain are regulated in the spine

Nociceptive pain is sensory in origin; Neuropathic pain can result if a nerve is severed, crushed or damaged...



... or if glial cells in the spine alter the chemistry of pain nerve synapses



Pain Nerve Pathways

"First Pain" (Acute)
Primarily A- δ fibers
(sharp/localized pain)

"Second Pain" (Chronic)
C fibers/ Polymodal Receptors
(achy/diffuse pain)

Thermal

Mechanical

Chemical

Heat

Cold

Types of Pain Transducers

Thermal

Mechanical

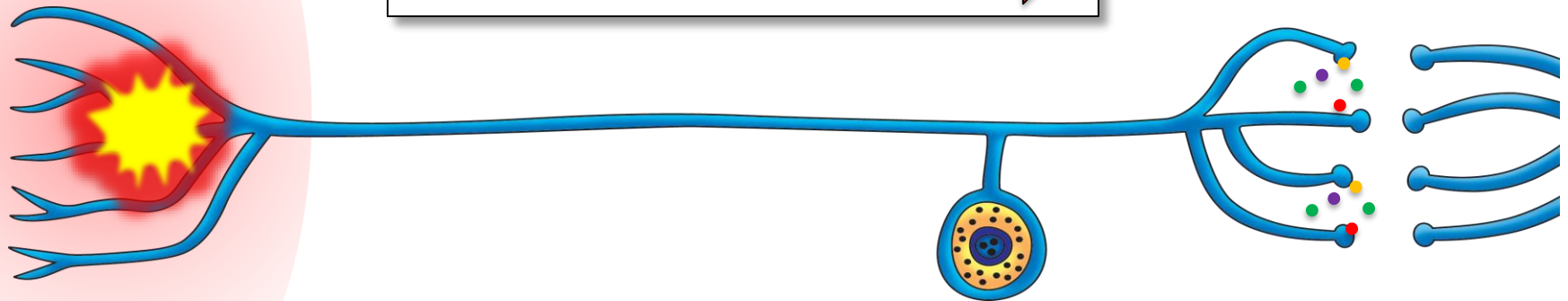
Chemical

"Silent"
(10-25%)

Nociceptor axons transmit signals both ways

← Inflammatory/ Immune signal

Pain signal →



Sensory
Transducers
Create a
Signal

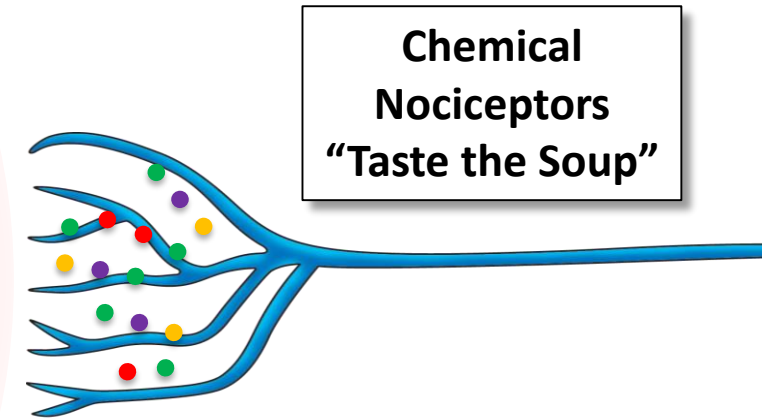
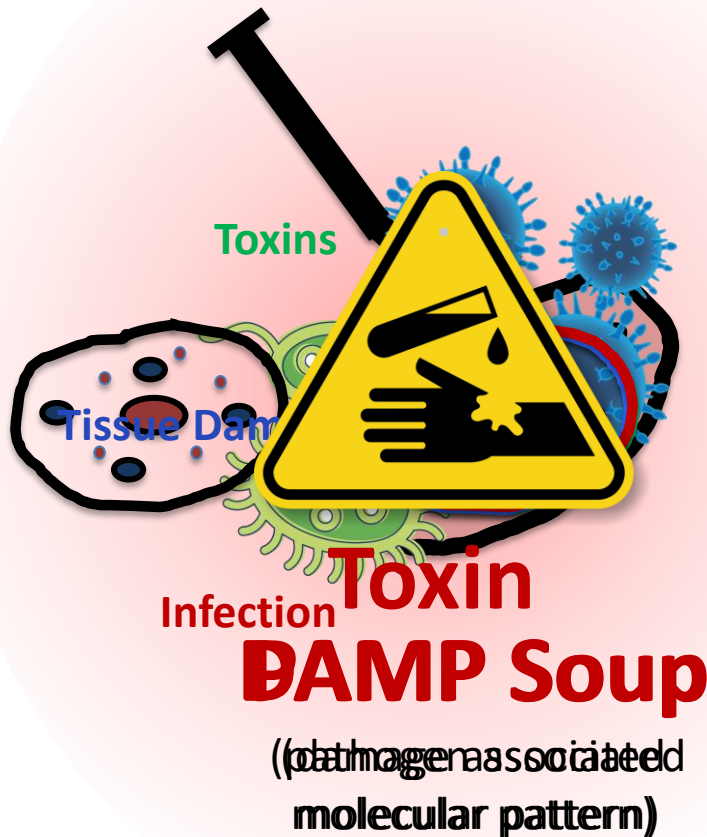
Pain and inflammation are the two
halves of the “unified defense
mechanism” (Chiu, 2012)

Synapses In
The Spine

Basbaum, 2009

Inflammatory Soup of the Day

C
a
p
i
l
l
a
r
y



The nociceptor initiates self-protective behavior and also orchestrates the immune response

Nociceptors Orchestrate The Healing Process

- **Working autonomously, nociceptors:**
 - Identify potential threats (damage, toxin or infection)
 - Initiate the inflammatory healing response
 - Cause capillaries to dilate and release white blood cells and a legion of chemicals
 - Activate mast cells, and program them to recycle damaged cells, fight pathogens or clean up toxins
 - Initiate cascade of trophic “chemical fertilizers” that make replacement cells grow

Pain Serves a Protective Function

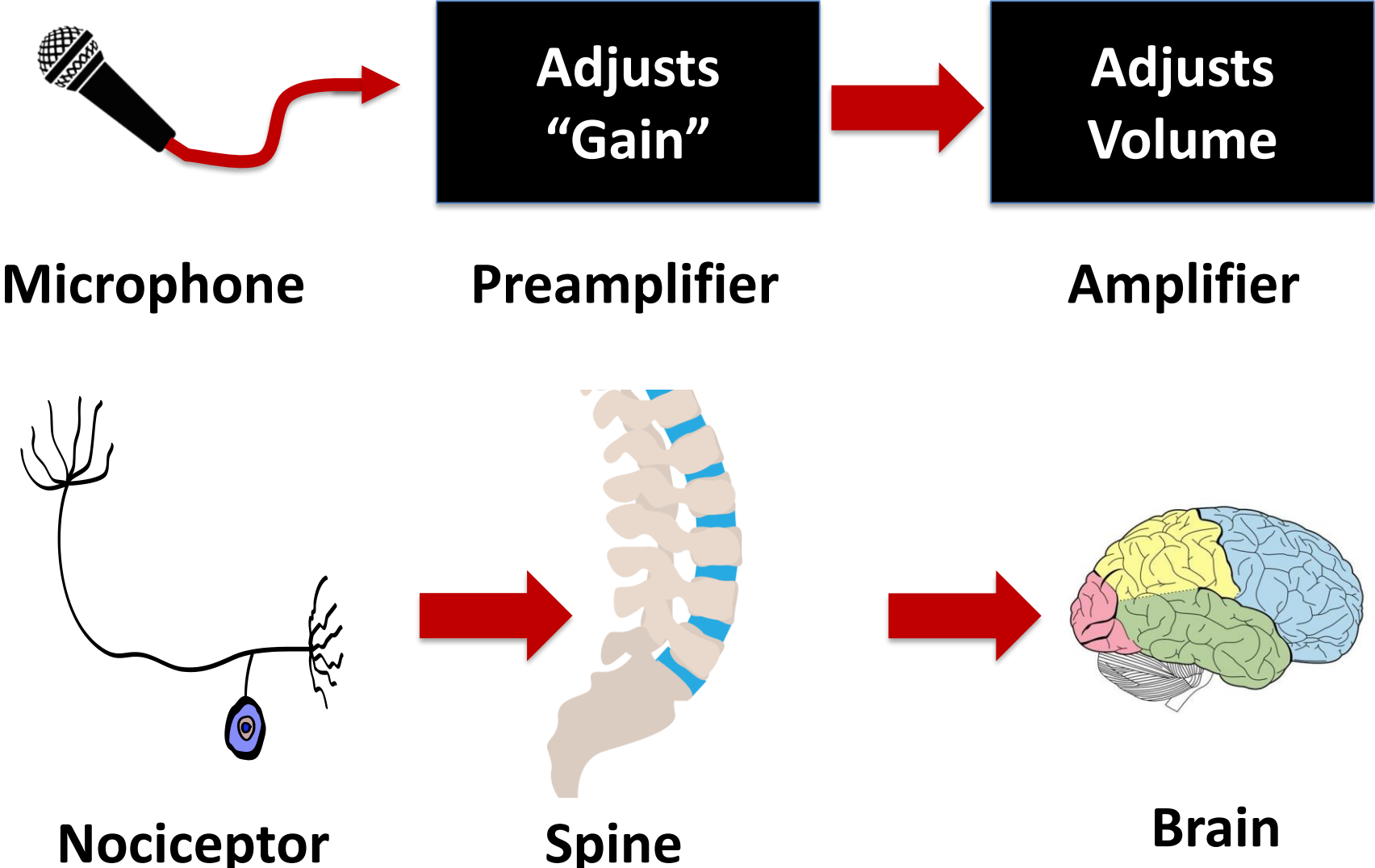
- In cooperation with the brain, nociceptors produce pain which:
 - Warns brain of potential danger
 - Triggers immediate self-protective reflexes
 - Activates the fight or flight response
 - Limits behavior during recovery
 - Basbaum, 2009; Ellis, 2013; Woolf, 2007; Chiu 2013; Matsuda, 2018

Spinal Pain Mechanisms



Gate vs Gain Control Theory And Circuits in the Spine

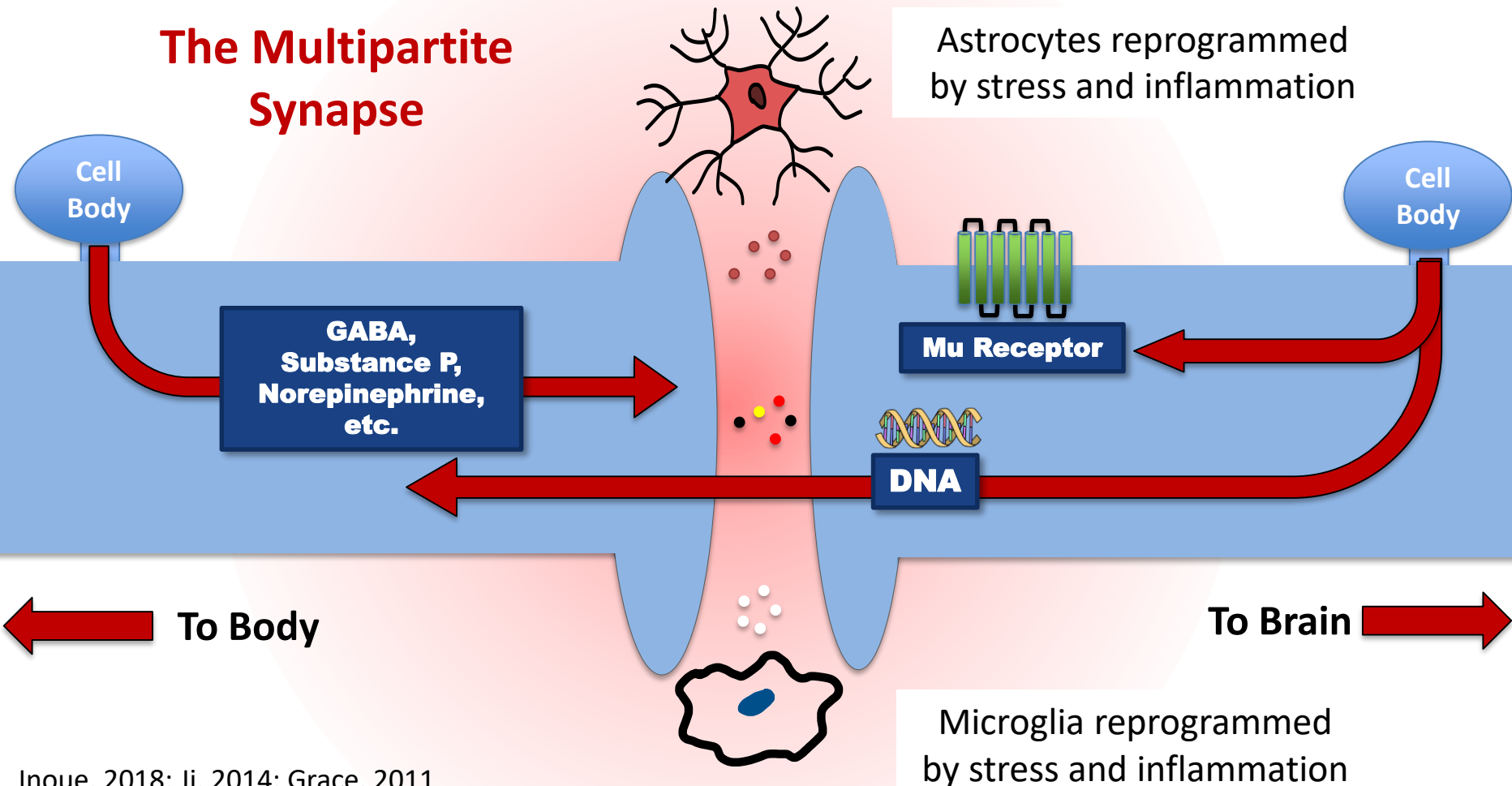
Gain Control: Pain Works Like a Microphone



Treede, 2016; Woolf, 2000

Nociplasticity: How Spinal Synapses Adjust “Gain”

The Multipartite Synapse



Inoue, 2018; Ji, 2014; Grace, 2011

Capillary

©2023 by Daniel Bruns, PsyD

Mechanisms of Nociceptivity

In the transition to chronic pain, our pain sensory system rebuilds itself and can become dysfunctionally sensitive.

This is more likely to happen when stress levels are high.

Spinal Plasticity and Memory

**Spinal plasticity enables spinal circuits
to remember past injuries via
enduring localized sensitization**

(Inoue, 2018; Rivat, 2016)

Spinal Plasticity and Memory

- Spinal “memories” increase the gain level, allowing the pain system monitor injured tissues, and be alert to re-injury
- These circuits automatically remember pain to protect vulnerable body parts, but these are “brainless” mechanisms, and may be dysfunctional
 - (Rome, 2000; Xanthos, 2014; Inoue, 2018)
- The brain & spine can influence/adjust this process
 - (Geuter, 2013)

Brain Pain Mechanisms



**How does the brain interpret the
pattern of nociceptor signals?**

The Pain Sensory System

Many parts of the brain are involved when you feel pain

©2013-19 Daniel Bruns, PsyD

Central Sensitization
The brain's pain center integrates these factors in the "pain neuromatrix" which sensitize you to pain)

Sensation and Movement
(self-protective behavior)

Stress/ Inflammatory Chemical Cascade
(CRF, ACTH, Cortisol, IL-6, etc.)

Emotion
(Depression, Anger & Anxiety)

Muscle Tension & Spasms
(knots in muscles)

Arousal
(I can't sleep)

Windup

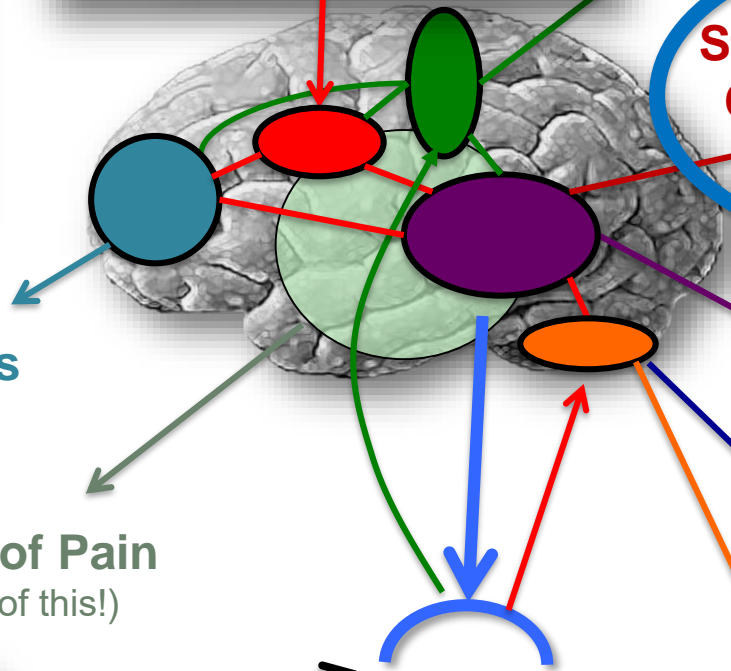
"C" Nerve Fibers
Chronic "Second Pain"
(broad pattern of dull, achy pain)

A-delta Nerve Fibers
Acute "First Pain"
(sharp, localized pain)

Pain Cognitions
(Will I get better??)

Memories of Pain
(I'm so sick of this!)

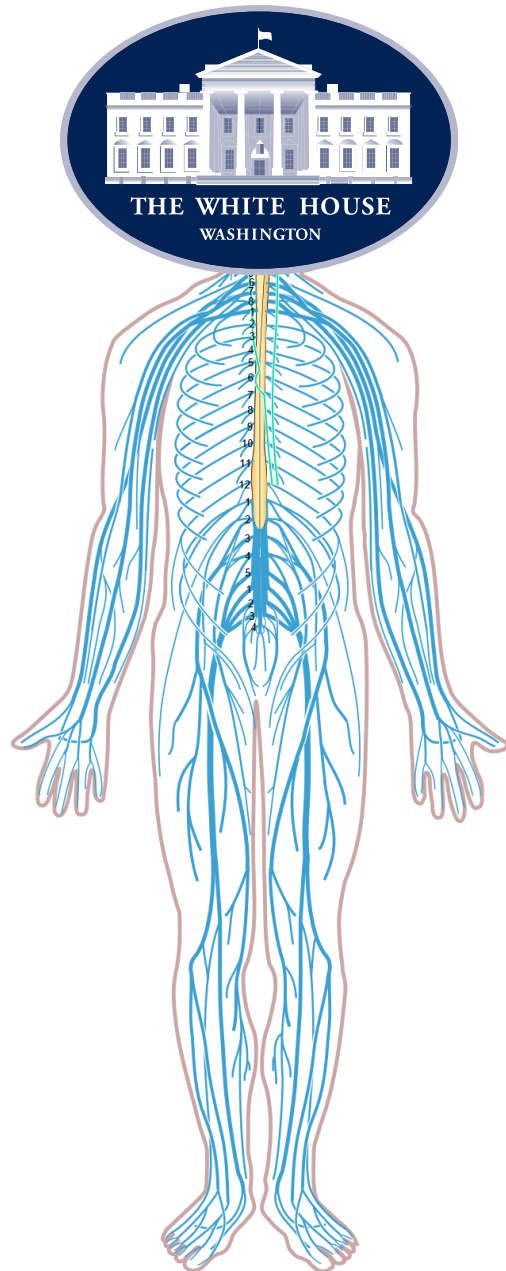
Sensory Gate Control:
Descending Neural Inhibition vs Windup



**Based On The Pattern of
Nociceptive Signals it Receives,**

**And In The Context of Cognition,
Mood, Memory and
Social Circumstances,**

**The Brain Constructs
the Feeling of Pain**



The Brain Cannot Dictate Pain Level By Itself

The Brain is like the President of the Pain Sensory System.

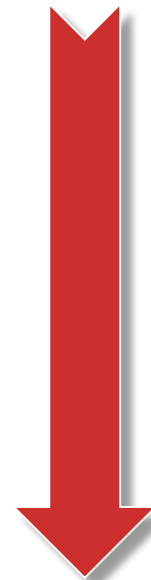
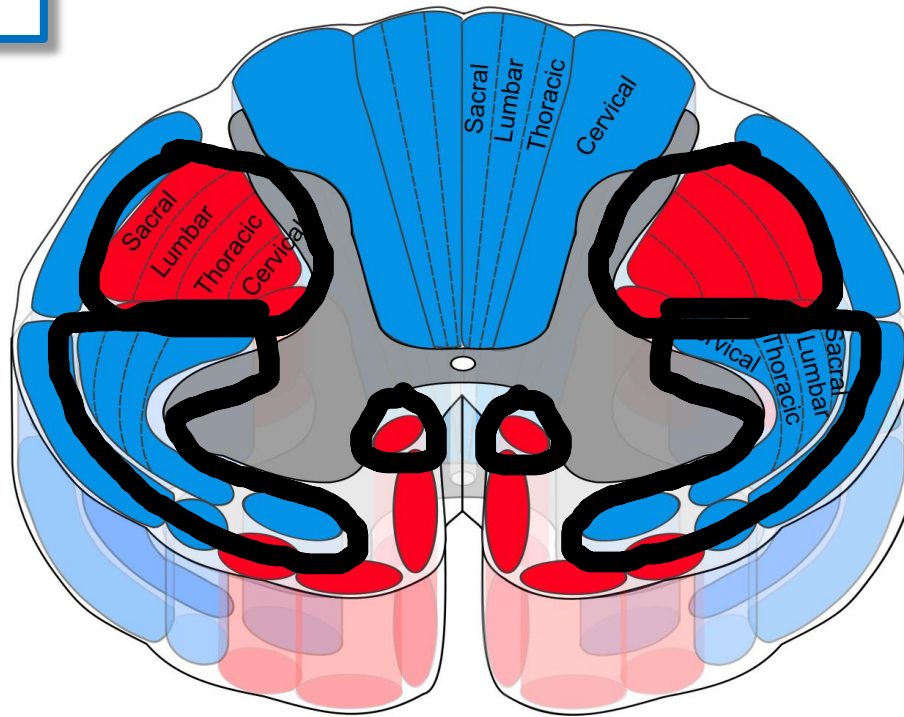
The Brain has a lot of regulatory power.

The Brain also has a lot of opposition from peripheral, spinal and metabolic mechanisms.

Pain: A Two-Way Street In The Spine

Blue
Afferent Nerve
Tracts

Red
Efferent Nerve
Tracts



Pain
Sensory Data

Pain
Hypotheses

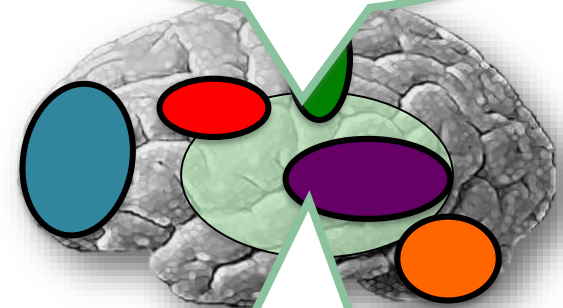
Re-educating Spinal Circuits

Ouch.

Uh oh!! This is my injured area! The problem is back!!

This injury is a catastrophe!!!!

this is a big deal.



Just relax.
Light exercise will be good for you.

Light exercise while calm helps reverse the effects of pain nociplasticity

Chronic Pain Changes the Nervous System

All pain disorders appear to involve a “nociplastic” reorganization of the pain sensory system

- Sensitized nociceptors
- Sensitized pain circuits in spinal ganglia
- Sensitized pain circuits in brain
- Reorganized brain functioning
- Objective changes to the brain including:
 - Signs of neurodegeneration
 - Decreased grey matter in prefrontal cortex
 - Memory impairment

This is the disease process of

ICD-11: Chronic Primary Pain



Opioid
Response
Network

How do you treat chronic pain without opioids?



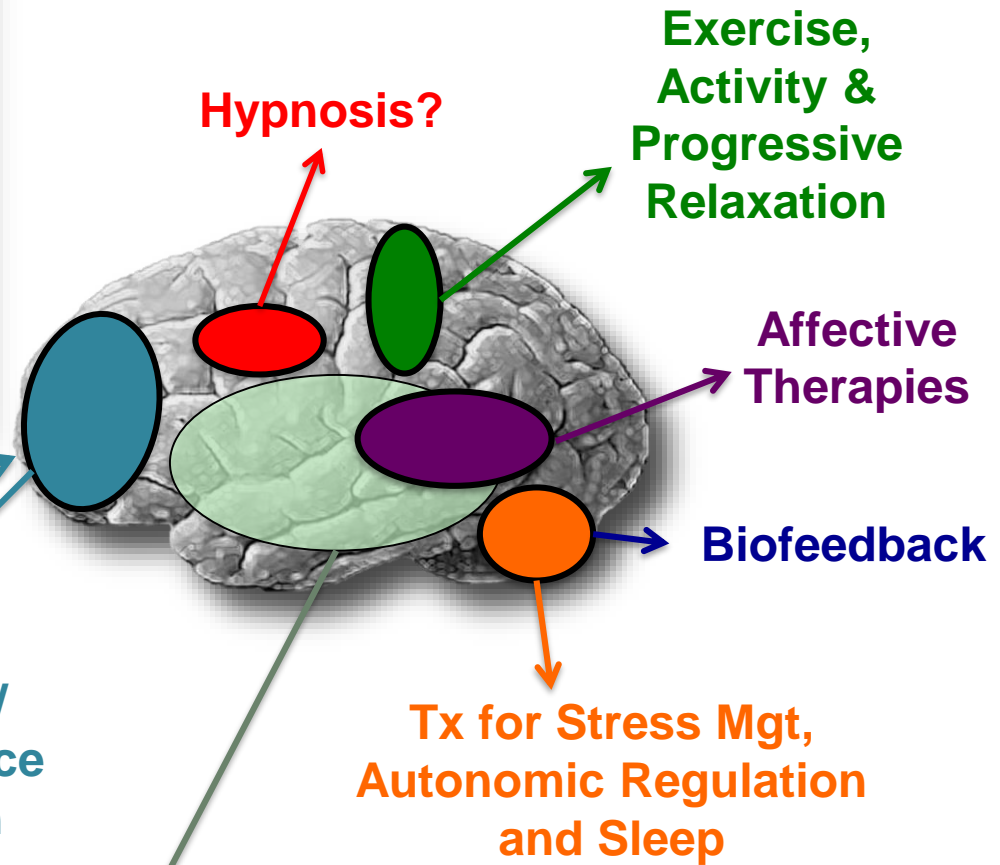
As Opposed Opioids: Psych Tx Targets Brain Functions to Improve Self Regulation

©2013 Daniel Bruns, PsyD



Cognitive
Therapies/
Neuroscience
Education

Mindfulness
Meditation



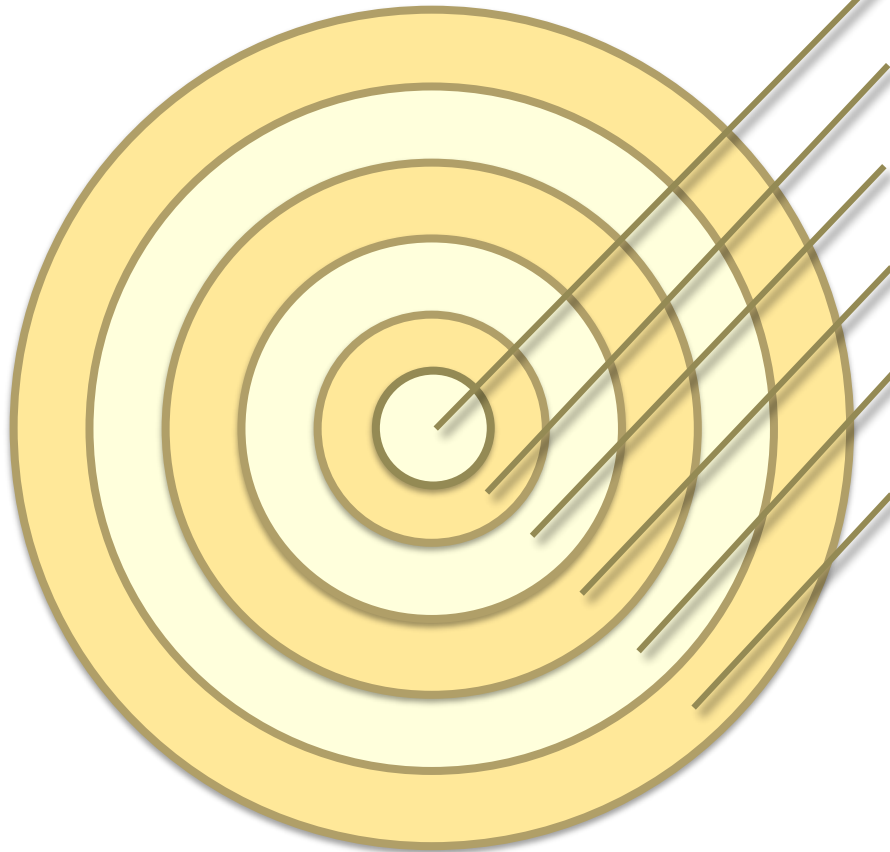
**Pain psychology
model of pain
treatment**

**How do you explain
this to patients?**



Like an Onion, Chronic Pain Has Layers

Over the course of time, chronic pain tends to develop several “layers”. Interdisciplinary treatment addresses all of these concerns.



Sensory pain (“nociceptive”) warns of actual or potential tissue damage

Nerve pain (“neuropathic”) due to nerve injury or disease is often difficult to locate and describe
Your **thoughts** alter how you perceive pain & injury.
It is dangerous? Or is it no big deal?

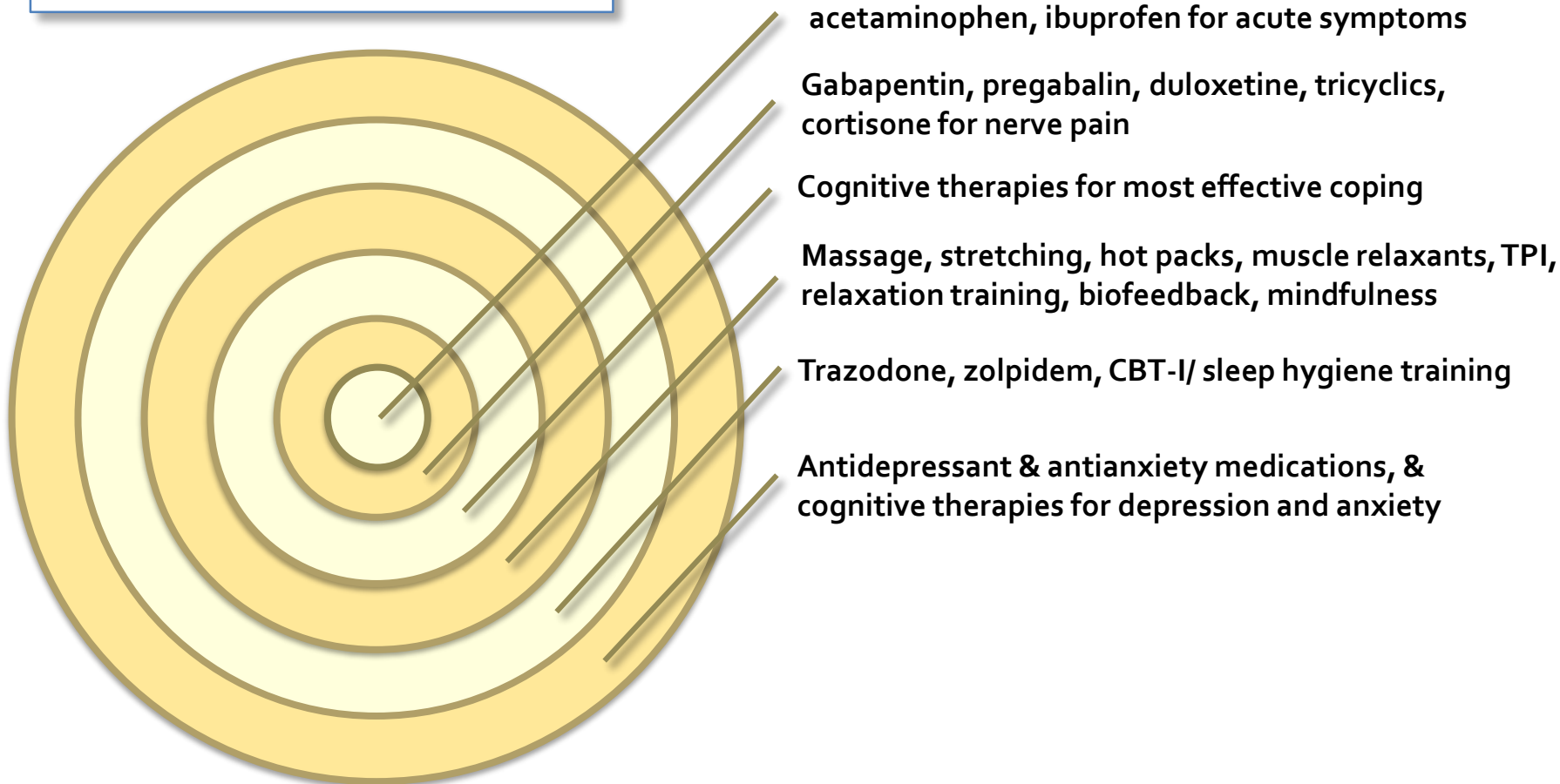
Stress-related muscle tension pain feels like “knots” in your muscles

Insomnia & exhaustion can delay the healing process, increase pain and reduce pain tolerance

Pain-related **anxiety, depression, & anger** increase pain and add to your suffering

Treating Pain One Layer at a Time

Pain is so complex that there is no one treatment that will address every layer. The most effective treatments for chronic pain involve treating it one layer at a time



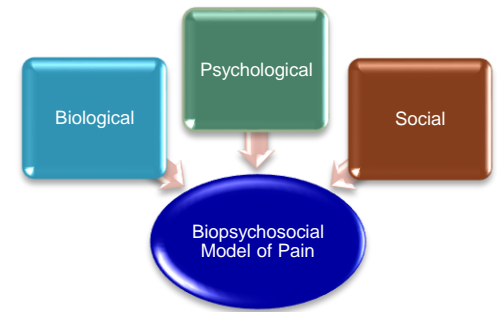
Advocating For Better Care for Pain and Opioid SUD

Is Interdisciplinary Care
Economically Feasible?



Opioid
Response
Network

What Happens When You Mandate The Biopsychosocial Model?



✦ Study of the Colorado Work Comp System

- Colorado WC system mandated biopsychosocial guidelines
- Gathered data on 29 million injured workers in 45 US states over 15 years
- Compared workers being treated by a biopsychosocial model vs ones that were not
- How did the biopsychosocial approach impact the cost of care and length of disability?
- (Bruns, Mueller and Warren, 2012)



Best Practice Model

Do the Best Thing!



Surgery/Injections

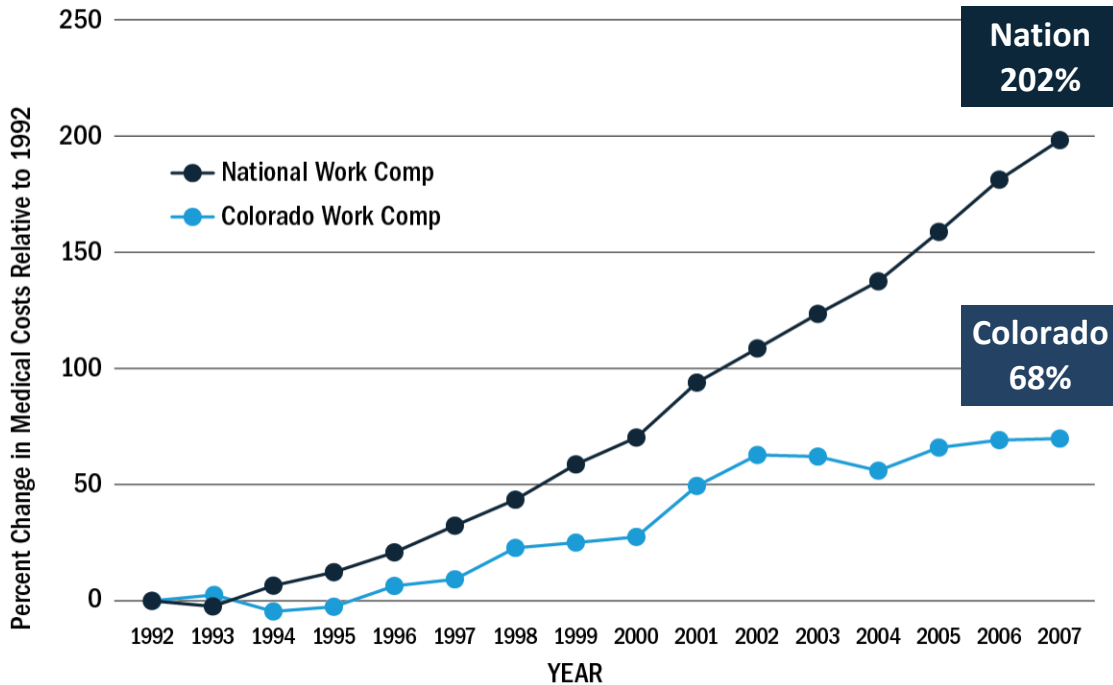
Medications

Physical therapies (DC/PT/OT)

Behavioral therapies



Colorado vs. National Medical Treatment Cost Increases

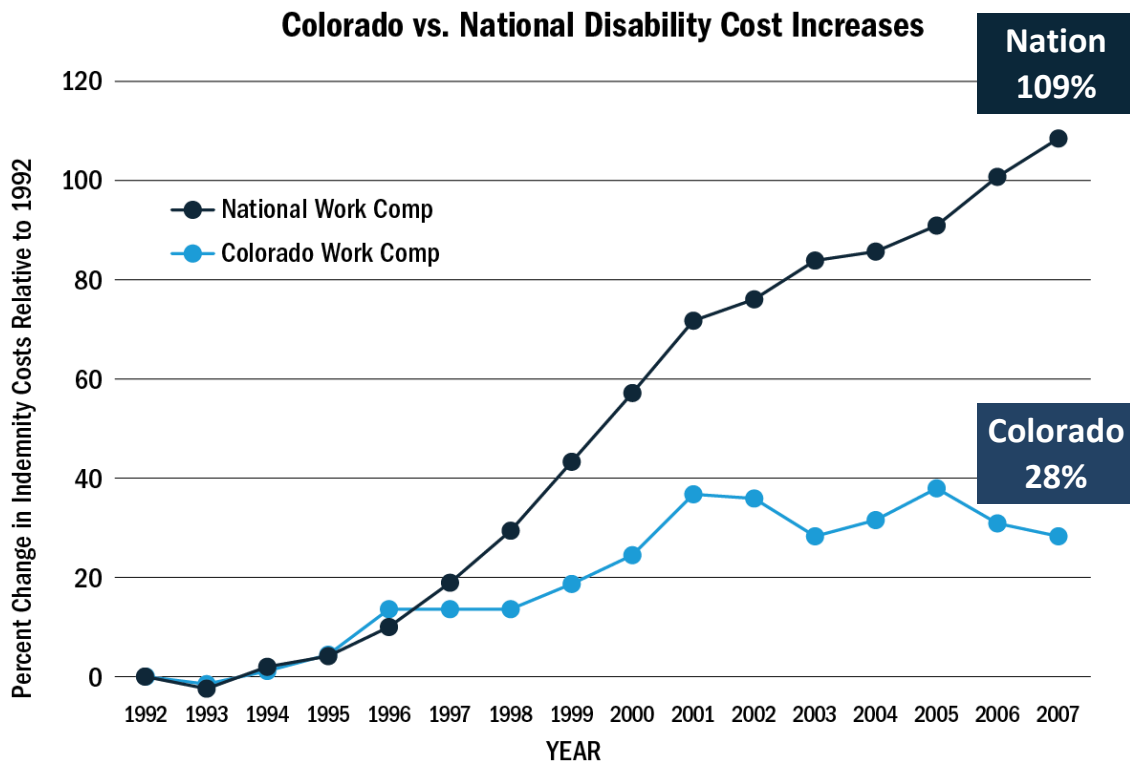


Adapted from Bruns, D., Mueller, K., & Warren, P. A. (2012). Biopsychosocial law, health care reform, and the control of medical inflation in Colorado. *Rehabilitation Psychology, 57*(2), 81–97. Copyright © 2012. American Psychological Association. All rights reserved.

Is Interdisciplinary Care More Expensive?

- Adding psychological treatments did not increase costs as feared. To the contrary, interdisciplinary care was associated with reduced costs.
- Compared to medical treatments, psychological treatments are very low risk, have a level of adverse events approaching zero, are often as effective as medical treatments, and are generally less expensive.





Using Disability Costs As An Outcome Proxy, Interdisciplinary Care Appeared to Reduce Impairment and Disability

This study used cost as a proxy for outcome, as costs were primarily determined by:

- amount of disability pay (cost here was a function of length of disability and receiving wage reimbursement) and
- amount of financial settlement (cost here was a function of degree of permanent impairment at the end of treatment).

Lower cost here suggested shorter term of disability and/or less impairment at end of treatment.

Adapted from Bruns, D., Mueller, K., & Warren, P. A. (2012). Biopsychosocial law, health care reform, and the control of medical inflation in Colorado. *Rehabilitation Psychology*, 57(2), 81–97. Copyright © 2012. American Psychological Association. All rights reserved.



**Estimated Colorado WC
cost savings in 2007 alone:**

\$859,000,000

Better care – Less money

Bruns, Mueller and Warren, 2012



**Opioid
Response
Network**

Conclusions

- ✧ Pain is a complex biopsychosocial condition
- ✧ Acute pain can evolve into a chronic primary pain condition, which is an ICD-11 nociplastic disease
- ✧ Effective treatment of chronic pain can reverse nociplasticity (Seminowicz, 2011)
- ✧ Interdisciplinary care is both better care, and economically feasible (Bruns, Mueller and Warren, 2012)



Conclusions

✧ The challenges are

- Develop better models of pain treatment that are less reliant on opioids
- Educate patients about this new way of thinking about pain
- Solve reimbursement problems
- Training the workforce in new interdisciplinary models of pain treatment



Questions?



Opioid
Response
Network

Bibliography

- ✦ Ahmad, F. B., Rossen, L. M., & Sutton, P. (2023). Provisional drug overdose death counts. National Center for Health Statistics. Retrieved from <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>
- ✦ Apkarian, A. V., & Scholz, J. (2006). Shared mechanisms between chronic pain and neurodegenerative disease. *Drug Discovery Today: Disease Mechanisms*, 3(3), 319–326. <https://doi.org/10.1016/j.ddmec.2006.09.006>
- ✦ Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. *Progress in neurobiology*, 87(2), 81–97. <https://doi.org/10.1016/j.pneurobio.2008.09.018>
- ✦ Barad, M. J., Ueno, T., Younger, J., Chatterjee, N., & Mackey, S. (2014). Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. *The journal of pain*, 15(2), 197–203. <https://doi.org/10.1016/j.jpain.2013.10.011>
- ✦ Basbaum, A. & Jessell, T. (2013). The perception of pain. In: *Principles of Neuroscience*, edited by E. Kandel, J. Schwartz, T. Jessell, S. Siegelbaum and A. Hudspeth. McGraw Hill
- ✦ Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell*, 139(2), 267–284. <https://doi.org/10.1016/j.cell.2009.09.028>
- ✦ Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuirheartaigh, R., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Science translational medicine*, 3(70), 70ra14. <https://doi.org/10.1126/scitranslmed.3001244>
- ✦ Bruns, D., Mueller, K., & Warren, P. A. (2012). Biopsychosocial law, health care reform, and the control of medical inflation in Colorado. *Rehabilitation Psychology*, 57(2), 81–97. <https://doi.org/10.1037/a0028623>



Bibliography

- ✦ Centers for Disease Control and Prevention. (2021, November 10). U.S. opioid dispensing rate maps. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Retrieved from <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>
- ✦ Chiu, I. M., Heesters, B. A., Ghasemlou, N., Von Hehn, C. A., Zhao, F., Tran, J., Wainger, B., Strominger, A., Muralidharan, S., Horswill, A. R., Bubeck Wardenburg, J., Hwang, S. W., Carroll, M. C., & Woolf, C. J. (2013). Bacteria activate sensory neurons that modulate pain and inflammation. *Nature*, 501(7465), 52–57. <https://doi.org/10.1038/nature12479M>.
- ✦ Chiu, I. M., von Hehn, C. A., & Woolf, C. J. (2012). Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nature neuroscience*, 15(8), 1063–1067. <https://doi.org/10.1038/nn.3144>
- ✦ Dahlhamer, J. M., Connor, E. M., Bose, J., Lucas, J. L., & Zelaya, C. E. (2021). Prescription Opioid Use Among Adults With Chronic Pain: United States, 2019. *National health statistics reports*, (162), 1–9.
- ✦ de Lange, F. P., Koers, A., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Meer, J. W., & Toni, I. (2008). Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain: a journal of neurology*, 131(Pt 8), 2172–2180. <https://doi.org/10.1093/brain/awn140>
- ✦ Derbyshire, S. W., Whalley, M. G., Stenger, V. A., & Oakley, D. A. (2004). Cerebral activation during hypnotically induced and imagined pain. *NeuroImage*, 23(1), 392–401. <https://doi.org/10.1016/j.neuroimage.2004.04.033>
- ✦ Descartes, R., Clerselier, C., La Forge, L., Schuyl, F. (1664). *L'homme et un Traitté de la ormotion du Foetus du Mesme Auteur*. Paris: Charles Angot.
- ✦ Eisenberger, N. I., & Lieberman, M. D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in cognitive sciences*, 8(7), 294–300. <https://doi.org/10.1016/j.tics.2004.05.010>



Bibliography

- ✦ Ellis, A., & Bennett, D. L. (2013). Neuroinflammation and the generation of neuropathic pain. *British journal of anaesthesia*, 111(1), 26–37. <https://doi.org/10.1093/bja/aet128>
- ✦ FDA, 2019. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. *Drug Safety Communications*.
- ✦ Gaskin, D. J., & Richard, P. (2012). The economic costs of pain in the United States. *The journal of pain : official journal of the American Pain Society*, 13(8), 715-724. doi:10.1016/j.jpain.2012.03.009
- ✦ Geuter, S., & Büchel, C. (2013). Facilitation of pain in the human spinal cord by nocebo treatment. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 33(34), 13784–13790. <https://doi.org/10.1523/JNEUROSCI.2191-13.2013>
- ✦ Grace, P. M., Rolan, P. E., & Hutchinson, M. R. (2011). Peripheral immune contributions to the maintenance of central glial activation underlying neuropathic pain. *Brain, behavior, and immunity*, 25(7), 1322–1332. <https://doi.org/10.1016/j.bbi.2011.04.003>
- ✦ Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., & Clauw, D. J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain : a journal of neurology*, 127(Pt 4), 835–843. <https://doi.org/10.1093/brain/awh098>
- ✦ Hallvik, S. E., El Ibrahim, S., Johnston, K., Geddes, J., Leichtling, G., Korthuis, P. T., & Hartung, D. M. (2022). Patient outcomes after opioid dose reduction among patients with chronic opioid therapy. *Pain*, 163(1), 83–90. <https://doi.org/10.1097/j.pain.0000000000002298>
- ✦ Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., Schnitzer, T. J., & Apkarian, A. V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain: a journal of neurology*, 136(Pt 9), 2751–2768. <https://doi.org/10.1093/brain/awt211>



Bibliography

- ✧ Inoue, K., & Tsuda, M. (2018). Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. *Nature reviews. Neuroscience*, 19(3), 138–152. <https://doi.org/10.1038/nrn.2018.2>
- ✧ Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. National Academies Press (US).
- ✧ Jensen M. P. (2010). A neuropsychological model of pain: research and clinical implications. *The journal of pain*, 11(1), 2–12. <https://doi.org/10.1016/j.jpain.2009.05.001>
- ✧ Jensen, K. B., Kosek, E., Wicksell, R., Kemani, M., Olsson, G., Merle, J. V., Kadetoff, D., & Ingvar, M. (2012). Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. *Pain*, 153(7), 1495–1503. <https://doi.org/10.1016/j.pain.2012.04.010>
- ✧ Jepma, M., Koban, L., van Doorn, J., Jones, M., & Wager, T. D. (2018). Behavioural and neural evidence for self-reinforcing expectancy effects on pain. *Nature human behaviour*, 2(11), 838–855. <https://doi.org/10.1038/s41562-018-0455-8>
- ✧ Ji, R. R., Nackley, A., Huh, Y., Terrando, N., & Maixner, W. (2018). Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. *Anesthesiology*, 129(2), 343–366. <https://doi.org/10.1097/ALN.0000000000002130>
- ✧ Ji, R. R., Xu, Z. Z., & Gao, Y. J. (2014). Emerging targets in neuroinflammation-driven chronic pain. *Nature reviews. Drug discovery*, 13(7), 533–548. <https://doi.org/10.1038/nrd4334>
- ✧ Liu, X., Li, L., Tang, F., Wu, S., & Hu, Y. (2014). Memory impairment in chronic pain patients and the related neuropsychological mechanisms: a review. *Acta neuropsychiatrica*, 26(4), 195–201. <https://doi.org/10.1017/neu.2013.47>



Bibliography

- ✦ Lobanov, O. V., Zeidan, F., McHaffie, J. G., Kraft, R. A., & Coghill, R. C. (2014). From cue to meaning: brain mechanisms supporting the construction of expectations of pain. *Pain*, 155(1), 129–136. <https://doi.org/10.1016/j.pain.2013.09.014>
- ✦ Lopresti A. L. (2017). Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. *The Australian and New Zealand journal of psychiatry*, 51(6), 565–582. <https://doi.org/10.1177/0004867417701996>
- ✦ Maixner, W., Fillingim, R. B., Williams, D. A., Smith, S. B., & Slade, G. D. (2016). Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. *The journal of pain*, 17(9 Suppl), T93–T107. <https://doi.org/10.1016/j.jpain.2016.06.002>
- ✦ Mansour, A. R., Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2014). Chronic pain: the role of learning and brain plasticity. *Restorative neurology and neuroscience*, 32(1), 129–139. <https://doi.org/10.3233/RNN-139003>
- ✦ Mäntyselkä, P., Kumpusalo, E., Ahonen, R., Kumpusalo, A., Kauhanen, J., Viinamäki, H., Halonen, P., & Takala, J. (2001). Pain as a reason to visit the doctor: a study in Finnish primary health care. *Pain*, 89(2-3), 175–180. [https://doi.org/10.1016/s0304-3959\(00\)00361-4](https://doi.org/10.1016/s0304-3959(00)00361-4)
- ✦ Matsuda, M., Huh, Y., & Ji, R. R. (2019). Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *Journal of anesthesia*, 33(1), 131–139. <https://doi.org/10.1007/s00540-018-2579-4>
- ✦ May A. (2008). Chronic pain may change the structure of the brain. *Pain*, 137(1), 7–15. <https://doi.org/10.1016/j.pain.2008.02.034>
- ✦ Melzack R. (2005). Evolution of the neuromatrix theory of pain. *The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. Pain practice : the official journal of World Institute of Pain*, 5(2), 85–94. <https://doi.org/10.1111/j.1533-2500.2005.05203.x>
- ✦ Melzack, R., & Katz, J. (2006). Pain in the 21st Century: The Neuromatrix and Beyond. In G. Young, A. W. Kane, & K. Nicholson (Eds.), *Psychological knowledge in court: PTSD, pain, and TBI* (pp. 129–148). Springer Science + Business Media. https://doi.org/10.1007/0-387-25610-5_7



Bibliography

- ✦ Mezei, L., Murinson, B. B., & Johns Hopkins Pain Curriculum Development Team (2011). Pain education in North American medical schools. *The journal of pain*, 12(12), 1199–1208. <https://doi.org/10.1016/j.jpain.2011.06.006>
- ✦ Mischkowski, D., Crocker, J., & Way, B. M. (2016). From painkiller to empathy killer: acetaminophen (paracetamol) reduces empathy for pain. *Social cognitive and affective neuroscience*, 11(9), 1345–1353. <https://doi.org/10.1093/scan/nsw057>
- ✦ Mischkowski, D., Crocker, J., & Way, B. M. (2019). A Social Analgesic? Acetaminophen (Paracetamol) Reduces Positive Empathy. *Frontiers in psychology*, 10, 538. <https://doi.org/10.3389/fpsyg.2019.00538>
- ✦ Oliva, E. M., Bowe, T., Manhapra, A., Kertesz, S., Hah, J. M., Henderson, P., Robinson, A., Paik, M., Sandbrink, F., Gordon, A. J., & Trafton, J. A. (2020). Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ (Clinical research ed.)*, 368, m283. <https://doi.org/10.1136/bmj.m283>
- ✦ Oliva, E. M., Bowe, T., Manhapra, A., Kertesz, S., Hah, J. M., Henderson, P., Robinson, A., Paik, M., Sandbrink, F., Gordon, A. J., & Trafton, J. A. (2020). Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ (Clinical research ed.)*, 368, m283. <https://doi.org/10.1136/bmj.m283>
- ✦ Ongaro, G., & Kaptchuk, T. J. (2019). Symptom perception, placebo effects, and the Bayesian brain. *Pain*, 160(1), 1–4. <https://doi.org/10.1097/j.pain.0000000000001367>
- ✦ Opioid settlement tracker, 2023. Global settlement tracker. <https://www.opioidsettlementtracker.com>
- ✦ O'Toole, M. S., Bovbjerg, D. H., Renna, M. E., Lekander, M., Mennin, D. S., & Zachariae, R. (2018). Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis. *Brain, behavior, and immunity*, 74, 68–78. <https://doi.org/10.1016/j.bbi.2018.04.005>
- ✦ Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X. J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, 161(9), 1976–1982. <https://doi.org/10.1097/j.pain.0000000000001939>



Bibliography

- ✦ Rivat, C., & Ballantyne, J. (2016). The dark side of opioids in pain management: basic science explains clinical observation. *Pain reports*, 1(2), e570. <https://doi.org/10.1097/PR9.0000000000000570>
- ✦ Rome, H. P., Jr, & Rome, J. D. (2000). Limbically augmented pain syndrome (LAPS): kindling, corticolimbic sensitization, and the convergence of affective and sensory symptoms in chronic pain disorders. *Pain medicine (Malden, Mass.)*, 1(1), 7-23. <https://doi.org/10.1046/j.1526-4637.2000.99105.x>
- ✦ Santo, L., & Schappert, S.M. (2022). Opioids prescribed to adults at discharge from emergency departments: United States, 2017–2020. *NCHS Data Brief*, no 461. Hyattsville, MD: National Center for Health Statistics. DOI: <https://dx.doi.org/10.15620/cdc:122879>
- ✦ Seminowicz, D. A., Wideman, T. H., Naso, L., Hatami-Khorousahi, Z., Fallatah, S., Ware, M. A., Jarzem, P., Bushnell, M. C., Shir, Y., Ouellet, J. A., & Stone, L. S. (2011). Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(20), 7540–7550. <https://doi.org/10.1523/JNEUROSCI.5280-10.2011>
- ✦ Shipton, E., Steketee, C., & Visser, E. (2023). The Pain Medicine Curriculum Framework-structured integration of pain medicine education into the medical curriculum. *Frontiers in pain research (Lausanne, Switzerland)*, 3, 1057114. <https://doi.org/10.3389/fpain.2022.1057114>
- ✦ Slavich, G. M., Shields, G. S., Deal, B. D., Gregory, A., & Toussaint, L. L. (2019). Alleviating Social Pain: A Double-Blind, Randomized, Placebo-Controlled Trial of Forgiveness and Acetaminophen. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*, 53(12), 1045–1054. <https://doi.org/10.1093/abm/kaz015>
- ✦ Soravia, L. M., Orosz, A., Schwab, S., Nakataki, M., Wiest, R., & Federspiel, A. (2016). CBT reduces CBF: cognitive-behavioral therapy reduces cerebral blood flow in fear-relevant brain regions in spider phobia. *Brain and behavior*, 6(9), e00510. <https://doi.org/10.1002/brb3.510>
- ✦ Staud, R., Robinson, M. E., & Price, D. D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *Journal of Pain*, 8(11), 893–901. <https://doi.org/10.1016/j.jpain.2007.06.006>



Bibliography

- ✦ Stephens, R., Atkins, J., & Kingston, A. (2009). Swearing as a response to pain. *Neuroreport*, 20(12), 1056–1060. <https://doi.org/10.1097/WNR.0b013e32832e64b1>
- ✦ Treede R. D. (2016). Gain control mechanisms in the nociceptive system. *Pain*, 157(6), 1199–1204. <https://doi.org/10.1097/j.pain.0000000000000499>
- ✦ U.S. Department of Health and Human Services (2016). National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain. Washington, DC: Department of Health and Human Services. Retrieved from https://www.iprcc.nih.gov/sites/default/files/documents/NationalPainStrategy_508C.pdf
- ✦ U.S. Department of Health and Human Services. (2019, May). Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. Retrieved from <https://www.hhs.gov/ash/advisory-committees/pain/index.html>
- ✦ U.S. Department of Health and Human Services. (2019, May). Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. Retrieved from <https://www.hhs.gov/ash/advisory-committees/pain/index.html>
- ✦ VanElzaker, M. B., Brumfield, S. A., & Lara Mejia, P. S. (2019). Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods. *Frontiers in neurology*, 9, 1033. <https://doi.org/10.3389/fneur.2018.01033>
- ✦ Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*, 156(4), 569–576. <https://doi.org/10.1097/01.j.pain.0000460357.01998.f1>
- ✦ WHO, 2023. WHO Model List of Essential Medicines. Geneva, World Health Organization.



Bibliography

- ✦ Willis, K. & Elmer, S. (2007). *Society, Culture and Health: an Introduction to Sociology for Nurses*. Sydney, Australia: Oxford University Press. ISBN 9780195559071.
- ✦ Willis, W. D. (2004). *Sensory mechanisms of the spinal cord (vol 1 & 2) 3rd edn*. Kluwer Academic/Plenum Publishers.
- ✦ Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science (New York, N.Y.)*, 288(5472), 1765–1769. <https://doi.org/10.1126/science.288.5472.1765>
- ✦ Xanthos, D. N., & Sandkühler, J. (2014). Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nature reviews. Neuroscience*, 15(1), 43–53. <https://doi.org/10.1038/nrn3617>
- ✦ Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain mechanisms supporting the modulation of pain by mindfulness meditation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(14), 5540–5548. <https://doi.org/10.1523/JNEUROSCI.5791-10.2011>

