U.S. Department of Health & Human Services • National Institutes of Health

National Center for Complementary and Integrative Health

Beyond opioids—Engaging endogenous pain modulation in the brain

M. Catherine Bushnell

Disclosures

- I have nothing to disclose
- The views presented here are mine and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the US Department of Health and Human Services

The opioid crisis has raised the question of how can we treat pain without taking drugs

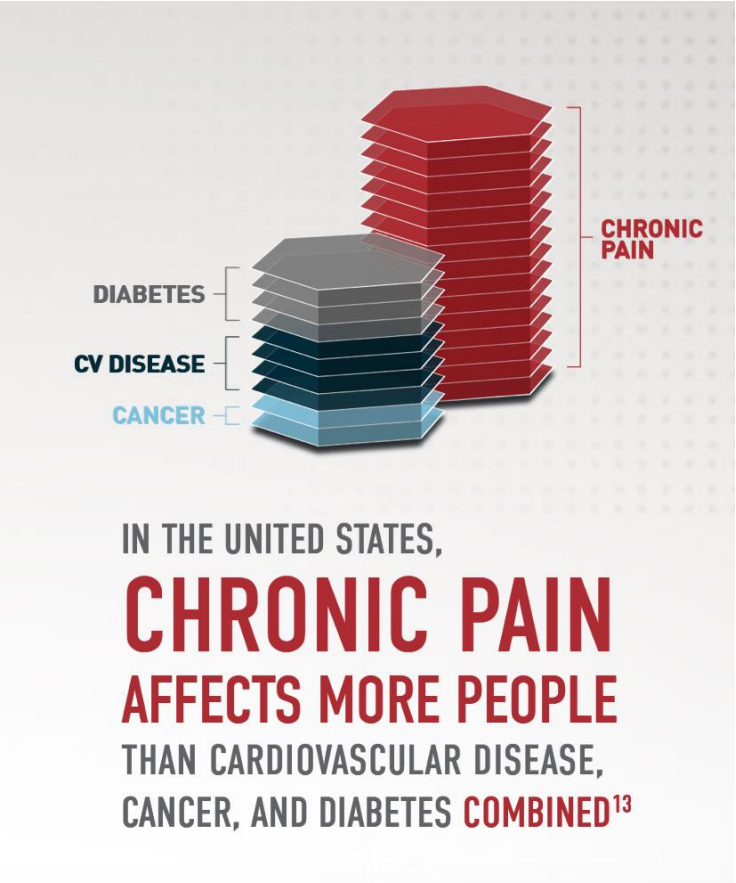
- At the National Center for Complementary and Integrative Health, we have a research program that examines how drugs work in the brain to reduce pain and how we can engage those systems without drugs.
- Today, I'll talk about how pain is processed in the brain
- How systems in the brain work to dampen or augment pain
- How chronic pain can change the brain
- Some lifestyle choices that can help reduce pain

Pain can be acute or chronic

We know how to treat acute pain, but we need to figure out better ways to manage chronic pain

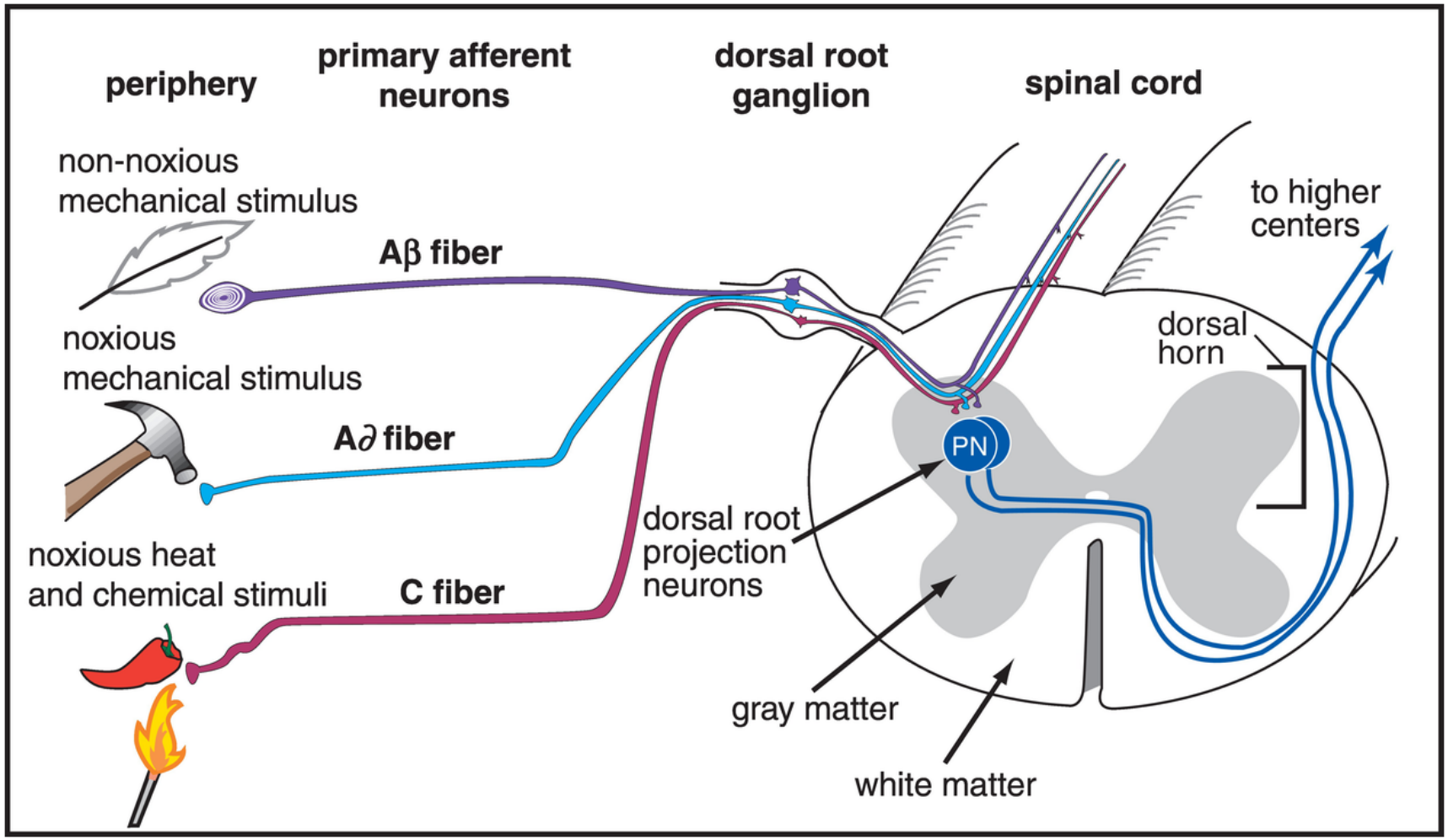
We need acute pain.

Chronic pain is a major problem

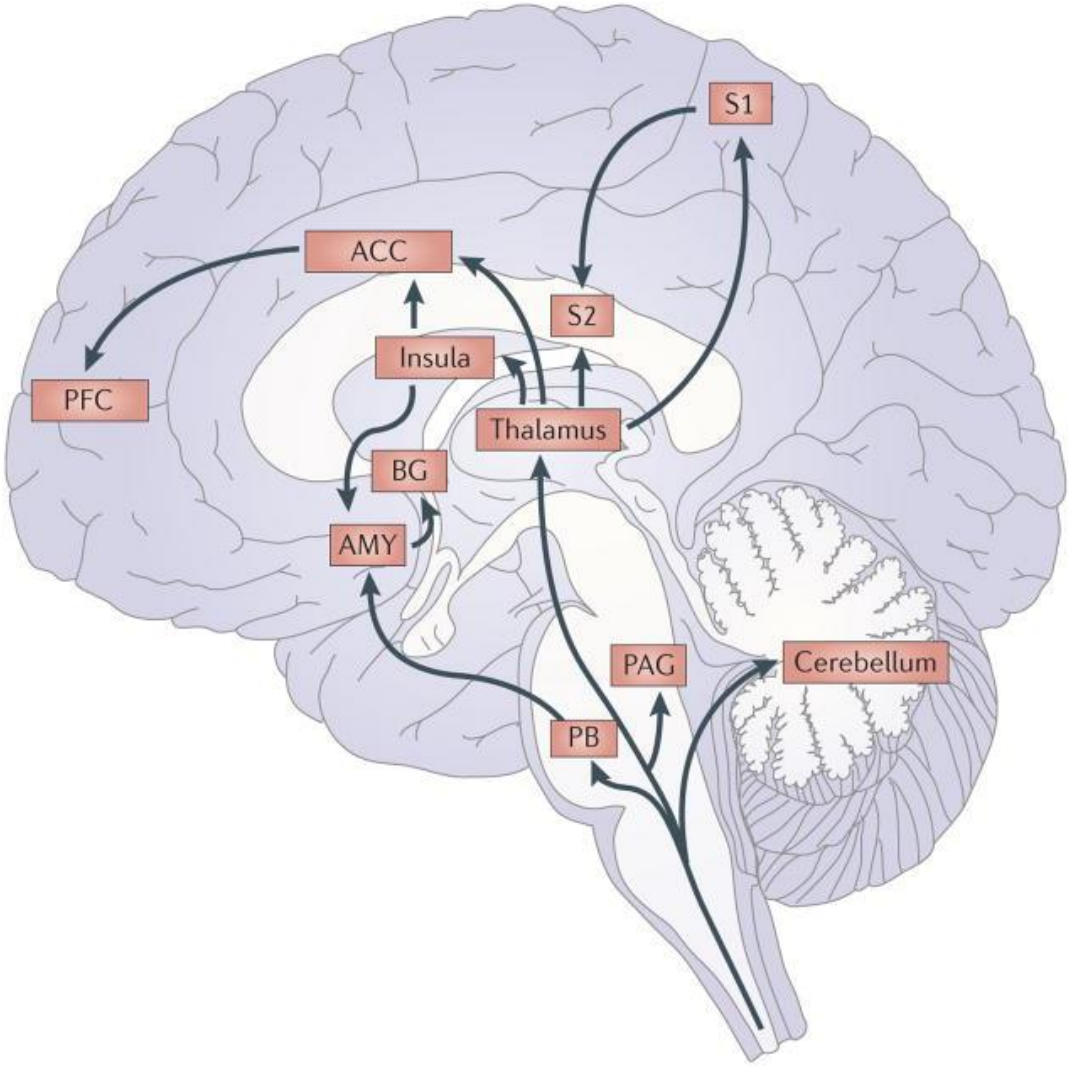


Dahlhamer et al, CDC Report 2018

So, what do we know about pain?



Multiple ascending pain pathways in brain



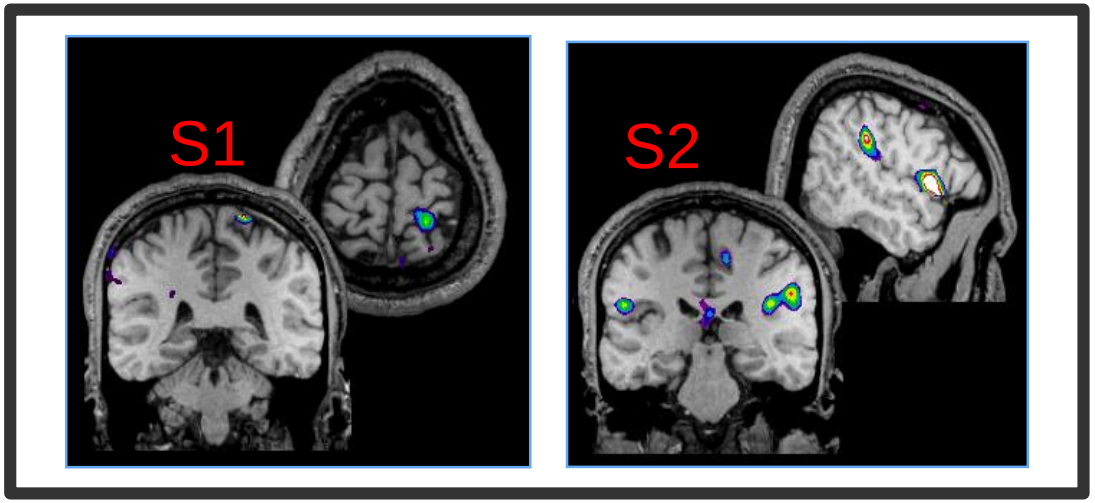
Bushnell et al. *Nat. Neurosci*. 2013

Multiple pain pathways correspond to the complexity of the pain experience

Pain sensation
Intensity
Quality--pricking, burning, aching)

Pain emotion
(unpleasant; suffering)

In the cerebral cortex, pain sensation and pain emotion are processed differently



MRI to detect brain activation correlated with pain sensation and unpleasantness

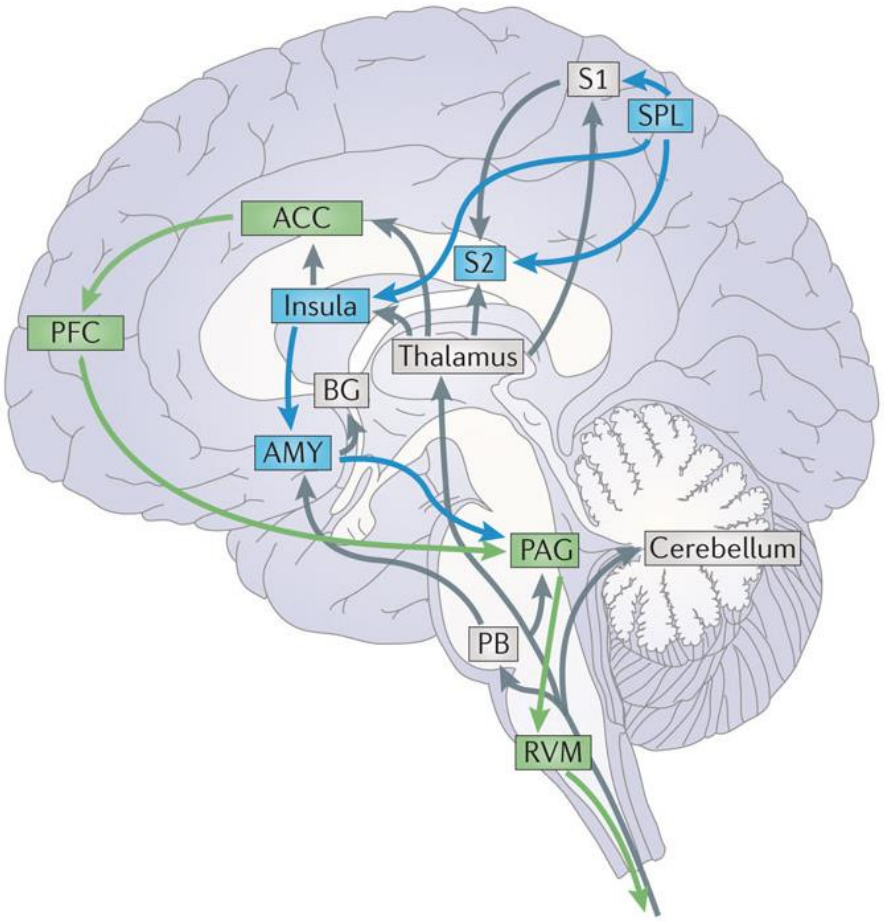
Pain sensation in somatosensory cortices

Pain emotions in emotional regions

People react very differently to the same painful stimulus

What accounts for individual differences in pain perception?

There are multiple descending pathways in brain that can dampen or enhance pain information

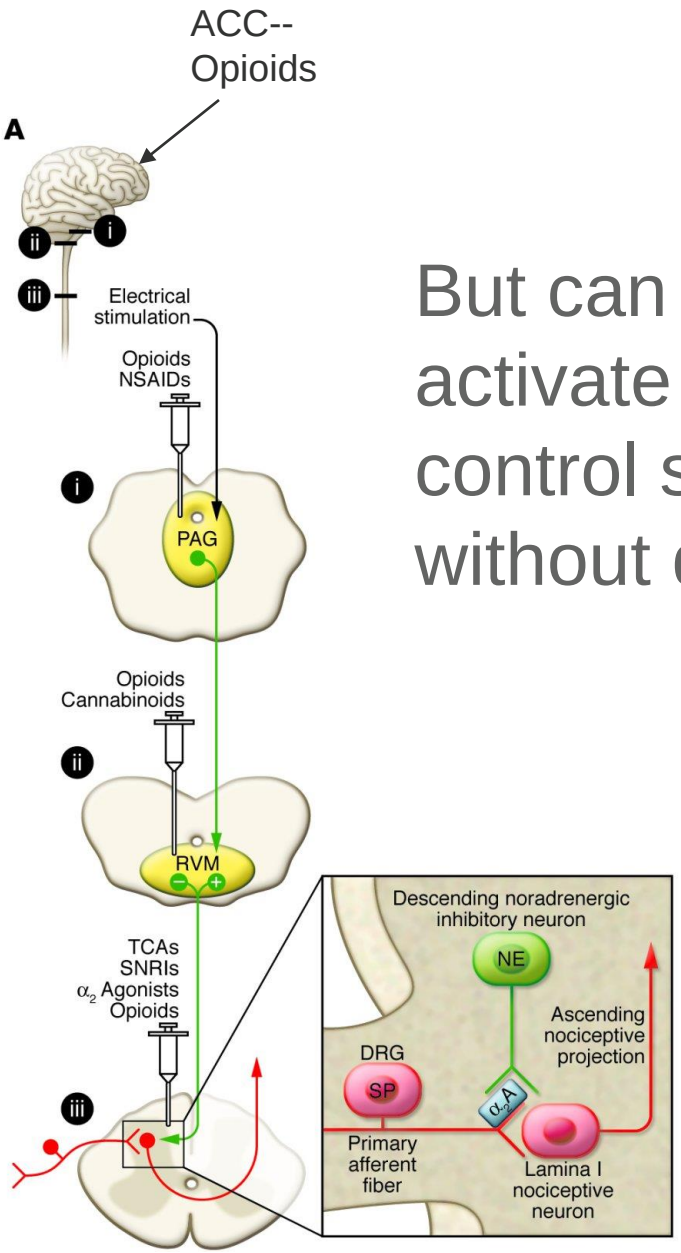


Nature Reviews | Neuroscience

Different people may have differing abilities to engage these systems.

Bushnell et al. *Nat. Neurosci*. 2013

Analgesic drugs, including opiates, work through activation of these pain modulation systems



But can we activate these control systems without drugs?

Ossipov et al, J. Clin. Investigation, 2010

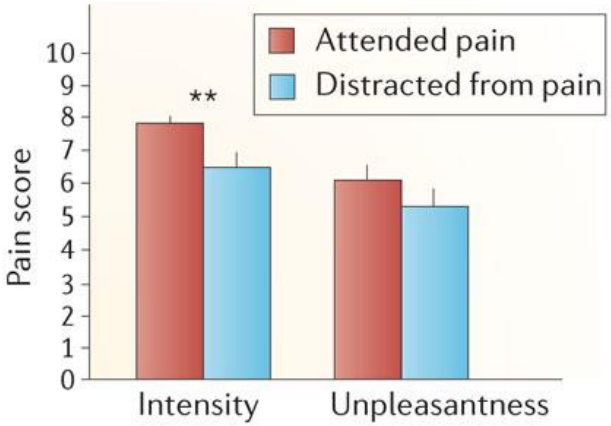
Psychological state can increase or decrease pain via descending pathways in the brain

Emotions

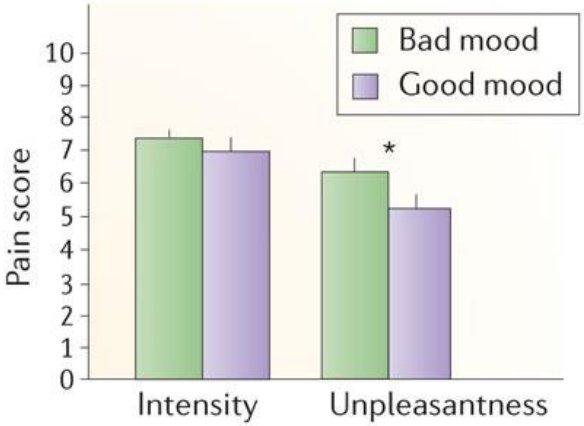
Attention/Distraction

Attention and emotions change different aspects of pain

Attentional modulation



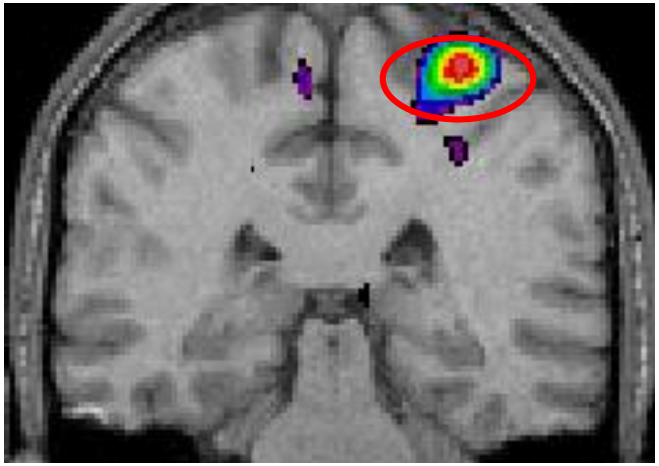
Emotional modulation



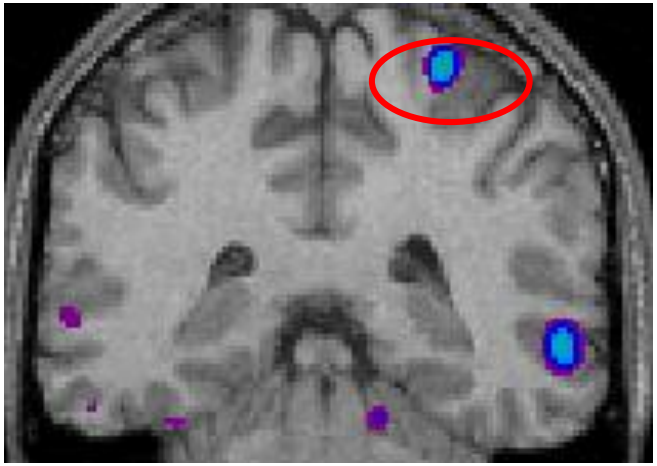
Bushnell et al. *Nat. Neurosci*. 2013

Attention Modulates Sensory pathways

Somatosensory cortex



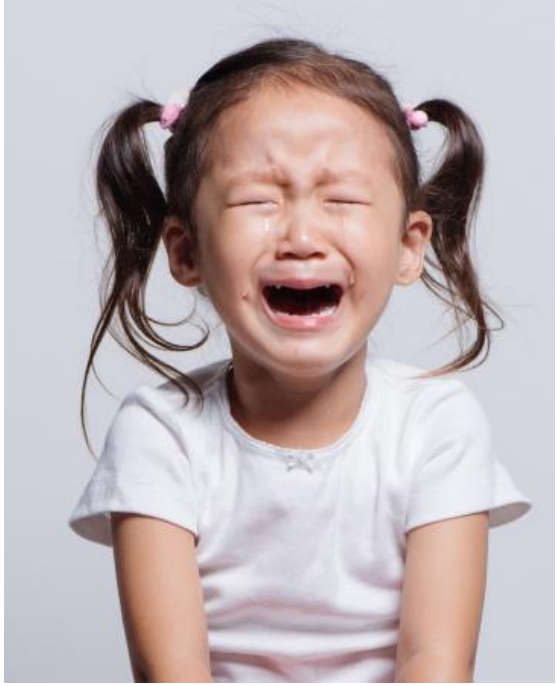
Attention to pain



Distraction from pain

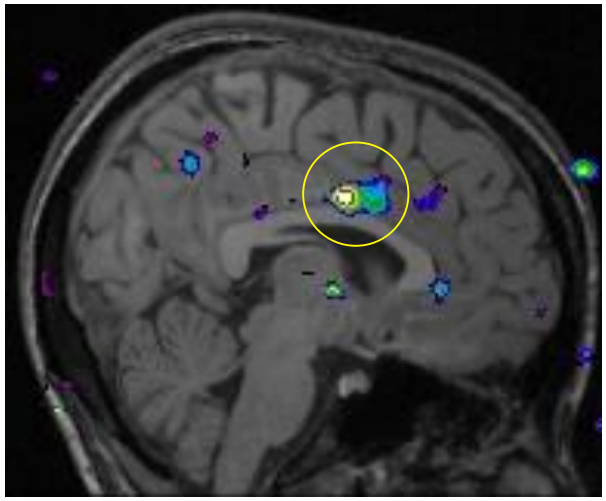
Bushnell et al. 1999

Mood alters emotional pathways

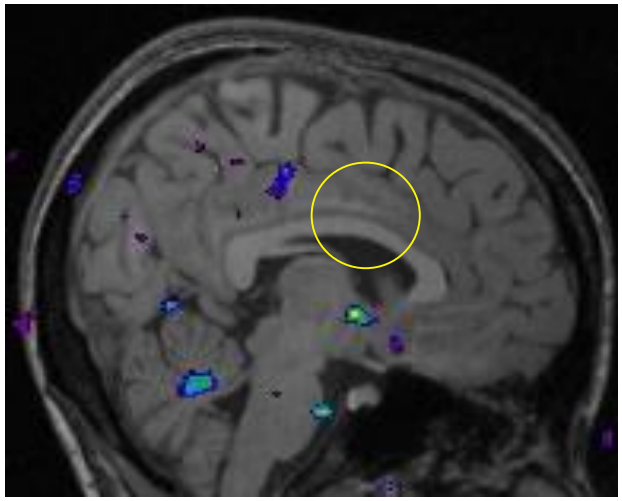


Villemure & Bushnell 2009

Anterior cingulate cortex



Bad mood + Pain

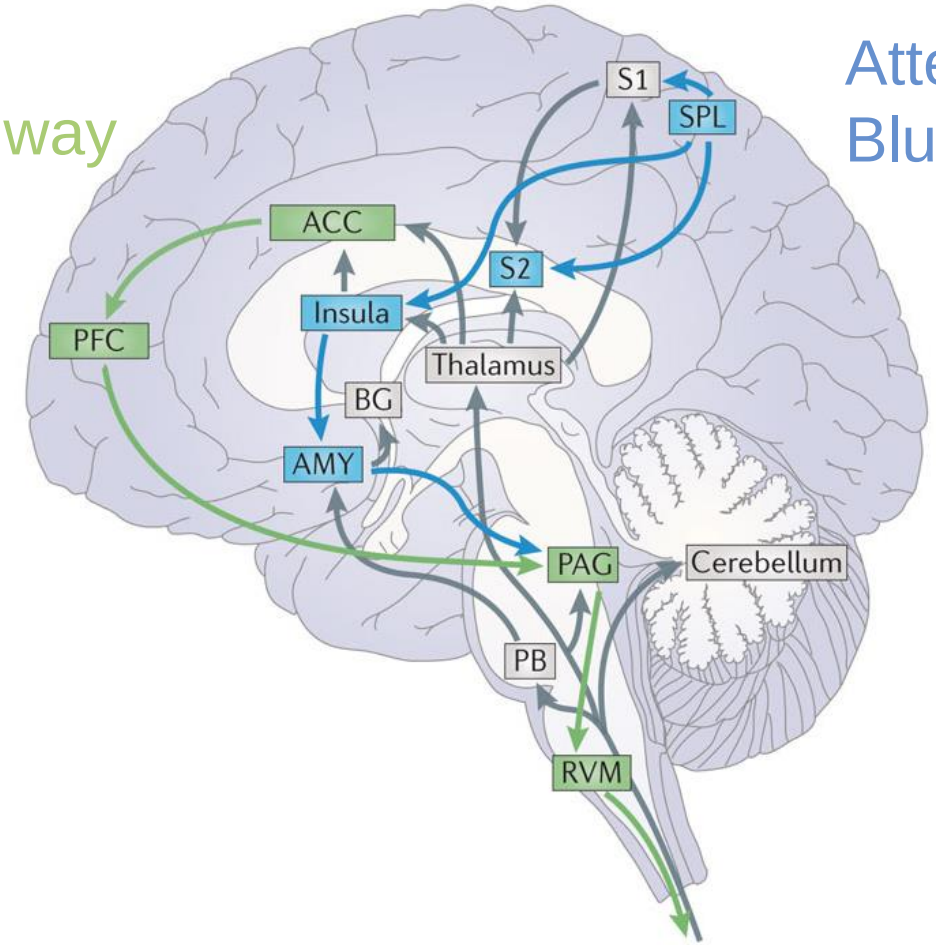


Good mood + Pain

Attention and emotions activate different modulatory circuitry in the brain

Emotions:
Green pathway

Attention:
Blue pathway

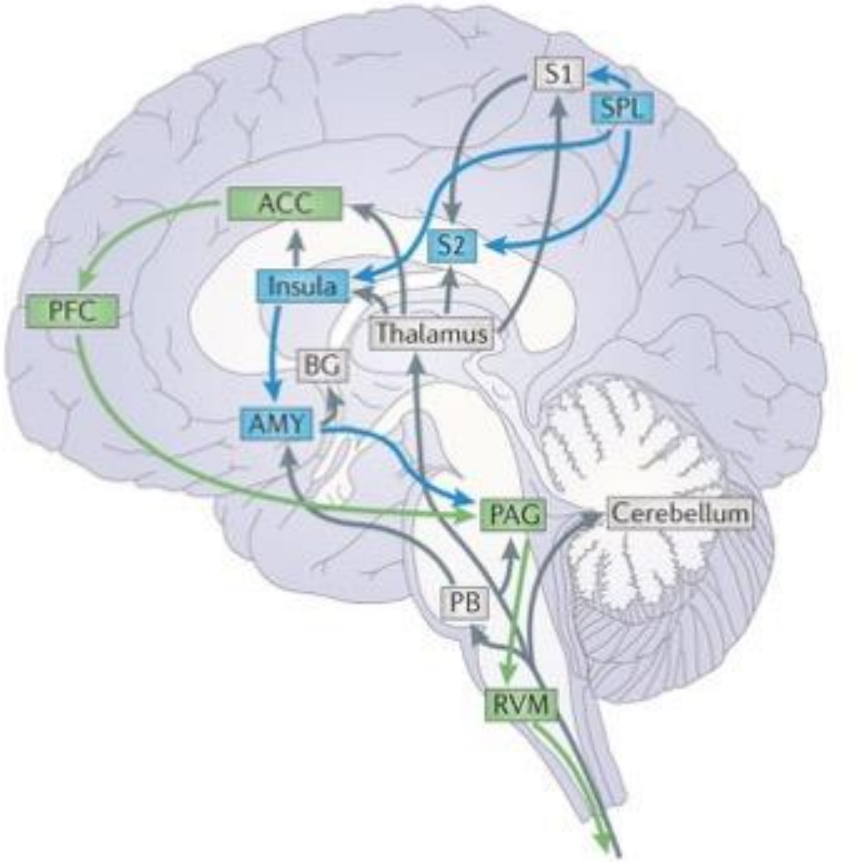


Bushnell et al. *Nat. Neurosci*. 2013

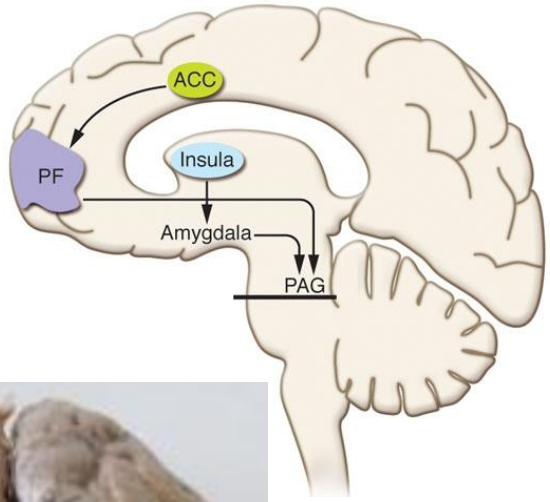
Nature Reviews | Neuroscience

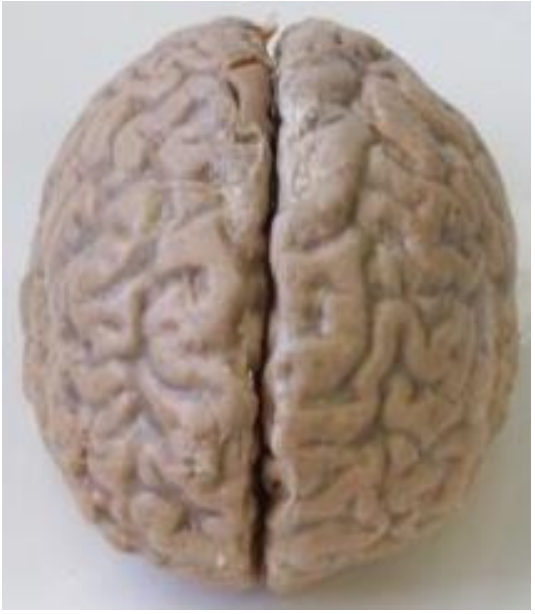
How does chronic pain affect endogenous pain regulation?

Descending pain-modulatory circuits disrupted in chronic pain patients



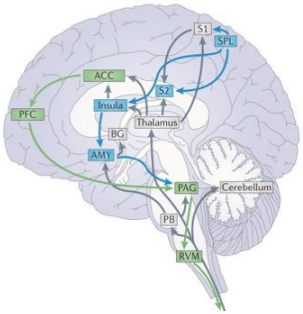
Nature Reviews | Neuroscience

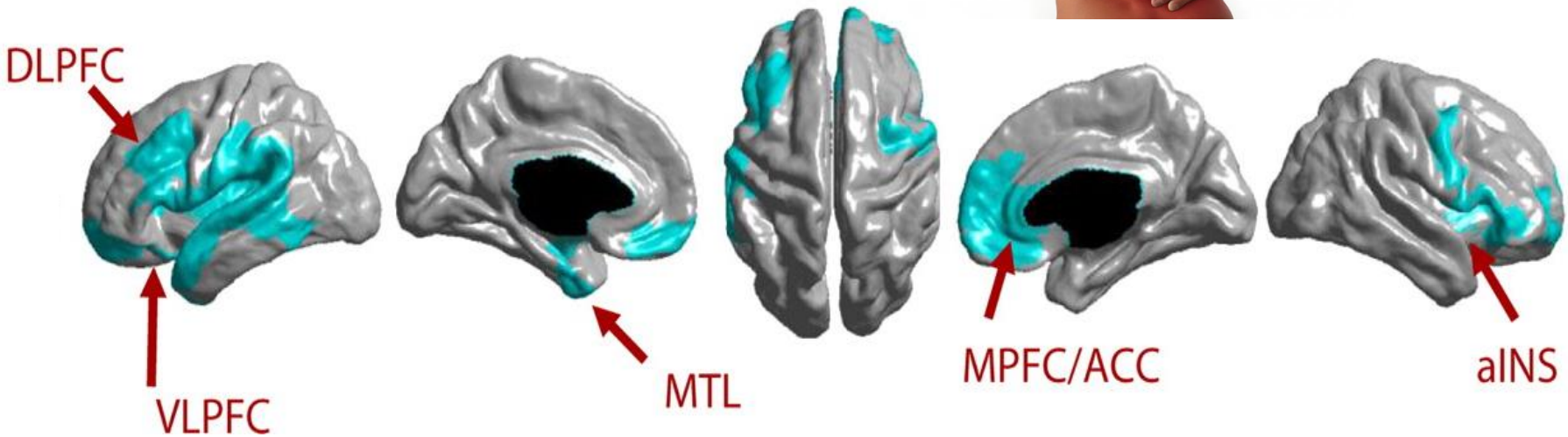




Chronic pain patients have reductions in brain gray matter, particularly in regions involved in pain modulation

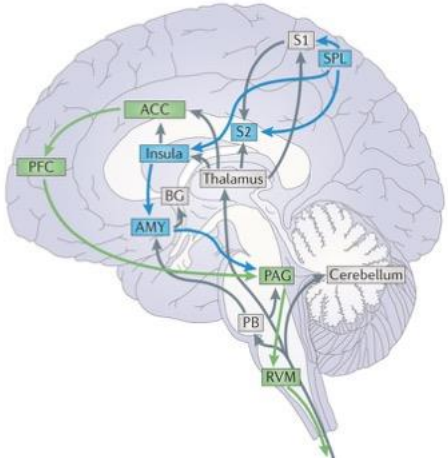
Chronic back pain patients have less gray matter in pain modulation regions of brain

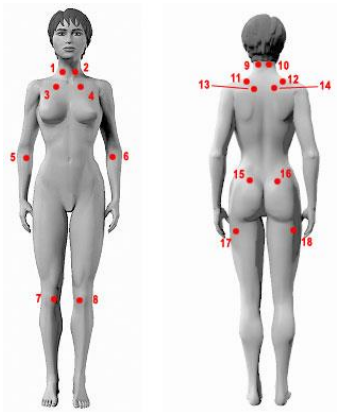


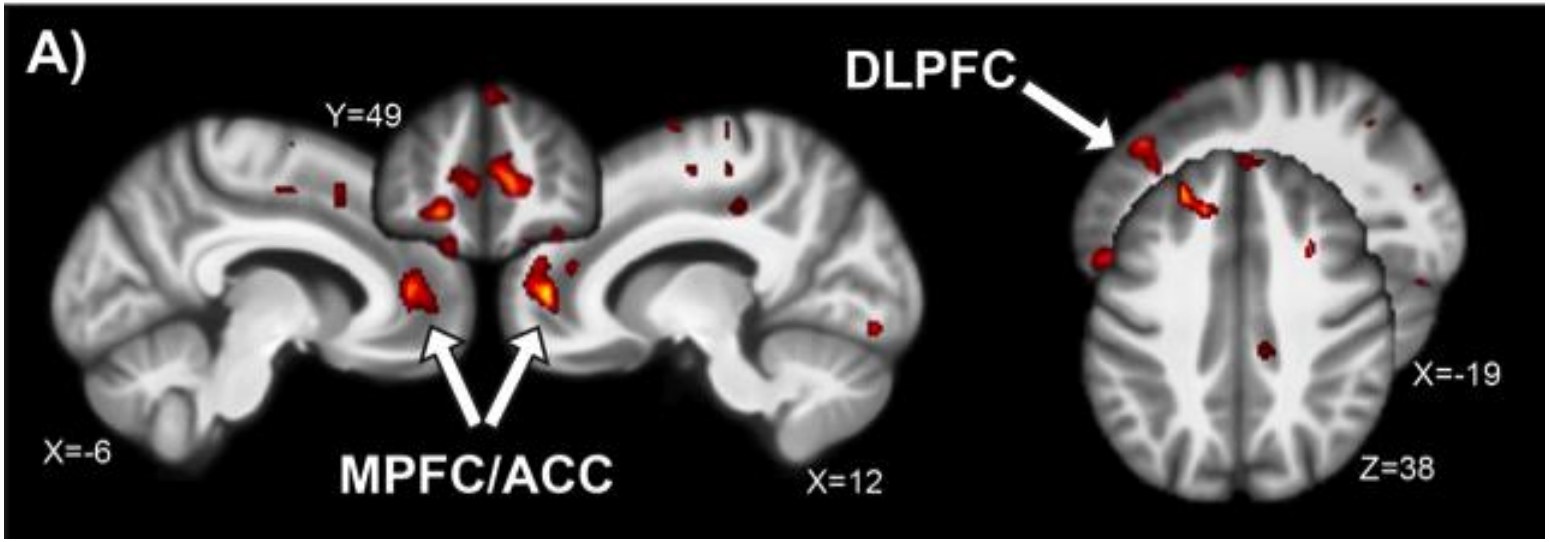


Seminowicz, Stone et al. *J. Neurosci*. 2011

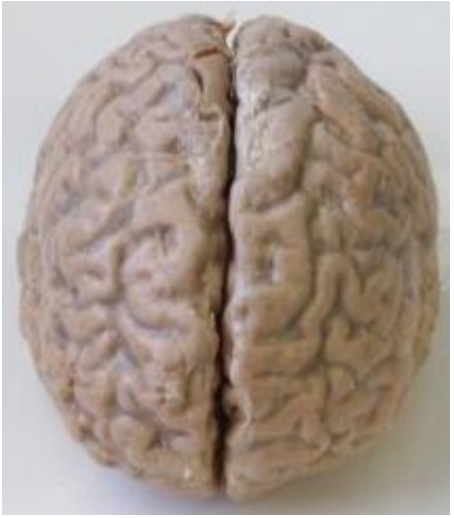
Similar gray matter reduction in fibromyalgia patients

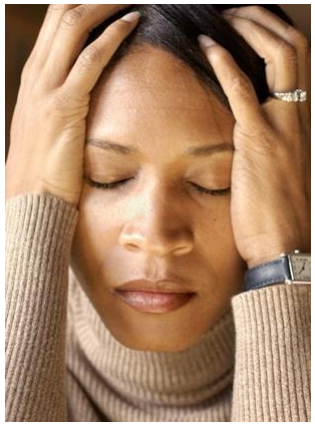






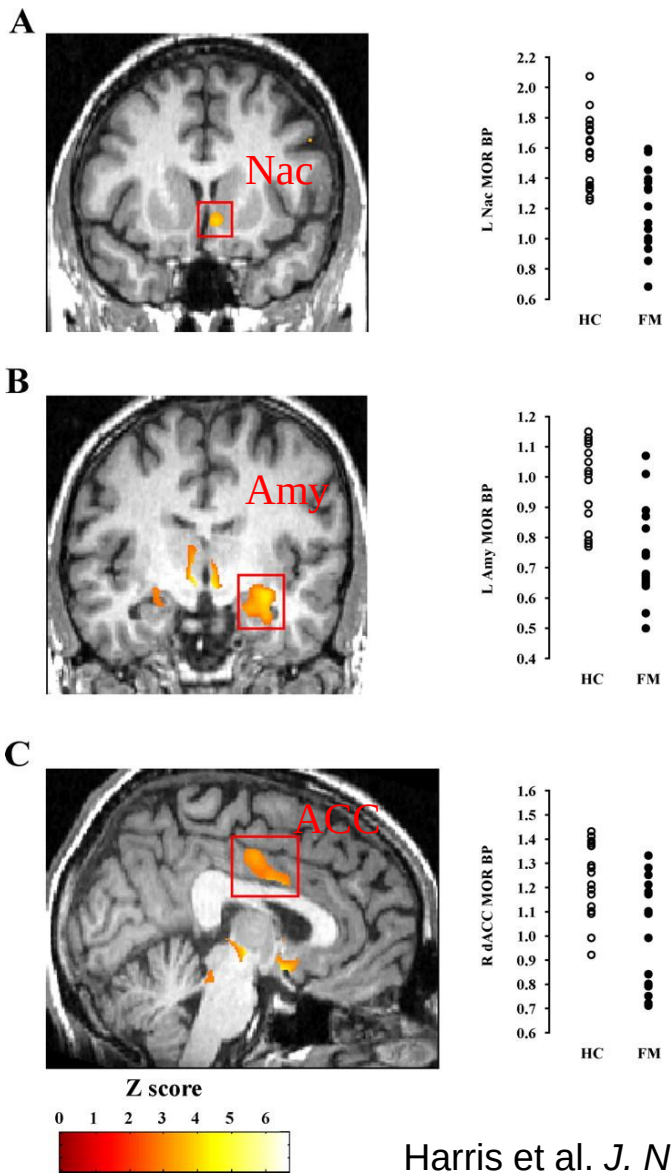
Ceko, Schweinhardt et al. *Neuroimage: Clinical,* 2013





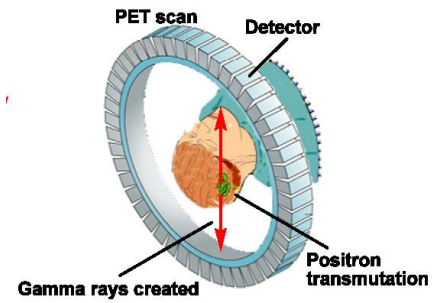
Chronic pain alters opioid receptors in the brain

Fibromyalgia patients have reduced opioid binding



Harris et al. *J. Neurosci.* 2007

Positron Emission Tomography



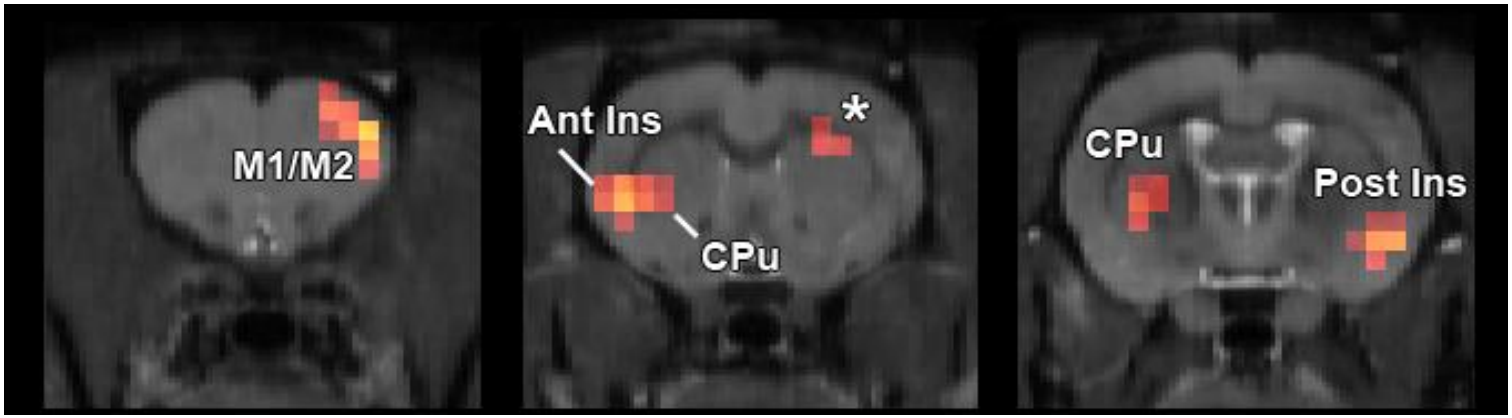
^{11}C-Carfentanil

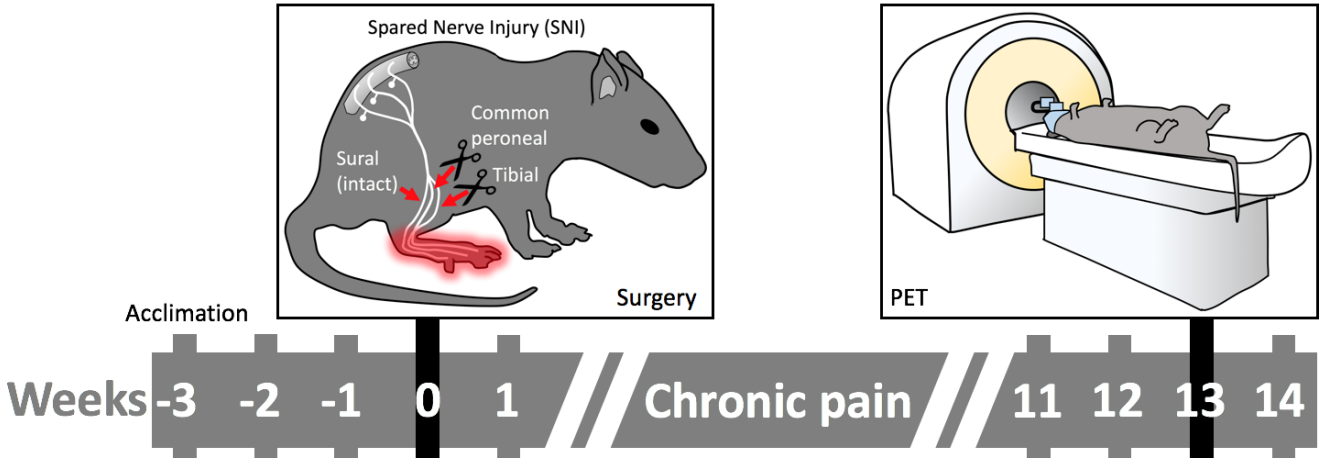
Mu opioid receptor agonist

Similar findings in other pain conditions, including arthritis, neuropathic pain, headache, complex regional pain syndrome

©2007 by Society for Neuroscience

As found in humans, reduced opioid binding in rat model of chronic pain





Thompson, Pitcher et al, *Pain* 2018.

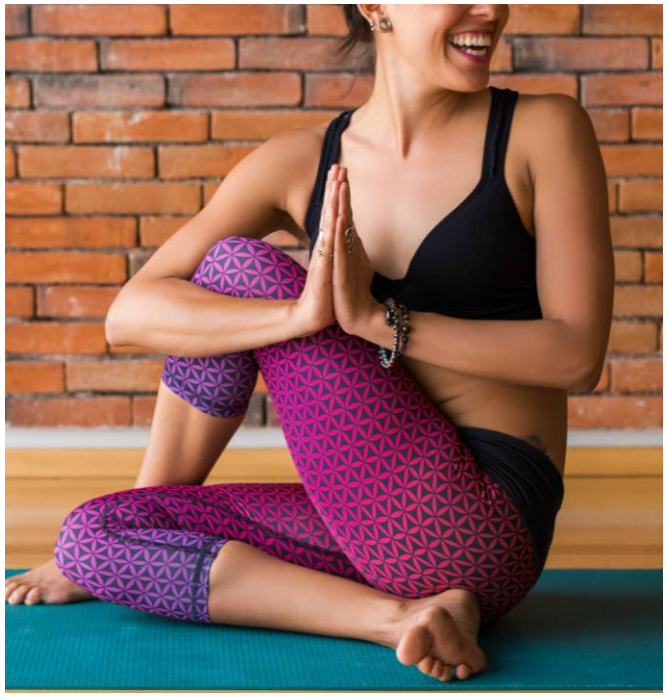
Given that pain modulatory systems may not be working as well in chronic pain patients as in health people, it is particularly important to find ways to engage these systems without resorting to opiates.

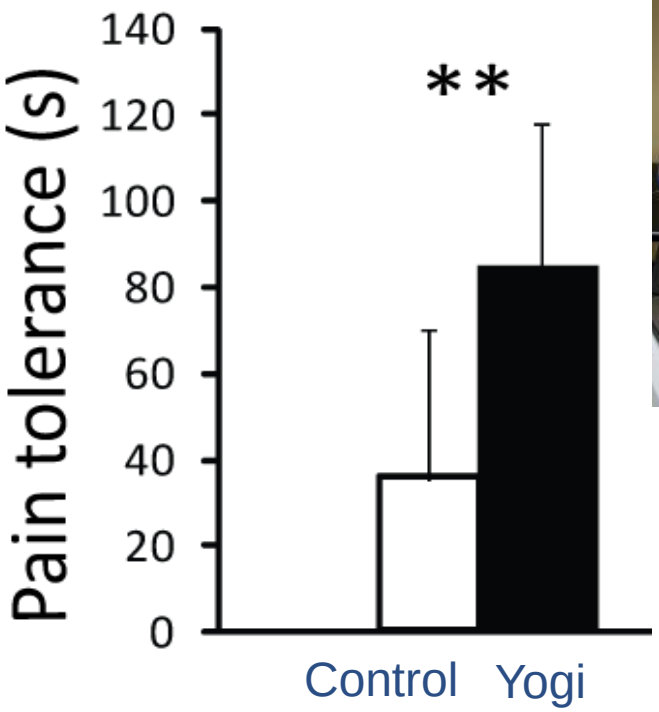
How can we engage pain modulatory systems without taking opioids?

Evidence that some lifestyle choices can help reduce the impact of chronic pain on the brain

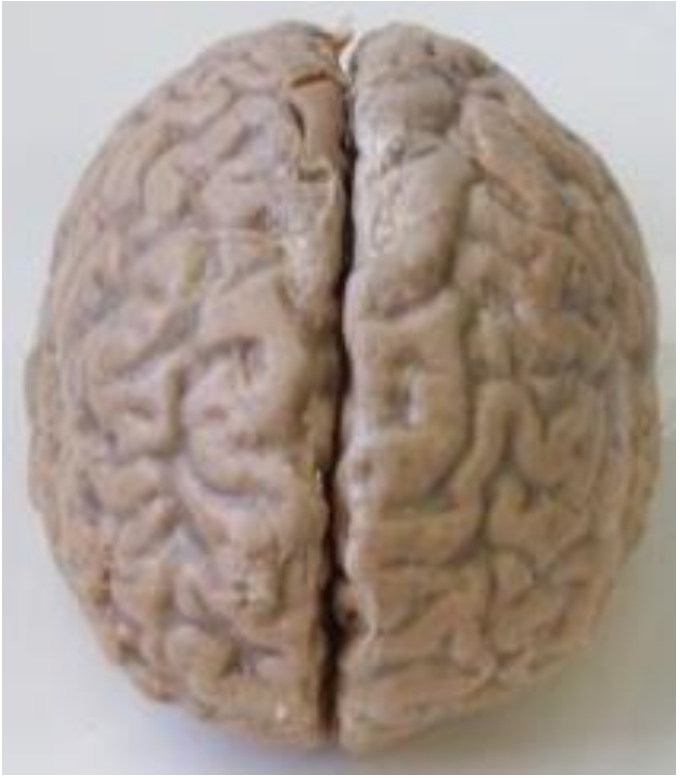
YOGA THERAPY FOR PAIN

Evidence that yoga practitioners have reduced pain perception



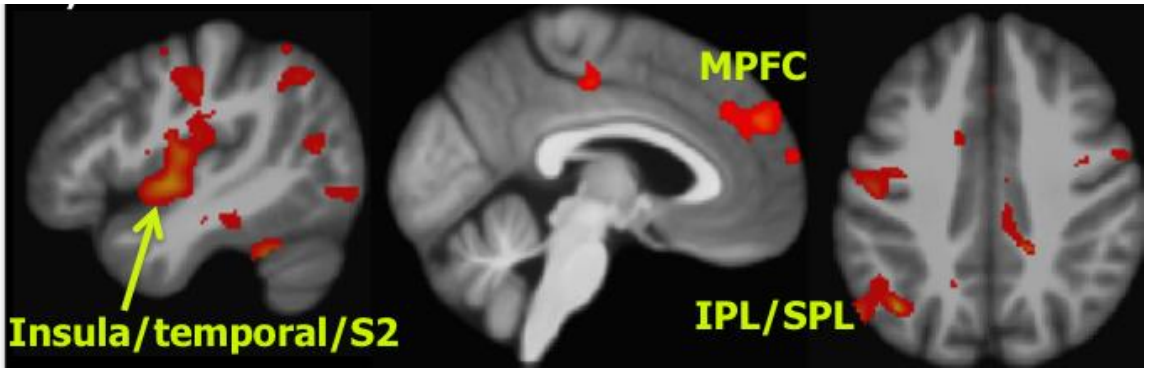


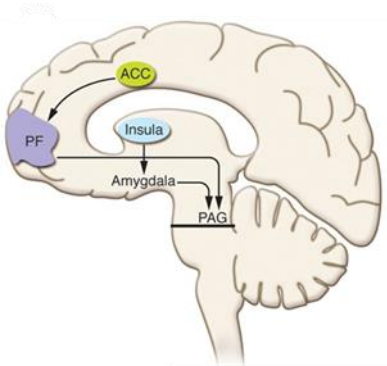
Villemure, Ceko et al, *Cerebral Cortex* 2014

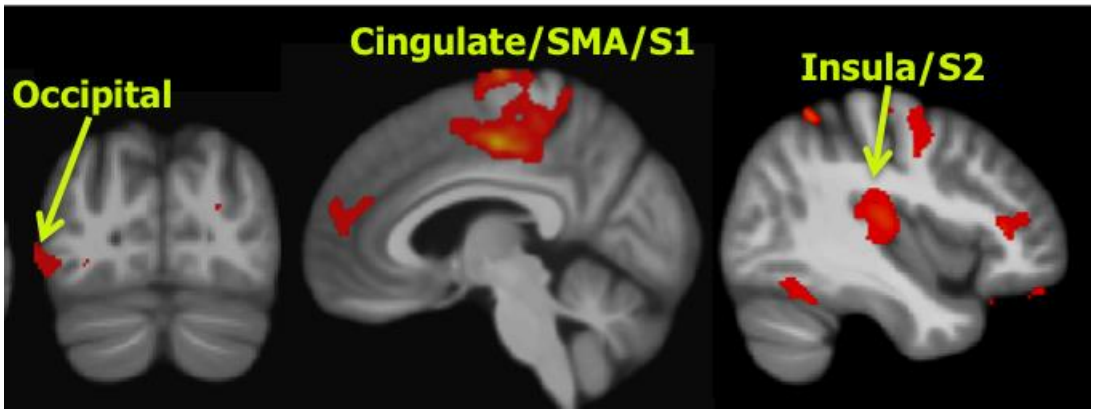


Practicing yoga has the opposite effect on the brain as does chronic pain

Yoga practitioners have more gray matter than controls in multiple brain regions, including regions involved in pain modulation



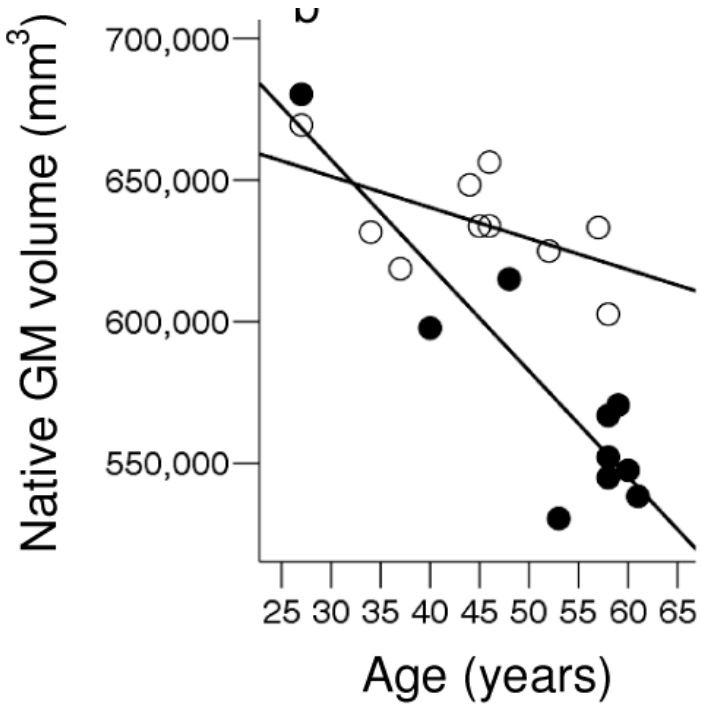




Villemure, Ceko et al, *Cerebral Cortex* 2014

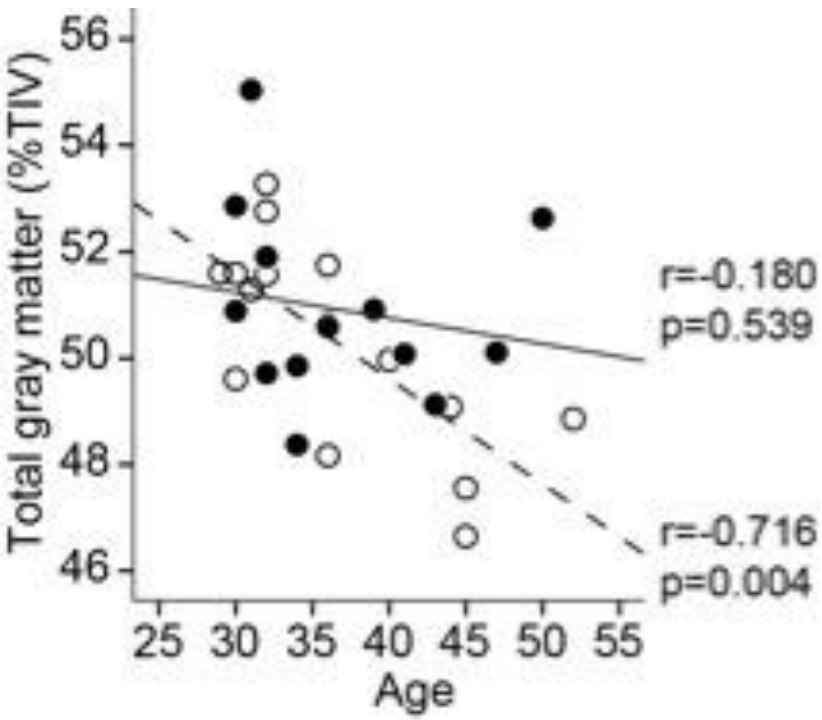
Yoga may protect against age-related gray matter loss

— Accelerated GM loss in chronic pain



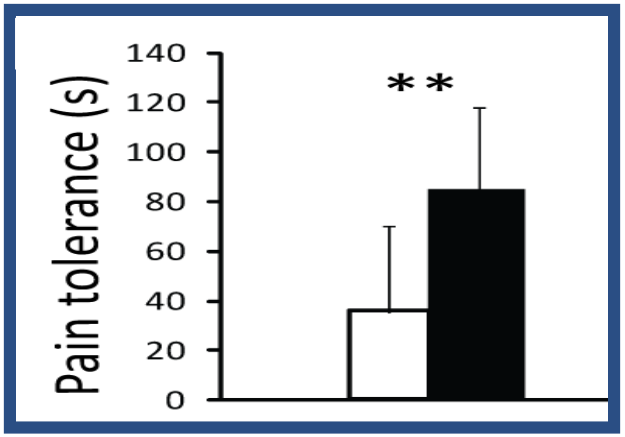
Kuchinad A, et al. *J Neurosci*. 2007.

— Decelerated GM loss in yogis

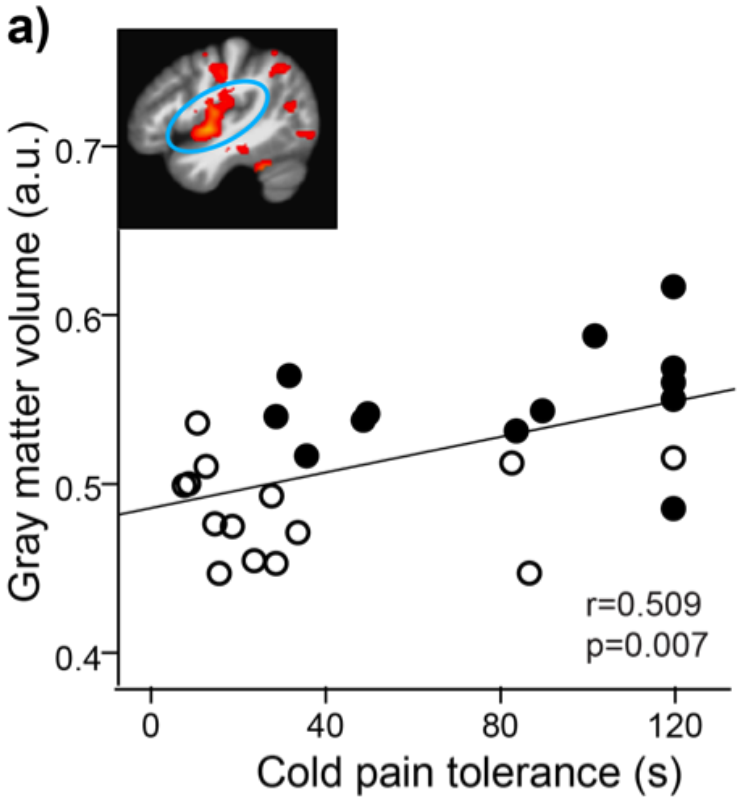


Villemure, Ceko et al, *Cerebral Cortex* 2014

Can increased gray matter account for increased pain tolerance in yogis?



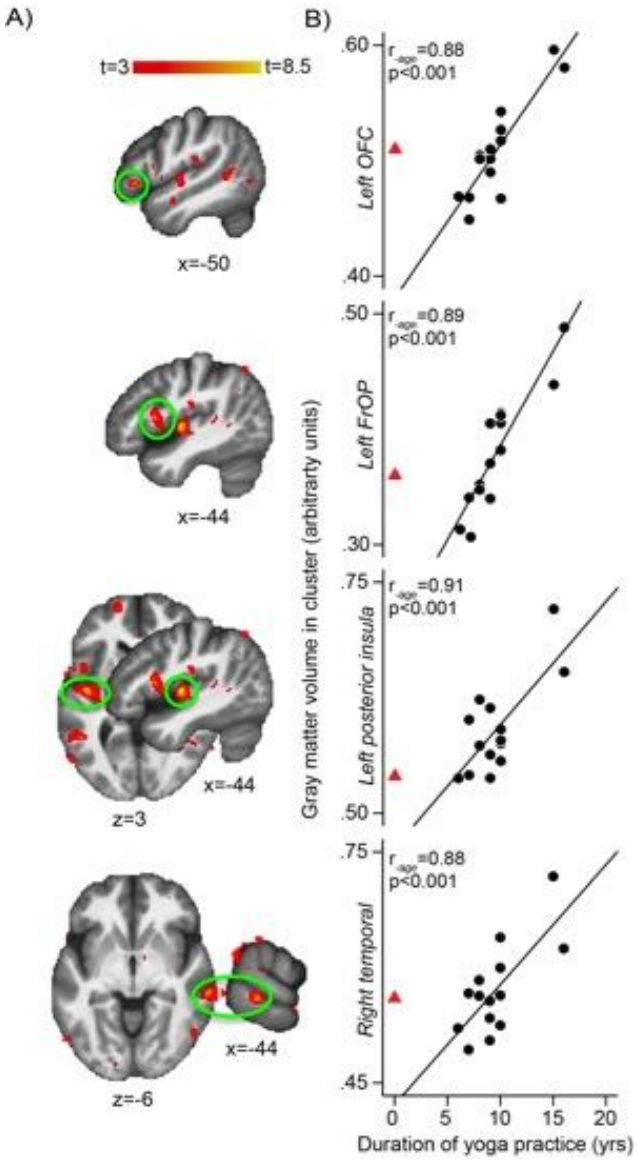
Insula gray matter size correlates with pain tolerance



Villemure. Ceko et al, *Cerebral Cortex* 2013

Yoga and gray matter increases: Cause or effect?

Are gray matter increases in yoga related to length of yoga practice?



Orbito-frontal

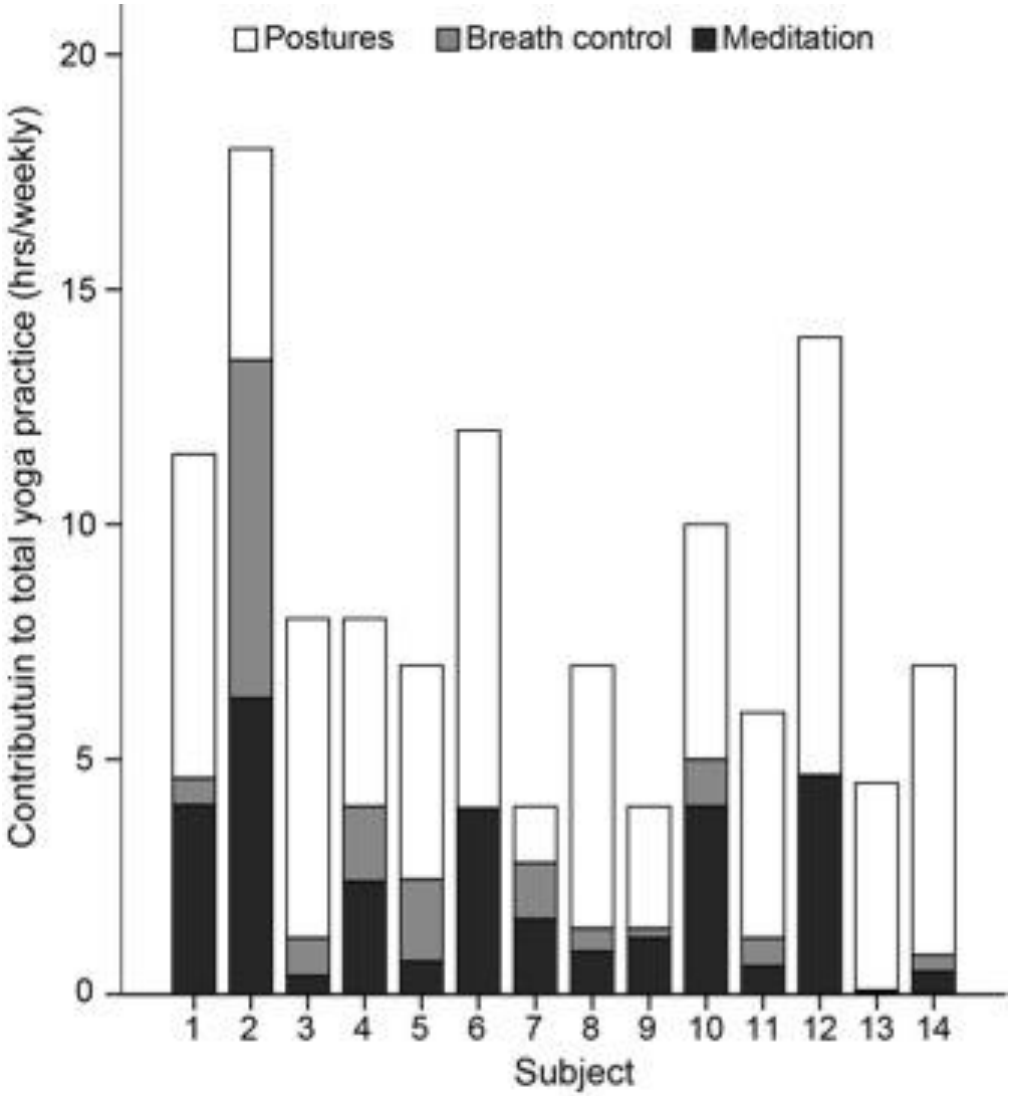
Frontal

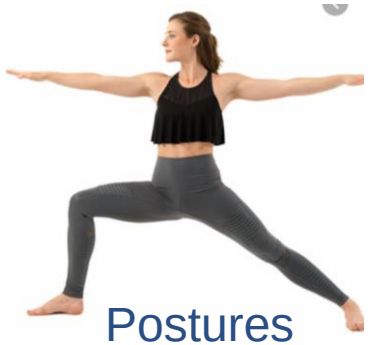
Insula

Temporal

Villemure, Ceko, Cotton et al, *2015*

Yoga practice is different for different people





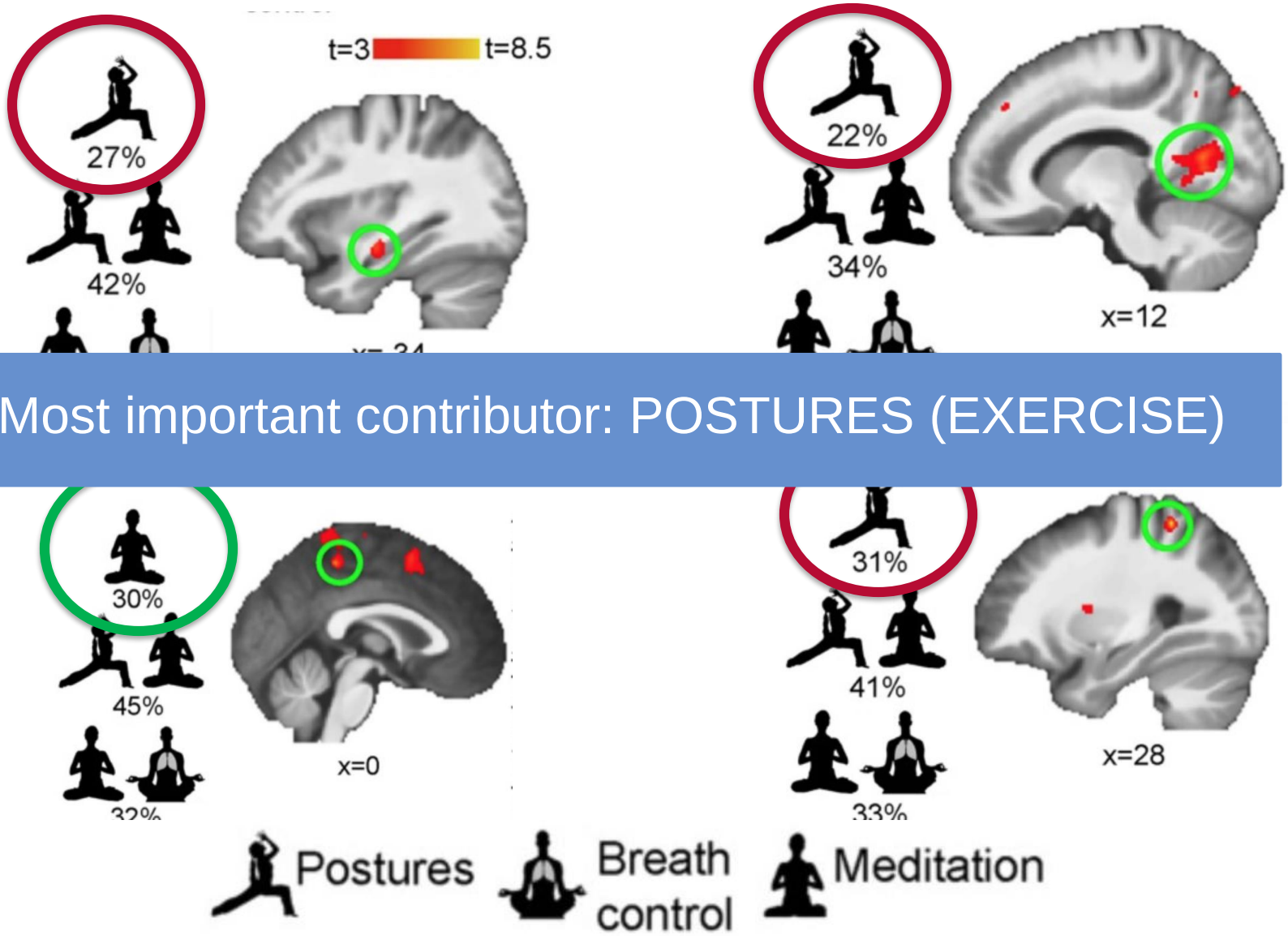
Postures

Breathing

Meditation

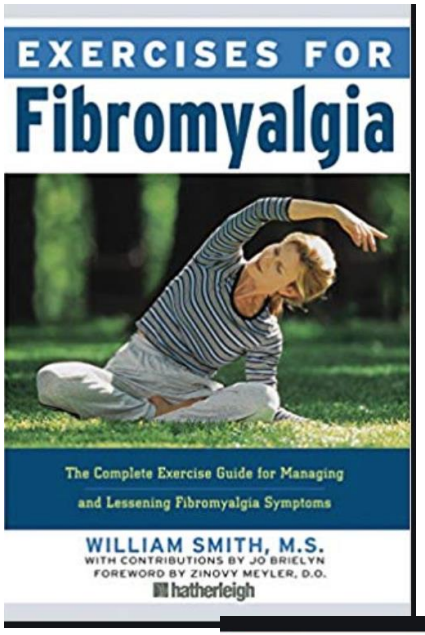
Villemure et al, *Front. Human Neuro.* 2015

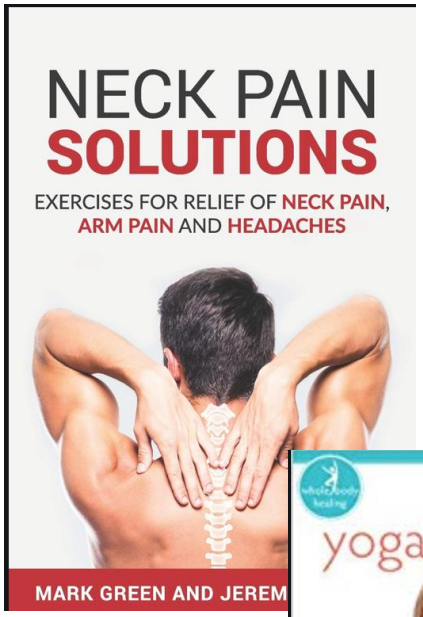
What aspects of yoga contribute to gray matter increases?

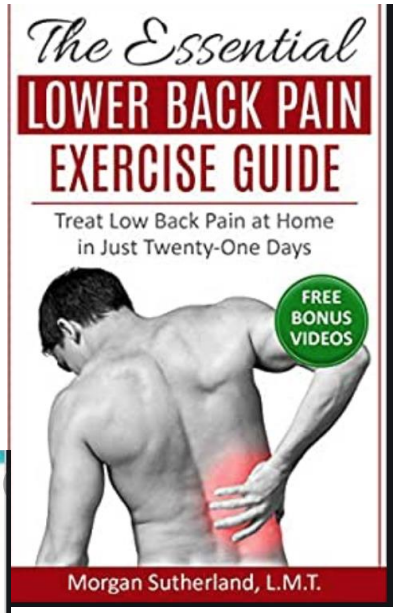


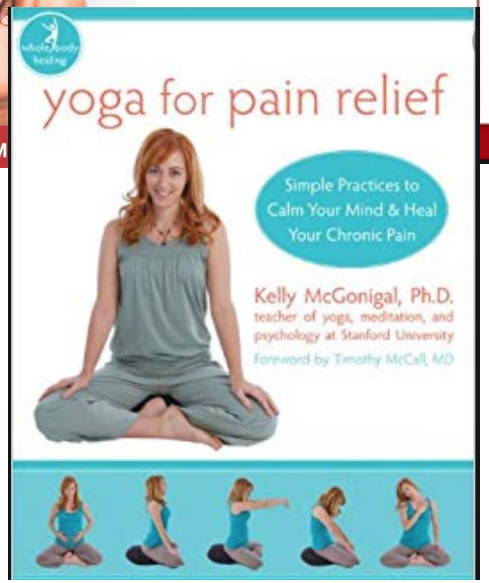
Most important contributor: POSTURES (EXERCISE)

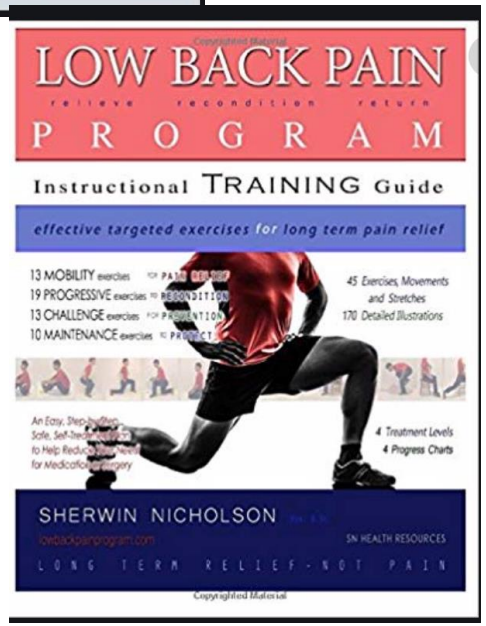
Growing evidence that people who exercise have reductions in chronic pain


EXERCISES FOR
Fibromyalgia
The Complete Exercise Guide for Managing
and Lessening Fibromyalgia Symptoms
WILLIAM SMITH, M.S.
WITH CONTRIBUTIONS BY JO BRIELYN
FOREWORD BY ZINOVY MEYLER, D.O.
hatherleigh


NECK PAIN
SOLUTIONS
EXERCISES FOR RELIEF OF NECK PAIN,
ARM PAIN AND HEADACHES
MARK GREEN AND JEREM


The Essential
LOWER BACK PAIN
EXERCISE GUIDE
Treat Low Back Pain at Home
in Just Twenty-One Days
FREE
BONUS
VIDEOS
Morgan Sutherland, L.M.T.


yoga for pain relief
Simple Practices to
Calm Your Mind & Heal
Your Chronic Pain
Kelly McGonigal, Ph.D.
teacher of yoga, meditation, and
psychology at Stanford University
Foreword by Timothy McCall, MD


LOW BACK PAIN
relieve recondition return
PROGRAM
Instructional TRAINING Guide
effective targeted exercises for long term pain relief
13 MOBILITY exercises
19 PROGRESSIVE exercises
13 CHALLENGE exercises
10 MAINTENANCE exercises
45 Exercises, Movements
and Stretches
170 Detailed Illustrations
4 Treatment Levels
4 Progress Charts
SHERWIN NICHOLSON
SN HEALTH RESOURCES
LONG TERM RELIEF-NOT PAIN
Copyrighted Material

HOW TO REDUCE
Chronic Pain
THROUGH EXERCISE
HotBodyHealth.com

Can exercise reduce chronic pain in anyone or are people who are willing and able to exercise essentially different have from those who don’t?

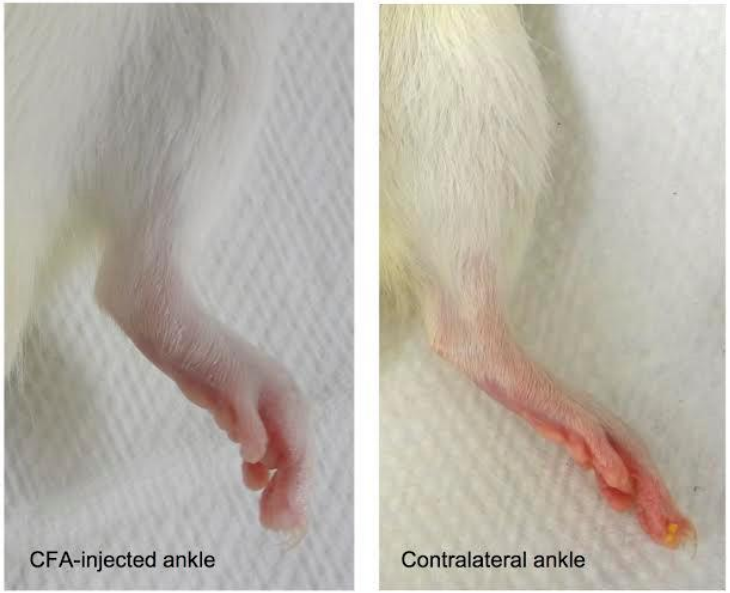
Can be tested using rodent models.

We can keep genetics and environment constant and only change amount of exercise.

Does moderate exercise reduce chronic pain?

Sent the rats to a "gym" for 1 hour/day, 5 days/week

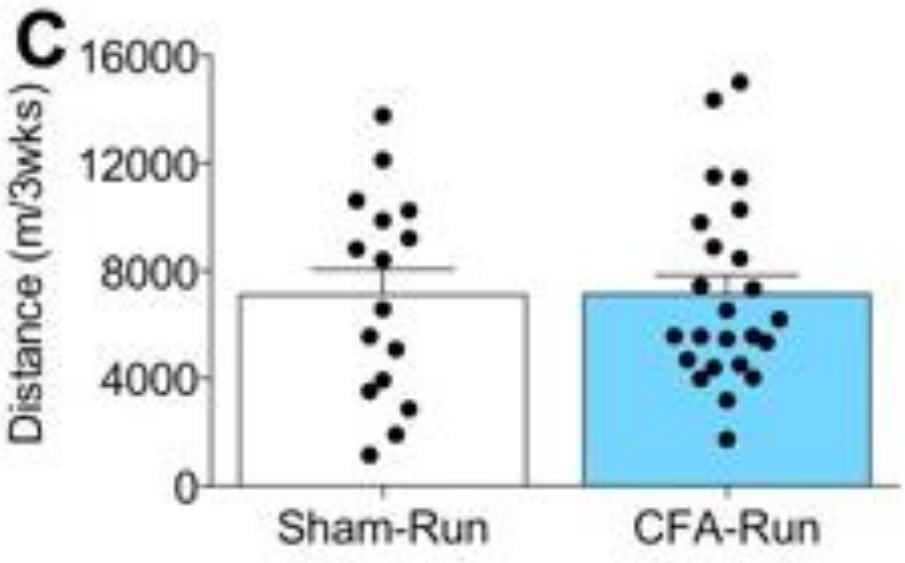
CFA inflammatory arthritis model in rats



Inject paw with Complete Freund's Adjuvant to create a permanent inflammation

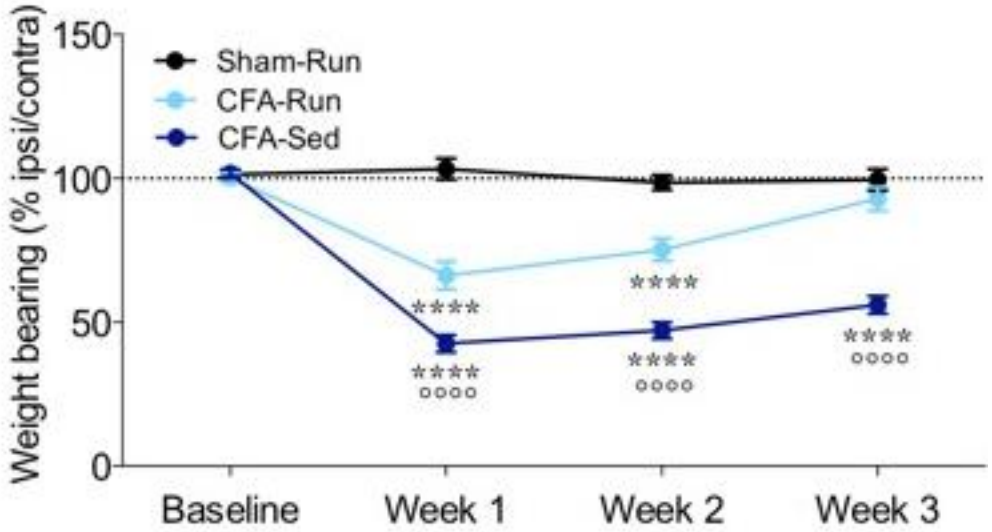
Pitcher MH et al. *J. Pain 2017*

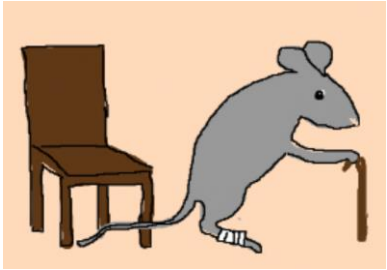
Will rats run if they are in pain?



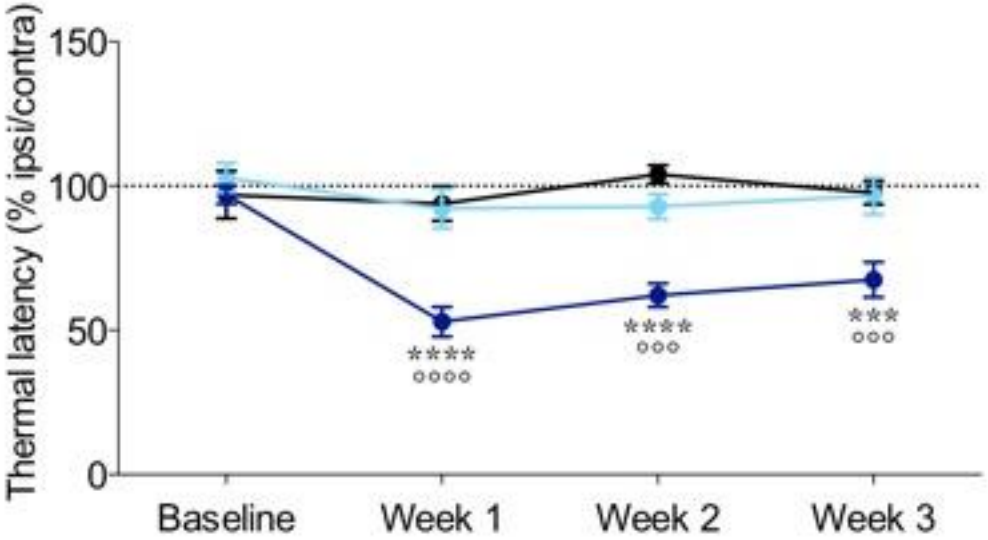
Pitcher MH et al. *J. Pain 2017*

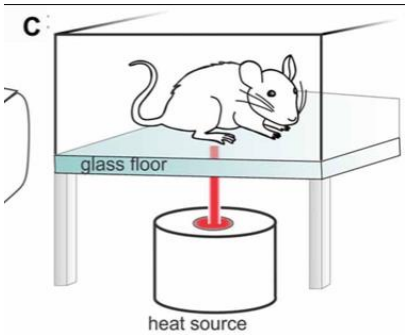
Voluntary exercise is analgesic





Weight bearing (limping)





Withdraw foot from heat

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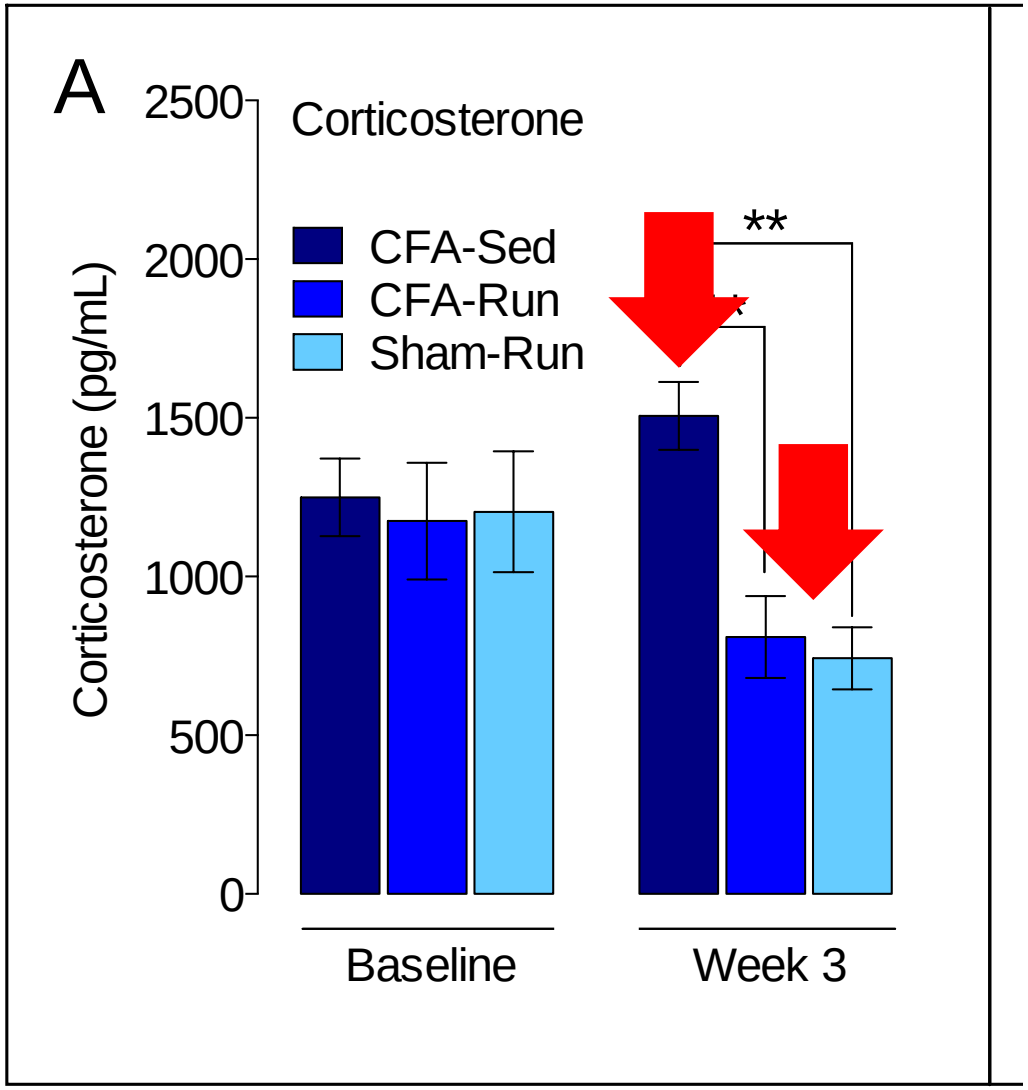
Measured stress levels through blood samples of corticosterone (cortisol)

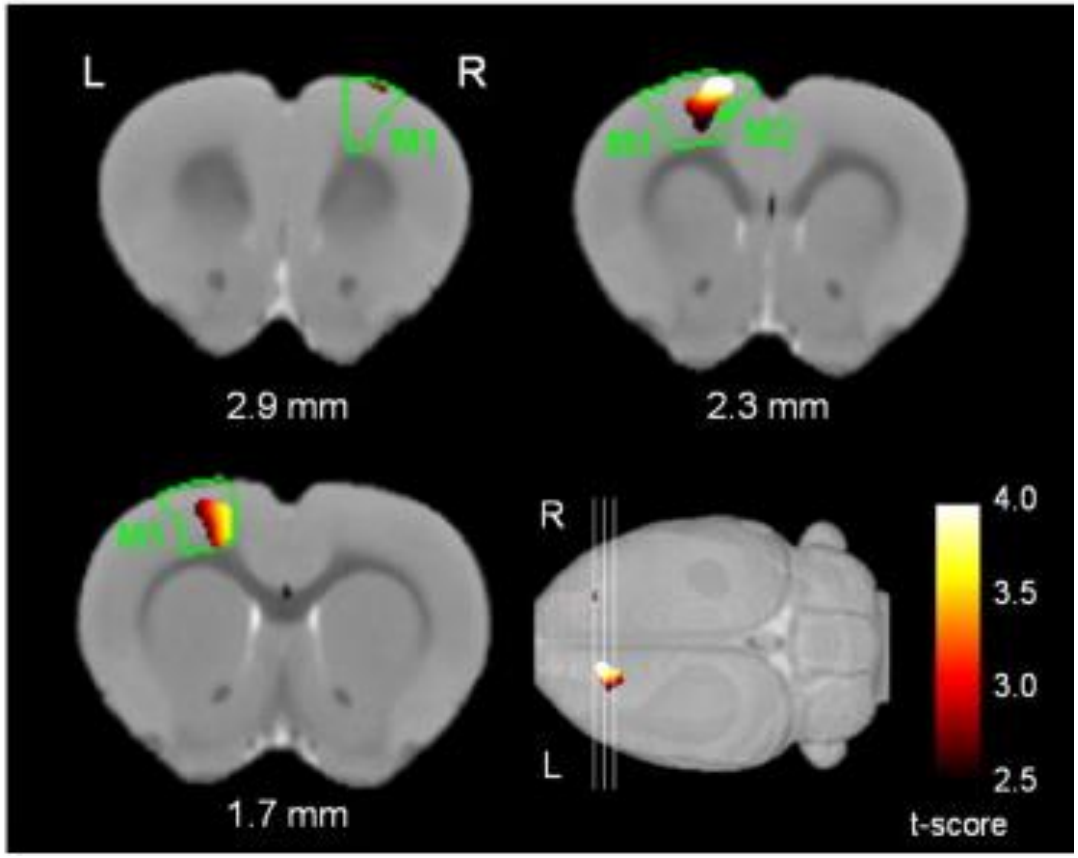


Injured animals that did not exercise showed increased stress

Voluntary running *reduced* stress to normal levels

Pitcher MH et al. *J. Pain 2017*

Voluntary running in rats increases gray matter in brain

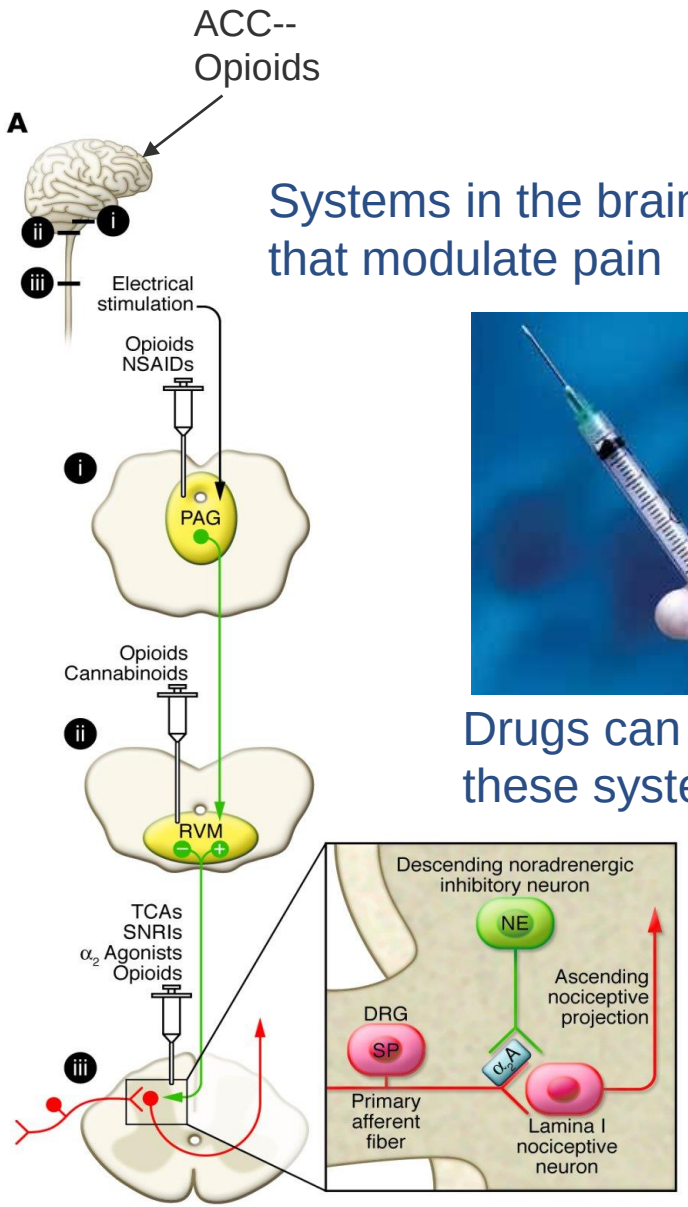


Rat brain

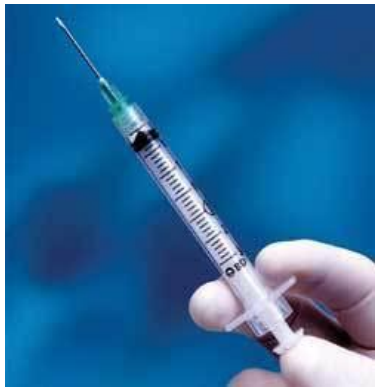
Colored blobs show regions of increased gray matter

Sumiyoshi et al NeuroImage 2014

Summary



Systems in the brain that modulate pain



Drugs can activate these systems

Activate same systems by attention and emotions

Active lifestyles can reduce chronic pain by accessing these systems and normalizing brain

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Lucie Low

Valerie Cotton

Thank you to the people who conducted these studies

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