

What is Placebo Analgesia: and how does it happen?

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Disclosure

- No Conflict of Interest

Chronic Pain: A Major Problem for Vets

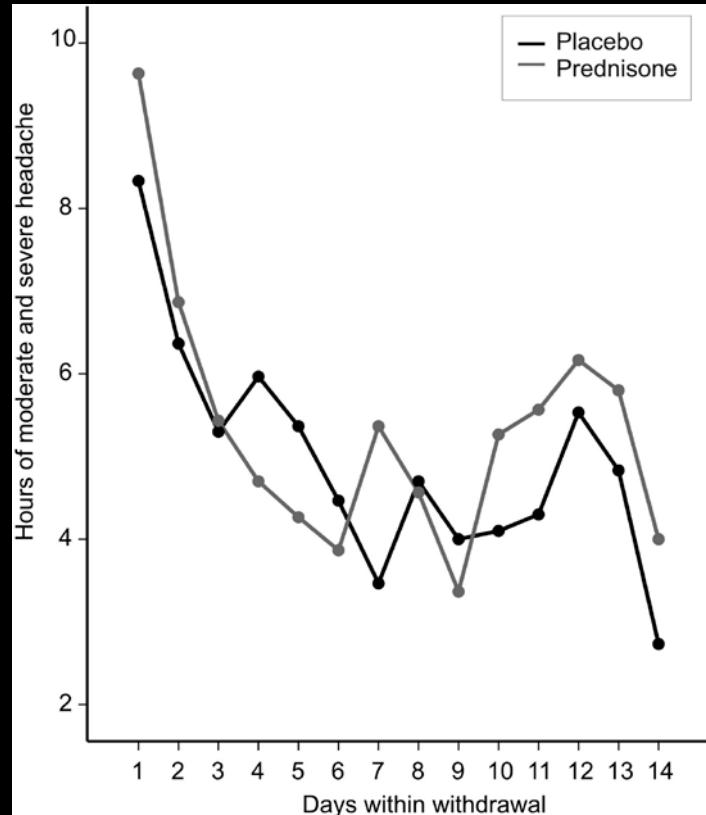
30% of the U.S. population suffers from chronic pain. The percentage of the veteran population with chronic pain is over 50%.

Institute of Medicine. (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

Improvement After Treatment

Negative outcomes common in placebo controlled clinical trials for analgesics

Medication
overuse
headache



Is the treatment ineffective
or is the placebo too
effective?

Is there even a
placebo effect here?

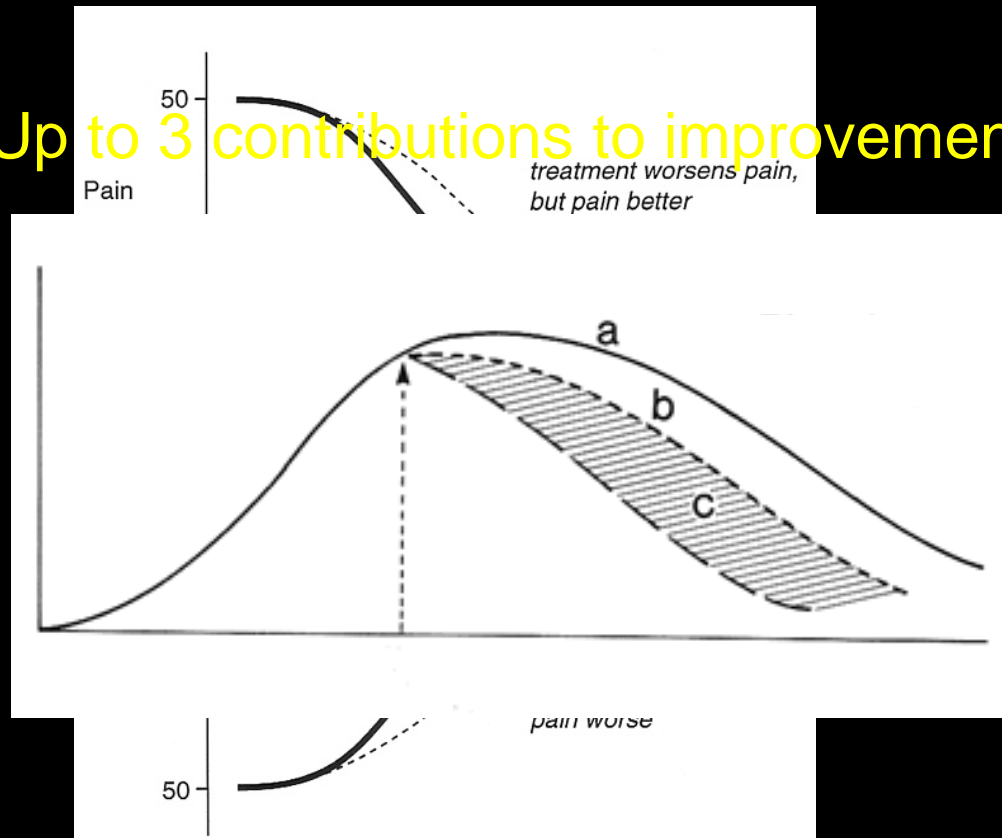
Rabe K et al. Cephalalgia
2012;33:202-207

Why Does Placebo Group Improve?

- Natural history
- Placebo response

Natural History: Why RCTs

Up to 3 contributions to improvement



- a: natural history
- b: placebo effect
- c: drug effect

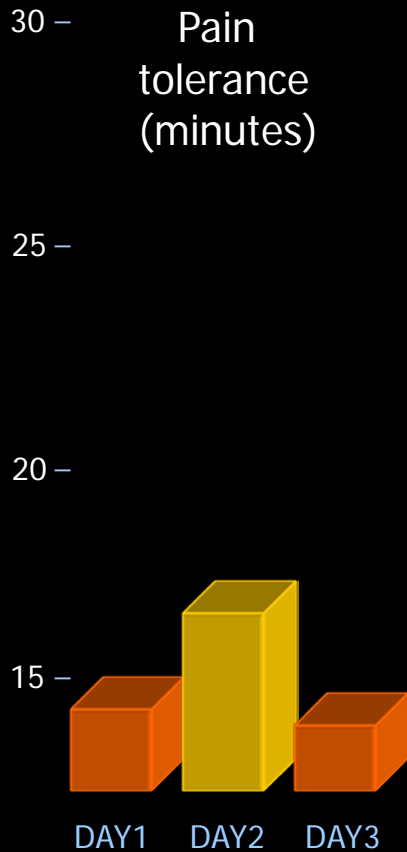
Pain severity

An individual placebo response is usually an inference, not an observation.

Do Placebo Effects Even Occur ?

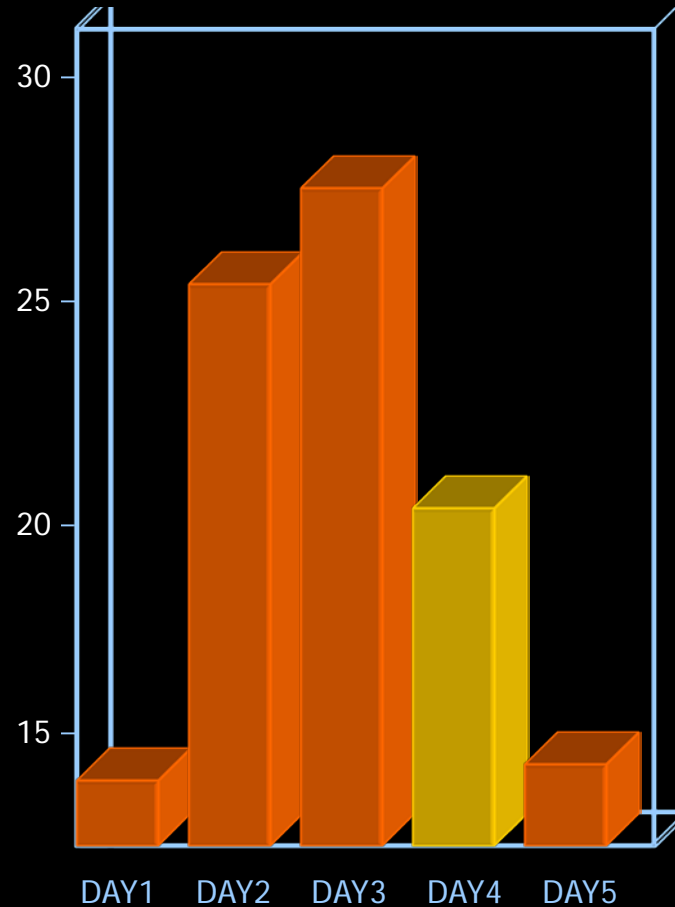
- Yes: Magnitude can be experimentally manipulated

Drug Conditioning



PLA

Expectation



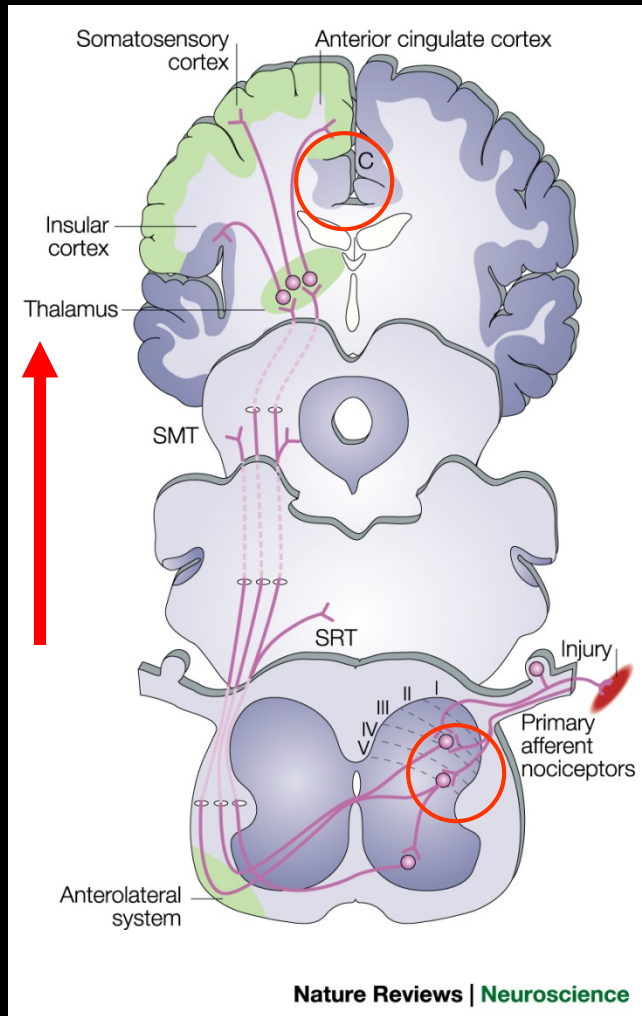
MOR MOR PLA

Conditioning
+ expectation

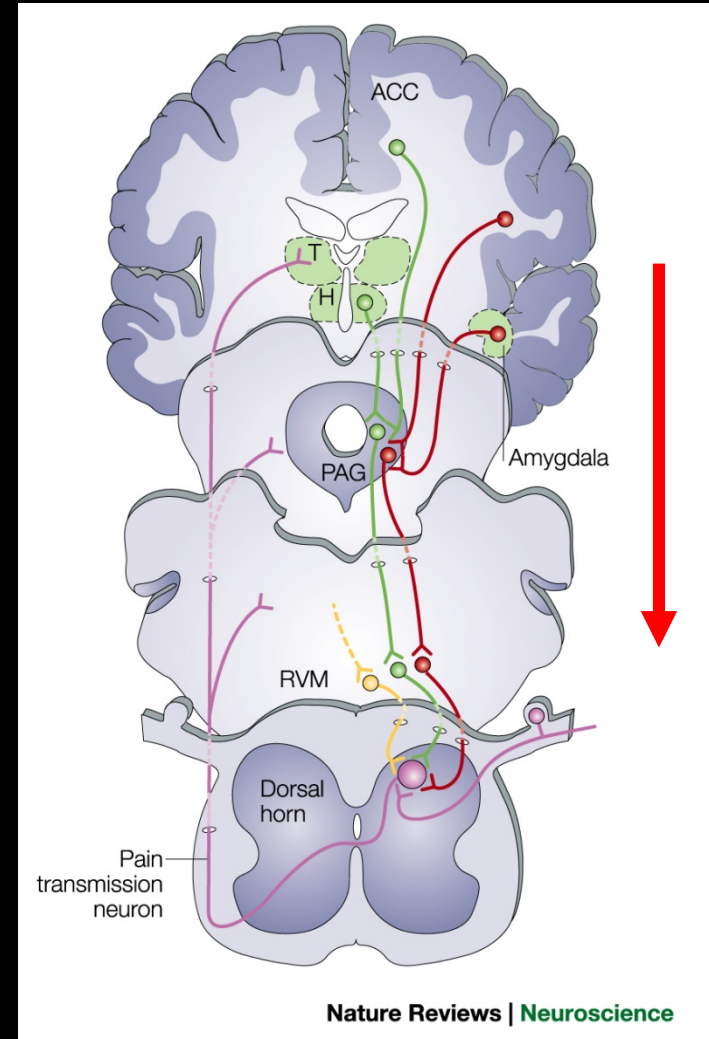
Benedetti F, et al
J Neurosci. 2007

How Does Expectation Inhibit Pain?

Transmission

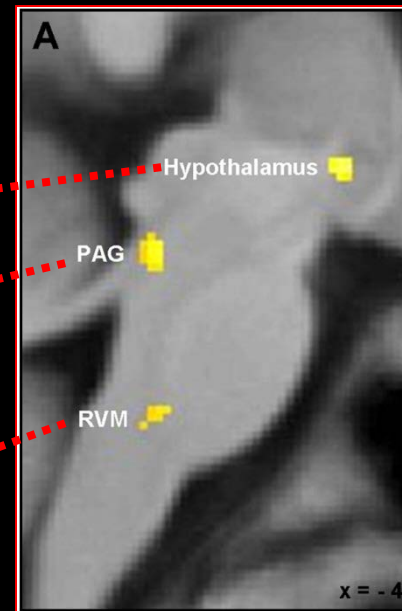
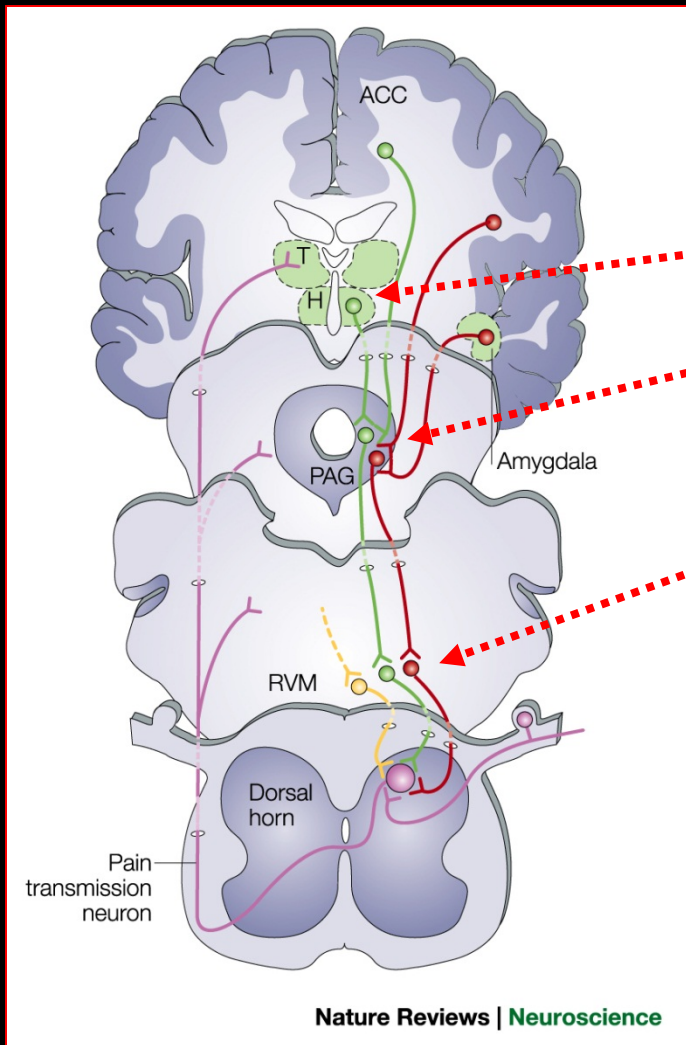


Modulation



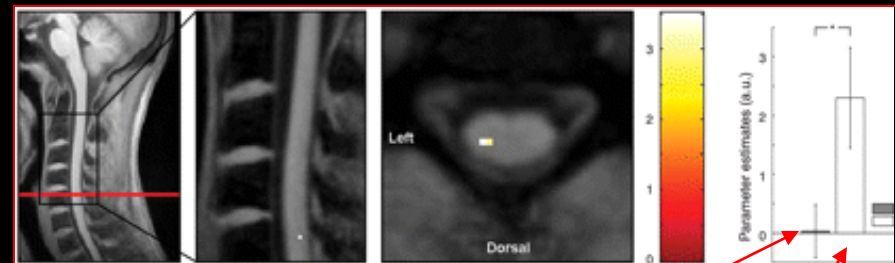
Fields, Nat Rev
Neurosci, 2004

Placebo Activates Human Pain Modulating Circuit



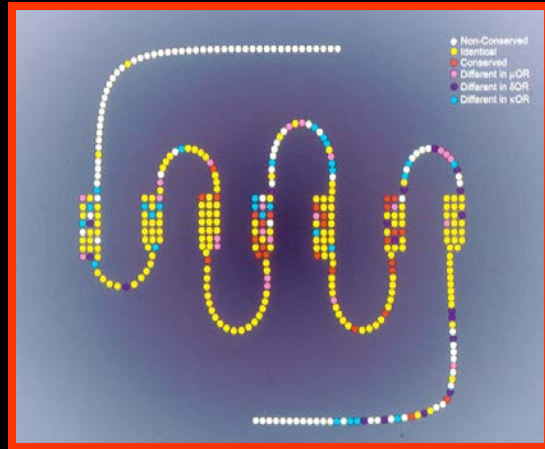
Eippert et al,
Neuron, 2009
Science, 2009

Reduces pain signal at spinal level

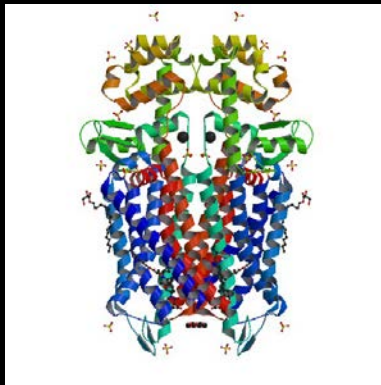


placebo control

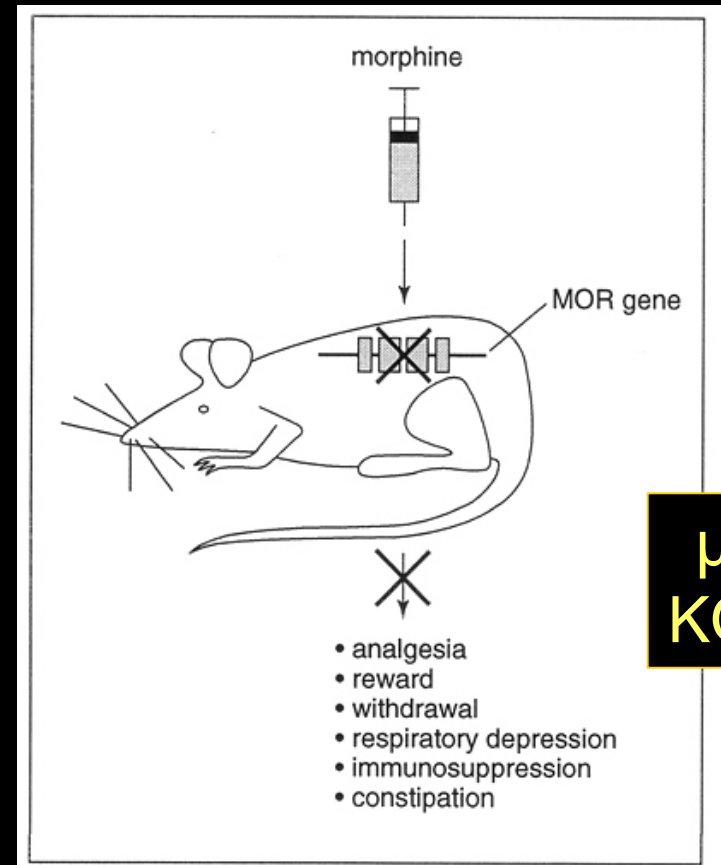
The Morphine (mu) Opioid Receptor



Opioid family of
7TMD GPCRs



Brian Kobilka
2012

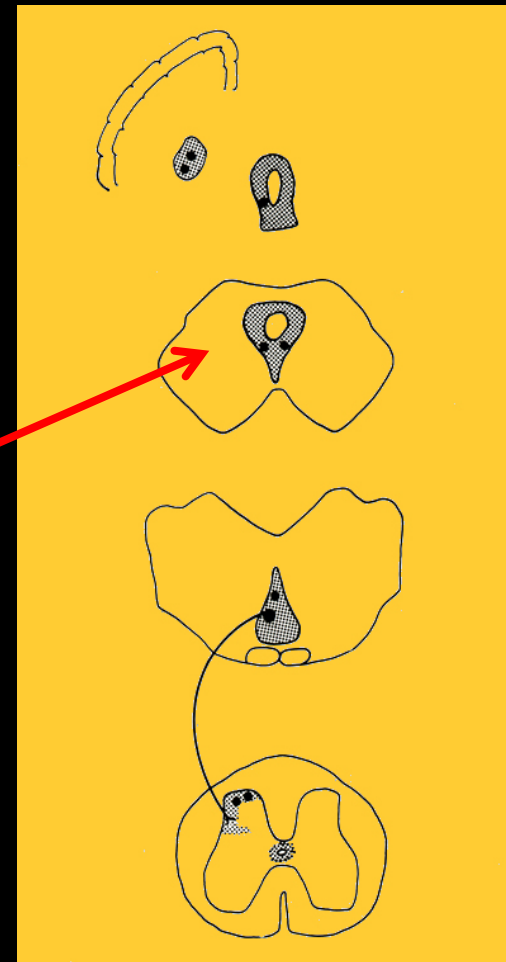
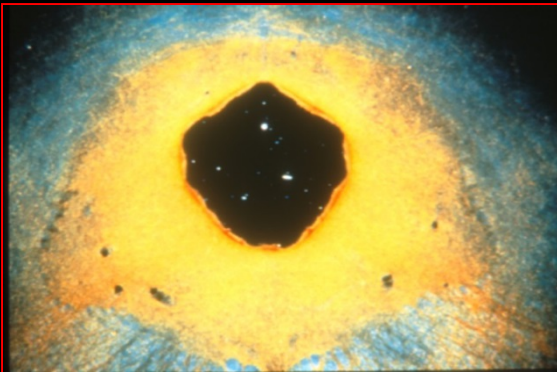


Endogenous opioids

Tyr-gly-gly-phe-met

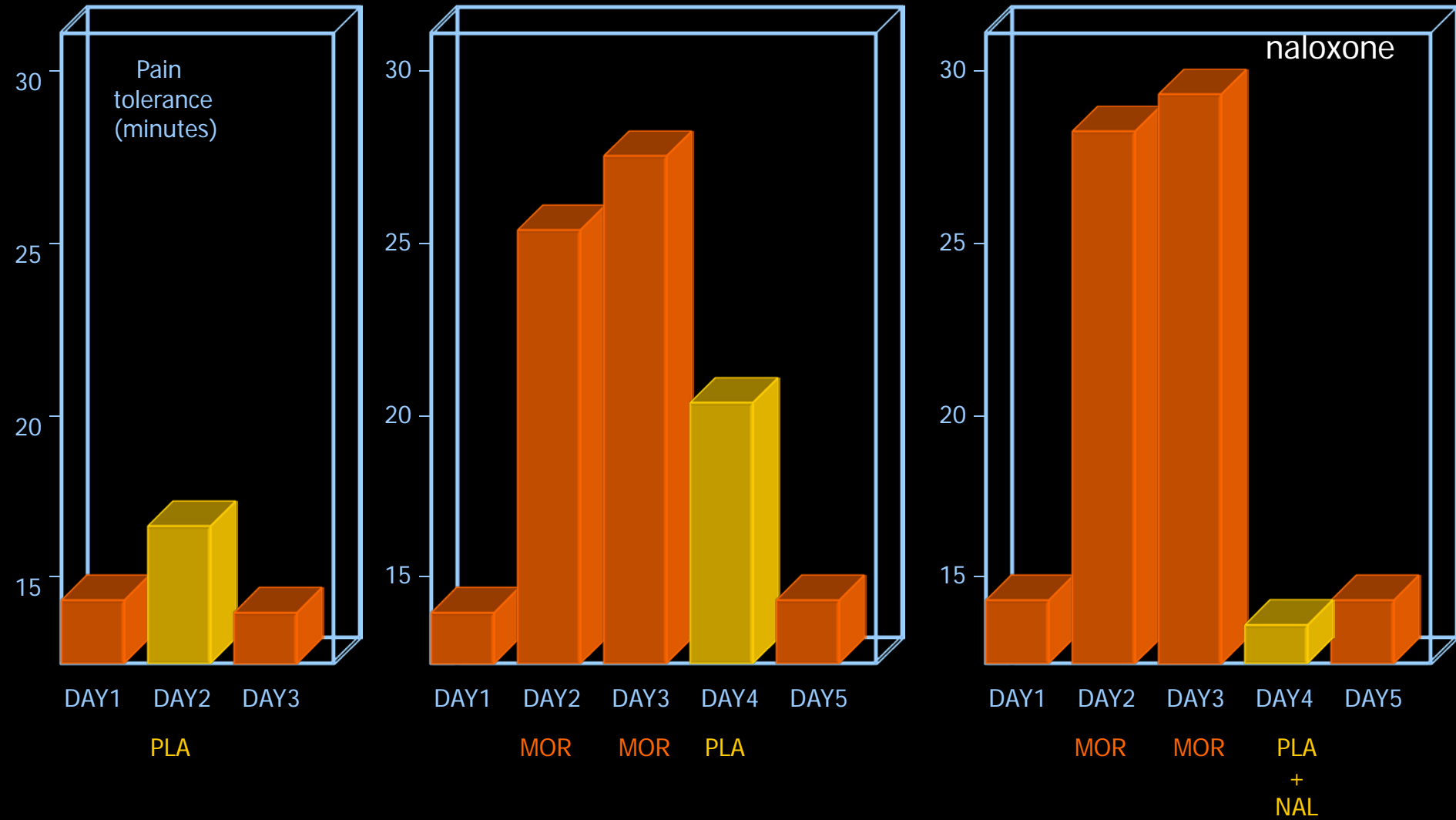
Tyr-gly-gly-phe-leu

Hughes & Kosterlitz, 1975



Does Placebo Analgesia Depend on Endogenous Opioids?

Naloxone Blocks Placebo

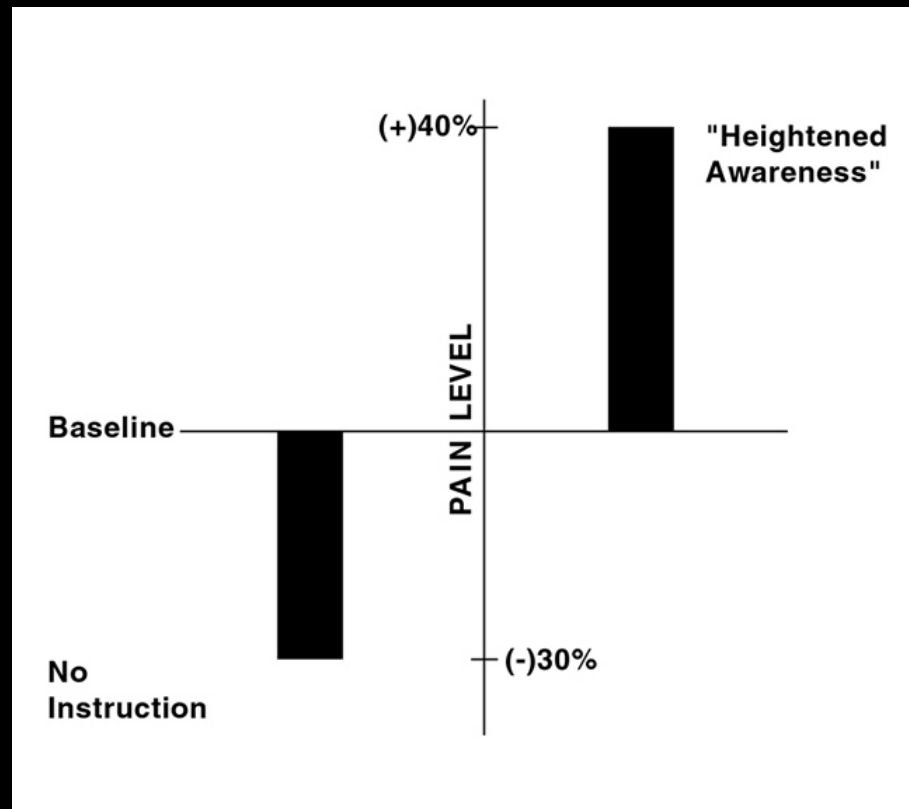


Benedetti F, et al
J Neurosci. 2007

Summary I

- Improvement after treatment can be due to:
 - Natural history
 - Expectation (Placebo response)
- Expectation of pain relief:
 - Engages descending opioid mediated pain modulating circuit

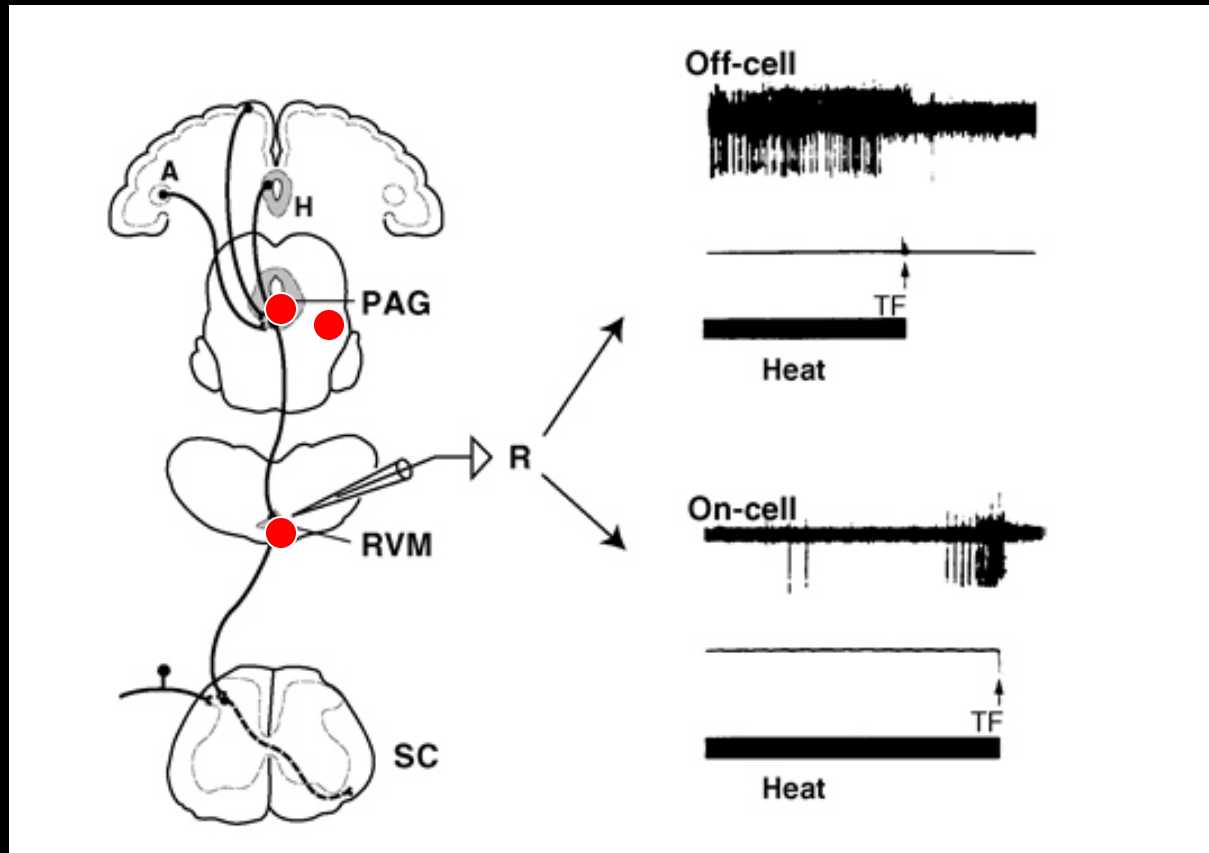
Expectation Can Also Increase Pain



Dworkin et al
Anesth Analg 1983

Pain Modulating Neurons

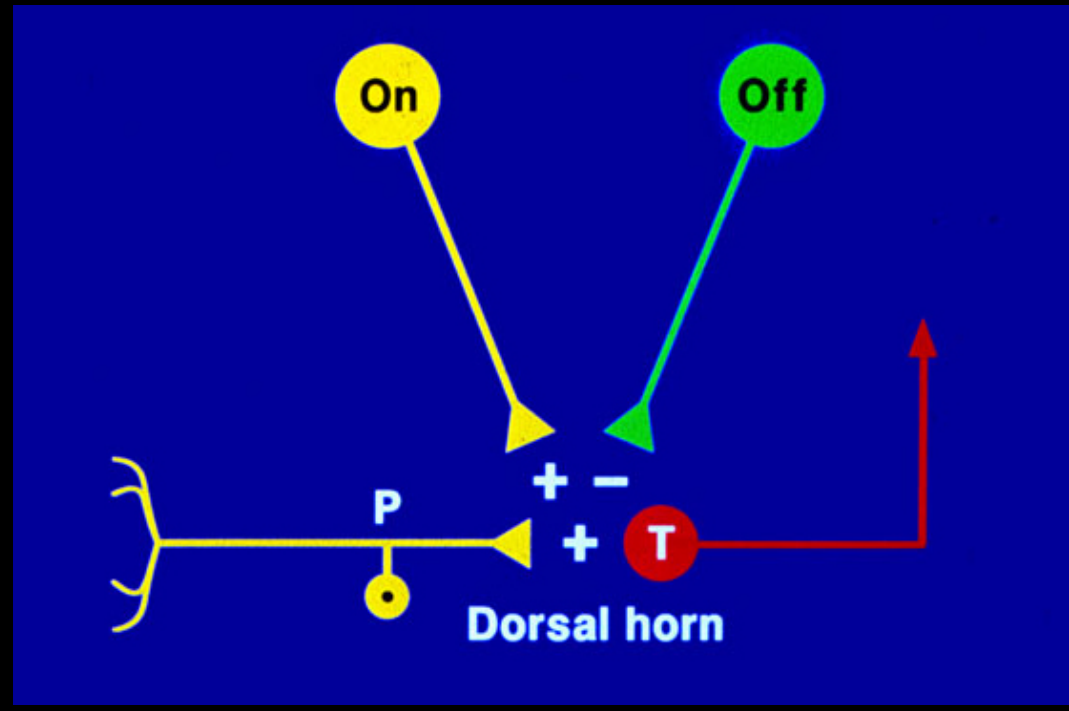
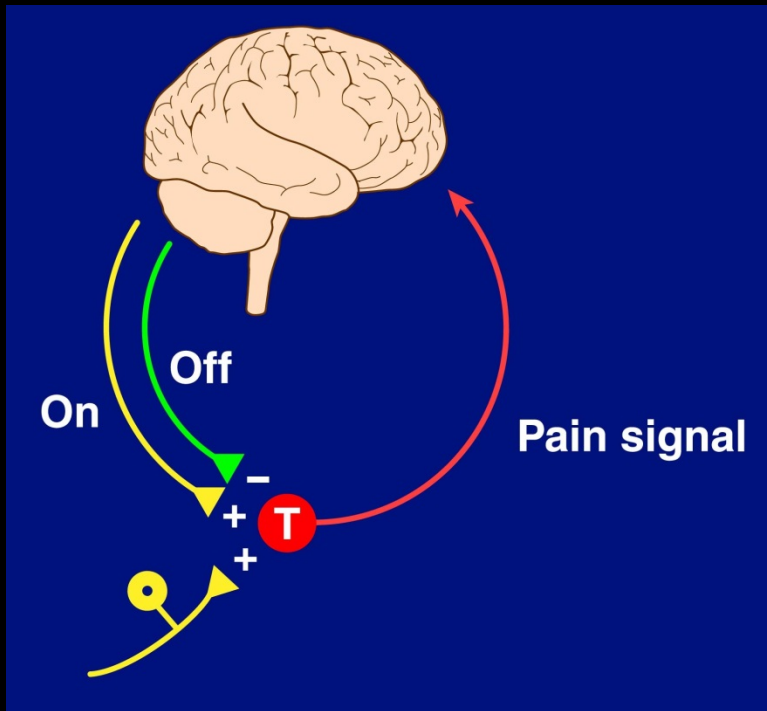
Control is Bidirectional



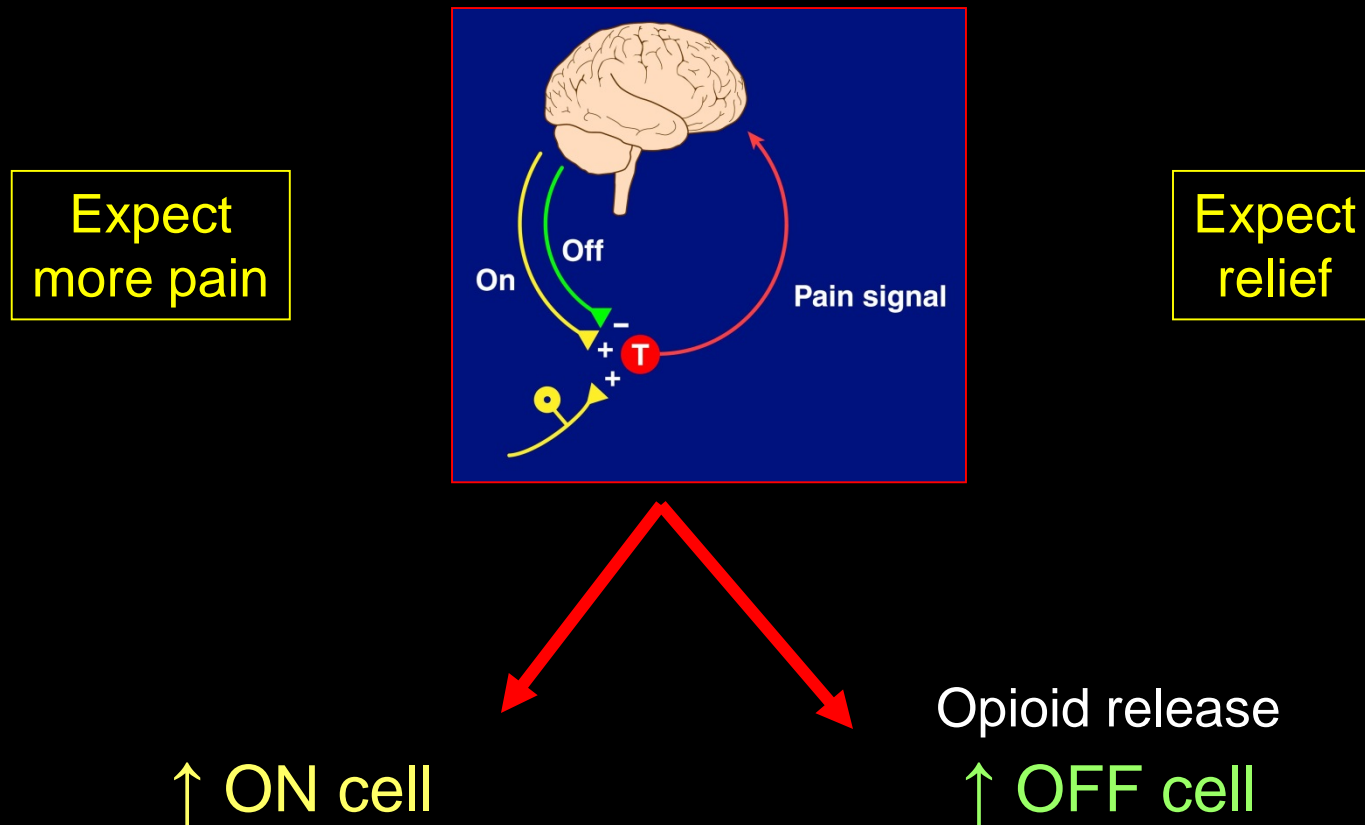
PAG
NCF
RVM

Fields e.g. (2004)
Nat Rev Neurosci

Centrally Generated Bidirectional Control of Pain

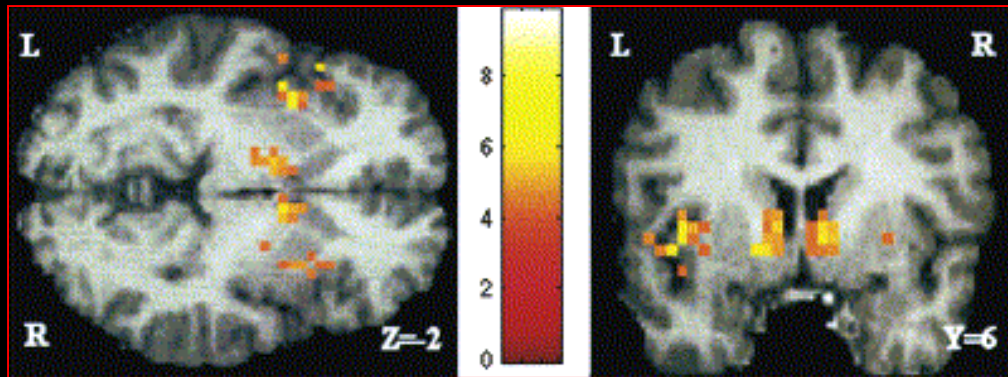


Expectations Can Facilitate or Inhibit Pain via Modulatory Circuit



What Drives ON and OFF Cells?

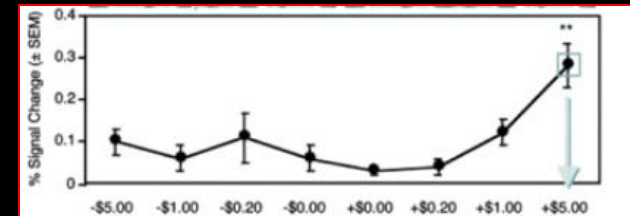
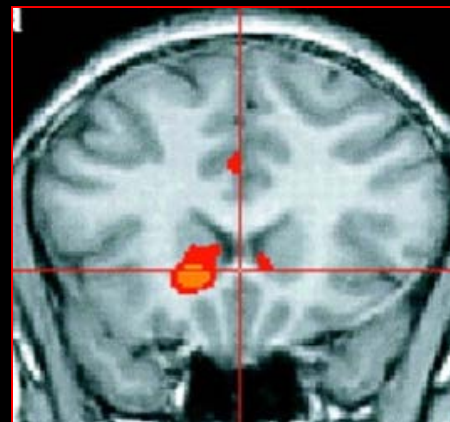
Both Pain and Reward Predictive Cues Activate Human Ventral Striatum



Jensen et al,
Neuron 2003

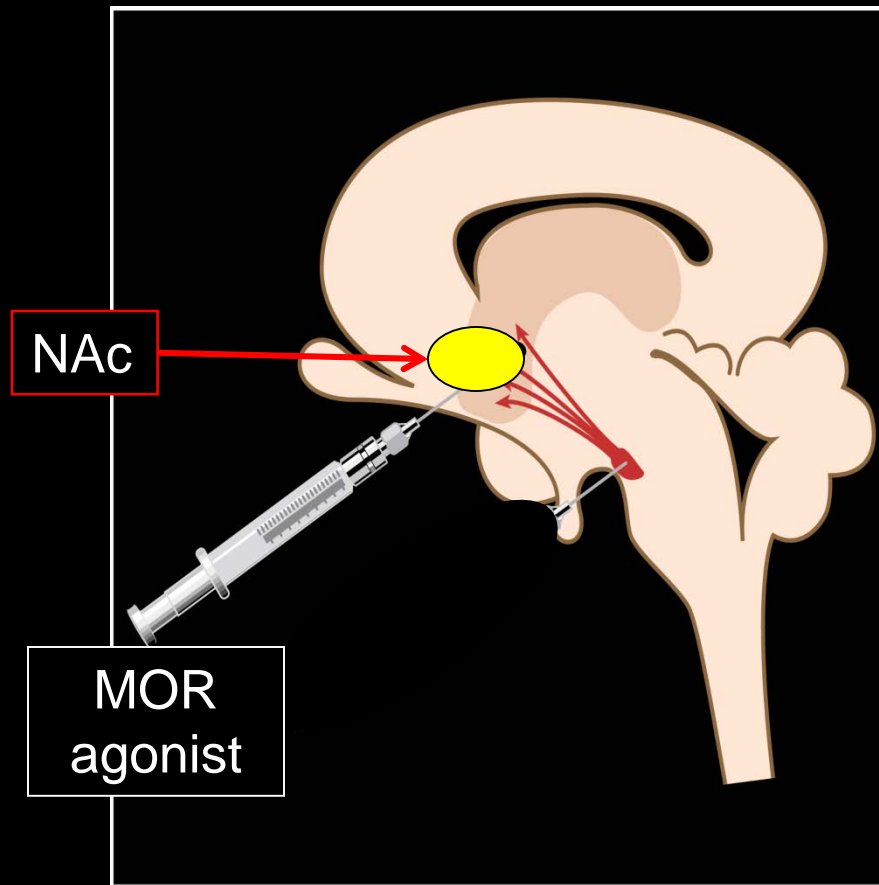
What does
this mean?

Reward
predictive
cue



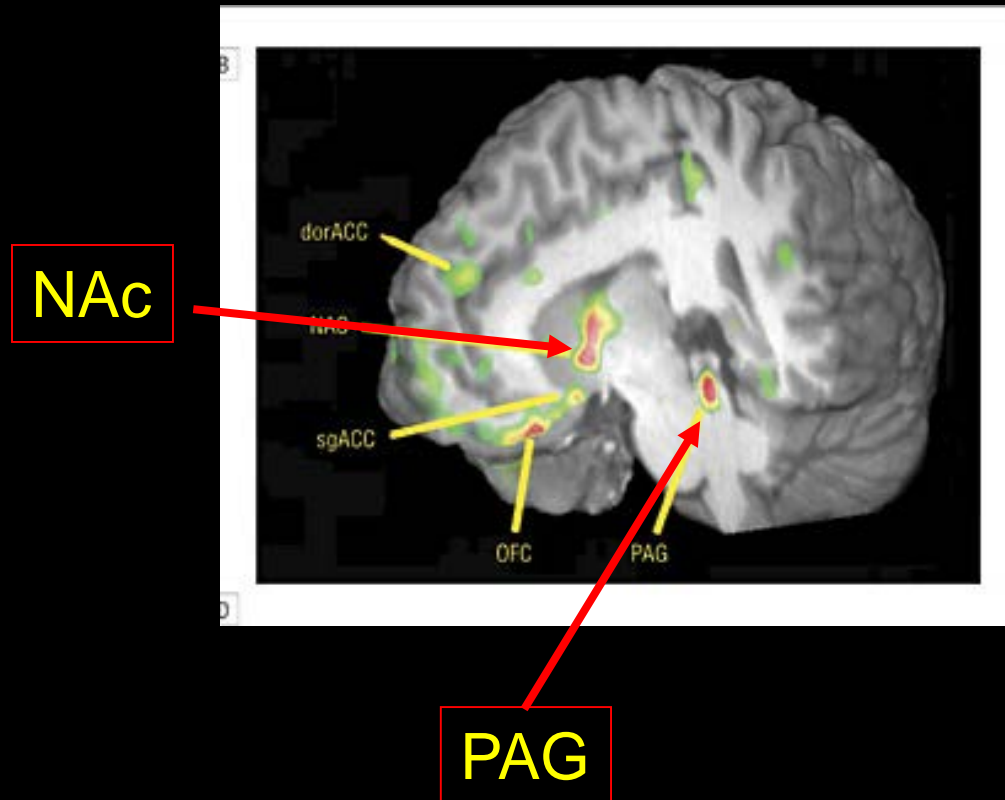
Knutson et al,
J. Neurosci 2001

Opioids in Nucleus Accumbens suppress pain



Franklin, Neurosci Biobehav. Rev, 1989
Altier & Stewart, JPET, 1998
Schmidt et al, Eur J Neurosci 2002

Placebo Release of Endogenous Opioids in Human NAc!



C¹¹ Carfentanil displacement

Scott, D. J. et al.
Arch Gen
Psychiatry 2008

Summary II

- Expectation is bidirectional:
 - Activates NAc; then modulatory circuit
 - Relief expectancy engages endogenous opioids

Active Analgesic Treatments Have an Expectation Component

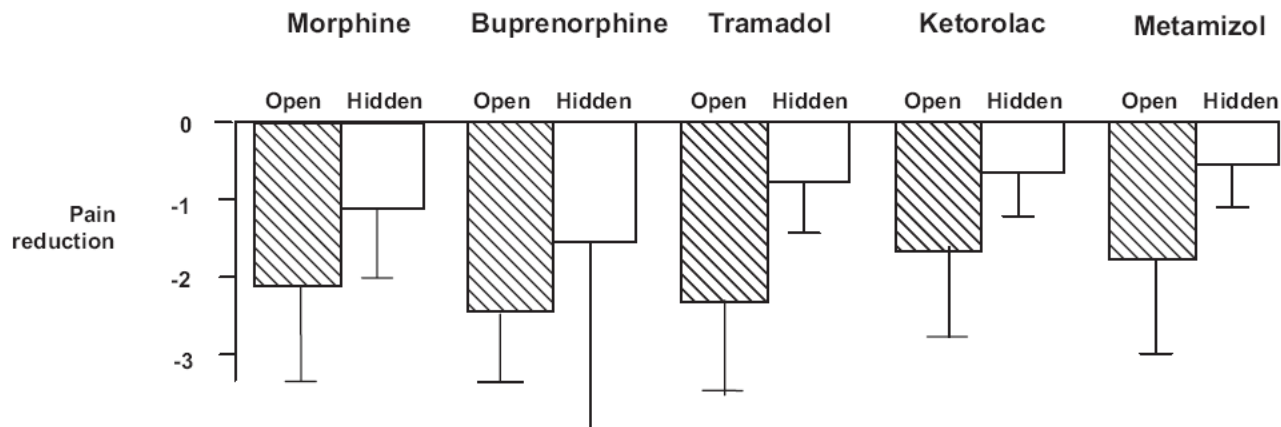


Figure 1

Comparison of analgesic effects of opioid (morphine, tramadol, buprenorphine) and nonopioid (ketorolac, metamizol) medications across hidden versus open intravenous injections in patients with postoperative pain. (Data are from Amanzio et al. 2001.)

Summary II

- All treatments include an expectation component
 - Can be analgesic (placebo) or hyperalgesic (nocebo)
- Expectations can change
 - Verbal instruction
 - Conditioning

Expectation Predicts Clinical Outcomes for Chronic Pain Patients

Table 3

Correlation matrix, mean, and SD of predictors and outcomes.

Variables*	Mean ± SD	1	2	3	4	5
1—Expected relief OM (0-100)	64.44 ± 26.29	1.00				
2—Expected improvement in quality of life OM	4.76 ± 0.91	0.62†	1.00			
3—Expected improvement in functioning OM	4.69 ± 0.99	0.58†	0.73†	1.00		
4—Changes in pain intensity (NRS)	0.85 ± 2.25	0.18†	0.14†	0.12†	1.00	
5—Changes in depressive symptoms (BDI)	1.46 ± 7.61	0.02	0.04‡	0.04	0.24†	1.00
6—Changes in pain interference (BPI)	0.76 ± 2.10	0.12†	0.12†	0.10†	0.59†	0.38†
7—Changes in pain catastrophizing (PCS)	4.19 ± 11.03	0.11†	0.09†	0.08†	0.38†	0.42†
8—Global impression of change	0.01 ± 0.88	0.23†	0.19†	0.17†	0.47†	0.31†
9—Satisfaction with treatment	4.21 ± 1.83	0.09†	0.09†	0.08†	0.17†	0.11†

* Positive values for variables 4 to 7 reflect improvements.

† $P < 0.001$.

‡ $P < 0.05$.

BDI, Beck Depression Inventory-I; BPI, Brief Pain Inventory; PCS, Pain Catastrophizing Scale.

N=2272, Pain Clinic Entry, data complete, 3 Canadian Pain Centers

Cormier et al (2016) Pain:330-338

Clinical Implications

- Assess patient expectations at intake
- Initial treatments carry over
 - Early success important
 - Repeated failure stacks the deck, even against 'effective' treatments

Acknowledgments

- RAC
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- NIH, University of California