

# The analgesia-addiction interface: Clinical and neurobiological issues

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# Drugs Commonly Used for Chronic Pain

- Opioids
- COX inhibitors
- 5HT/NE reuptake inhibitors (*TCA*s, *SNRI*s: *Venlafaxine*, *Duloxetine*, *Tramadol*)
- Triptans (5HT<sub>1b/d</sub> agonists)\*
- Anticonvulsants (pregabalin, gabapentin, topiramate, etc.)\*

\* ? Broad spectrum analgesics

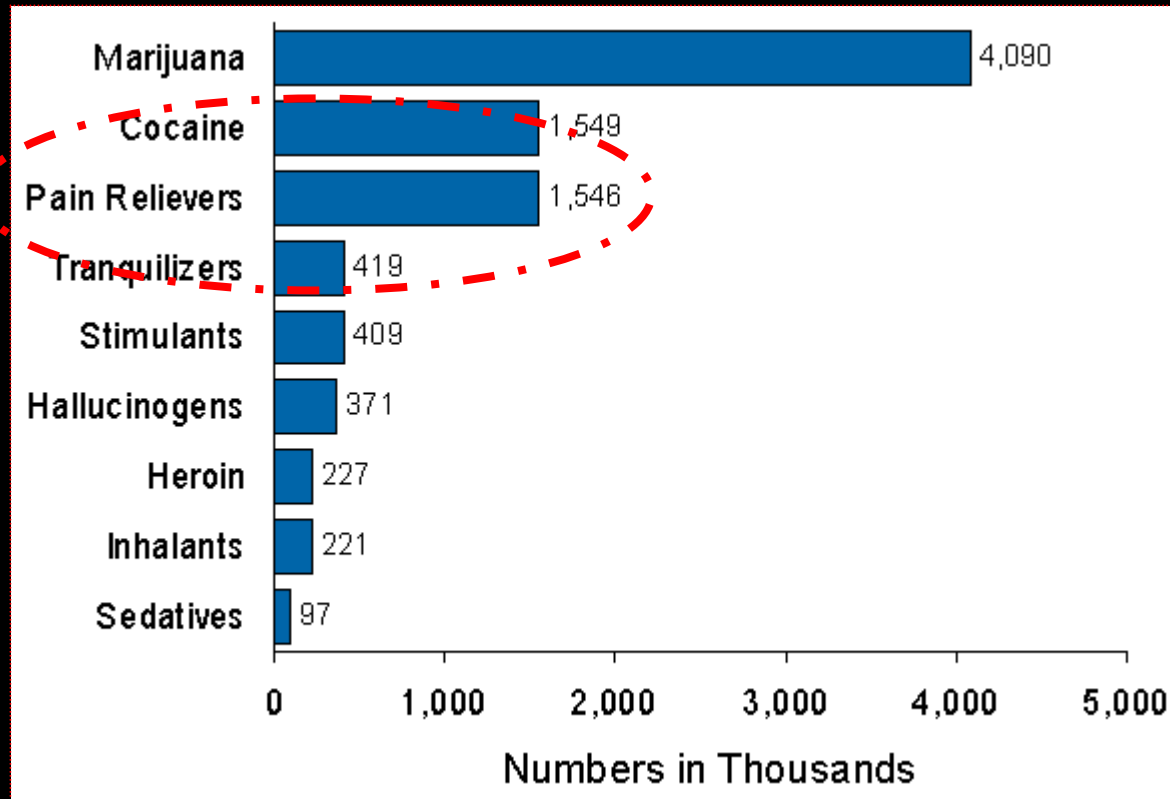
Many patients have residual pain when non-opioid options are exhausted.

Opioids are currently the most potent, and broadest spectrum analgesics.

# On the other hand

- Opioid efficacy past three months unproven
- Side effects (sedation, nausea, constipation, urinary retention)
- Tolerance and dependence (hyperalgesia)
- Abuse potential

# Substance abuse: the scope



2005,  
SAMSA website


ca. 30 million heavy drinkers,  
120 million smokers  
Most individuals are polysubstance users

# Question for the clinician:

Why is my patient continuing to take opioids?

- Effective analgesia
- Relieve symptoms of physical dependence
- Patient has become addicted
- Substance abuse antedated treatment
- Patient never had pain

# Prescription opioids: two user groups



Pain treatment  
with opioids



Prescription opioid  
abuse

Millions of people in both groups

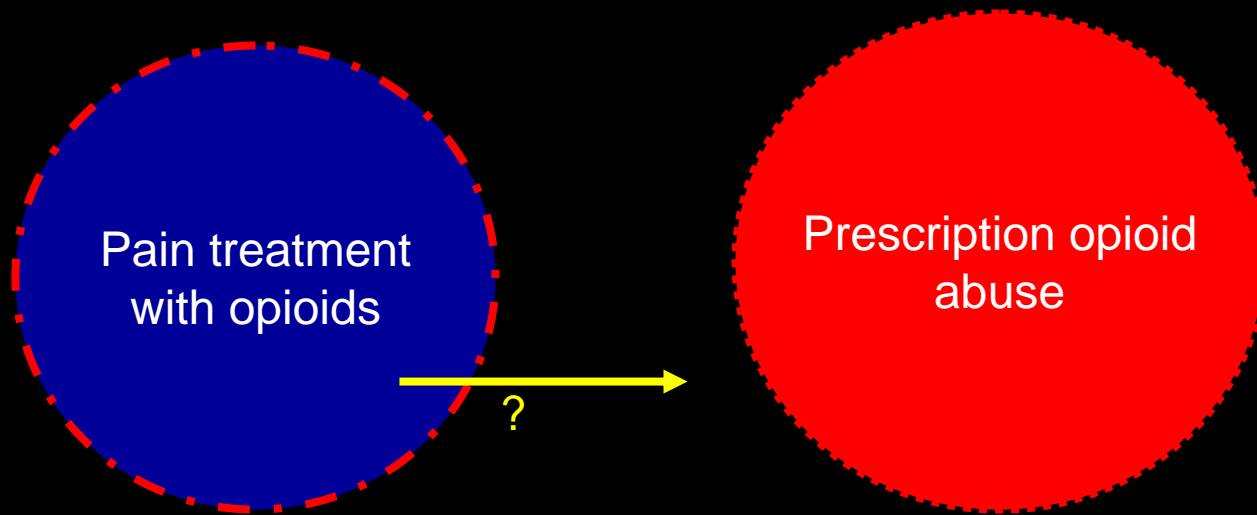
# The clinical conundrum

- Patient reports inadequate pain relief
- Risk of creating drug abuse.
- Patient with history of drug abuse
  - Legitimate pain complaint?
  - Deception to obtain drugs?



# The Doctor's Dilemma:

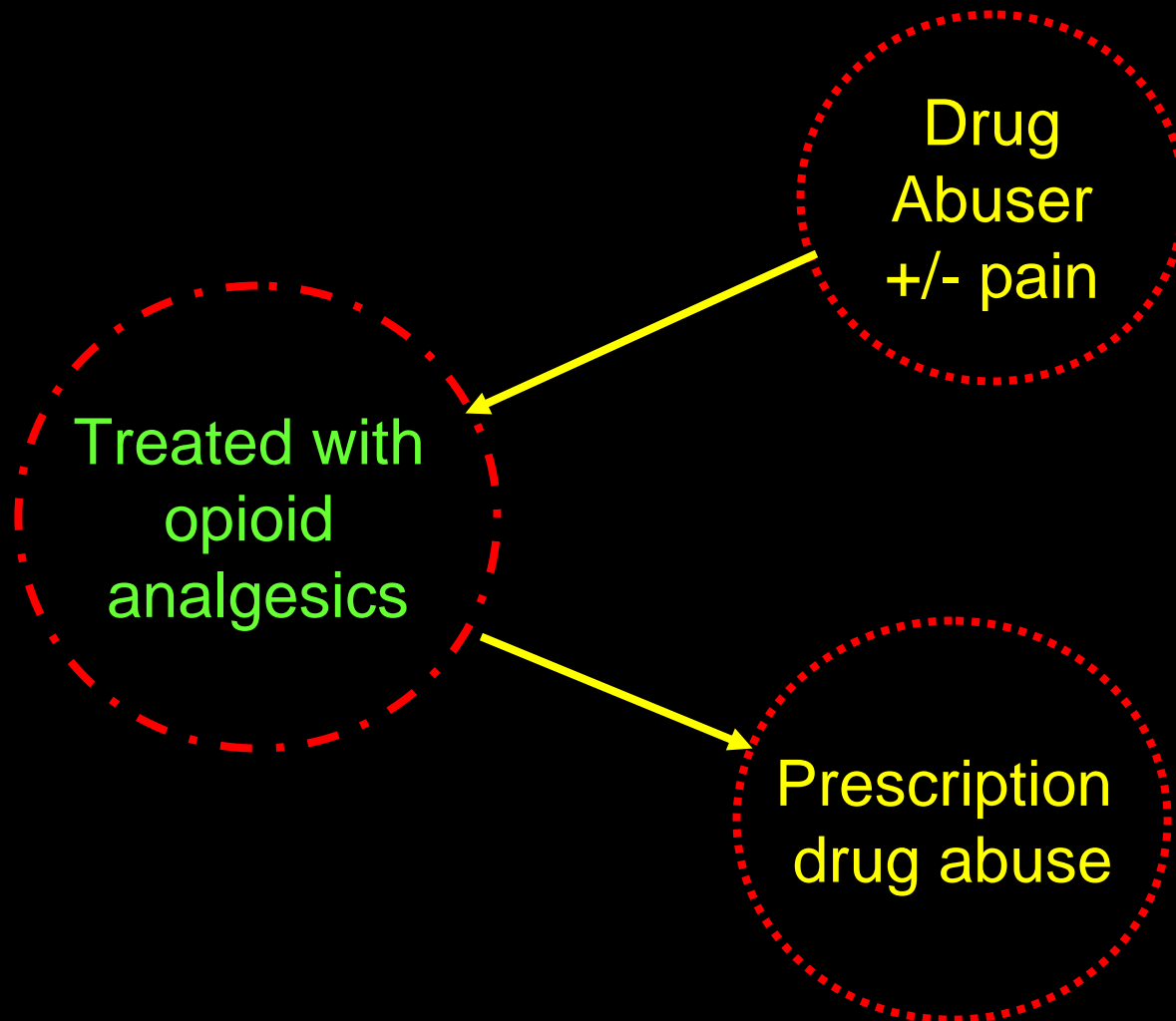
Does pain treatment cause opioid abuse?



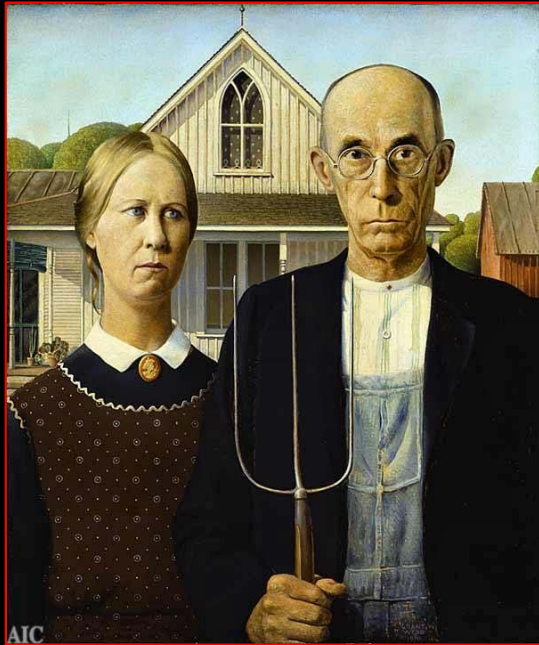
# New abuse rates relatively low when opioids used to treat CNCP

- Mark Sullivan— SE area Vets; Edlund et al, Pain in press.  
2% ( ca. 300/15000) overall incidence (25% non-opioid Sub Abuse, 67% Mental health Dx)

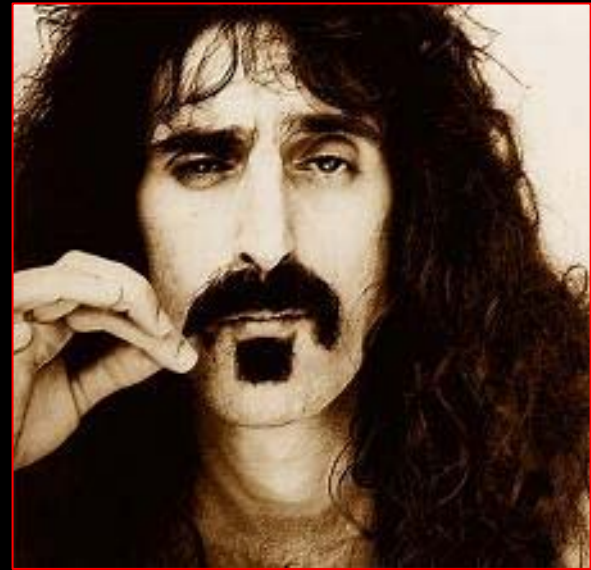
# Some substance abusers become opioid abusers when treated with opioids



# Know your patient



“Doc, only Dilaudid works for me.”



“Doctor, John doesn’t like to take drugs”

# Patient evaluation and monitoring

- Screening instruments (Kirsch, Managed Care 16, Supplement 3, February, 2007)
- Urine toxicology
- Steve Passik: Aberrant drug taking behaviors—  
record keeping

# The Future

- Genetic screens
- Endophenotyping, functional imaging

# How can we improve pain therapeutics?

- Better non-opioid analgesics
- Non-pharmaceutical approaches (CBT, etc.)
- Opioids with reduced tolerance and dependence (DOR antagonists, adjuvants)
- Potent, non-rewarding analgesics

# Properties of an Ideal Analgesic

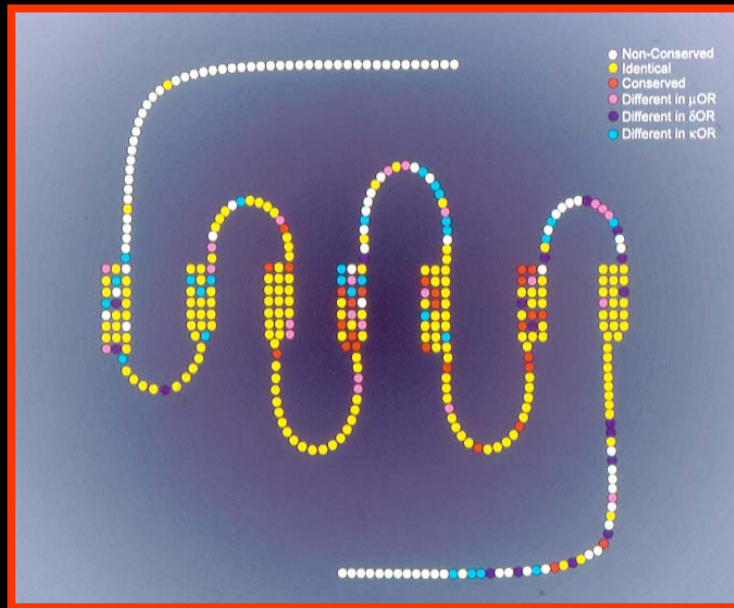
The holy grail of pain research

- Completely safe & totally effective
- Works on all pains
- Tolerance does not develop
- Non-addicting

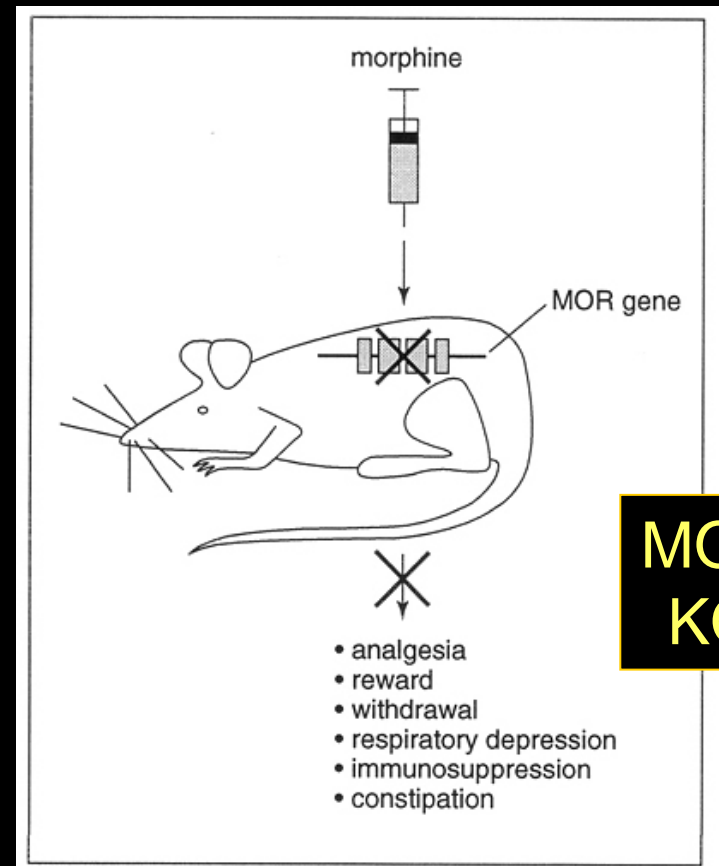


What about opioids; can we separate analgesia and reward?

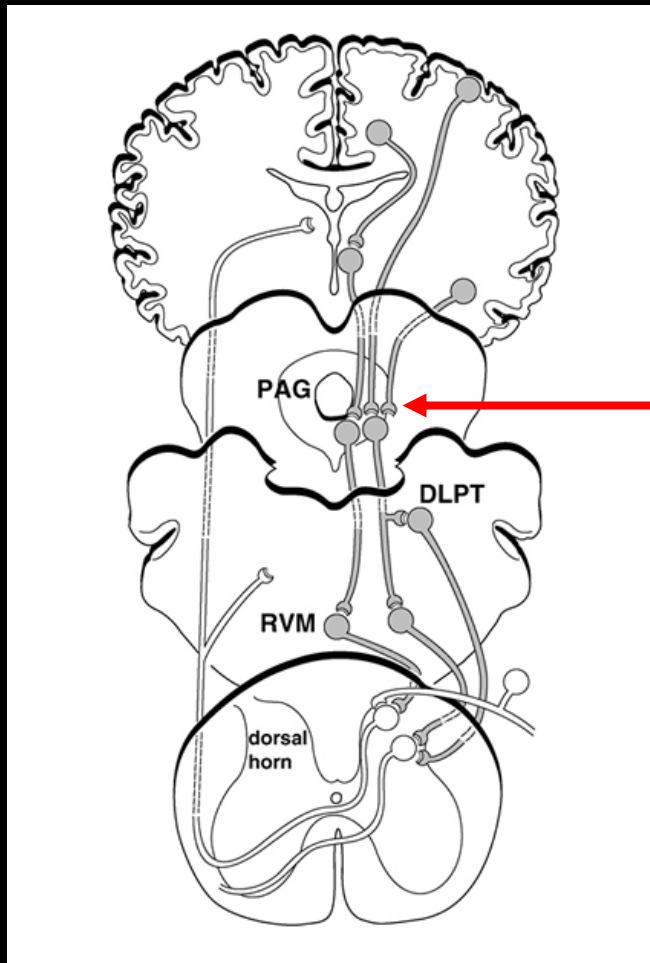
# The same receptor mediates both



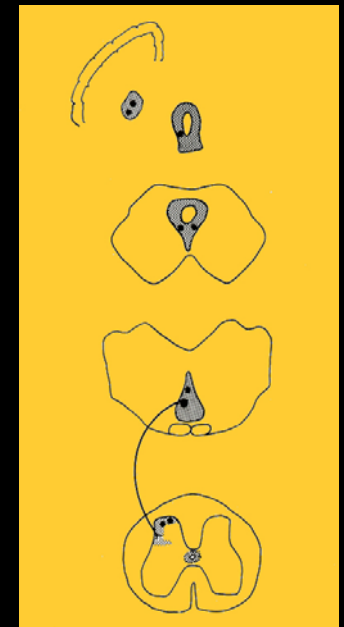
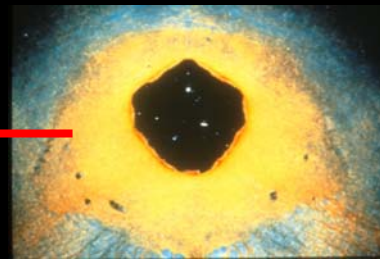
Opioid family of  
7TMD GPCRs



# Opioid analgesia circuit



Leu-enk

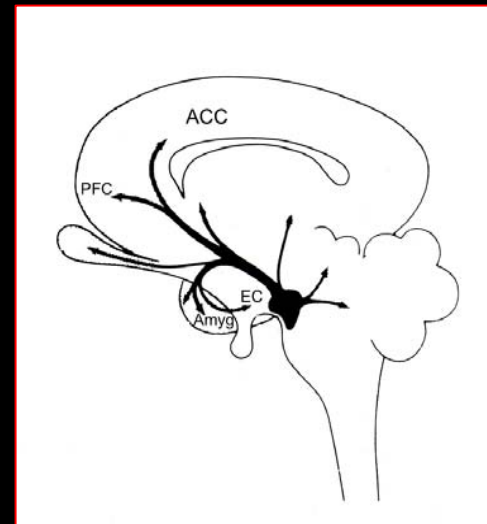
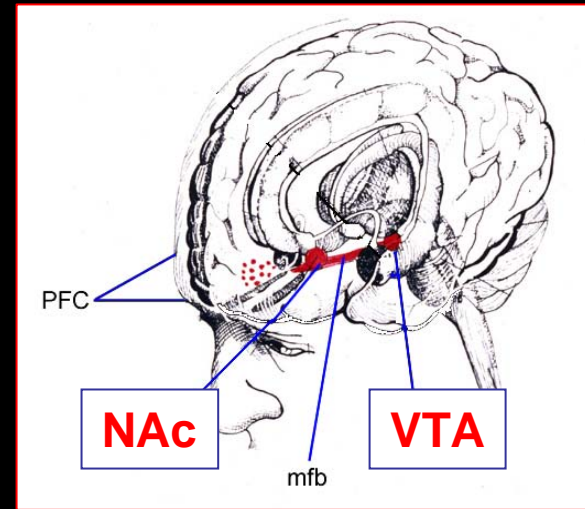
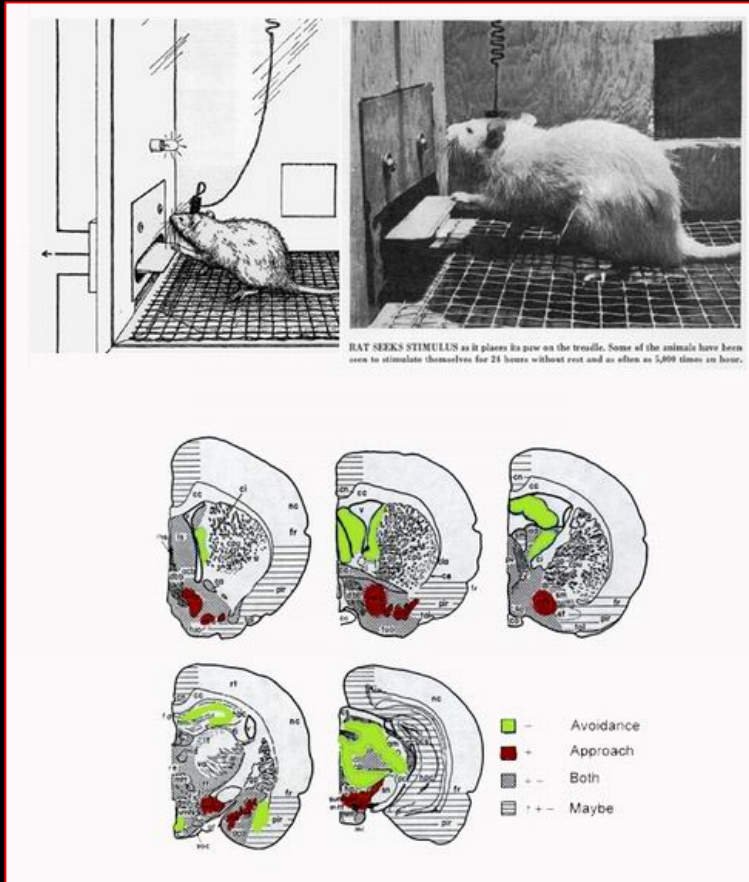


Tyr-gly-gly-phe-met

Tyr-gly-gly-phe-leu

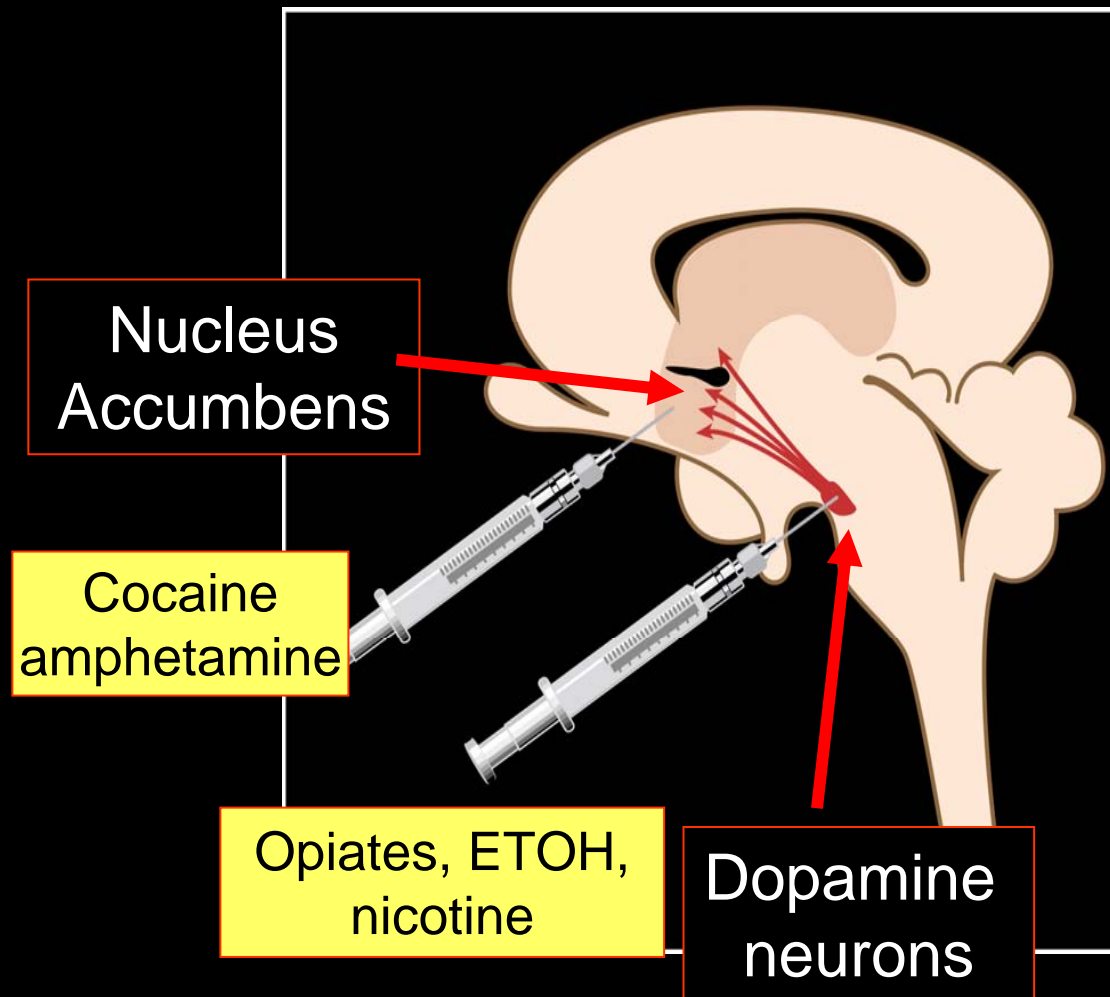
Hughes & Kosterlitz, 1975  
Basbaum & Fields, 1976

# Mesolimbic reward circuit

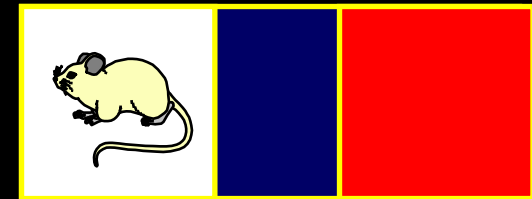
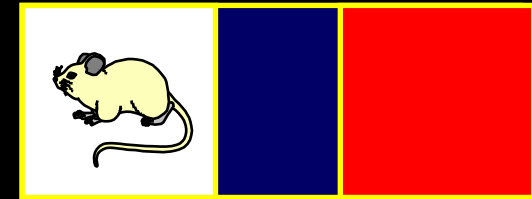
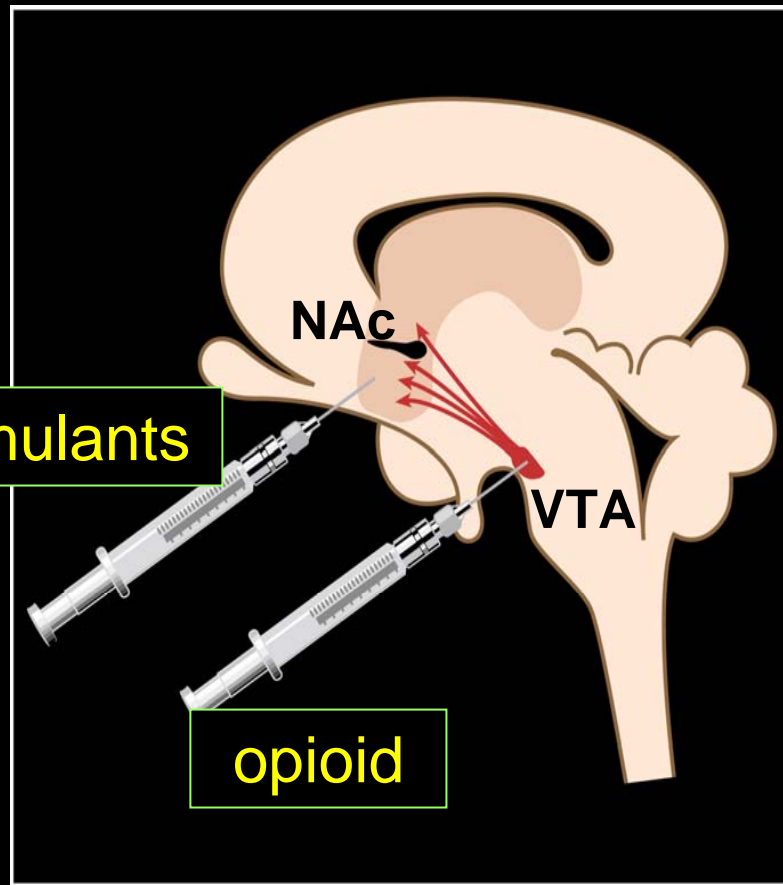


Olds & Milner, 1954  
McGill / Hebb lab

# Rats self administer drugs directly into the reward circuitry



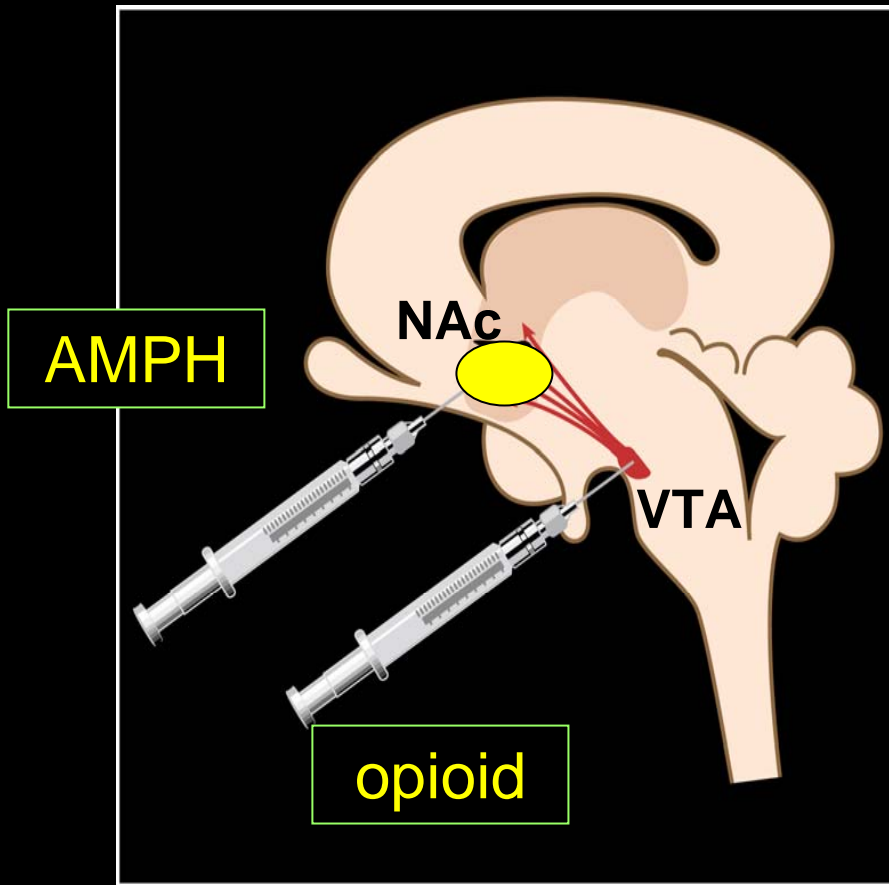
# Reward circuit produces analgesia



Analgesia and drug reward Blocked by NAc DA antagonists

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

# Psychostimulants potentiate opioid reward



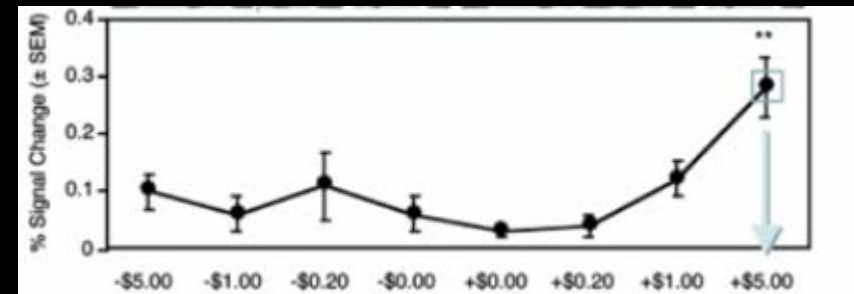
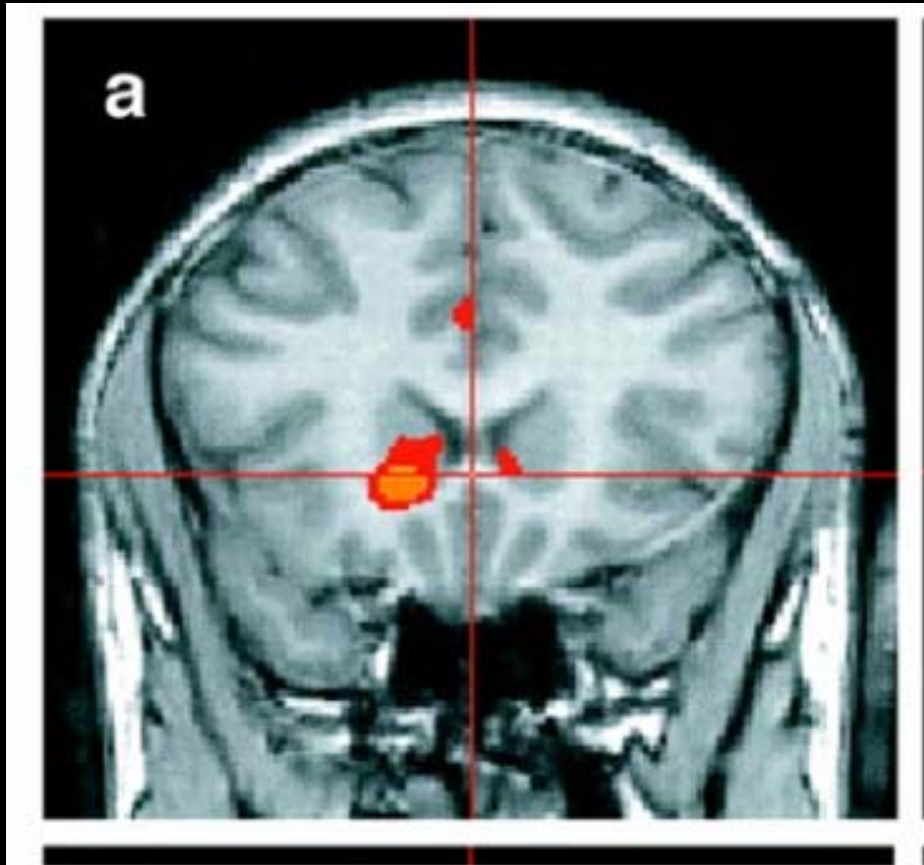
Blocked by Dopamine  
antagonists in NAc

# We need to know how the reward circuitry produces analgesia

- **If** we can uncouple these processes, we may have better analgesics.



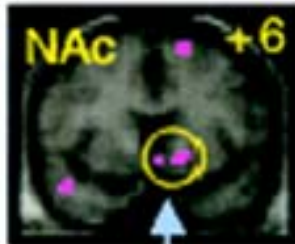
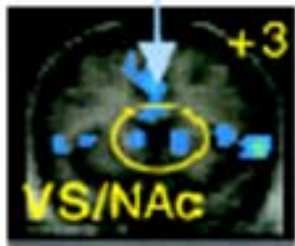
# Human NAc activity correlates with magnitude of monetary reward



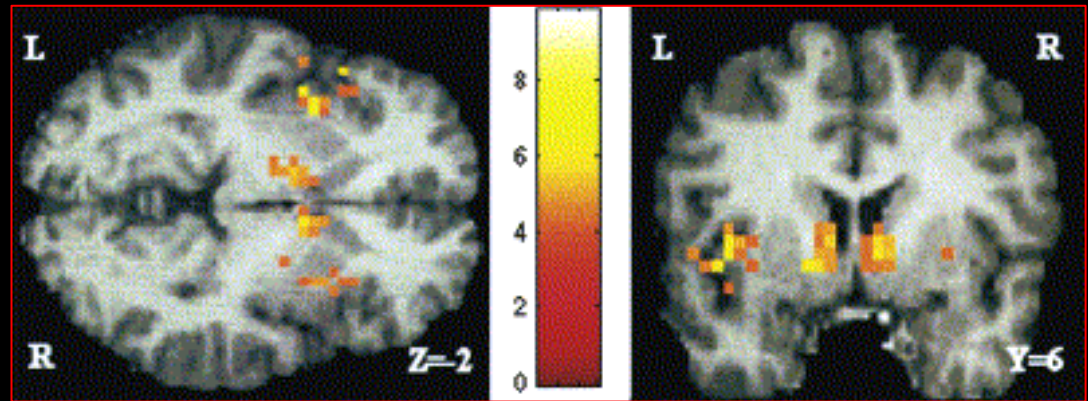
Knutson et al, J. Neurosci 2001

# Noxious stimuli and pain predictive cues activate human ventral striatum

Noxious thermal Stimulus

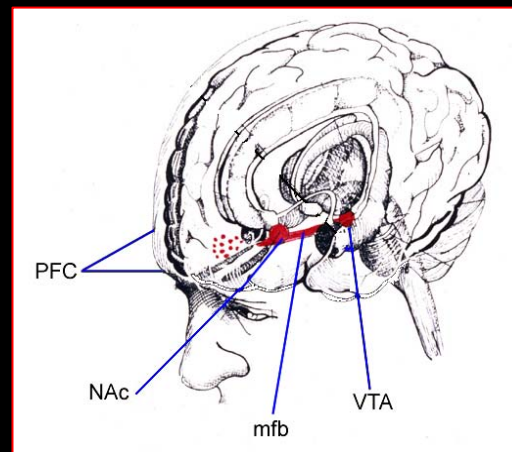


Becerra et al,  
Neuron, 2001

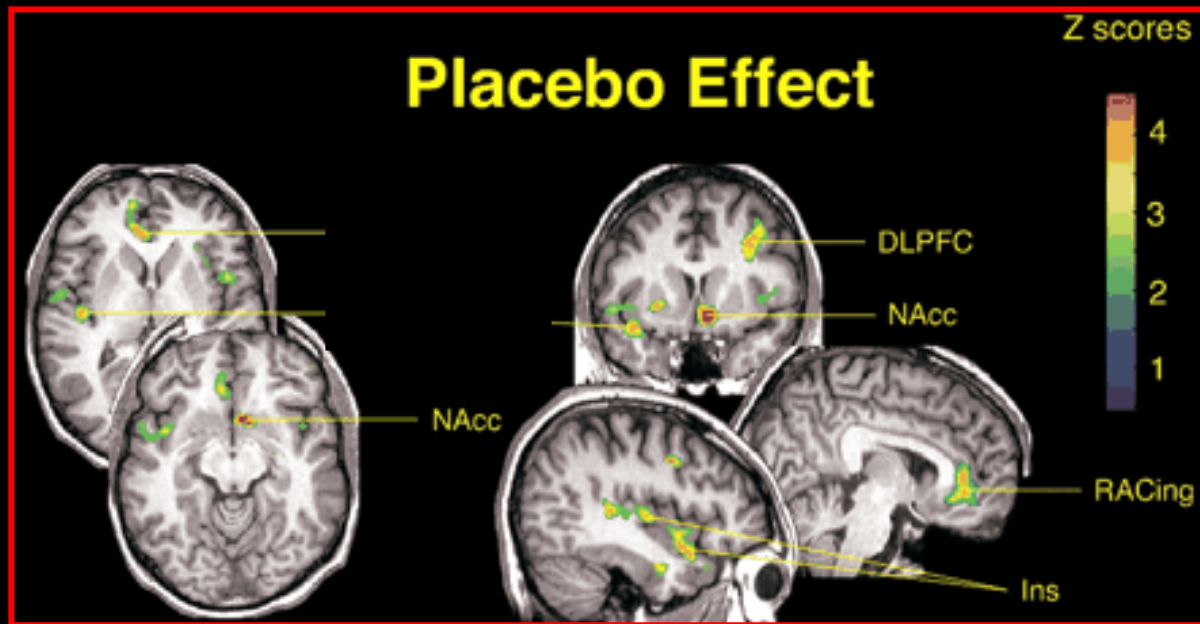


Pain predictive cue

Jensen et al,  
Neuron, 2003

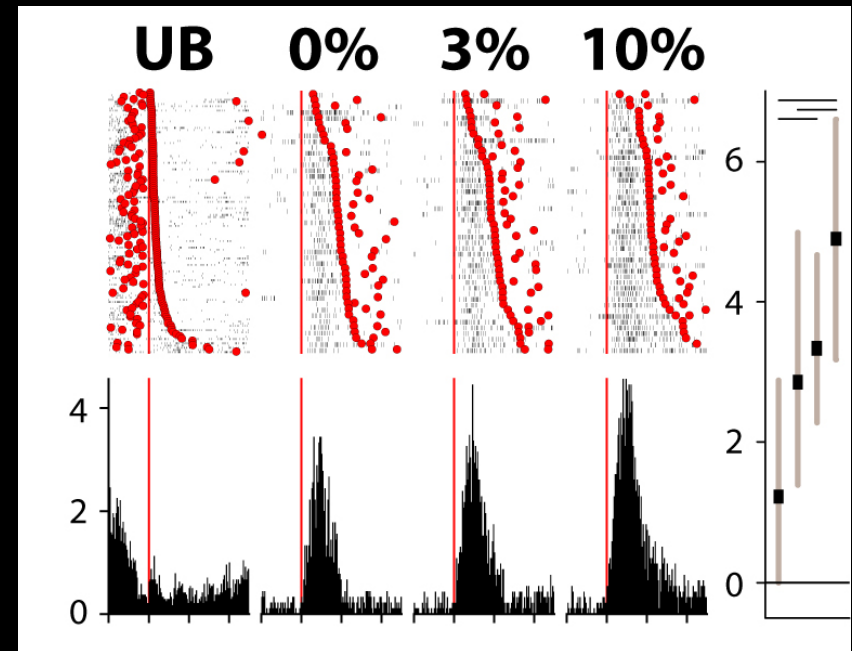
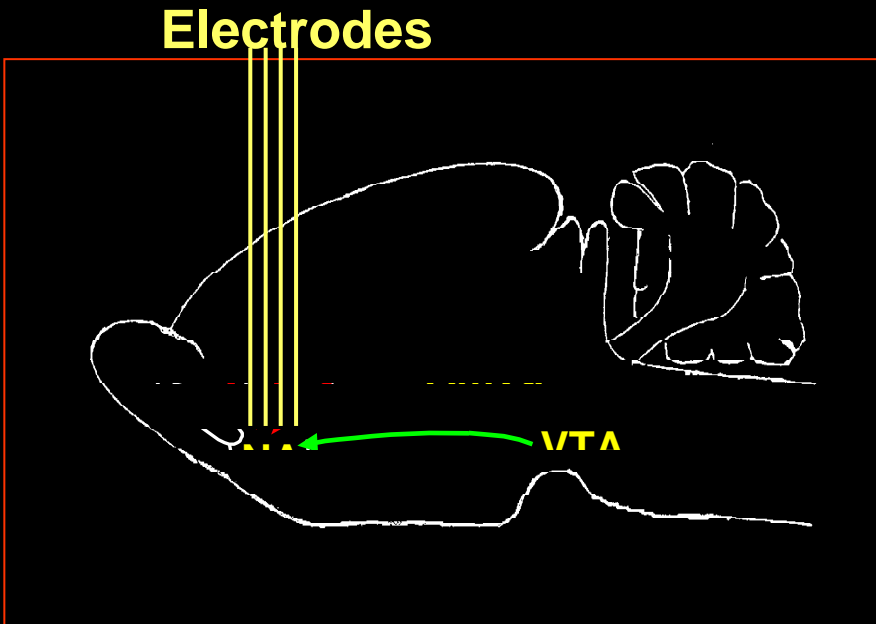
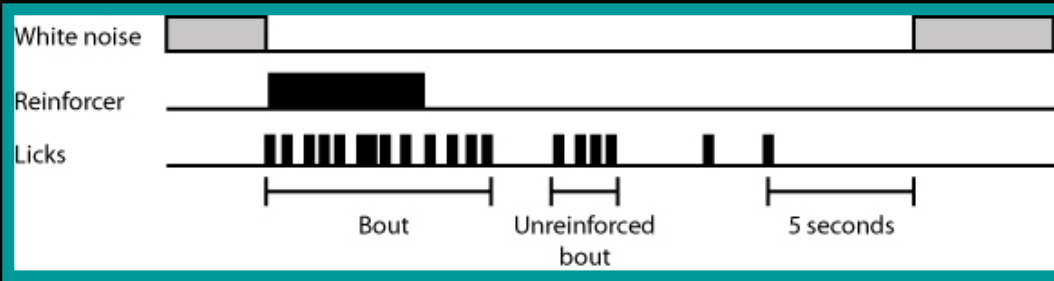


# Expectation of pain relief leads to opioid release in NAc



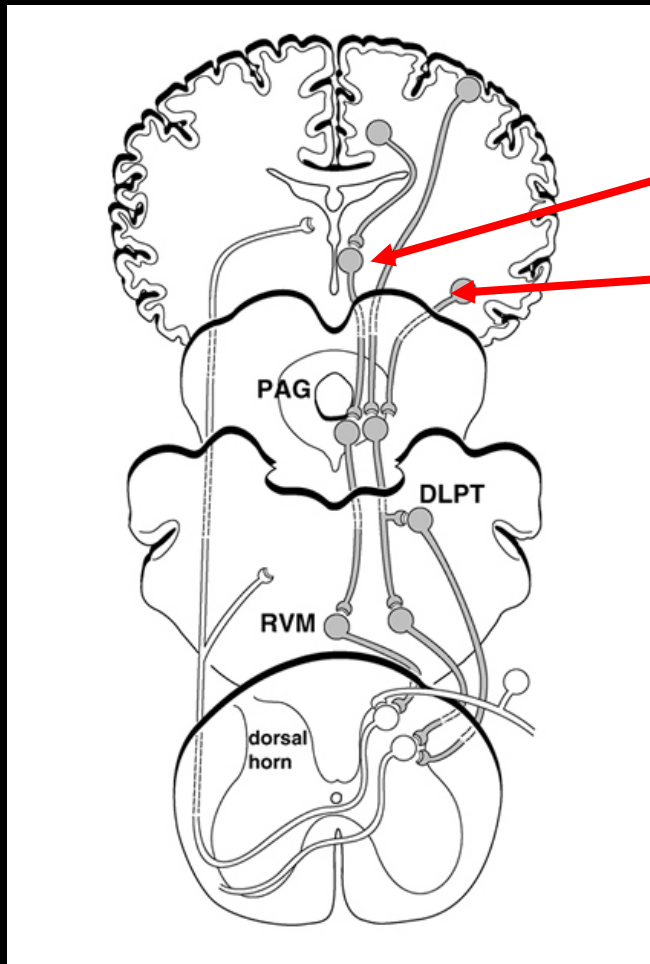
Zubieta et al, J. Neurosci, 2005

# NAc neurons encode reward value



Sharif Taha

# How is reward circuit linked to pain modulating pathway?



hypothalamus

amygdala

What are the relevant non-opioid Neurotransmitters?

Becerra et al, Neuron, 2001

# Summary

- Opioids are essential for treating moderate to severe pain
- Neurobiologists are making progress in reducing opioid tolerance and dependence
- Opioids are rewarding; this has created a growing non-medical demand for prescription opioids
- Opioid addiction is a disease
- Understanding how opioids produce reward and analgesia will lead to better analgesics and treatments for addiction.

# Thanks

- NIDA, NINDS and the NIH pain consortium,
- The AMA
- Allan Basbaum, Jon Levine, Mary Heinricher, Mike Morgan, ZZ Pan, Sharif Taha
- State of California Alcoholism and Addiction Research Program, Gallo Research Center, Wheeler Center, University of California