Enhancing Translation in Preclinical Assessment of Pain*

or….”what can a 6” furry creature tell us about human pain?”

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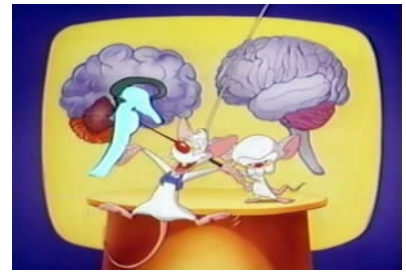


http://www.youtube.com/watch?v=snO68aJTOpM

What can we learn in animal studies that may offer increased confidence in filtering targets going forward?

The problem – lots of new information about neurobiology of pain,

many "high impact" papers in premier journals

…..but limited impact on treatment of human pain;

Clinical trials have not been very successful;

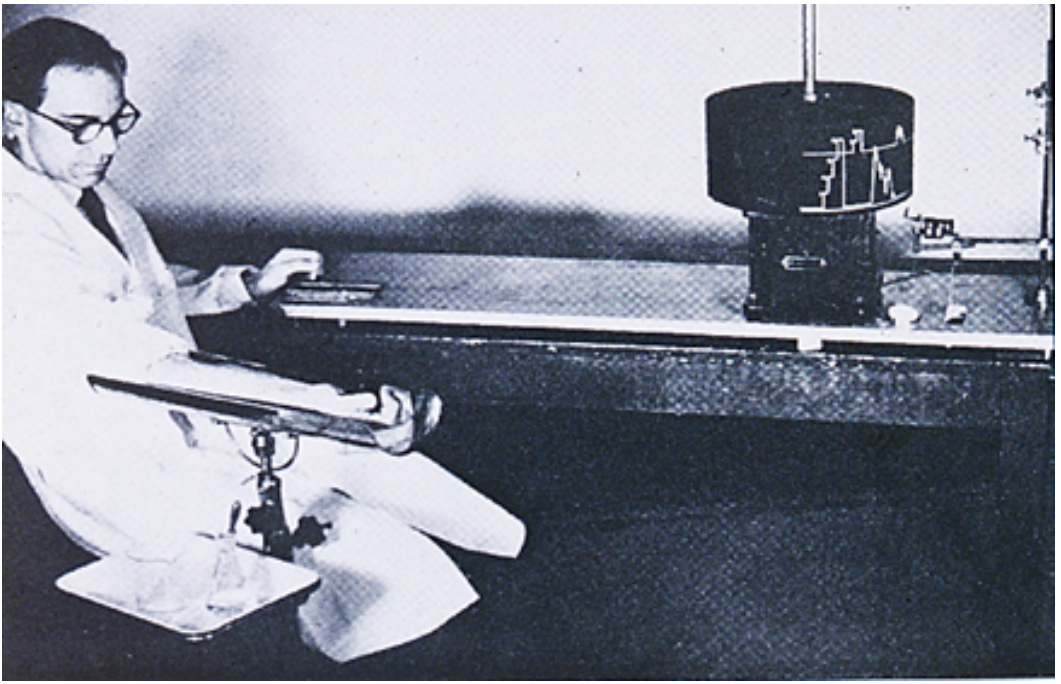
Loss of confidence in the validity of preclinical pain studies!!

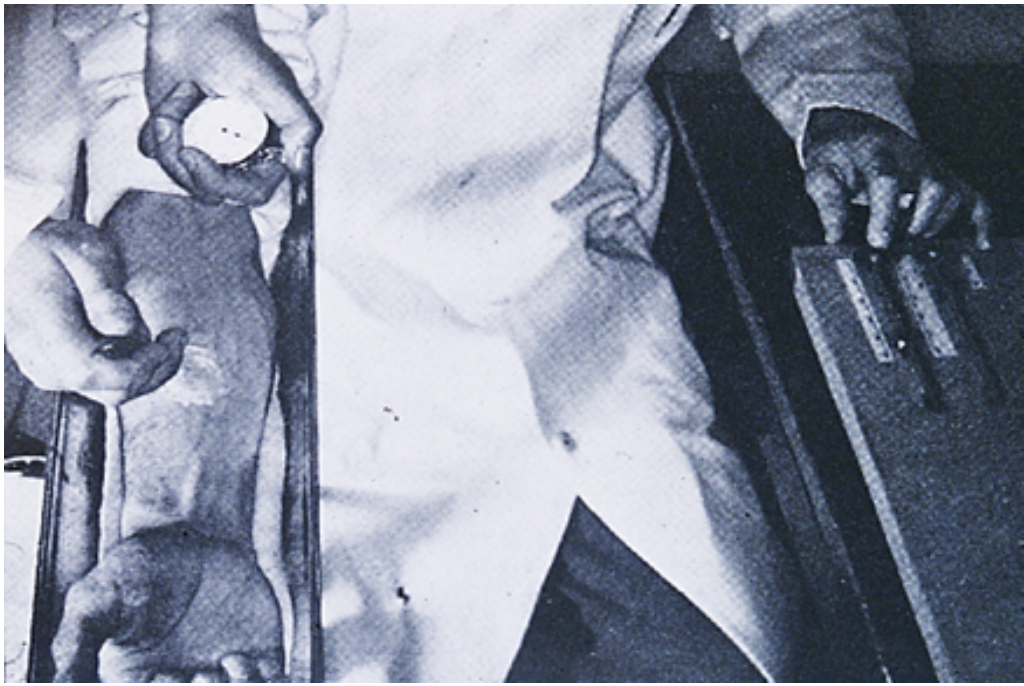
"Animal models are not predictive" - has become **a sound bite**!!

Question is too complex for a superficial answer;

- **lack of knowledge of clinical pain mechanism – what are we translating to?**
- compounds with poor tolerability that do not allow mechanistic conclusion;
- inability to invalidate targets clinically, etc.

Somatosensation and nociception crosses species!!





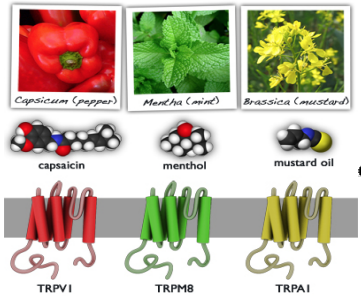
Activation of nociceptors produces sensations of pain in humans.

- NGF
- bradykinin
- noxious heat and mechanical stimulation
- capsaicin

Blocking activation or transmission in nociceptor prevents pain experience in humans

- CIP due to mutations in TRKA receptors, Nav1.7 channel

We have learned much that is relevant to man



Transduction

Heat

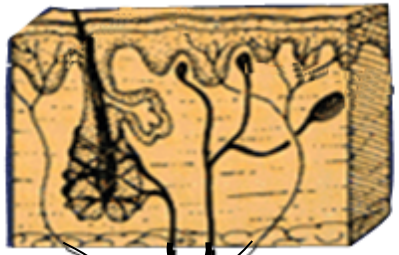
TRPV1, TRPV2
TRPV3, TREK-1

Mechanical

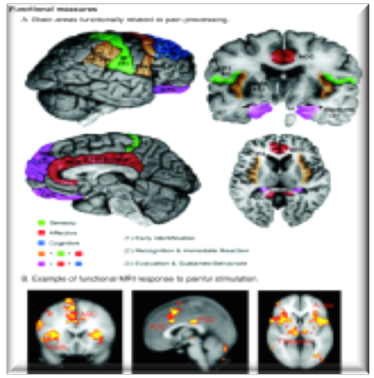
MDEG
DRASIC
TREK-1

Cold

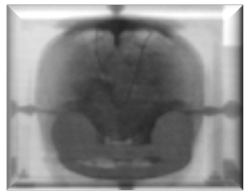
TRPM8, TRPA1



Perception
Cortex



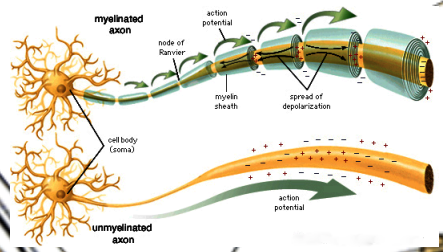
Endogenous Opioids



Intra-PAG
stimulation
in Human

Modulation
Limbic (amygdala)
Midbrain/medulla

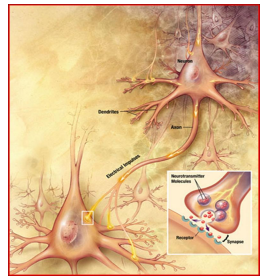
Transmission
Sensory Fibers
(touch, pain)



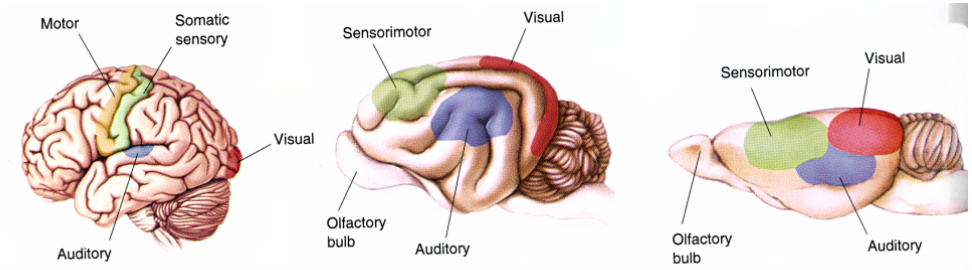
From Brain

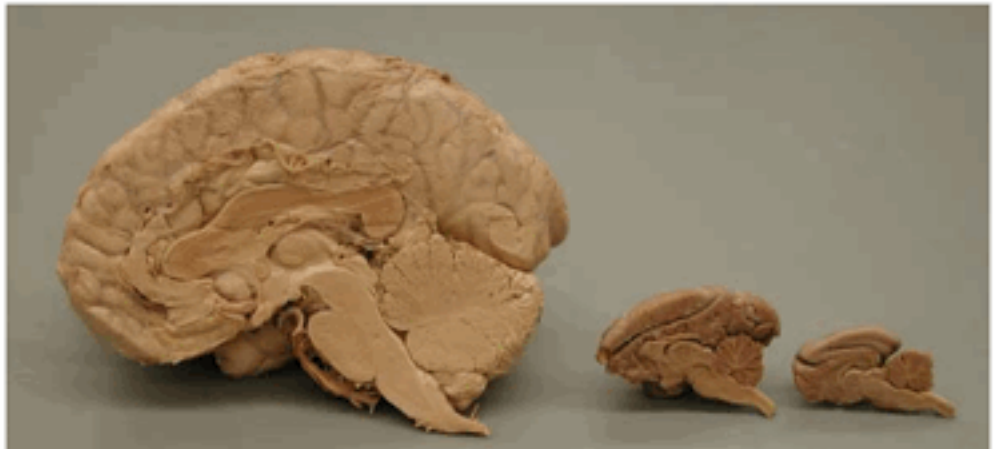
To Brain

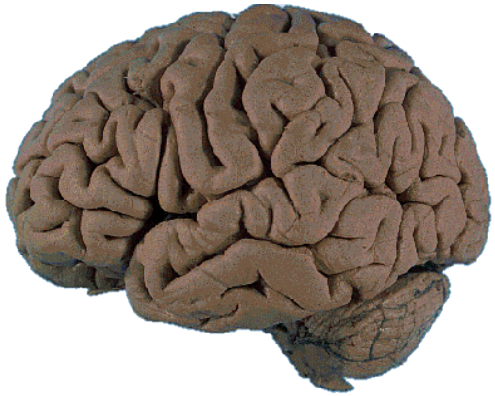
Transmission
Spinal Cord



Animal models have limitations that must be acknowledged a priori!!







Behavioral measures of "pain" are problematic for chronic pain

Hypersensitivity: most behaviors measure spinal reflexes (withdrawal), spino-bulbospinal reflexes (jumping, stretching) or simple behaviors (vocalization, biting, licking, guarding).

These behaviors can often be performed in decerebrate animals!

Chronic pain patients exhibit spontaneous (non-evoked) pain.

The prevalence of hypersensitivity is thought to be less than the prevalence of spontaneous pain – but important!!

Pain involves supraspinal processing (*emotion, cognition and learning*).

Complex pain behaviors: aggression, food intake, locomotion, weight bearing, posture and gait, facial grimace, burrowing, wheel running, reduction in quality of life (anhedonia, anxiety, depression, cognitive deficits, memory impairment, negative affect, sleep disruption)….but, are these measuring mechanisms relevant to modulation of pain?? This has to be demonstrated experimentally.

Operant measures of pain: Negative reinforcement/CPP; PEAP; self-administration of analgesic drugs

One possibility is that operant models may offer potential translational advantages

Where can we go to increase confidence in preclinical studies – do animals feel "pain" in some analogous way as humans?

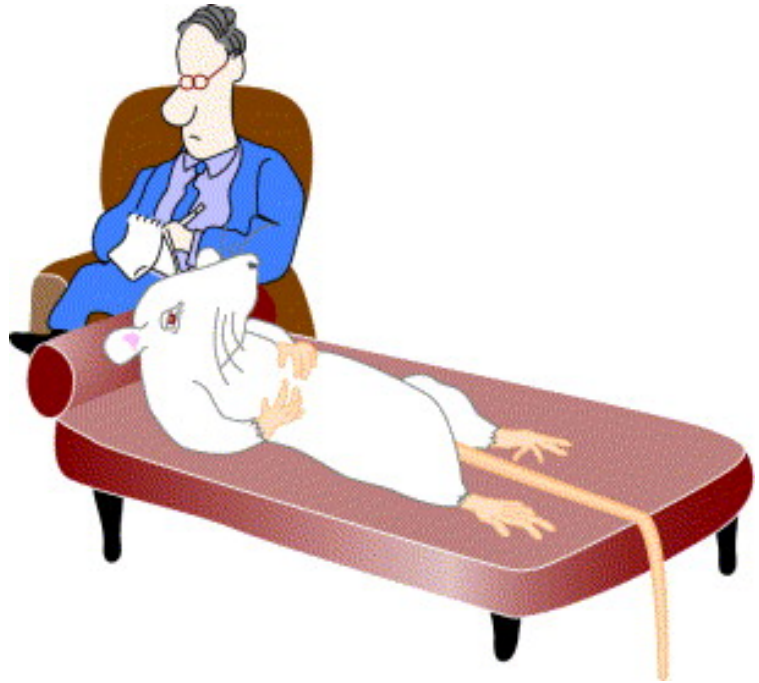
Pain is vital to survival - congenital insensitivity to pain reduces life expectancy).

Pain is an important part of body's defense system to:

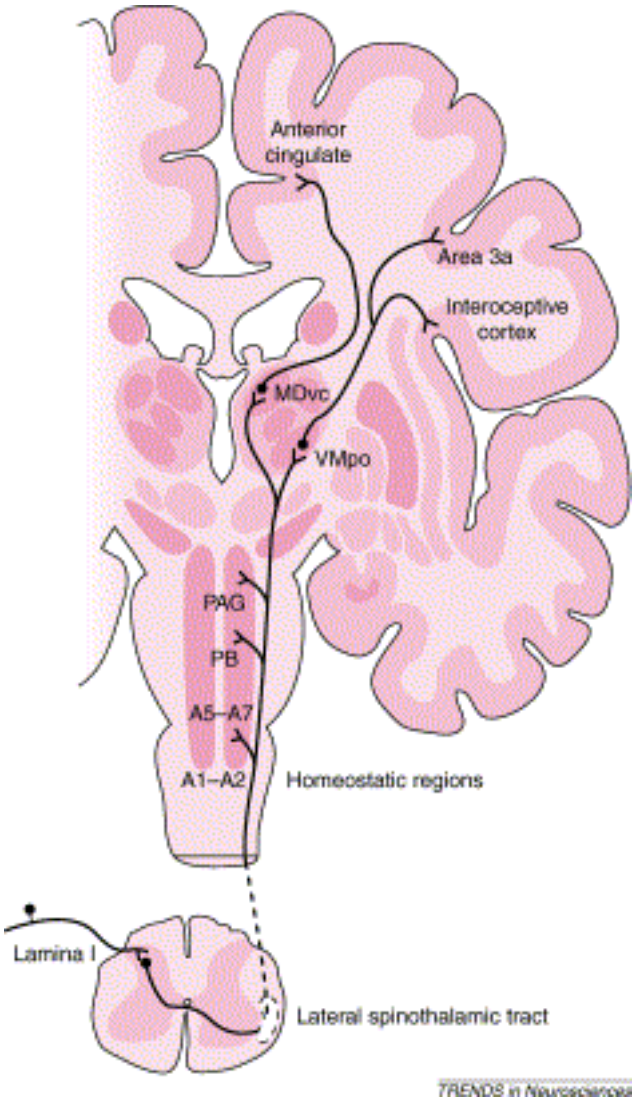
- **withdraw from damaging situation (reflexive reaction)**
- **protect the affected body part while it heals (ongoing pain)**
- **avoid similar harmful situations in the future (learning)**

Human pain is a multidimensional subjective feeling (Melzack and Casey, 1968):

- **sensory-discriminative (sense of the intensity, location, quality and duration of the pain)**
- **affective-motivational (unpleasantness and urge to escape the unpleasantness)**
- **cognitive-evaluative (cognitions such as appraisal, cultural values, distraction and hypnotic suggestion)**



Homeostatic afferent pathway for pain



Interoceptors: nociceptors, (osmotic pressure, heart rate, blood pressure, volume, concentration of minerals, CO_2….)

Lamina I neurons project to homeostatic sites in the brainstem (the parabrachial nucleus (PB) and the PAG) and to the **thalamus**: the posterior part of the ventral medial nucleus (VMpo) and the ventral caudal part of the medial dorsal nucleus (MDvc).

The VMpo conveys modality-specific sensory representation of pain to **interoceptive cortex** (the insula) and to area 3a in the sensorimotor cortex **(feeling)**.

The MDvc integrates lamina I input with brainstem homeostatic activity (from PB and PAG) and produces behavioral drive in the **anterior cingulate cortex (motivation)**.

Craig AD., Trends Neurosci. 2003
A new view of pain as a homeostatic emotion.

Increased translational relevance of pain research?

A.D. Craig, Nat. Rev. Neurosci. 2009

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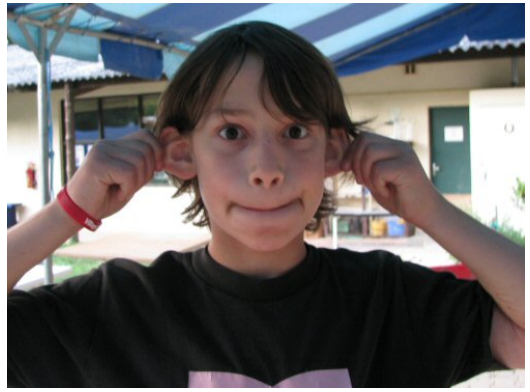

Nociceptors: receptors, channels, intracellular signaling…
Neurotransmitters: glutamate, opioids
Pain pathways: main ascending and descending pathways.
Descending facilitation and inhibition from the RVM discovered in rat tail-flick test and confirmed in humans.

Mesolimbic reward pathway: dopamine
Behavior: motivation

Pain is an aversive state that motivates behavior to seek relief

Opinion TRENDS in Neurosciences Vol.26 No.6 June 2003 303

A new view of pain as a homeostatic emotion

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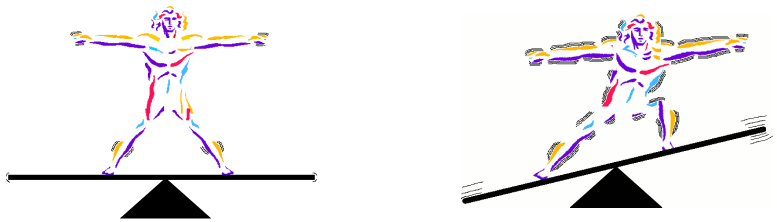
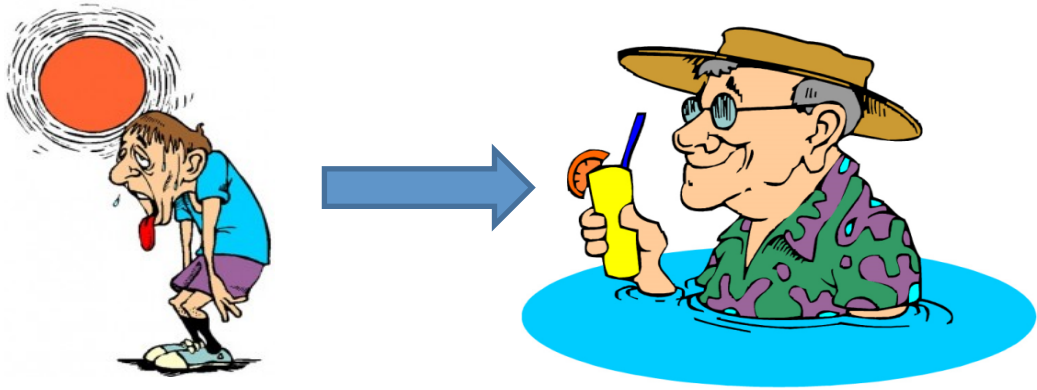


"…the human feeling of pain is both a distinct sensation and a motivation – that is, a specific emotion that reflects homeostatic behavioral drive similar to temperature, itch, hunger, and thirst."

Negative reinforcement can be used in animals to "unmask" pain that is "just there"!!



Imbalance/Discomfort
Tonic Aversive State

Relief is rewarding

Relief of pain can be conceptualized as a reward!!

Reinforcement:
An event that will increase the likelihood of a behavior.

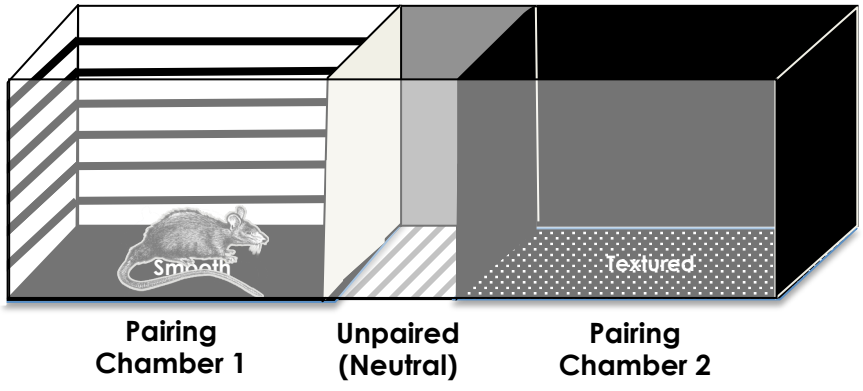
Negative Reinforcement:
An increase in the future frequency or likelihood of behavior due to the removal of an aversive stimulus.

Pain relief is a prime example of negative reinforcement.
Associating a specific event (i.e. taking a medication) with removal of an ongoing stimulus (i.e. pain) will increase the behavior of taking the medication.

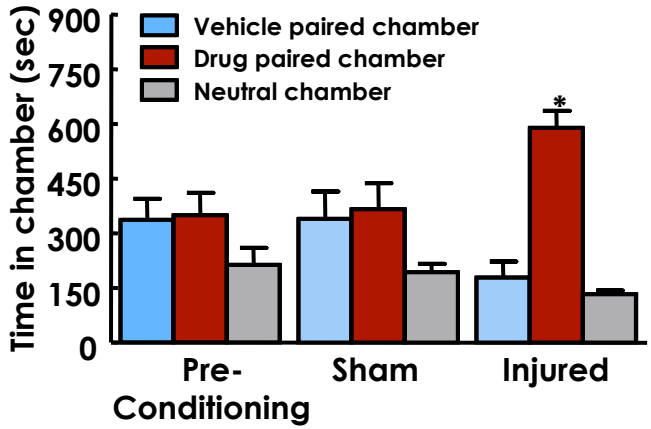
Unmasking spontaneous pain through negative reinforcement

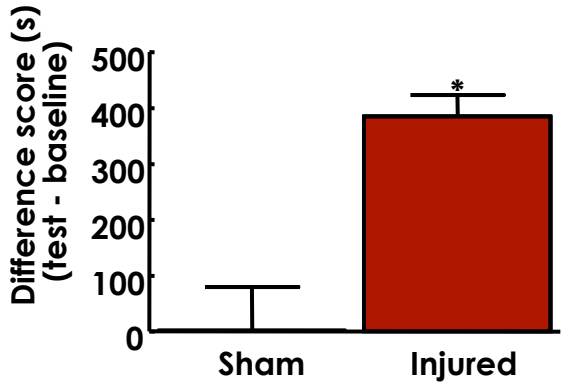
Conditioned place preference (CPP) - Pairing a context with a treatment that produces pain relief will result in increased time spent in that context.

- CPP will be observed only if the aversive state induced by chronic pain is present – unmasks pain that is just there.
- CPP will be observed only if the treatment relieves the aversive state – mechanism.
- CPP can be demonstrated in animals with *complete denervation of the hindpaw* – the aversive state is not generated by ambulation within the testing chamber;
- CPP can be demonstrated with peripheral nerve block and spinal treatments – i.e., drugs that are not rewarding in the absence of pain can become rewarding in the presence of chronic pain (relief of pain as a reward).



Visual, tactile and odor cues





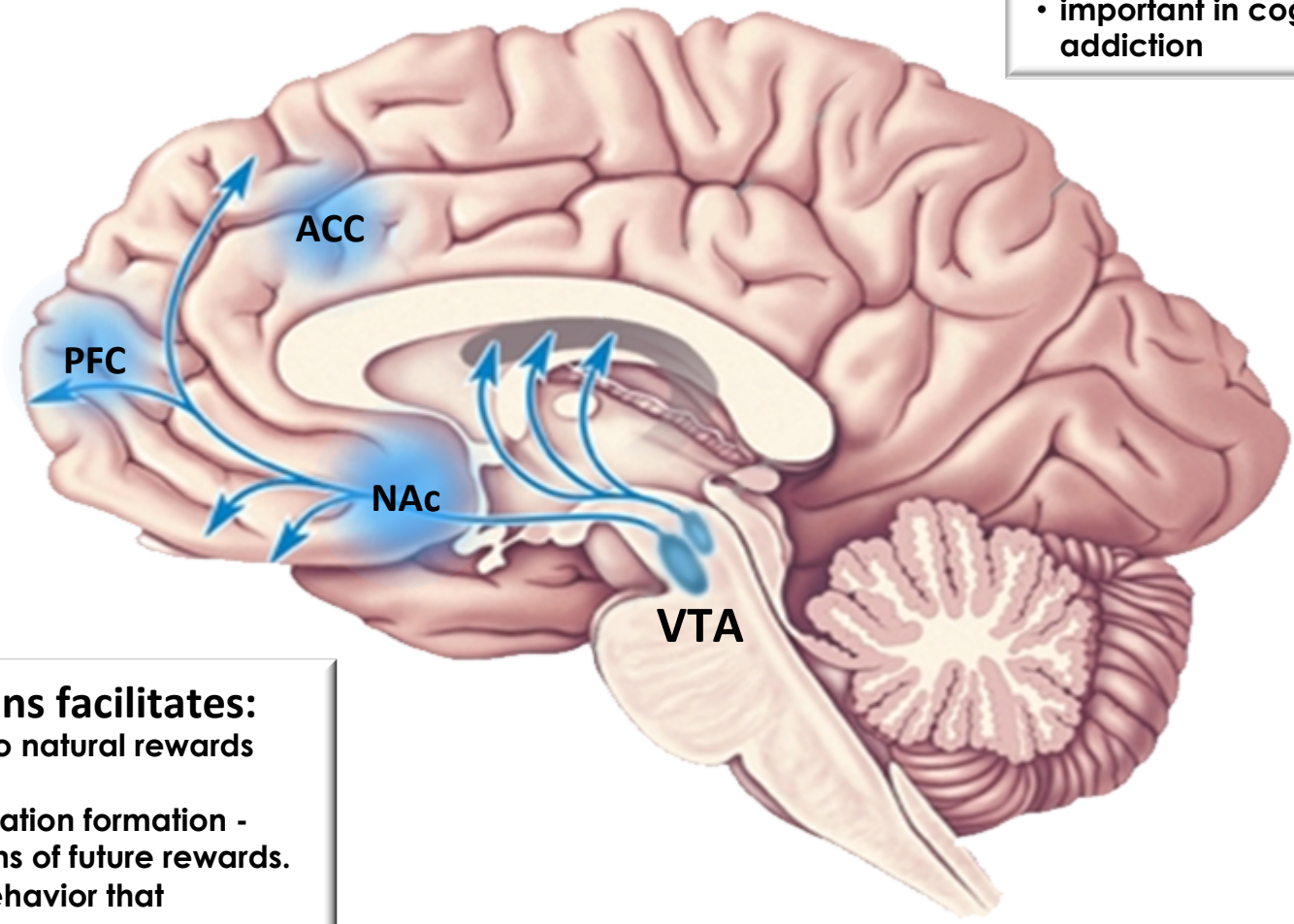
Mesocorticolimbic Dopamine Reward/Valuation Pathway

Prefrontal Cortex
Anterior Cingulate Cortex

- suppression of actions that do not contribute to an optimal outcome.

Ventral Tegmental Area (VTA)

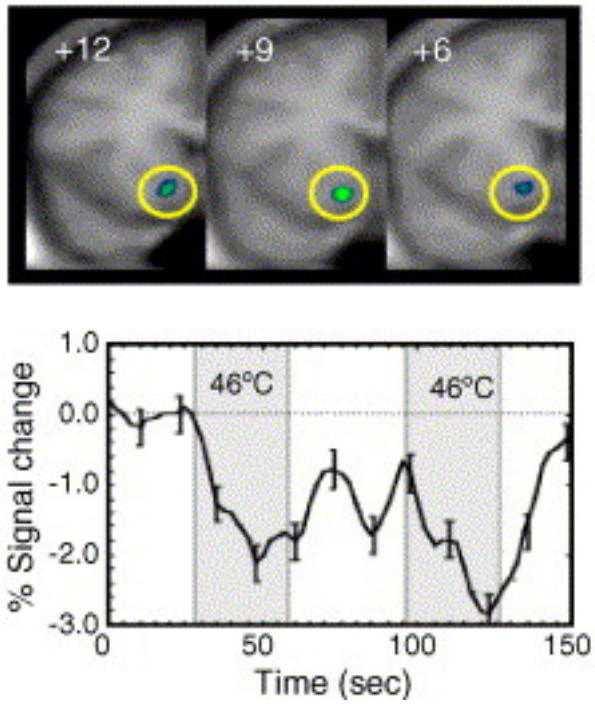
- the origin of the dopaminergic cell bodies of the mesocorticolimbic system
- implicated in the drug and natural reward circuitry of the brain
- important in cognition, motivation, drug addiction



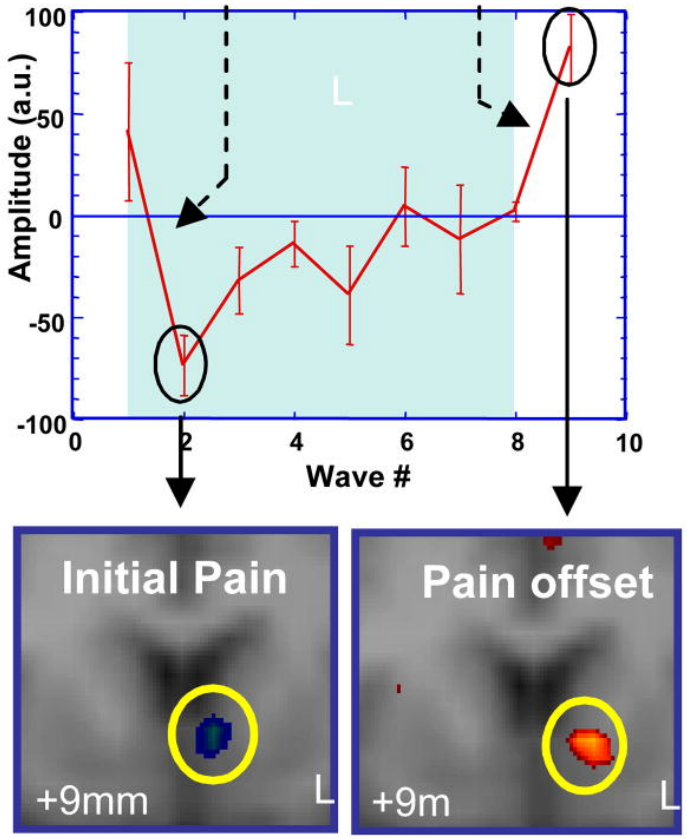
Nucleus accumbens facilitates:

- Reward (pleasure) to natural rewards and drugs of abuse.
- Learning and association formation - enhances predictions of future rewards.
- Reinforcement of behavior that maximizes reward.
- Valuation and decision making

Pain and pain relief have opposite effects on nucleus accumbens activation



Noxious thermal stimulus (46 °C) to the hand decreases activity of the nucleus accumbens.

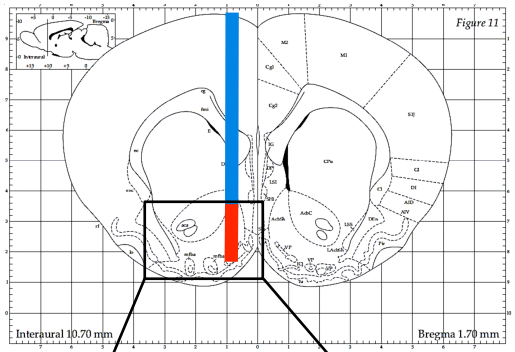


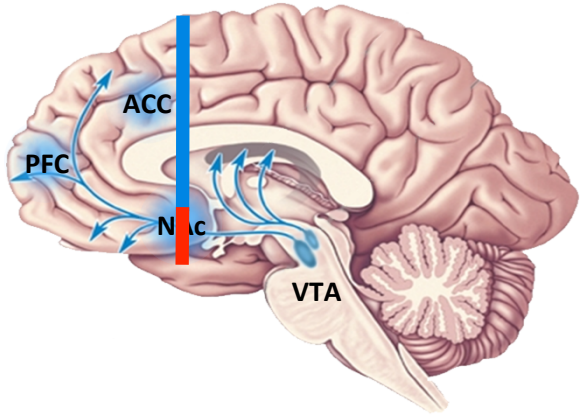
Negative signal change with pain onset and a positive signal change with pain offset in the NAc.

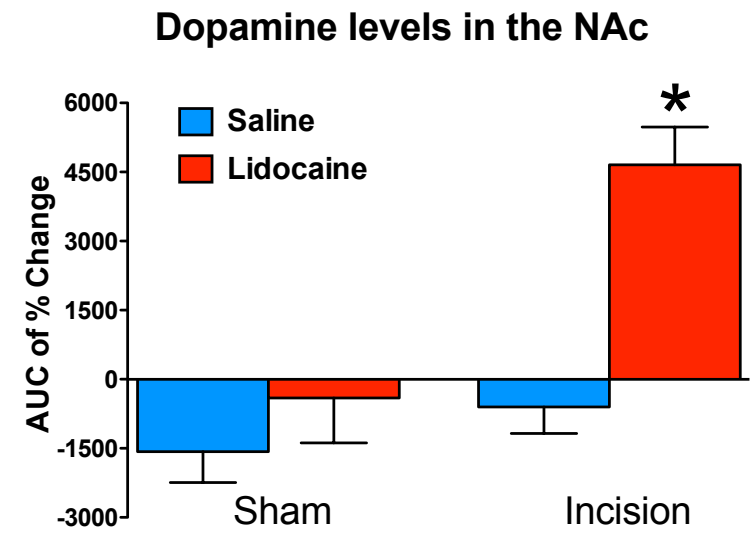
Aharon I, Neurosci Lett. 2006

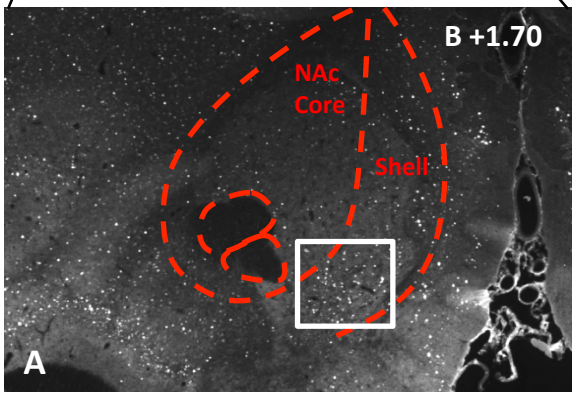
Becerra L, Eur J Pain. 2008

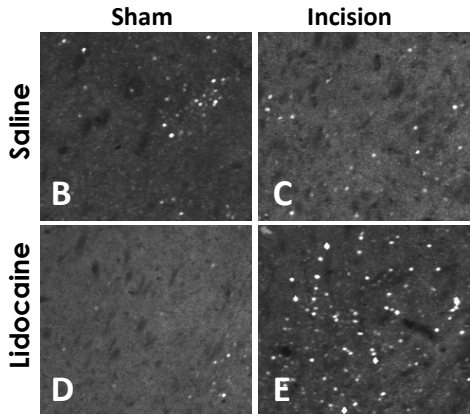
Pain relief elicits release of dopamine in the nucleus accumbens

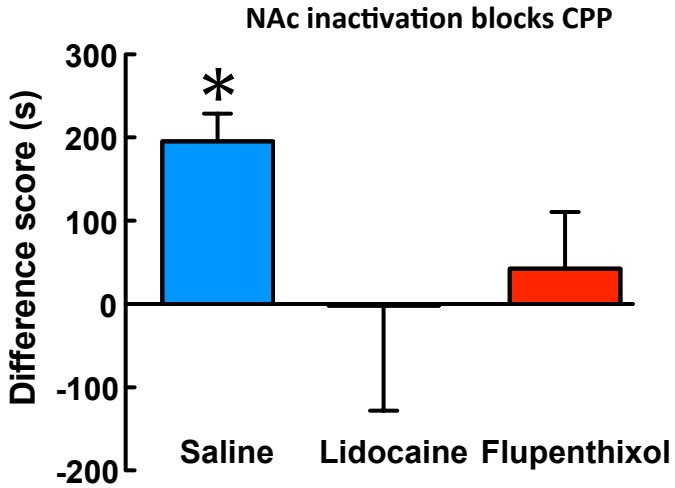












We still need to learn from animals!!

- Drug testing in humans may be unethical, is expensive and subjective;
- Genetic information may only go so far and no guarantee that success will apply broadly to pain patients;
- Targets may, or may not be, druggable and/or safe
  - (is anosmia a concern with Nav1.7 blockade?)
- New mechanistic hypotheses must be generated, molecules must be discovered and prioritized prior to going to man;

Improved *filtering* of pain targets necessary -

Increased confidence may arise from understanding how pain impacts circuits that are likely to be conserved across species!!

Effective treatments regardless of molecular target and site of action must be reflected in the brain!!

Hurdles to progress

- What are we trying to “translate” to? – Need for clear definitions and use of terms –
  - What do we mean by analgesia? Is tanezumab an analgesic?
- Why are we so focused on blocking pathways (antagonists, inhibitors), rather than agonists
  - Target engagement and side effects
- Are we using animal models to study mechanism or disease?
  - How many models of mechanism do we need?
- How do we avoid “irrational exuberance” about a target?