

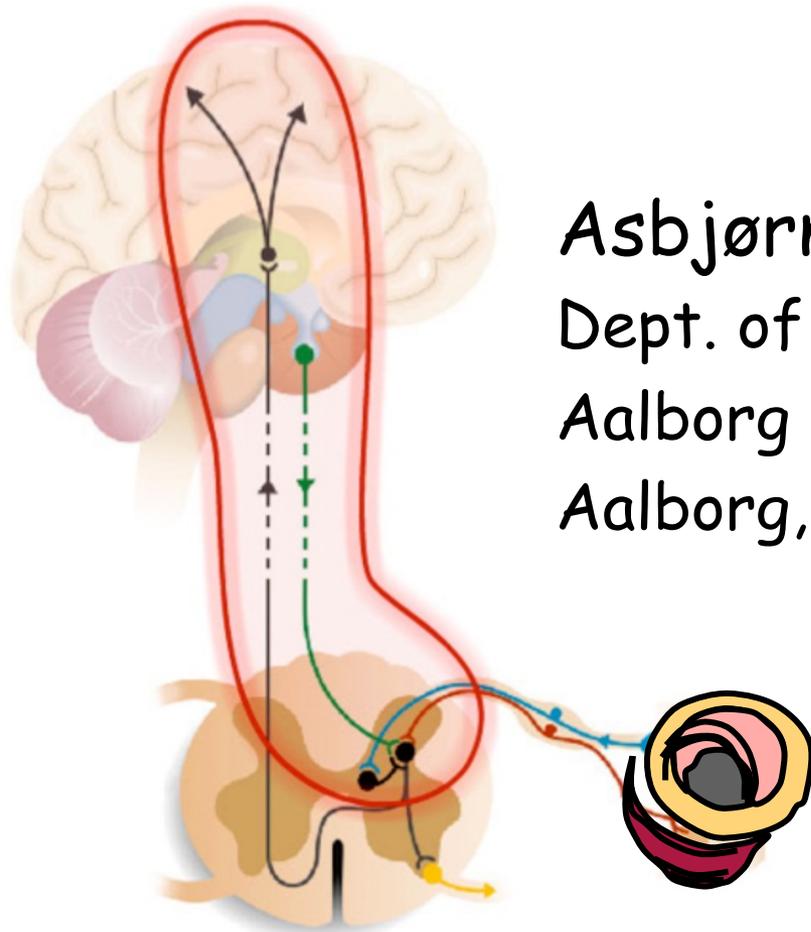
# Human pain experiments as an alternative to animal models

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Aalborg, Denmark

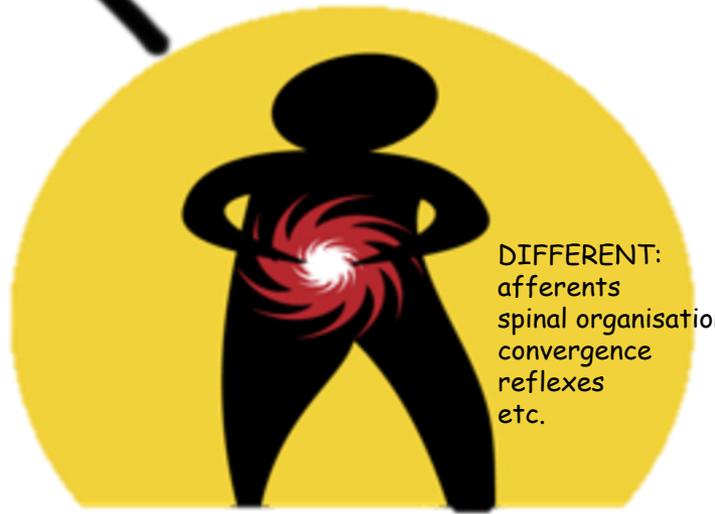


# SPECIALIAL



Visceral specific changes?

Visceral pain



DIFFERENT:  
afferents  
spinal organisation  
convergence  
reflexes  
etc.

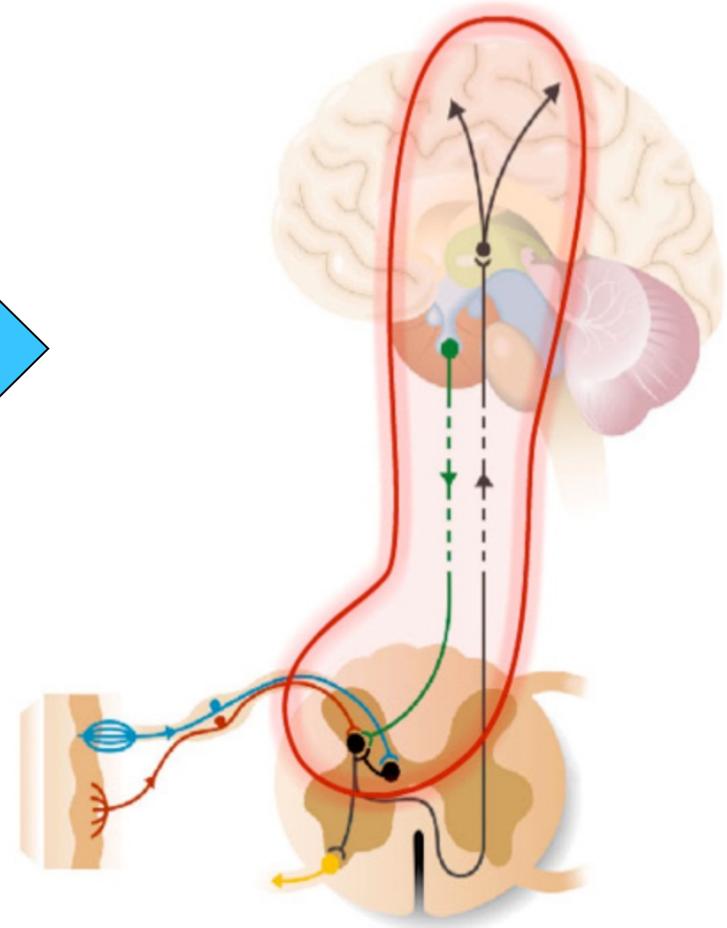
# The approach to visceral pain studies



animal studies

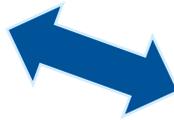
clinical studies

experimental human studies



# Confounders in clinical pain

Job situation



Psychological: Fear, anxiety



Previous experience



Fever, malaise  
tiredness, nausea



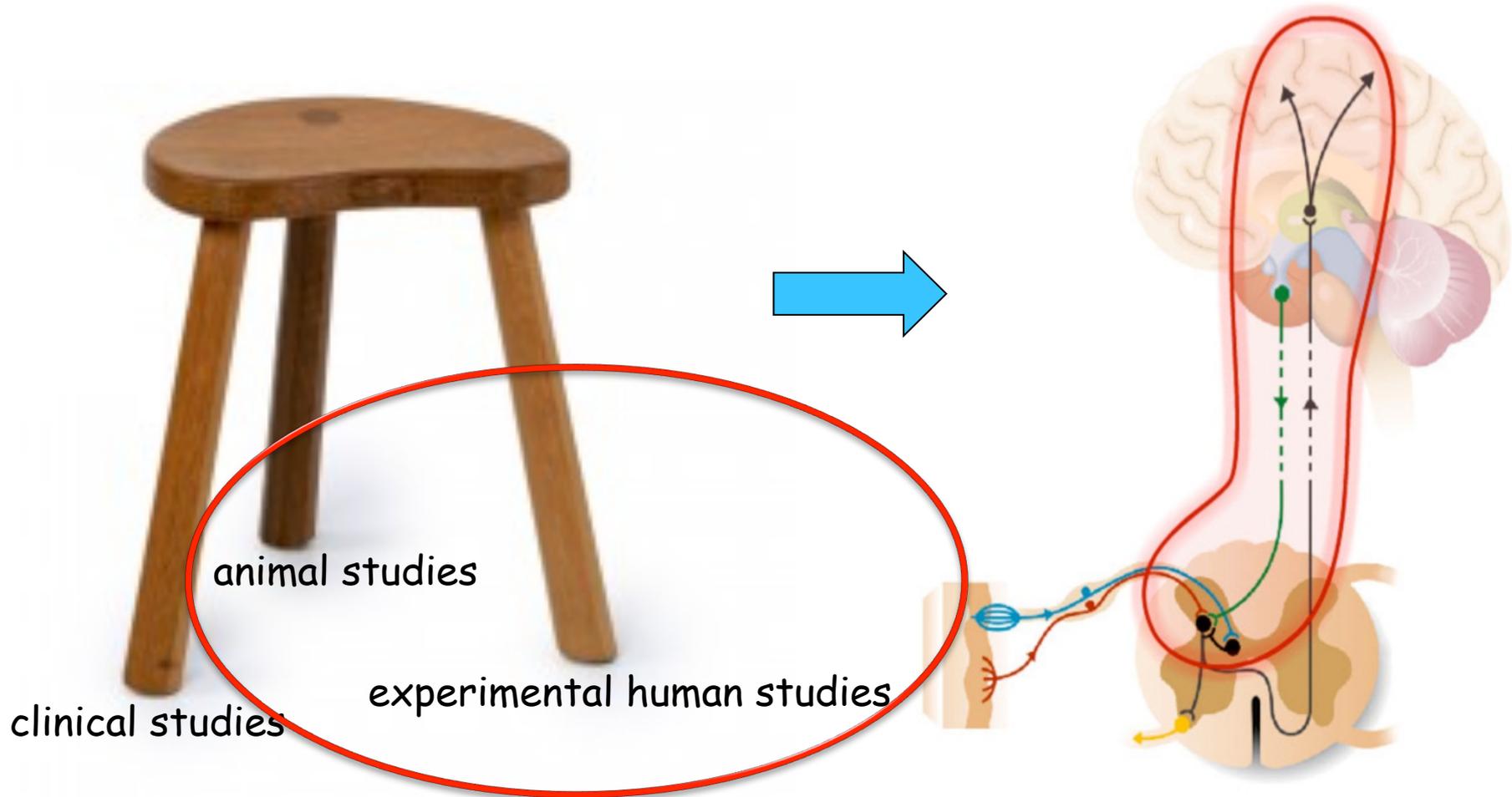
Pain intensity



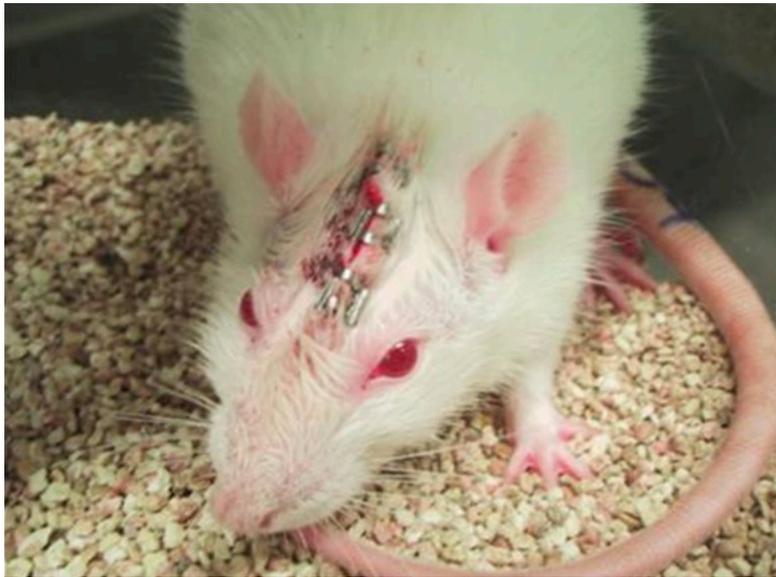
Side effects from medication

Symptoms from other organs

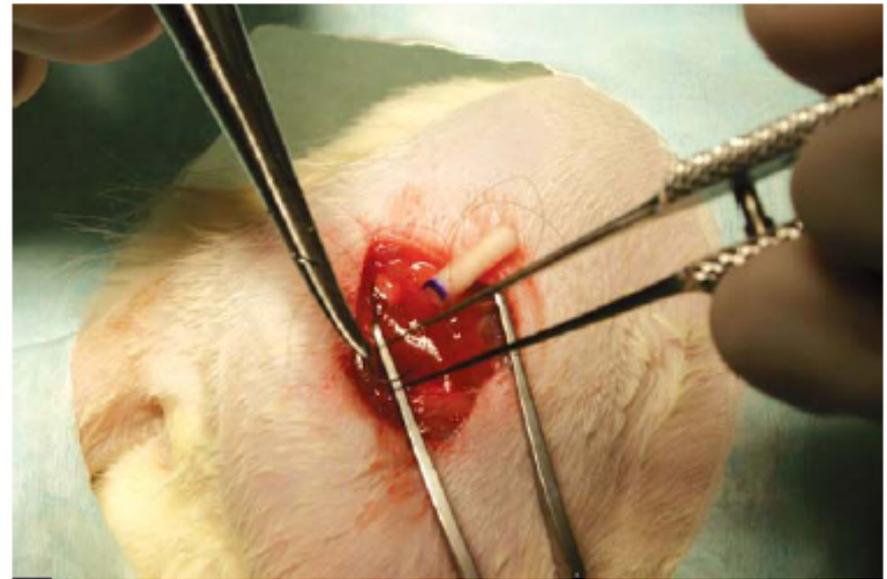
# The approach to visceral pain studies



# Animal models in pain research

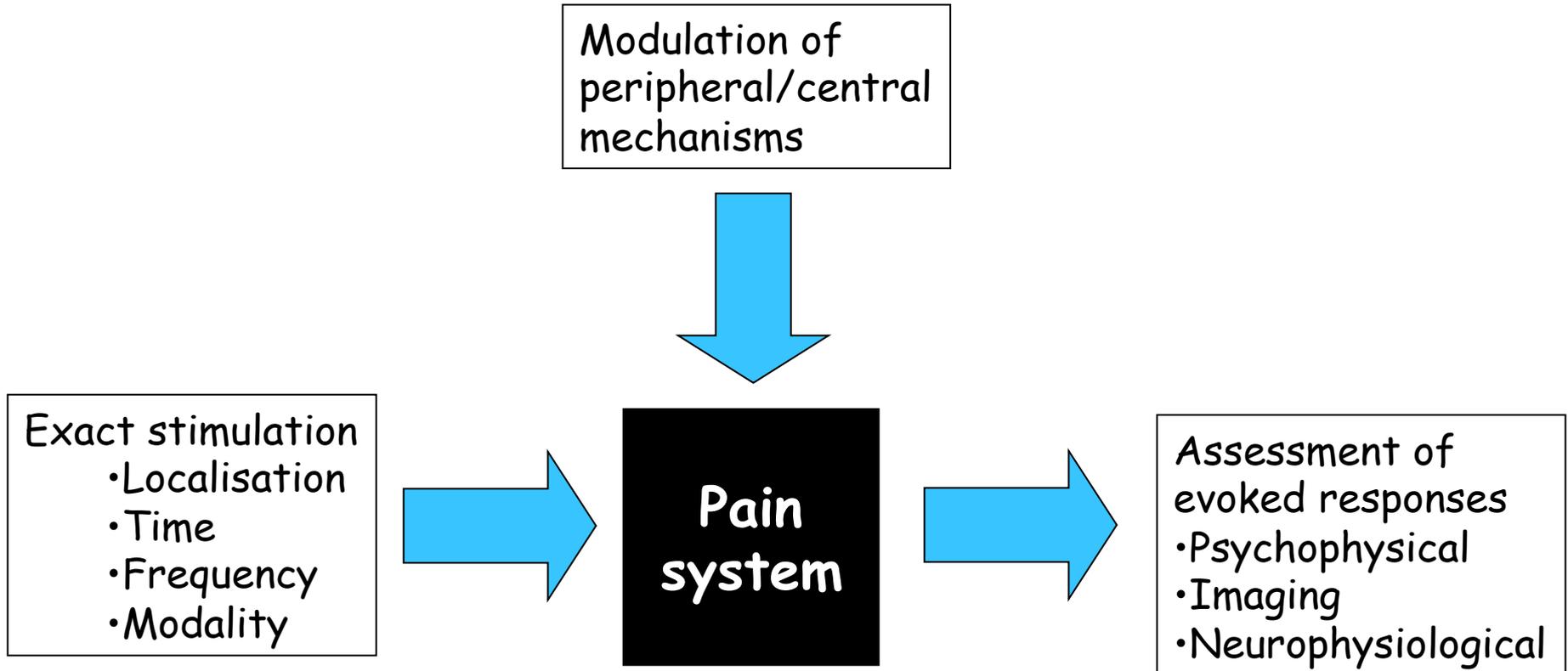


Direct placement of brain electrodes



Sciatic nerve resection

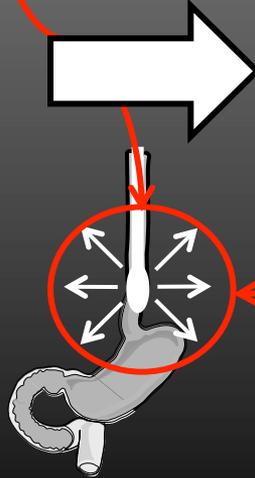
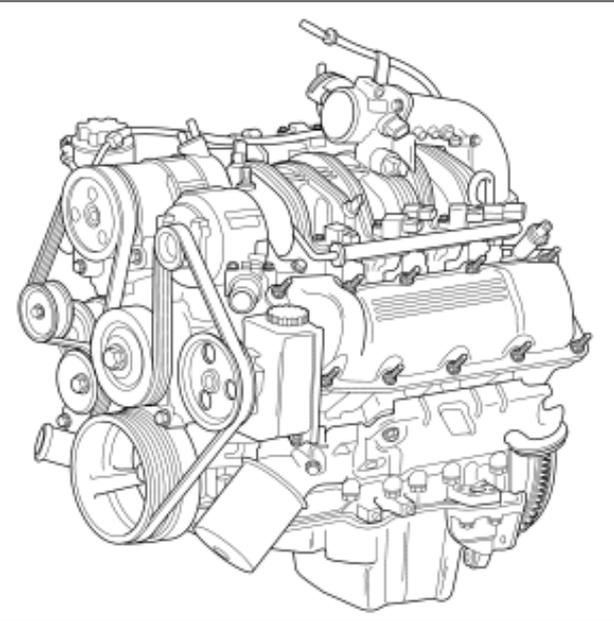
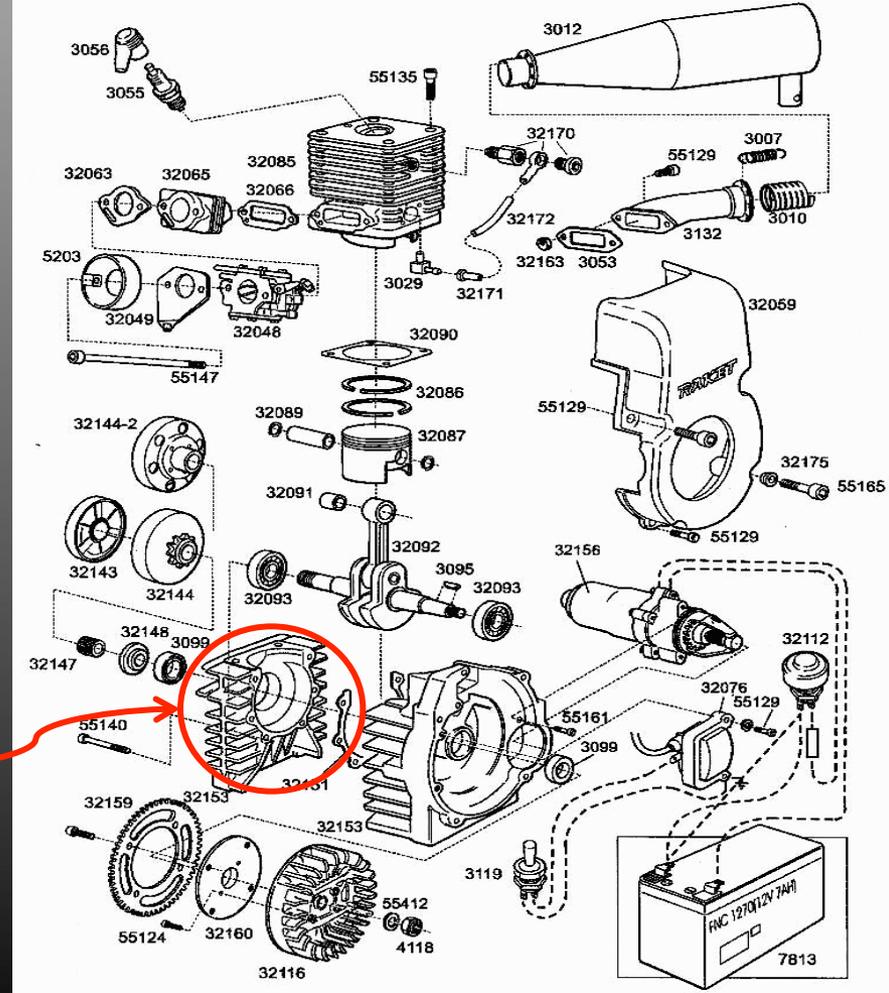
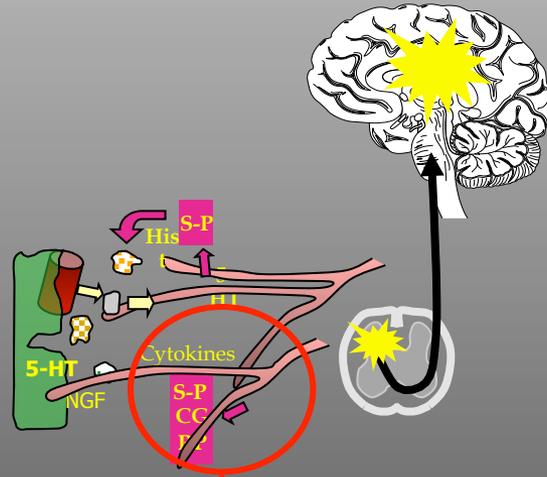
# The concept for human experimental pain



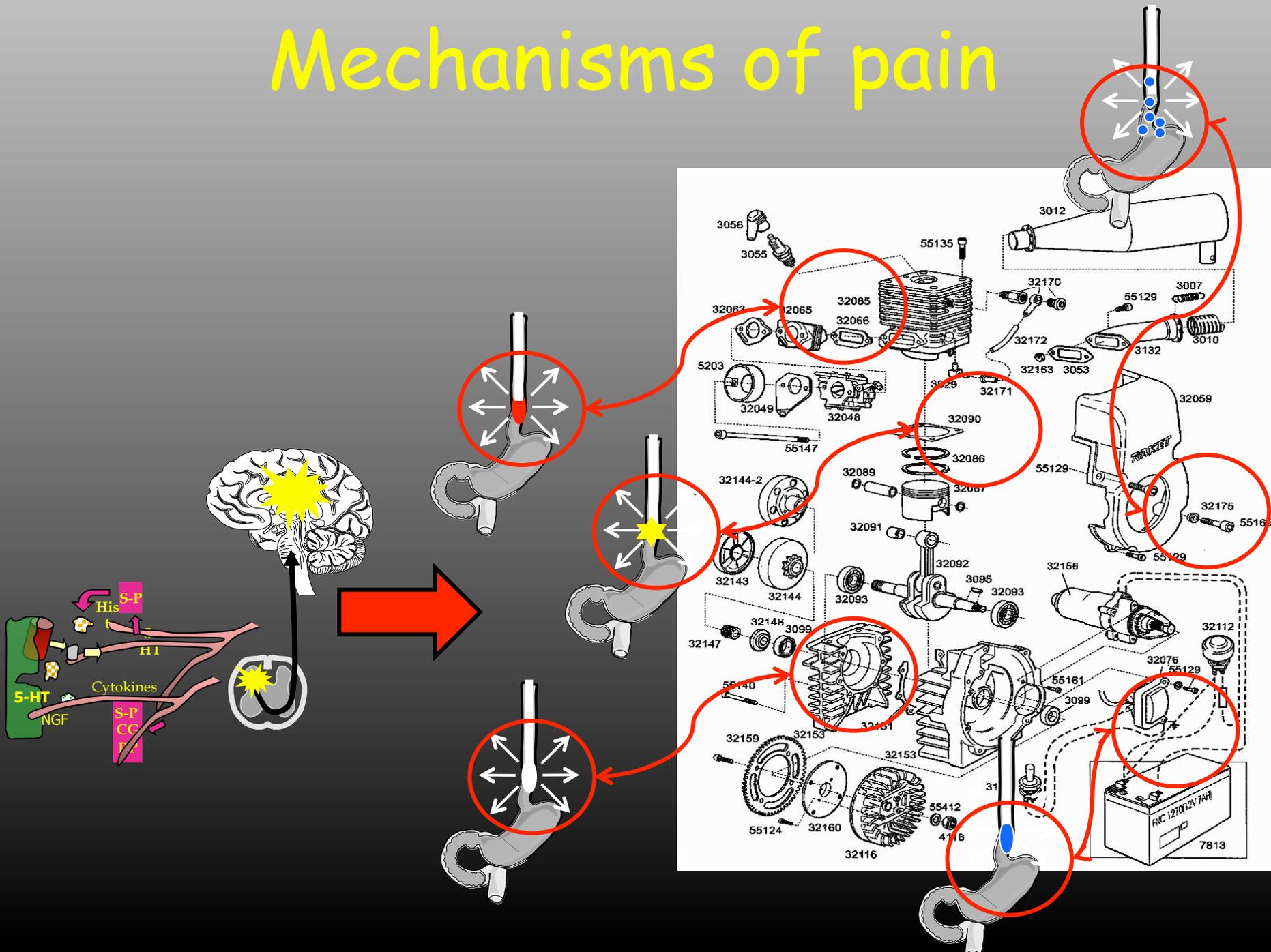
# Bridging experimental to clinical findings



# One example: mechanisms of pain



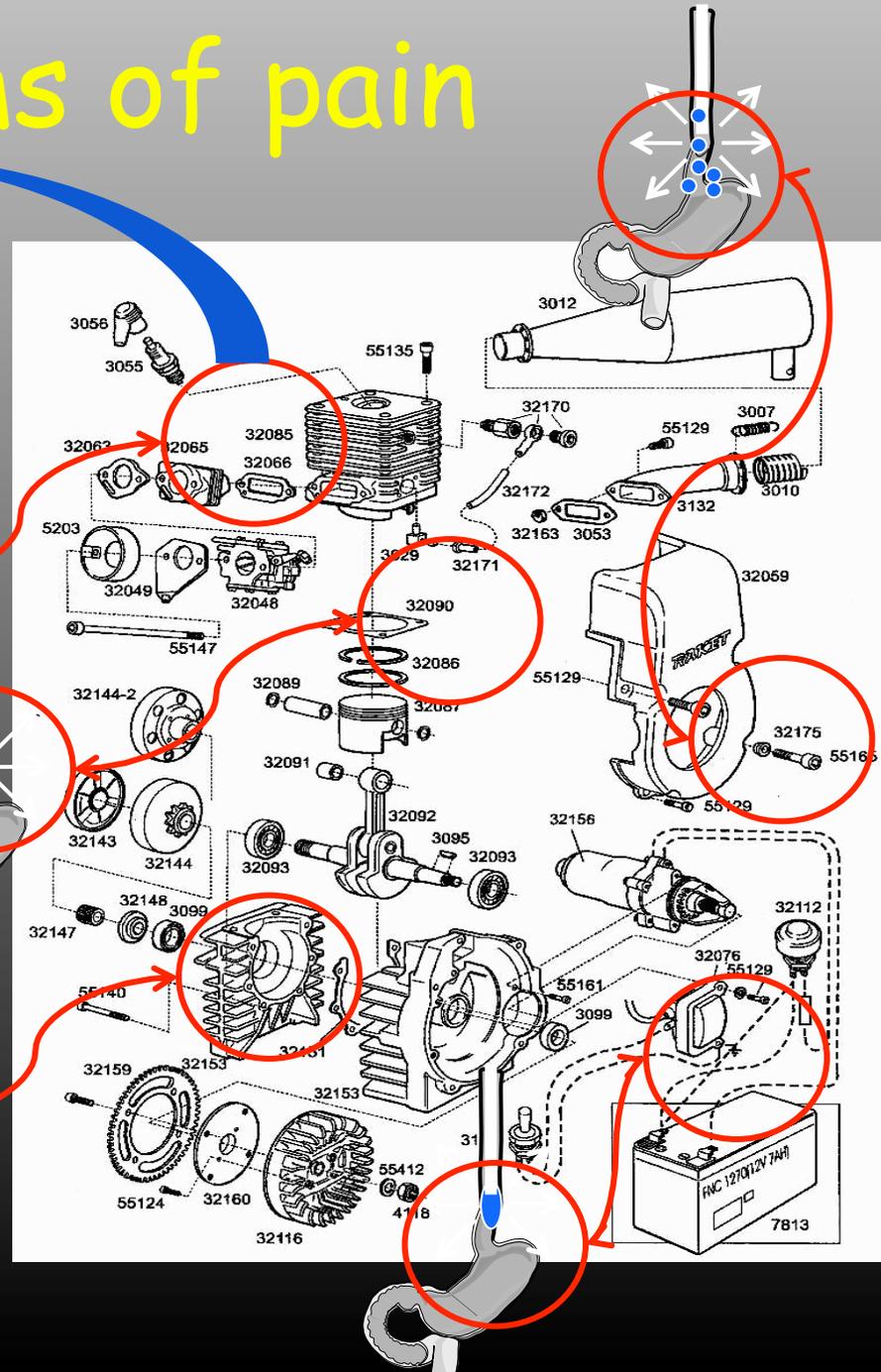
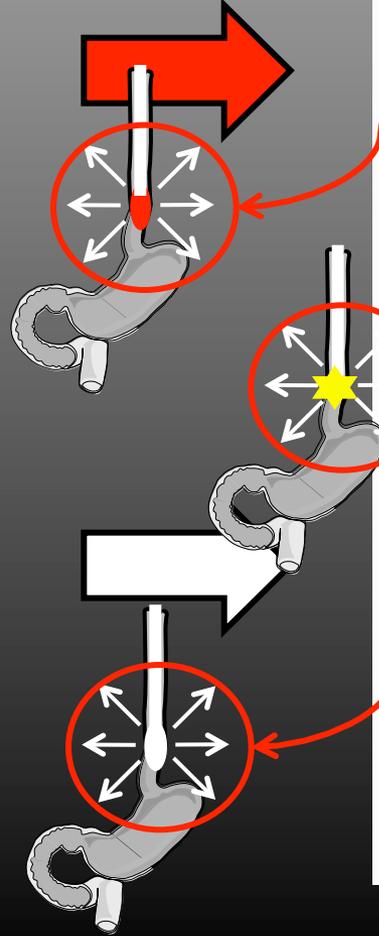
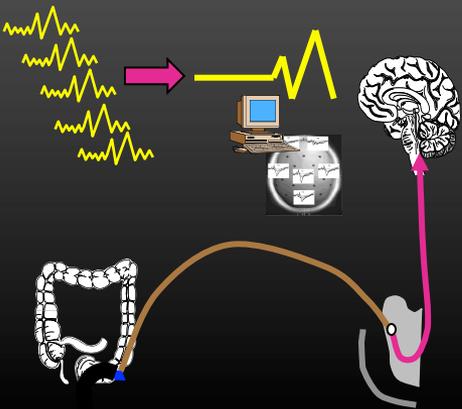
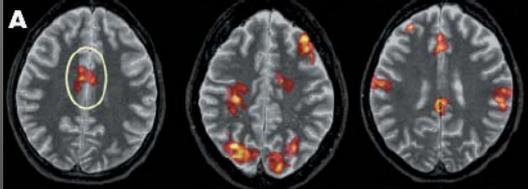
# Mechanisms of pain



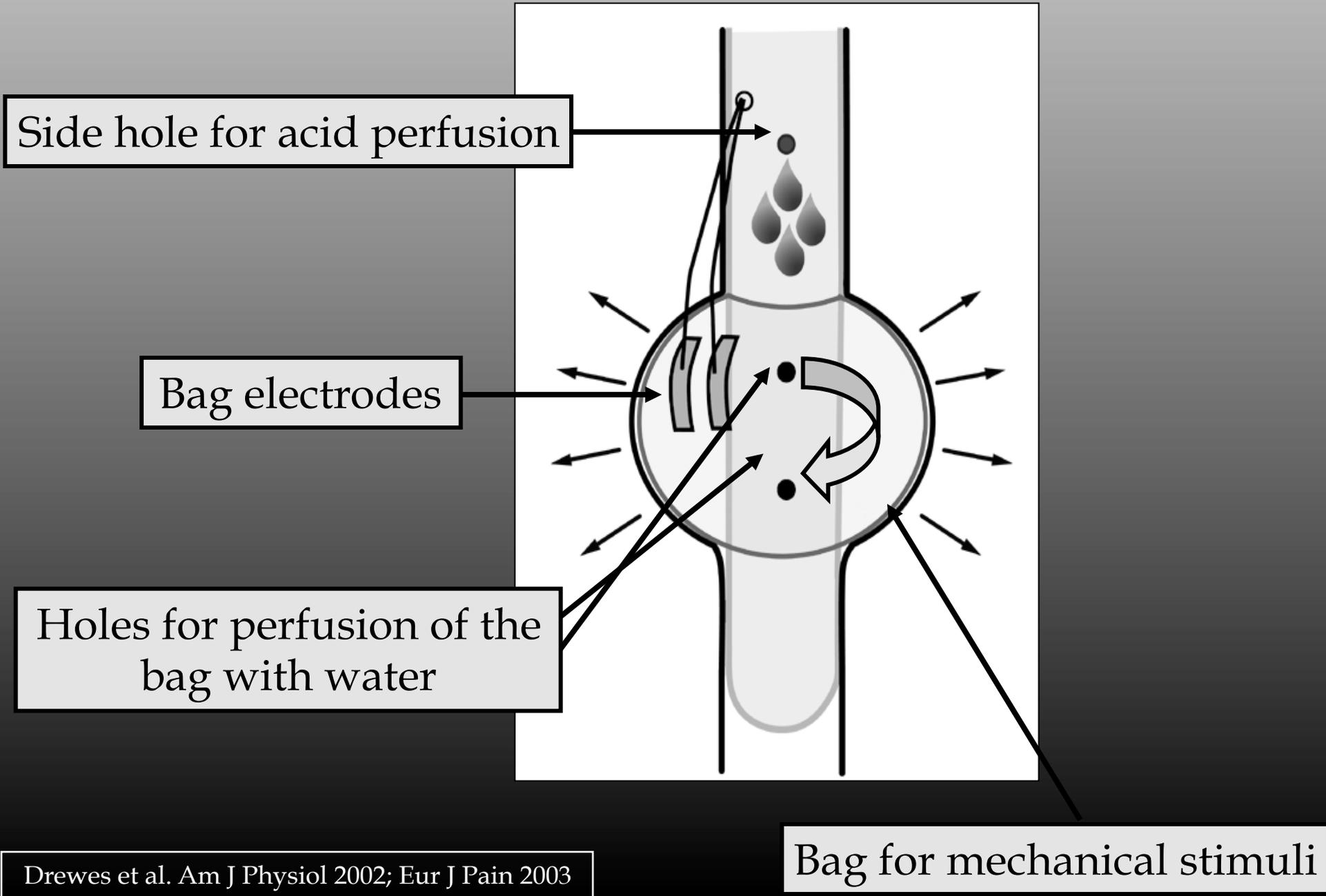
# Mechanisms of pain

- Flickering
- Quivering
- Pulsing
- Throbbing
- Beating
- Pounding

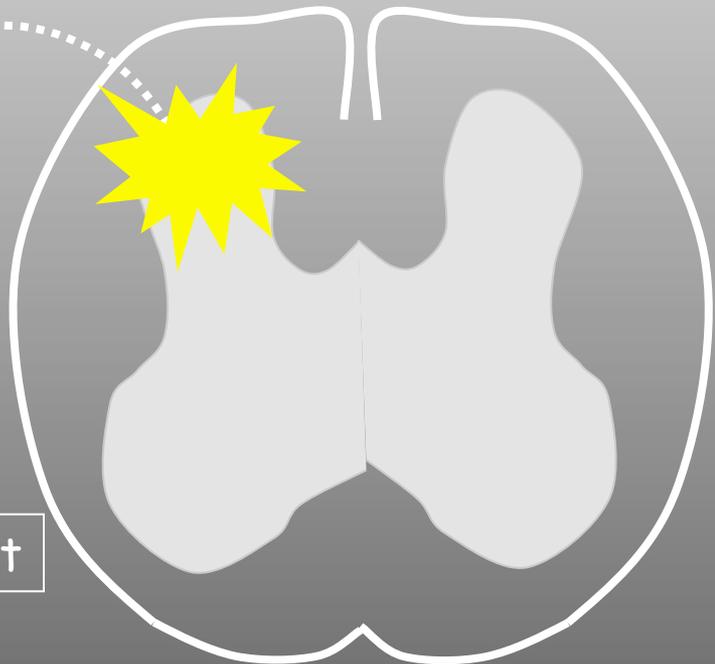
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# Multimodal stimulation - mimicking the clinical situation



ALTHOUGH SIMPLIFIED:  
Different layers  
Different receptors  
Different nerves



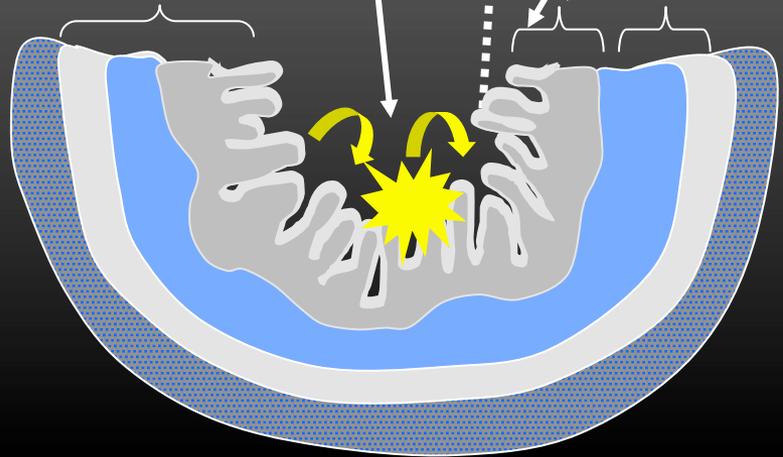
Electrical

Sensitisation with acid

Cold

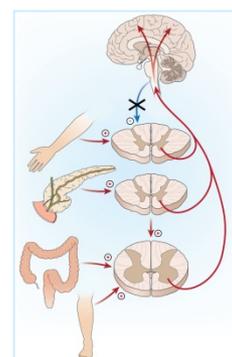
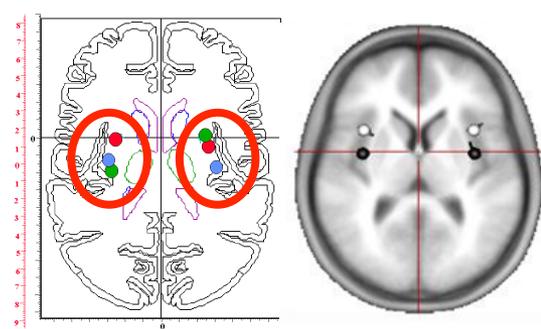
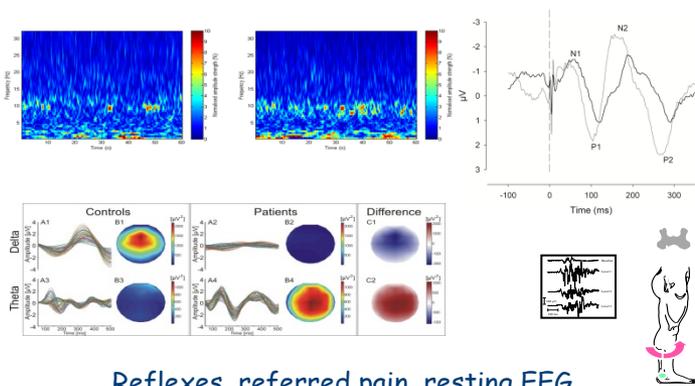
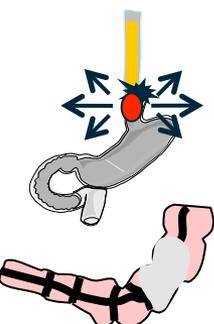
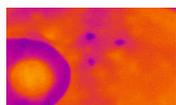
Heat

Mechanical



# CNS- assessment used at Mech-Sense Aalborg University Hospital

## SENSORY SYSTEM & ELECTROPHYSIOLOGY



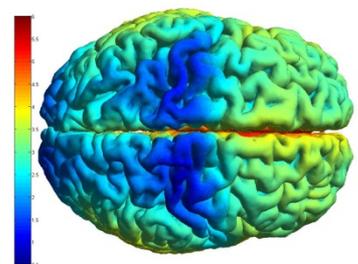
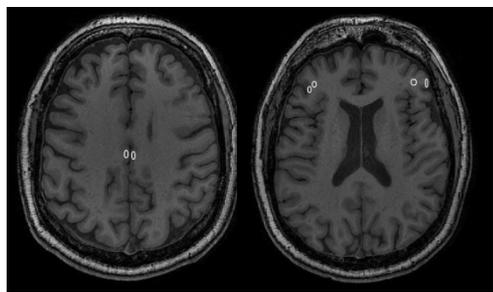
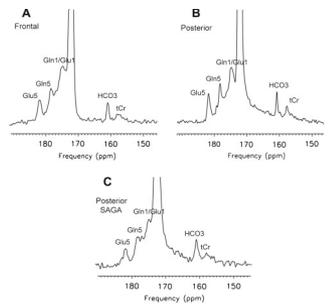
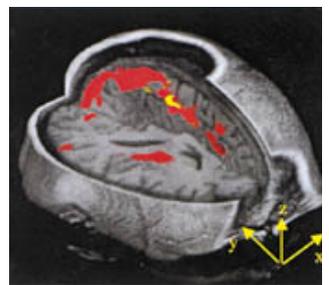
Sensory/autonomic system

Reflexes, referred pain, resting EEG & evoked brain potentials

Brain electrical sources

Descending control

## BRAIN IMAGING



BOLD, arterial spin labelling

Spectroscopy

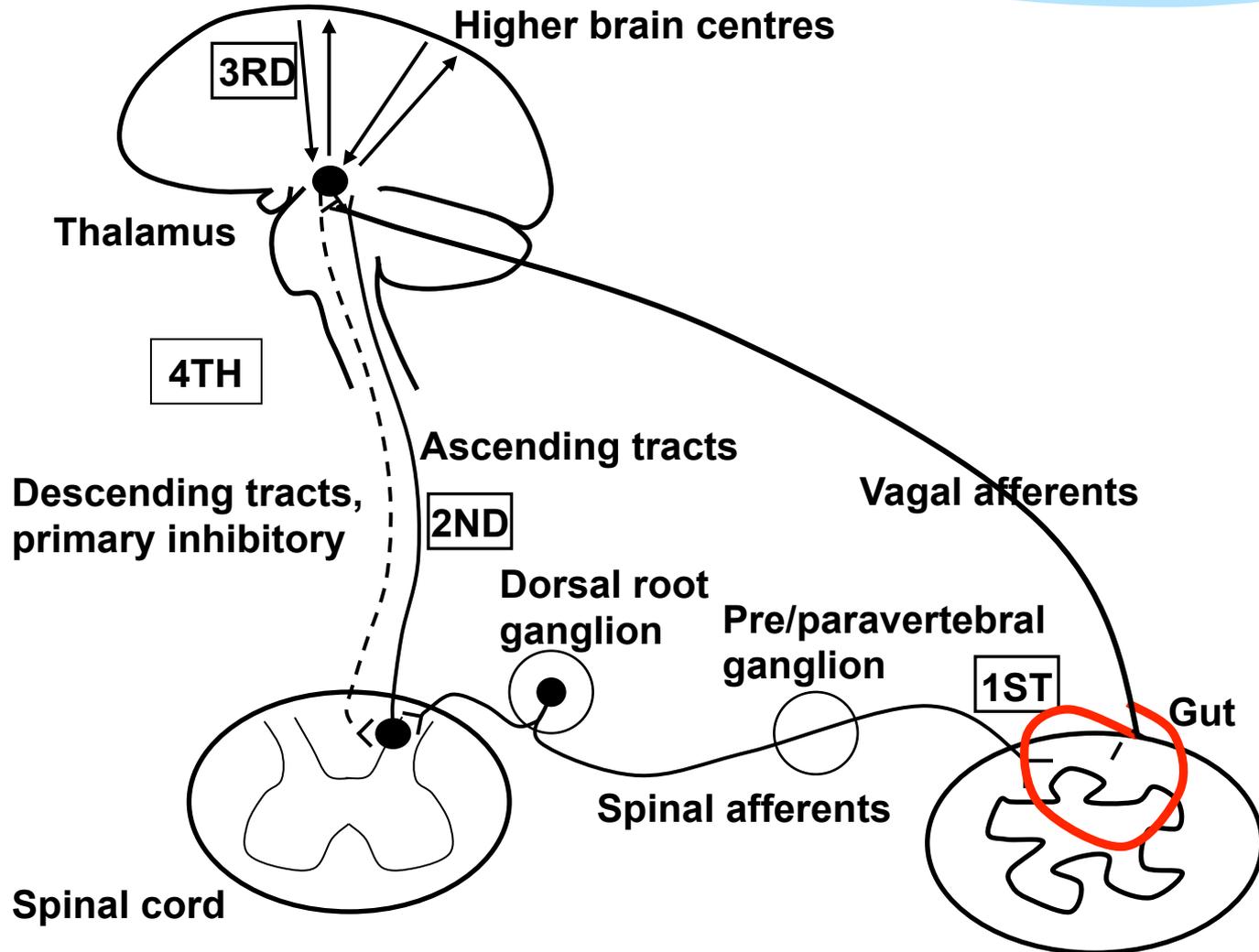
Diffusion tensor imaging

Cortex volumetry

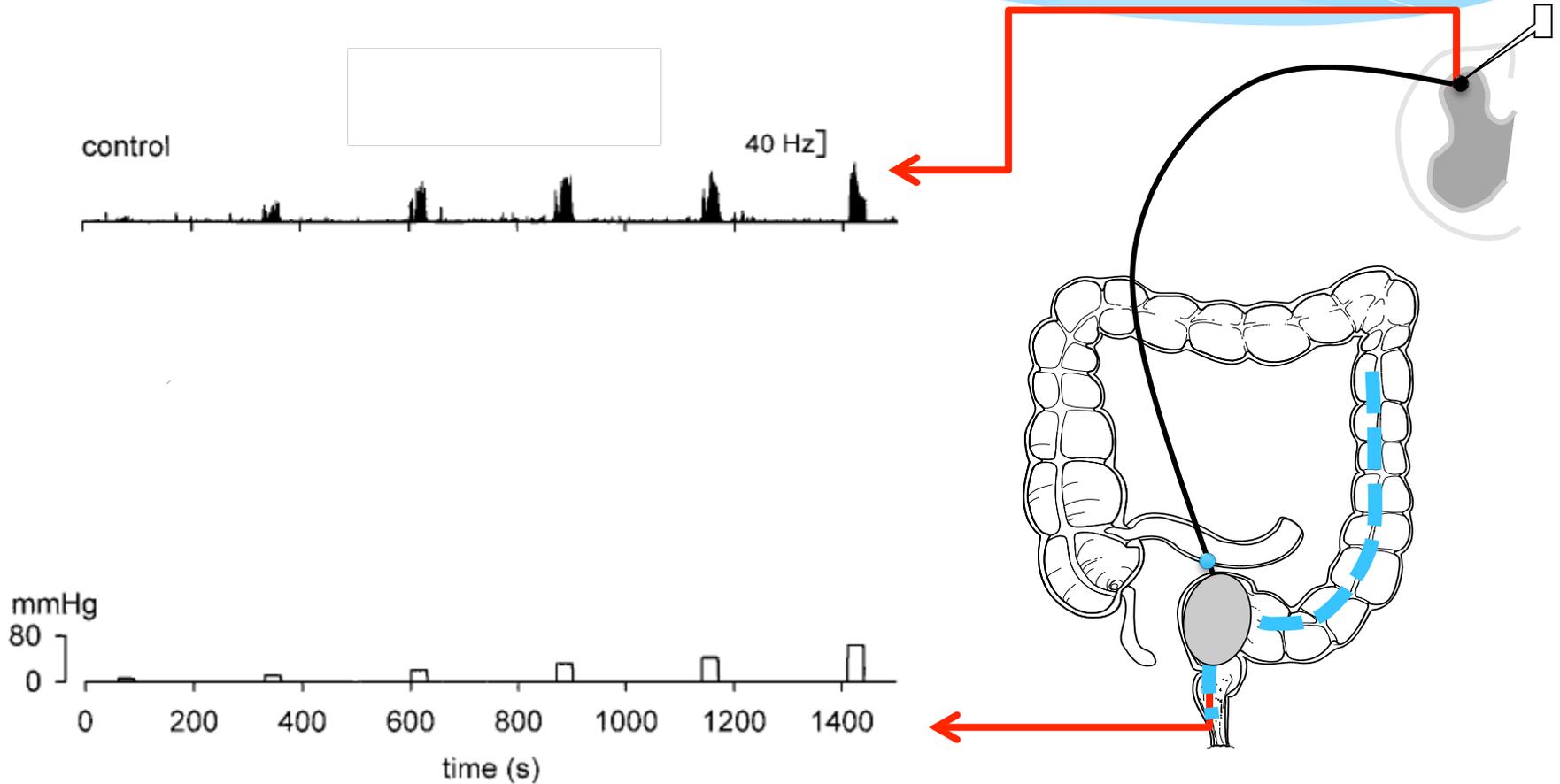
# Animal vs. human pain studies



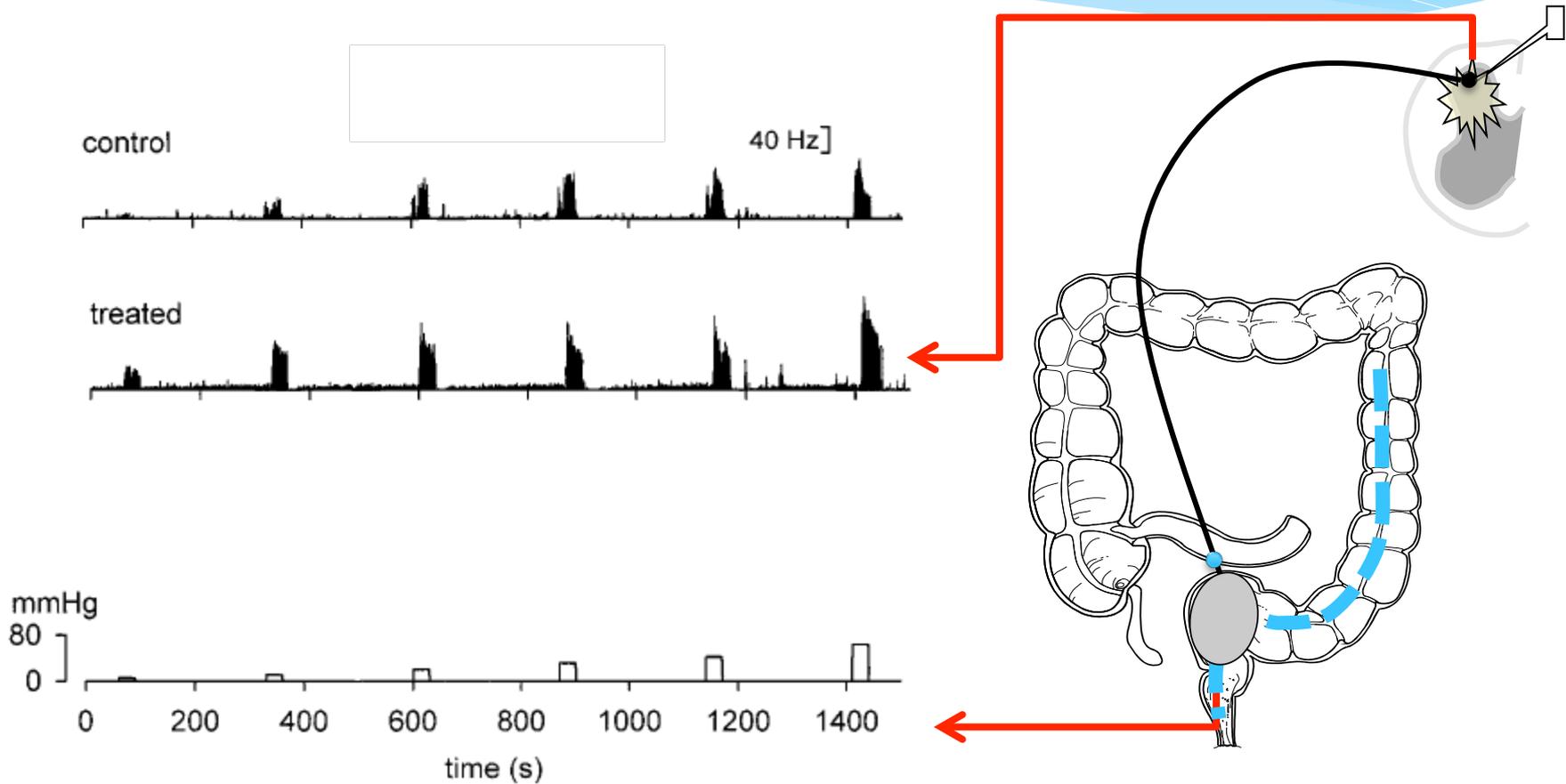
# The peripheral nerves



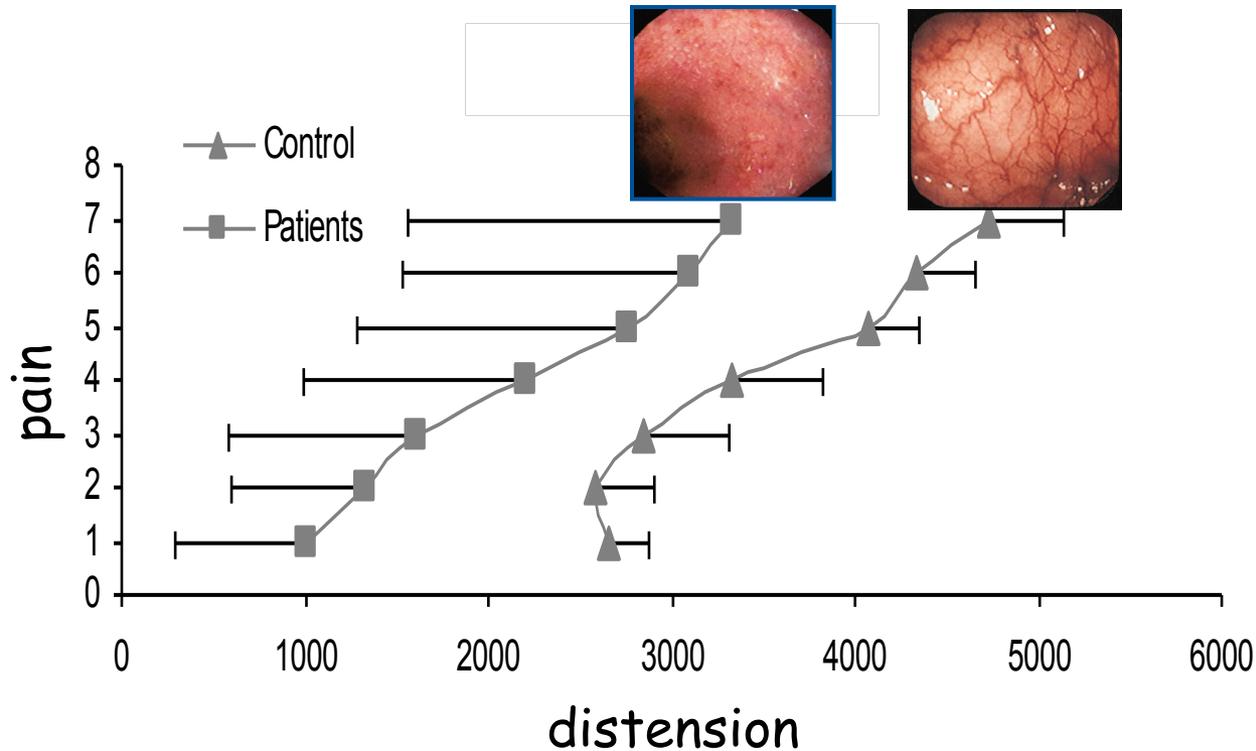
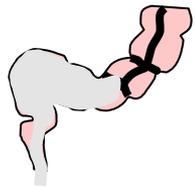
# Animal study: Peripheral sensitization



# Animal study: Peripheral sensitization

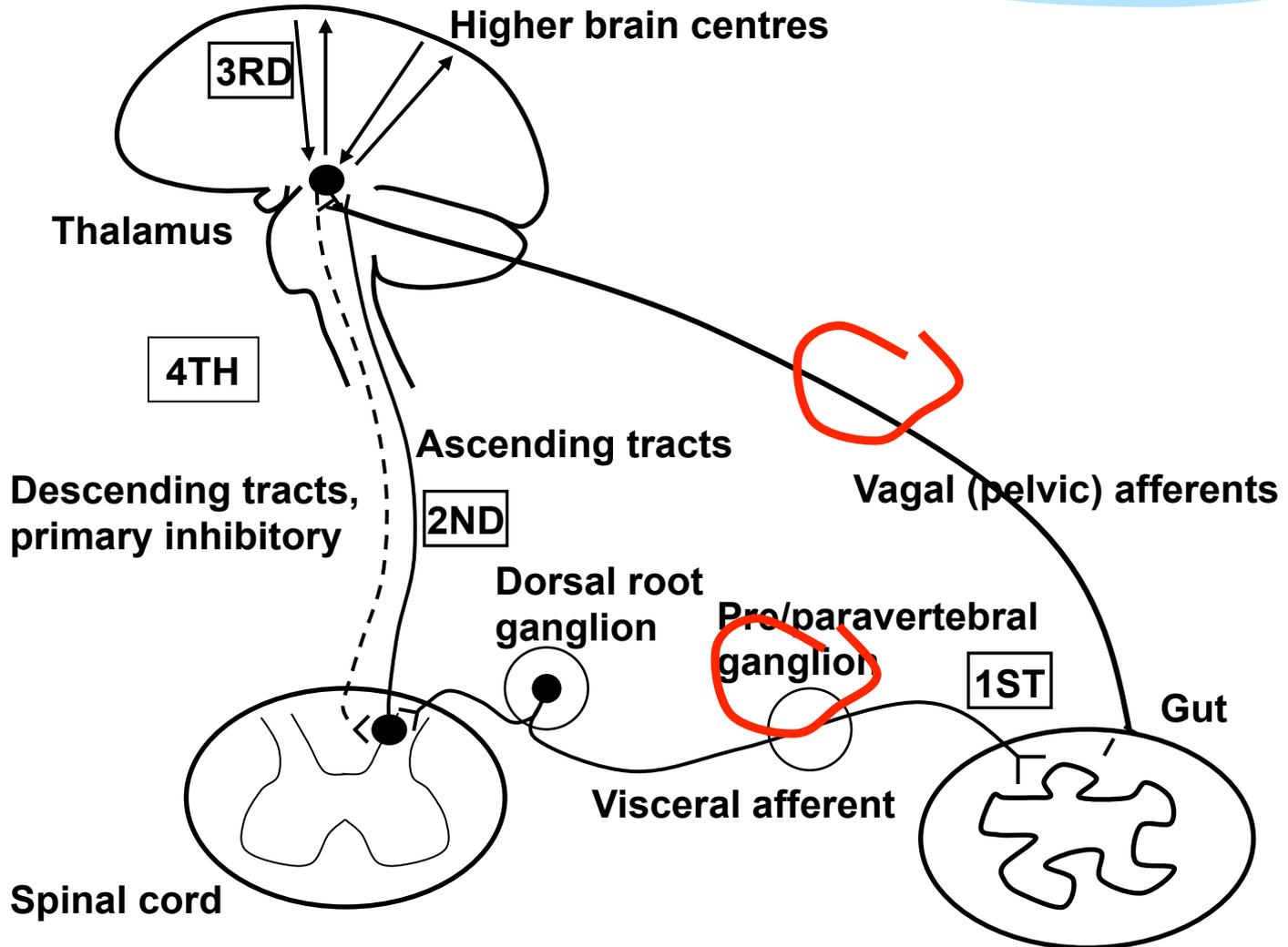


# Human experimental study: patients with inflammation due UC

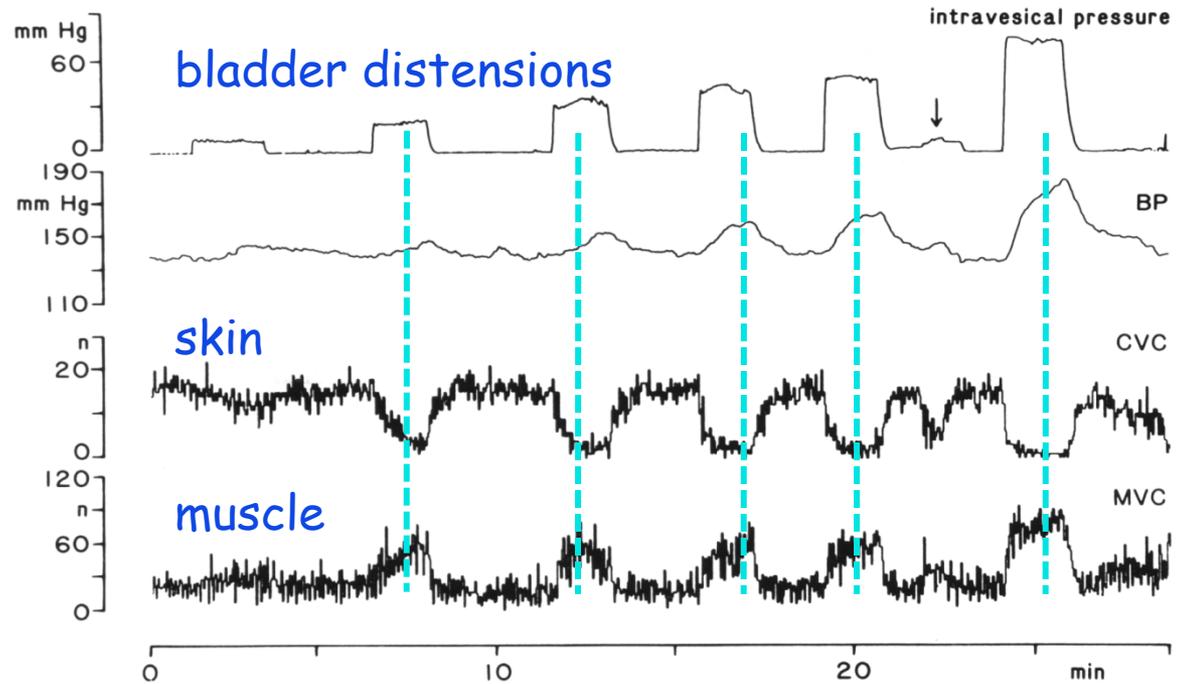
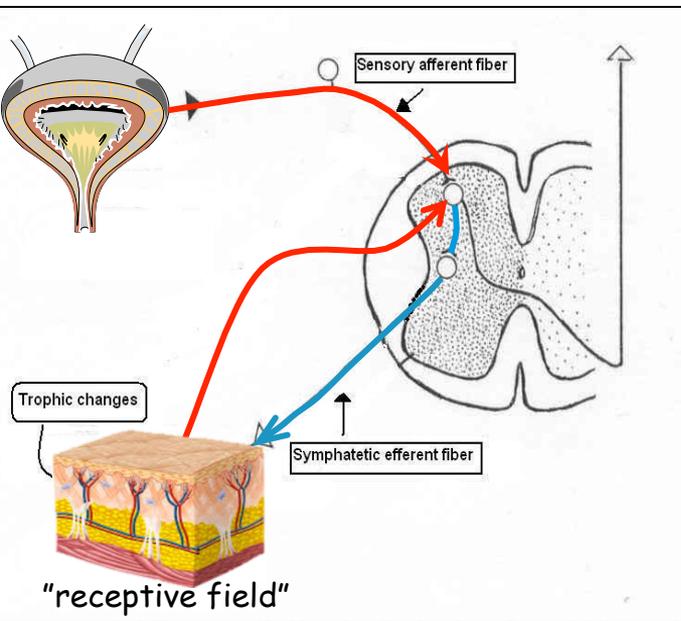


No central integration of the pain response  
- the hyperalgesia mainly of peripheral origin

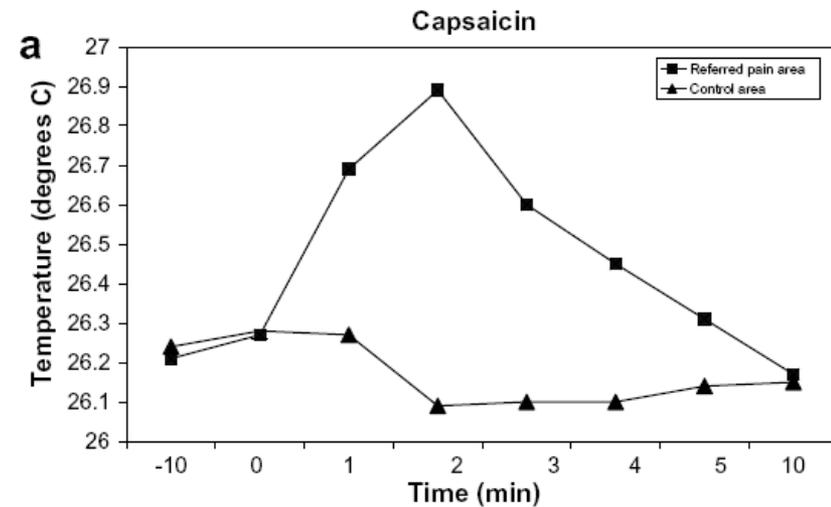
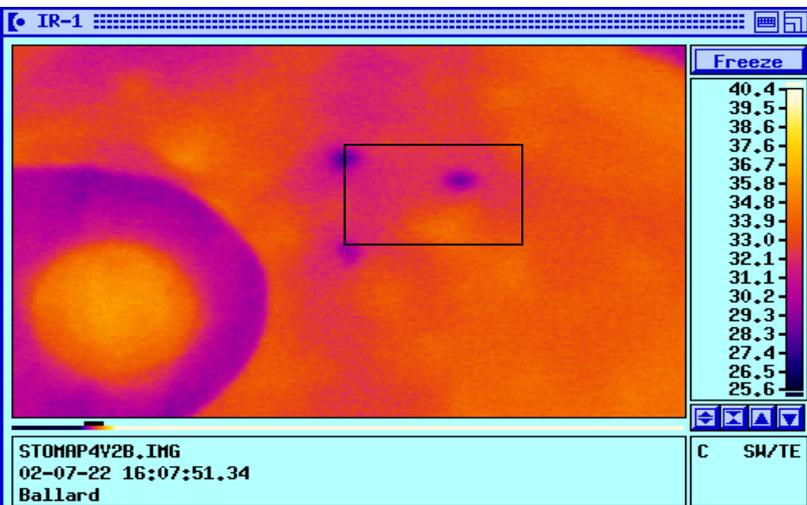
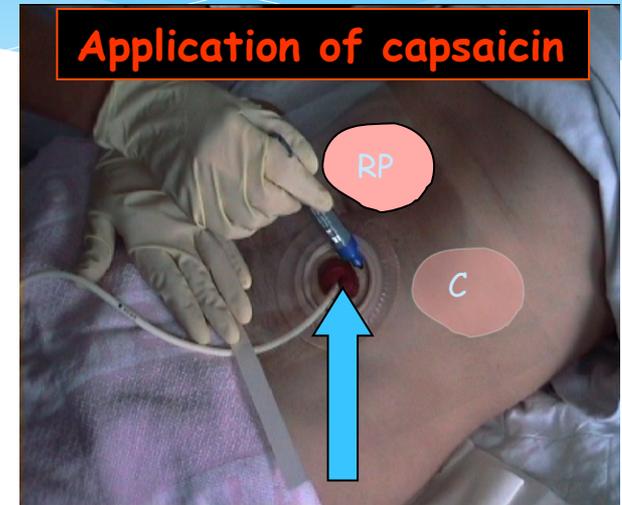
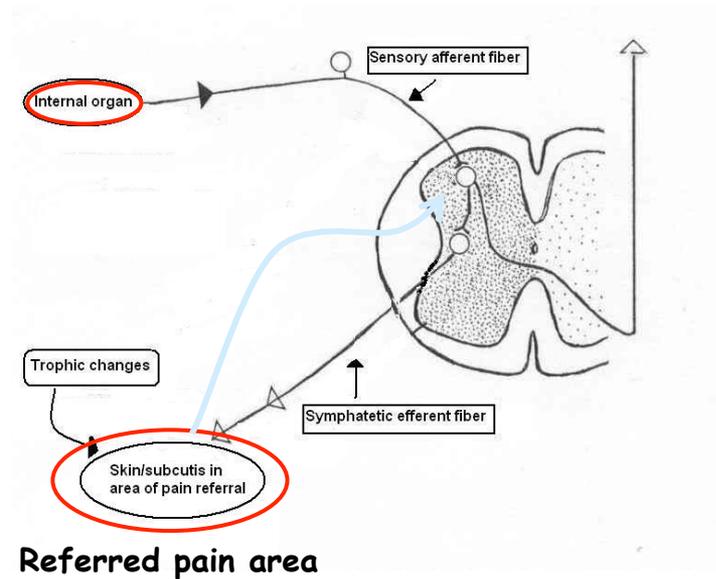
# The autonomic nervous system



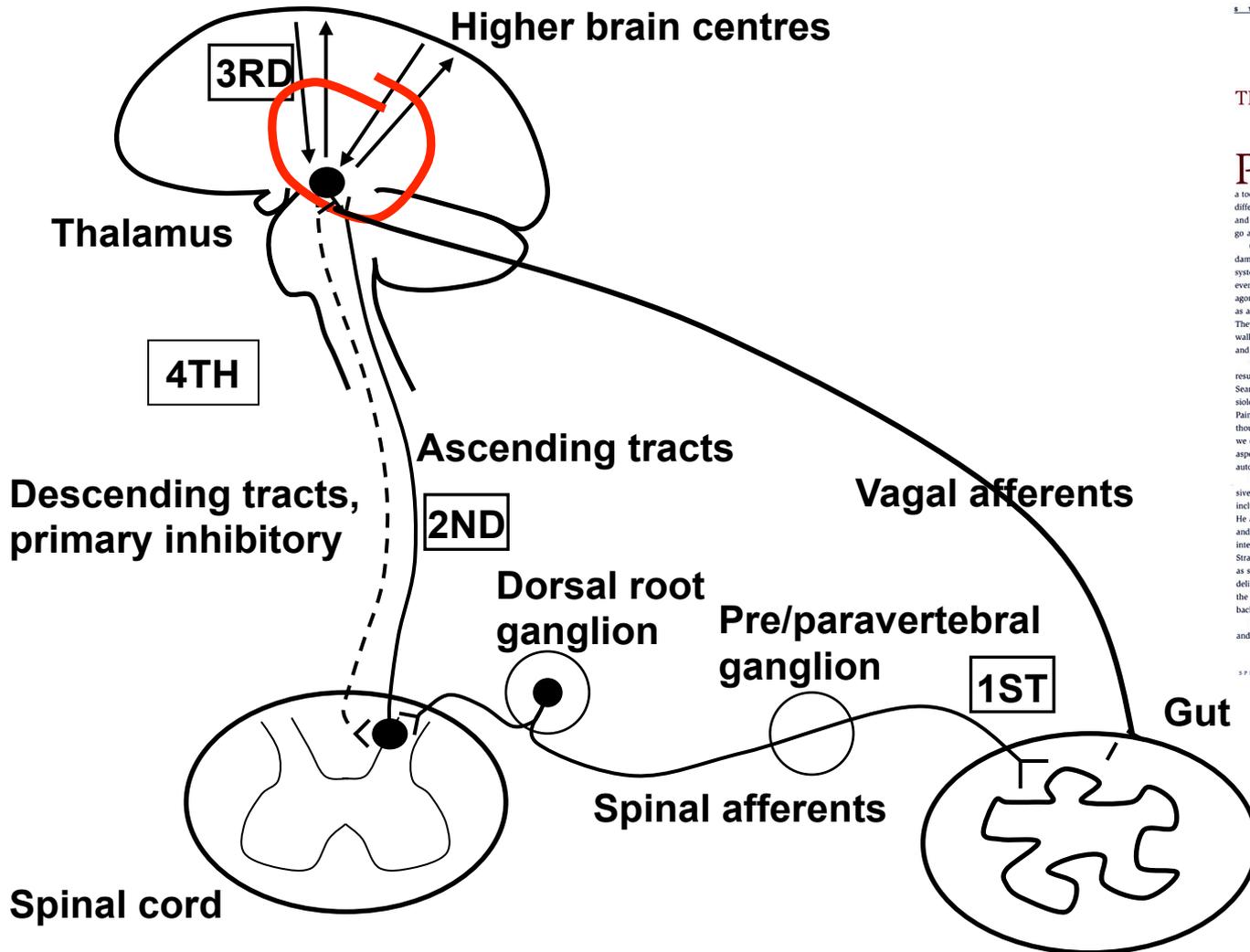
# Animal study



# Human experimental study



# The brain level - complexity increases



STANFORD UNIVERSITY MEDICAL CENTER

PAIN

## THE Pain IS IN THE Brain

Pretty much everyone has experienced pain at one time or another—from hitting a misplaced finger with a hammer, pulling a muscle, suffering from a toothache, or taking an unexpected fall. But there's a different kind of pain that affects the nerves in our bodies, and it can cause unbearable pain that never seems to go away.

Chronic pain can stem from headaches, cancer, arthritis, damage to the peripheral nerves or to the central nervous system, or no discernible cause. The condition can make even simple acts, such as walking or putting on a shirt, agonizing. People with this kind of pain often describe it as a tingling, or pins and needles, or like an electric shock. They say they feel like their skin is on fire or like they are walking on silvers of glass. Each person's pain is individual and virtually indescribable.

"Chronic pain is difficult to diagnose because it's the result of a neural disruption rather than an injury," says Sean Mackey, MD, PhD, an assistant professor of anesthesiology and the associate director of Stanford's Division of Pain Management. "It's also difficult to treat because even though we can prescribe medication to control the pain, we often don't have a real cure. Our goal is to address all aspects of the condition and help give people back their autonomy and control of their life."

Dr. Mackey is coordinating an integrated, comprehensive program that deals with a variety of pain, including chronic conditions and pain related to cancer. He and his associates assess the type and degree of pain and develop the best treatment, from pharmacological interventions to psychological and physiological therapies. Strategies can include state-of-the-art medical tools, such as surgery, radiofrequency, and implantable medication delivery systems, as well as holistic approaches that utilize the mind-body connection, such as acupuncture, biofeedback, and mental imaging.

Dr. Mackey's focus is in functional neuroimaging (fMRI) and outcomes research. Using magnetic resonance imaging

and other imaging tools allows him to pinpoint which areas of the brain are activated by pain stimuli as well as track their response to various therapies. He has found that different kinds of pain activate different regions of the brain and that learned behaviors (such as anticipating a lab-induced pinprick) show up in another region altogether.

"Imaging shows that the perception of pain is truly in the brain," he says. "We get to peer inside the brain and unlock some of its mysteries. We have been able to isolate the structures in the brain that respond to stimuli and have found that sensory perception, for example, activates a different area than emotional perception. We are in the process of measuring these responses to understand the cognitive aspects of pain."

Part of his research involves a sort of neurofeedback, in which patients observe where and how much their brain "lights up" in response to pain and learn to use conscious controls over the activated area. He is also using fMRI on the spinal cord to observe how medication affects neural communication before the pain message reaches the brain. ■

### Why Does It Hurt?

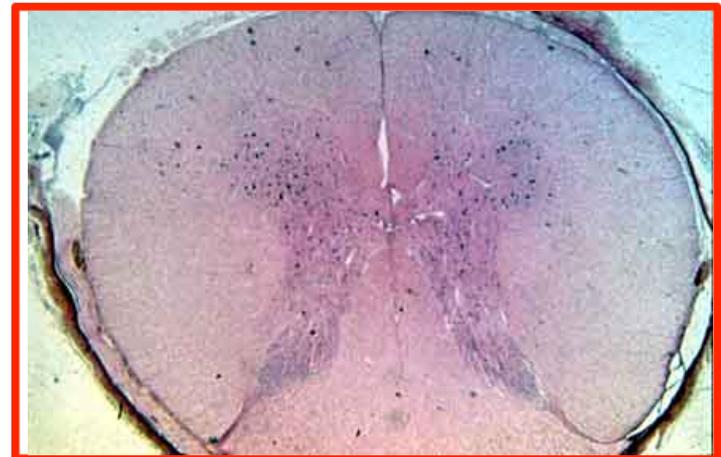
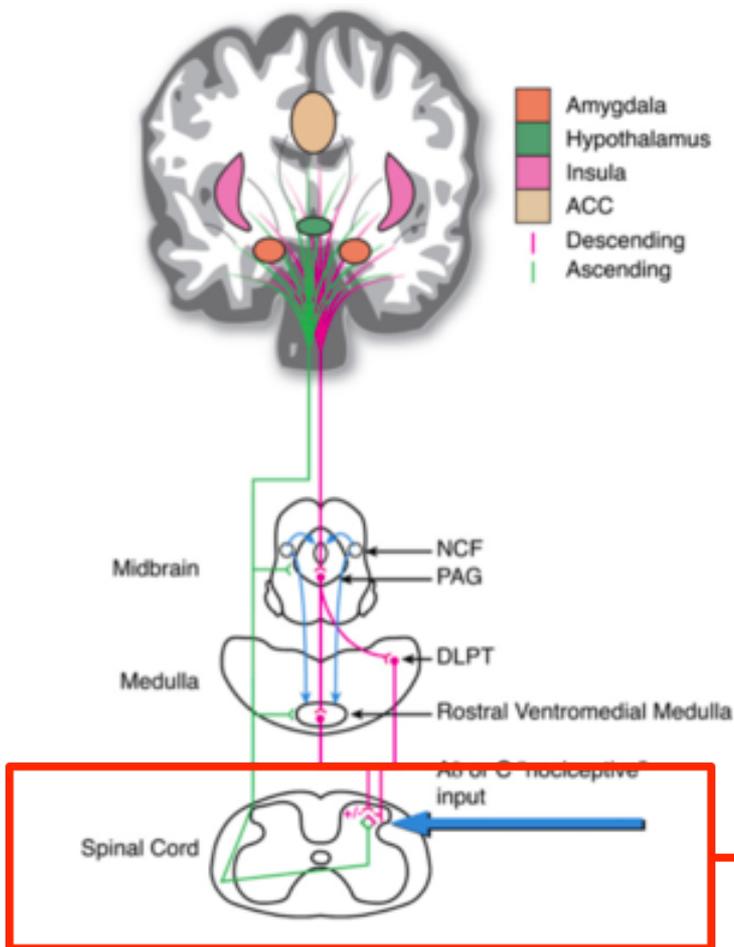
Pain is a complicated process that involves an intricate interplay between a number of important chemicals found in the brain and spinal cord. In general, these chemicals, called neurotransmitters, send nerve impulses from one cell to another. Specialized nerve cells called nociceptors are activated by external events, such as heat or a pinch, or by damaged cells and carry the information to the central nervous system, where it is perceived as pain.

The spinal cord acts as a sort of relay center where the pain signal can be blocked, enhanced, or modified before it is relayed to the brain. Most pain messages are delivered to the thalamus, which plays a key role in relaying messages between the brain and parts of the body. From there the signals are passed along to the cortex, the headquarters for complex thoughts.

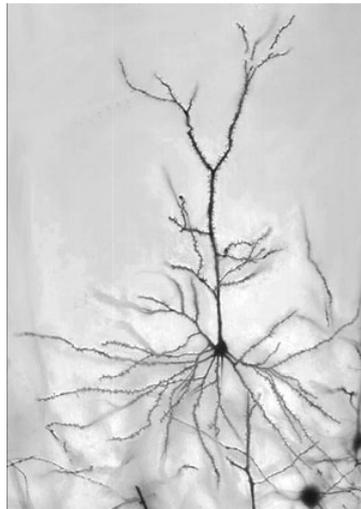
SPRING 2005 • CENTER FOCUS

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# Spinal cord research in animals



# Animal brain studies



- stimulation
- surgery
- dissection
- tracer studies
- etc

# Imaging of human pain

1. BOLD

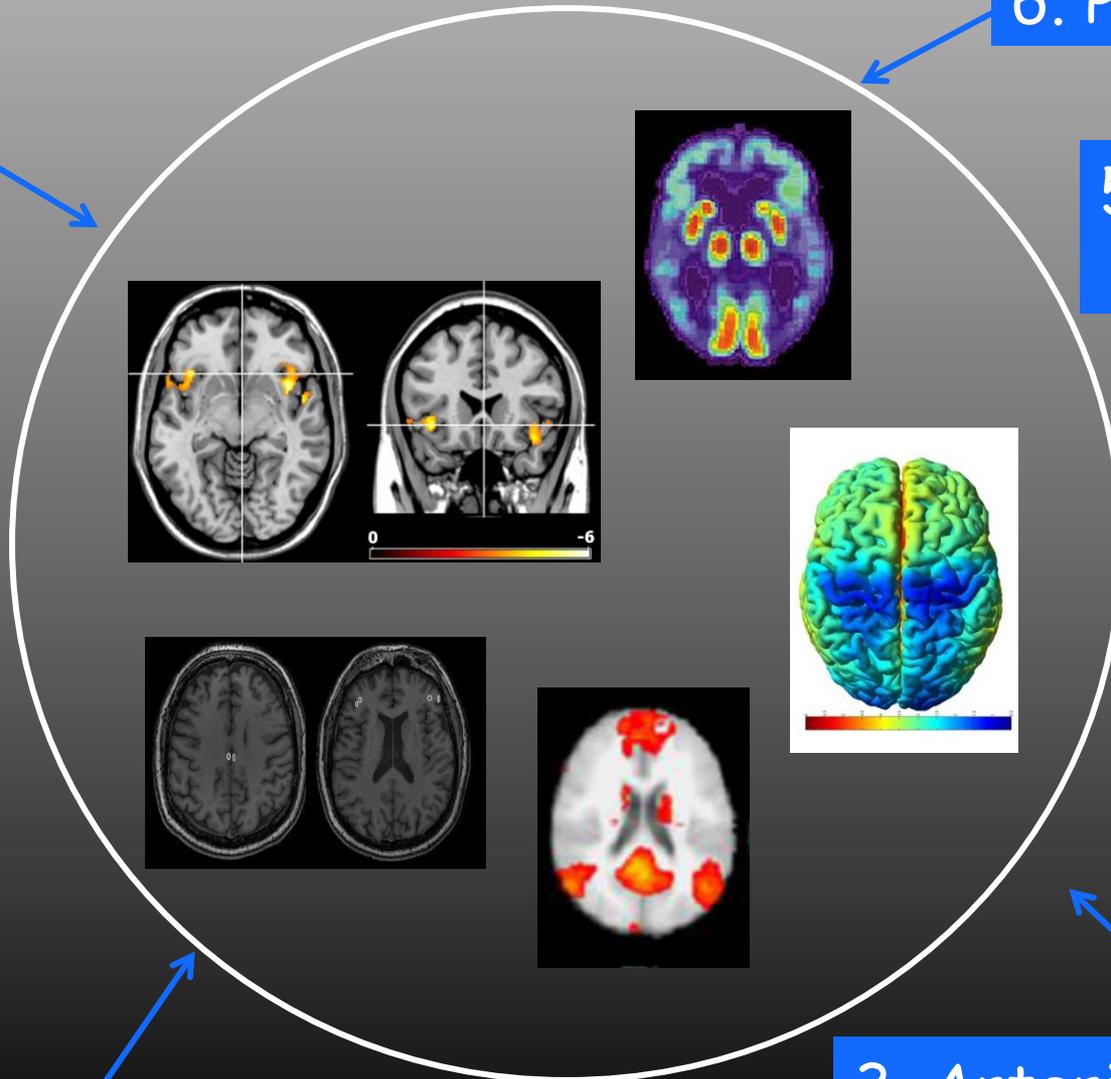
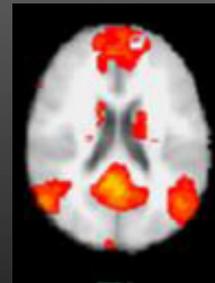
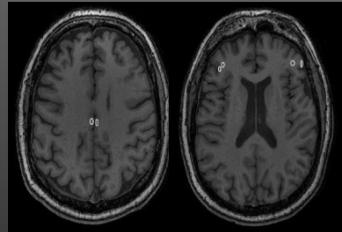
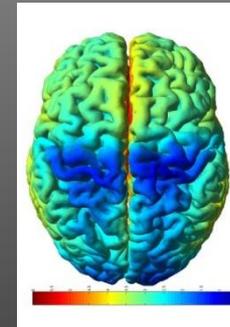
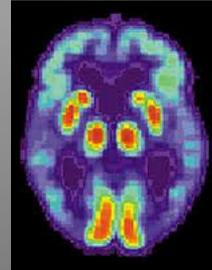
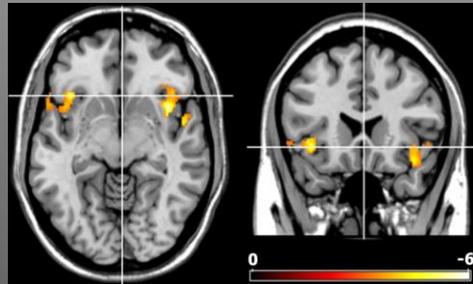
6. PET

5. Resting stage fMRI

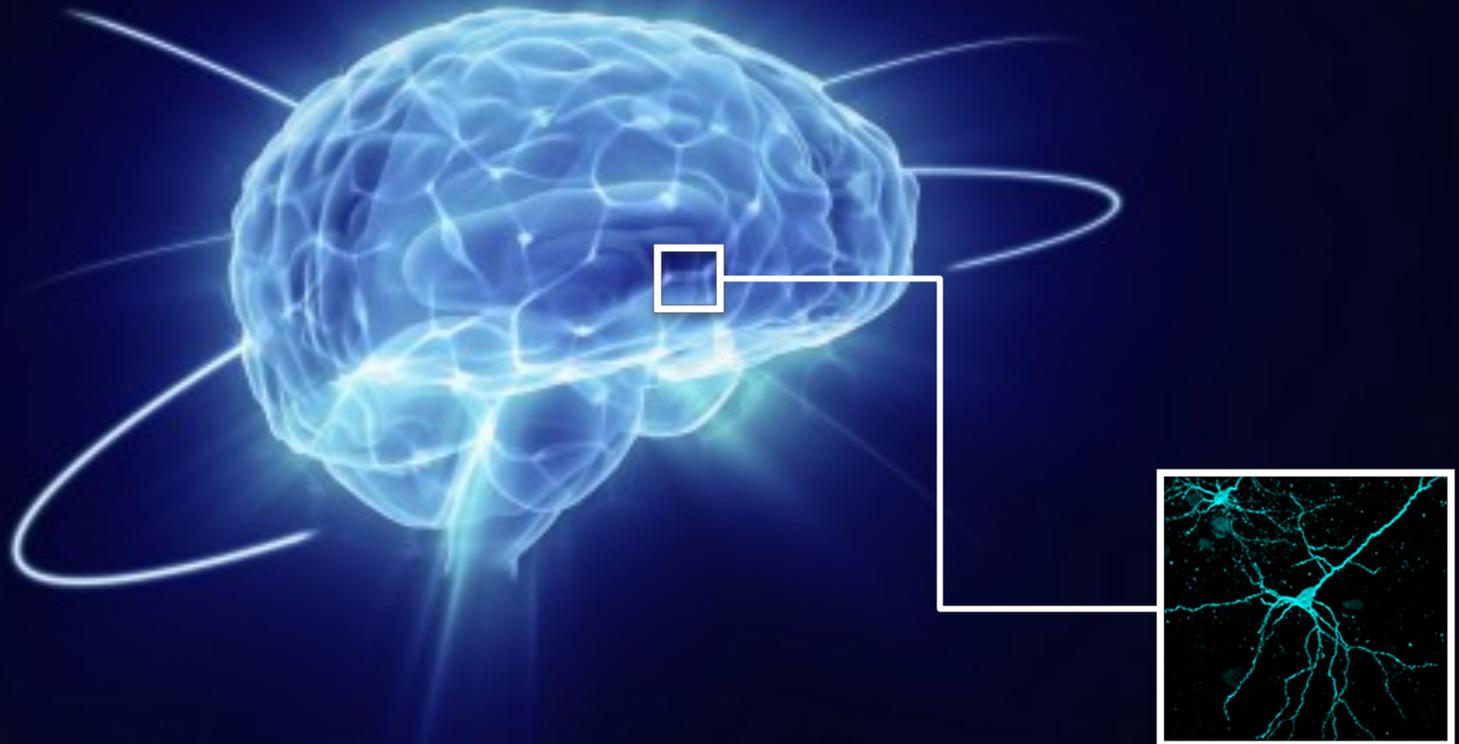
4. Volumetry

3. Arterial spin labelling

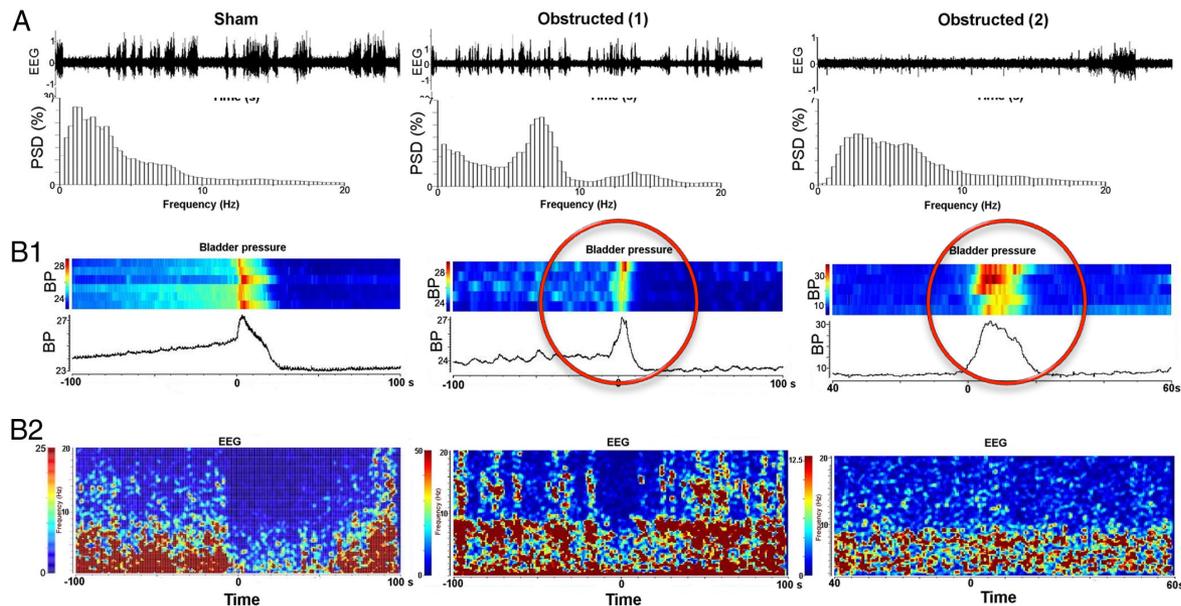
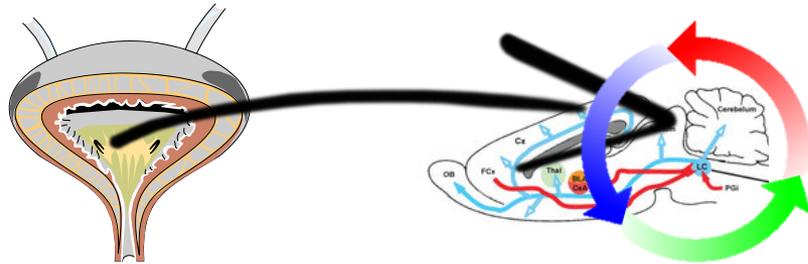
2. Diffusion tensor imaging



# Direct brain signalling - electrical activity

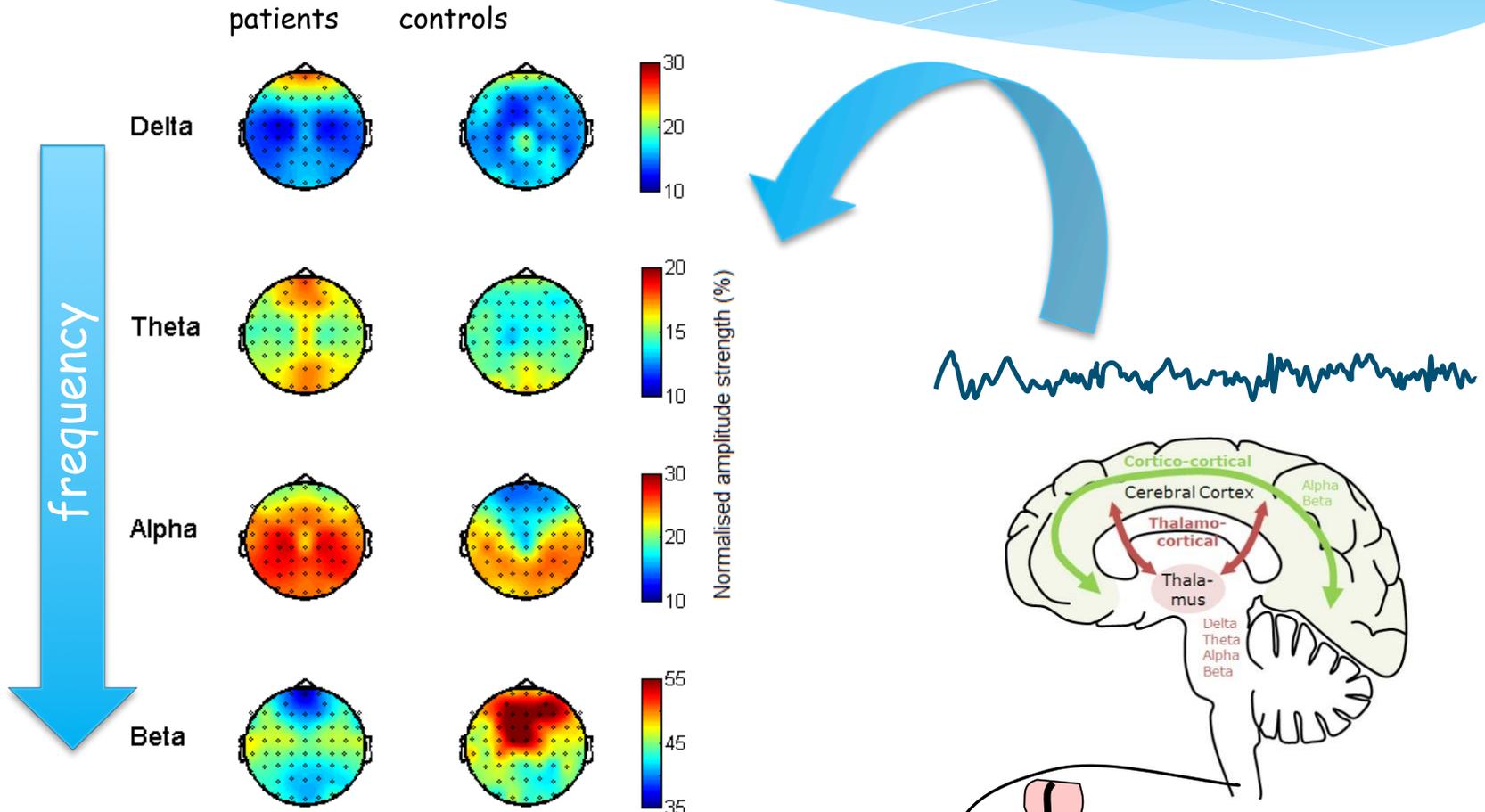


# Animal studies - an example

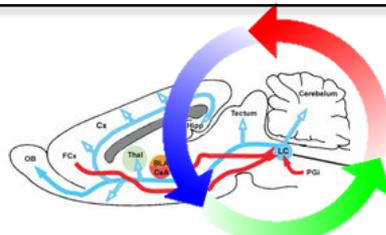


Bladder distension in rats results in neural hyperactivity in locus coeruleus with specific abnormalities in the EEG circuits (decreased low frequency and increased theta (6-8Hz) activity)

# A comparable human study



Slowed EEG rhythmicity was seen in patient (N= 31) with painful chronic pancreatitis  
 Theta (like in neuropathic pain) was independent on opioids and aetiology

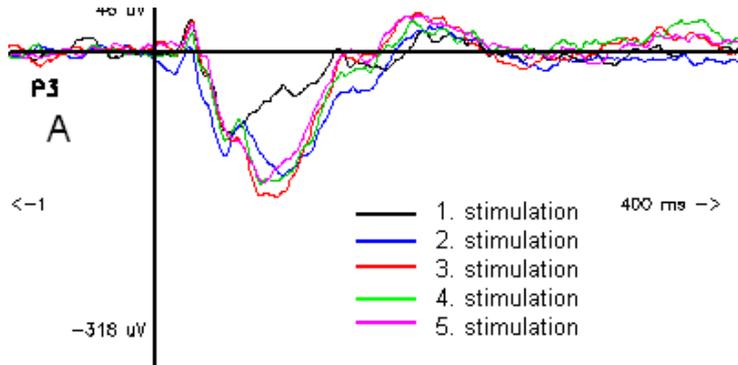


Drewes et al. World J Gastroenterol 2008  
 Olesen et al. Eur J Gastroenterol Hepatol 2011

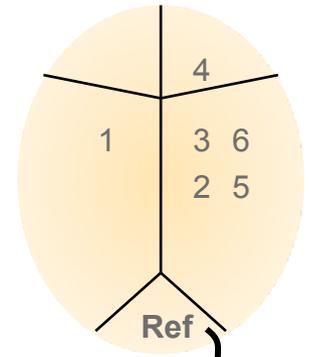
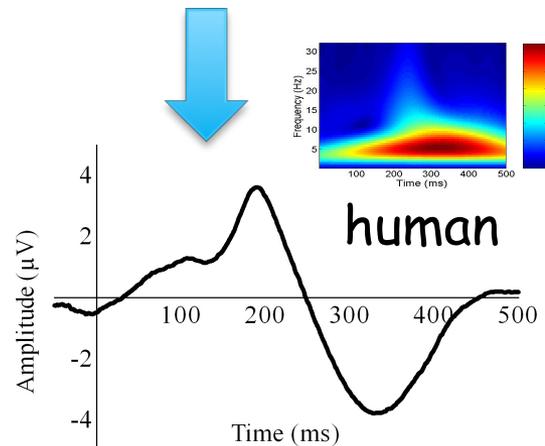
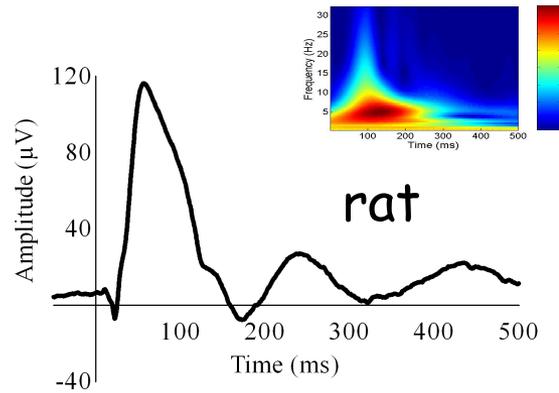
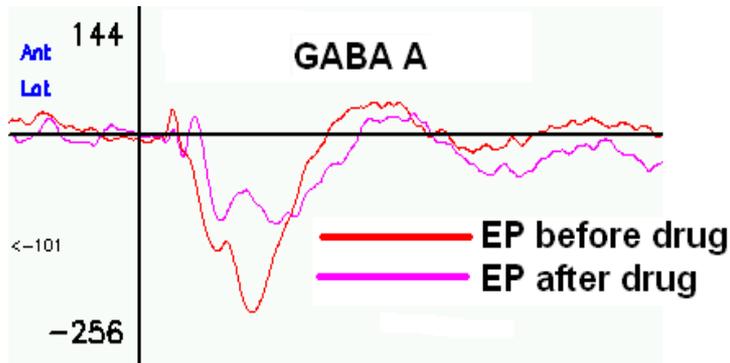
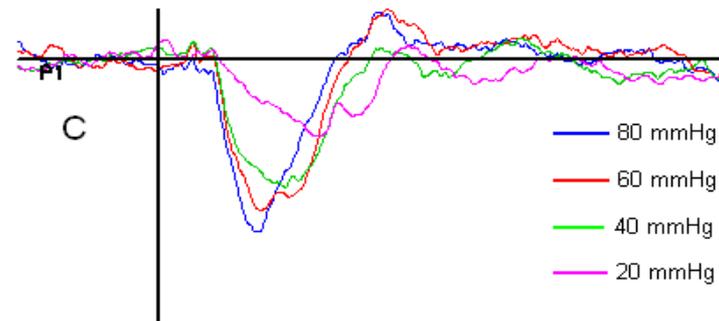
# Pain models in drug development



# Brain studies and drug development

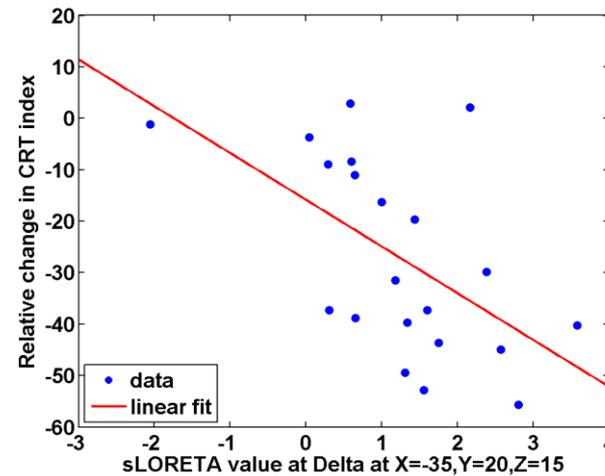
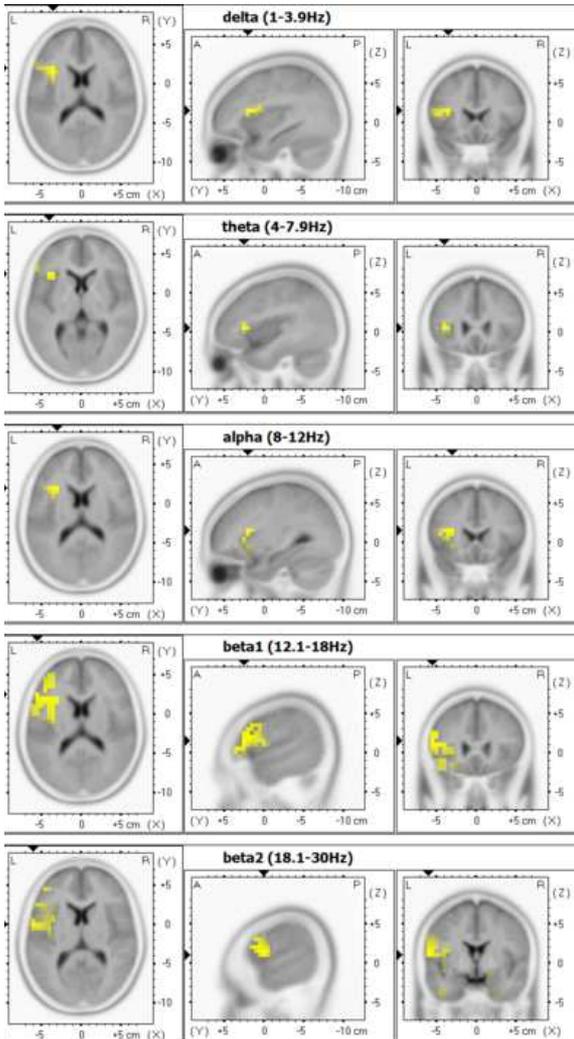


Different stimulation intensities



5 x 60 rectal distensions

# Source localization of human resting EEG



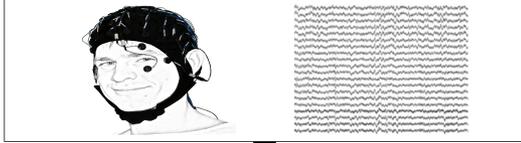
Frontal and insula oscillated more strongly after remifentanyl  
Activity at delta band was correlated with reaction time

# The global outcome

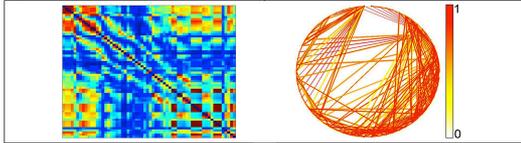


# Graph theoretical solutions

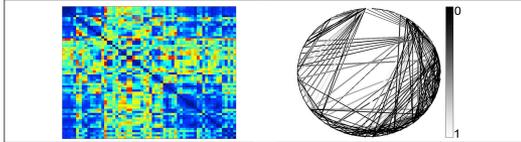
## A) EEG recordings



## B) Coherence measures

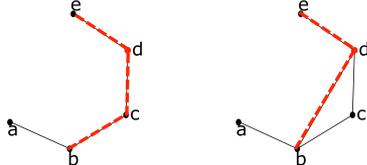


## C) Graph theory

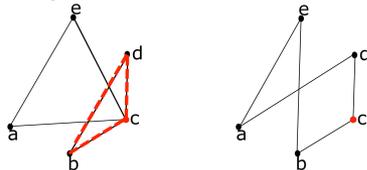


## D) Graph measures

### i) Characteristic path length



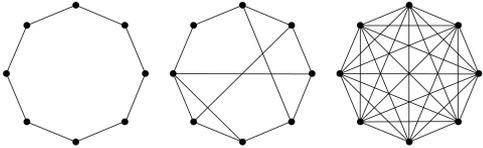
### ii) Clustering coefficient



### iii) Small-world networks

perfect order

random order



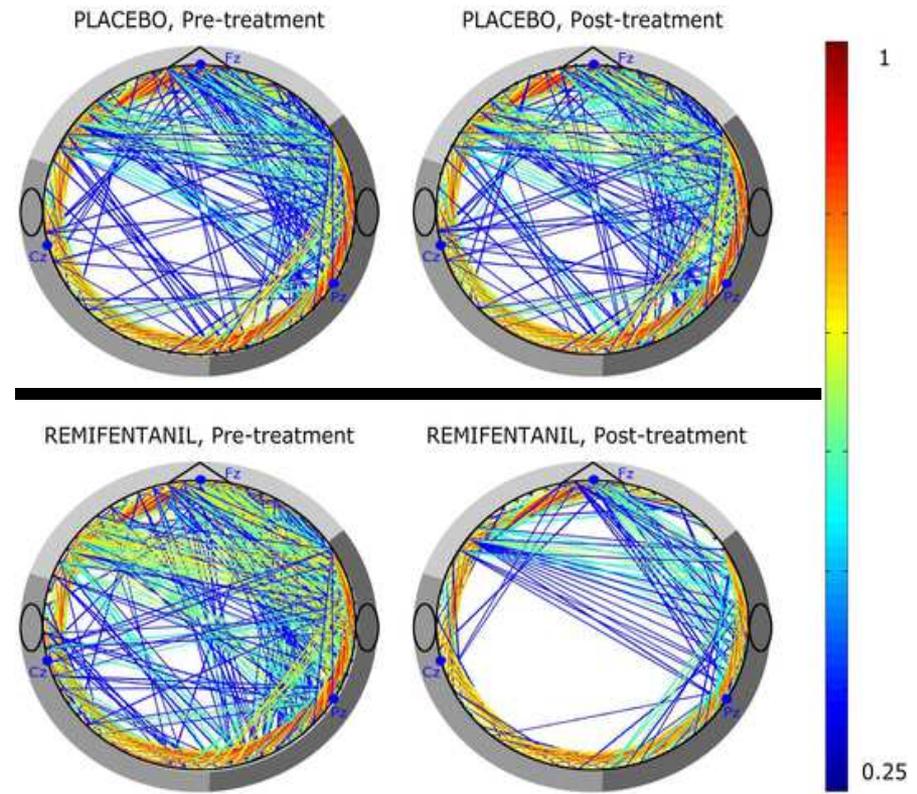
low path length  
high clustering

Remifentaniol:

Path length ↑

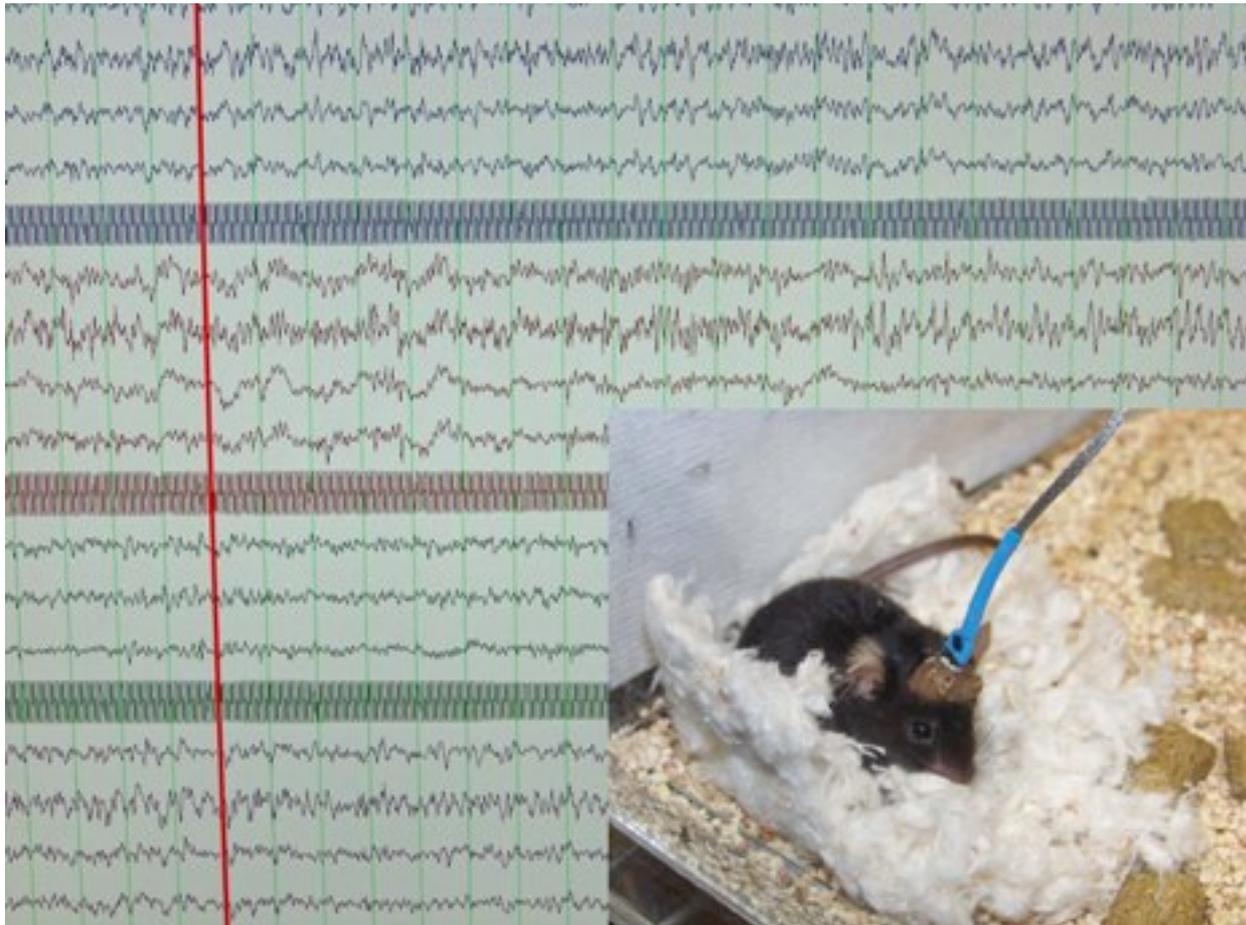
Clustering coefficient ↓

Small worldness ↓



Networks after placebo and remifentaniol

# Complex assessment of the pain system



# Levels of interactive studies in human pain

5. Resting and pain evoked EEG

8. MR resting stage networks & spectroscopy

4. Brain source modelling

3. Spinal potentials

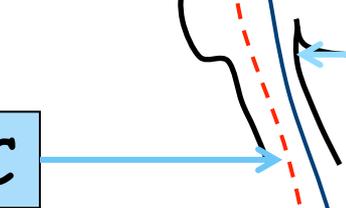
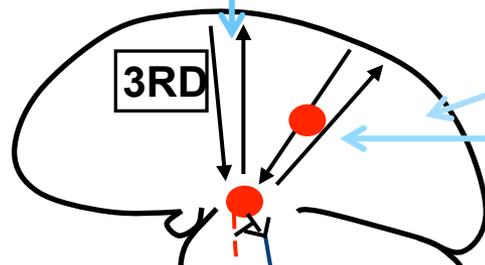
1. QST

6. CPM/DNIC

7. Offset analgesia

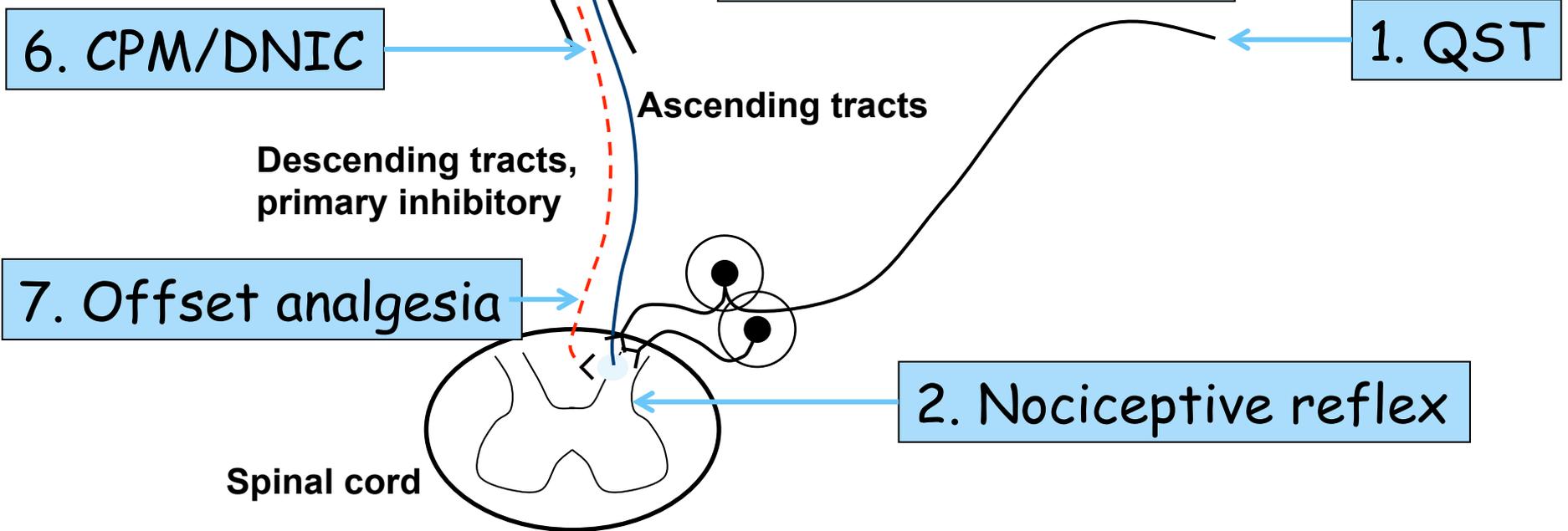
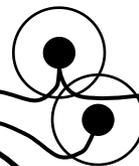
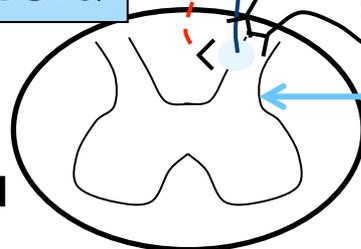
2. Nociceptive reflex

Spinal cord

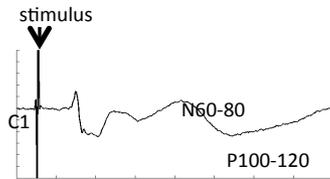


Ascending tracts

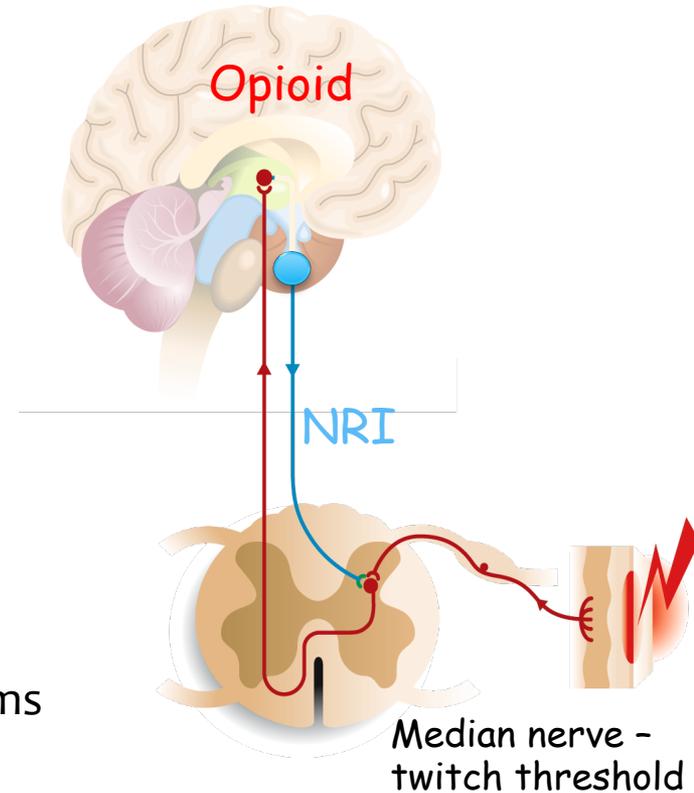
Descending tracts,  
primary inhibitory



# Brainstem sensory processing opioid vs. antidepressive (& placebo)



Venlafaxine treatment resulted in changes in sensory processing in the brain stem



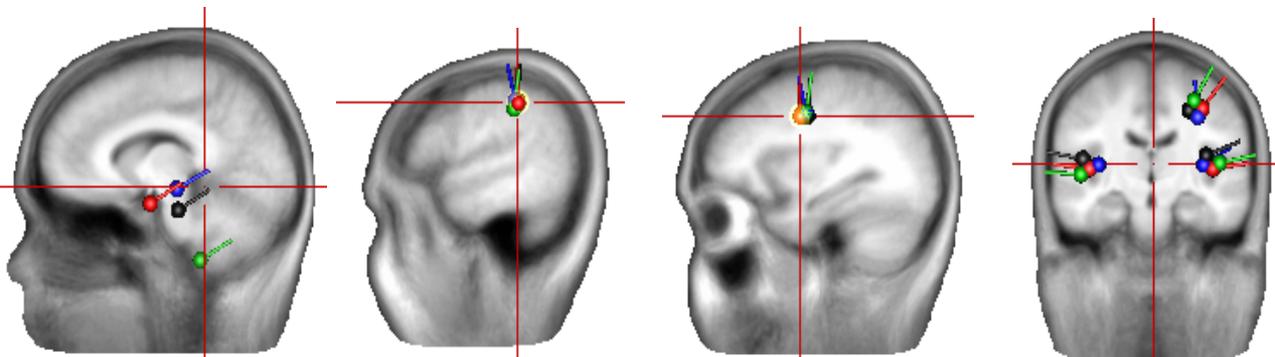
- Baseline
- Placebo
- Oxycodone
- Venlafaxine

14-18ms

20-25ms

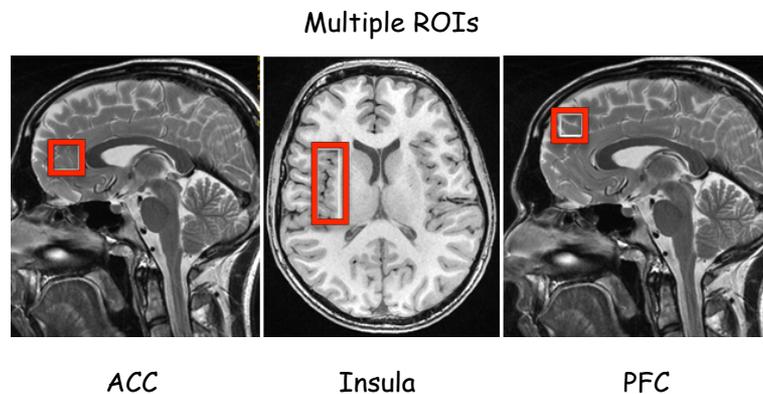
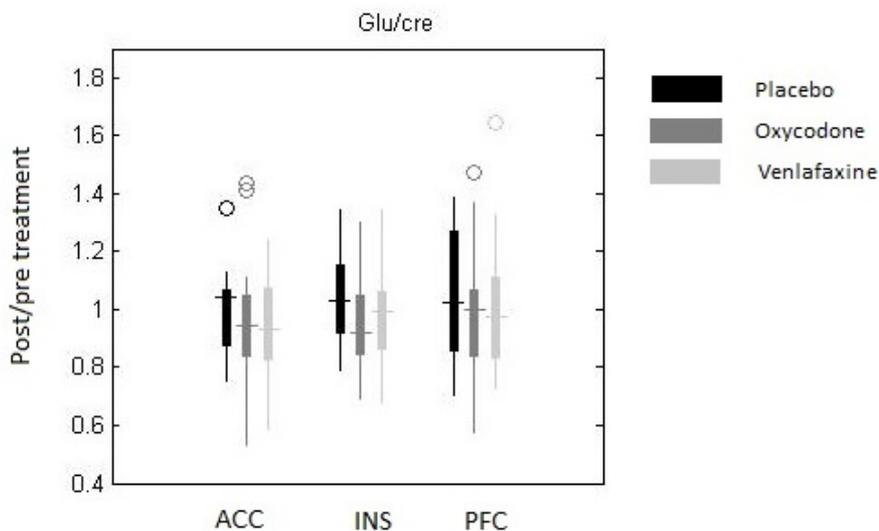
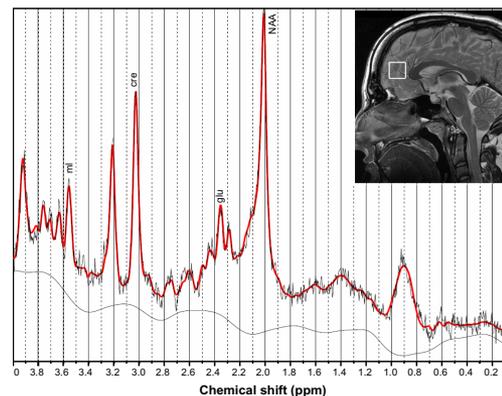
30-45ms

50-150ms



# Multi-voxel spectroscopy opioid vs. antidepressive (& placebo)

Opioid treatment decreased glutamate levels in the "pain matrix"





# Analgesics and animal studies

## PROS

1. Basic physiological studies have demonstrated many pharmacological mechanisms
  1. receptor types
  2. pain mechanisms
  3. side effects
  4. tolerance
  5. combination therapy
  6. rotation
  7. etc



## CONS

1. Animal studies are mainly based on motor reflexes or behavioral responses, whereas pain is a net result of complex sensory, affective, and cognitive processing
2. Major differences between the effects of drugs across species (and even strains), and this limits generalization of findings to man
3. Many of the models are also optimized for success the construct validity (translability) is often limited
4. In fact, only one painkiller (ziconotide) has ever gone from bench to bedside)

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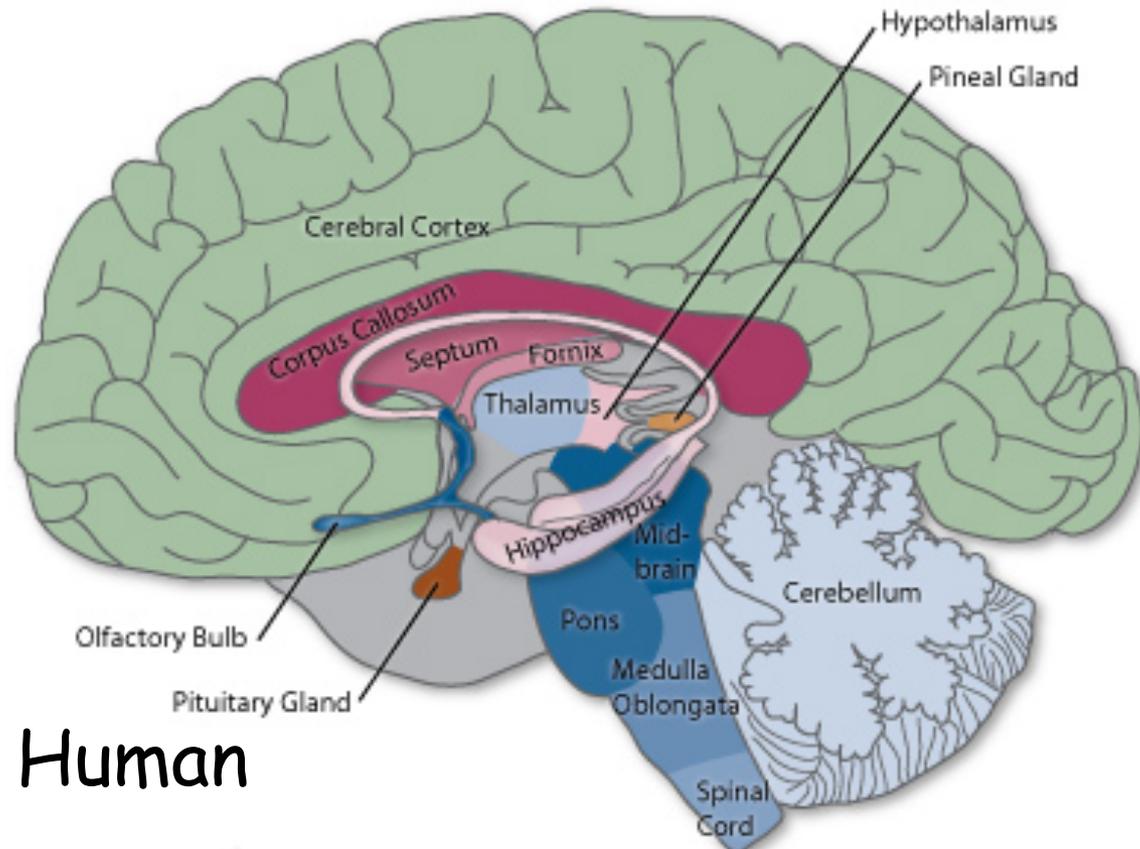
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# Species differences

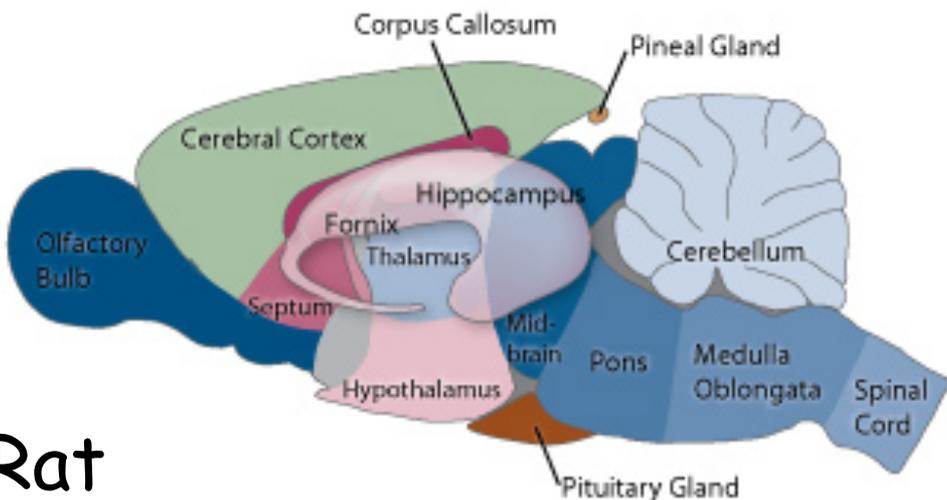


????





Human



Rat

