Temperature, noxious stimuli
Nociceptors are mechano-chemical receptors

- Free nerve endings
- Tissue damage
Compound action potential and modality

FIG. D-1  Schematic diagram of a peripheral nerve with sensory and motor branches. Stimulation or recording at site A involves both sensory and motor axons, at site C sensory axons only, and at B both sensory and motor axons, since the motor nerve has many sensory axons.
Compound action potential and modality
Compound action potential and modality

**FIG. D-1** Schematic diagram of a peripheral nerve with sensory and motor branches. Stimulation or recording at site A involves both sensory and motor axons, at site C sensory axons only, and at B both sensory and motor axons, since the motor nerve has many sensory axons.
Erlanger and Gasser

Humans:
Pressure blocks touch but not pain
Cocaine blocks pain but not light touch

Frog Nerve:
Pressure blocks large fibers (fast conducting)
Cocaine blocks small, slow fibers

Quindi?...
So fiber size is related to modality
Aα, Aβ
Fine-touch fiber
C fiber
Aδ, C

Dorsal column
Spinothalamic tract
Inhibitory interneuron
Noxious stimulus

Touch

Cognitive activities

Primary afferent neurones (\(A_\beta\) fibres)

Primary afferent neurones (\(A_\delta\) and \(C\) fibres)

Nociceptors

Mechanoreceptors

Descending pathway

Dorsal horn

Dorsal root ganglion

Spino-thalamic tract

Sensory cortex

Limbic system

Thalamus

Secondary afferent neurones

Ventral horn

apologies to artist for no credit  :( 
The only pain supportable pain... is the pain of others

Oscar Wilde
Pain is an alarm signal
Congenital absence of pain
Surgical treatment of untreatable pain
Pain intensity-related activation of the primary somatosensory cortex. Multiple regression analyses of PET scans of cerebral blood flow reveal that the contralateral primary somatosensory cortex (SI) exhibits activation which is significantly related to the perceived intensity of noxious thermal stimuli (upper left image). Activation differences are somatotopically appropriate and are located in a zone consistent with the upper arm.
Pain intensity-related activation of the anterior cingulate cortex. Multiple regression analyses of PET scans of cerebral blood flow reveal that multiple regions of the anterior cingulate cortex (ACC) exhibit activation which is significantly related to the perceived intensity of noxious thermal stimuli (upper left image). Numerous lines of evidence indicate that the anterior cingulate cortex is involved in the processing of affective components of pain. However, activation of this region in a manner related to a sensory-discriminative feature of pain (i.e., pain intensity) suggests a broader role in the processing of pain.

Pain intensity-related activation of the insular cortex. Multiple regression analyses of PET scans of cerebral blood flow reveal that the insular cortex exhibits activation which is significantly related to the perceived intensity of noxious thermal stimuli (upper left image). Much like the anterior cingulate cortex, this brain region has significant connections with both the prefrontal cortex and amygdala, and may play an important role in imparting meaning to the experience of pain.
Primary SS cortex and ACC+Ins cortex activated in proportion to pain.

So why discriminative/affective distinction? Largely based on lesion effects.
activation of ACC and INS correlated with affective dimension of pain

Pain empathy activates ACC

Anti-pain substances reduce pain (of course) but also activation of ACC – INS
Relation between receptors and pain not so simple as shown here!!
Nociceptors

- Nociceptors are special receptors that respond only to **noxious** stimuli and generate nerve impulses which the brain interprets as “pain”
- Free nerve endings
- Tissue damage
Although “pain pathways” from the skin have been identified, it is incorrect to suppose that a specified quantity of nociceptor impulses travels in an uninterrupted stream to cerebral cortex to produce a proportional quantity of pain. Rather, a given level of nociceptor activation can produce dramatically different subjective experiences under different conditions. A soldier charging into battle may not even notice injuries that would, under other circumstances, produce exceptional pain.

At the opposite end of the spectrum, a chronic pain syndrome can exist even without abnormal activity in skin nociceptors. It is the central processing of nociceptor signals, not their mere presence, that gives rise to the sensory and affective experience. Understanding pain thus requires understanding how the stream of impulses arriving from the nociceptors is processed by the rest of the nervous system. And, as pointed out by Melzack, the subjective experience of pain, more than the experience any other signal originating in a sensory organ, is modulated by social, cultural, and personal factors.
pain

GATE CONTROL
Pain modulation
  personal history
  culture
  stress

suggestion (placebo)
Placebo effect  (prof. Fabrizio Benedetti, Univ. Torino)

1. Pain suppression not from active ingredients but from expectations.
2. Patient must expect and believe.
3. Patient must know that they are receiving treatment
4. No effect if unaware (communication and visualization)
Endogenous Opioids

- leucine-enkephalin (leu-enkephalin)
- methionine-enkephalin (met-enkephalin)
- beta-endorphin
- alpha-neoendorphin
- dynorphins
A  PRE-OPPIO MELANOCORTINA (POMC)

Segnale NH₂ → γ-MSH → ACTH → β-MSH β-END COOH
  α-MSH CLIP β-LPH

B  PRE-ENCEFALINA

Segnale NH₂ → 1 2 3 4 5 6 7 COOH
  Met-ENK (Arg-Gly-Leu)  Leu-ENK (Arg-Phe)
  Peptide E

C  PRE-DINORFINA

Segnale NH₂ → βNeo-END DIN A DIN B
  1-8 13 14-29 COOH
  α-Neo-END 1-17
Placebo effect  (prof. Fabrizio Benedetti, Univ. Torino)

1. Pain suppression not from active ingredients but from expectations.
2. Patient must expect and believe.
3. Patient must know that they are receiving treatment
4. No effect if unaware (communication and visualization)
Placebo acts through endogenous opioids

**Endogenous Opioids**

- leucine-enkephalin (leu-enkephalin)
- methionine-enkephalin (met-enkephalin)
- beta-endorphin
- alpha-neoendorphin
- dynorphins
Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain

Markus Rütgen, Eva-Maria Seidel, Giorgia Silani, Igor Riečansky, Allan Hummer, Christian Windischberger, Predrag Petrovic, and Claus Lamm

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Abstract

Significance

Empathy is of major importance for everyday social interaction. Recent neuroscientific models suggest that pain empathy relies on the activation of brain areas that are also engaged during the first-hand experience of pain. These models rely on rather unspecific and correlational evidence. Here, we show that inducing pain analgesia also reduces pain empathy, and that this is associated with decreased activation of empathy-related brain areas. We then document that blocking placebo analgesia via an opioid antagonist also blocks placebo analgesia effects on pain empathy. This finding suggests that pain empathy is grounded in neural responses and neurotransmitter activity related to first-hand pain.
Moreover...

Placebo can increase effectiveness of «active» ingredients

Cancelled by Nalaxone (morphine antagonist)

NOCEBO
break
Spinal cord and sensory pathways
Spinal Cord

White matter (axons) and grey matter (neurons and unmyelinated fibers)

In white matter, various ascending and descending tracts

In grey matter, varies layers where sensory and motor integration occurs
A, a, b fibers

right side of brain  left side of brain

5. Sensory pathway reaches the cerebral cortex for conscious perception

right side of brain  left side of brain

4. Sensory pathway continues with second neuron projection

right side of brain  left side of brain

3. Sensory axon enters the spinal cord and synapses with brain

right side of brain  left side of brain

2. Action potential in sensory neuron

right side of brain  left side of brain

1. Sensory endings in skin

right side of brain  left side of brain

0. Lower motor neuron causes contraction of the target skeletal muscle

right side of brain  left side of brain

6. An upper motor neuron from the cortex executes a motor command

right side of brain  left side of brain

7. The upper motor neuron contacts a lower motor neuron in the spinal cord

right side of brain  left side of brain

apologies to artist for no credit : ( 
To get to the brain, there are numerous pathways, but two general classes:

The dorsal column system
    large fibers that ascend directly to the brain stem

The anterolateral column system
    small fibers cross the spinal cord and – after several synapses – ascend
to the brain stem or else directly to the thalamus (also called ‘spinothalamic tract’)

Spinothalamic system:

i. Pathway directly to thalamus and reticular formation
ii. Small/Medium fibers
iii. Small/medium conduction velocity (Aδ, C)
iv. Nociceptive and thermal stimuli
v. Lower "place specificity" – medium-large receptive fields
vi. Reduced topographical organization
vii. Reduced “synaptic security”
viii. Stability expansion in the course of evolution
* Temperature and pain

* Damage causes severe deficit in temperature and pain sensation
Touch sensation...
Passive or active?
active sensing

brain

world
Brain show

Reverse correlation under free viewing of a feature film

Post-central sulcus
Somatosensory hand-related region

1.5T GE scanner.
TR = 3000, TE = 55, FOV 24 cm2, matrix 80 x 80.
short break...

then... more about pain
Dorsal column system:
i. Pathway through brain stem and thalamus
ii. Medium/Large fibers
iii. High conduction velocity (Aα, Aβ)
iv. Innocuous stimuli
v. "place specificity" – small receptive fields
vi. Elevated topographical organization
vii. “synaptic security”
viii. Progressive expansion in the course of evolution
* Tactile analysis

* Damage causes severe deficit in tactile discrimination and recognition