Neurobiological aspects of pain in childhood

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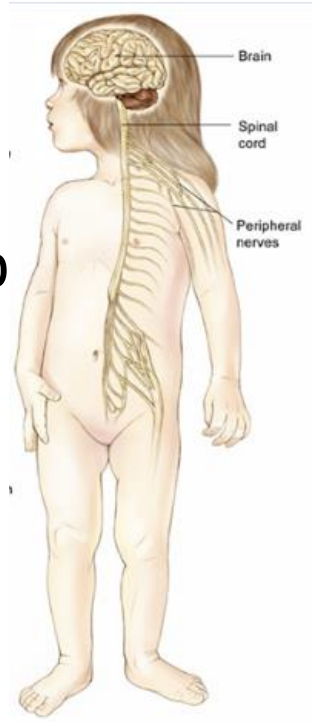


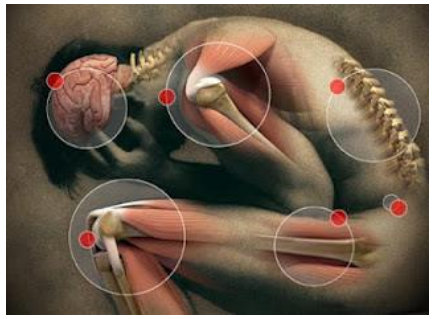
The purpose of pain

- Caused by actual or potential injury or tissue damage
- Defence mechanism
- Warning, protection
- Escape
- Rest, healing
- Learning
- Preserves life

In many cases pain is not protective

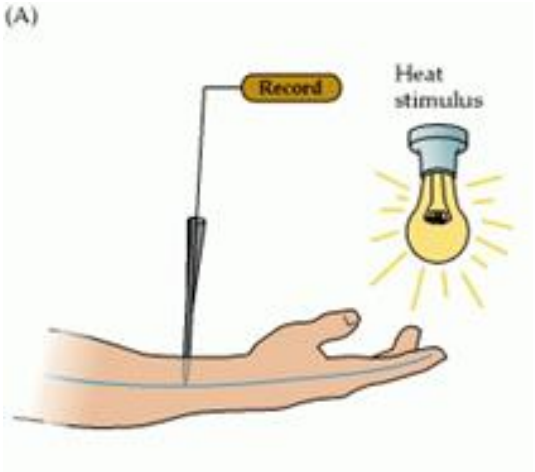
- Pain arises spontaneously
- Elicited by normally innocuous stimuli (touch)
- Exaggerated and prolonged response to noxious stimuli
- Spreads beyond the area of injury
- Clinical pain is unpredictable and frequently poorly related to injury
- Is amplified or even generated by the central nervous system

Pain can also be maladaptive



- Too prolonged to act as a warning
- No possibility of escape
- Nothing is learned from it
- Causes great suffering
- Does not preserve life
- Lead to depression, anxiety, lack of mobility and social isolation

Pain is triggered by nociceptors – but does not result from a straight path to the brain



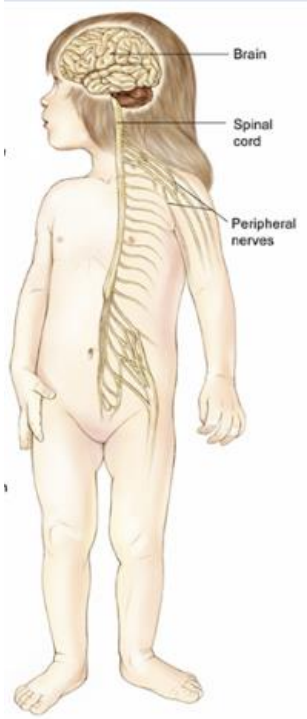
Signals from
two main nociceptor groups:
A deltas – short sharp pain
C fibres – dull, aching pain

Central component to pain

A major contribution is made by the **central nervous system** in generating pain

This central component is of fundamental importance when considering clinical pain

It is therefore difficult to predict pain on the basis of injury or damage

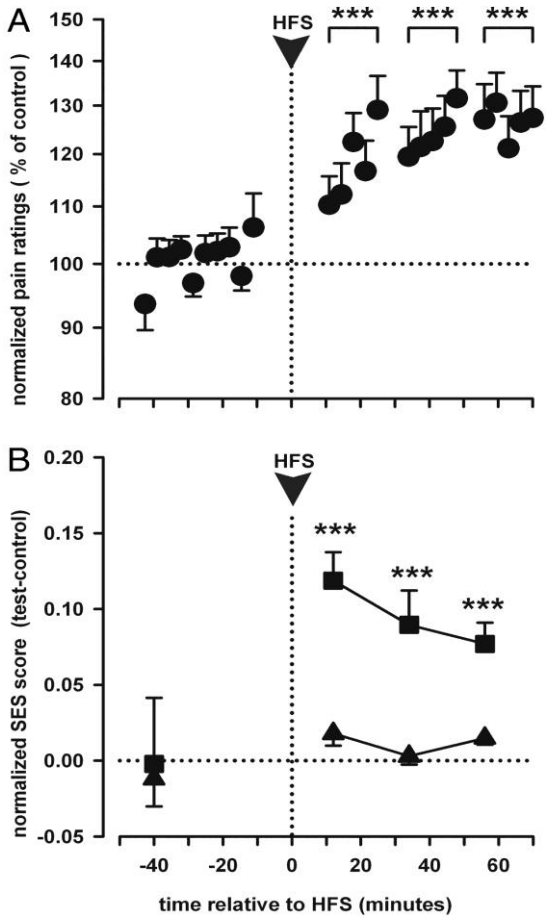


Central sensitization

- A mechanism whereby pain is amplified or even generated by the central nervous system
- An increase in excitability of central neurons such that normal inputs evoke exaggerated responses.
- Results from synaptic and circuit plasticity in the CNS.
- A form of 'learning' whereby the CNS pain processing is altered.
- Maintained 'state' of central sensitization beyond the resolution of a peripheral injury
- 'Latent' central sensitization following previous injury

Woolf CJ. Pain. 2011 152:S2-15. Latremoliere A & Woolf CJ (2009) J. Pain 10 895-926.

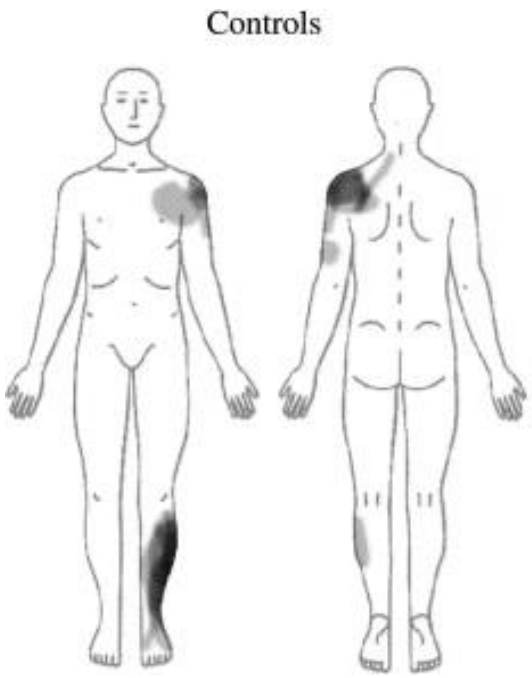
Demonstrating a central component to pain in human volunteers: wind-up amplification



Hansen, N. et al. J Neurophysiol 97: 2559-2563 2007

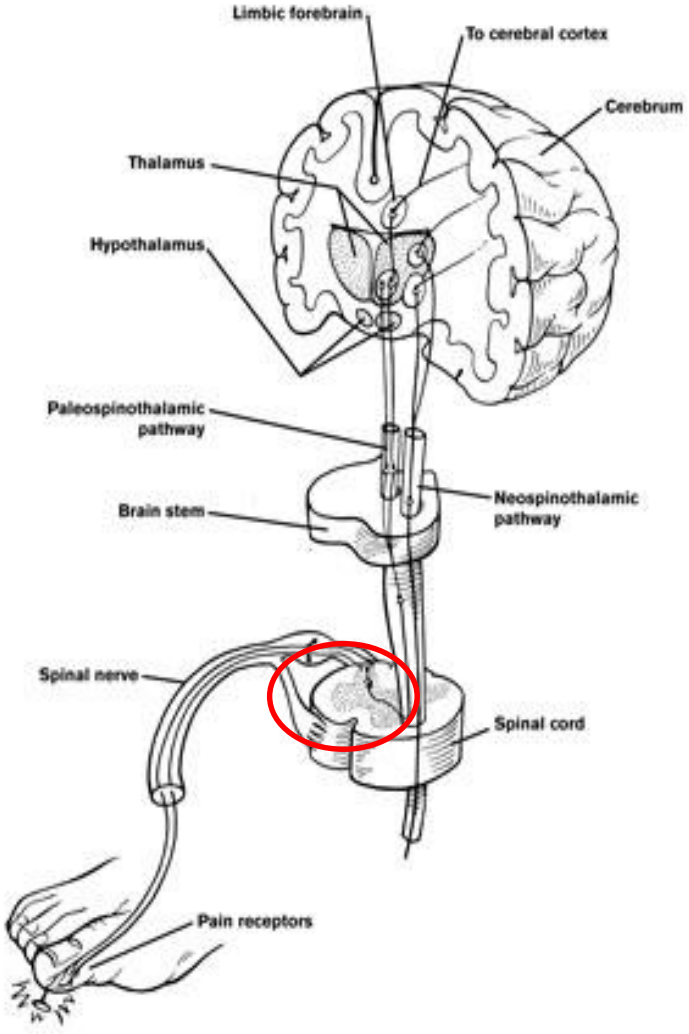
In chronic pain patients, central sensitization has become an established state

Experimental tests on chronic pain patients

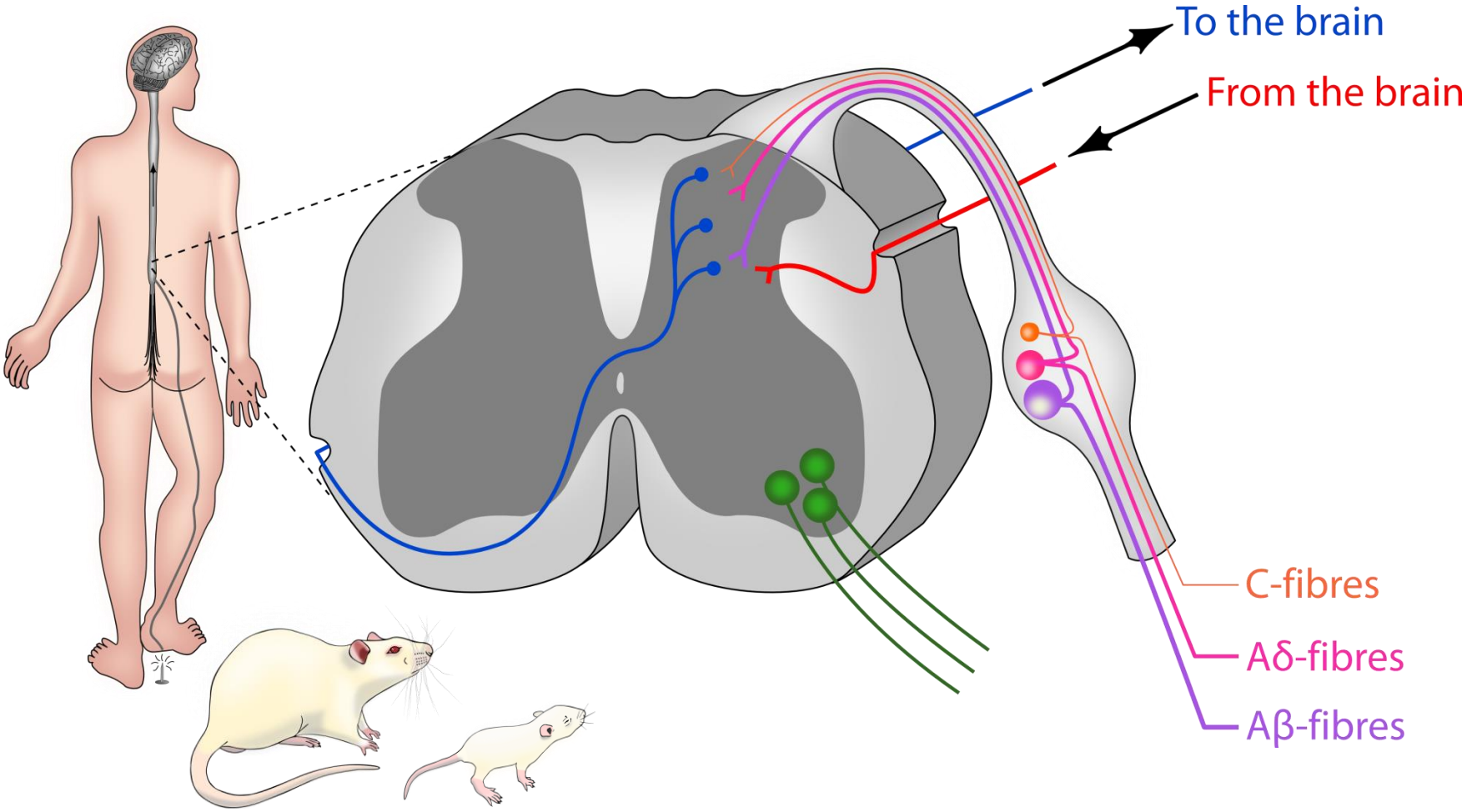


O'Neill et al European Journal of Pain 11, 2007, 415-420

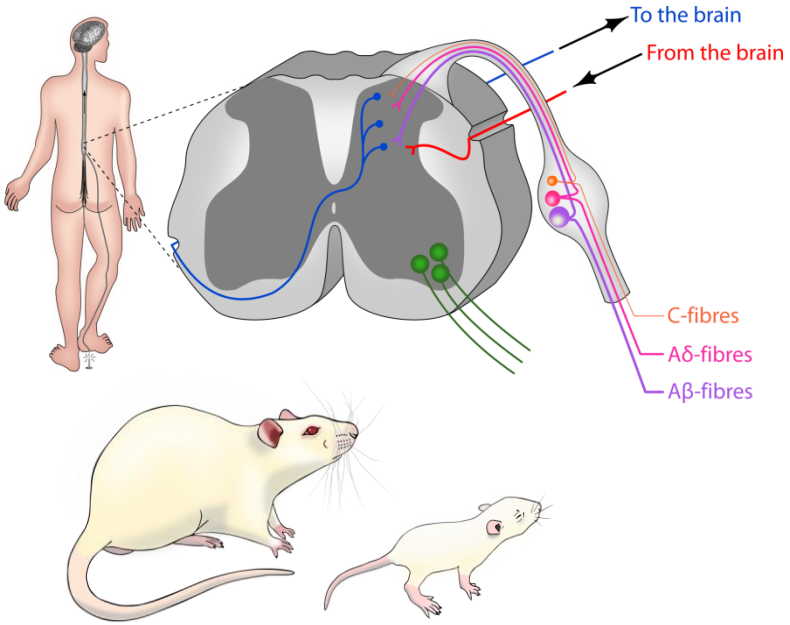
Pain is processed at different levels of the nervous system

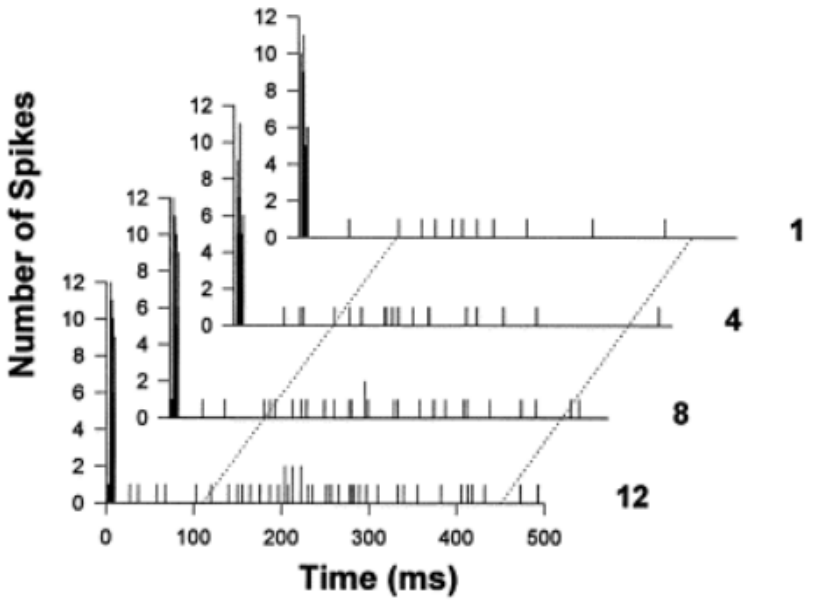


Pain experience is a result of active processing in the central nervous system



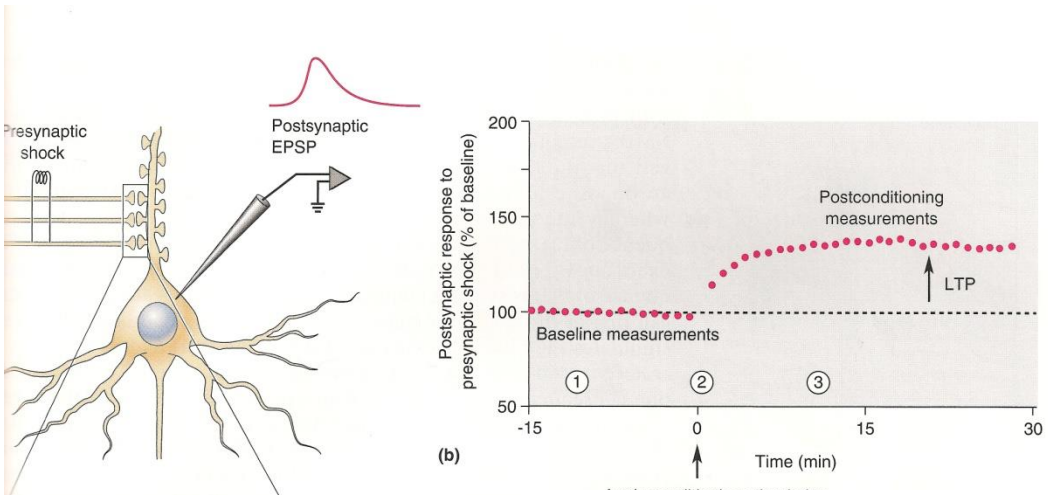
Dorsal horn – first nociceptor synapses in the central nervous system; first site of change



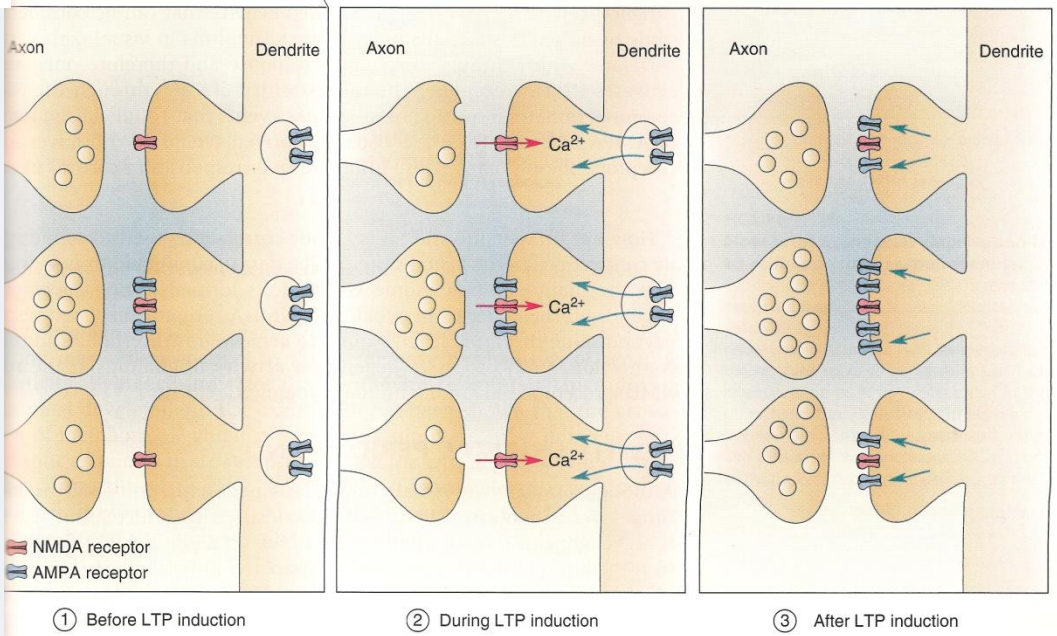


Repeated C fibre stimulation causes ‘wind-up’ of dorsal horn cell activity

Neuronal mechanism of central sensitization

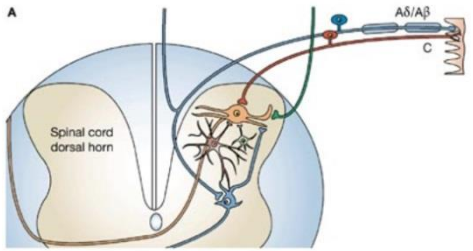


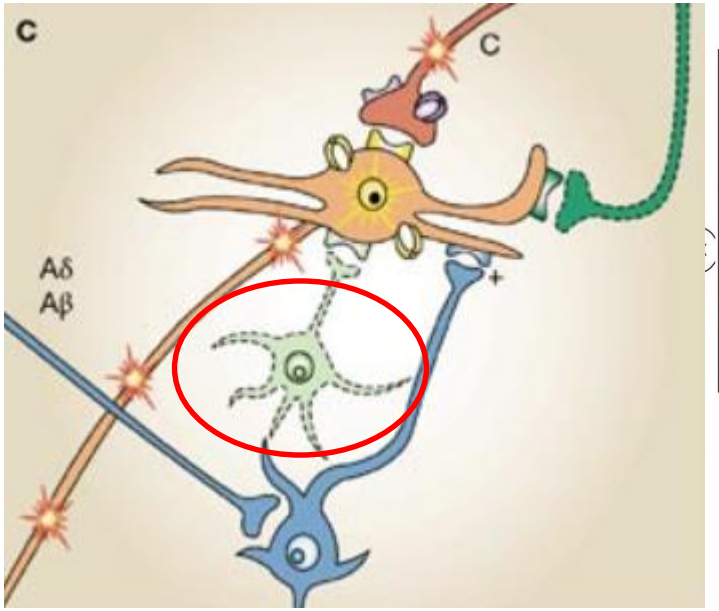
C fibre nociceptor stimulation

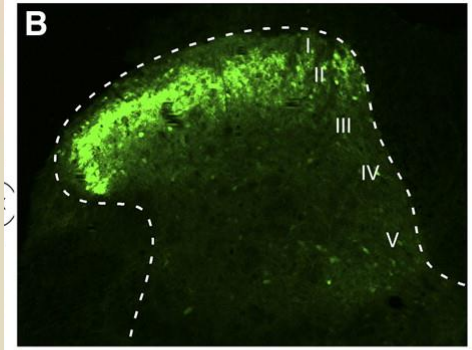


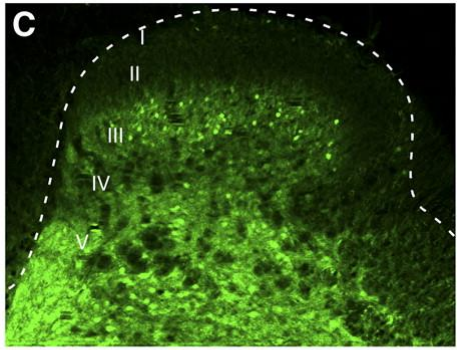
LTP (long term potentiation): strengthens synaptic transmission

Disinhibition contributes to central sensitization







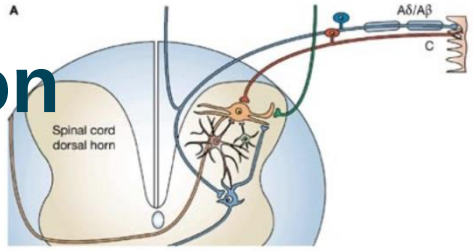


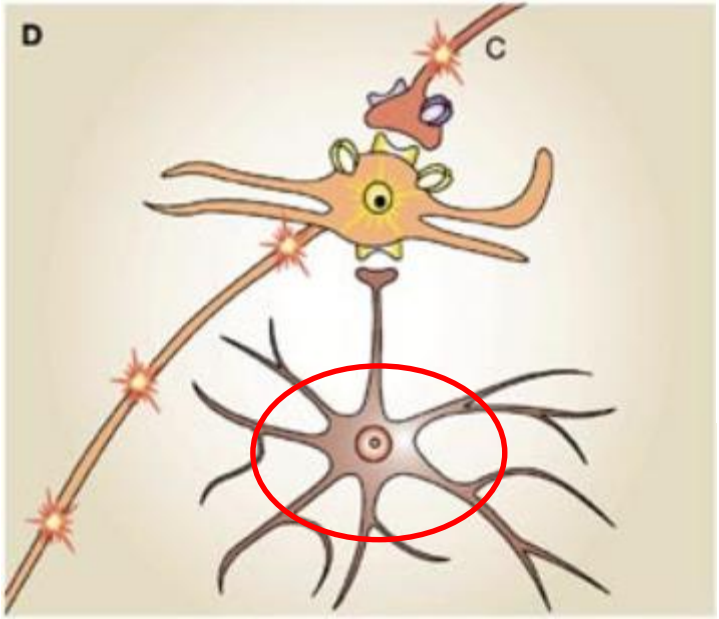
GABA glycine

Inhibitory neurotransmitters become less effective at controlling sensory Input. Therefore activity in pain circuits increases

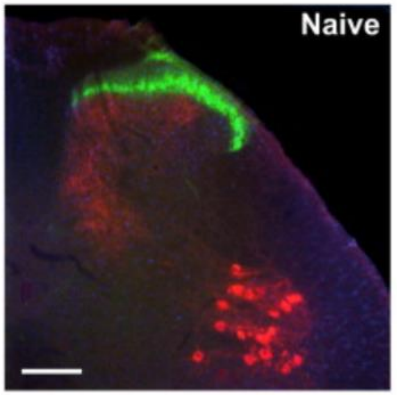
…..but this inhibition is already weak in the young spinal cord

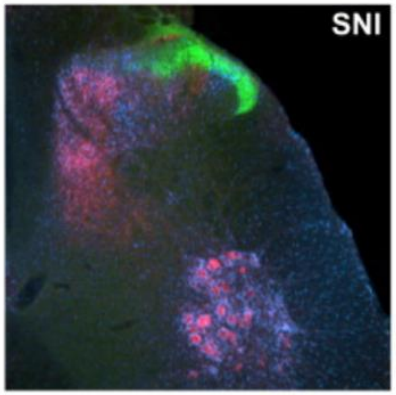
Glial immune activation contributes to central sensitization





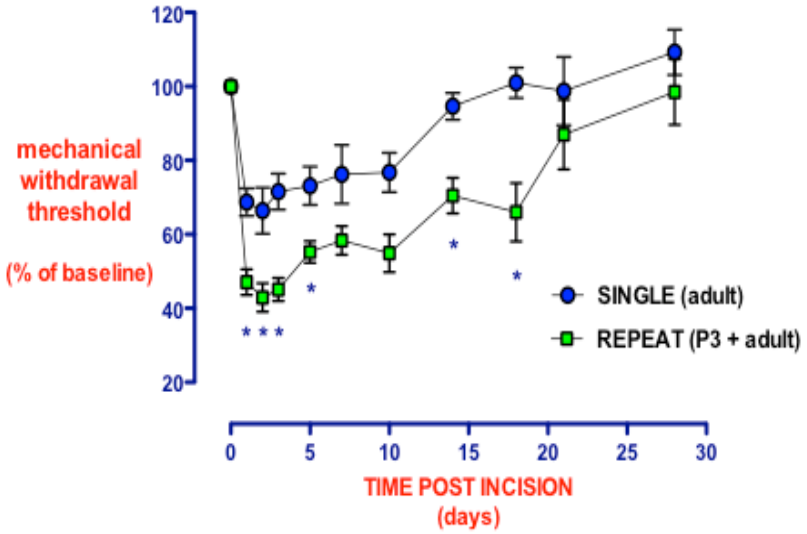
…but the glial responses in young spinal cord appear to retain a ‘memory’



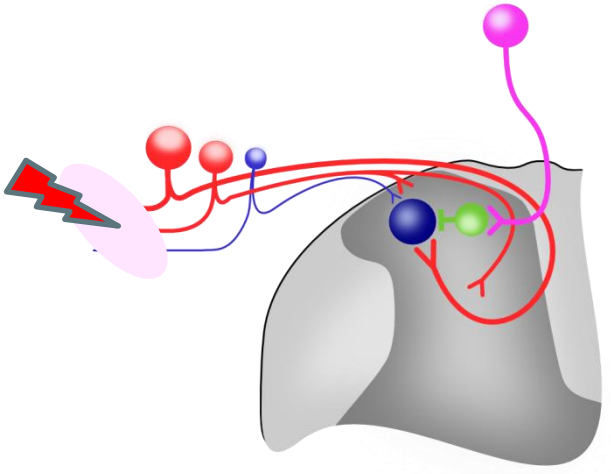


Microglial activation (blue) among the sensory terminals (green & red). Release local cytokines and activate pain circuits

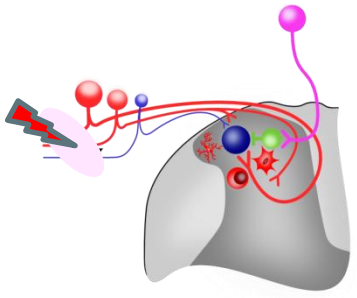
Previous injury in early life can 'prime' pain circuits – enhancing central sensitization



Prevented by local immune suppression



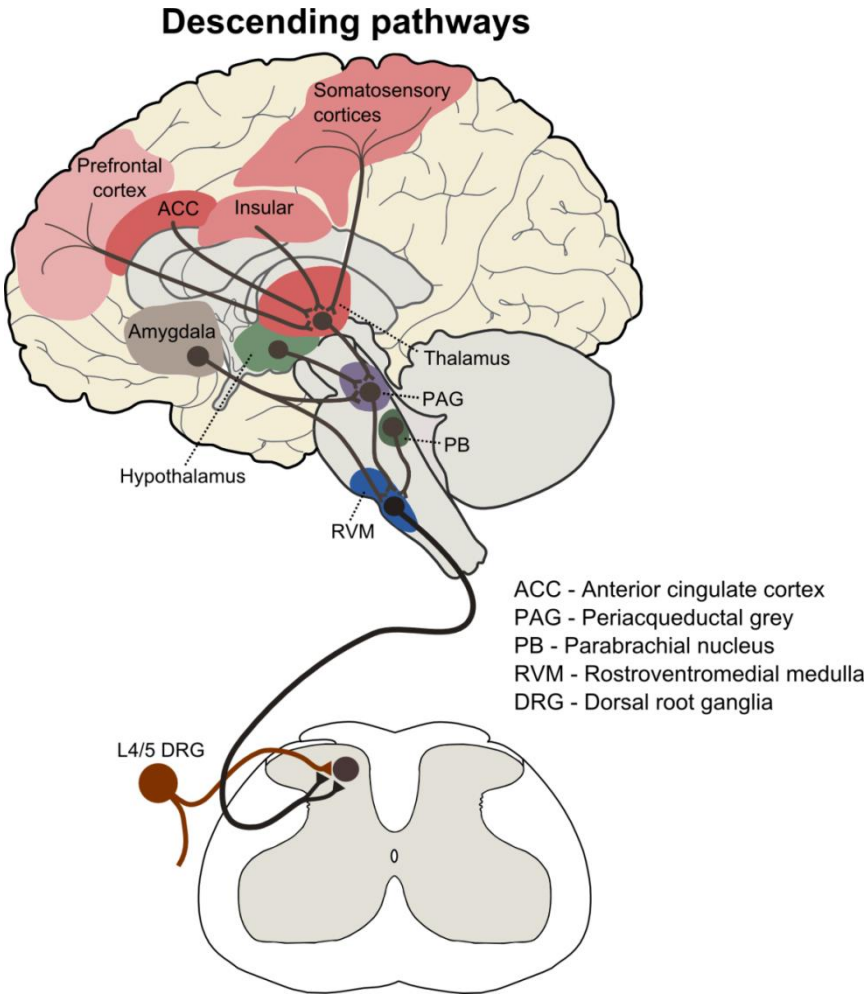
Synaptic changes in dorsal horn circuits



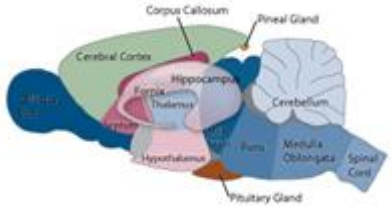
Changing neuroimmune profile

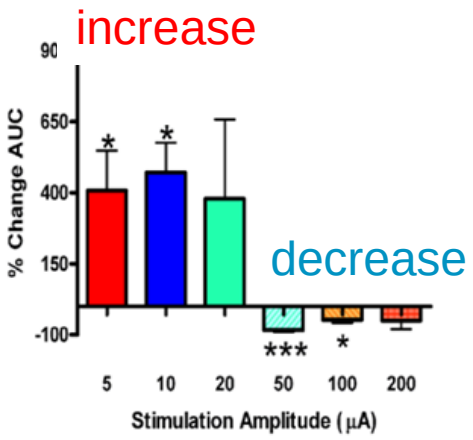
Torsney C et al., 2002, Li J et al., 2009, Beggs S et al., 2012

Descending control of spinal pain processing

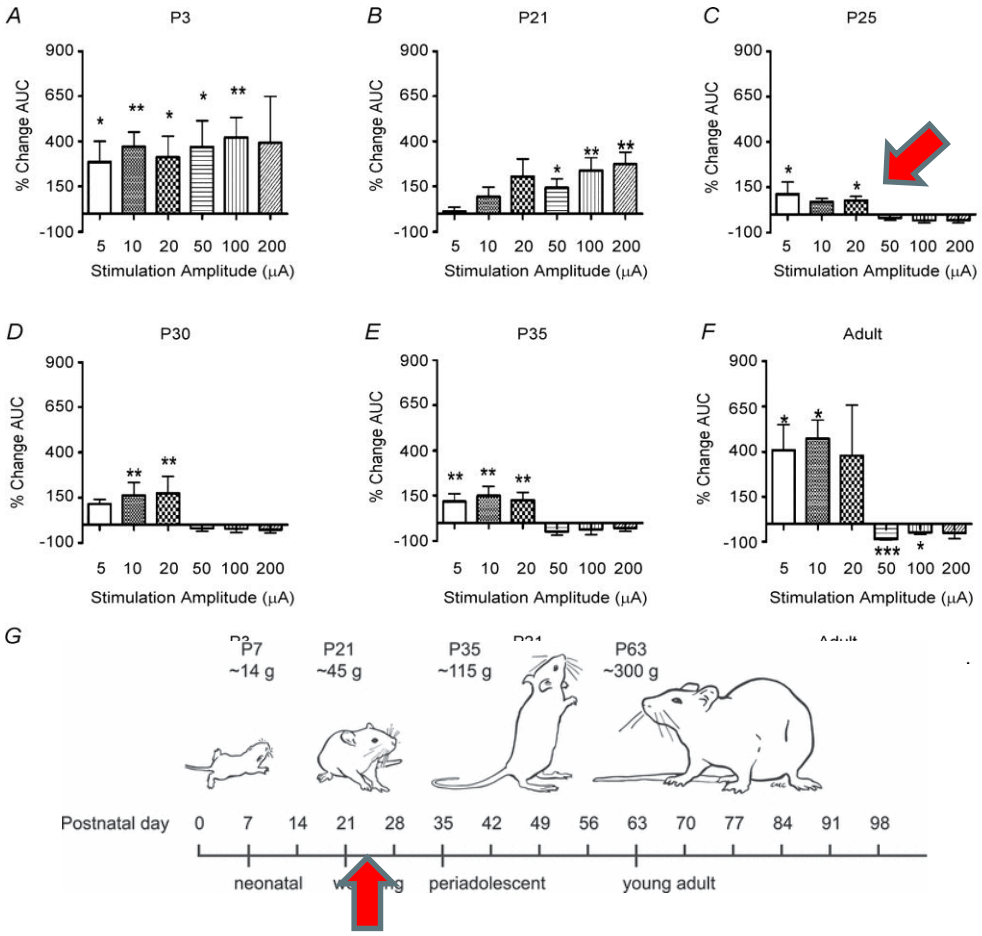


modelled in the rat





Late maturation of descending inhibition in childhood



Hathway et al (2009) J Physiol. 587:2927-35

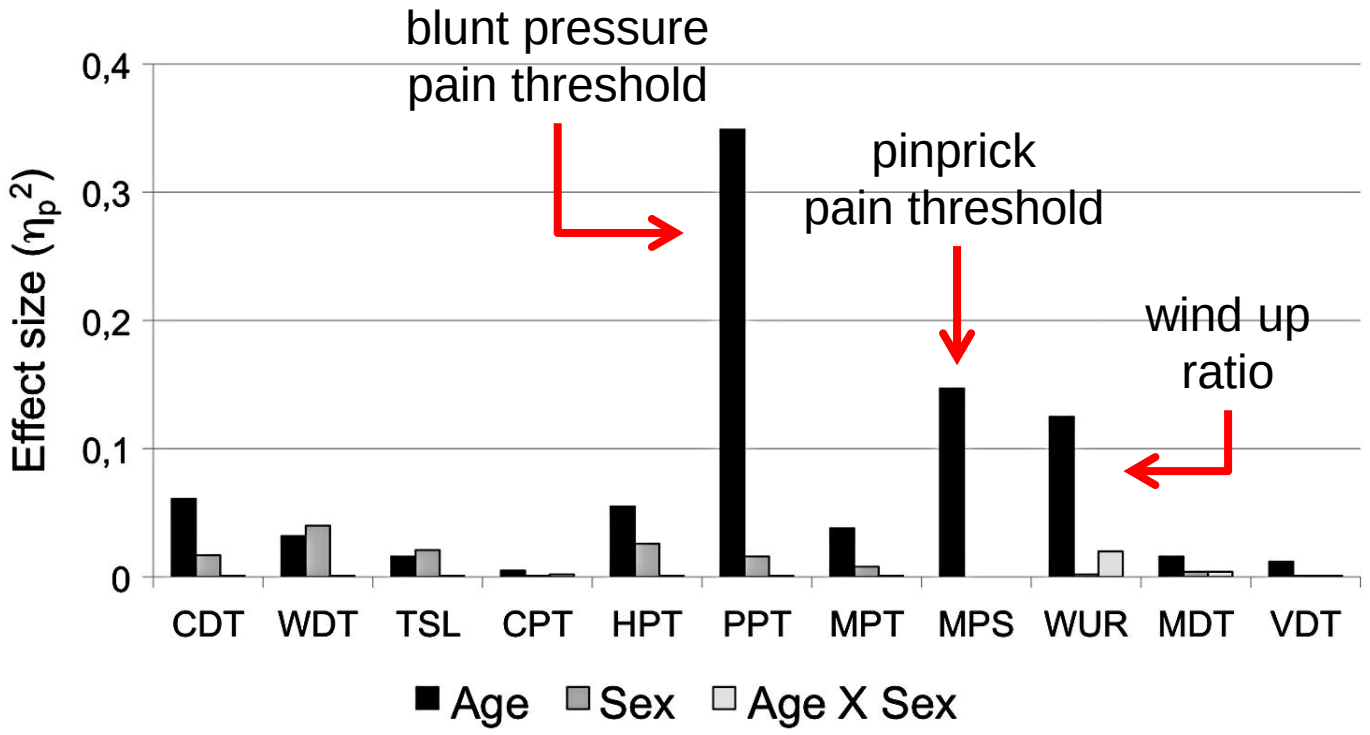
Predictions of childhood pain from animal data

- A ‘open’ system. Less natural inhibition within pain circuits
- Central sensitization likely to be a very strong component of pain
- Descending control weaker, less easy to control pain centrally
- Pain may be primed by earlier tissue damage through glial-immune changes

To test this we need objective measures of pain in children

- Pain in children is not the same as in adults
- Central nervous system is still developing
- Different CNS regions mature at different ages
- Developmental aspects will affect pain quality, intensity, duration and importantly, endogenous pain control.
  - Quantitative sensory testing
  - Evoked potentials
  - fMRI

Children are more sensitive to noxious stimuli than adolescents

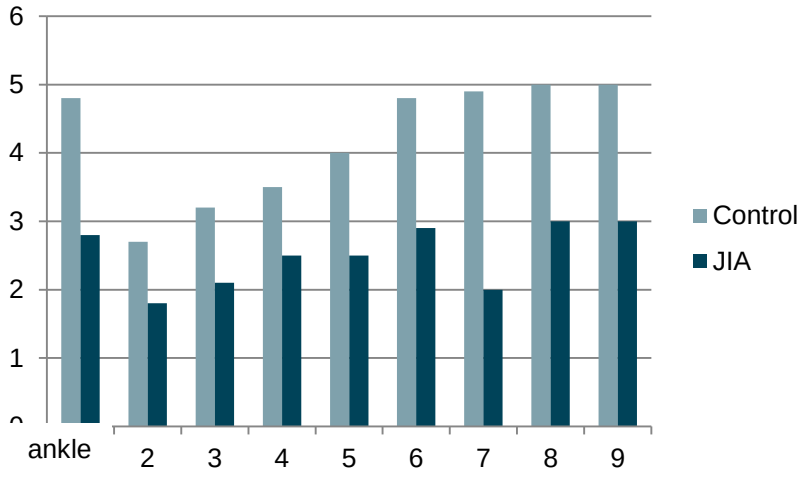


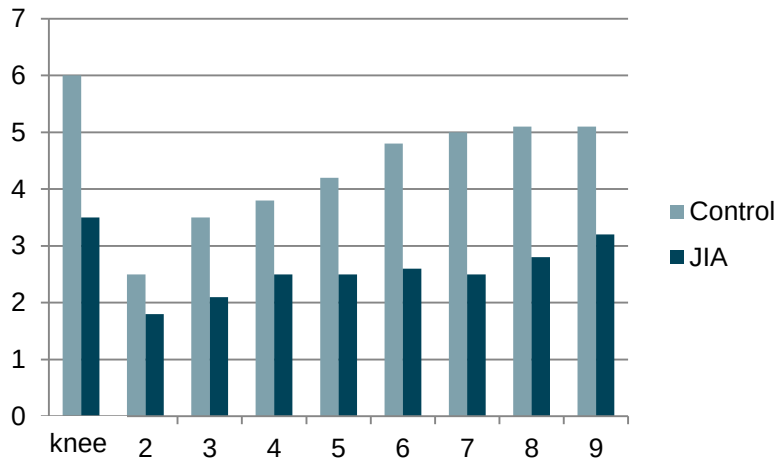
Developmental differences between 7 & 14-year-olds using quantitative sensory testing (QST)

Blankenburg et al., Pain. (2011)152:2625-31, Hirschfeld et al., Neuropediatrics (2012) 43:10-6

Reduced pain thresholds in joint inflammatory disease

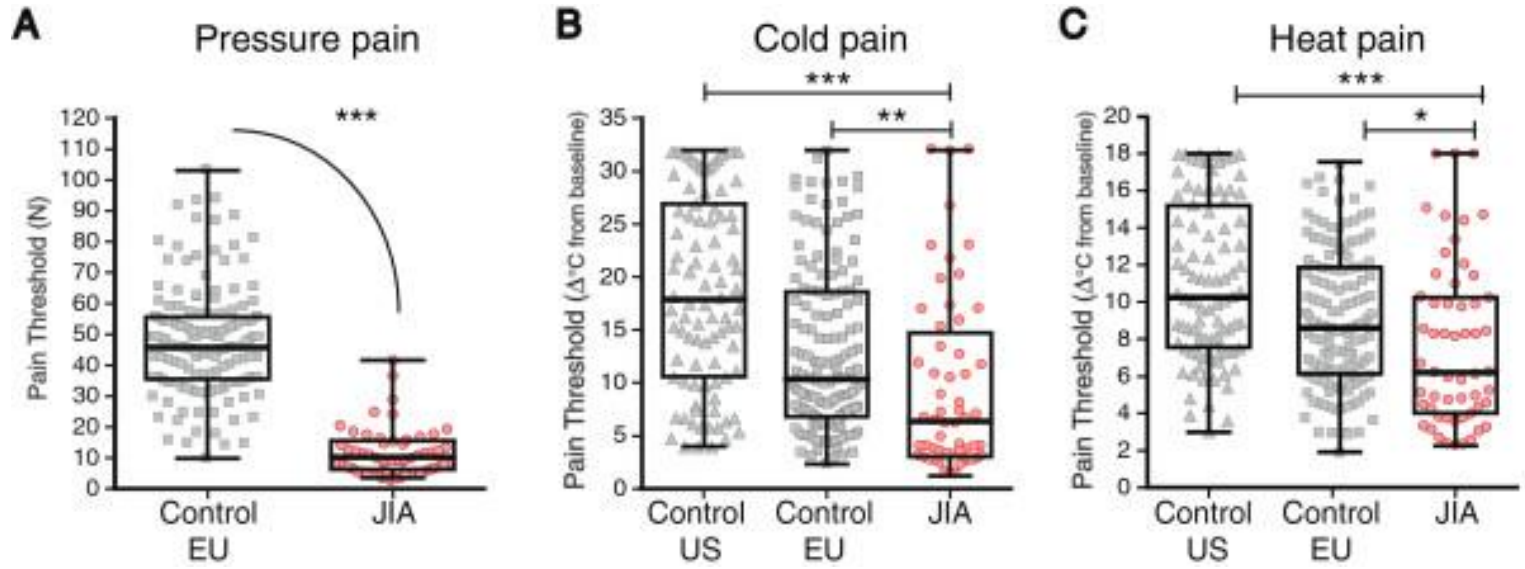
- 17 patients 6-17 with ankle and knee joint inflammation compared to 69 controls
- Pain thresholds lower in all tested sites, inflamed and non-inflamed





Hogeweg et al., 1985 Pain 62:11

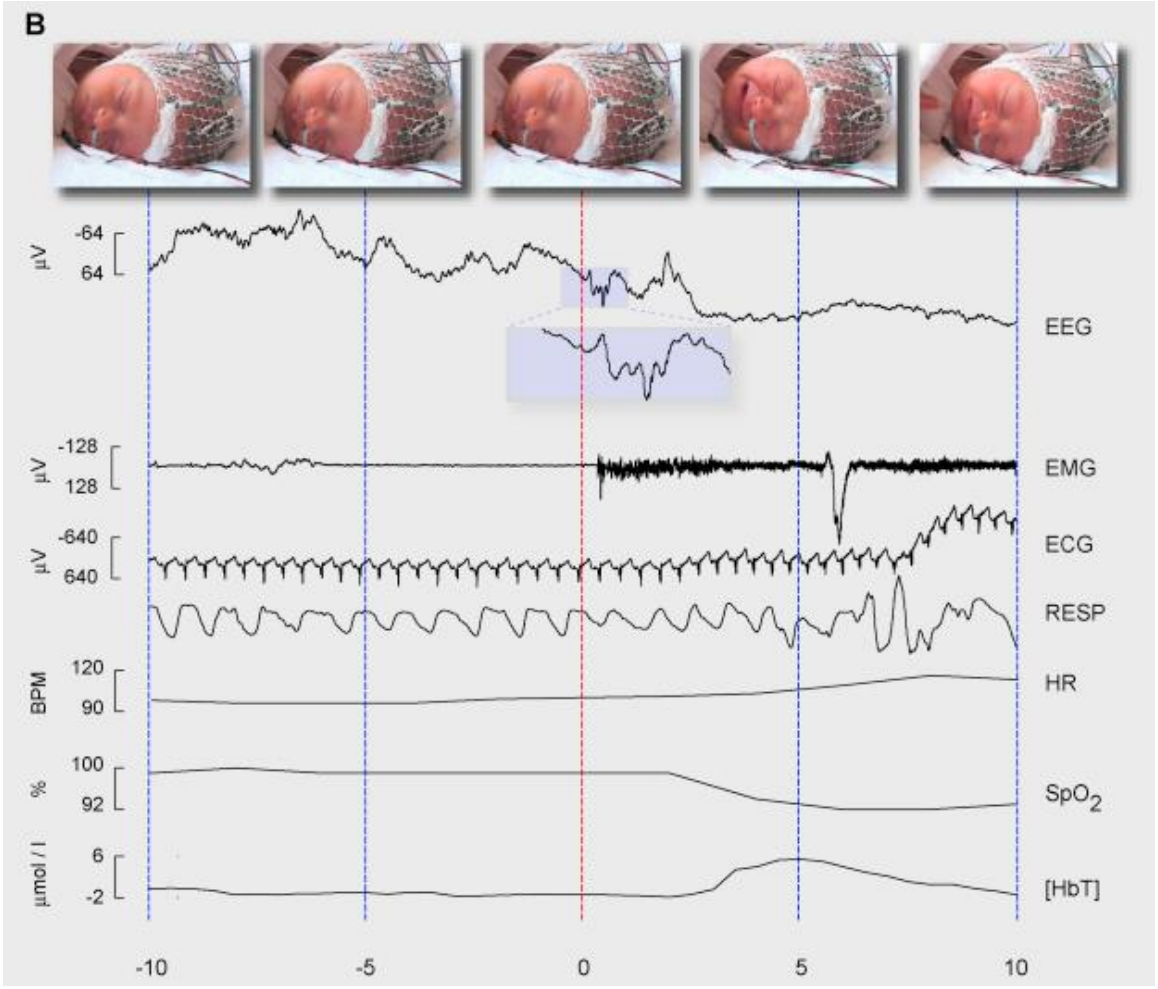
Pain is not always related to active disease state



Noxious thresholds for pressure, cold and heat pain at thenar eminence. Joint inflammatory disease patients (n = 58), and controls (EU, n = 151; US, n = 92). Patients were hypersensitive to all modalities.

Cornelissen L et al., Pediatr Rheumatol Online J. 2014 Sep 6;12:39.
Consolaro A Ravelli A Nature Reviews Rheumatology 9, 447-448 (2013)

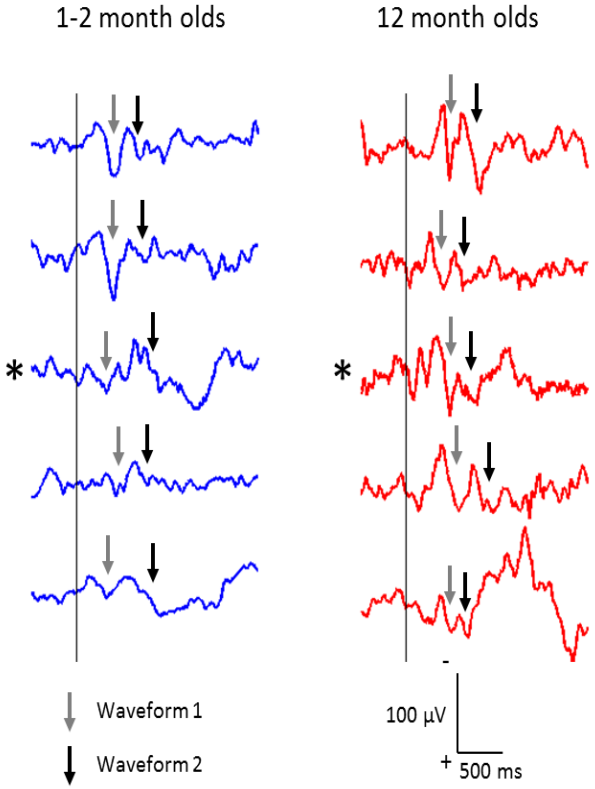
Recording pain activity from the cortex with EEG electrodes

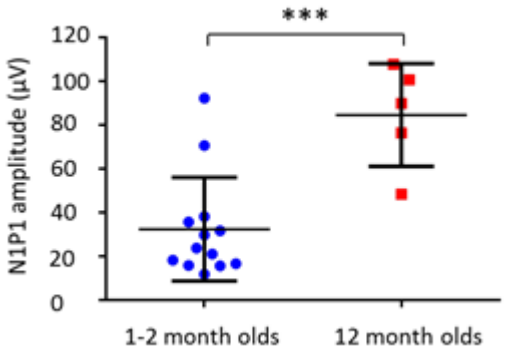


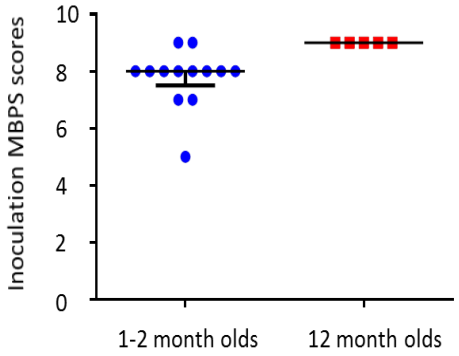
Worley et al., J Neurosci Methods 2012; 205: 252–257

Pain is not always related to behaviour

Innoculation needle prick: EEG and behavioural score

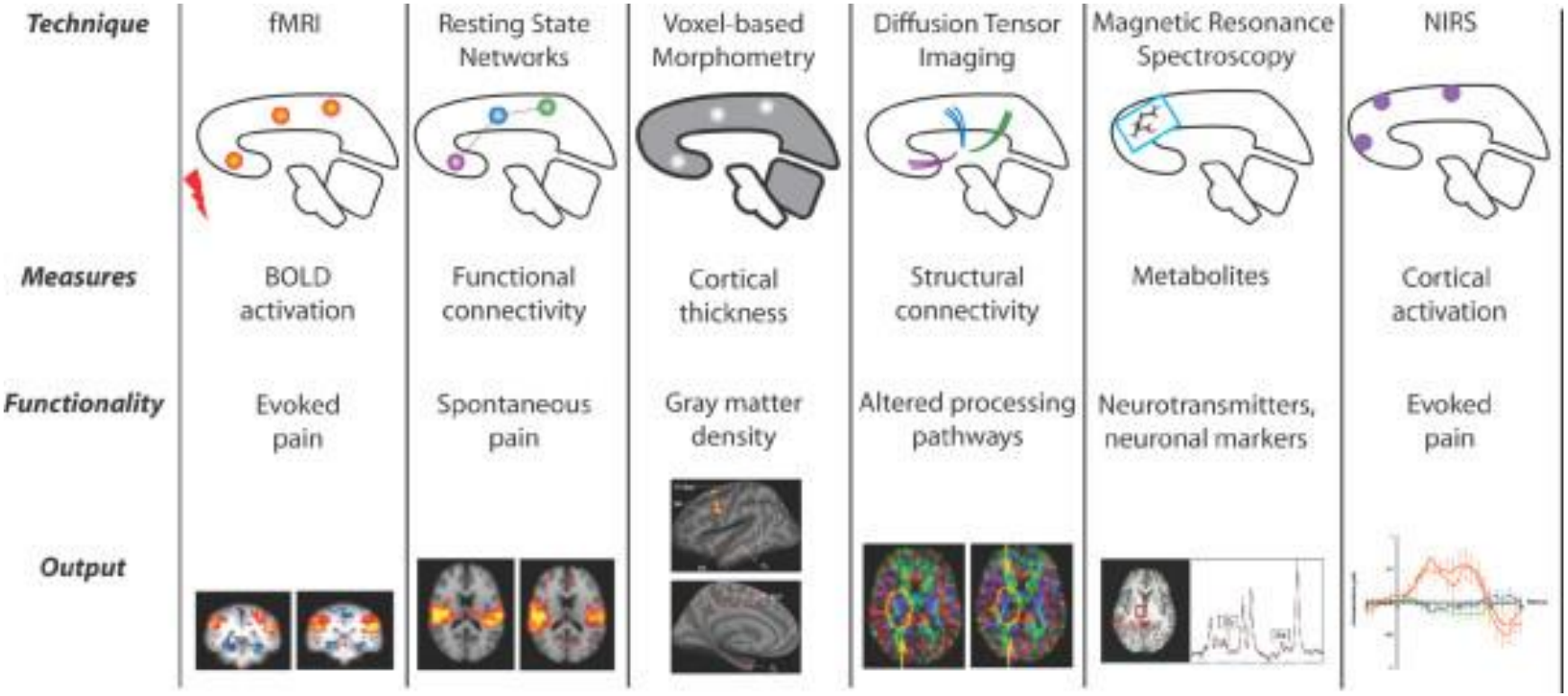






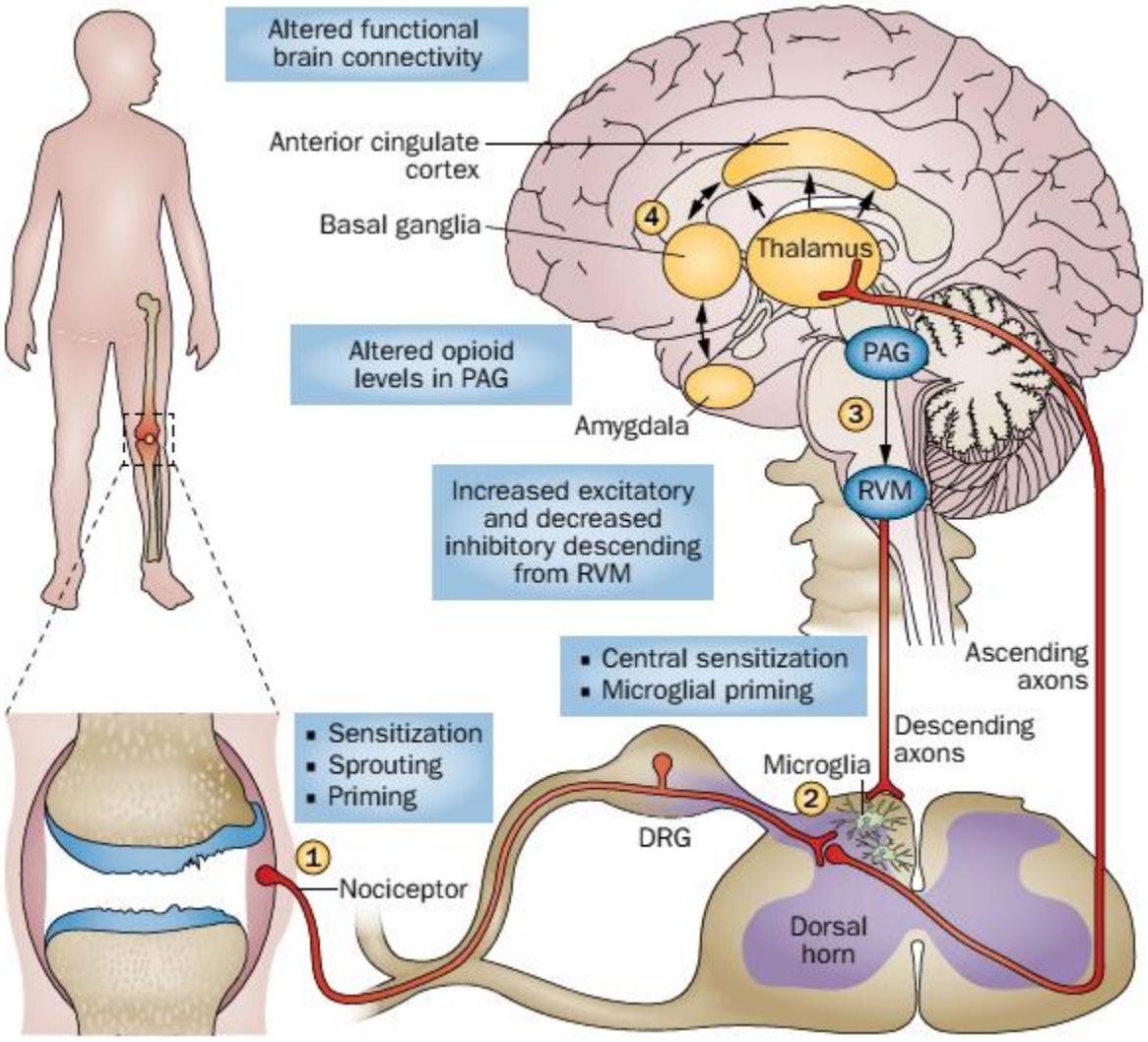
Verriotis et al. Pain (2014) in press

Studying connectivity in the child's brain



Sava et al., Mol Pain. 2009 16;5:30.

A child's chronic pain



De Lalouvière LL et al., 2014 10(4):205-11

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