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

Demonstrating a central component to pain in human volunteers: wind-up amplification
In chronic pain patients, central sensitization has become an established state

Experimental tests on chronic pain patients

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

LTP (long term potentiation): strengthens synaptic transmission

C fibre nociceptor stimulation
Disinhibition contributes to central sensitization

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

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

ACC - Anterior cingulate cortex
PAG - Periaqueductal grey
PB - Parabrachial nucleus
RVM - Rostroventromedial medulla
DRG - Dorsal root ganglia

increase

decrease

% Change AUC

Stimulation Amplitude (μA)
Late maturation of descending inhibition in childhood

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)

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.

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

Studying connectivity in the child’s brain

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A child’s chronic pain
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