Filmpje: Pijnprikkel
### Development of pain system

#### Gestational age (weeks)

<p>| 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Perception | | | | | | | | | | | | | | | | | | | | | |
| Cutaneous sensory perception | | | | | | | | | | | | | | | | | | | | | |
| Myelination | Nerve tracts in the Spinal Cord and Brain Stem | Internal Capsula | Corona Radiata | | | | | | | | | | | | | | | | | |
| EEG Patterns | | | | | | | | | | | | | | | | | | | | | |
| Intermittent | Pattern I EEG Synchronous | Pattern II EEG | Pattern III EEG | Pattern IV EEG | | | | | | | | | | | | | | | | | |
| Cortical maturation | | | | | | | | | | | | | | | | | | | | | |
| Neuronal Migration | | | | | | | | | | | | | | | | | | | | | |
| Dendritic Arborization | | | | | | | | | | | | | | | | | | | | | |
| Synaptogenesis with Thalamocortical Fibres | | | | | | | | | | | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Representative receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>TrkA</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>BKα</td>
</tr>
<tr>
<td>Serotonin</td>
<td>γ-HT3</td>
</tr>
<tr>
<td>ATP</td>
<td>P2X5</td>
</tr>
<tr>
<td>H⁺</td>
<td>ASIC3/TRPV1</td>
</tr>
<tr>
<td>Lipids</td>
<td>PGE2, IC81/1, TRPV1</td>
</tr>
<tr>
<td>Heat</td>
<td>TRPV1/VRL1</td>
</tr>
<tr>
<td>Cold</td>
<td>TRPV8</td>
</tr>
<tr>
<td>Pressure</td>
<td>DEG/ENaC</td>
</tr>
</tbody>
</table>
Neuro-anatomy

Adapted from: [Anatomy Textbook](source)

- Adult
- Neonate

C-fibers
A-β fibers
Spinal Cord
Neurotrophins and nociceptor development

Schematic diagram of the synaptic changes that take place in the superficial laminae of the dorsal horn over the first 2–3 postnatal weeks

Activity-dependent development in spinal cord sensory connections

Influencing factors in a clinical setting

- Environment?
- Medication
- Opioids/sedatives?
- Maternal Separation?
- Stress?
- Bias? doctors/nurses
What outcome data should at least be assessed?

- Detection thresholds?
- Pain thresholds?
- Suprapain sensitivity?
**Neonatal period**

**Surgery group (n=57)**
- ≤ 3 months of age
- Abdominal/ thoracic surgery

**Mechanical ventilation group (n=53)**
- Artificial ventilation >5 days
- No morphine

**ECMO group (n=60)**
- Meconium aspiration / sepsis
- Morphine >5 days

**Follow-up**
Guidelines Dutch Paediatric Association for follow up of critically ill newborns

**Prospective**
- Illness
- Development
- Hospital admissions
- Surgical procedures

**Outcome**
- Detection threshold
- Pain threshold
- Suprapain threshold

*Schouw et al. In preparation*
Neonatal period

- **Surgery group (n=57)**
  - ≤ 3 months of age
  - Abdominal/ thoracic surgery

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  - Artificial ventilation >5 days
  - No morphine

- **ECMO group (n=60)**
  - Meconium aspiration / sepsis
  - Morphine >5 days

8-9 years

- **Controls (n=57)**
- **Controls (n=53)**
- **Controls (n=60)**

**Outcome**
- Detection threshold
- Pain threshold
- Suprapain threshold

*Schouw et al. In preparation*
Assessment pain sensitivity: three different body locations

Postoperative

ECMO

Respiratory insufficiency
Neonatal pain exposure: developmental window

Premature neonate

Term born neonate

2-3 months old

hypo sensitive thermal detection & hyper sensitive pain than term born counterparts

Hypothetical sensitive thermal detection & Hyper sensitive pain than when operated upon at 2-3 months of age
Tissue damage during a critical period of newborns can cause prolonged alterations in somatosensory function, which last into adult life…

• Conclusion: mainly based on studies in animals
• Pain studies in human infants: max. follow-up ≤ 3 years
Descending pathways

[Diagram showing brain structures and pathways]
Gate Control Theory
Are (pre)term born children capable of processing pain at a cortical level?

Slater et al. 2006
Sensitisation versus Habituation

![Bar chart showing the percent of infants tested with sensitized and habituated reflexes across different PCA (wks) ranges.](chart.png)

- Sensitized reflex
- Habituated reflex

Percent of infants tested

- <27.0
- 27.5-29.5
- 30.0-32.0
- 32.5-34.5
- 35.0-37.0
- 37.5-39.5

PCA (wks)
THE PROBLEM OF SENSITISATION AND SENSITIVITY

• Effects of previous potentially painful events on
  – pain threshold
  – distribution of opioid receptors
  – neurophysiological parameters
  – long-term behavioural problems

• Genetic heterogeneity
  – genetic defects → transgenic mice
  – DNA fingerprints → mutation analysis
THE PROBLEM OF SENSITISATION

Experimental approach in newborn rats

Human experience in the newborn period

Ruda MA et al. Science 2000;289:628-630
DIFFERENT DRUGS, SAME ULTIMATE EFFECT

DRUGS OF ABUSE hit various targets in the brain, but all directly or indirectly enhance the amount of dopamine signaling in the nucleus accumbens, thereby promoting addiction. Knowledge of the targets raises ideas for therapy (see box on opposite page).

NICOTINE induces VTA cells to release dopamine into the nucleus accumbens.

COCAINES AND RELATED STIMULANTS block dopamine uptake or increase dopamine release by the terminals of VTA cells and thus increase dopamine signaling in the nucleus accumbens.

Dopamine-releasing VTA neuron

MANY DRUGS, including cocaine, amphetamine (speed), morphine and alcohol, can alter the responses of nucleus accumbens and VTA cells to glutamate in long lasting ways. Those changes contribute to drug cravings by heightening memories of past drug experiences even after the substance is no longer used.

Glutamate receptor

Dopamine transporter

Cocaine

Nucleus accumbens neuron

CREB

Biphasic neurotransmitter made by neurons

OPIATE DRUGS mimic some of dopamine's actions in nucleus accumbens cells

OPiates (opium, heroin and their relatives) enhance dopamine release by quelling neurons that would otherwise inhibit dopamine-secreting neurons.
**Delta FosB: A Key to Craving**

1. Dopamine signaling leads to production of the protein delta FosB (ΔFosB).

2. ΔFosB represents a drug-memorizing switch and activates specific genes (different from those activated by CREB).

ΔFosB accumulates in neurons, leading to tolerance and, in the drug's absence, discomfort that only more drug can cure. But CREB activity falls within days when not boosted by repeated doses. In contrast, ΔFosB concentrations stay elevated for weeks after the last drug exposure. An CREB activity, declines, the dangerous long-term sensitizing effects of ΔFosB come to dominate.
Research needs
(NIH\FDA conference april 2004)

• Empiric foundations for composite measures in the youngest neonates (22-26 weeks)
• Understanding autonomic responses and how they change in the youngest neonates
• Need for assessment scales for chronic\ongoing pain
• PK\PD data of all analgesics
• Incorporate models which show patterns of response
Pediatric pain, the research agenda: future (2005-?)
Solutions are near and “far away”

Profound cognitive impaired

- children

- multidrug effect

elderly people

- f-MRI
- tolerance and addiction
- routine PET-scan