Development of nociception and pain

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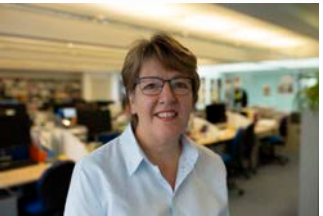

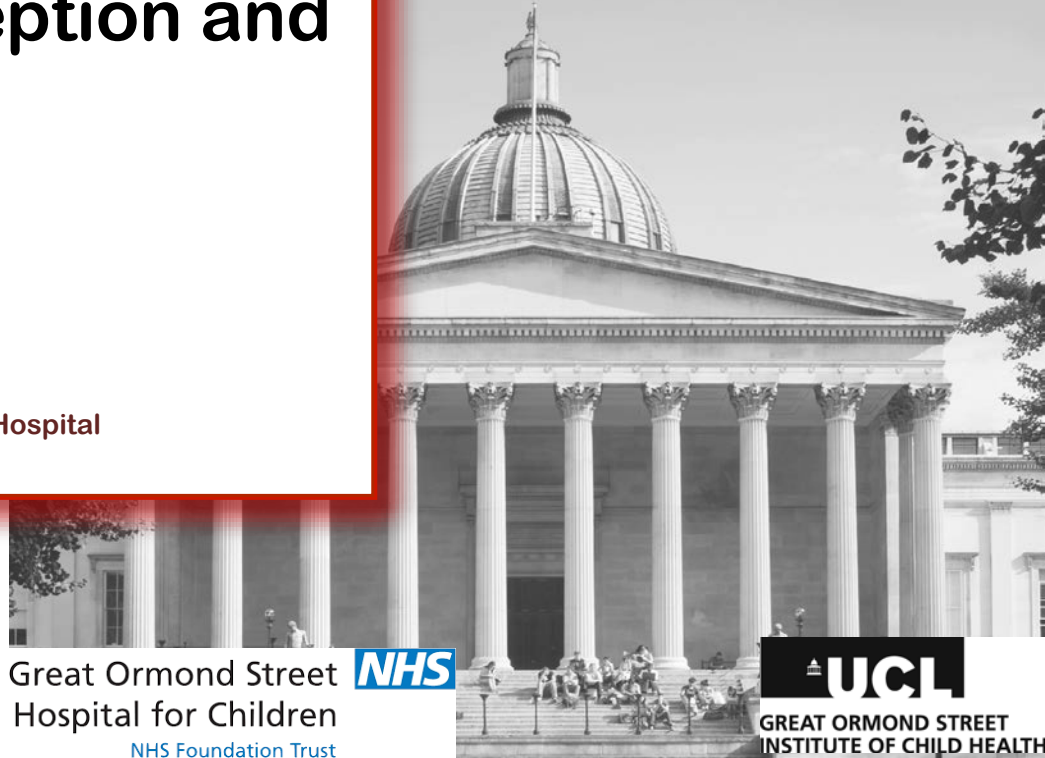

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Summary

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- **definitions**
  - nociception and pain
- **developing nociceptive pathways**
  - balance of excitation and inhibition
- **analgesia**
  - maintaining balance
- **type of injury**
  - mechanisms and targets

NO CONFLICTS OF INTEREST TO DECLARE

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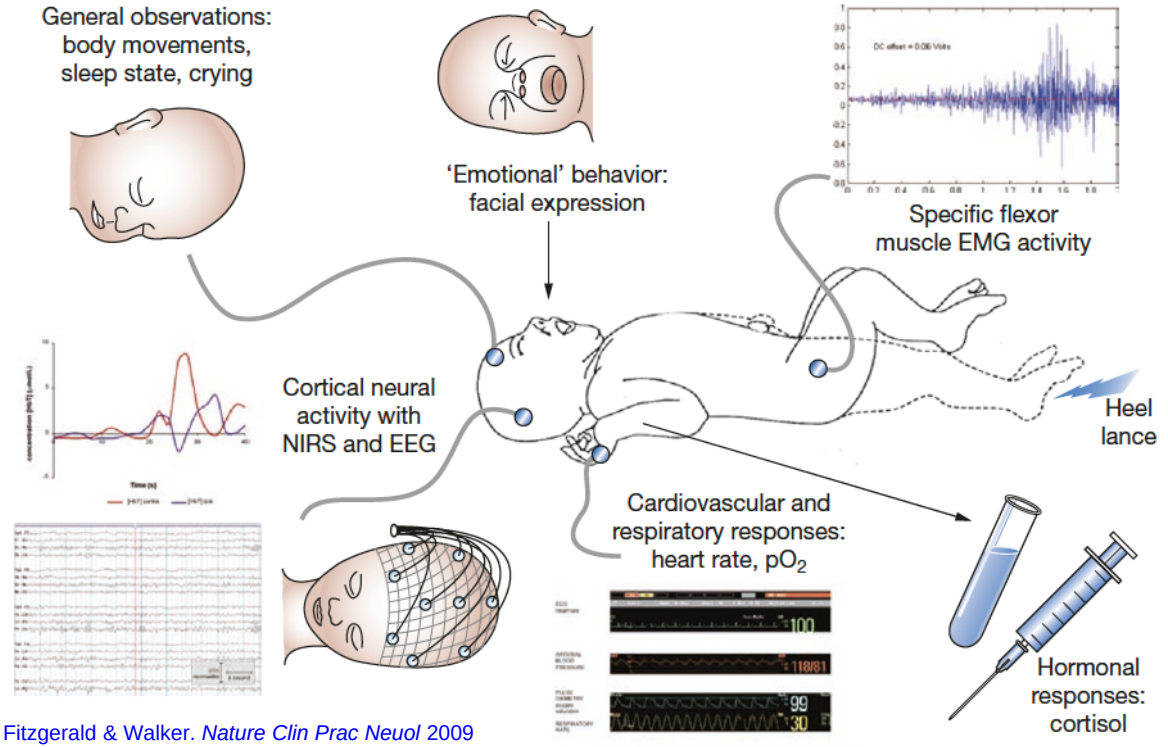
Nociception

- neural process of encoding noxious stimuli
- neurophysiological response
  - functional after birth
  - periphery to cortex
- plus…
  - behaviour
  - autonomic
  - stress response



Fitzgerald & Walker. *Nature Clin Prac Neuol* 2009

Nociception and Pain

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Pain

- unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage

IASP Revised Definition

Raja et al. *Pain* 2020

Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons

Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain

Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being

https://www.iasp-pain.org/publications/iasp-news/iasp-announces-revised-definition-of-pain/
http://s3.amazonaws.com/rdcms-iasp/files/production/public/images/Infographic_20200708_5_5_Final.pdf

Developing nociceptive pathways

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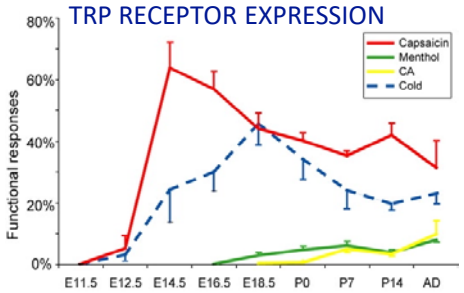
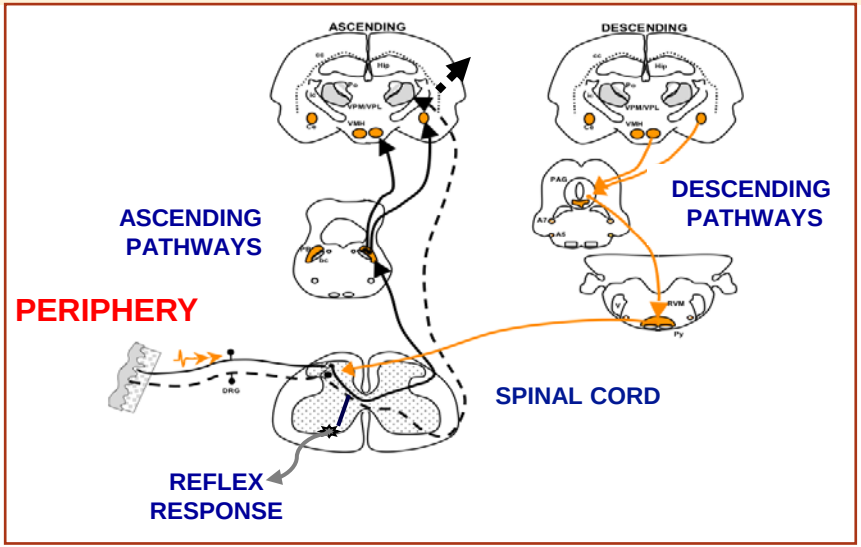
RESPONSE

- nociceptors transduce noxious stimuli
  - mechanical
  - thermal
  - chemical



Hjerling-Leffler et al. *J Neurosci* 2007



SENSITISATION

- primary hyperalgesia

Developing nociceptive pathways

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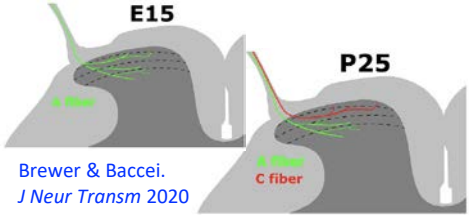
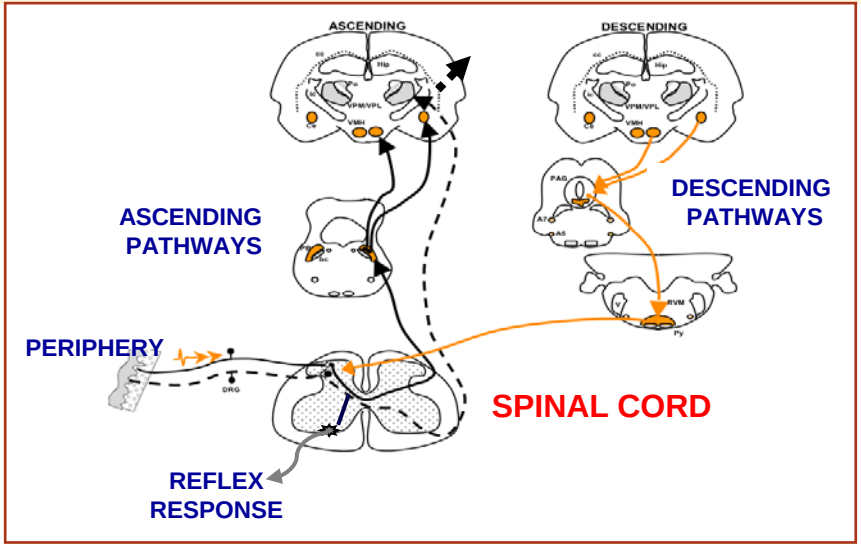
ALTERED STRUCTURE

- A and C fibres



Brewer & Baccei.
J Neur Transm 2020



ACTIVATE ASCENDING PATHWAYS

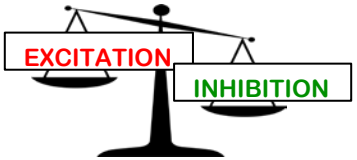
NMDA RECEPTORS

- expression

	P0–P7	P7–P22	Adult
Spinal cord	$++^{(2,4,5)}$		$+^{(2,4,5)}$
Dorsal horn	$+/-^{(2)}/+^{(4)}$	$+^{(2,4)}$	$+^{(1,2,3,4,6)}$
Ventral horn	$++^{(25)}/+^{(2,7)}$	$+/-^{(2,7)}/+^{(4)}$	$+/-^{(1,4,6,7)}$

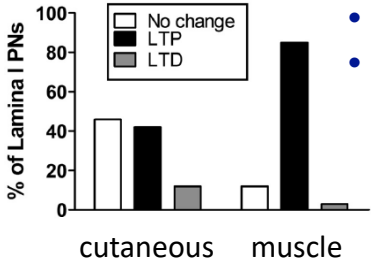
- subunit composition

de Geus et al. *Devt Neurobiol* 2020



CENTRAL SENSITISATION

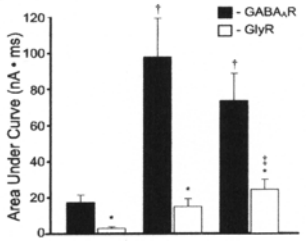
- muscle & cutaneous afferents
  - increased AMPA-R
  - increased glutamate release



Li & Baccei.
J Neurosci 2017

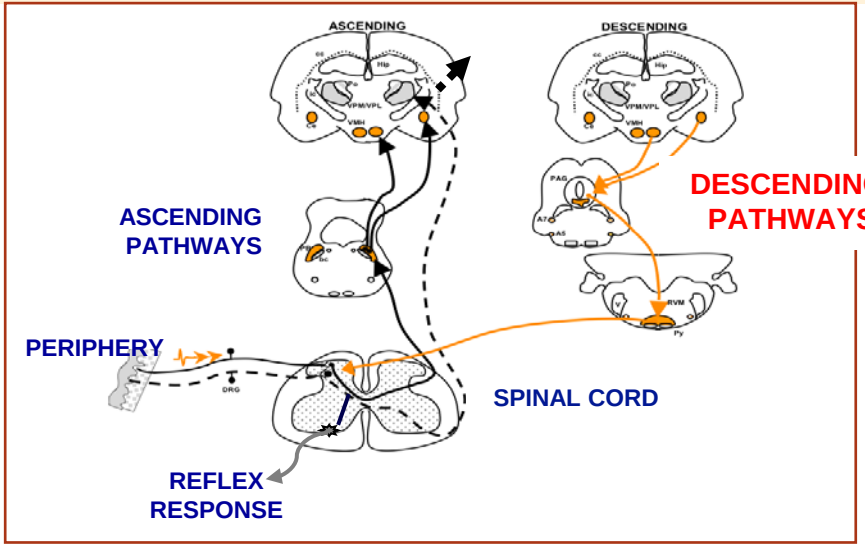
GABA, GLYCINE

- delayed maturation



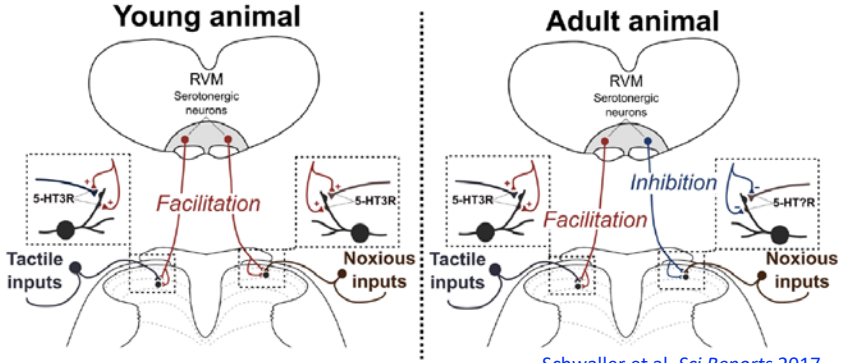
Baccei et al. *J Neurosci* 2004

Developing nociceptive pathways



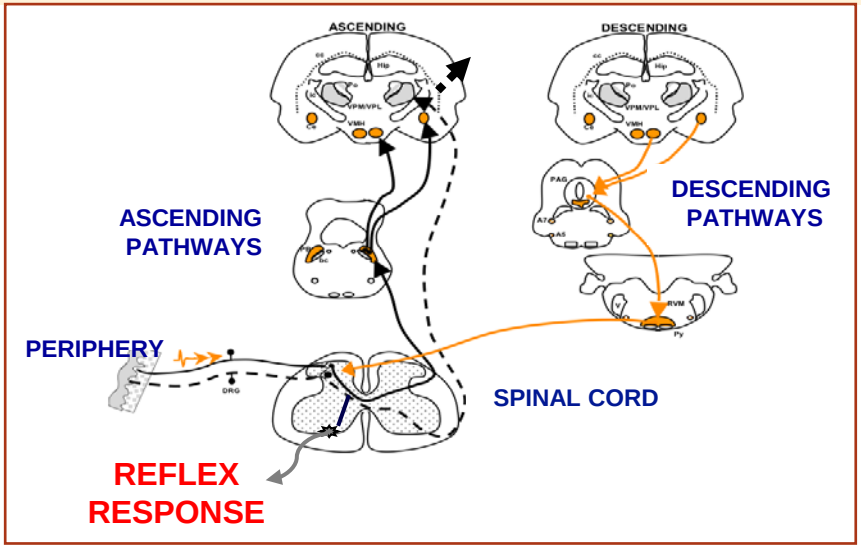
FACILITATION / INHIBITION

- delayed maturation of descending inhibition
  - *opioid*
    Kwok et al. *Pain* 2024
  - *serotonin*

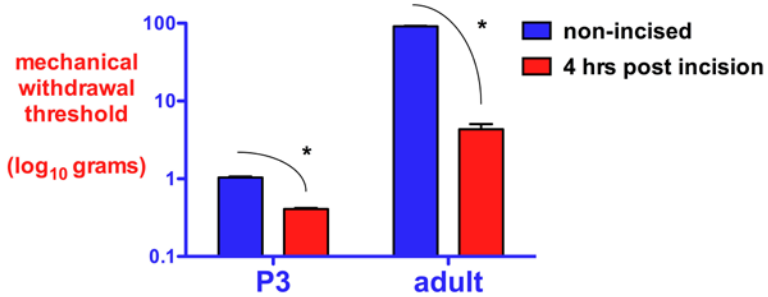


Schwaller et al. *Sci Reports* 2017

Developing nociceptive pathways



REFLEX
- low threshold
- poorly 'tuned'
  - generalized responses
- injury
  - increased sensitivity



Walker et al. *Pain* 2009

Impact of developmental age

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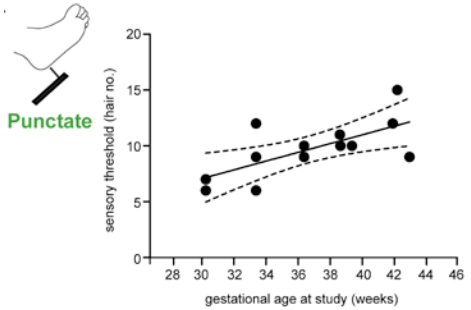
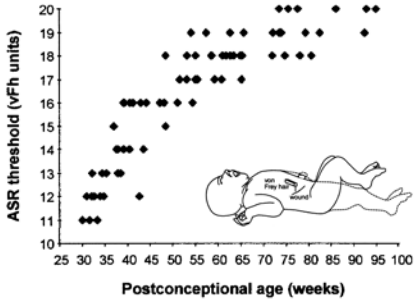
- **baseline varies with age**
  - normal development
  - impact of injury

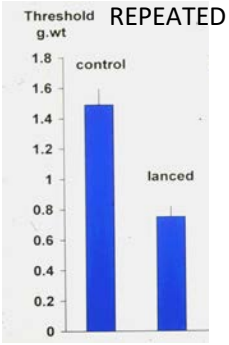
REFLEX THRESHOLDS



Cornelissen et al. *PLoS One* 2013



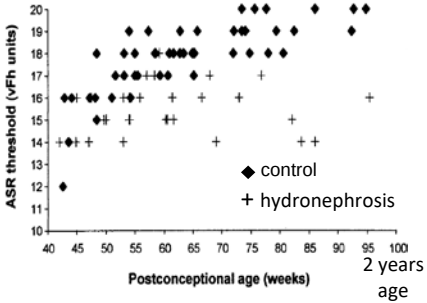
Andrews et al. *Pain* 2002a



REPEATED HEEL LANCE

Fitzgerald et al. *Pain* 1989

HYDRONEPHROSIS



Andrews et al. *Pain* 2002a

Impact of developmental age

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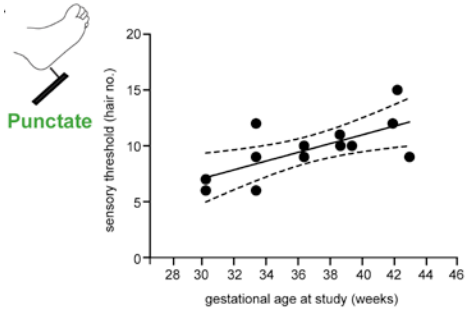
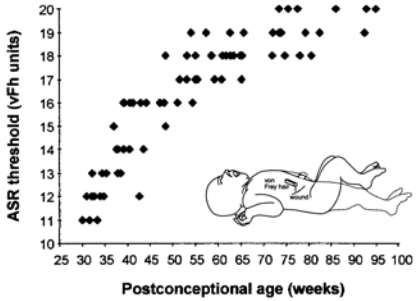
- **baseline varies with age**
  - normal development
  - impact of injury
- **analgesic efficacy**
  - age-dependent variability
  - pre vs post
  - injured vs un-injured

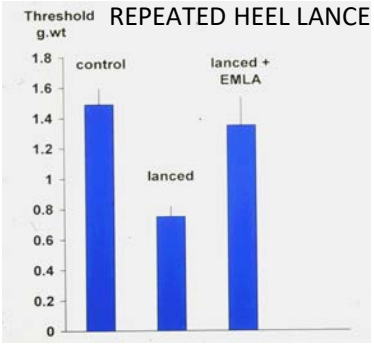
REFLEX THRESHOLDS



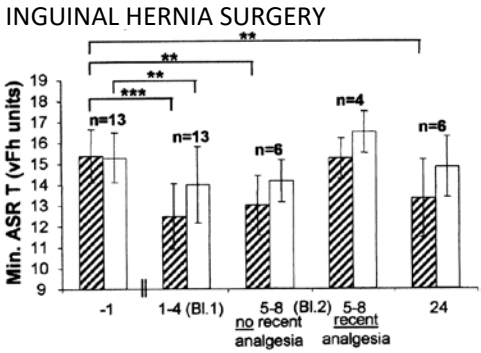
Cornelissen et al. *PLoS One* 2013



Andrews et al. *Pain* 2002a



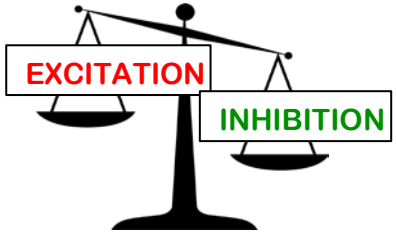
Fitzgerald et al. *Pain* 1989

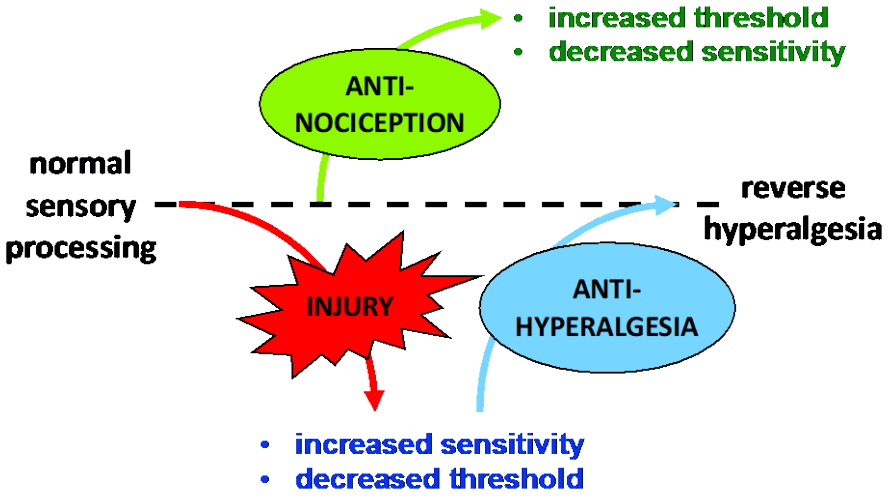


Andrews et al. *Pain* 2002b

Analgesia

- **balance impact of noxious input**
  - enhance inhibition / reduce excitation
- **requirement**
  - anti-nociceptive
  - reduce / reverse hyperalgesia
- **postnatal age**
  - efficacy and safety





Analgesia : balancing activity

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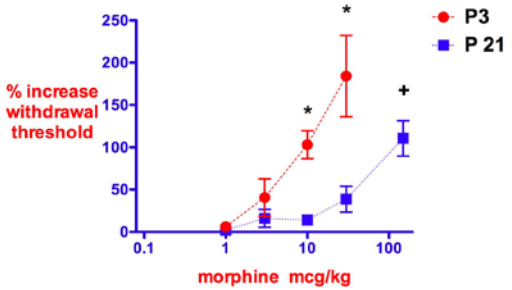
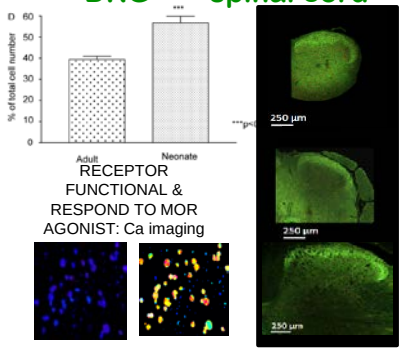
- **distribution / function of receptors**
  - dose-response

OPIOIDS



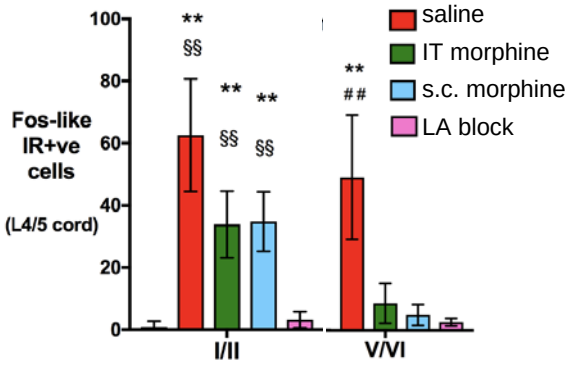
Westin et al. *Anesthesiol* 2010

DRG spinal cord

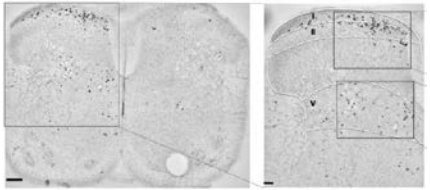


RECEPTOR FUNCTIONAL & RESPOND TO MOR AGONIST: Ca imaging

Nandi et al. *Pain* 2004;
Moriarty et al. *Br J Anaesth* 2018



SURGICAL INJURY
activated neurons in spinal cord



Moriarty et al. *Br J Anaesth* 2018

Analgesia : balancing activity

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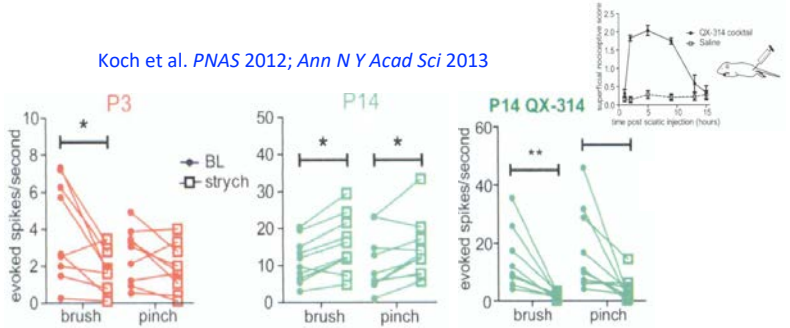
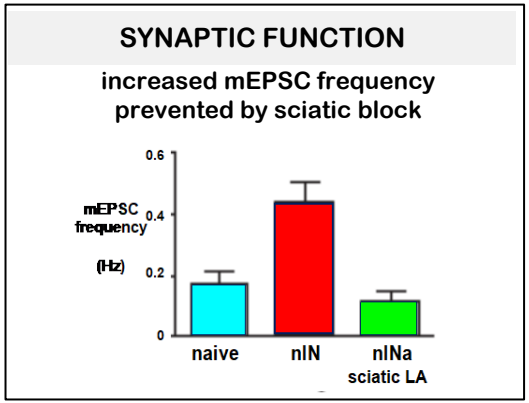
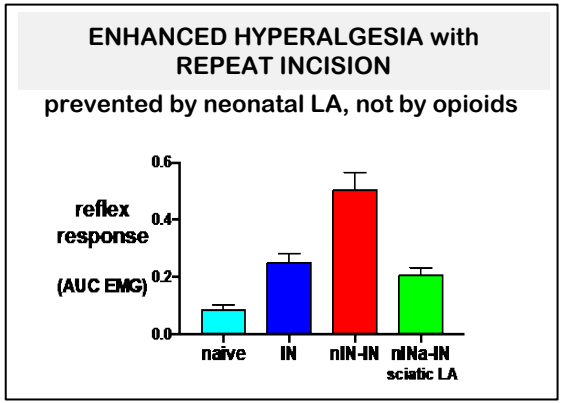
- **distribution / function of receptors**

- **activity-dependent maturation**
  - suppress normal input in absence of injury
    - delay inhibitory maturation
  - excess nociceptive input / injury
    - alter spinal circuits and function
    - LA : preventive analgesia

Koch et al. *PNAS* 2012; *Ann N Y Acad Sci* 2013







Li et al. *J Neurophysiol* 2009; Walker. *Pain* 2017; Moriarty et al. *Br J Anaesth* 2018

Analgesia : balancing activity

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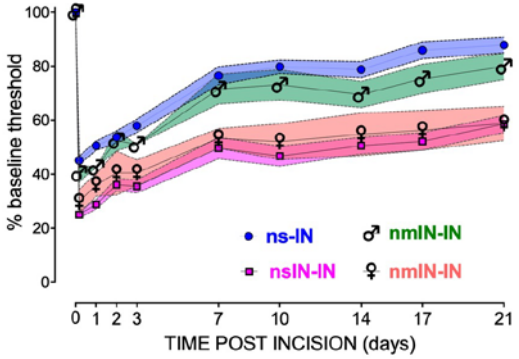
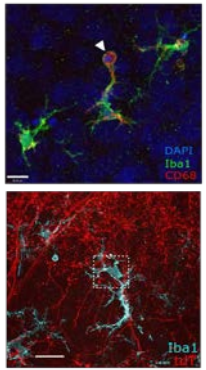
- **distribution / function of receptors**
- **activity-dependent maturation**
- **specific developmental roles**
  - microglia
    - influence neuronal excitability
      - inhibitors : sex-dependent
    - phagocytic role
      - shape synaptic circuits
      - inhibit : alter baseline sensitivity

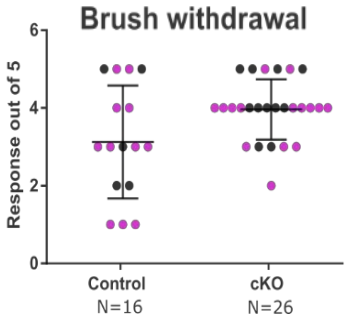
MICROGLIAL INHIBITION

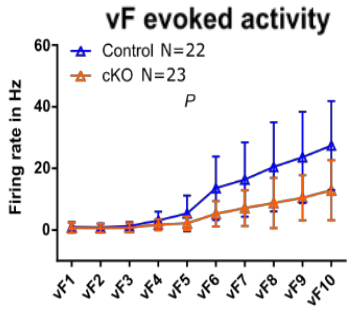


- adult: reduce incision-induced hyperalgesia
- neonate: prevent enhanced re-incision response
- *males only*

Moriarty et al. *J Neurosci* 2019







Xu et al. https://doi.org/10.1101/2021.03.22.436389

Analgesia : balancing activity

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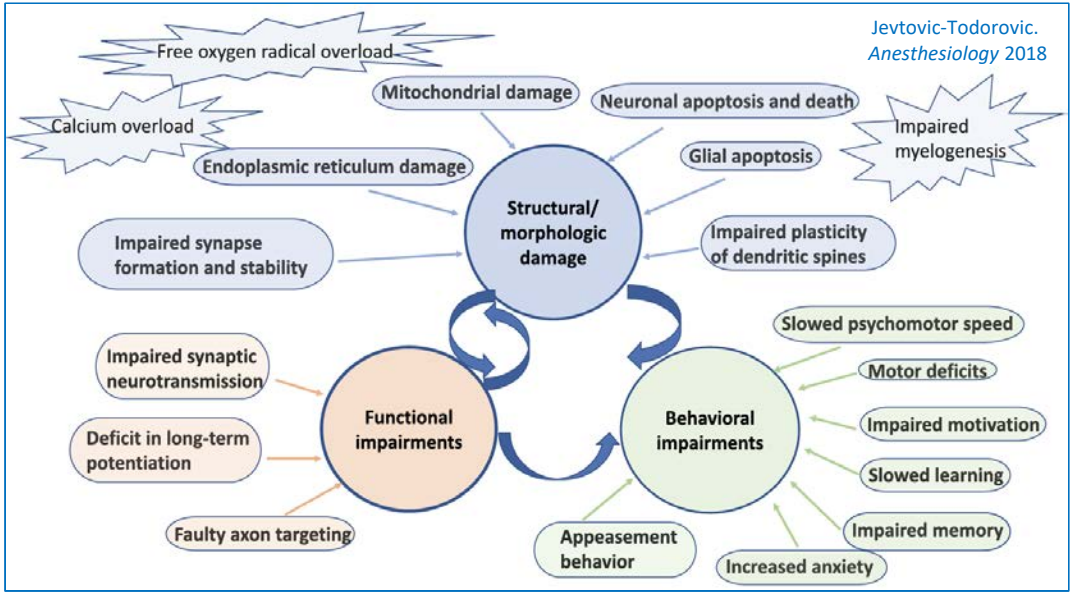
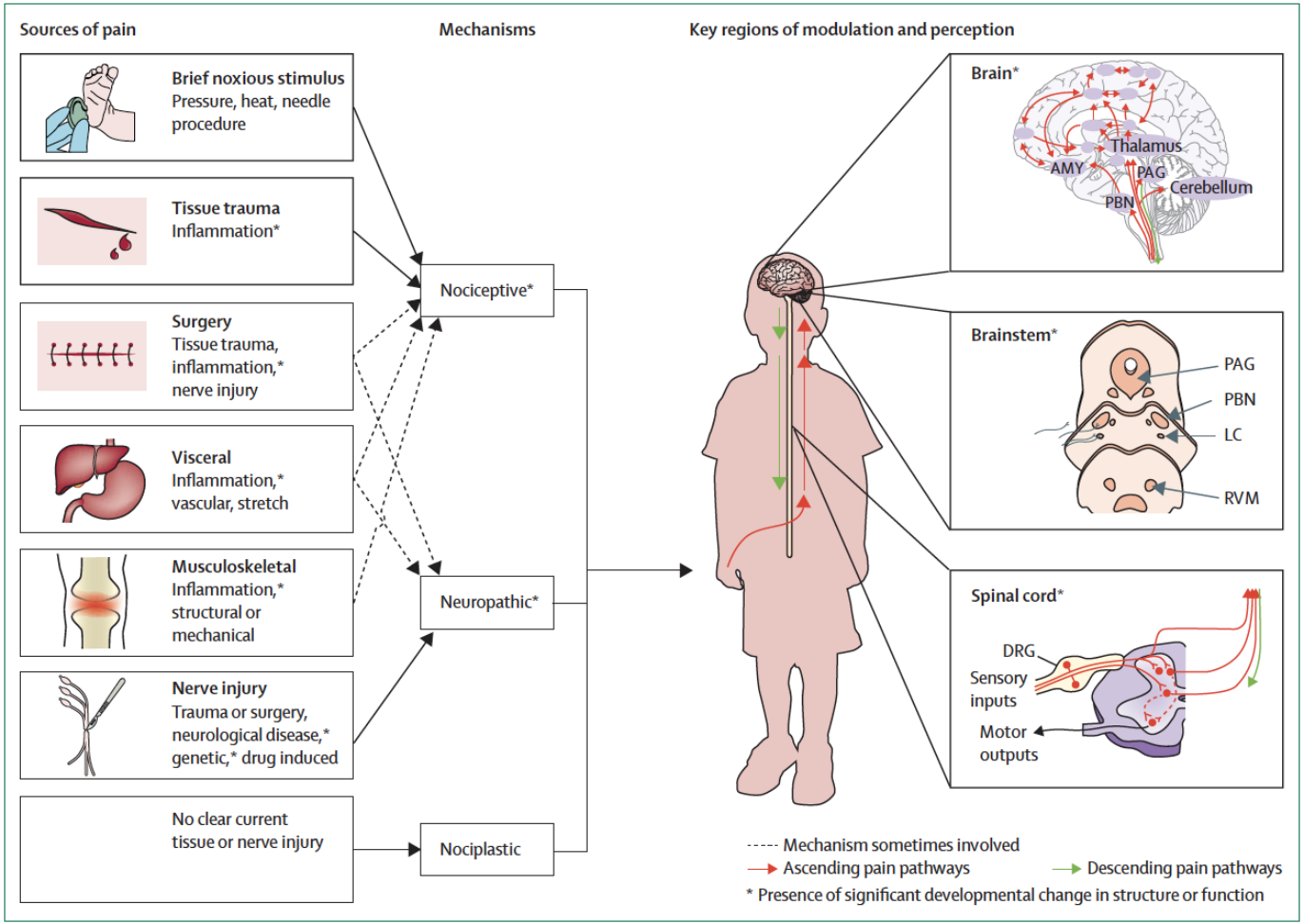
- **distribution / function of receptors**
- **activity-dependent maturation**
- **specific developmental roles**
- **developmental toxicity / safety**
  - link structure and function
  - tissue ↔ behaviour



Type of injury



procedural pain

- anti-nociceptive effect
- minimise hyperalgesia/ cumulative impact

surgery

- potential to intervene before injury
  - skin, muscle, nerve, bone, viscera

nerve injury

- trauma
  - delayed emergence
- chemotherapy
  - neuropathy
  - acute : mucositis
  - GD-2 antibodies

Eccleston et al. **2021**
Lancet Child & Adolescent Health Commission
doi: 10.1016/S2352-4642(20)30277-7