PainScience

Pain and Anaesthesia

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Disclosures

- Pain Specialist
  - Salaried WA Health & Joondalup
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- Adjunct Academic Appointments
  - UWA/NDU/Curtin
- Don't accept travel or accomodation from industry
  - Do accept education/food/wine
- No financial relationships with anything discussed here

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Overview

- Background and Epidemiology
- Definitions
- Physiology
- Neuroimmuno pharmacology
- Management of the chronic pain patient
- Anaesthesia for pain procedures

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Background

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What is pain?

"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (IASP)

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Pain versus Nociception

- Pain is the higher level perception
- Nociception is the transmission of a signal
- Compare with hearing
  - Sound versus Music
  - You don't need sound to hear music, or nociception to feel pain.

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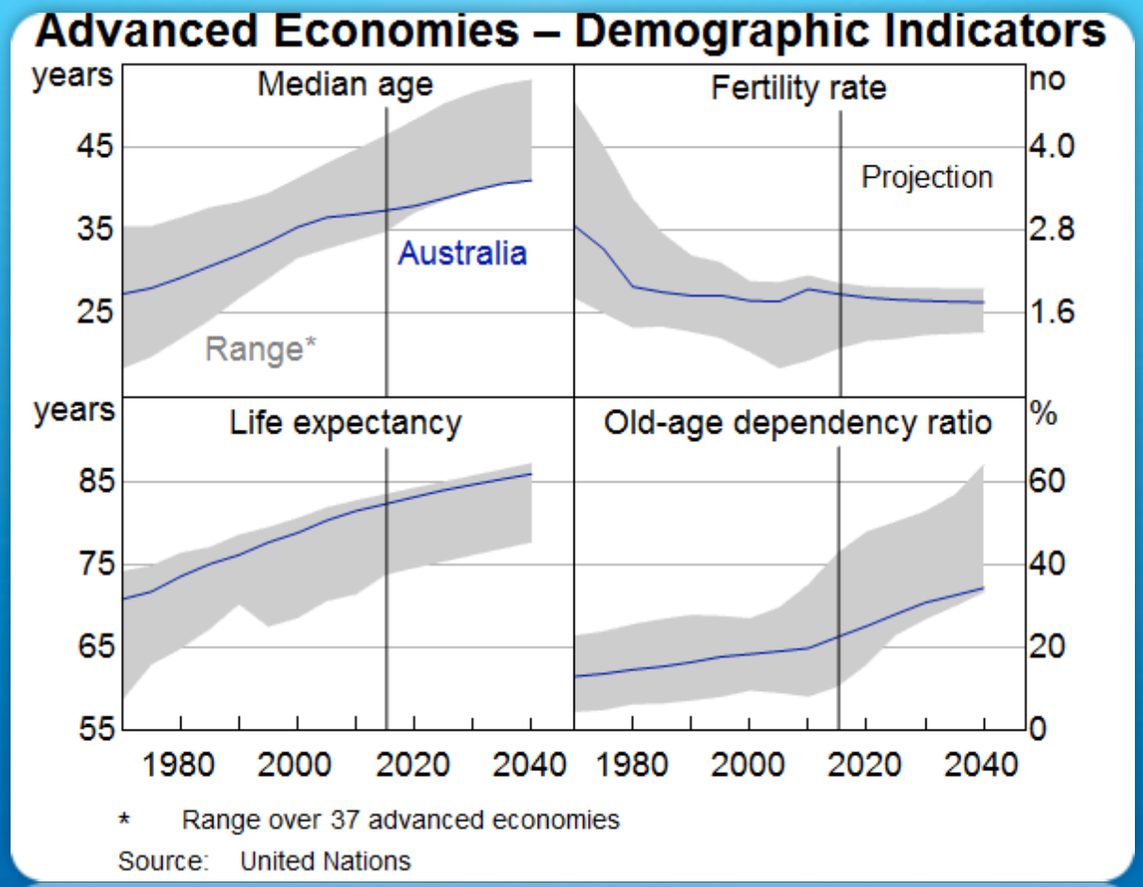
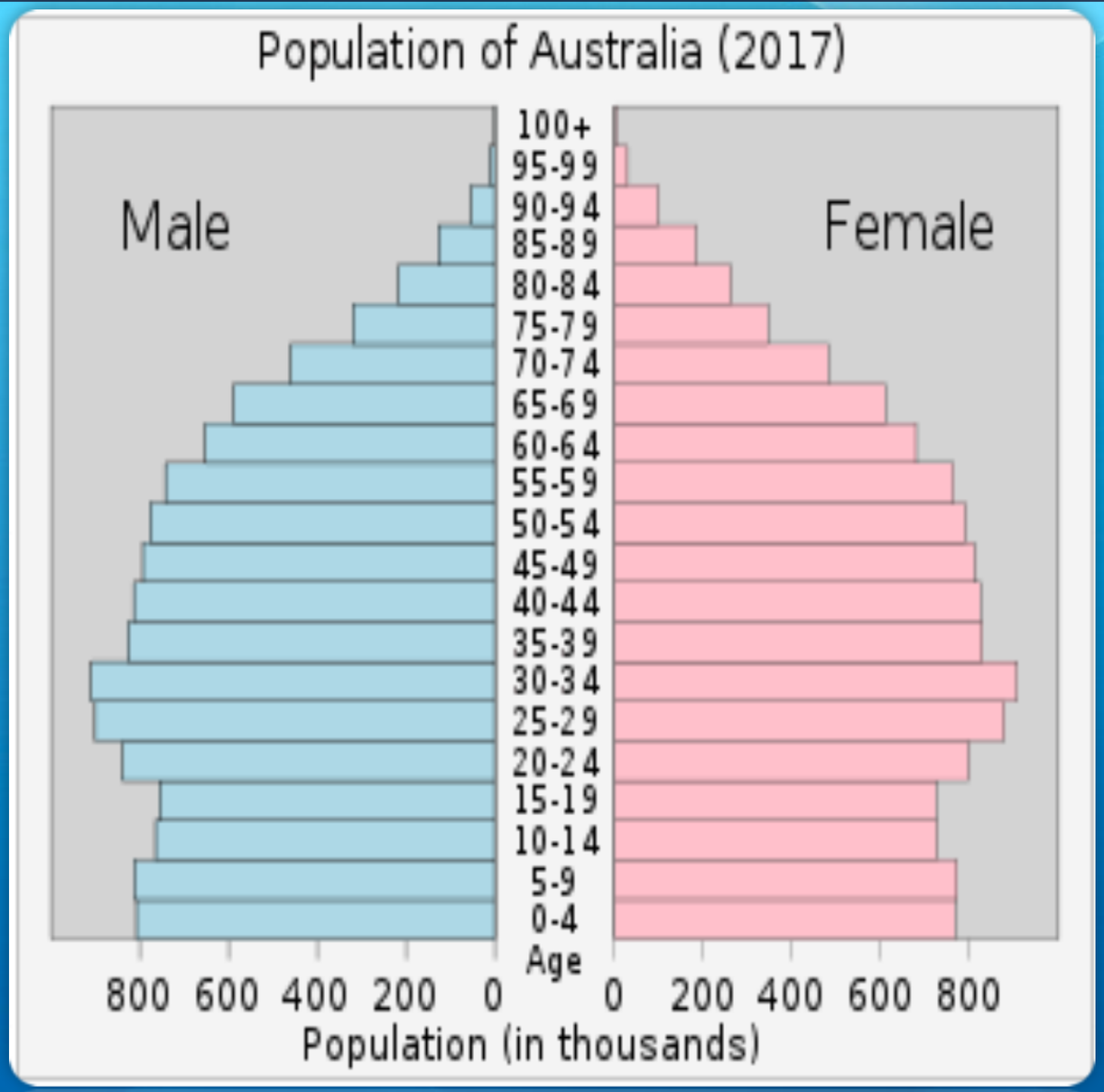
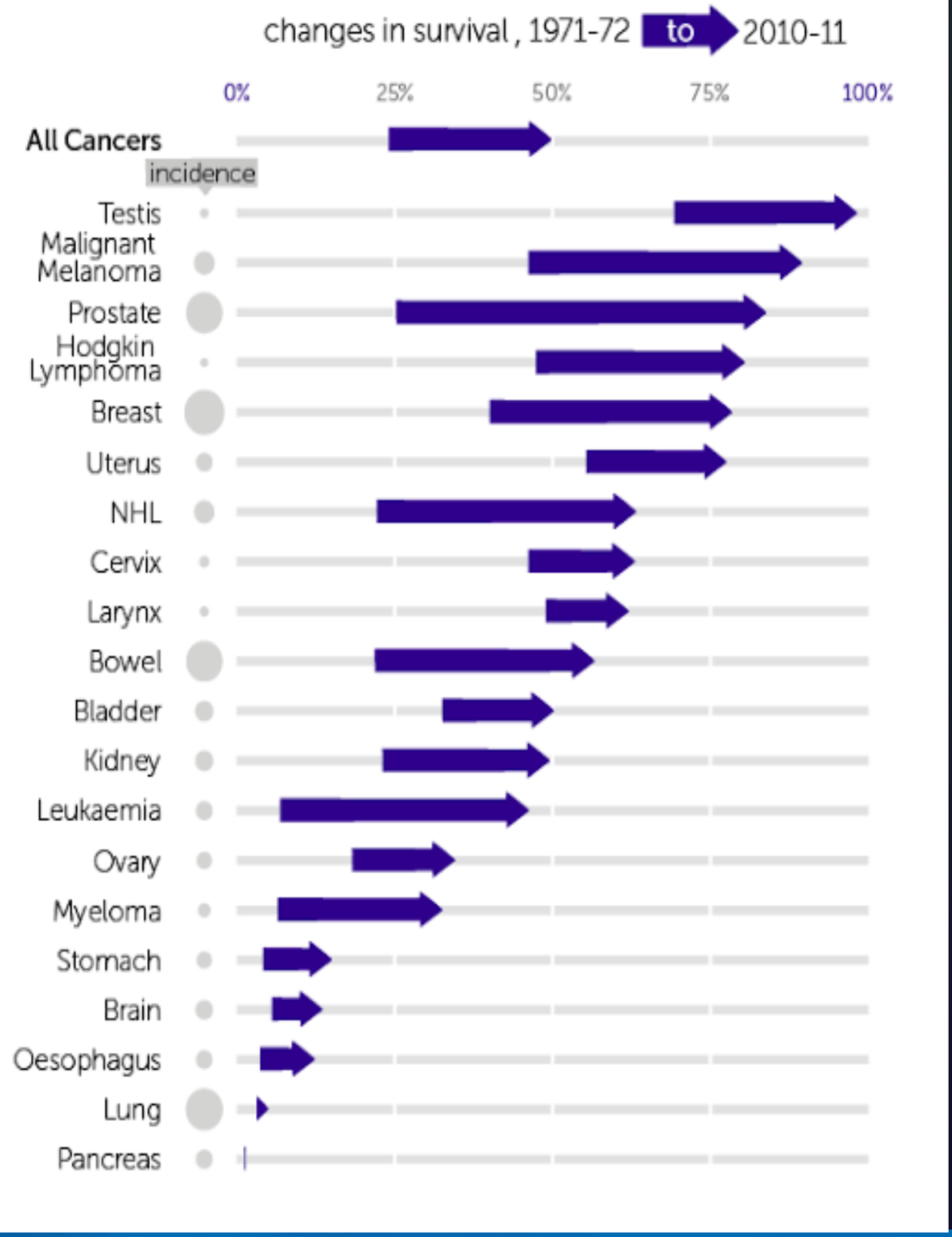
The Lucky Country

We do appear to be the lucky country...







CANCER MANAGEMENT IS

Treatments have changed

Survival has improved

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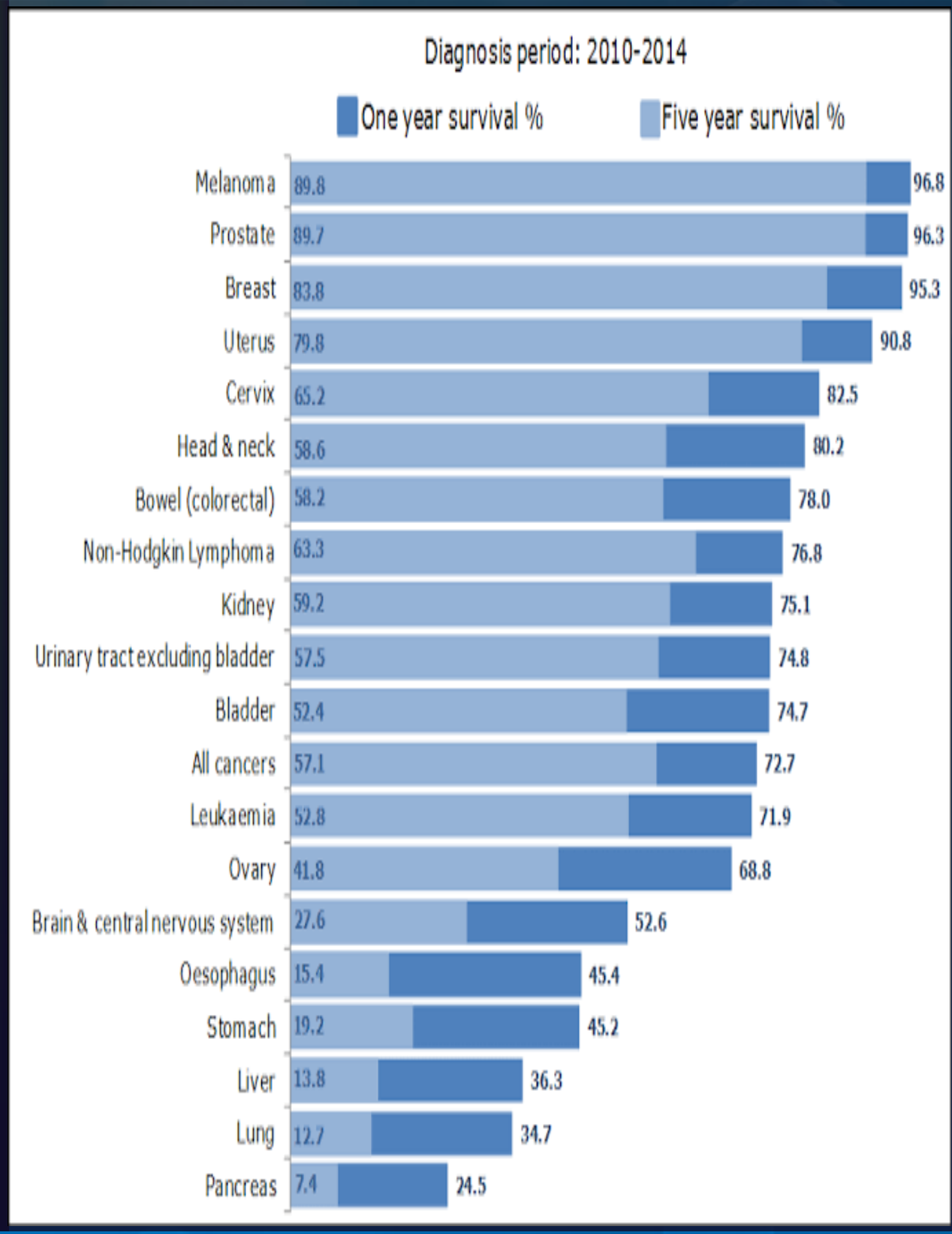
Now we have survivors

Which is fantastic

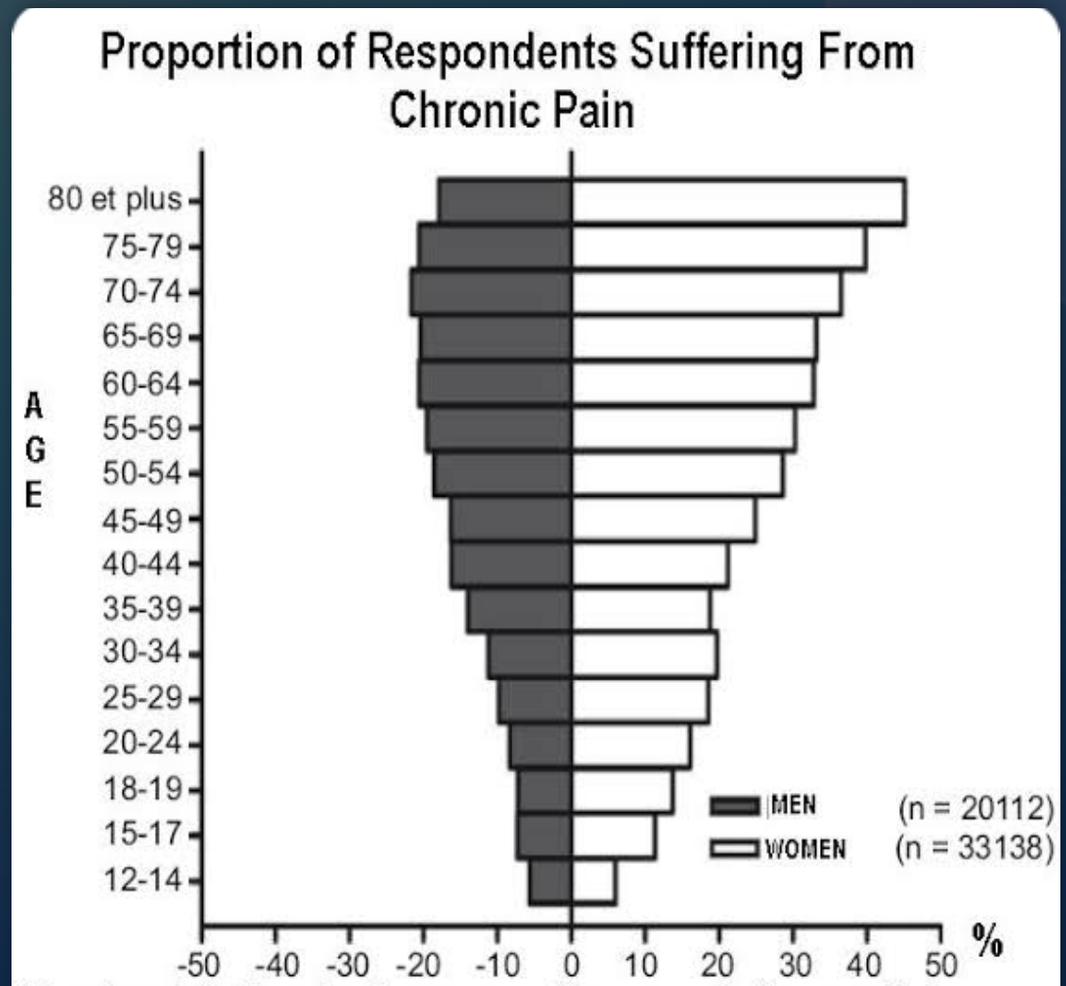
But often painful due to

- Cancer
- Surgery
- Chemotherapy
- Radiotherapy



DEMOGRAPHICS OF PAIN

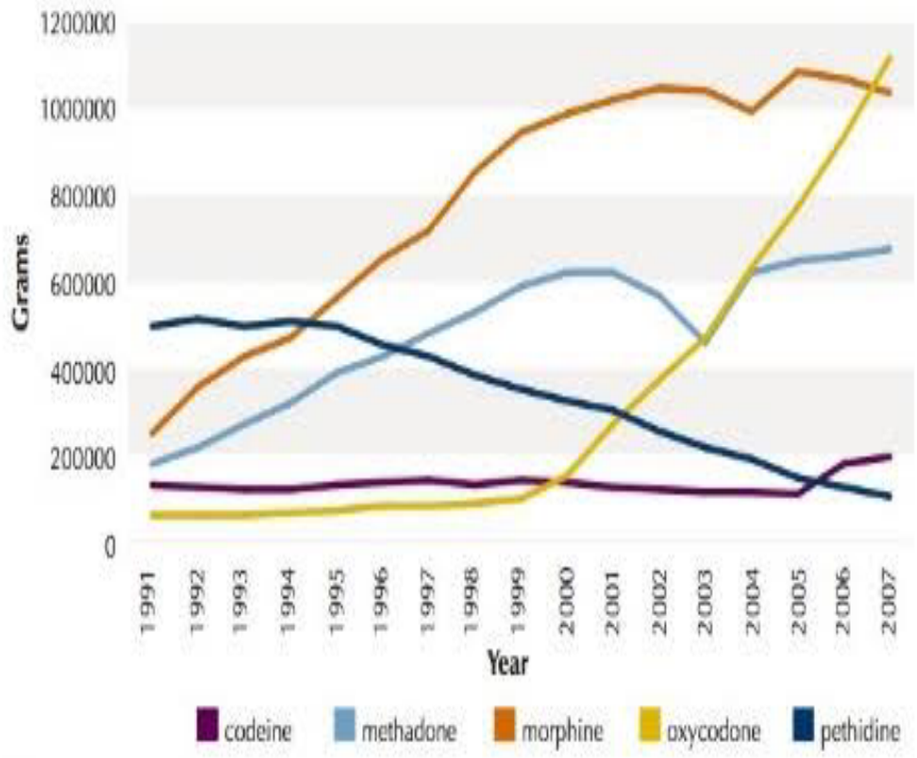
- Pain as a problem is related to
  - Age
  - Sex
  - And other things



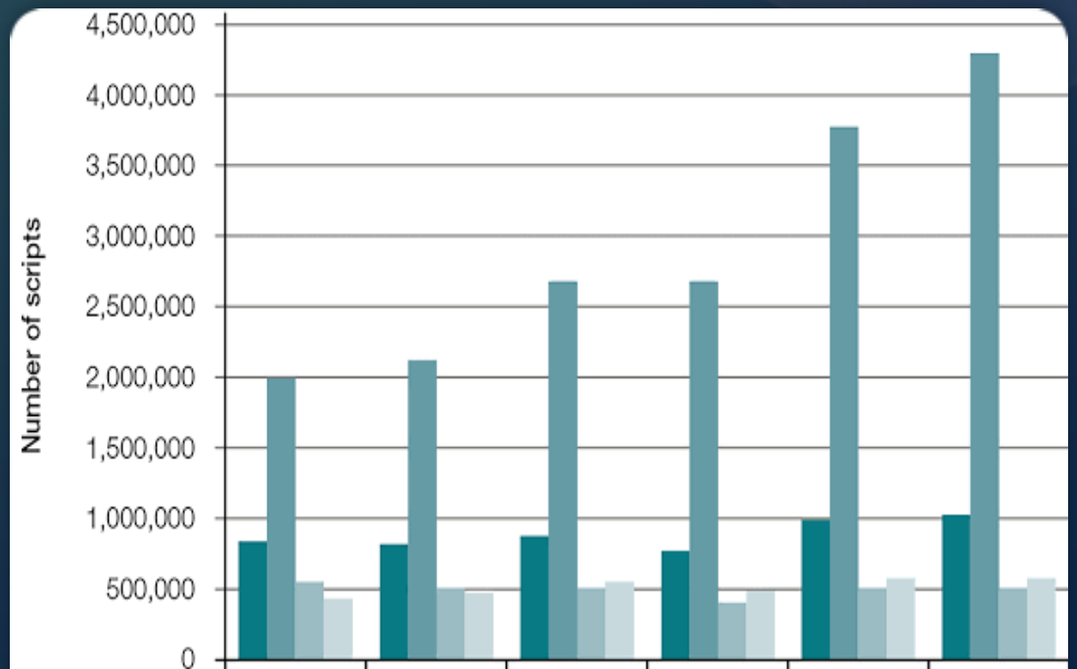
Chronic pain in Canada: do women suffer more pain than man? J. Barcellos de Souza et al. Douleur analg. (2009) 22:134-139

But we have treatments for pain

Figure 4: Pharmaceutical opioid base supply (grams) Australia from 1991-2007



Source: Dobbin 2008, Morphine, Unpublished paper provided to the Drugs and Crime Prevention Committee. Data extracted from the National Drug-control System (NDS) domestic transaction data by the Commonwealth Department of Health and Ageing.



	2010	2011	2012	2013	2014	2015
Tramadol	943,393	925,248	990,949	875,566	1,108,062	1,135,477
Oxycodone	2,104,477	2,226,766	2,787,544	2,779,078	3,875,103	4,405,382
Morphine	653,840	601,456	623,296	509,322	599,609	609,637
Fentanyl	533,891	578,893	654,710	582,076	682,558	682,070

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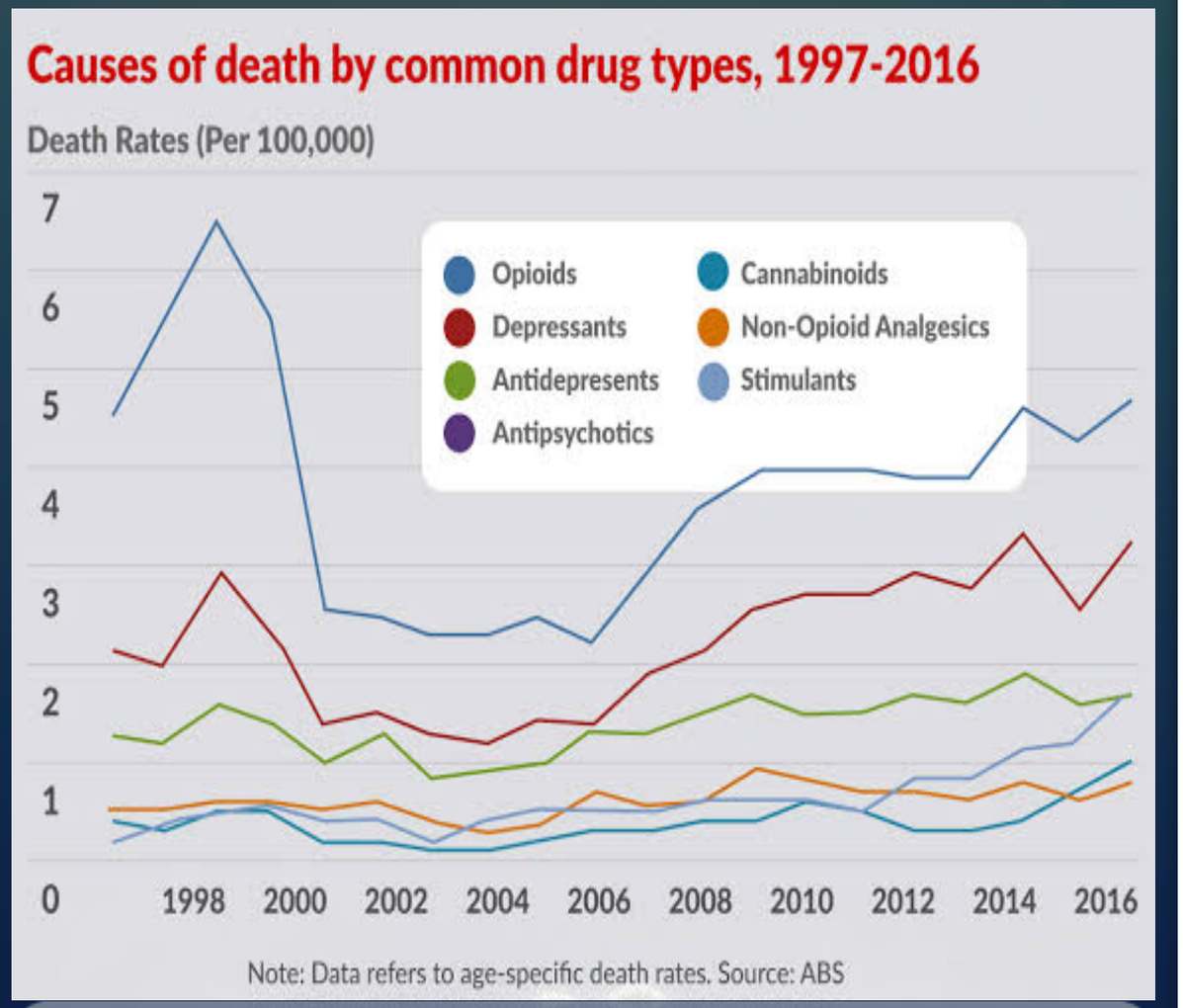
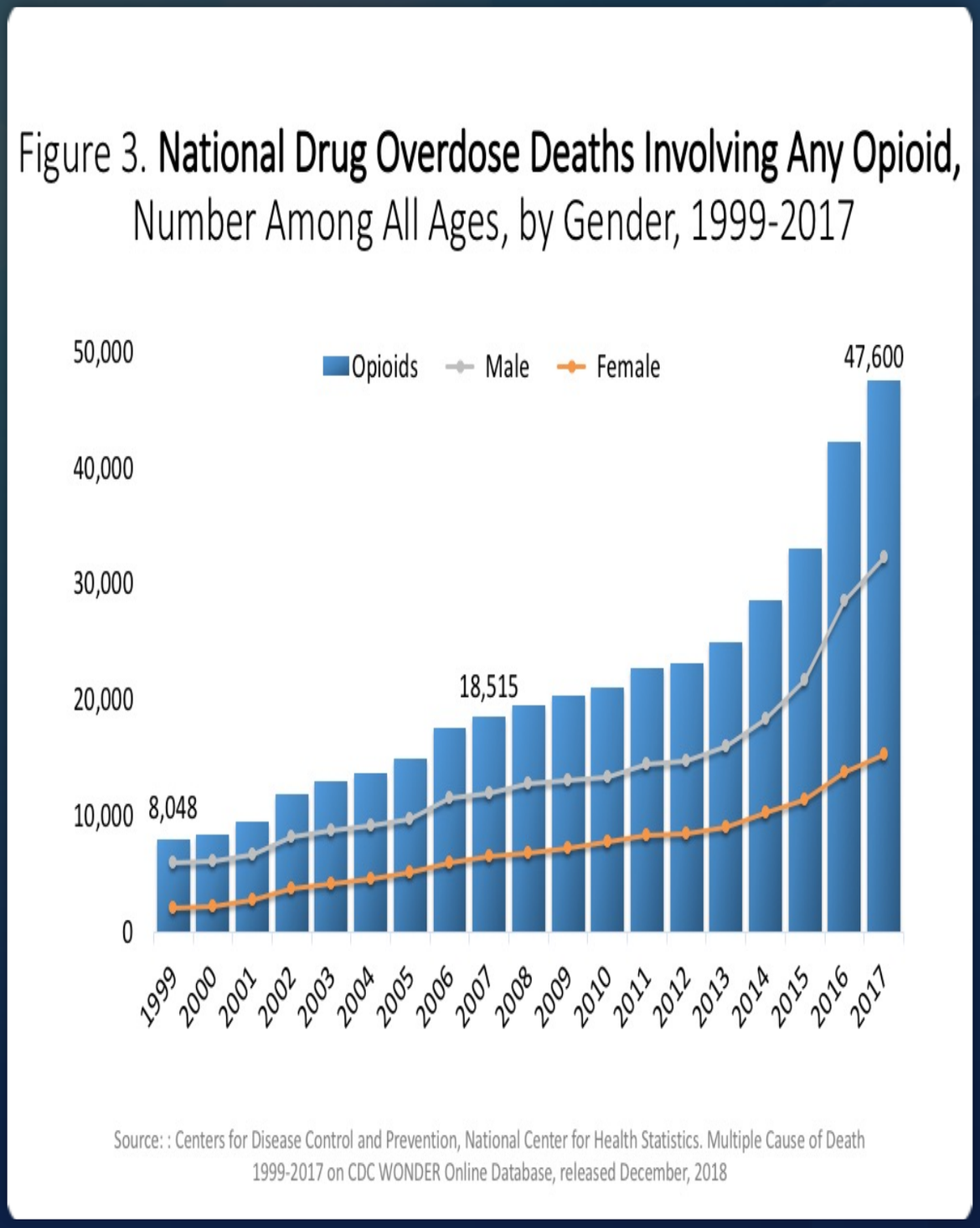
But the cure comes at a cost





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POLITICS & LEGALITIES

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THE CHANGING FACE OF THE PHARMACEUTICAL INDUSTRY

New York Times

2nd May, 2019

https://www.nytimes.com/2019/05/02/health/insys-trial-verdict-kapoor.html

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nytimes.com

The New York Times

Distributor Faces Federal Criminal Charges Over Opioid Crisis

The charges against the wholesaler, Rochester Drug Cooperative, and two of its former executives marked a new tactic for prosecutors in tackling the epidemic of addiction to prescription painkillers.

Laurence F. Doud III, who had served as chief executive of Rochester Drug Cooperative, surrendered to Drug Enforcement Administration agents on Tuesday.

THIS ISN'T A ONE OFF

New York Times

23 April 2019

https://www.nytimes.com/2019/04/23/nyregion/opioid-crisis-drug-trafficking-rochester.html

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US medical group that pushed doctors to prescribe painkillers forced to close

- **American Pain Society accused of being pawn of big pharma**
- **Group took nearly $1m from leading opioid manufacturers**

▲ By 2012, more than 250m opioid prescriptions a year were dispensed in the US, enough to provide every American adult with 30 days of pills. Photograph: Jessica Hill/AP

Medical Society Bankrupcy

25th may 2019

https://www.theguardian.com/us-news/2019/may/25/american-pain-society-doctors-painkillers

"The fifth vital sign"

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FACULTY OF PAIN MEDICINE - RECOGNITION OF CHANGE

- GENERATIONAL CHANGE IN FPM AGAINST OPIOIDS
  - LACK OF EVIDENCE OF BENEFIT/ EVIDENCE OF HARM
  - Drive to look at alternatives
    - Non-opioids and non-traditional opioids.
    - Procedural interventions

FPM
ANZCA
Fellow of the Faculty of Pain Medicine

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Background Summary

- We are getting older
  - We have more age related diseases, including cancer
  - We have more cancer survivors
- Pain is a growing problem
- Opioid treatments have been rising
  - Deaths are rising with and from this
  - Increasing recognition of the issues with opioids

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Definitions

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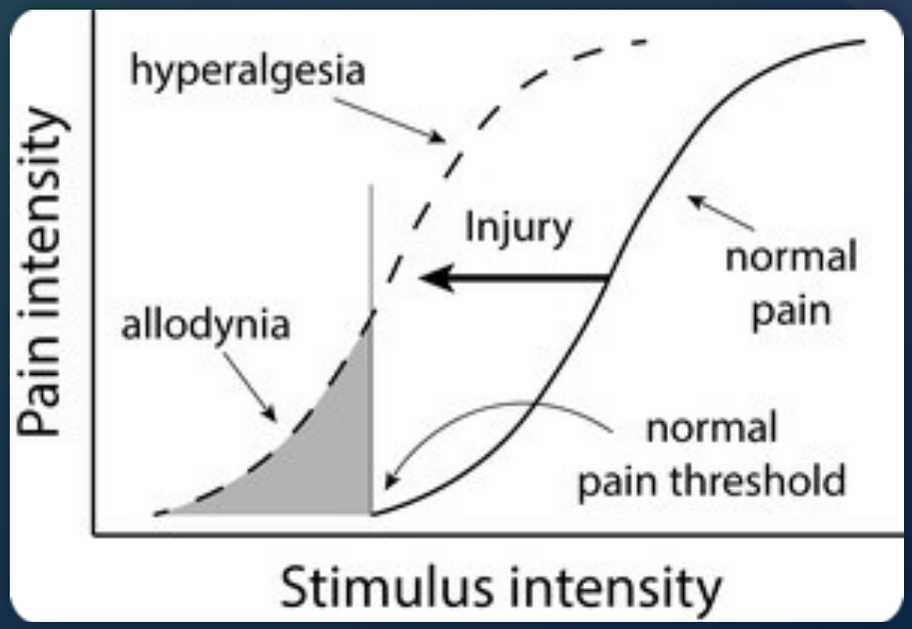
Types of pain

- Nociceptive
  - Pain from tissue injury
- Nociplastic
  - Pain from altered nociception
- Neuropathic
  - Pain from nerve injury

Signs

- Allodynia
  - Pain without tissue injury
- Hyperalgesia
  - Excess pain to injury
- Hyperpathia
  - Pain due to repetitive stimulation



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Pain Physiology

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Pain Pathways

Descartes had a pretty fair idea of the basics

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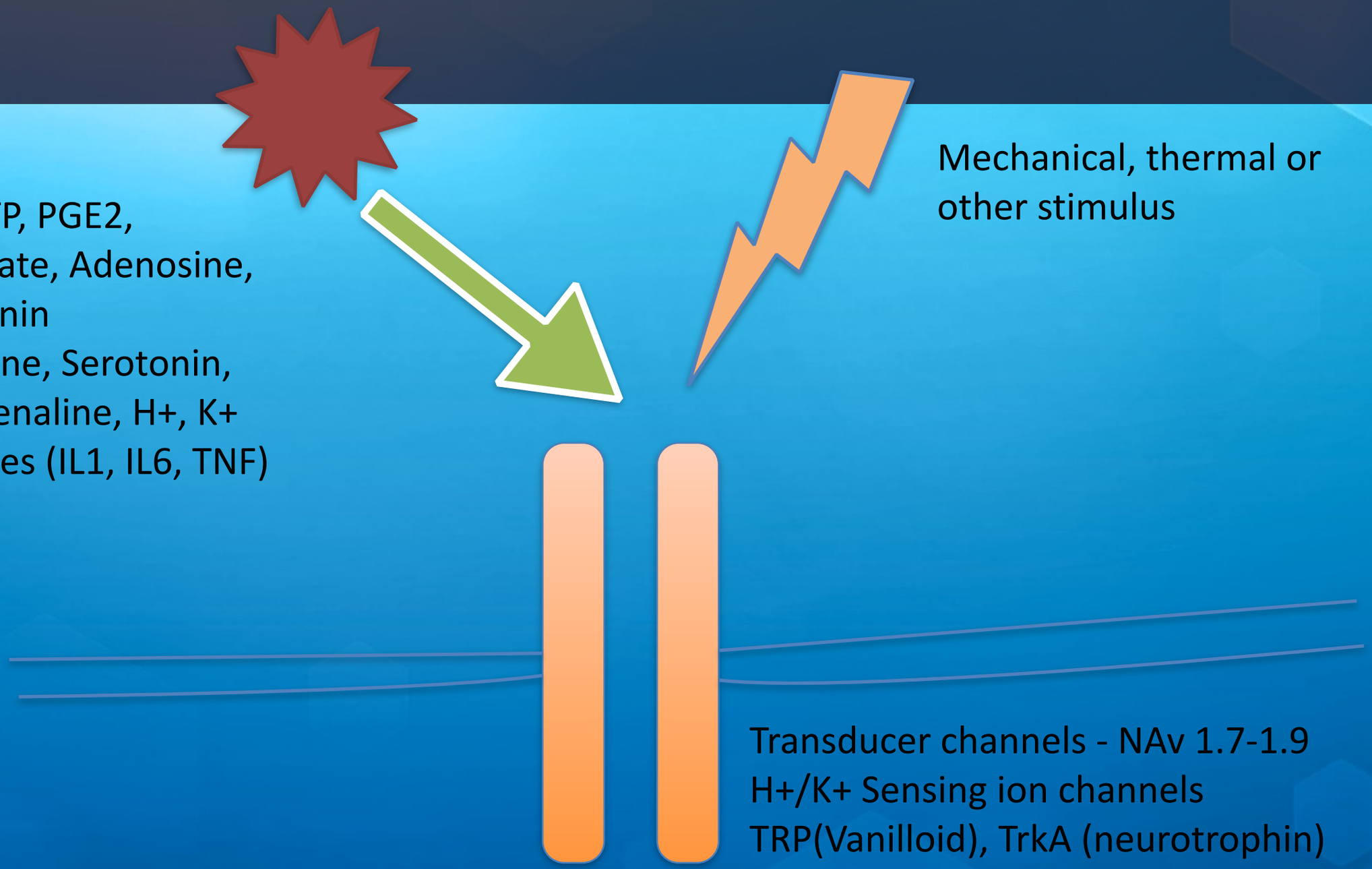
Nociception



AcH, ATP, PGE2,
Glutamate, Adenosine,
Bradykinin
Histamine, Serotonin,
Noradrenaline, H+, K+
Cytokines (IL1, IL6, TNF)

Mechanical, thermal or
other stimulus

Transducer channels - NAv 1.7-1.9
H+/K+ Sensing ion channels
TRP(Vanilloid), TrkA (neurotrophin)

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What happens after nociception

Fibres	Aδ	C	Aβ
Threshold	Low & High	High	Pathological
Stimulii	Thermal Mechanical	Thermal Mechanical Chemical	Mechanical Light Touch
Diameter	2-5 µm	0.5-2 µm	5-10 µm
Conduction Velocity	10-30 m/s	0.5-2 m/s	30-60 m/s

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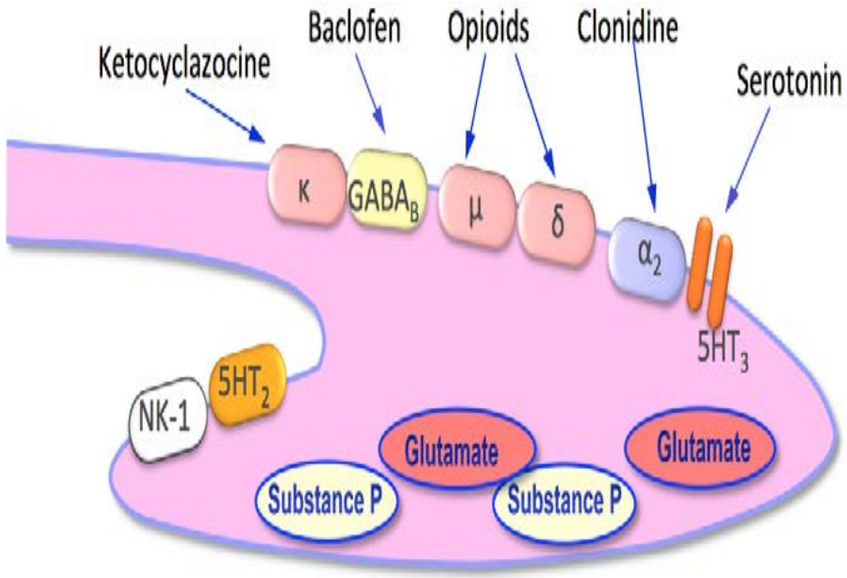

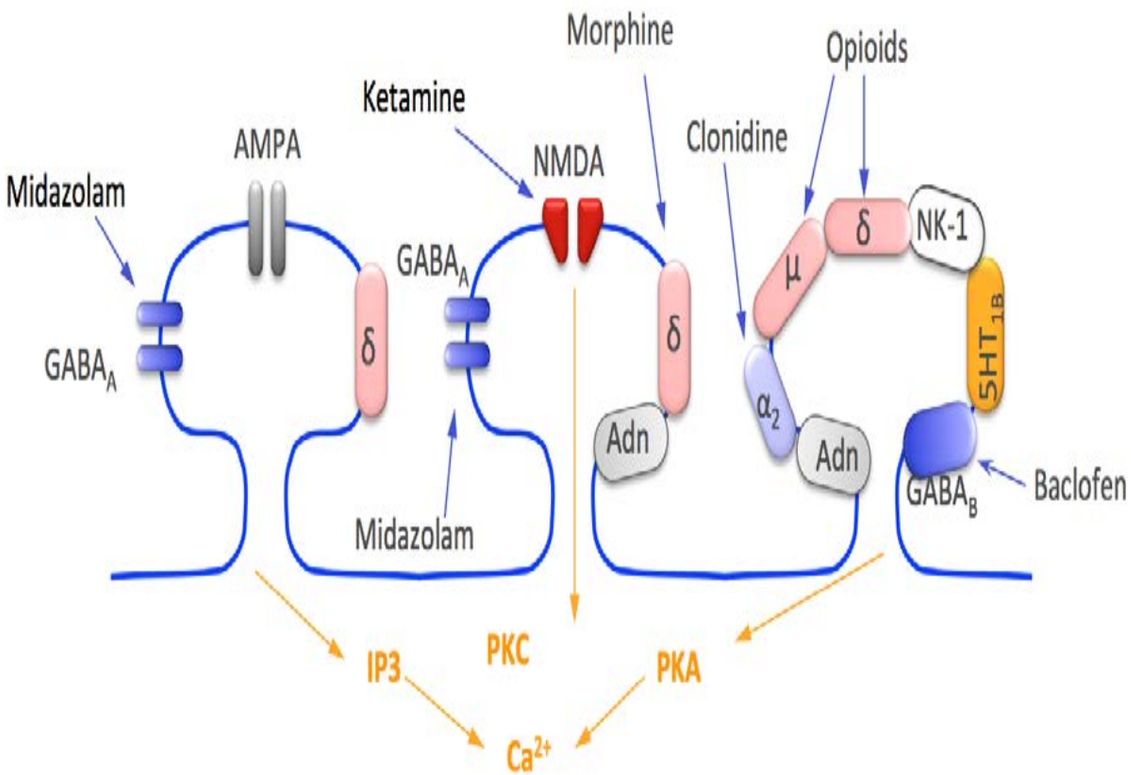

First order Synapse

spinal cord (Lamina II, V)

Presents most of our pharmacological opportunities

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The Dorsal Horn

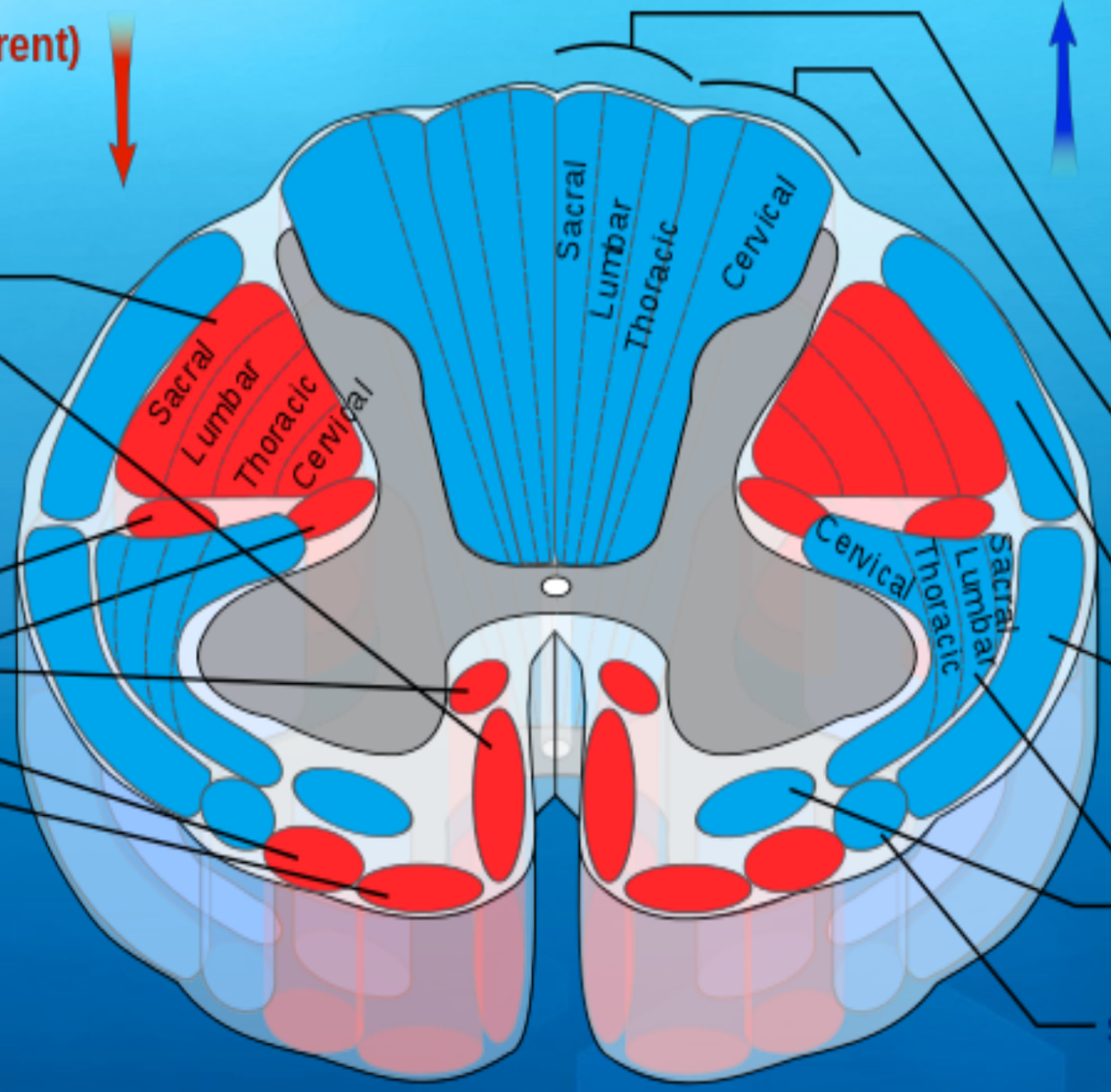
Motor and descending (efferent) pathways (red)

Pyramidal tracts

- Lateral corticospinal tract
- Anterior corticospinal tract

Extrapyramidal Tracts

- Rubrospinal tract
- Reticulospinal tracts
- Olivospinal tract
- Vestibulospinal tract



Sensory and ascending (afferent) pathways (blue)

Dorsal Column Medial Lemniscus System

- Gracile fasciculus
- Cuneate fasciculus

Spinocerebellar Tracts

- Posterior spinocerebellar tract
- Anterior spinocerebellar tract

Anterolateral System

- Lateral spinothalamic tract
- Anterior spinothalamic tract
- Spino-olivary fibers

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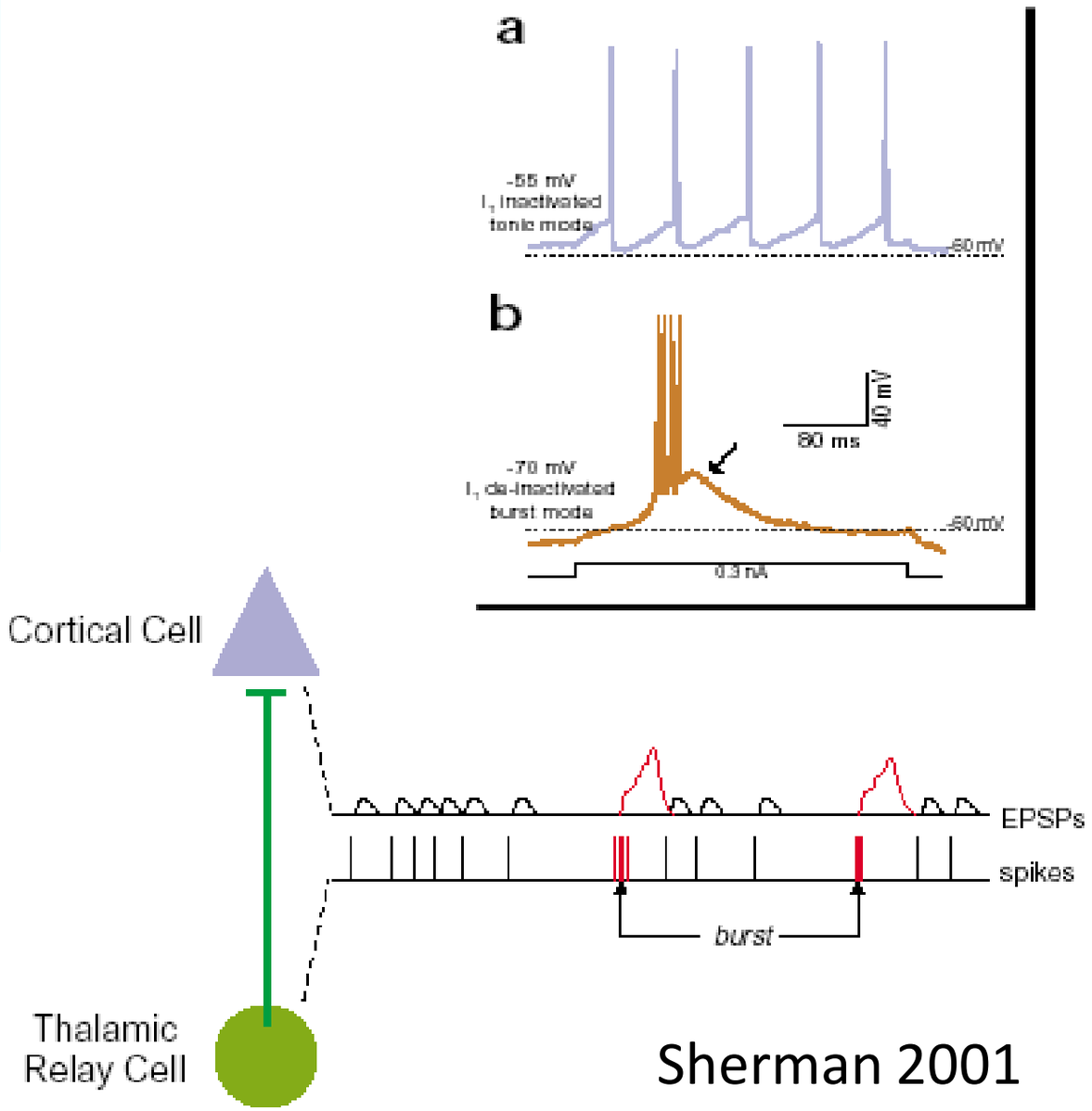

SIGNALLING OF PAIN

Burst mode is signal detector

Tonic is feature detector

Sherman 2001

Cooper 2006

Burst has a non-linear response

Lisman 1997

Sherman 2001

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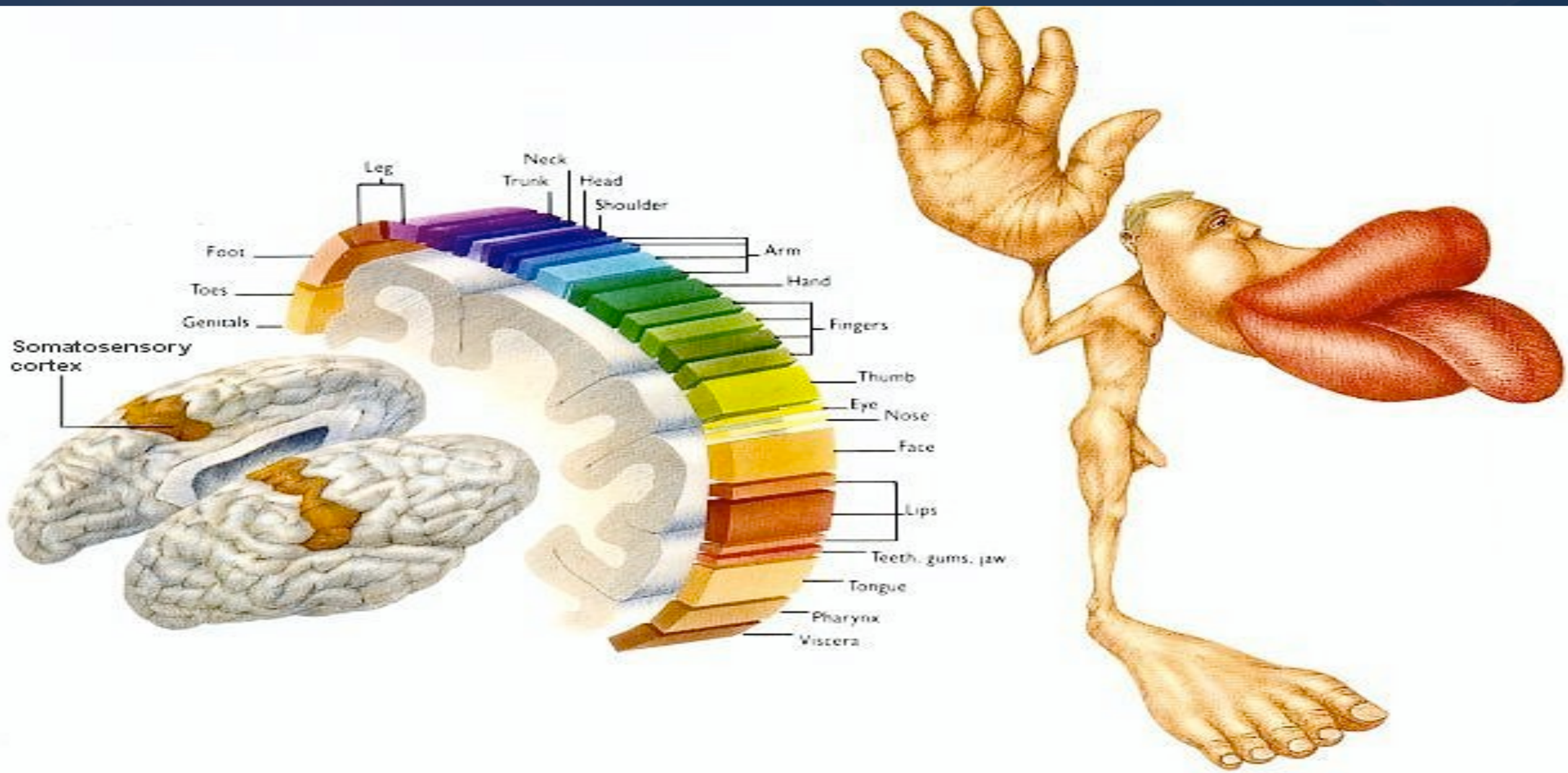
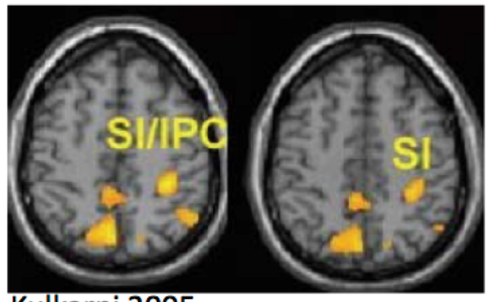
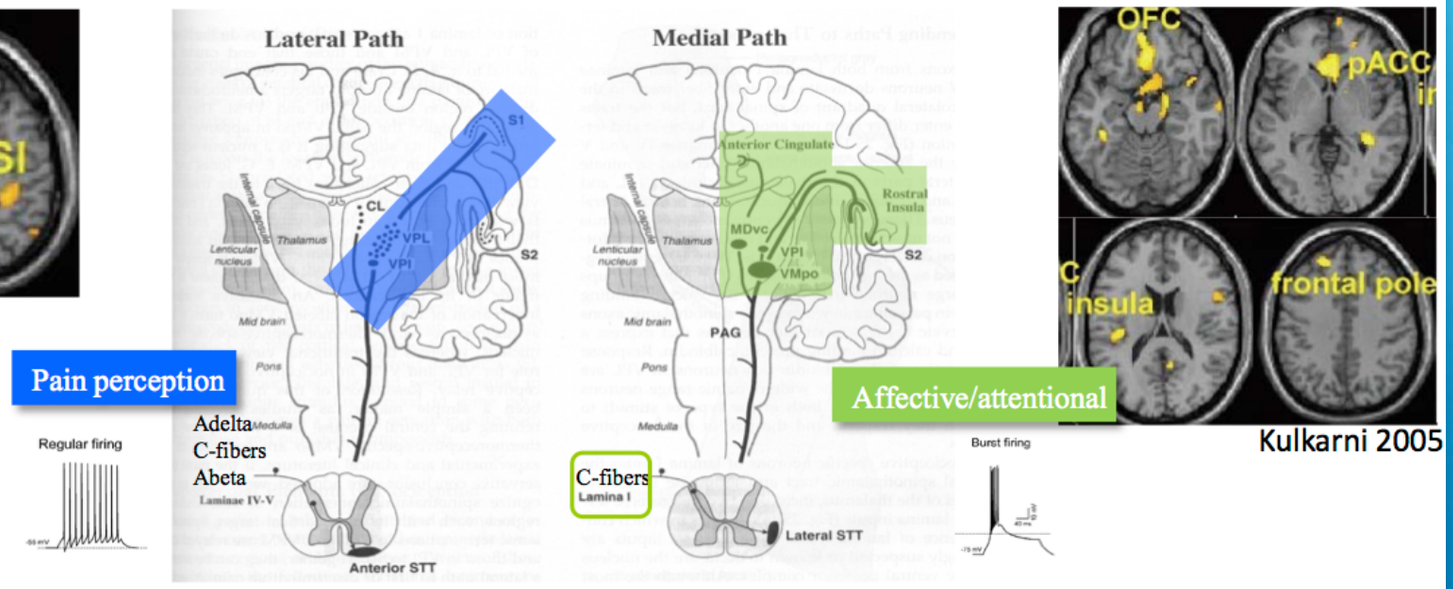
Somatosensory Cortex



Two Pain Pathways



Kulkarni 2005



Kulkarni 2005

Lateral System (Pain Perception)

WDR neurons

Firing in tonic mode

Lamina I, V-VI

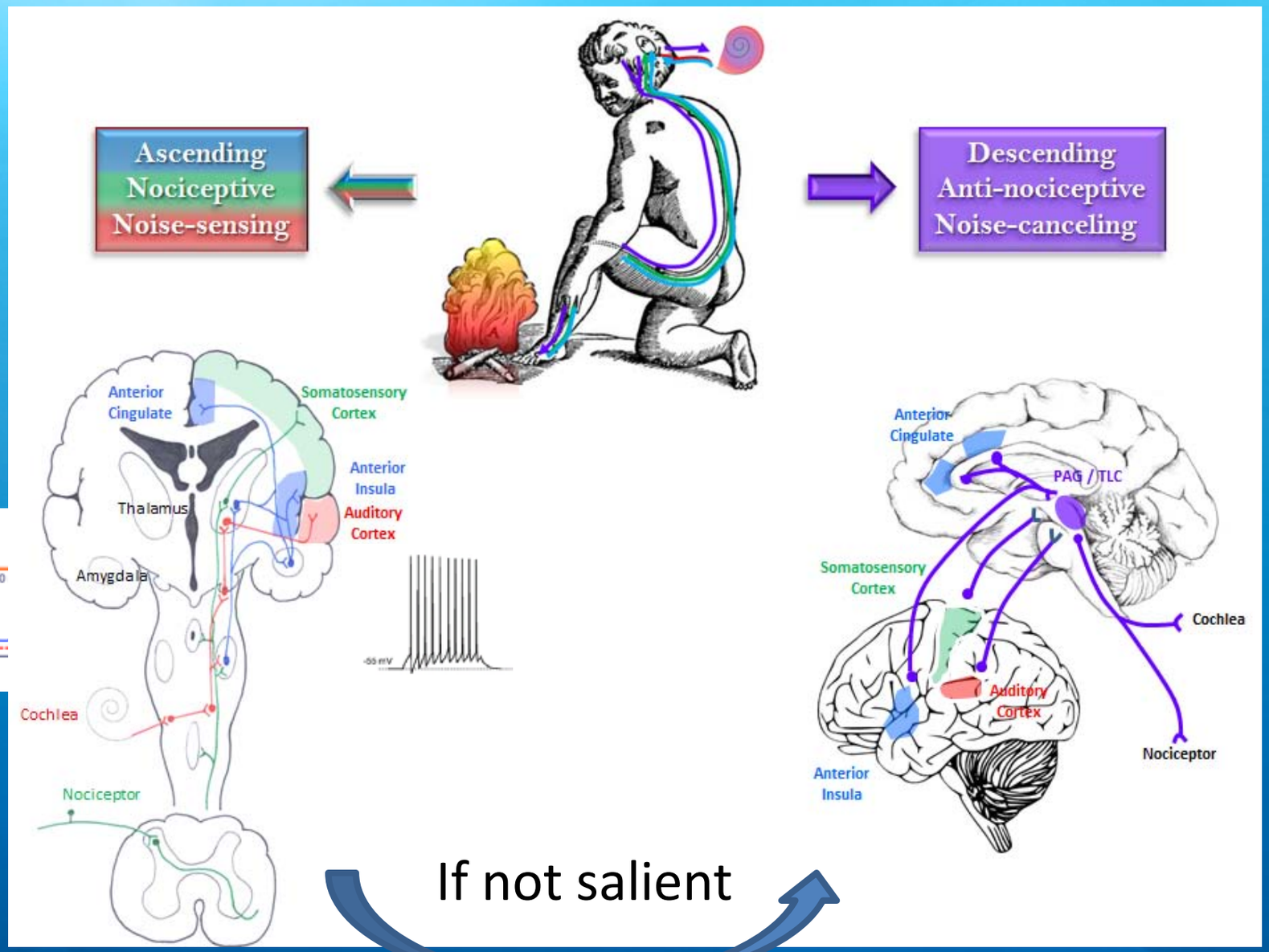
Medial System (Affective)

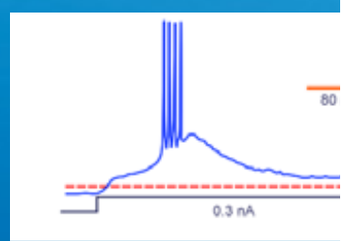
Nociceptive neurons

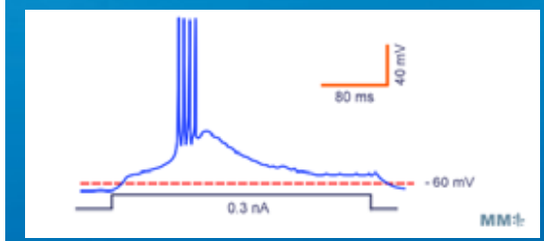
Fire in burst

Lamina I

Descending Pathways







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Glia and Pain

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Neuronal Activity

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Neurons don't float

- 10% of cells in the brain are neuronal
- 90% are glia.
  - Astrocytes
  - Microglia
  - Satellite Glial Cells
  - Others (Oligodendrocytes, Ependymal cells)
- Glia aren't just scaffolding

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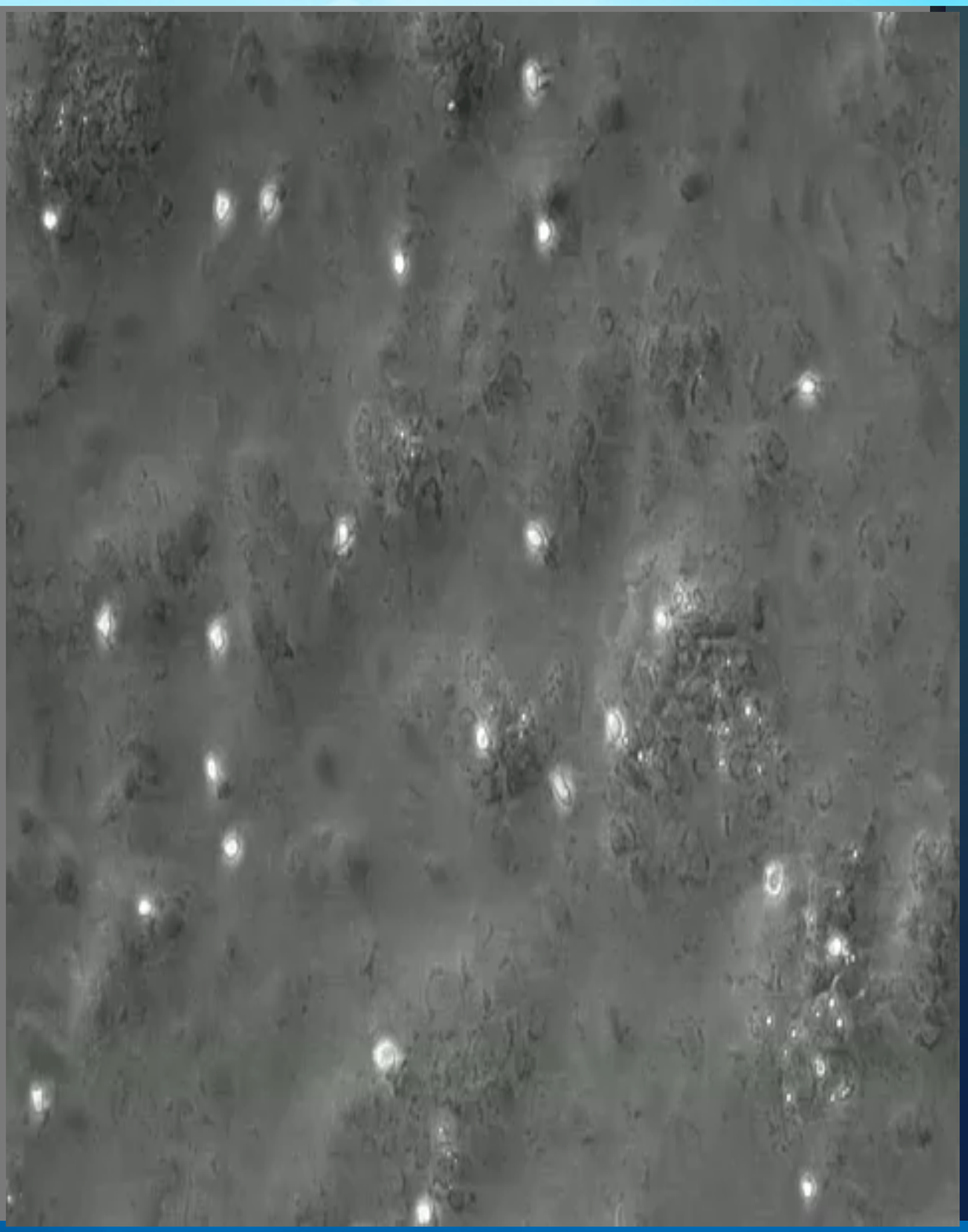

Microglia

Constantly survey the brain

Touch every part of the brain 3x / hour

Rapidly respond to injury

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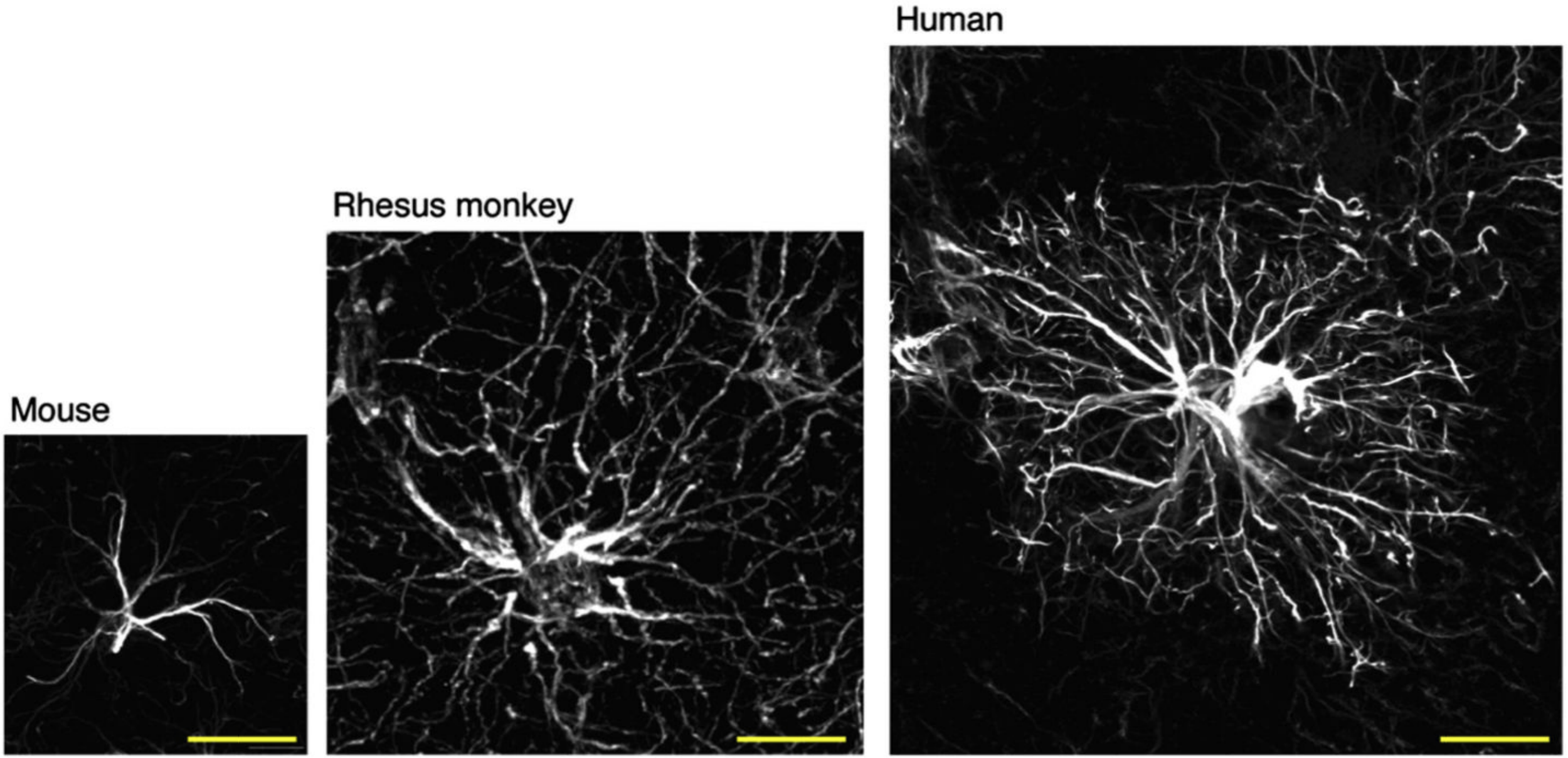
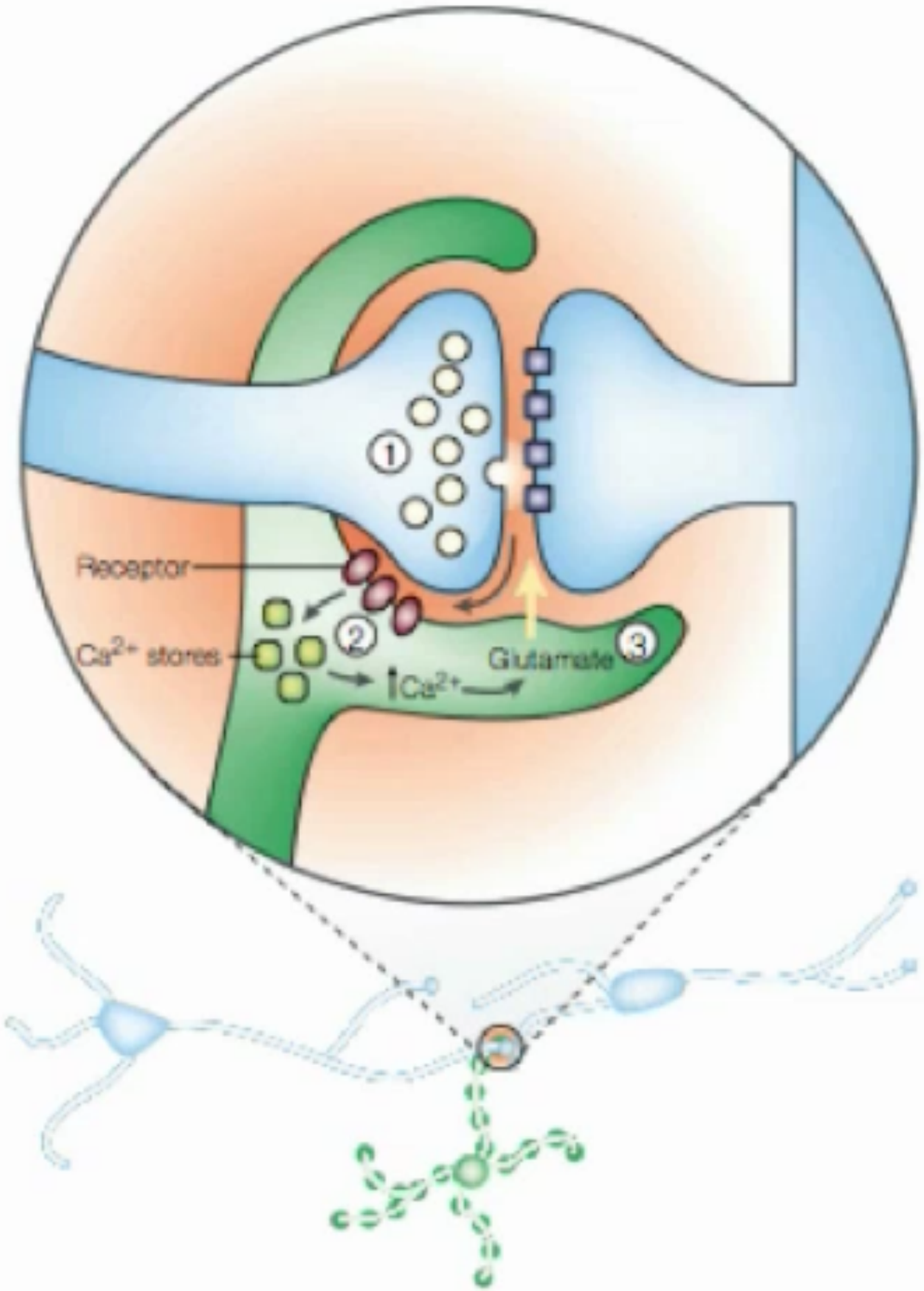
Astrocytes





Astrocytes

The tripartite synapse

- Astrocytes modify the transmission of signals

Glutamate take up by

- GLAST
- GLT-1

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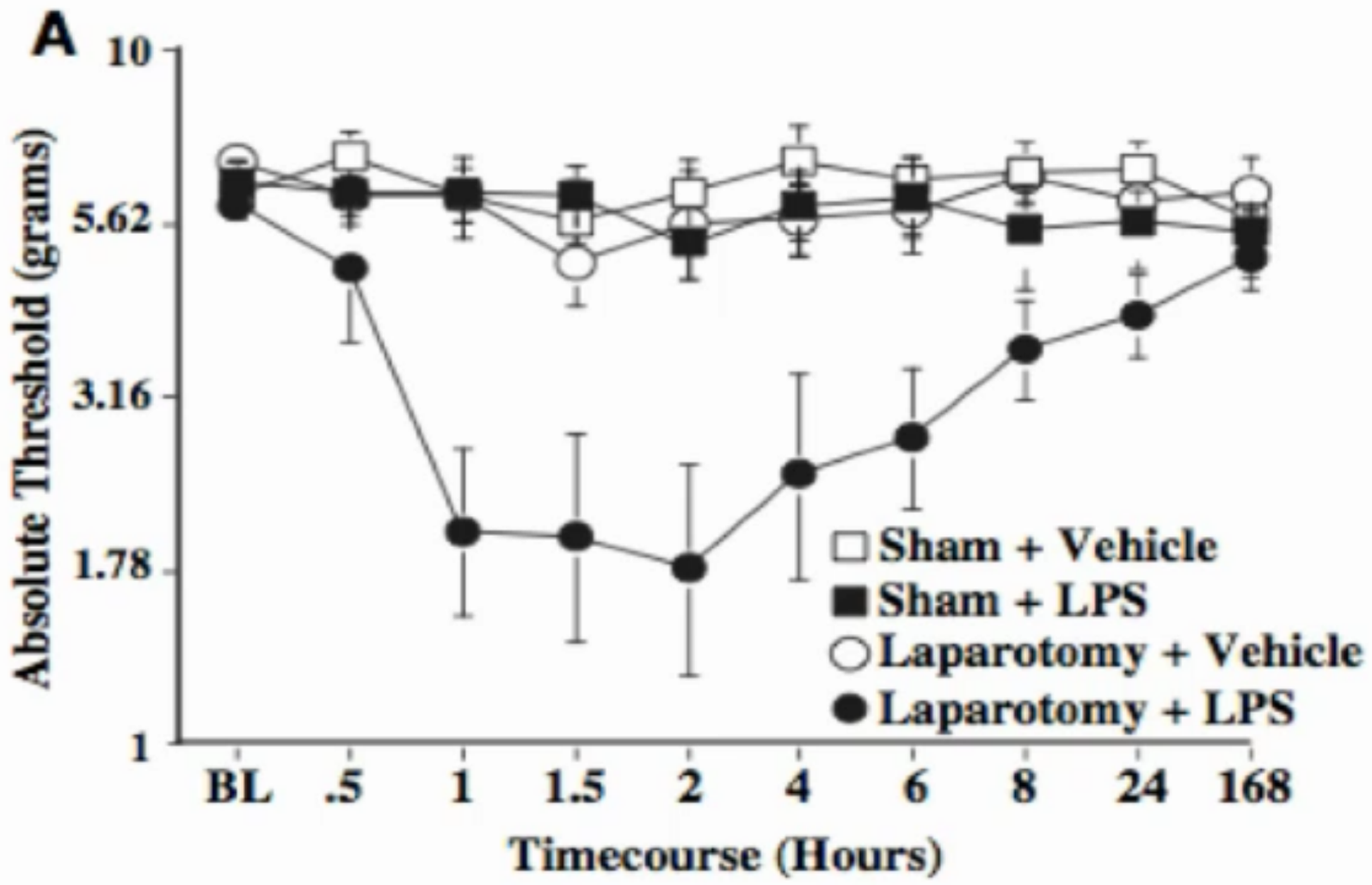
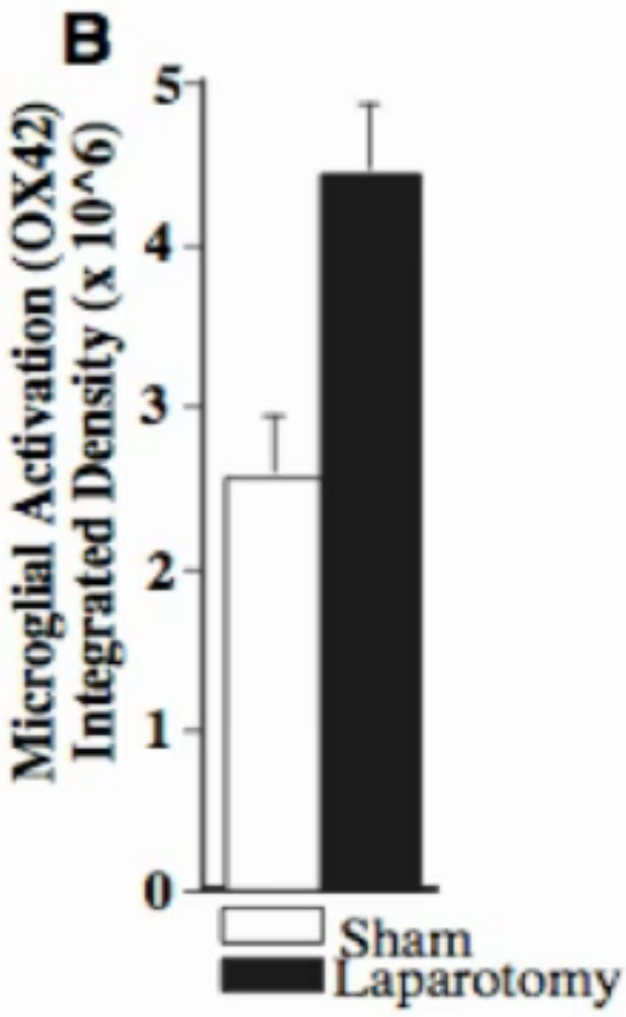
Allodynia 2-hit hypothesis





Hains et al, 2011

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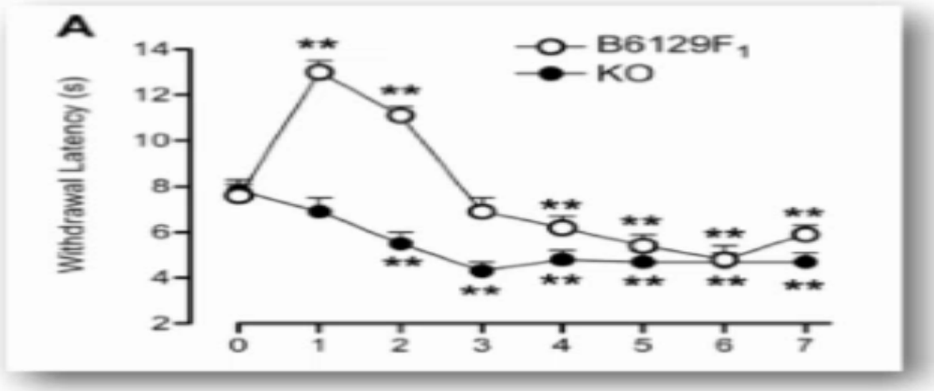
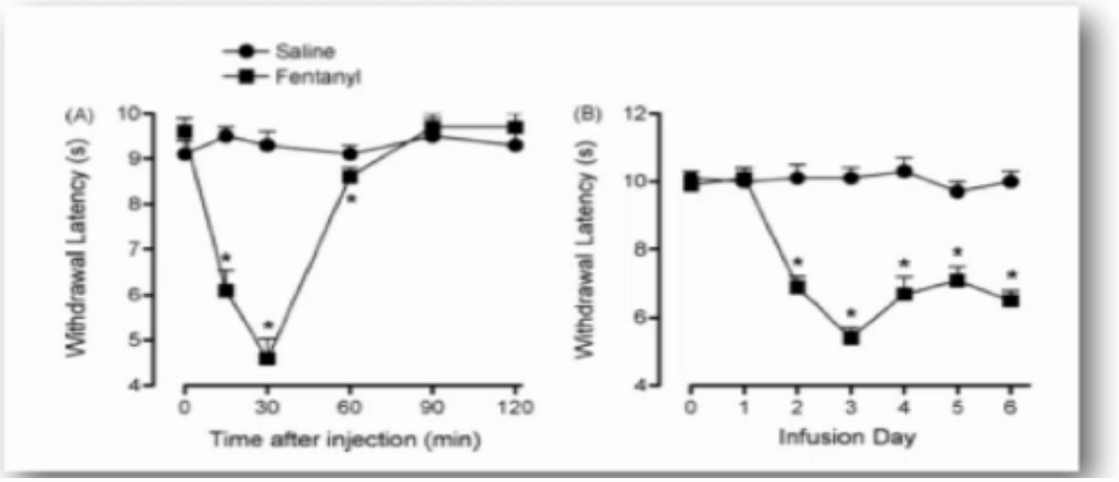
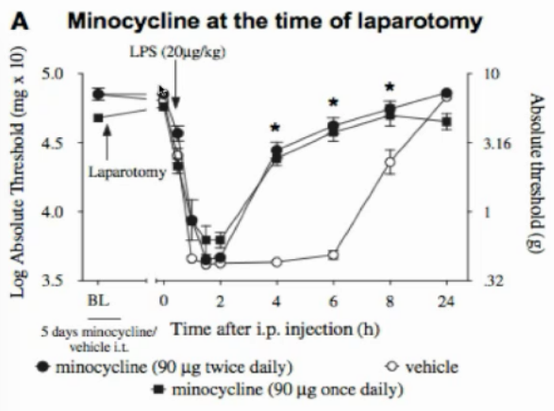
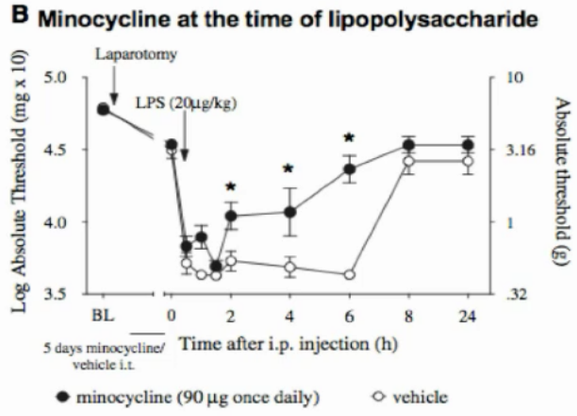
Juni et al 2007



Waxman et al 2009







MINOCYCLINE BLOCKS THIS

Minocycline blocks microglial activation

Blocking microglia blocks allodynia (in rats)

Also, TLR4 knockout mice have less pain

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Opioids & Glia

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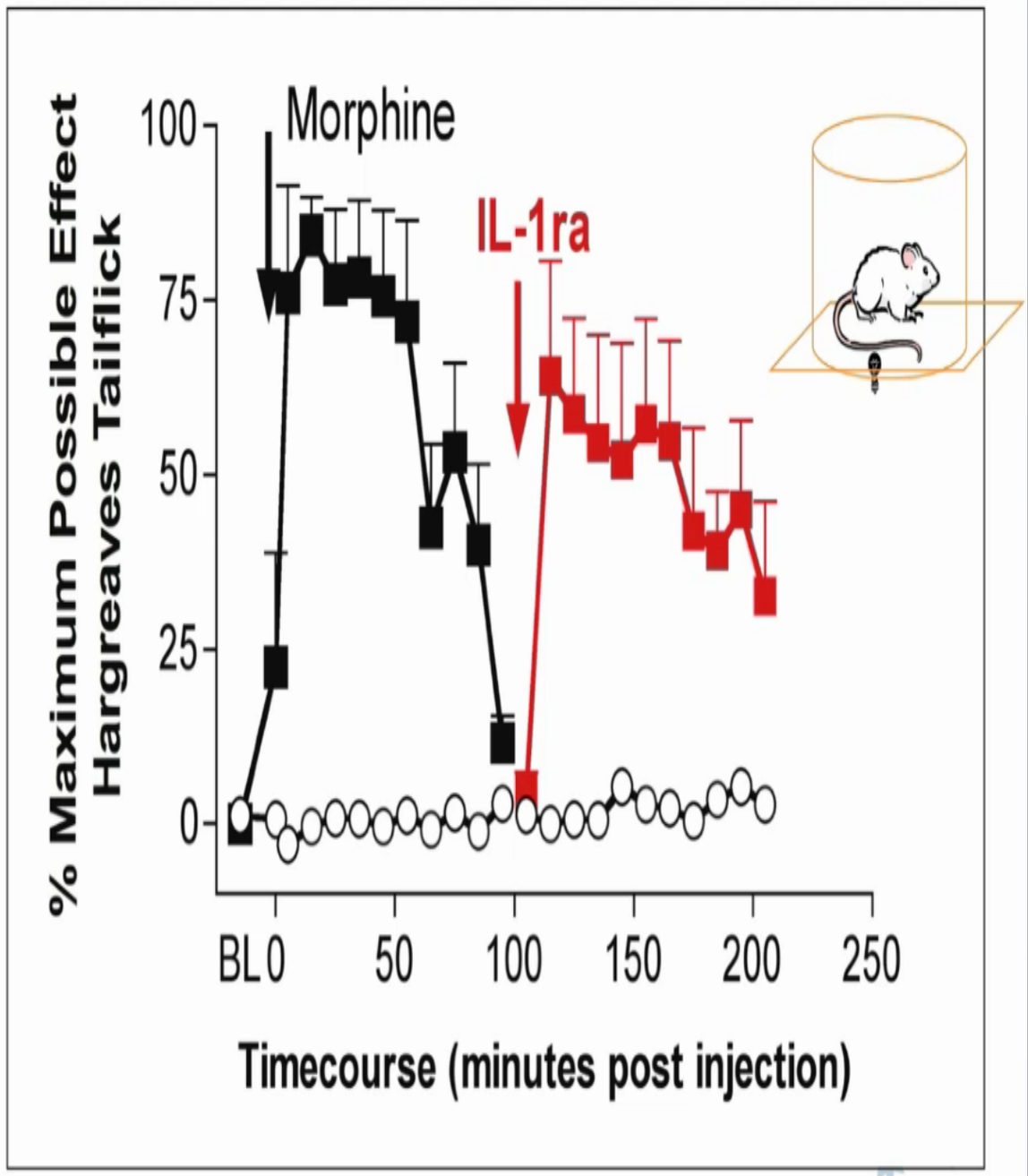

Hutchinson et al 2008

BLOCKING IL-1 RESTORES ANALGESIA

Morphine antagonises its own action

The mechanism for antagonism isn't via opiate receptors

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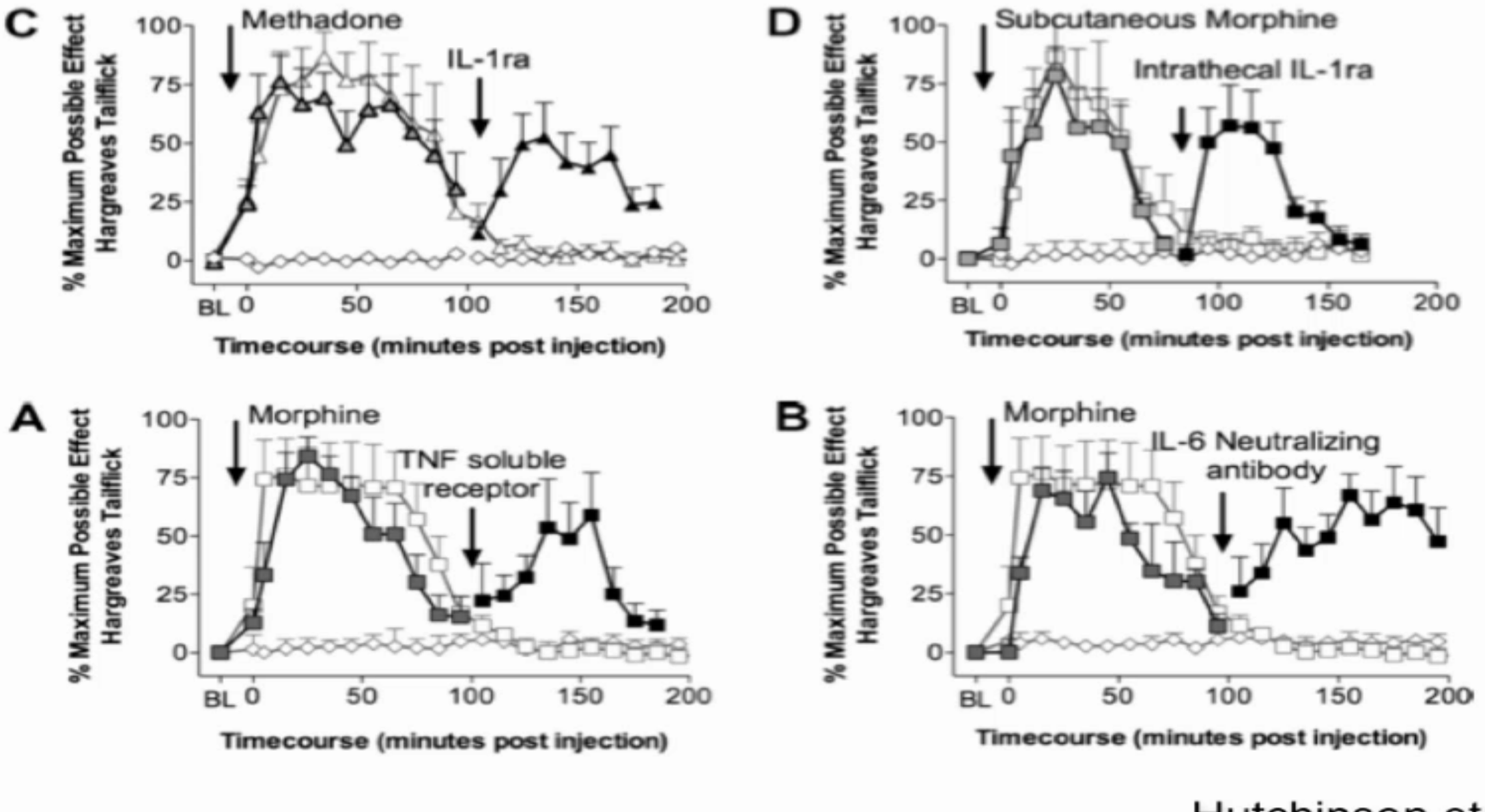
Its not just morphine and IL-1



Hutchinson et al 2008

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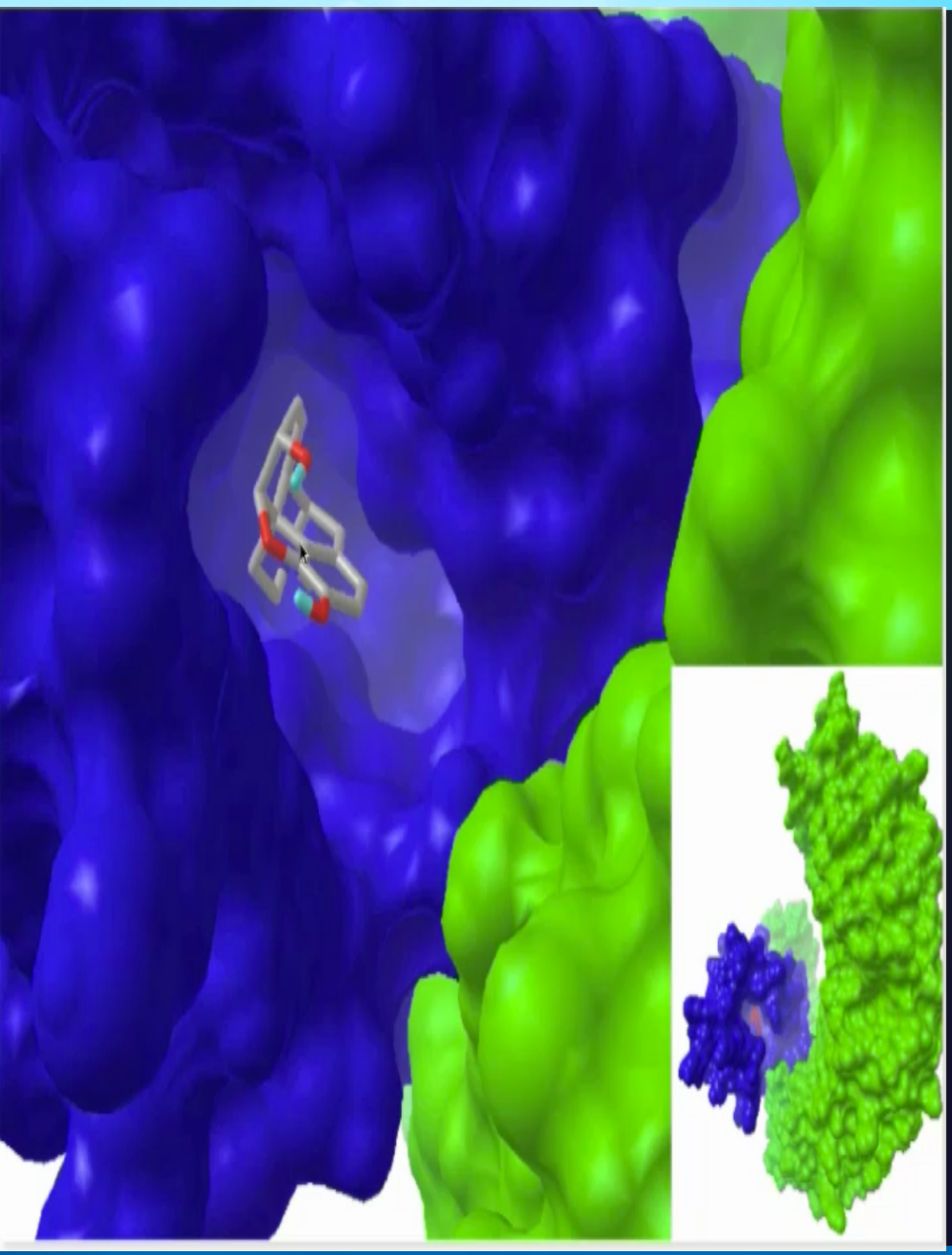

Morphine and TLR-4

Morphine binds the same site as LPS in the MD2 accessory protein to TLR-4

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Chronic Pain & Perioperative Medicine

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Preoperative Assessment

Opioids for chronic pain are bad

- But this is not the time to fix that
- Estimate daily morphine equivalents

Factors that will complicate anaesthesia:

- Anxiety
- Impaired DNIC
- Device therapy

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Neuropathic pain medications

- Gabapentinoids. (Pregabalin/Gabapentin)
- SNRI's (Duloxetine/venlafaxine)
- Atypical opioids (Tapentadol/Buprenorphine)

Other Pain Medications

Weight loss management

GLP-1 RA's.

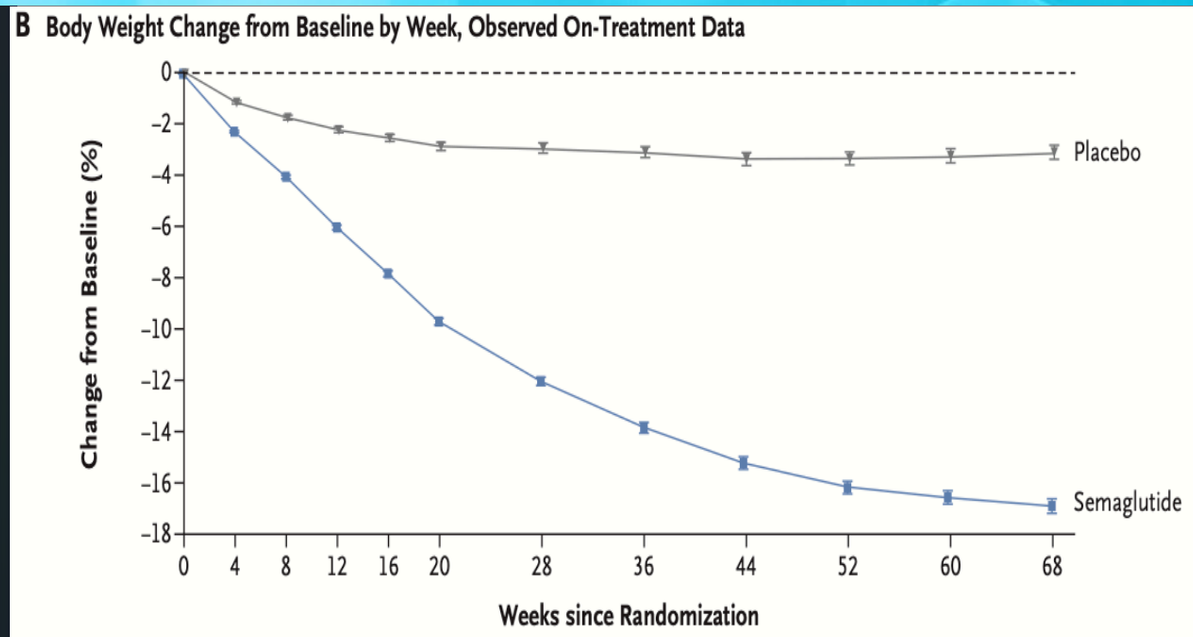
- (Semaglutide/liraglutide/dulaglutide)

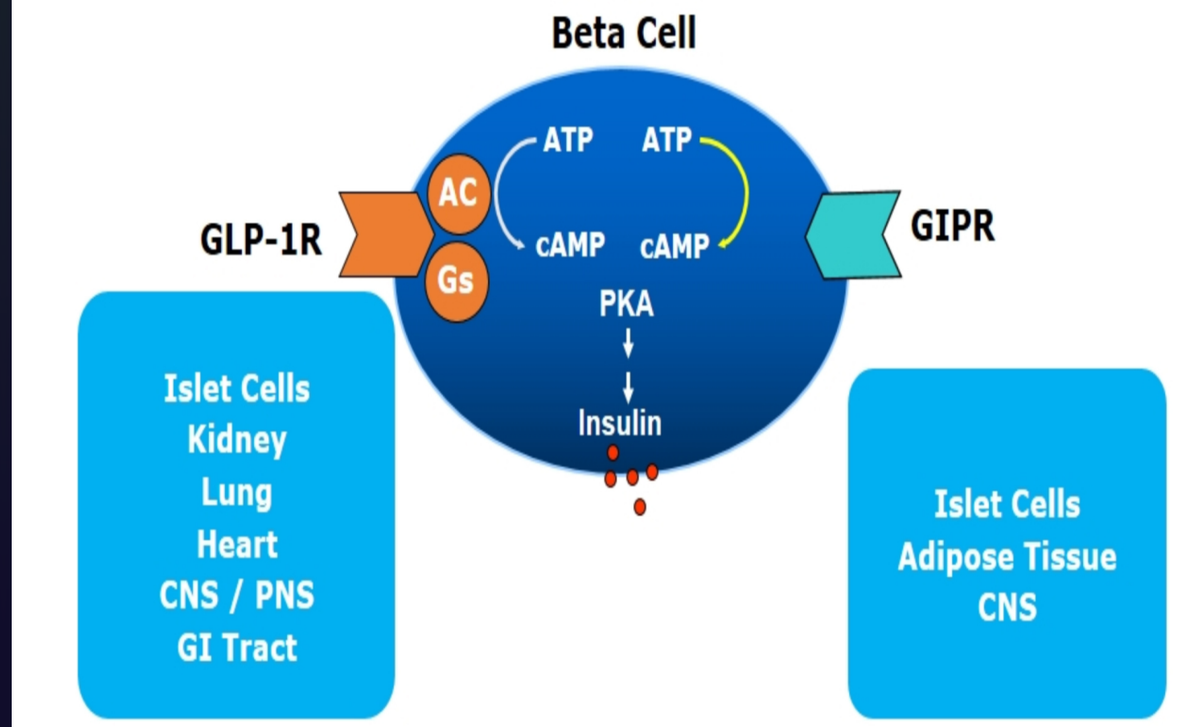
Twincretins

- Tirzepatide (coming soon)

Off label medications

- Low dose naltrexone





Intraoperative management

May well need high doses of opioids

Can titrate at the start to get an idea

Blocks and ketamine are your friends

And remifentanil is not

Parenteral methadone can be a good choice also

Acute dosing of methadone is easy

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Postoperative Management

Limit Fentanyl/Morphine/Oxycodone/ Hydromorphone. Consider instead:

- Tapentadol
- Buprenorphine
- Ketamine

May need bigger doses

- Sometimes this can lead to surprises.

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Complex Regional Pain Syndrome

Causes:

Peripheral musculoskeletal

- Fractures 45%
- Sprains 18%
- Elective surgery 12%

Nerve injury

Idiopathic - 10%

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Budapest Criteria

Consensus meeting in 2003

Improvement on previous IASP criteria

- Sensitivity 85%
- Specificity: 69%
  - 3 Symptoms
  - 2 Signs

IASP Clinical Budapest Criteria in diagnosing CRPS

1. Continuing pain that is disproportionate to any inciting event

2. At least one symptom reported in at least three of the following categories:

Sensory	Hyperesthesia or allodynia
Vasomotor	Temperature asymmetry, skin color changes, skin color asymmetry
Sudomotor	Edema, sweating changes, sweating asymmetry
Motor/trophic	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)

3. At least one sign at time of evaluation in at least two of the following categories:

Sensory	Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
Vasomotor	Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry
Sudomotor	Evidence of edema, sweating changes or sweating asymmetry
Motor/trophic	Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)

4. No other diagnosis can better explain the symptoms and signs

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Anaesthesia for Pain Procedures

Tips for doing a pain list

- Not all patients are opioid tolerant
  - Many are anxious
  - Some are sensitised
- Generally just need sedation +/- Ketamine
- Some procedures affect autonomics
  - Epidurals often have local anaesthetic
  - Sympathectomies
  - Neuromodulation

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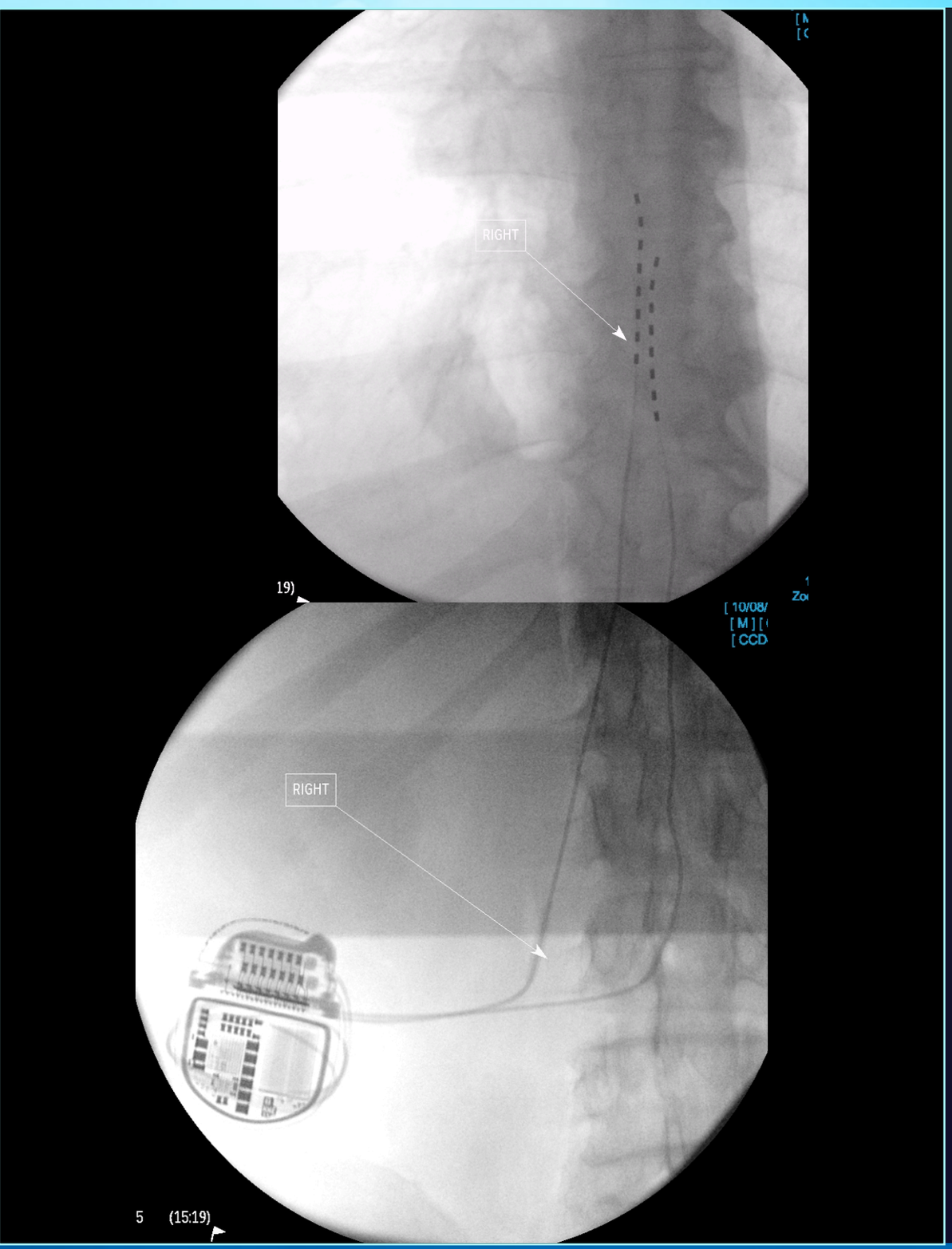

Anaesthesia for Neuromodulation

Prone positioning

Trials don't hurt much

May do on table testing

Permanent's are a small operation

Usually general anaesthesia

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Summary

- Background and Epidemiology
- Definitions
- Physiology
- Neuroimmuno pharmacology
- Management of the chronic pain patient
- Anaesthesia for pain procedures