PainScience

Pain Management

&

The problem with opioids

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Disclosures

- Employment:
  - SCGH and Joondalup as employee in pain medicine
  - PainScience - private practice
- University
  - Adjunct positions with NDU, Curtin, UWA
- Industry
  - No conflicts / disclosures / financial interests
  - Don’t accept industry travel/accomodation.

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Outline

History, demographics and politics

Review of pain physiology

Glia and pain

Role of opioids in pain management

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Demographics

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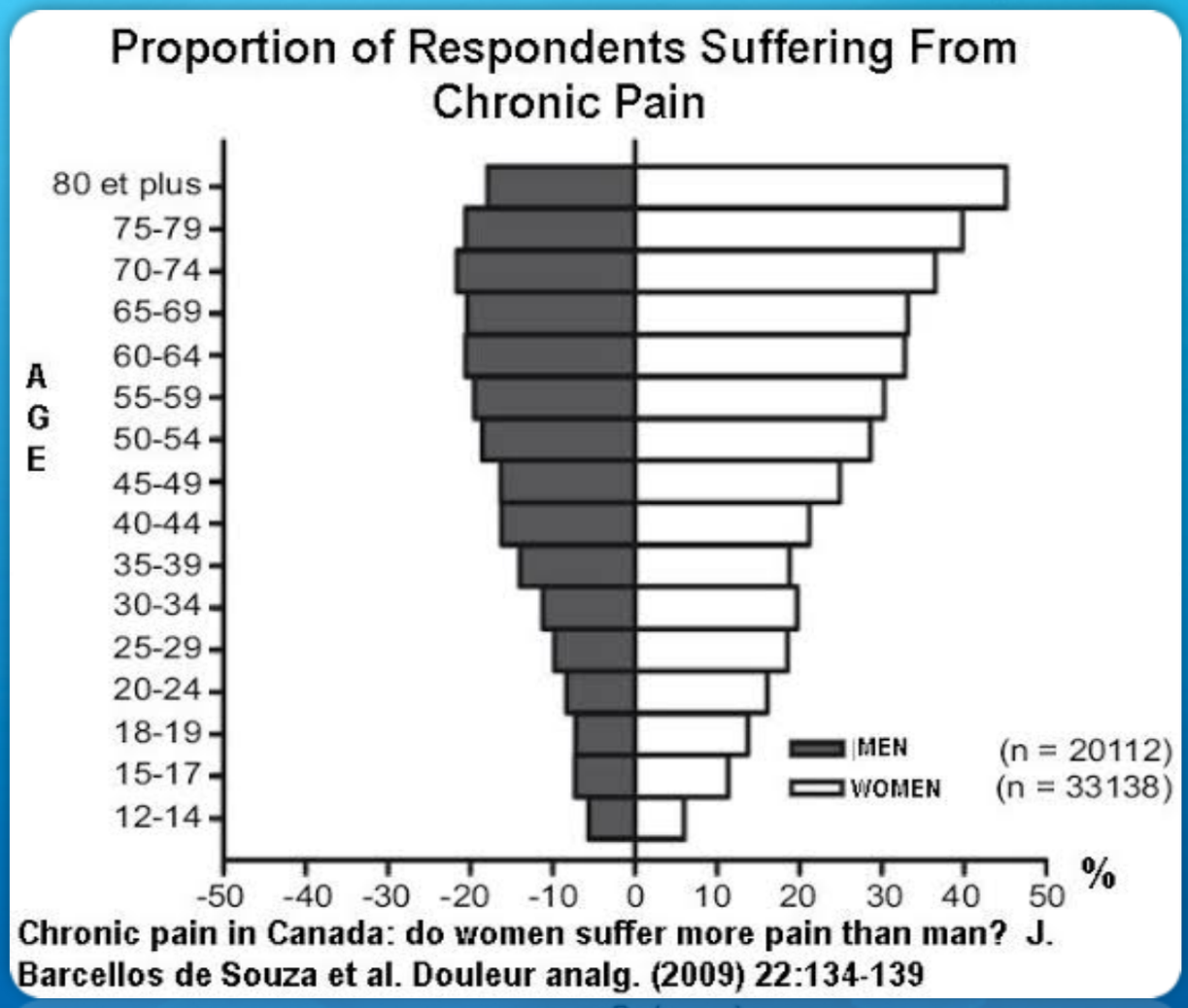
Demographics of Pain

Pain has a definite association with:

- Age
- Gender
- And some other things



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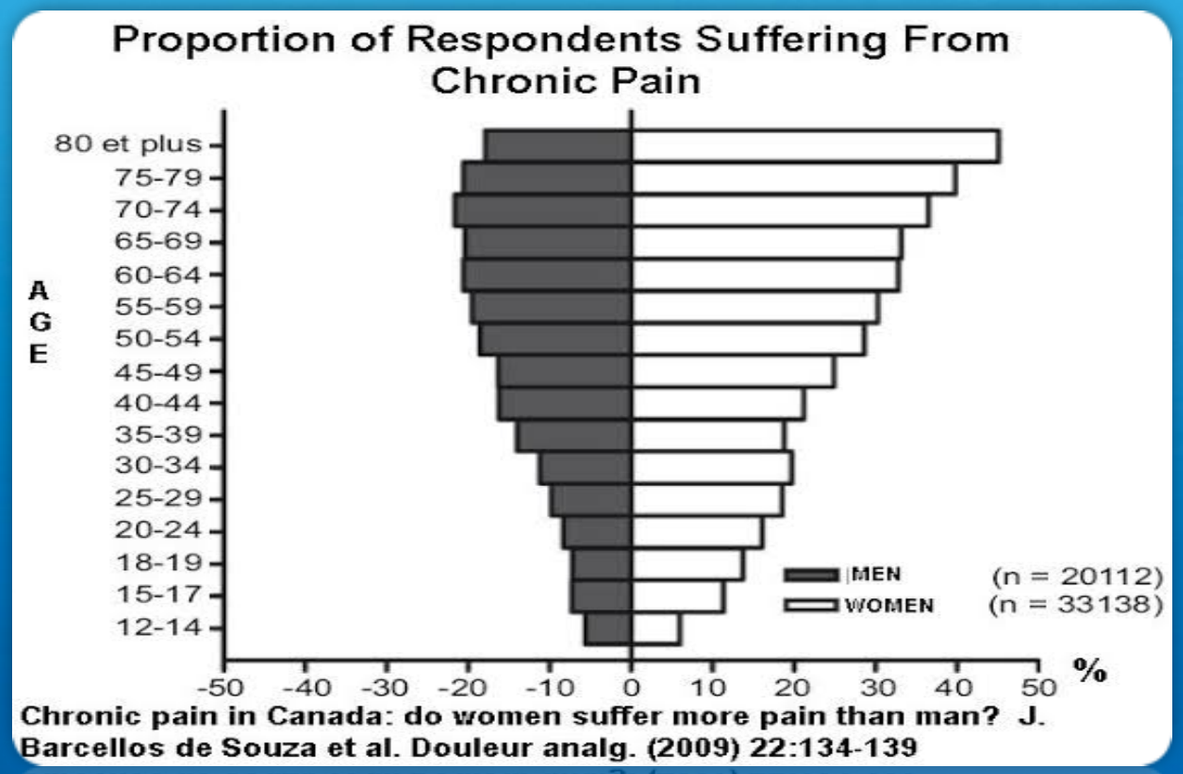
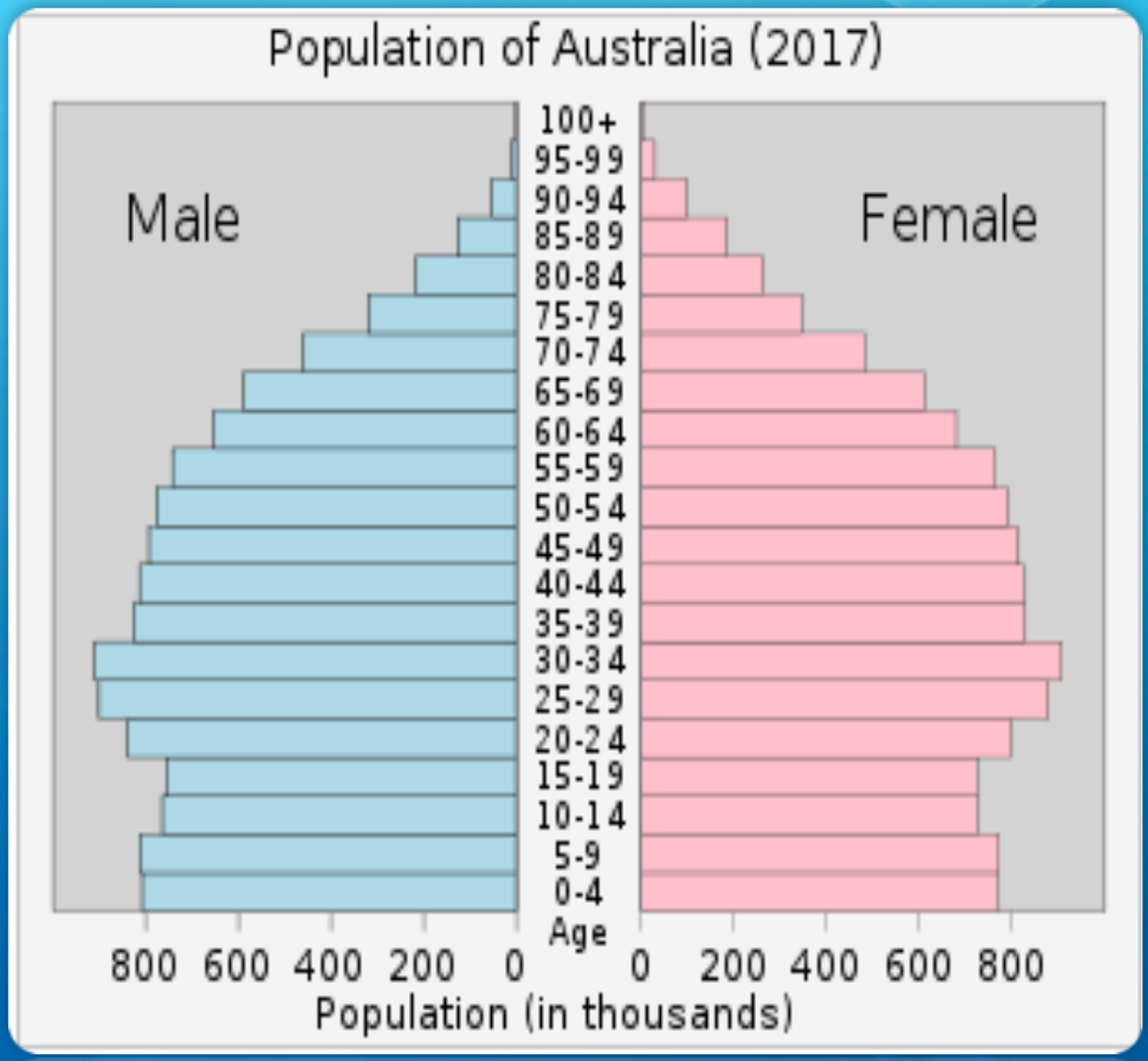
Pain is an increasing problem

Mainly because its age related.





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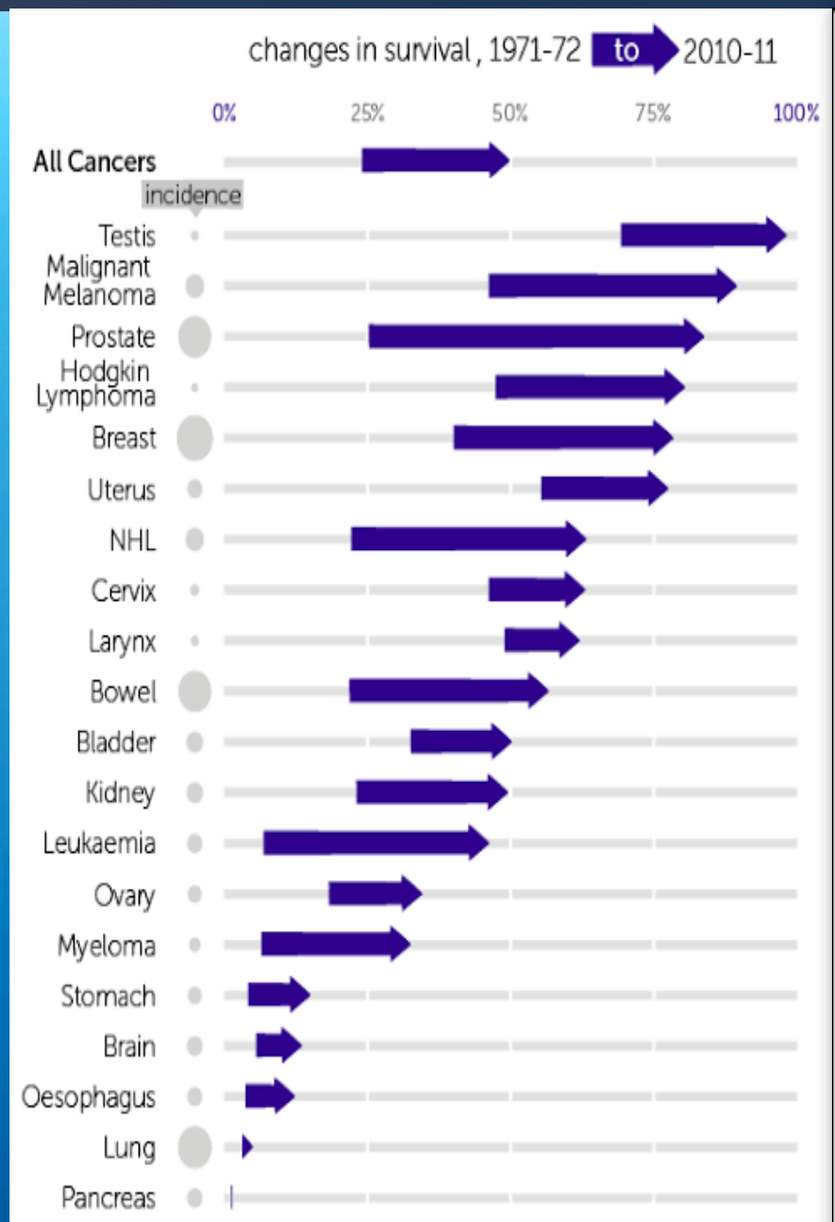
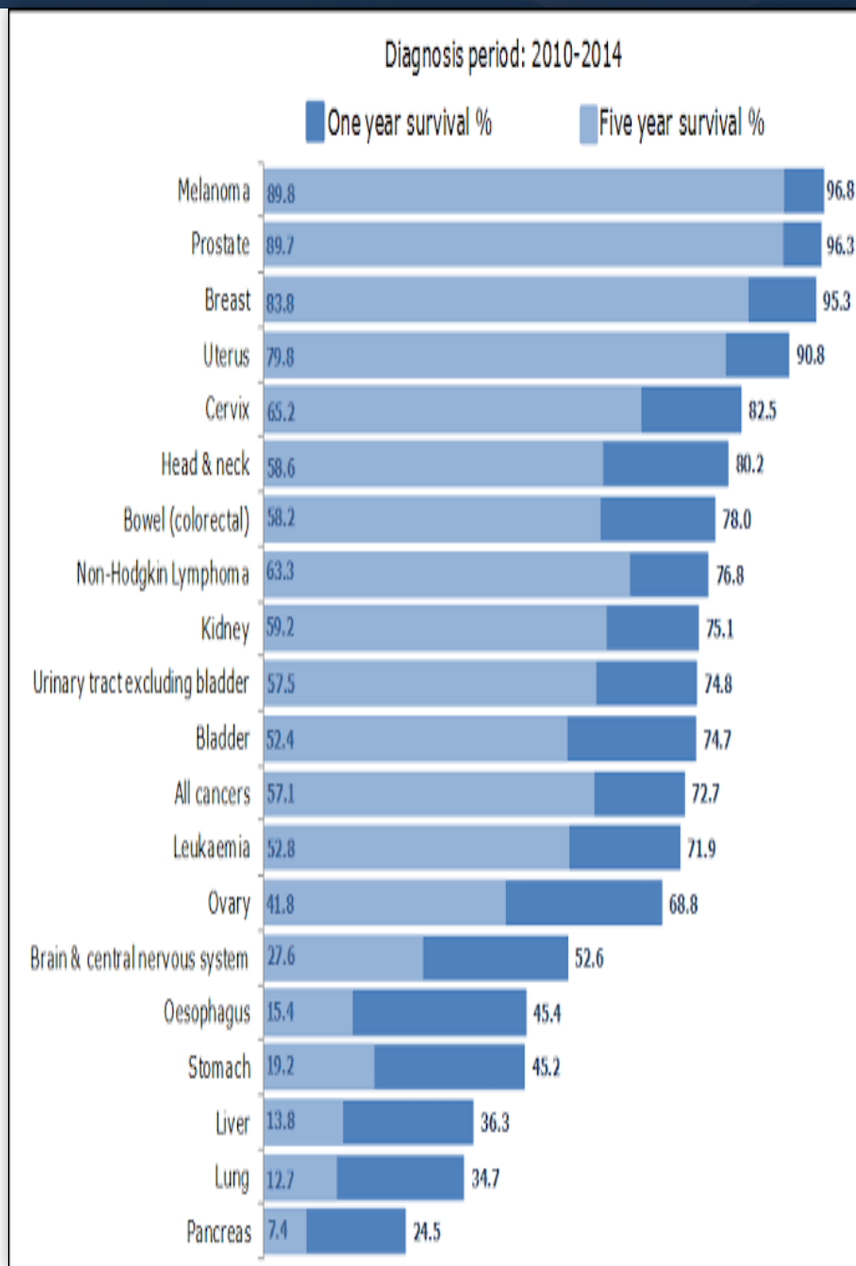
CANCER PAIN IS A BIG CONTRIBUTOR

Survival is improving.

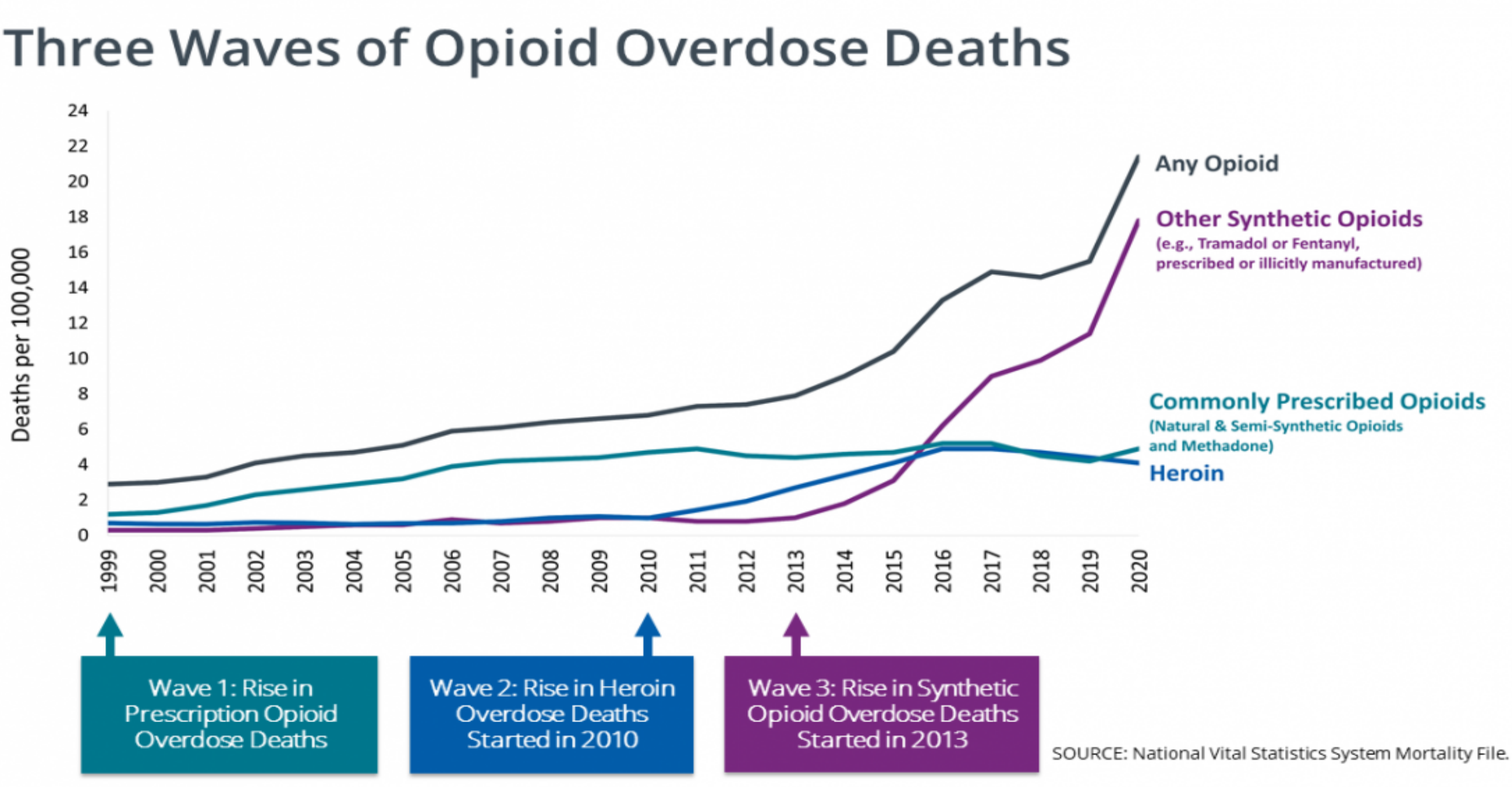
Pain is increasing. Due to

- The underlying cancer
- Surgery pain
- Radiotherapy
- Chemotherapy





But the cure comes at a cost



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Summary of Demographics

Pain is a growing problem

- Opioid treatments have been rising
- Deaths are rising with and from this

We are getting older

- More age related diseases that cause pain
- Degenerative diseases
- cancer - with more cancer survivors

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History and politics

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nytimes.com

The New York Times

Top Executives of Insys, an Opioid Company, Are Found Guilty of Racketeering

John Kapoor, the founder of Insys Therapeutics, at federal court in Boston.

Steven Senne/Associated Press

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

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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Australian Government

Changes to opioid prescribing

- Second opinion for longer term opioid use
- Restrictions on fentanyl patches
- Real time prescription monitoring

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FACULTY OF PAIN MEDICINE - RECOGNITION OF CHANGE

Generational change in the FPM against high dose opioids

LACK OF EVIDENCE OF BENEFIT/ EVIDENCE OF HARM

Drive to look at alternatives

Non-opioids and non-traditional opioids.

Procedural interventions

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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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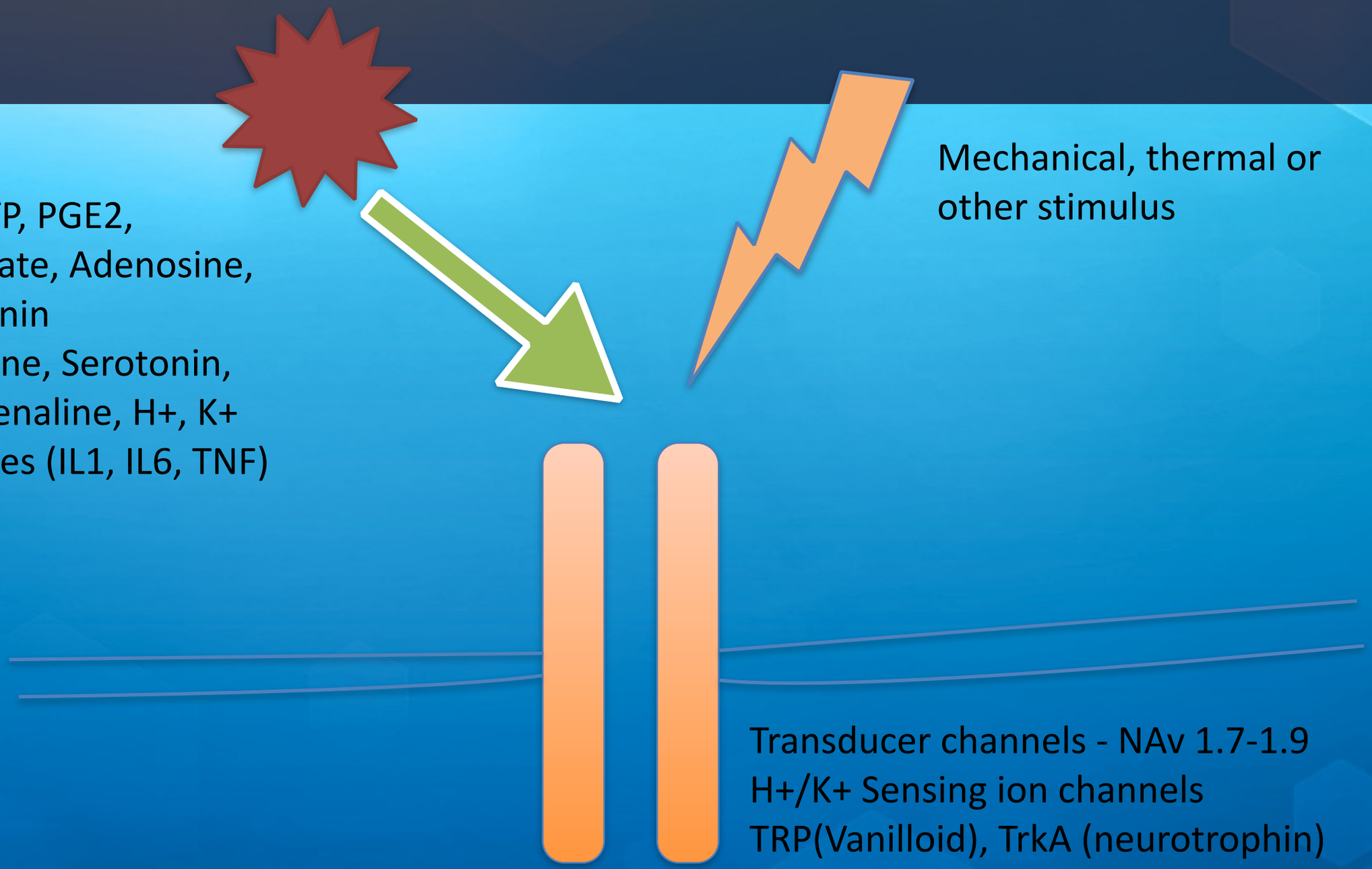
Nociception



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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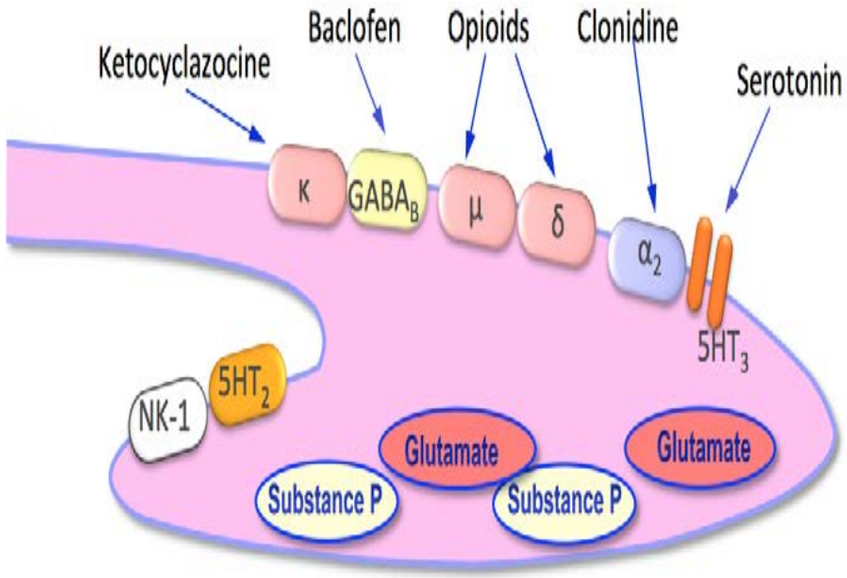

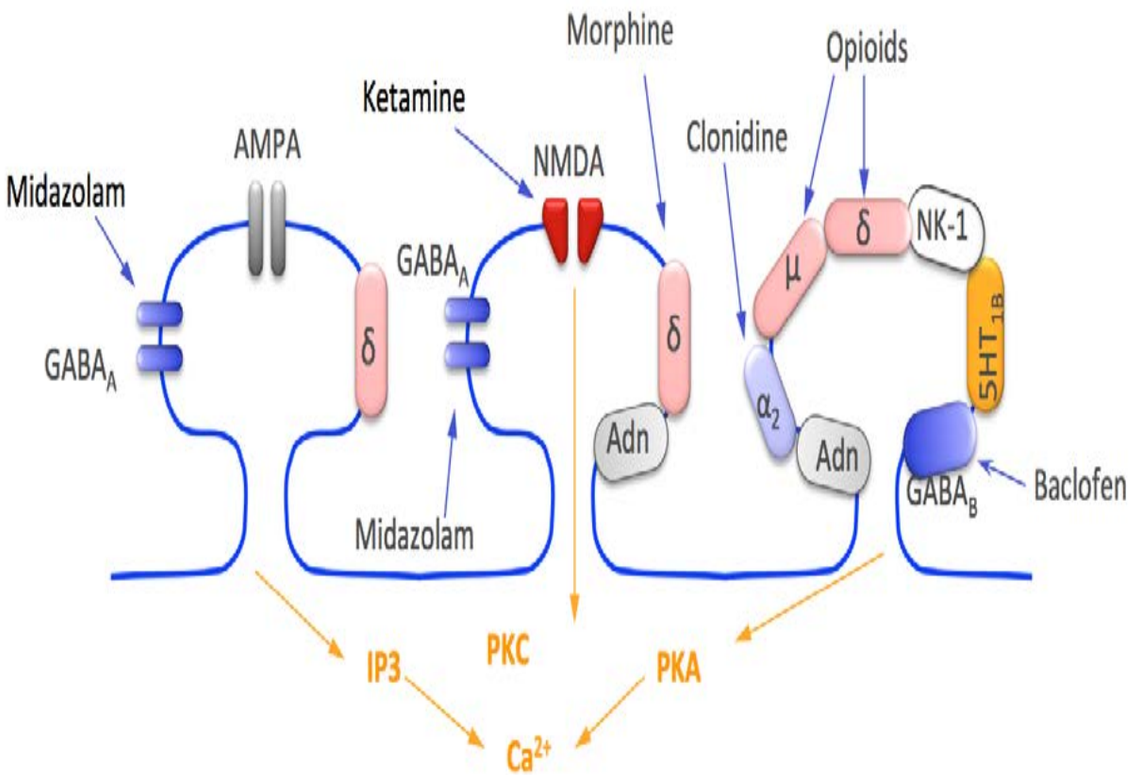

First order Synapse

spinal cord (Lamina II, V)

Presents most of our pharmacological opportunities

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The Dorsal Horn

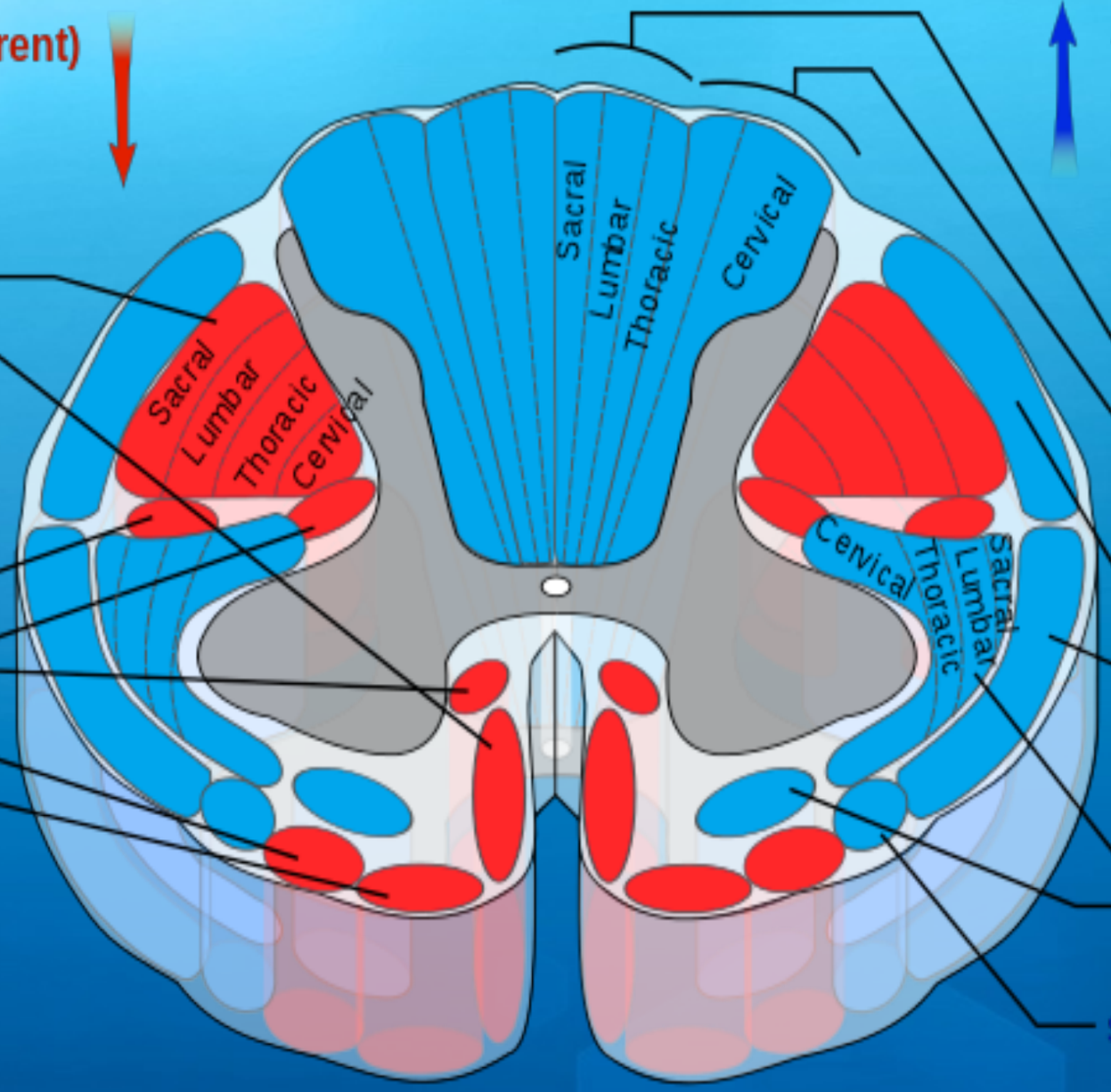
Motor and descending (efferent) pathways (red)

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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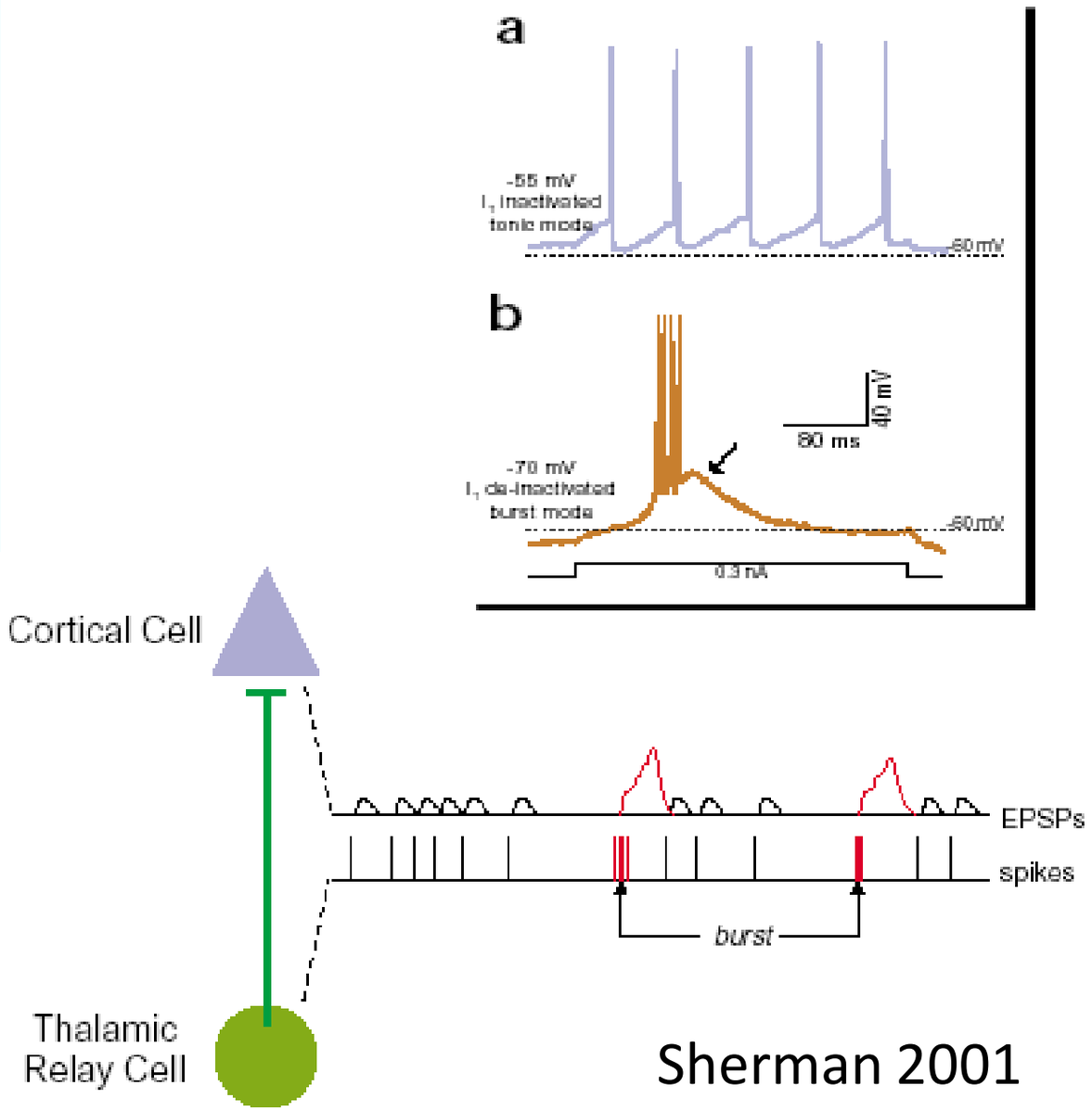

SIGNALLING OF PAIN

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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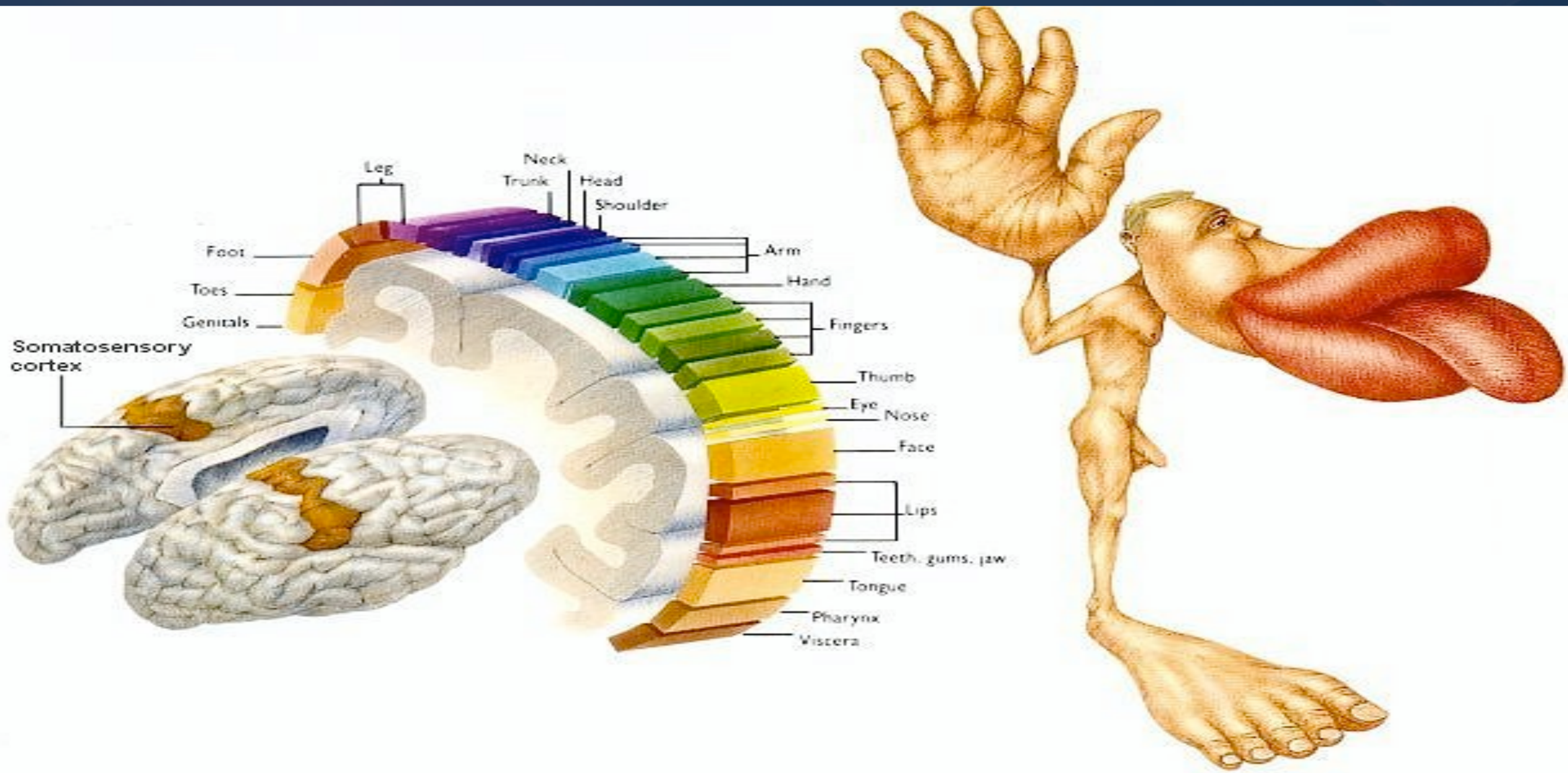
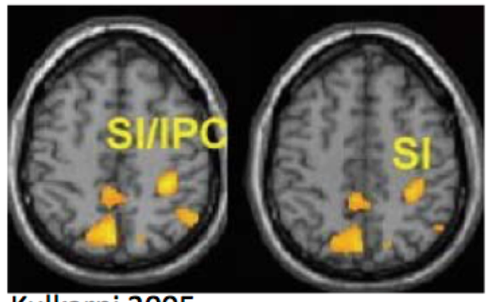
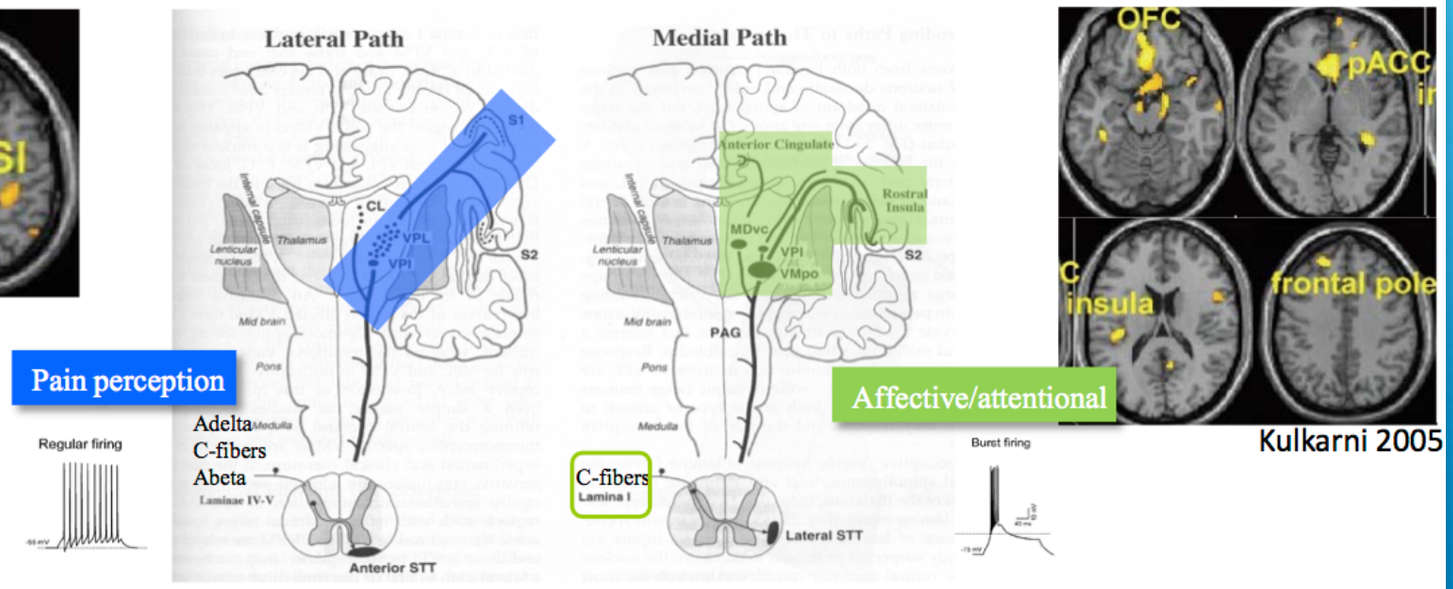
Somatosensory Cortex



Two Pain Pathways



Kulkarni 2005



Kulkarni 2005

Lateral System (Pain Perception)

WDR neurons

Firing in tonic mode

Lamina I, V-VI

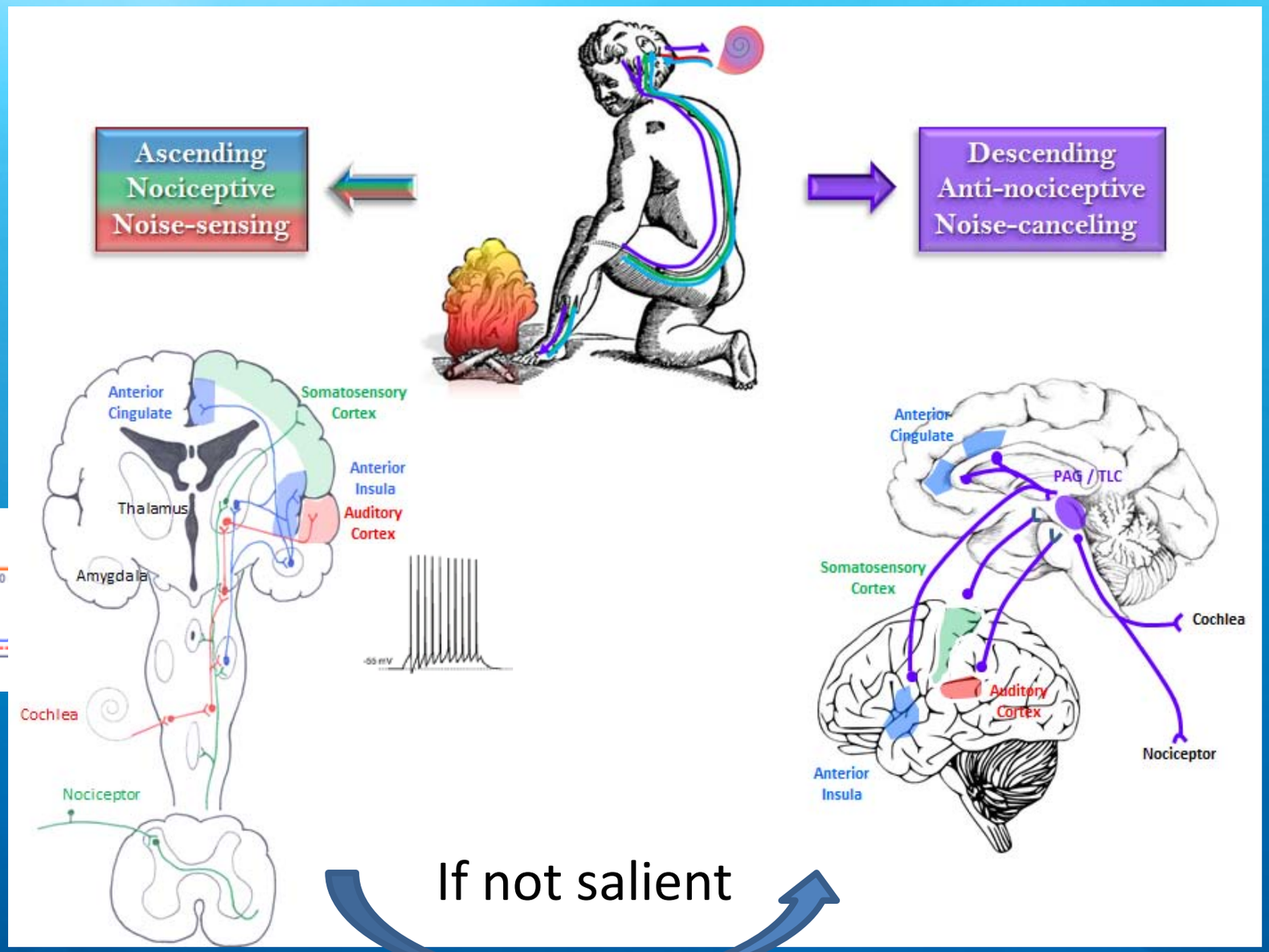
Medial System (Affective)

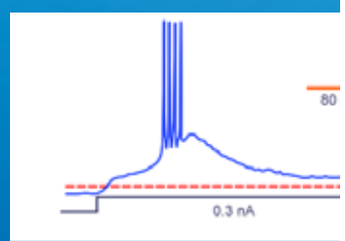
Nociceptive neurons

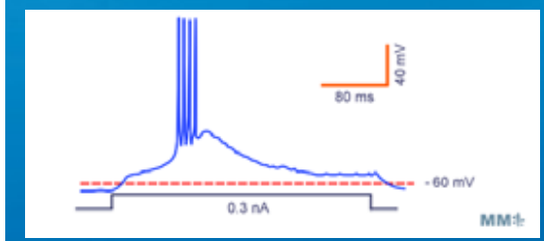
Fire in burst

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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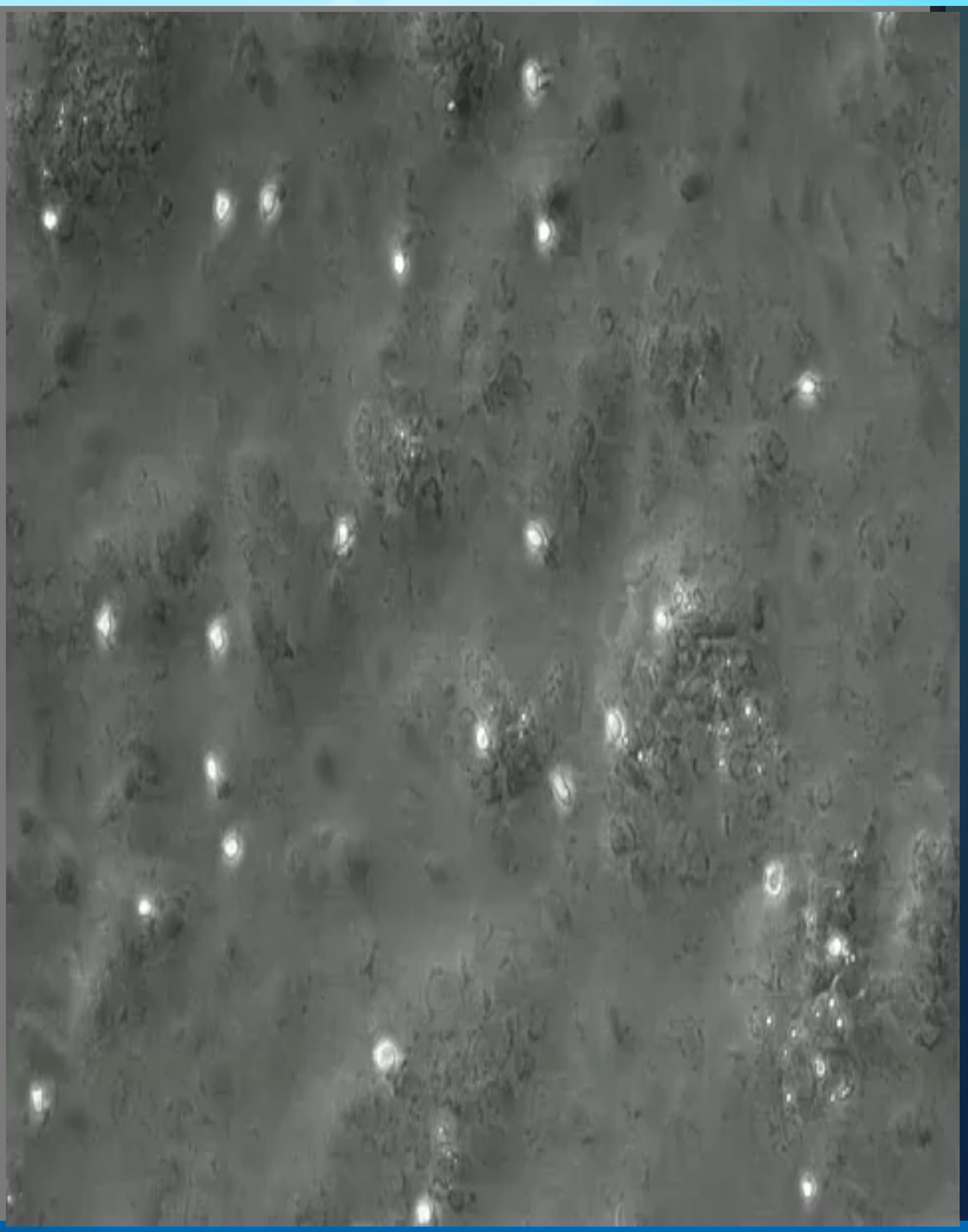

Microglia

Constantly survey the brain

Touch every part of the brain 3x / hour

Rapidly respond to injury

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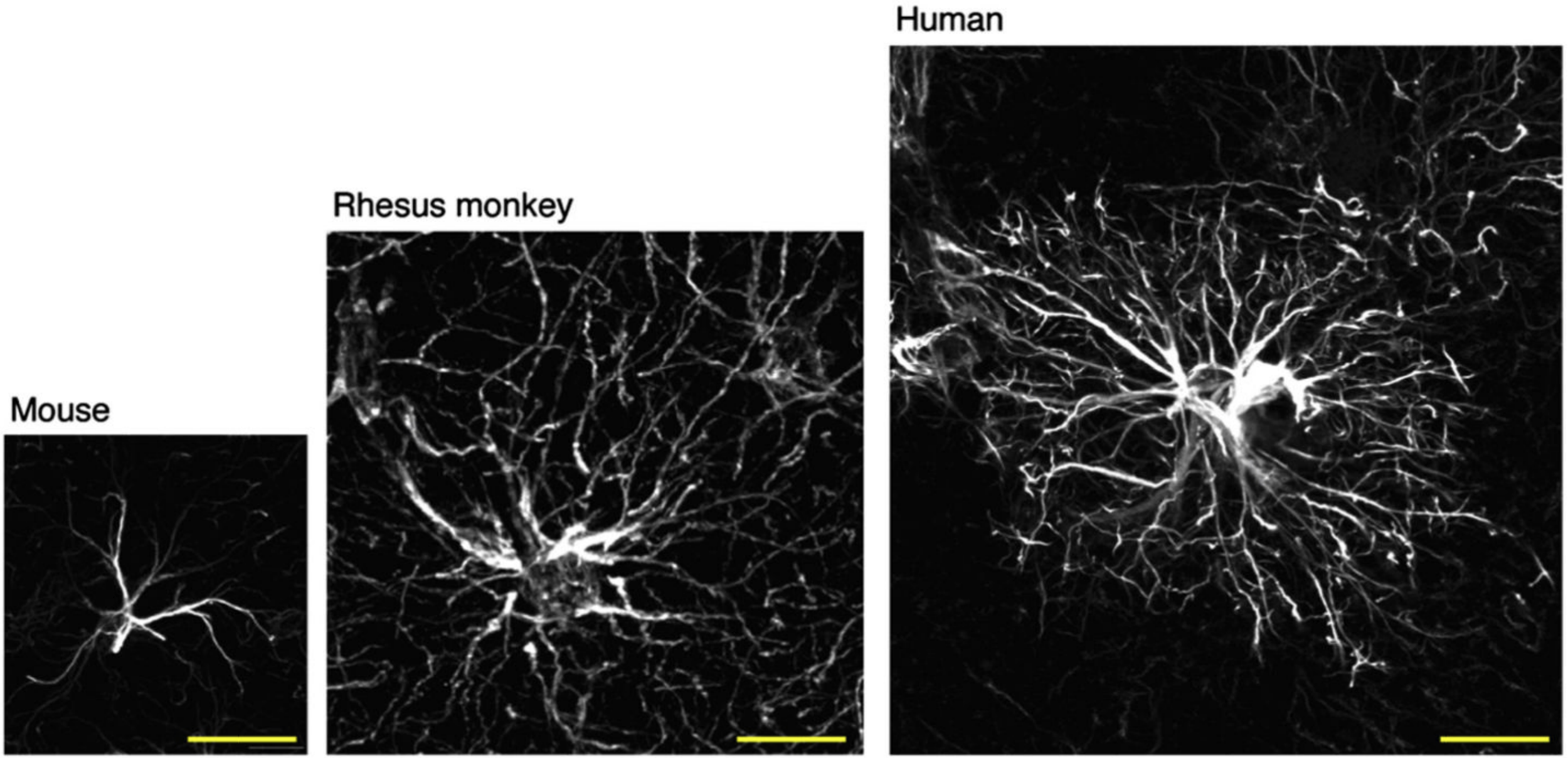
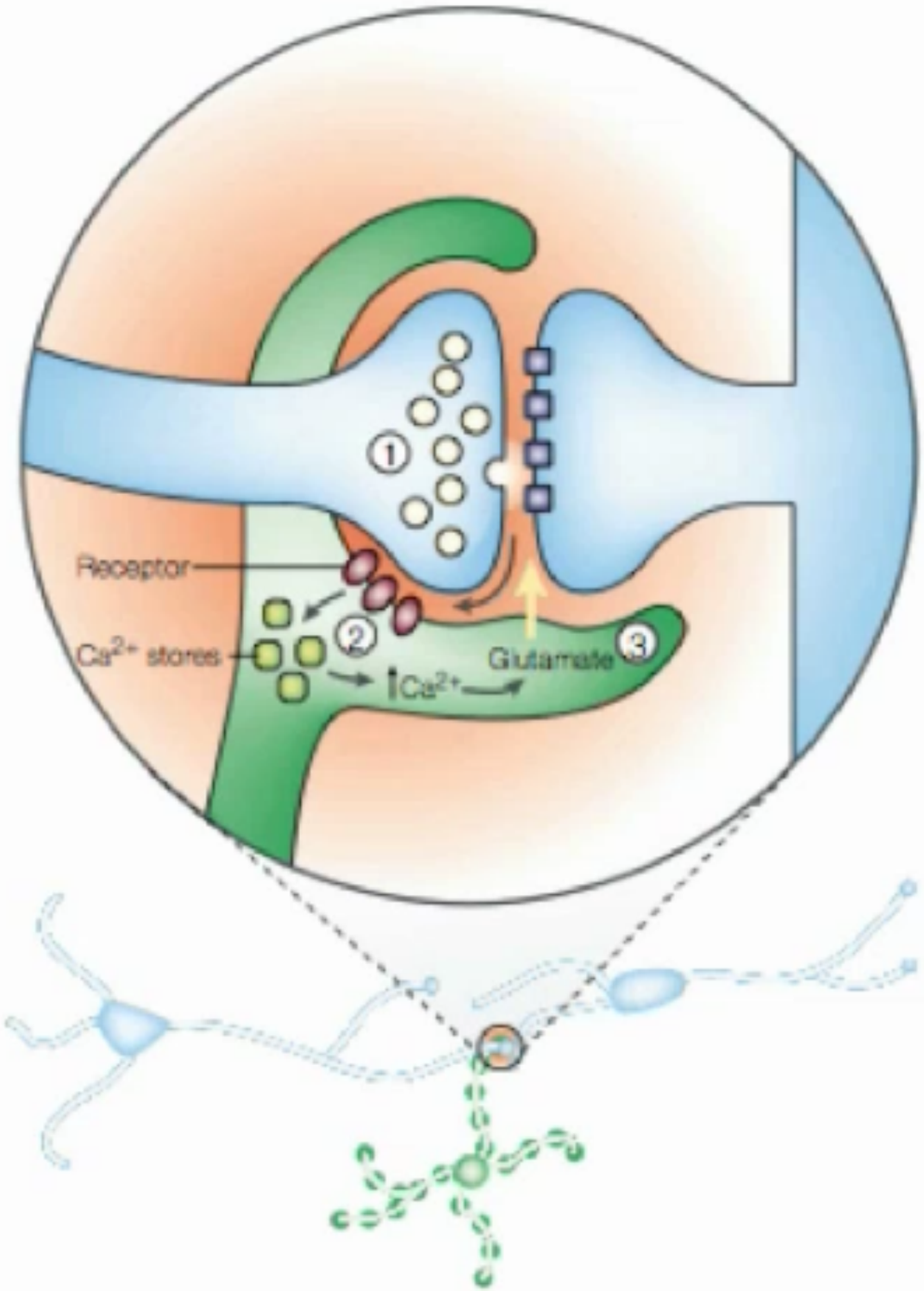
Astrocytes





Astrocytes

The tripartite synapse

- Astrocytes modify the transmission of signals

Glutamate take up by

- GLAST
- GLT-1

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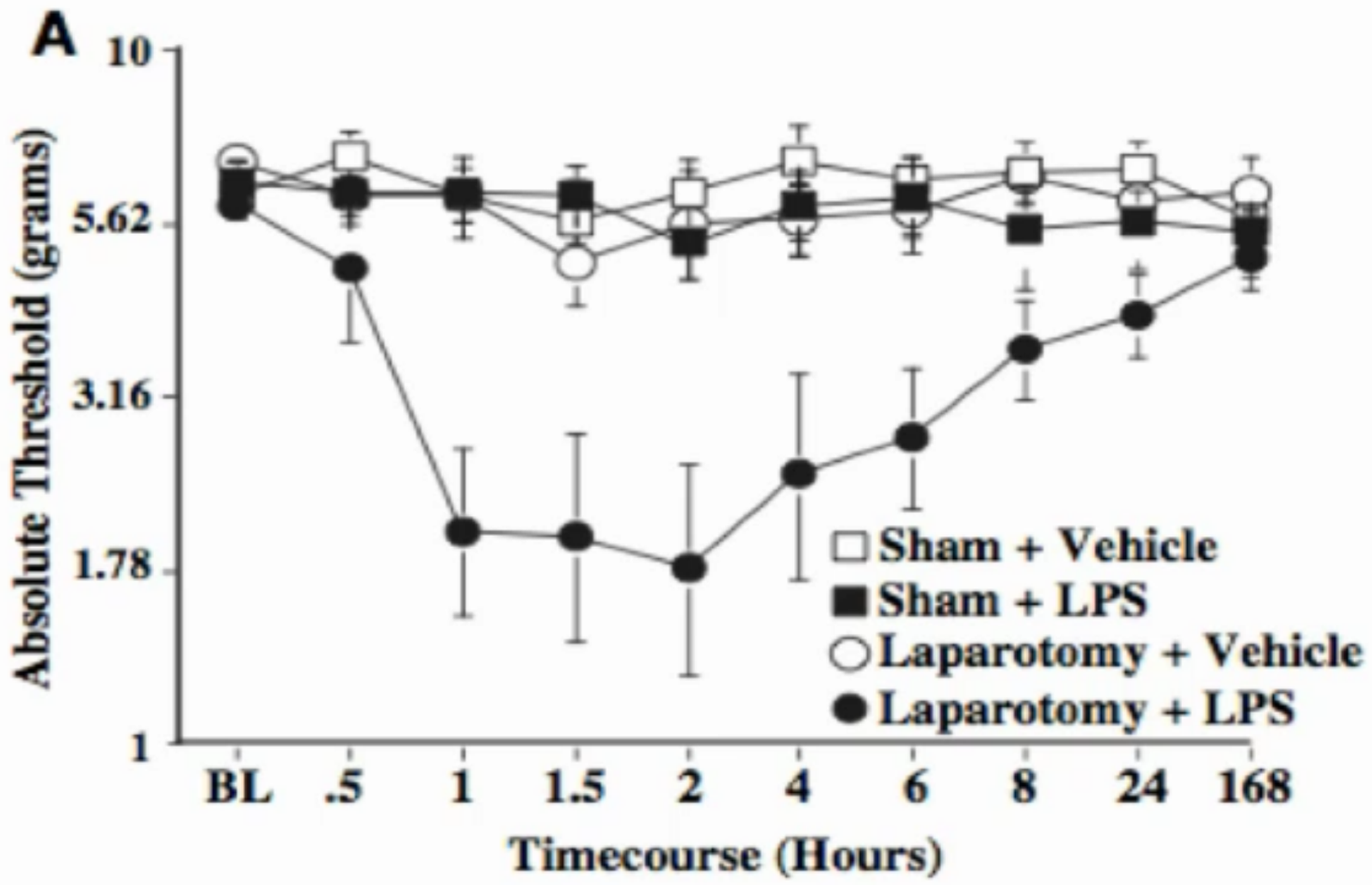
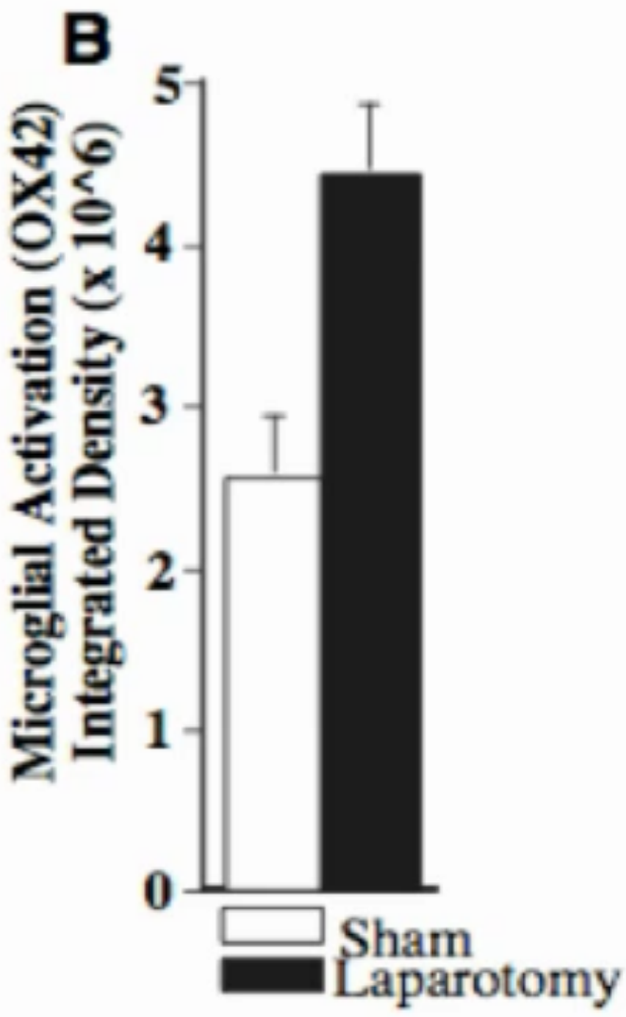
Allodynia 2-hit hypothesis





Hains et al, 2011

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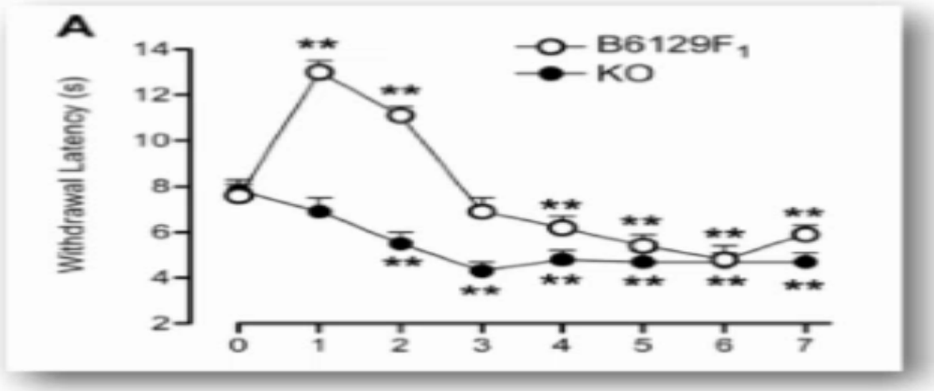
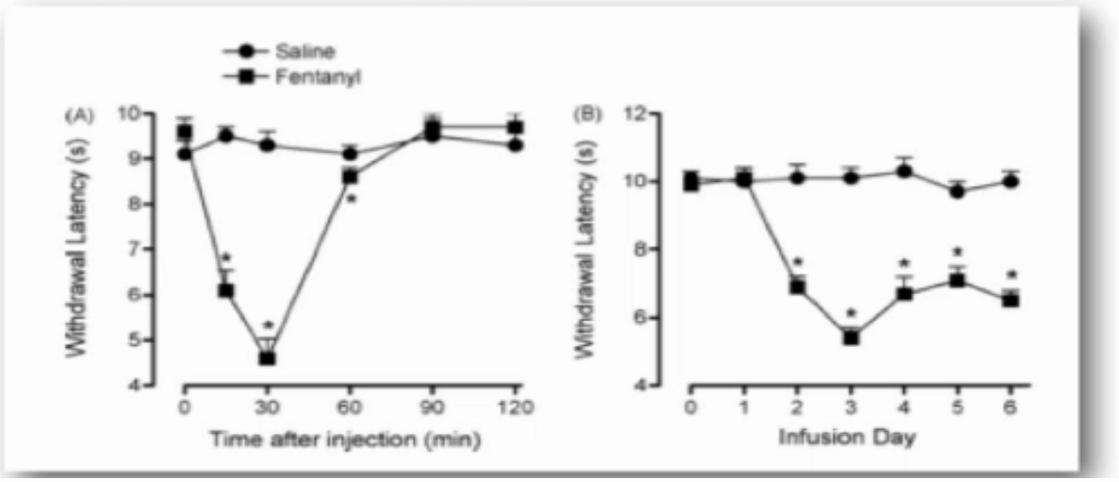
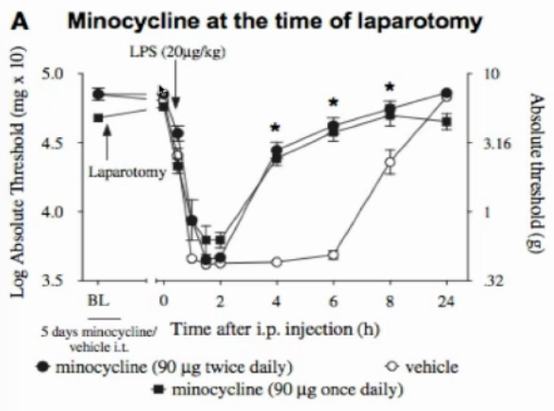
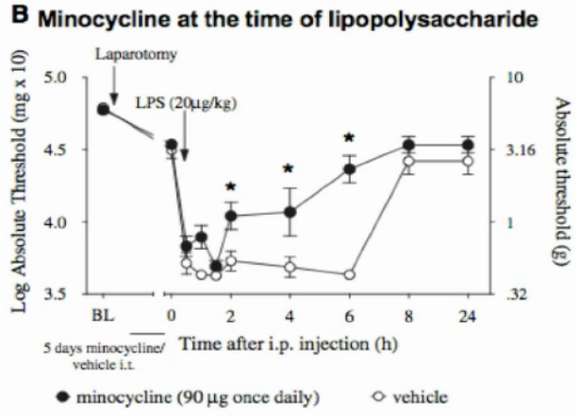
Juni et al 2007



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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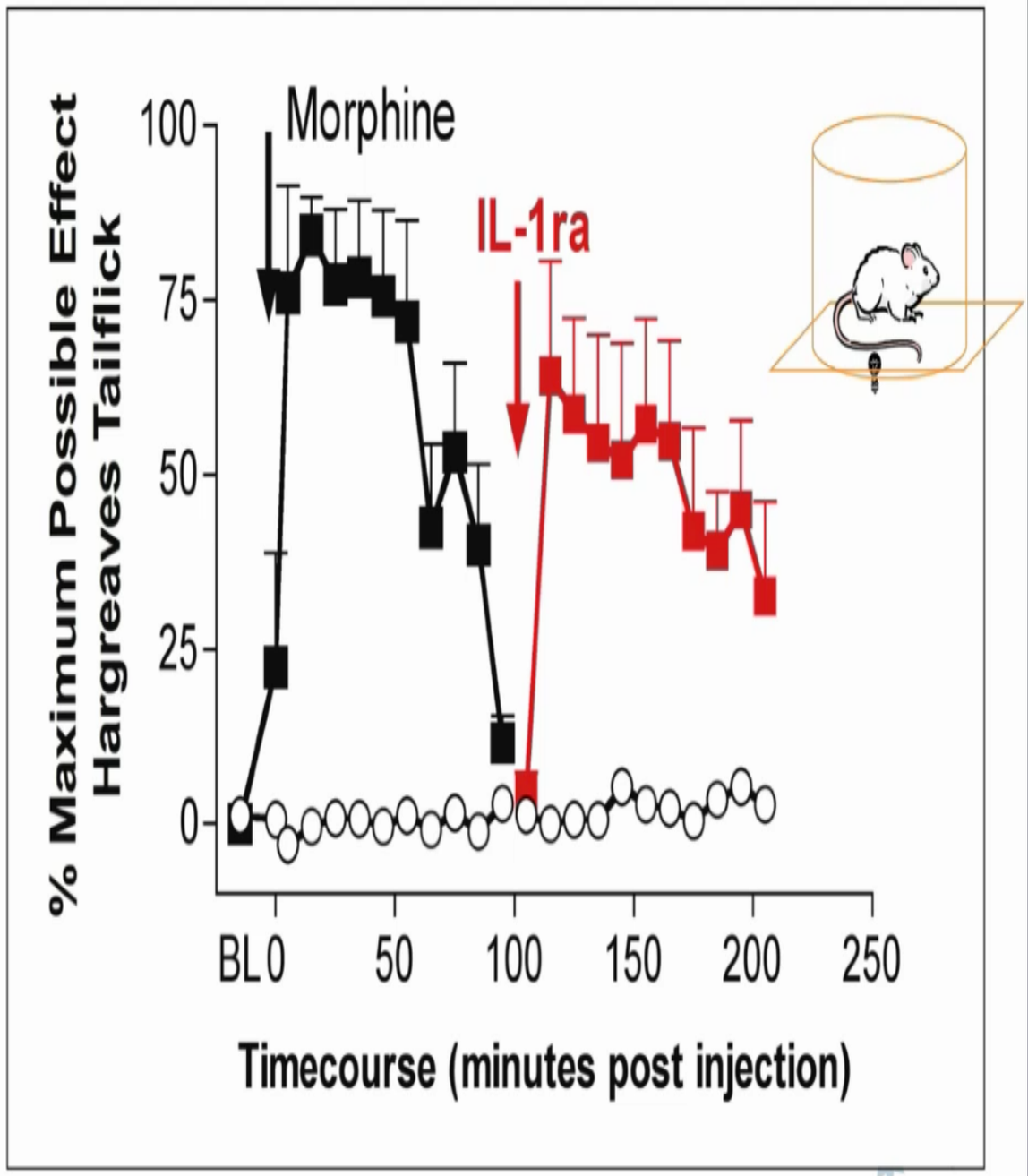

Hutchinson et al 2008

BLOCKING IL-1 RESTORES ANALGESIA

Morphine antagonises its own action

The mechanism for antagonism isn't via opiate receptors

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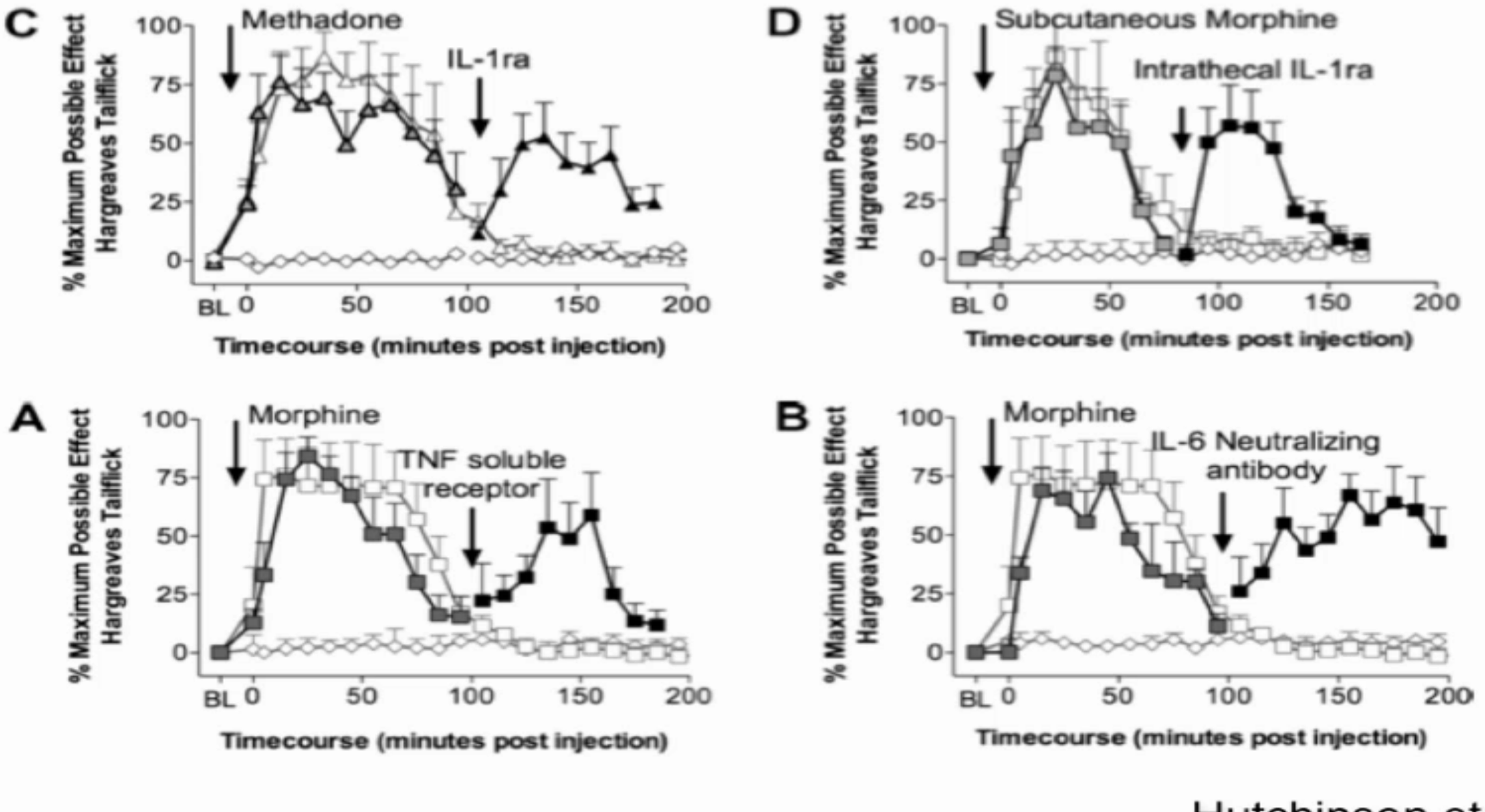
Its not just morphine and IL-1



Hutchinson et al 2008

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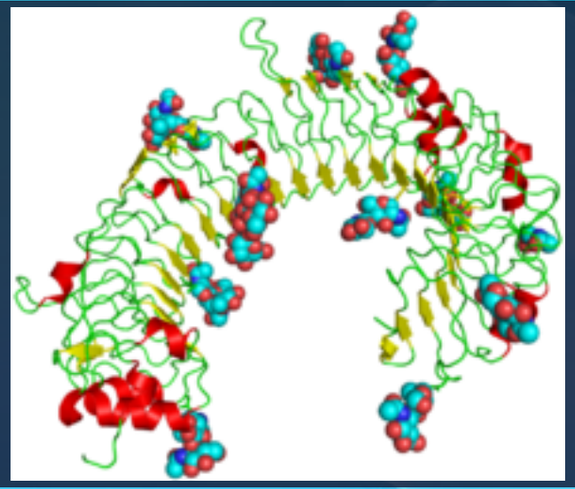
Toll Like Receptors



Part of innate immune system

- Pre-formed response to pathogens
- Present in most species
- Modulate an inflammatory response

TLR-4 is preformed towards lipopolysaccharide as a target.

Receptor	Ligand
TLR-1	Bacterial Lipoprotein
TLR-2	Gram positive Bacteria
TLR-3	Viruses
TLR-4	Gram negative Bacteria
TLR-5	Toxoplasma
TLR-6	Mycoplasma
TLR-7	RNA viruses
TLR-8	RNA Viruses
TLR-9	Bacteria, DNA virus
TLR-10	???
TLR-11, 12	Toxoplasma,
TLR-13	Bacterial Ribosome

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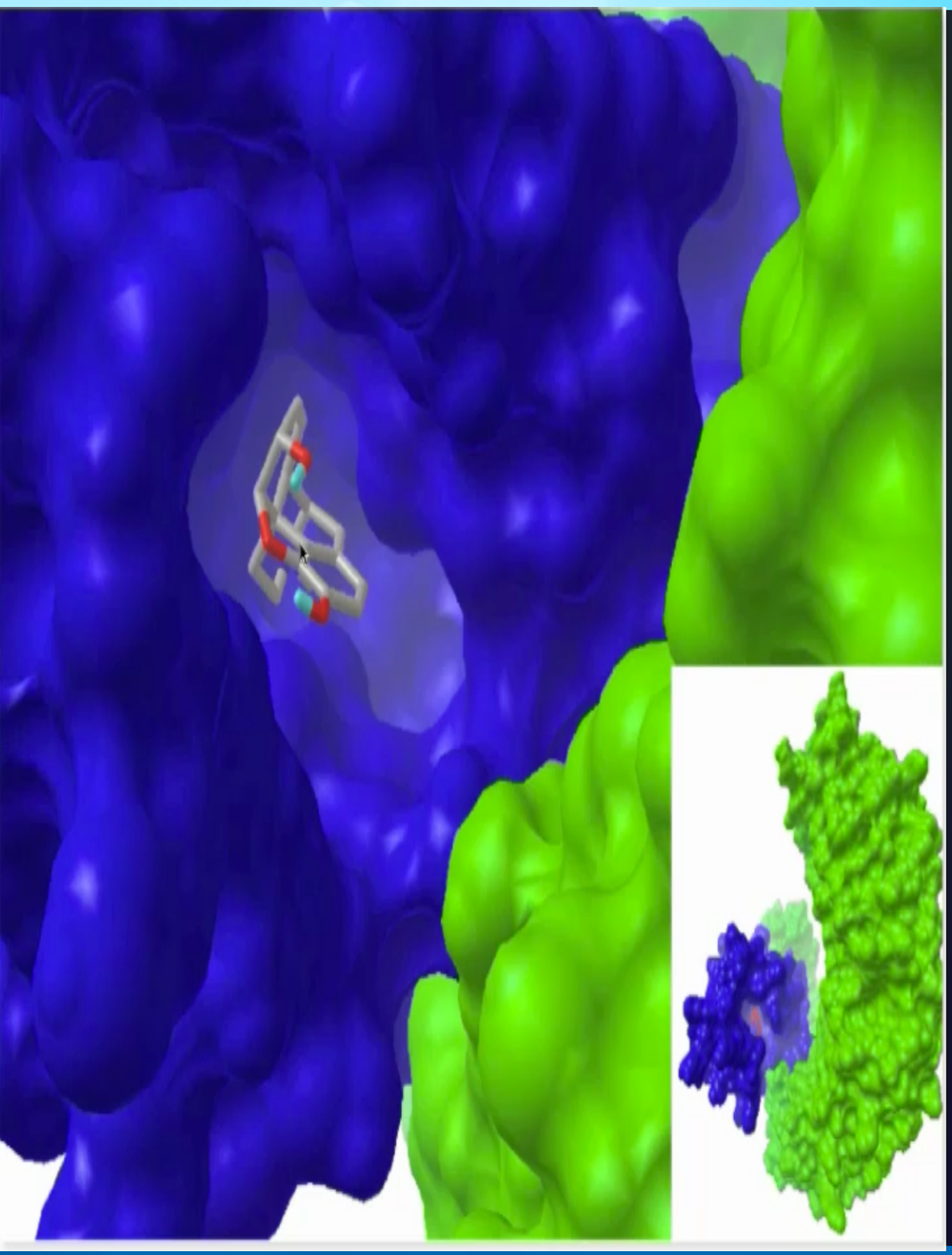

Morphine and TLR-4

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

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Summary

Pain messaging is modulated at the spinal cord level

Glutamate is the main pain messenger

Removal of glutamate messaging is impaired with neuroinflammation

Opioids cause neuroinflammation, probably via TLR-4 activation.

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Do Opioids Work?

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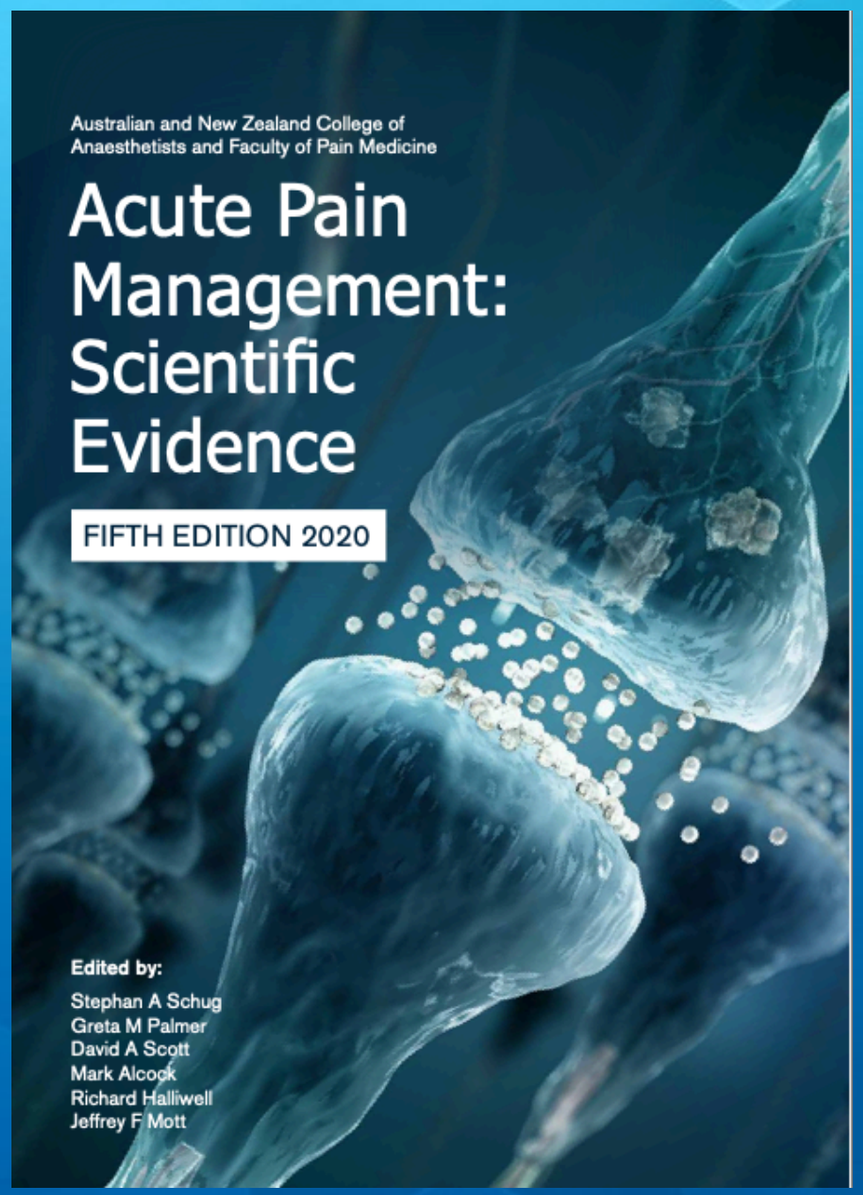
Efficacy of opioids

Clearly effective in acute pain

- Good Evidence base
- Duration of therapy?

HTTPS://WWW.ANZCA.EDU.AU/APSME5



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Opioids for chronic neuropathic pain

Opioids do provide clinically relevant pain relief (>50% reduction) in some neuropathic pain conditions.

- Very limited evidence base
- Not always generally applicable
- Only for some people
- Need to discount placebo response.

Sommer S et al. Opioids for chronic non-cancer neuropathic pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. Eur J Pain. 2020;24:3–18.

DOI: 10.1002/ejp.1494

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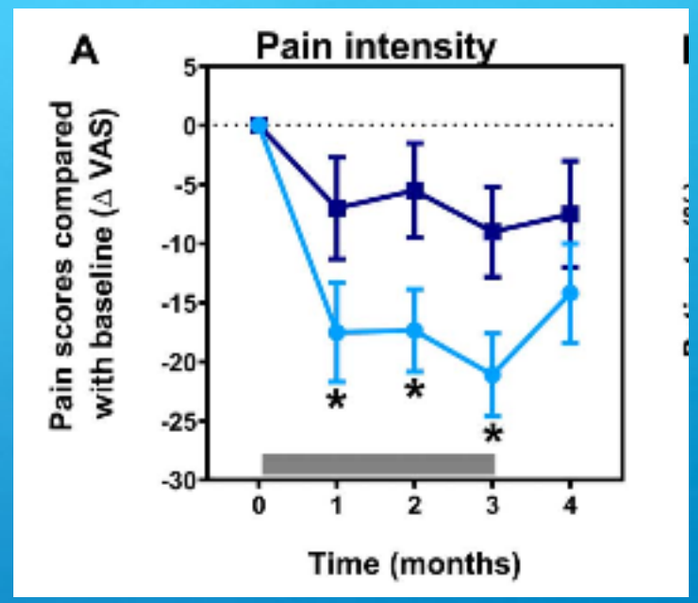
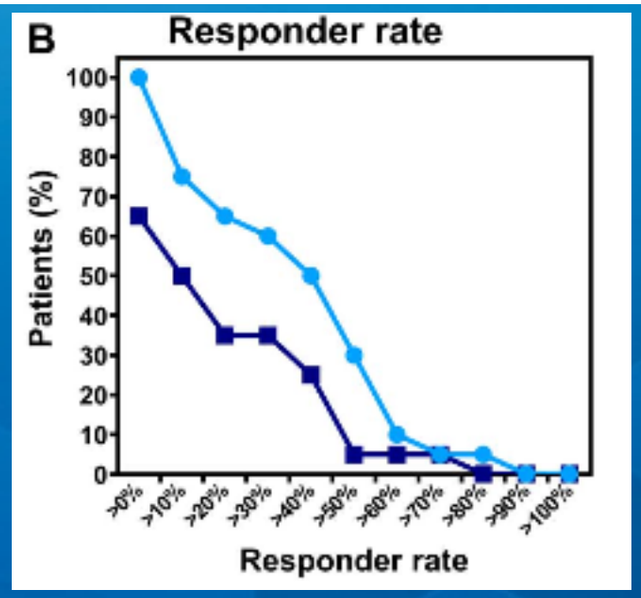
Opioids for chronic pain

Opioids do work - for some people

- Good Evidence base
- Efficacy decreases over time
- Subgroup do benefit.

- In this study significant reduction in temporal summation of pain





Van De Donk T et al. Tapentadol treatment results in long-term pain relief in patients with chronic low back pain and associates with reduced segmental sensitization Pain Reports 5(2020) e877
http://dx.doi.org/10.1097/PR9.0000000000000877

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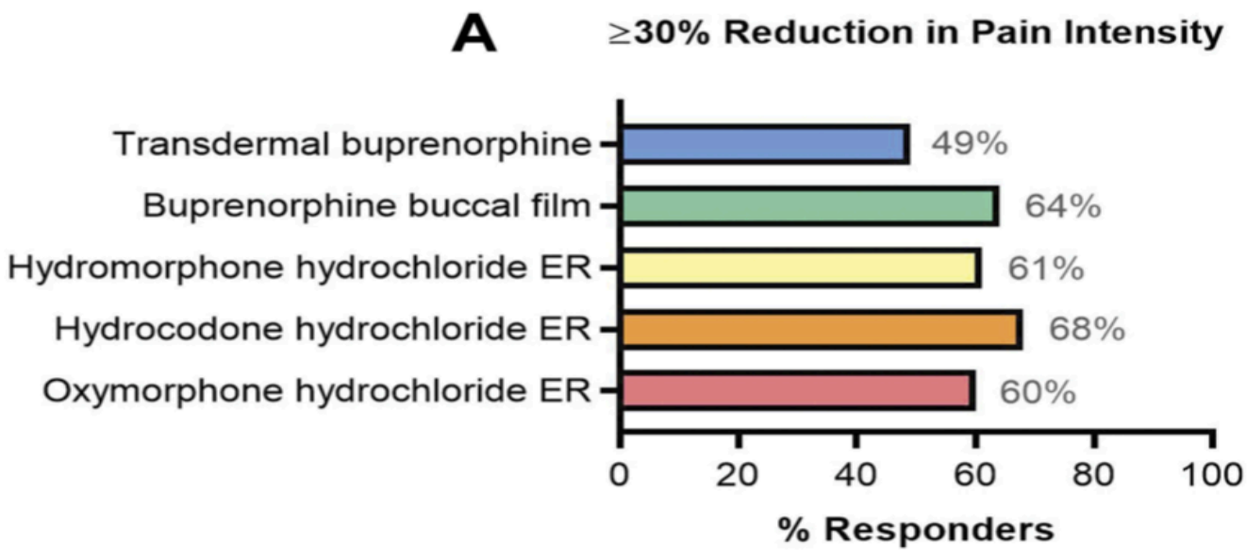
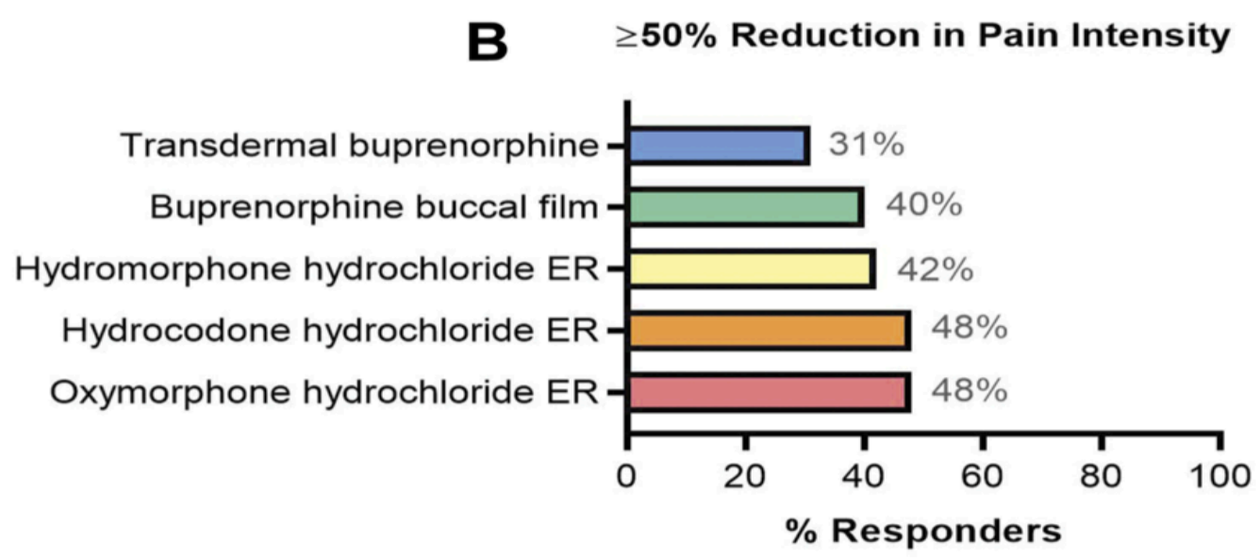
Are they all the same?

More likely to get long term response with some opioids in some people.

Safety And Efficacy Of The Unique Opioid Buprenorphine For The Treatment Of Chronic Pain
Pergoliaai Jr and Raffa. Journal of Pain Research 2019:12 3299–3317
http://doi.org/10.2147/JPR.S231948

Meta-analysis 33 studies - mostly transdermal buprenorphine





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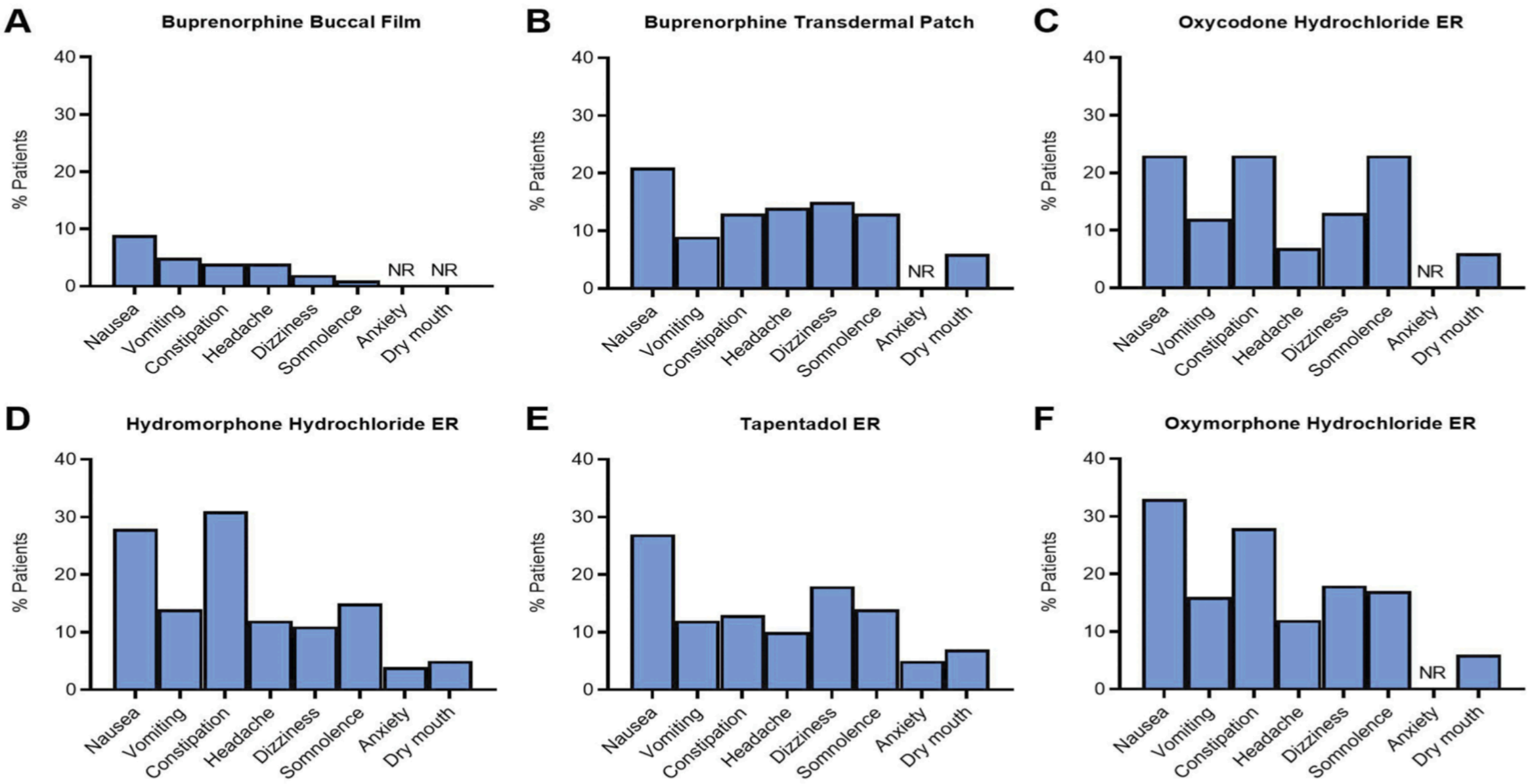
SIDE EFFECTS ARE QUITE DIFFERENT



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Are Opioids Safe?

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Opioids are not all the same

Mortality figures (amongst other data) do seem to vary depending on opioid used.

Event	Opioid Prescribed				
	Hydrocodone Bitartrate (n=6275)	Codeine Phosphate (n=6275)	Oxycodone Hydrochloride (n=6275)	Propoxyphene Hydrochloride (n=6275)	Tramadol Hydrochloride (n=6275)
All-cause mortality					
No. of events	32	57	60	49	46
Person-years	1120	793	959	1510	1272
IR (95% CI)	3 (2 to 4)	7 (5 to 9)	6 (5 to 8)	3 (2 to 4)	4 (3 to 5)
RR (95% CI)	1 [Reference]	2.53 (1.70 to 3.76)	2.25 (1.52 to 3.34)	1.32 (0.88 to 1.98)	1.44 (0.96 to 2.17)
RD (95% CI)	1 [Reference]	4 (2 to 5)	3 (2 to 5)	1 (–0.3 to 2)	1 (–0.1 to 2)

The Comparative Safety of Opioids for Nonmalignant Pain in Older Adults
Solomon D et al. Arch Intern Med. 2010;170(22):1979-1986

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Some people are at increased risk

Well established social risk factors

- Familial abuse
- Drug and alcohol use history

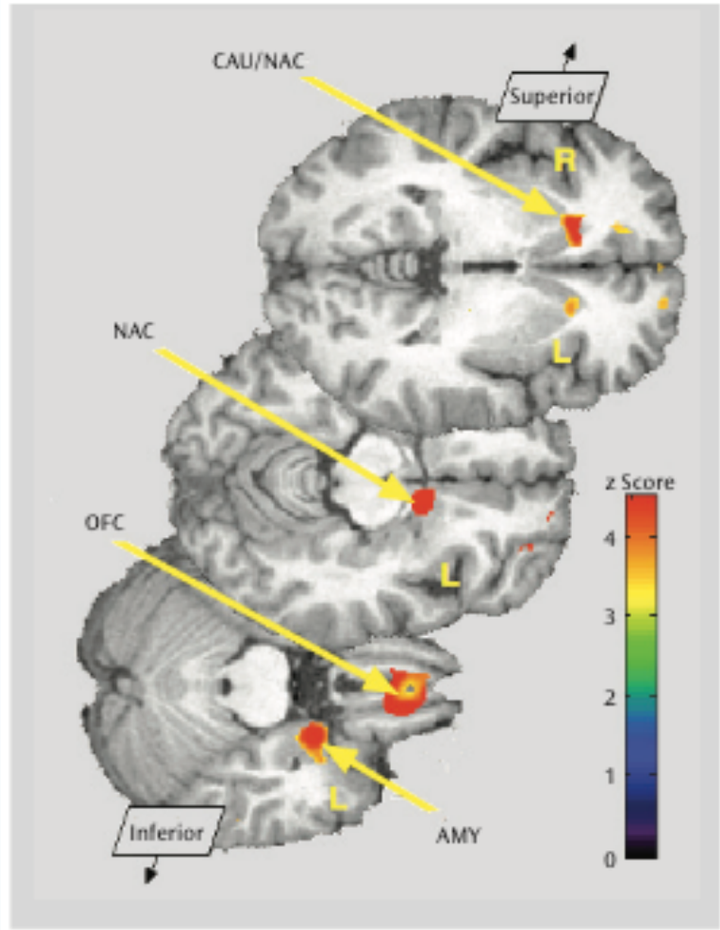
50% of risk is environmental

There are underlying biological drivers for opioid risks

- Borderline Personality Disorder has different μ opioid receptor expression

Dysregulation of Regional Endogenous Opioid Function in Borderline Personality Disorder
Prossin A et al. Am J Psychiatry 167:8, August 2010

FIGURE 2. Greater Regional μ-Opioid BP_{ND} in Patients With Borderline Personality Disorder Relative to Healthy Comparison Subjects[a]



[a] Significant z score color values are superimposed over an anatomically standardized magnetic resonance image in axial views. Image data are displayed in radiological convention so that the upper side of the image corresponds to the right side of the brain. CAU=nucleus caudate; NAC=nucleus accumbens; OFC=orbitofrontal cortex, AMY=amygdala.

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Reduced life expectancy

Substantial reduction in life expectancy in people on long term opioids.

Approximately 6x mortality compared to population in one study

Large impact in younger people

Lewer D et al. Journal of Psychiatric Research
Volume 130, November 2020, Pages 435-440
https://doi.org/10.1016/j.jpsychires.2020.08.013

PainScience

Worse outcomes with Surgery

Chronic opioid use prior to abdominal surgery is associated with

- Longer length of stay
- Higher cost of hospitalisation
- More complications
- More readmissions
- No change in discharge destination

Annals of Surgery. 2017 Apr; 265 (4) : 695-701.

Preoperative Opioid Use is Independently Associated With Increased Costs and Worse Outcomes After Major Abdominal Surgery.

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Opioid Safety

Opioids are not equally safe for all people

Not all opioids are equally safe

Longer term use carries higher risk

Higher doses carry higher risk

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Is it safe to stop opioids?

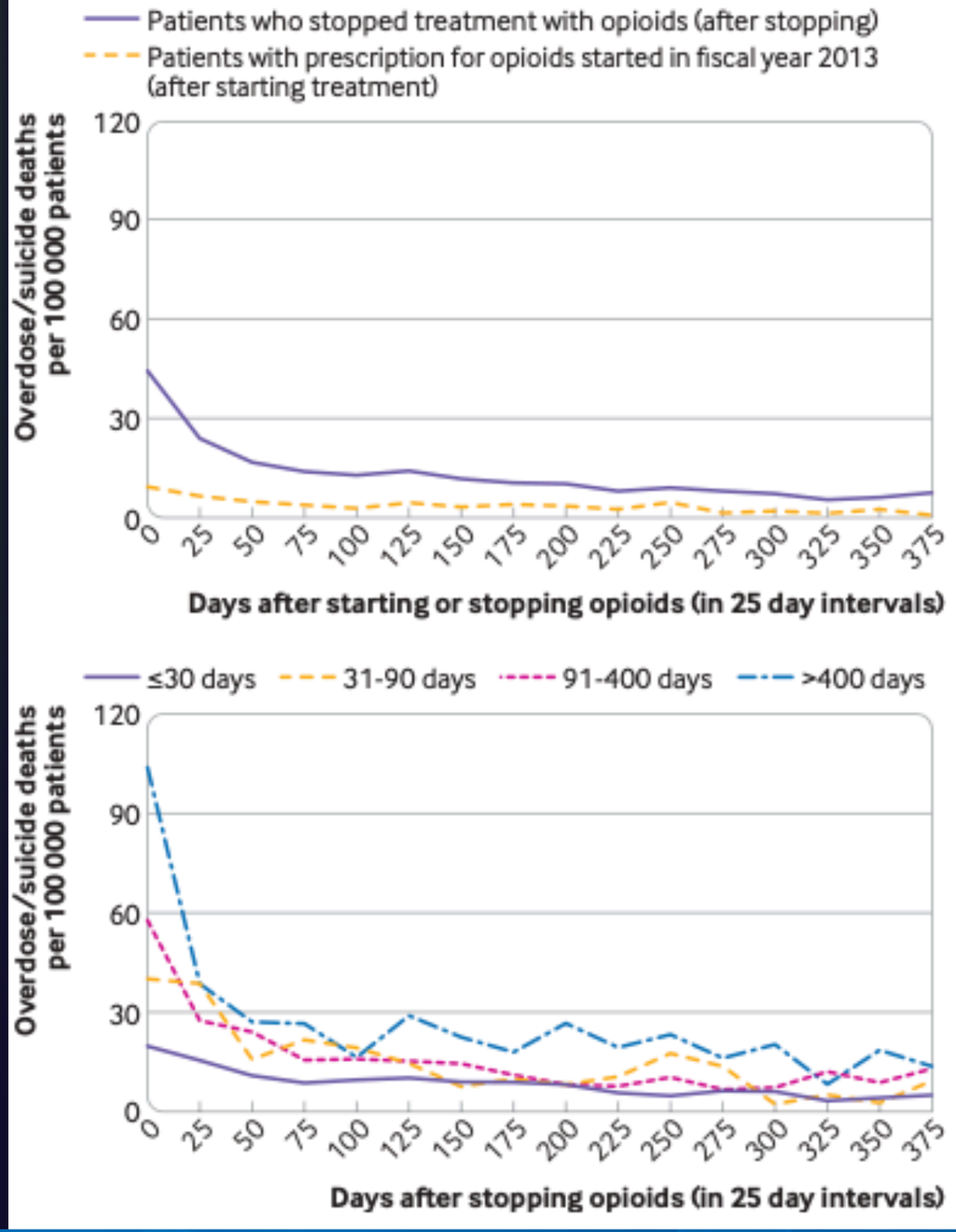
Risks of stopping

Evidence for cessation of opioids is mixed.

Risk of harm exists.

- Increased risk of suicide
- Worse if treated for longer

BMJ 2020;368:m283 | doi: 10.1136/bmj.m283



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Are there alternatives?

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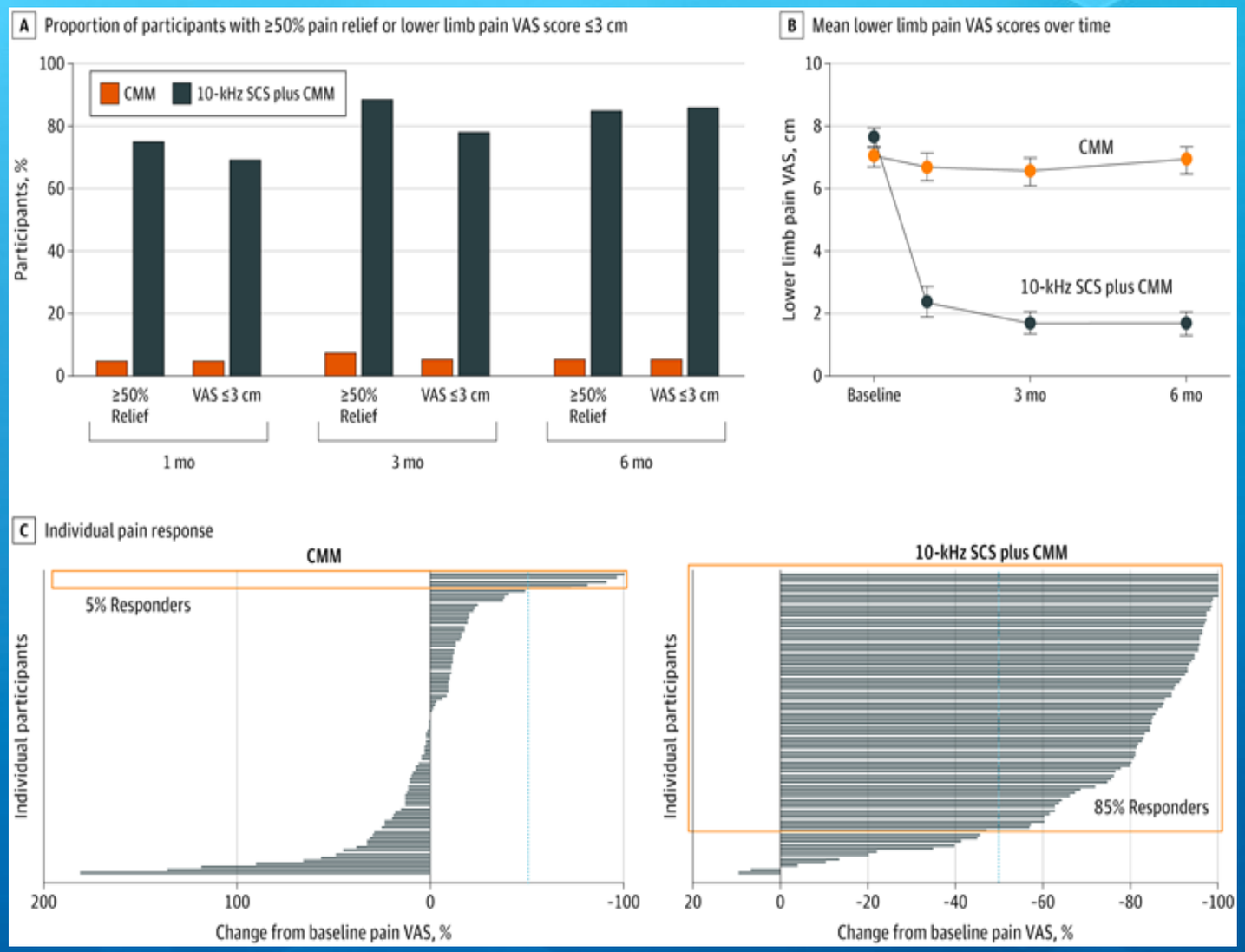
Diabetic Neuropathic Pain

Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy

Petersen EA et al.
JAMA Neurol. 2021; 78(6):687-698

Probably treating ischaemia as well as neuropathic pain.



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Summary
The problem with Opioids

- They work well for some things
  - Mostly shorter term acute and cancer pain
- They work much less well for chronic pain
  - But they still work for some
  - Not all opioids are the same
  - Stopping opioids carries a risk
- They cause neuro-inflammation and pain