The transition of Acute Post-operative pain to Persistent Postoperative Pain: Is it a burden?

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Mental Health and Neuroscience
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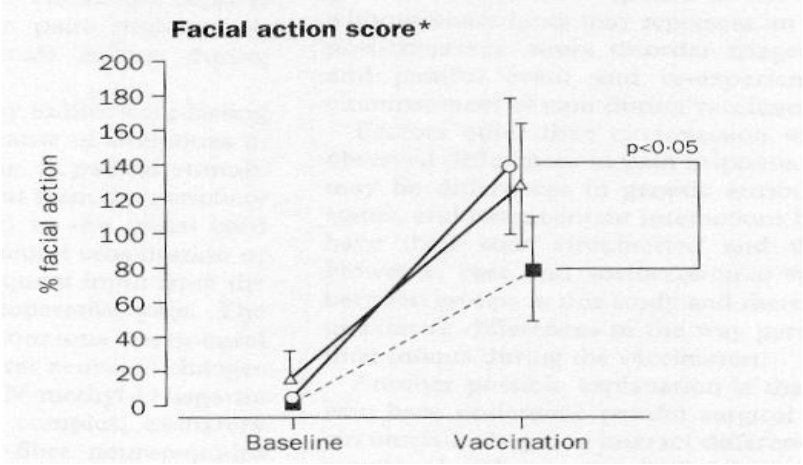
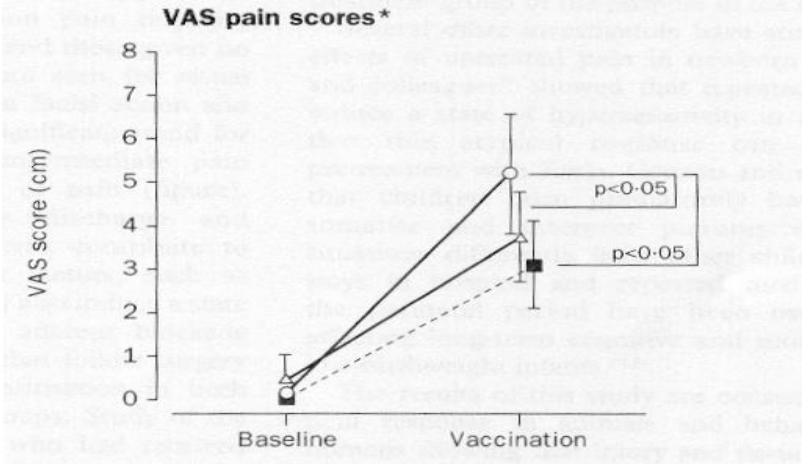
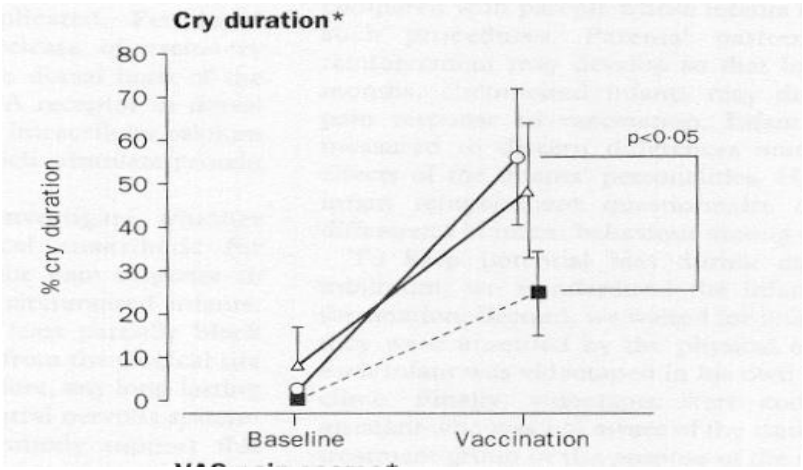
Long term implications: Hyperalgesia

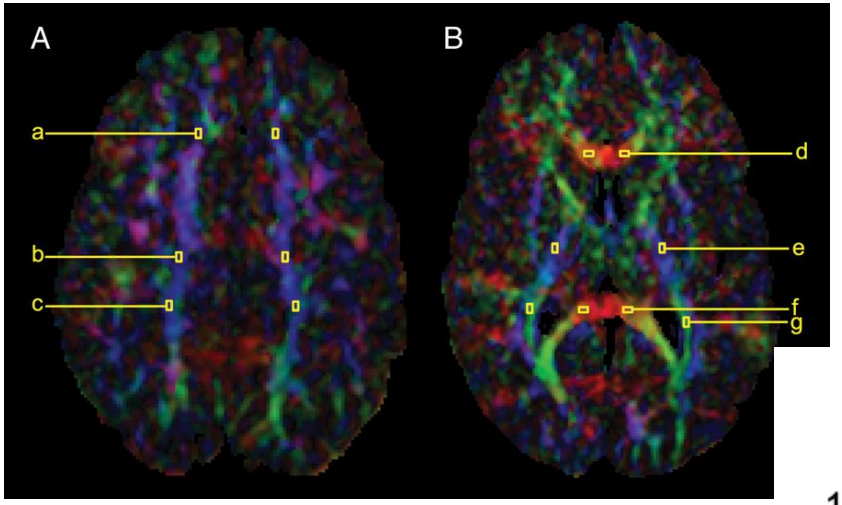


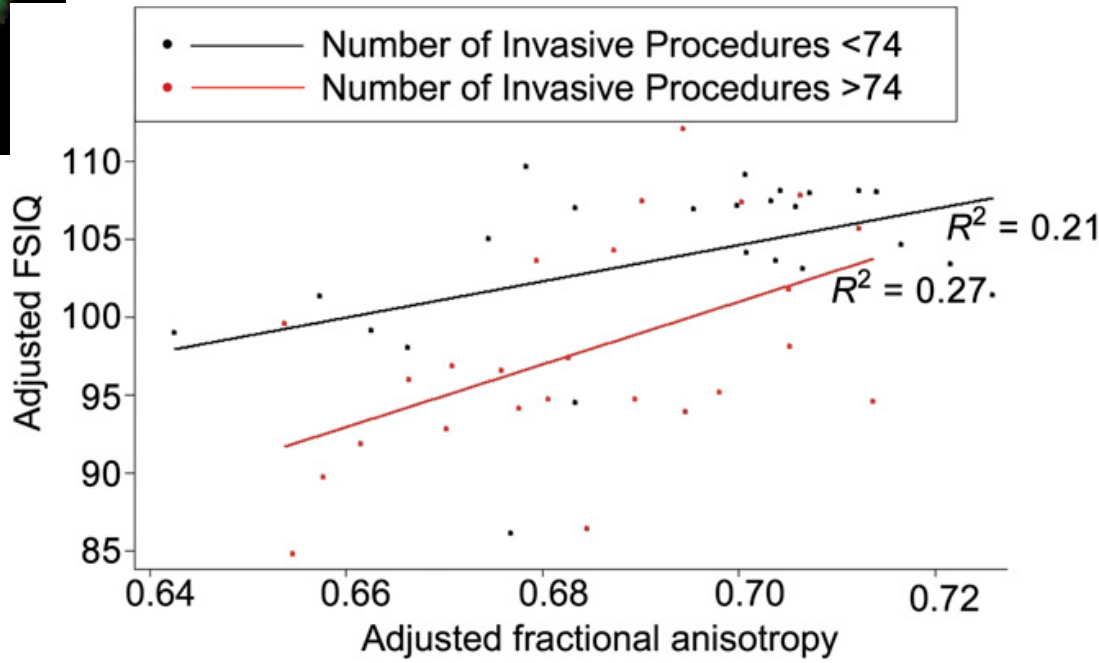




Taddio et al. The Lancet 1997; 349, 599 - 603.

Invasive procedures in Preterm children: Brain and cognitive development at school age





Vinall et al. Pediatrics 2014;133:412-421

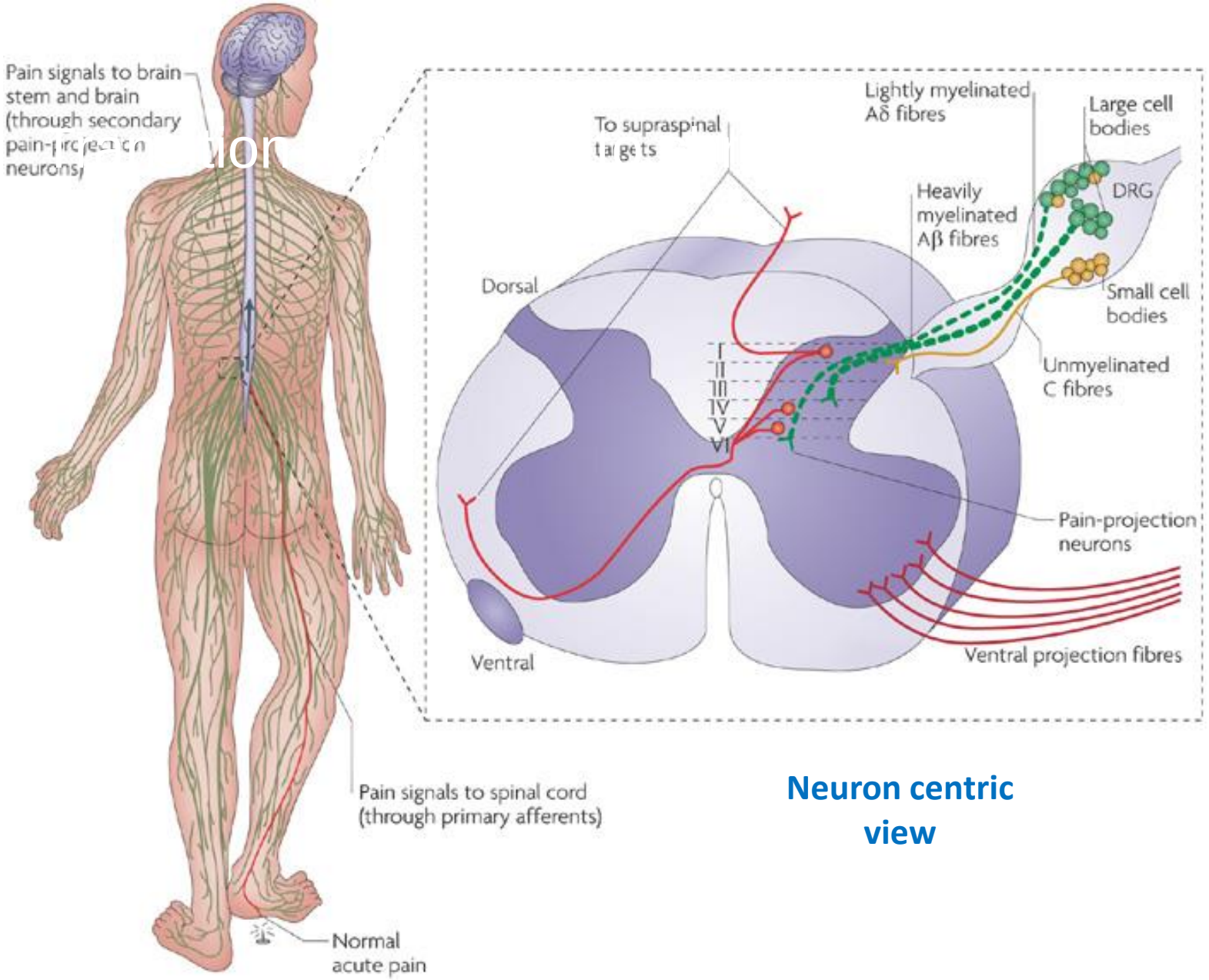
chronic post surgical pain

- The pain must develop after a surgical procedure
- The pain is of at least two months duration
- Other causes for the pain have been excluded
- The possibility that the pain is from a pre-existing condition has been excluded

Macrea & Davies, 1999

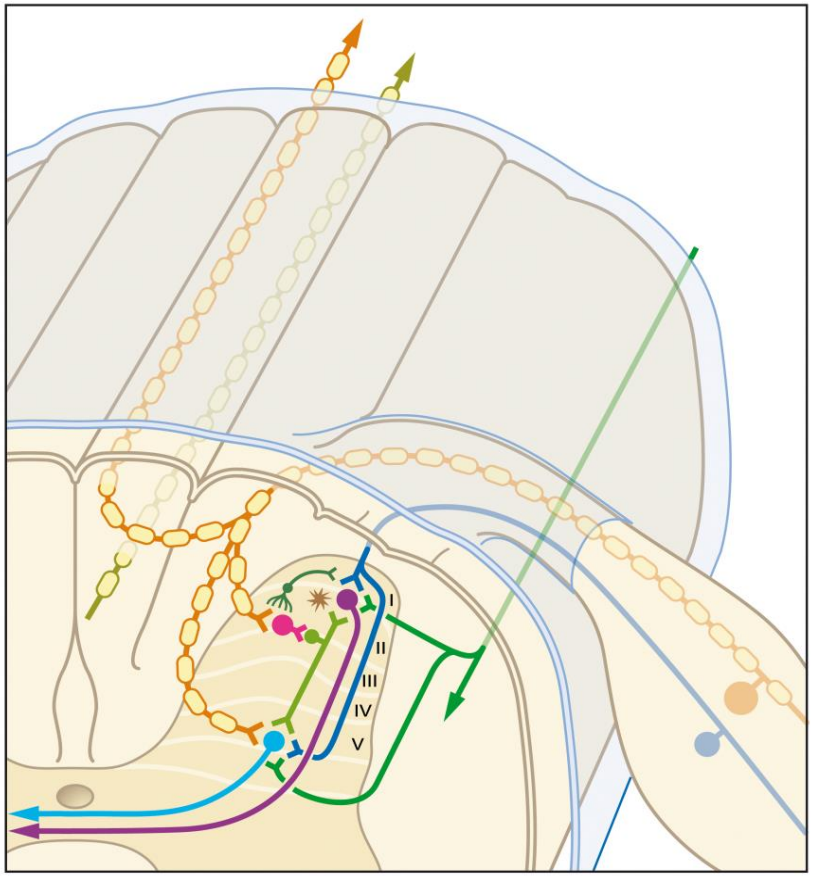
prevalence persistent post surgical pain

	Kehlet 2006	Macrea 2008	Niraj & Rowbotham 2011	Lavand'homme 2011
Amputation	30-50	50-85	27-30	50-85
Thoracotomy	30-40	5-65	52	16-21
Cardiac surgery	30-50	30-55	44	-
Breast surgery	20-30	20-50	48	47
Hip surgery		12	28	12
Hernia repair	10	5-35	12	12
Ceasarean section	10	6		4-10



Neuron centric view

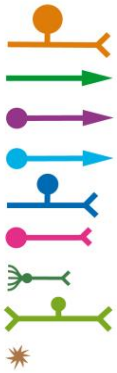
Milligan,Watkins, Nature Reviews Neuroscience 10, 23-36 (2009)



From a neuron centric view to a neuron-glial view

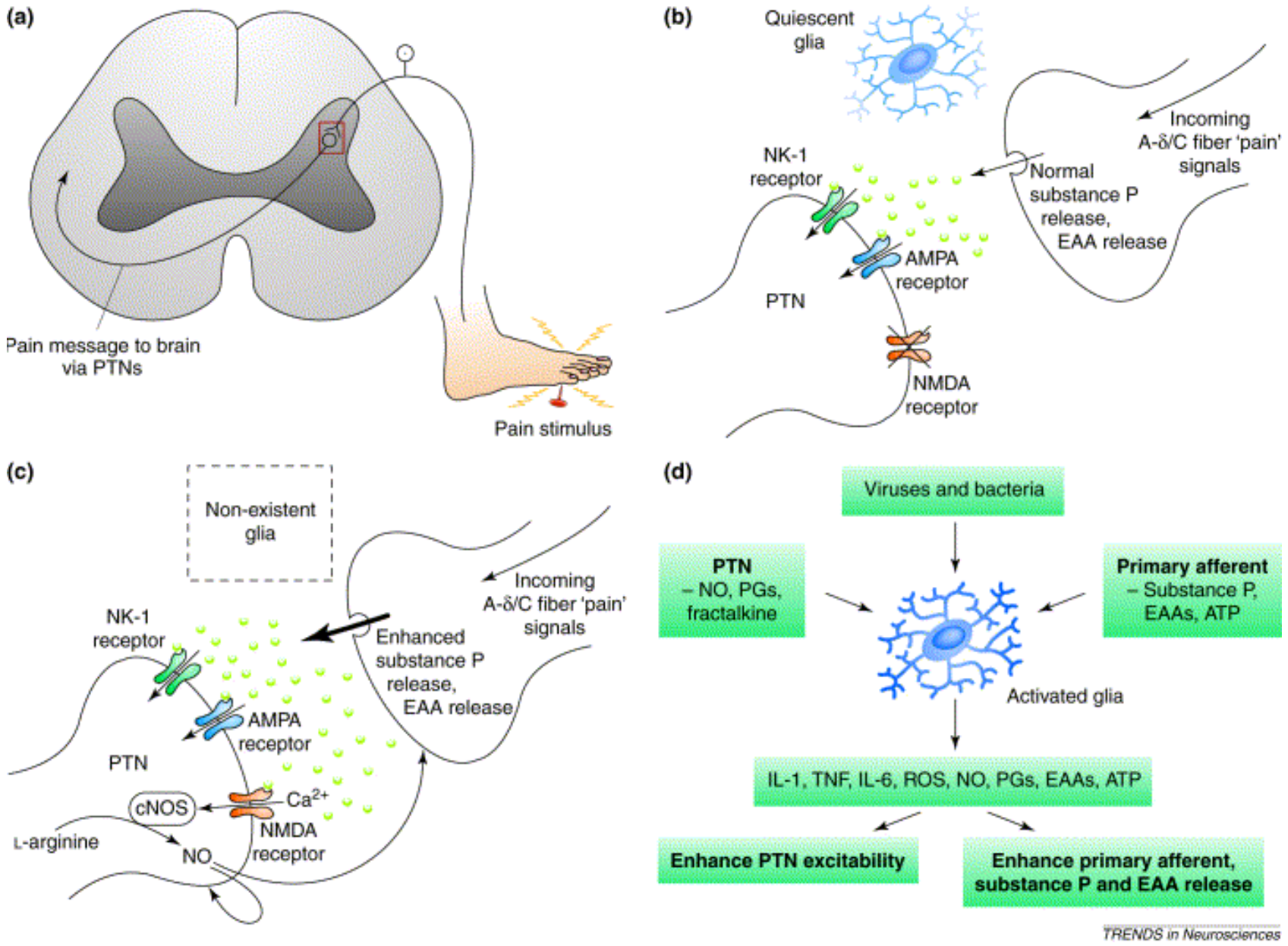
Microglia

Astroglia



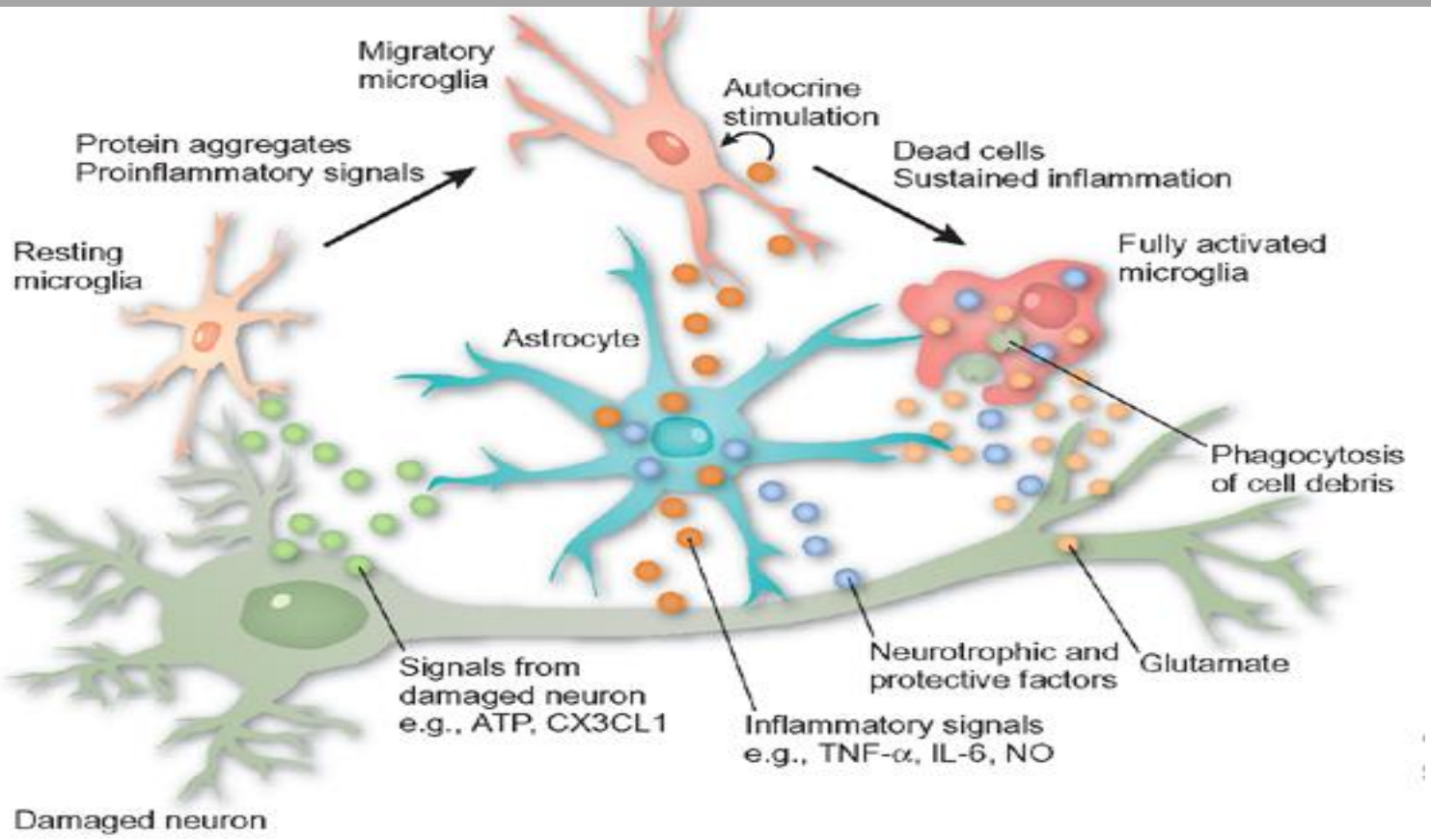
A-fiber afferent
descending (supraspinal) axon
Nociception-specific projection neuron
Wide-dynamic-range projection neuron
Nociceptor/ C-fiber afferent
PKC-γ interneuron
Inhibitory interneuron
Excitatory interneuron
glial cell

Berger JV, Knaepen L, Janssen SP, Jaken RJ, Marcus MA, Joosten EA, Deumens R. 2011 Cellular and molecular insights into neuropathy-induced hypersensitivity for mechanism-based treatment approaches
Brain Res Rev. 67(1-2):282-310



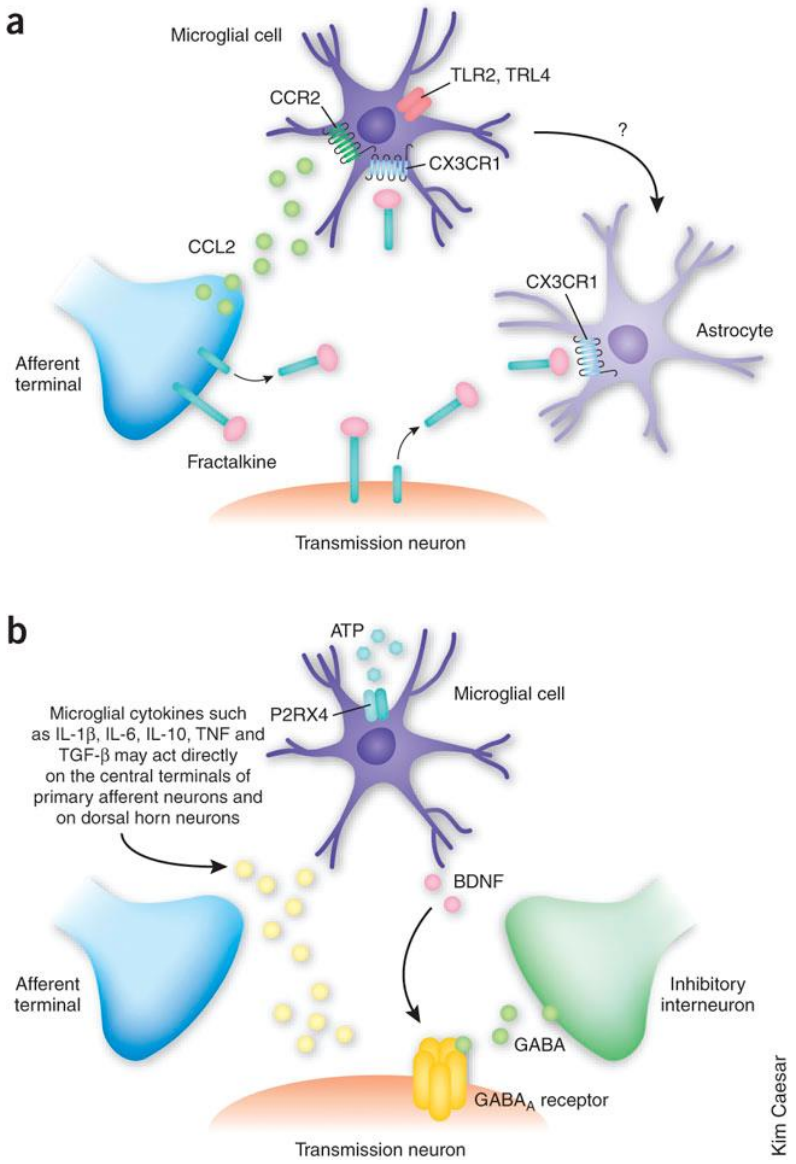
Watkins et al: Trends in Neuroscience 2001, 24: 450-55

Transition from acute to chronic Pain



First stage: microglia activation → Second stage: astroglial activation

From: Monk PN and Shaw P (2006) Nat.Med. 123, 885-887



The first stage: Activation of Microglia

1. Chemokines: CCL2/CCR2

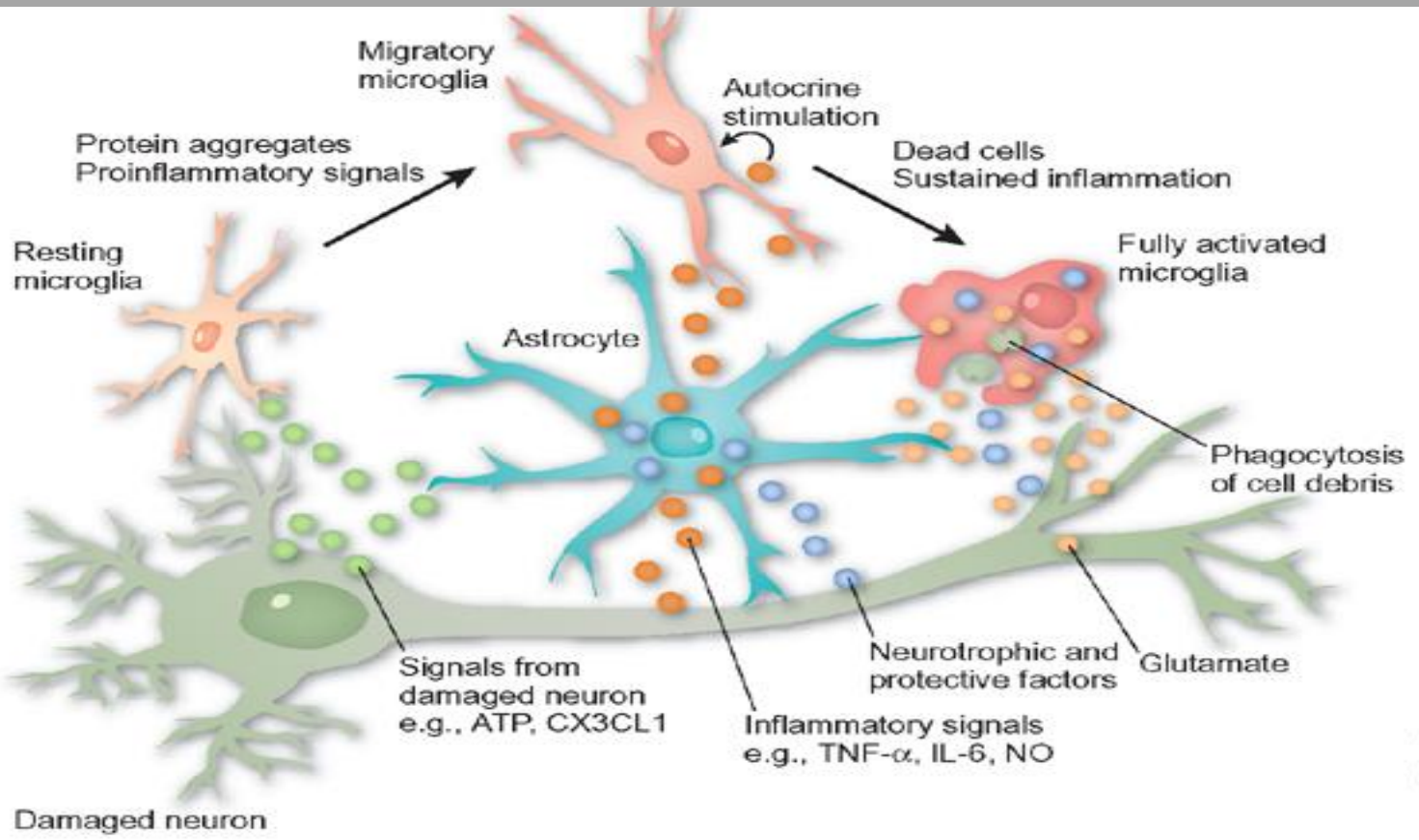
2. ATP and Purinergic receptors

3. Toll like receptors

Activated microglia and pain?

The neuropathic pain triad: neurons, immune cells and glia
Joachim Scholz & Clifford J Woolf
Nature Neuroscience 10, 1361 - 1368 (2007)

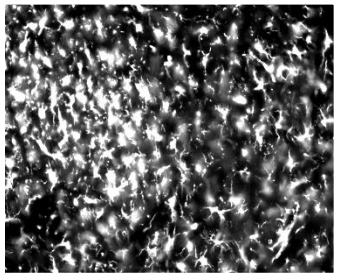
Transition from acute to chronic Pain

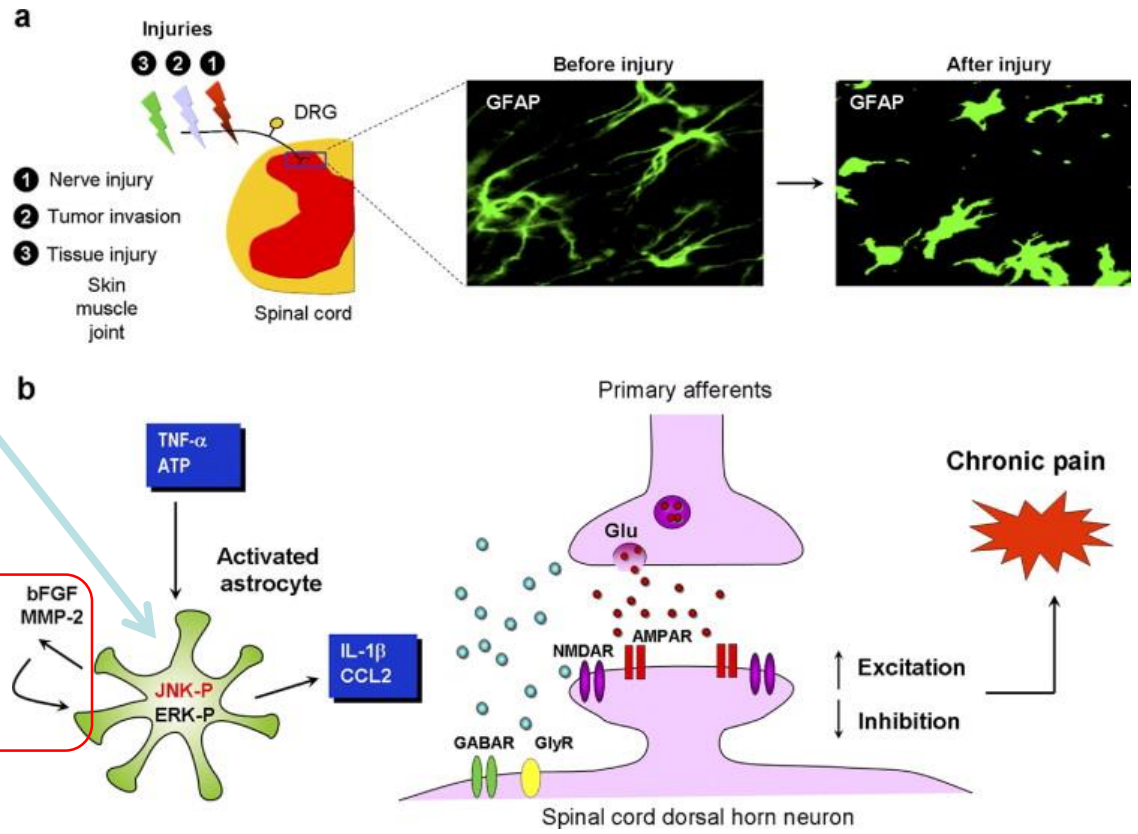


onset	First stage: microglia activation ATP - P2X4 – p38MAPK – BDNF- NMDA	→ **IL-18**	Second stage: astroglial activation Il-1B bFGF maintenance

From: Monk PN and Shaw P (2006) Nat.Med. 123, 885-887

Activated astrocytes and Pain



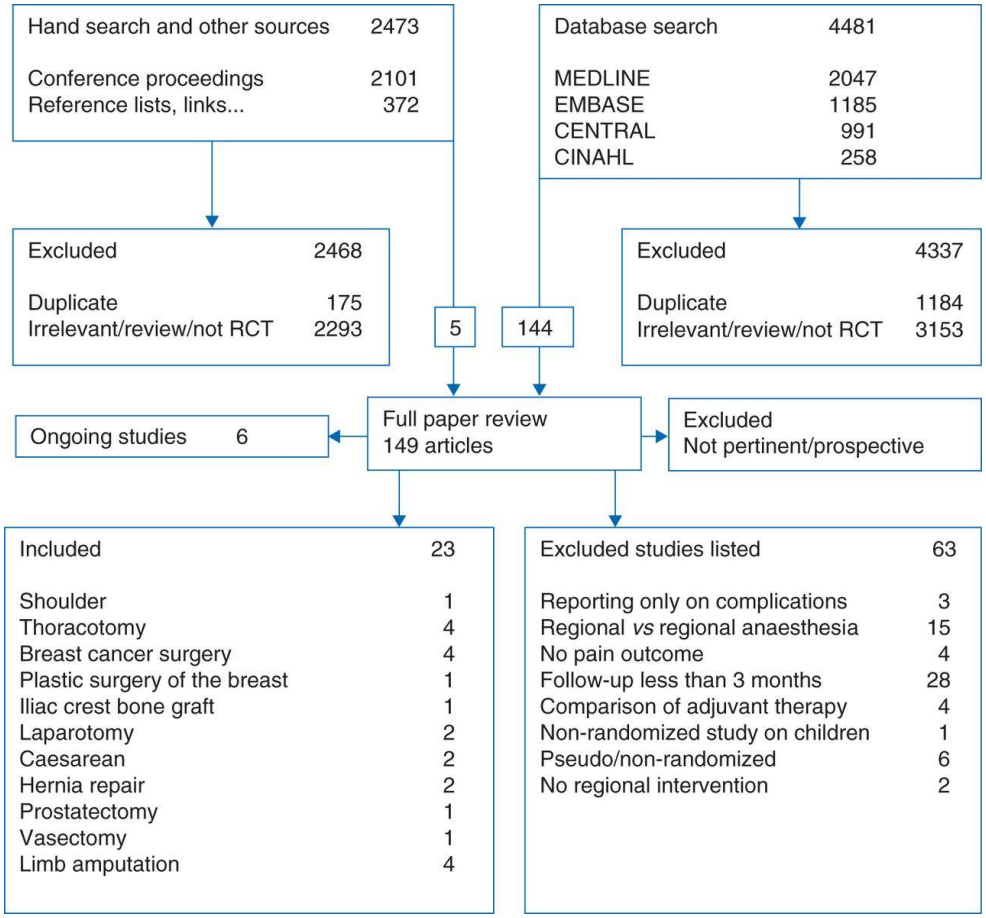


Astrocytes maintain the central sensitization proces among other things

Autocrine loop: bFGF
CS induction: Il-1B

Gao Y-J and Ji R-R (2010) Targeting astrocyte signaling for chronic pain. Neurotherapeutics 7: 482-493

Regional anaesthesia to prevent chronic pain after surgery

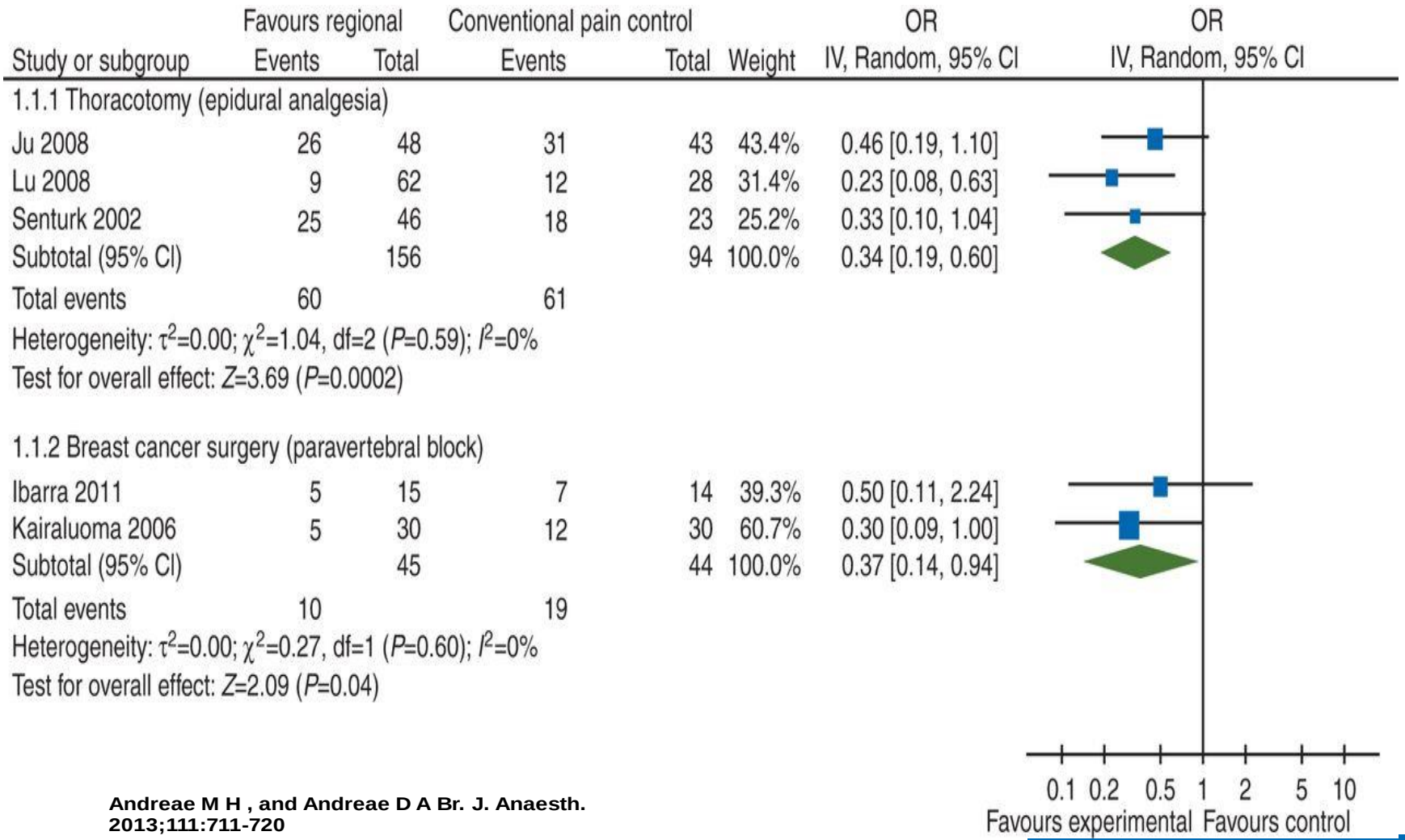


Andreae M H , and Andreae D A Br. J. Anaesth. 2013;111:711-720

BJA British Journal of Anaesthesia

Forest plot favoured epidural anaesthesia for the prevention of PPP

outcomes at 6 months after thoracotomy with an OR of 0.33 (95% CI 0.20–0.56) and paravertebral block for breast cancer surgery with an OR of 0.37 (95% CI 0.14–0.94), respectively



Andreae M H , and Andreae D A Br. J. Anaesth. 2013;111:711-720

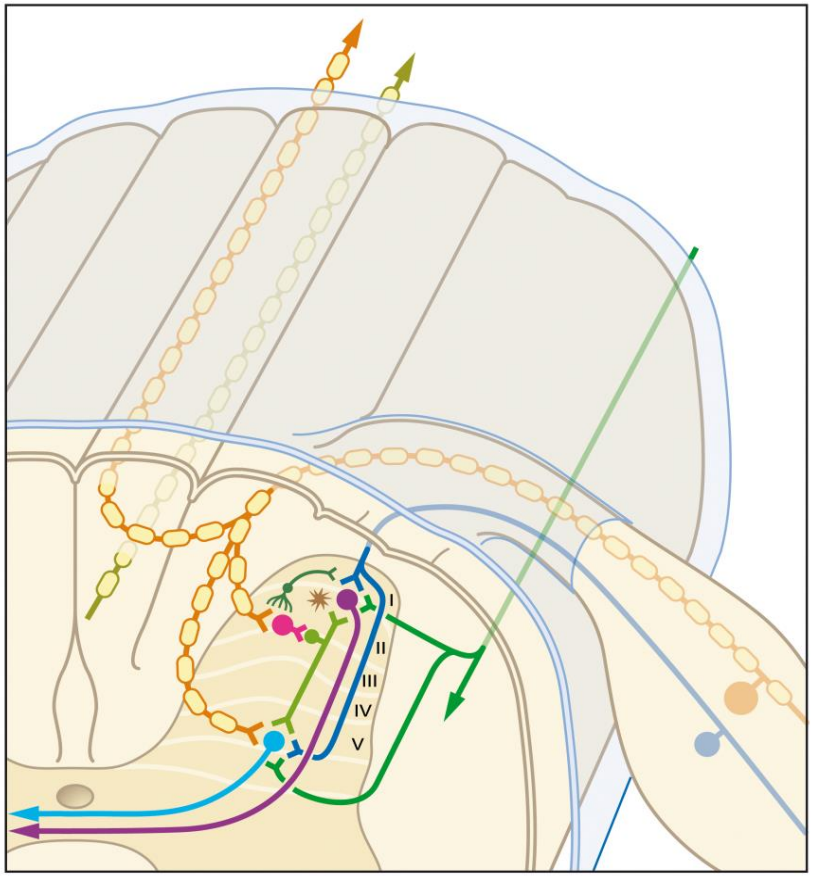
BJA British Journal of Anaesthesia

As such therapeutic or pharmacological manipulation of the glial cells in the central nervous system, and in particular in neuropathic pain, has, despite the major pre-clinical improvements, **not yet resulted into clinical applicable therapies**
(Basbaum et al.,(2009) Cell 139, 267-284)

Pharmacotherapy for the prevention of chronic pain after surgery in adults

1.Luis Enrique Chaparro[1], et al. Published Online: 24 JUL 2013

We identified 40 RCT for various pharmacological interventions including intravenous ketamine (14RCTs), oral gabapentin (10RCTs), oral pregabalin (5RCTs), non-steroidal anti-inflammatories (3RCTs), intravenous steroids (3RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3RCTs), oral mexiletine(2RCTs), intravenous fentanyl (1RCT), intravenous lidocaine (1RCT),oral venlafaxine (1RCT) and inhalednitrousoxide(1RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is<100 participants per treatment arm), which could lead to the overestimation of treatment effect



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descending (supraspinal) axon
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Nociceptor/ C-fiber afferent
PKC-γ interneuron
Inhibitory interneuron
Excitatory interneuron
glial cell

Early growth response 1 (EGR1) by a 23-BP DNA decoy (AYX1)

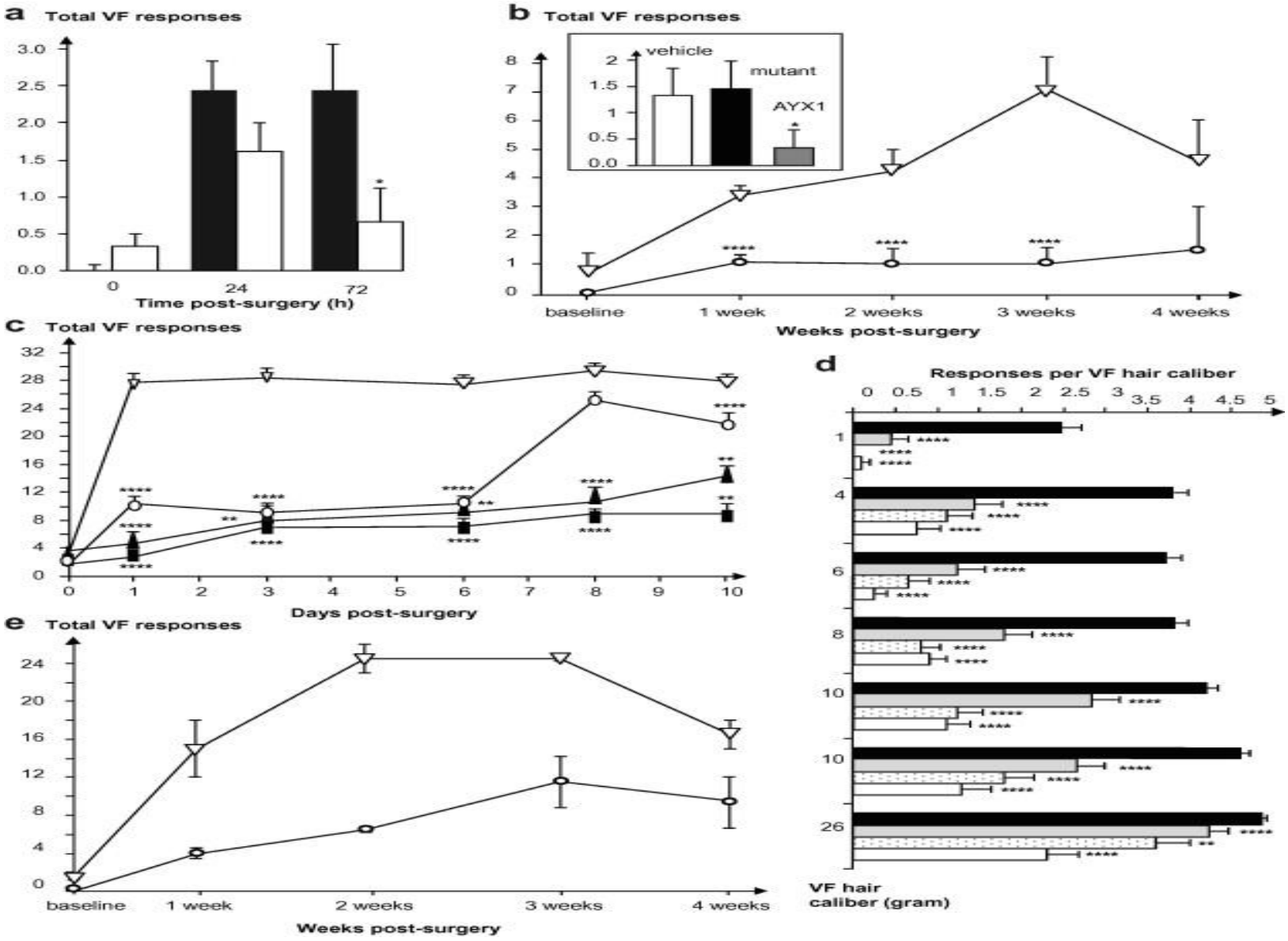
From a neuron centric view to a neuron-glial view

Microglia

Astroglia

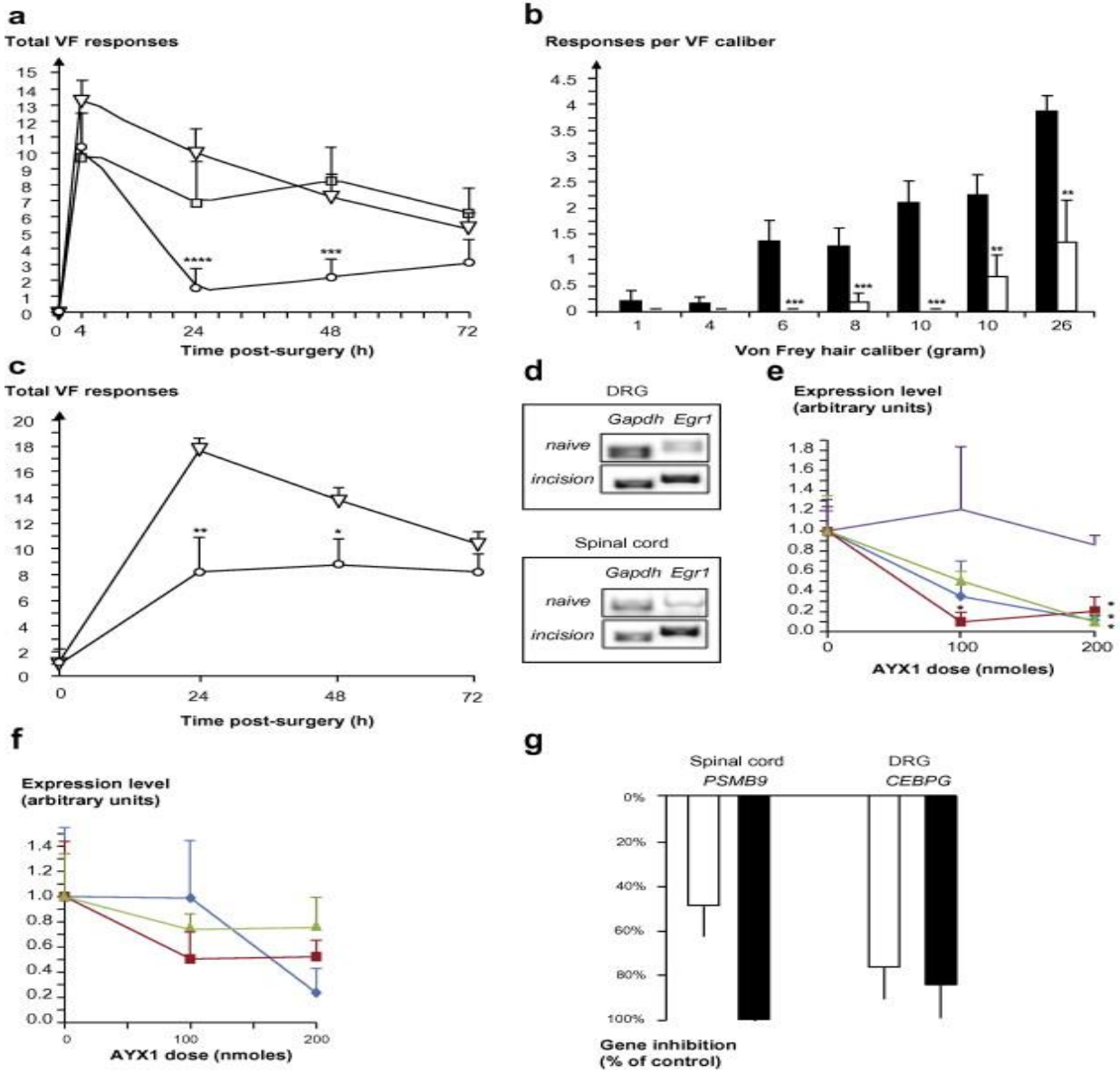
Berger JV, Knaepen L, Janssen SP, Jaken RJ, Marcus MA, Joosten EA, Deumens R. 2011 Cellular and molecular insights into neuropathy-induced hypersensitivity for mechanism-based treatment approaches **Brain Res Rev**. 67(1-2):282-310

AYX1 efficacy in the CFA model



From: Mamet et al. (2014) Pain 155, 322-333

Initial demonstration AYX1 in the plantair incisional model



From: Mamet et al. (2014) Pain 155, 322-333

Is this a clinical applicable therapy?

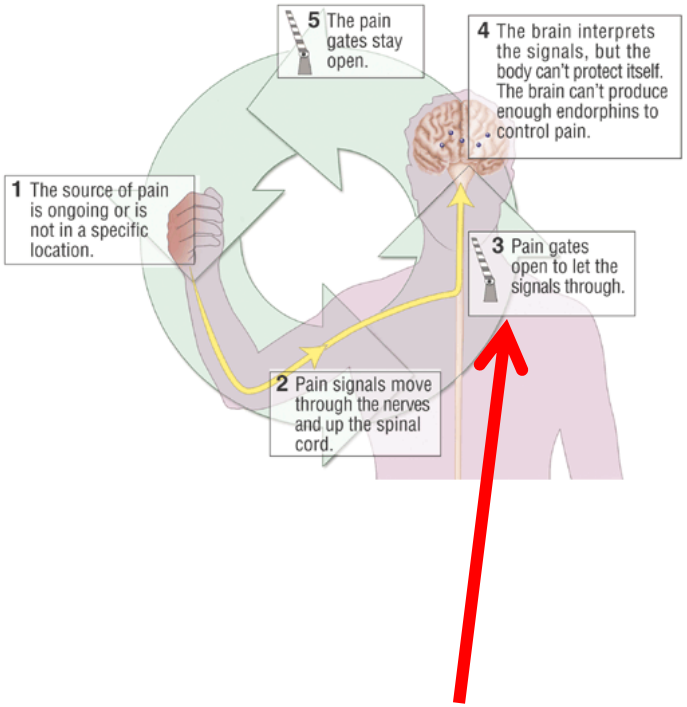
RS Ulrich, 1984
View through a window may influence recovery from surgery. Science 224:4220-421

Patients with window view on nature
(Enriched Environment)

facing a brick building wall
(Restricted Housing)

shorter hospital stay
use of less analgesic
less complain to the staff

Yes, enriched (healing) housing is a clinical applicable therapy and affects the neuron-glia interaction



Is this a clinical applicable therapy?

RQ: **Is it possible to modulate such a complex glial-neuron interaction as noted during the transition from acute to chronic pain without using pharmacological interventions?**

Answer: **Yes, it seems that housing does change the complex glial-neuron interaction and interferes with the transition from acute to chronic pain.**

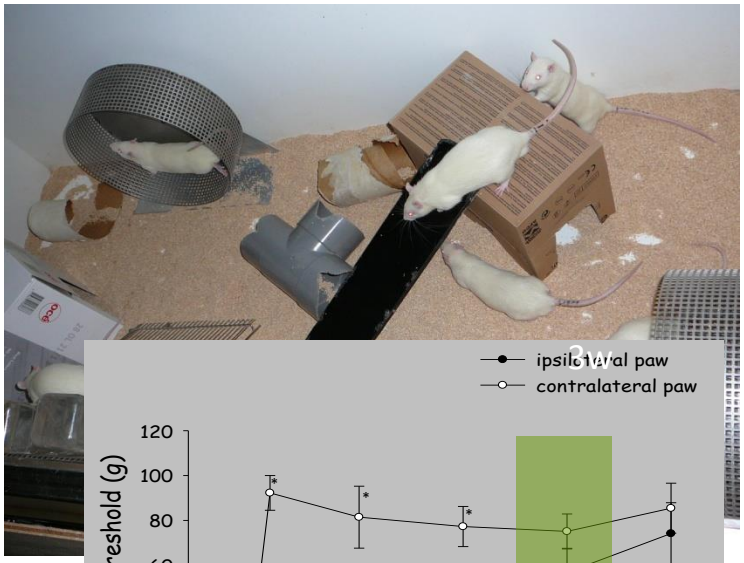
Modulation of the glia-neuron interaction: non-pharmacological?

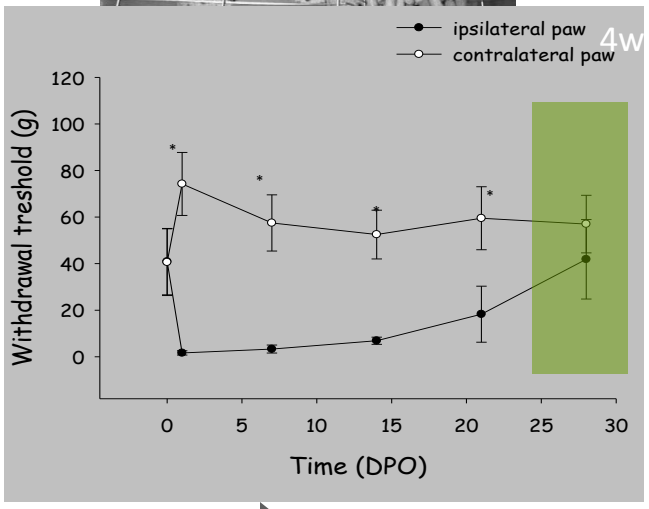
T=0:

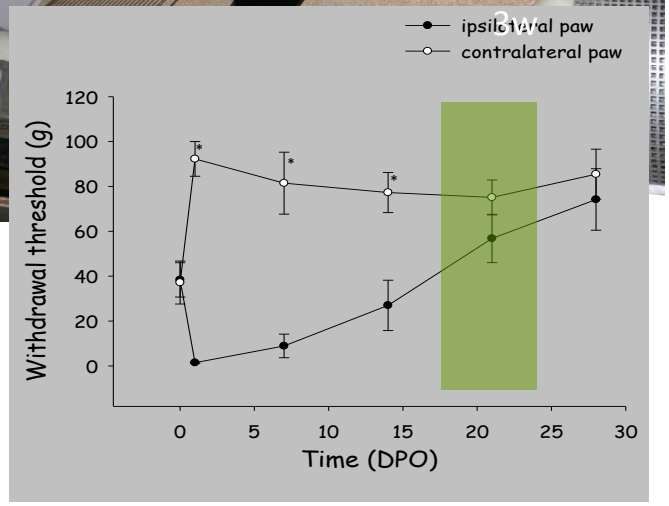
injection of 2mg of carrageenan in the right knee of the rat

Restricted Environment

Enriched Environment







Reduction in the duration of pain

Anne Gabriel (2009): Effect of housing in an enriched environment on the recovery from experimental inflammatory pain.

Modulation of the glia-neuron interaction: non-pharmacological?

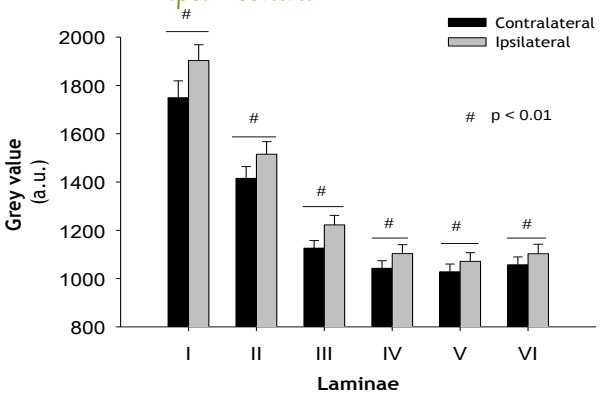
T=0:
injection of 2mg of carrageenan in the right knee of the rat

Restricted environment

Enriched environment

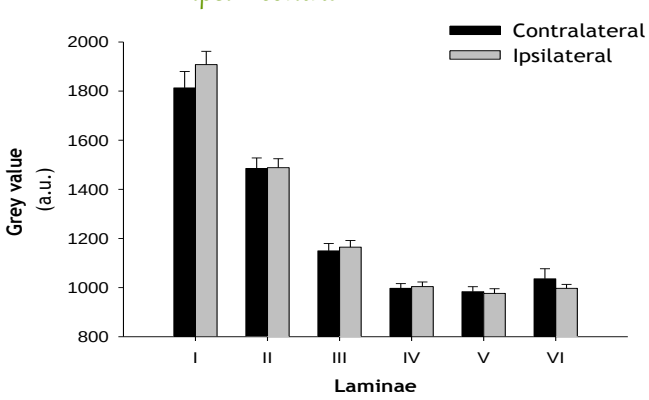
GFAP Intensity at DPO21

ipsi > contra



EE balances GFAP density between the ipsi- and contralateral sides

ipsi = contra



predictors of persistent post surgical pain

- ☑ **study 1**:
  1490 hospitalized patients, various surgical procedures
  6 months follow-up

- ❑ **study 2**:
  1000 day surgery patients, various surgical procedures
  12 months follow-up

- ❑ **Study 3:**
  500 patients with hysterectomy
  3 & 6 months follow-up

surgery

follow-up

preoperative assessment

acute

6 months

Annals of Surgery • Volume 245, Number 3, March 2007

Somatic and Psychologic Predictors of Long-term Unfavorable Outcome After Surgical Intervention

Madelon L. Peters, PhD, Micha Sommer, MD,† Janneke M. de Rijke, PhD,†*
Fons Kessels, MD, MSc,‡ Erik Heineman, MD, PhD,§ Jacob Patijn, MD, PhD,†
*Marco A. E. Marcus, MD, PhD,† Maarten van Kleef, MD, PhD,† and Johan W. S. Vlaeyen, PhD**

Outcome:
increased pain at follow-up

Predictors:

surgery-related & clinical

- ❑ demographics: sex, age, education
- ❑ pre-operative pain, ASA grade
- ❑ duration of surgery
- ❑ type of operation: minor, intermediate, major
- ❑ anatomical site
- ❑ type of anesthesia (general, locoregional, both)

psychological

- ❑ surgical fear
- ❑ pain catastrophizing
- ❑ optimism
- ❑ self-efficacy

main predictors:
odds ratio's

	Study 1
More extensive operation	2.6
Duration of surgery	2.0
Pre-operative pain	
Acute Pain Intensity	3.2
Surgical Fear	1.9
Catastrophizing	(+)
Optimism	(+)

Clin J Pain • Volume 28, Number 9, November/December 2012

Preoperative Anxiety and Catastrophizing

A Systematic Review and Meta-analysis of the Association With Chronic Postsurgical Pain

Maurice Theunissen, MSc, Madelon L. Peters, PhD,† Julie Bruce, PhD,‡ Hans-Fritz Gramke, MD, PhD,* and Marco A. Marcus, MD, PhD**

29 studies included: 16 positive association
13 no association
0 negative association

pooled OR: 2.1
(95% CI: 1.5 – 3.0)
N=14

consistent predictors

- type of procedure
- younger age
- pre-operative pain
- high levels of acute pain
- psychological factors (anxiety, negative cognitions & expectations)
- (genetic factors)
- (pain sensitivity / pain modulation capacity (QST, CPM))

Eur J Pain **16** (2012) 901–910

Development of a risk index for the prediction of chronic post-surgical pain

A. Althaus[1], A. Hinrichs-Rocker[1], R. Chapman[2], O. Arránz Becker[3], R. Lefering[1], C. Simanski[4], F. Weber[5], K.-H. Moser[6], R. Joppich[7], S. Trojan[7], N. Gutzeit[1], E. Neugebauer[1]

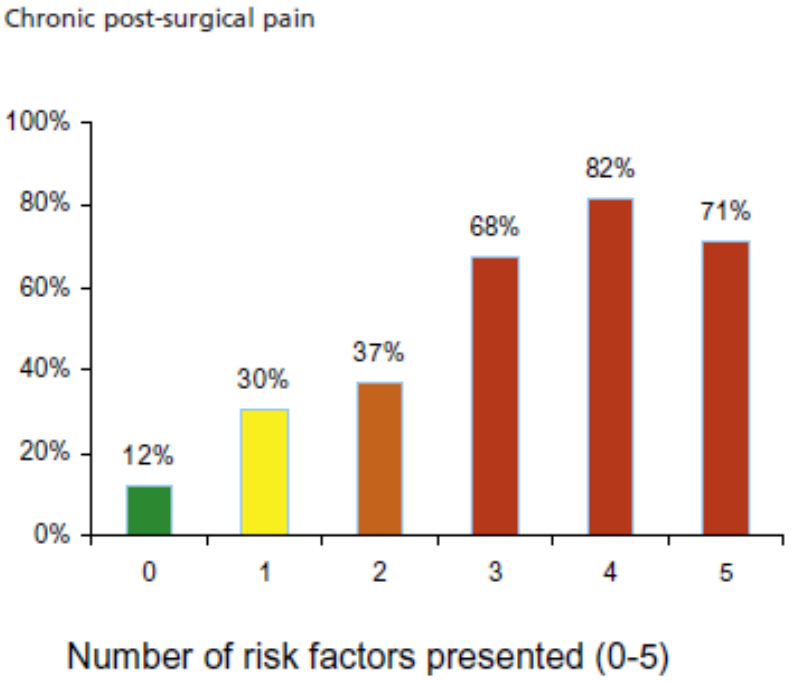
pre-operative pain in the operating field

other chronic pre-operative pain

post-surgical acute pain

capacity overload

comorbid stress symptoms



The Journal of Pain, Vol 14, No 8 (August), 2013: pp 854-864

Are Psychological Predictors of Chronic Postsurgical Pain Dependent on the Surgical Model? A Comparison of Total Knee Arthroplasty and Breast Surgery for Cancer

Anne Masselin-Dubois,*,† Nadine Attal,*,†,‡ Dominique Fletcher,*,†,‡,§ Christian Jayr,¶ Aline Albi,¶ Jacques Fermanian,|| Didier Bouhassira,*,†,‡ and Sophie Baudic*,†,‡

- TKA n=89; breast: n=100
- PPSP: average pain at 3 months ≥ 3 (0-10 scale)
- Neuropathic pain: DN4 at 3 months ≥ 3 (0-7 scale)

Predictors PPSP:

- older age
- acute post-operative pain (day 2)
- state anxiety & catastrophizing

acute pain → <u>Acute Pain Service</u>

Ready et al. 1988

Maier et al 1994

< 20 %

of all patients should experience severe pain after 1997

< 5 % by 2002

Audit Commission (UK), London 1997

Working together

A defenition what is quality. An agreement how to work together and all should have the same passion to reach that goal.