Acute and Chronic Pain Management Practice in the New Millennium

18 August 2012

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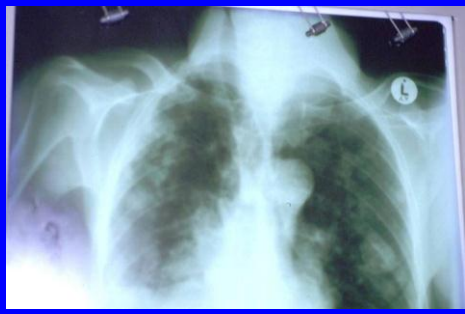
New Millennium

- A - Introduction
- B – Pain Conduction
- C – Peripheral and Central Sensitisation
- D – Brain Imaging
- E – Cognitive Modulations of Pain
- F – Genetics
- G – New Drugs
- H – Neuropathic Pain
- I - New Delivery Systems
- J – Neuromodulation
- K – Perioperative Pain
- L – Cancer Therapy
- M - Conclusion

A - Introduction

Acute Pain

Clinical Pain
Relief Service

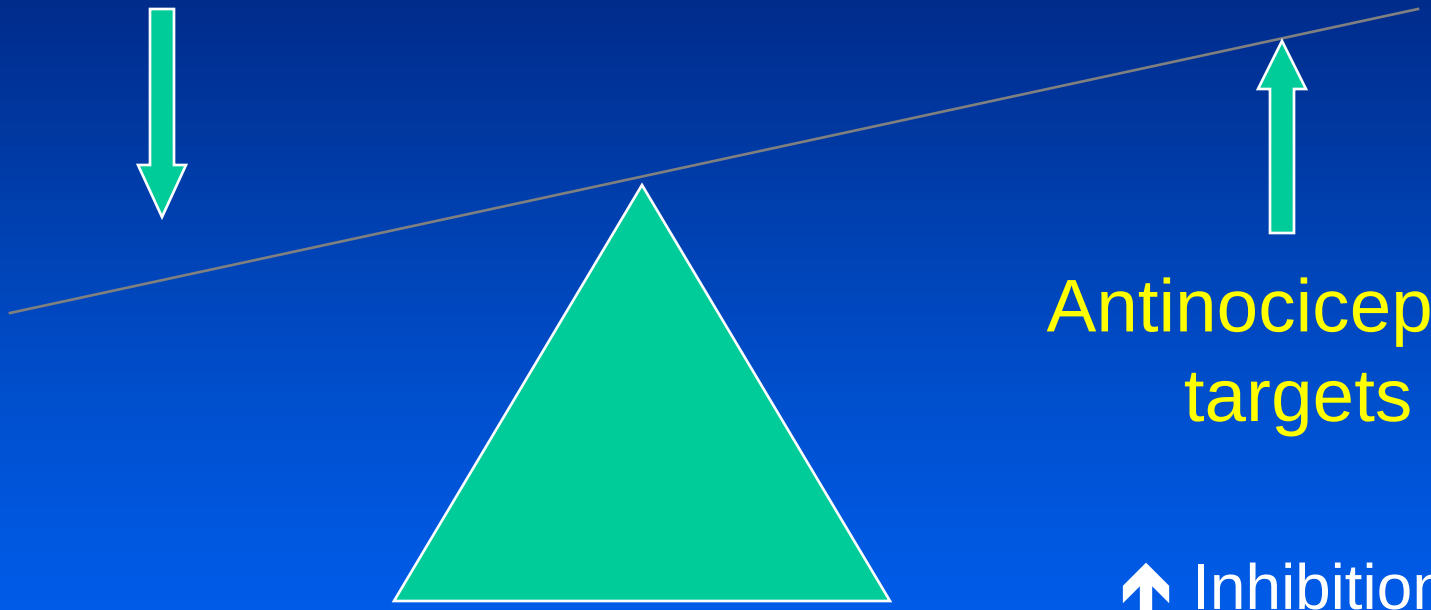


Chronic Pain

Cancer Pain

Enhanced Pain Management

Pronociceptive targets

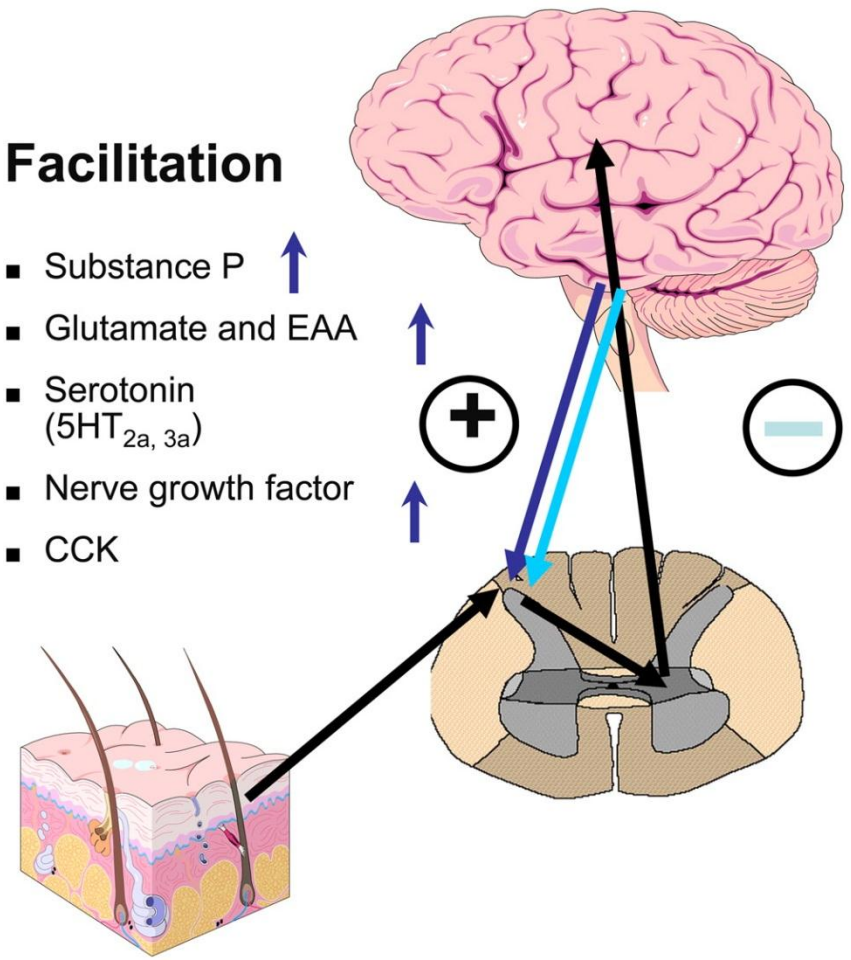


Antinociceptive targets

Inhibition

Excitation

Neural Influences on Pain and Sensory Processing



Facilitation

- Substance P
- Glutamate and EAA
- Serotonin ($5HT_{2a, 3a}$)
- Nerve growth factor
- CCK

Inhibition

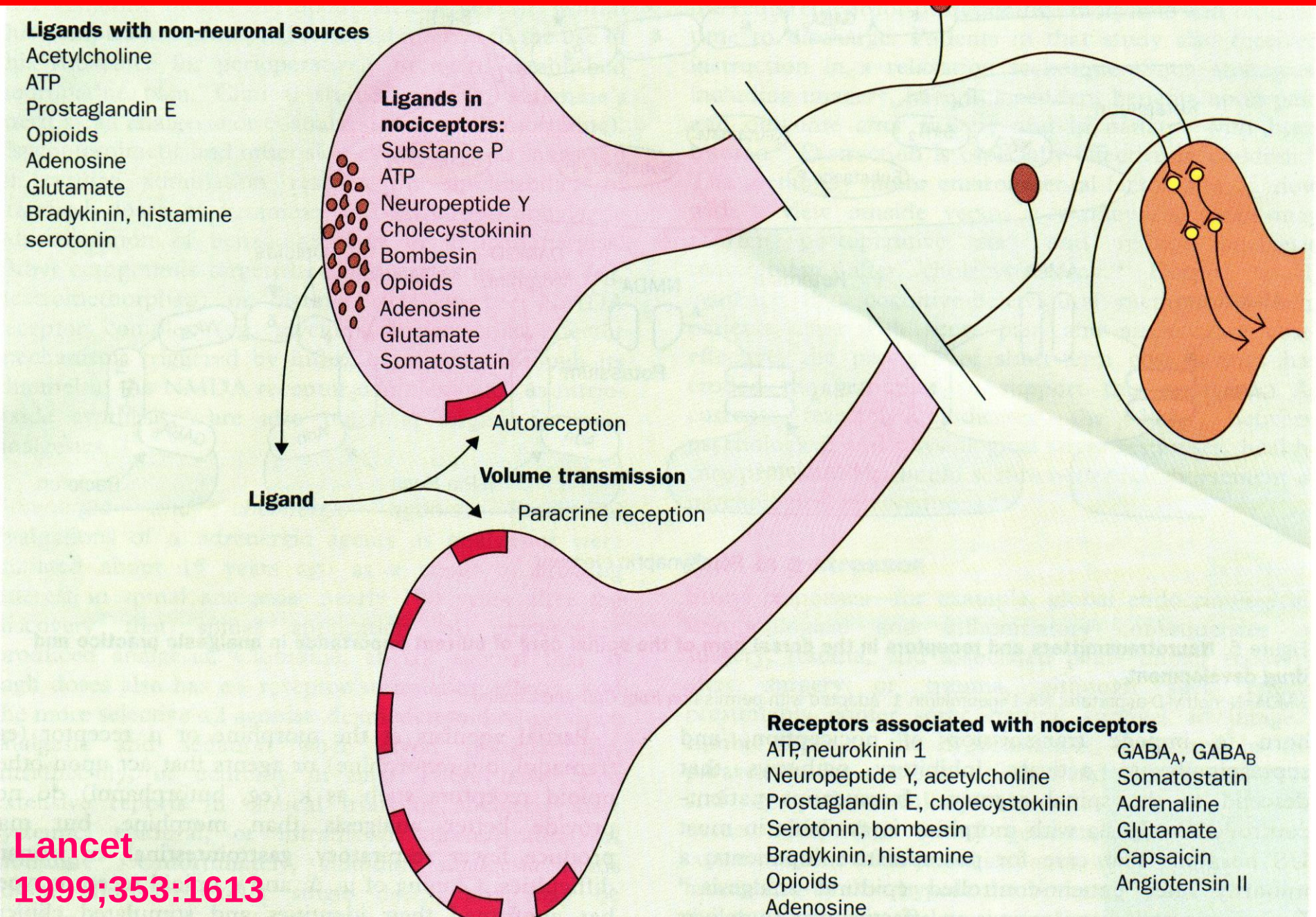
- Descending anti-nociceptive pathways
- Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
- Opioids
- GABA
- Cannabanoids
- Adenosine

(Phillips K. Best Pract Res Clin Rheumatol 2011;25(2):141-54)

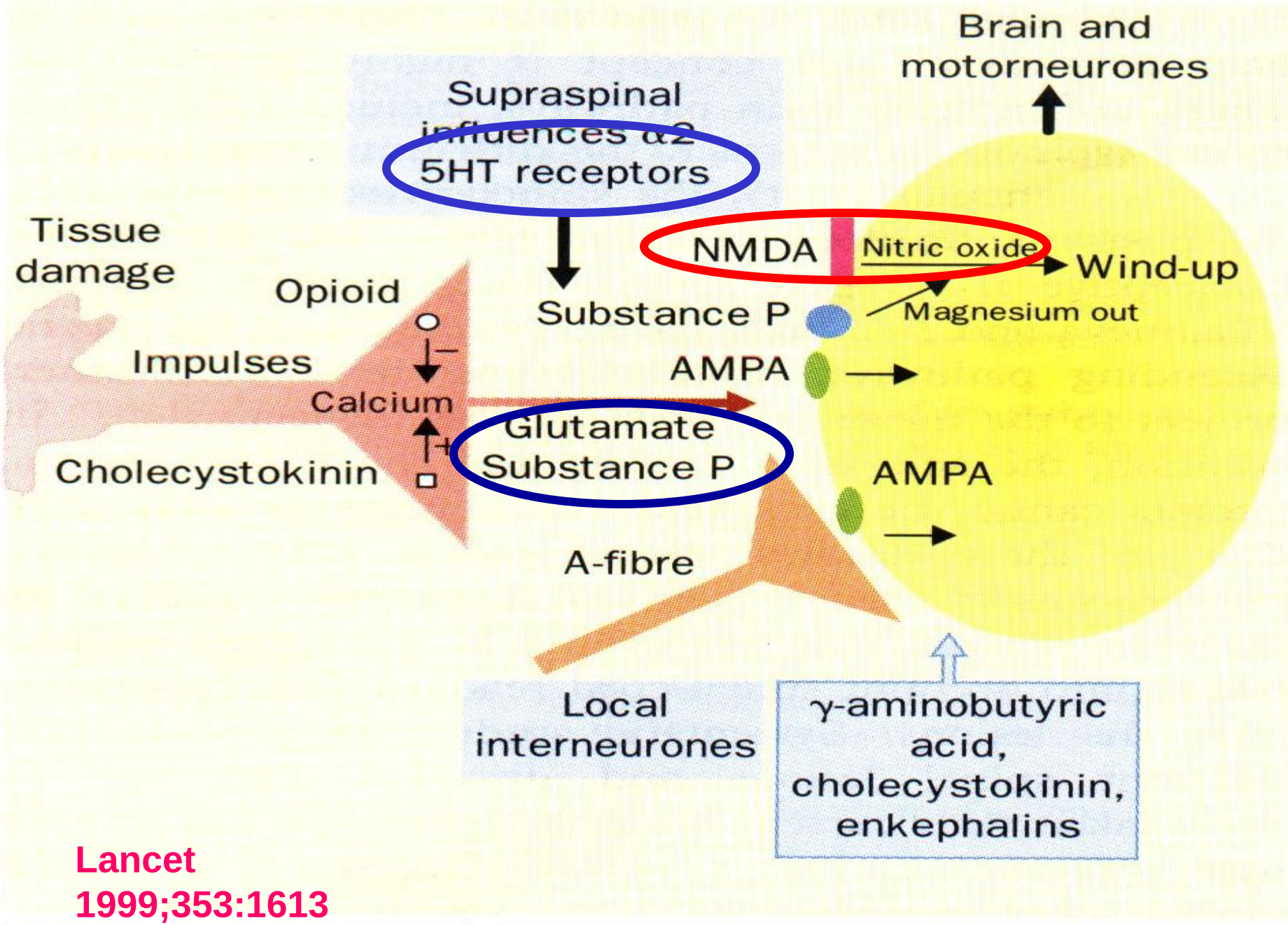
A - Introduction

- One in six New Zealanders (16.9%) suffer from chronic pain - data from the 2006/07 New Zealand Health Survey (Dominick C. NZ Med J 2011;124(1337):63-76)
- 48% used some form of medical treatment
- Prevalence increased with age from 8.6% to 28.1%
- Chronic pain represents a major health issue in New Zealand

B. Pain Conduction



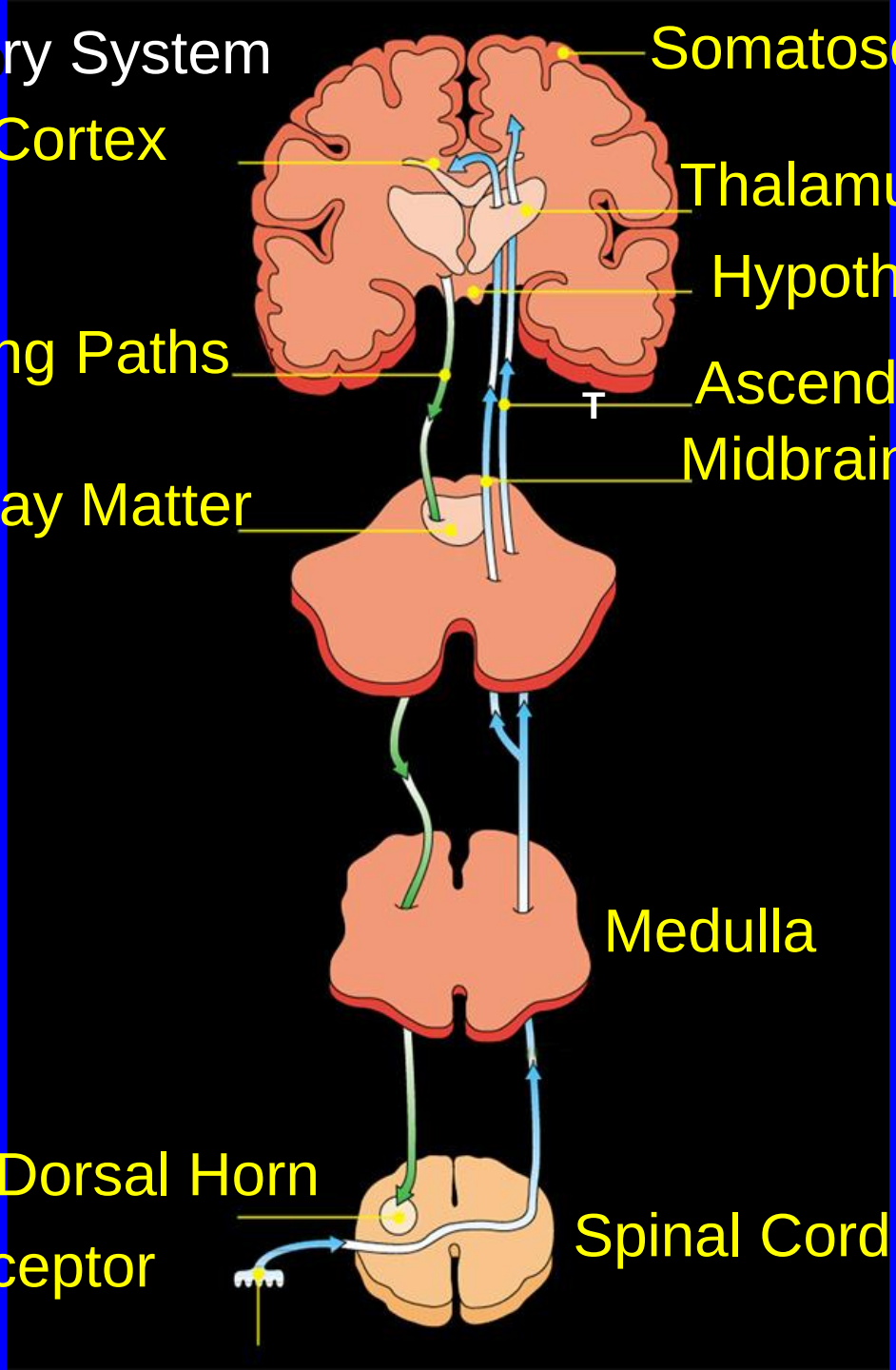
Lancet 1999;353:1613



Lancet 1999;353:1613

Interactions between different excitatory and inhibitory systems in the spinal cord

The Somatosensory System

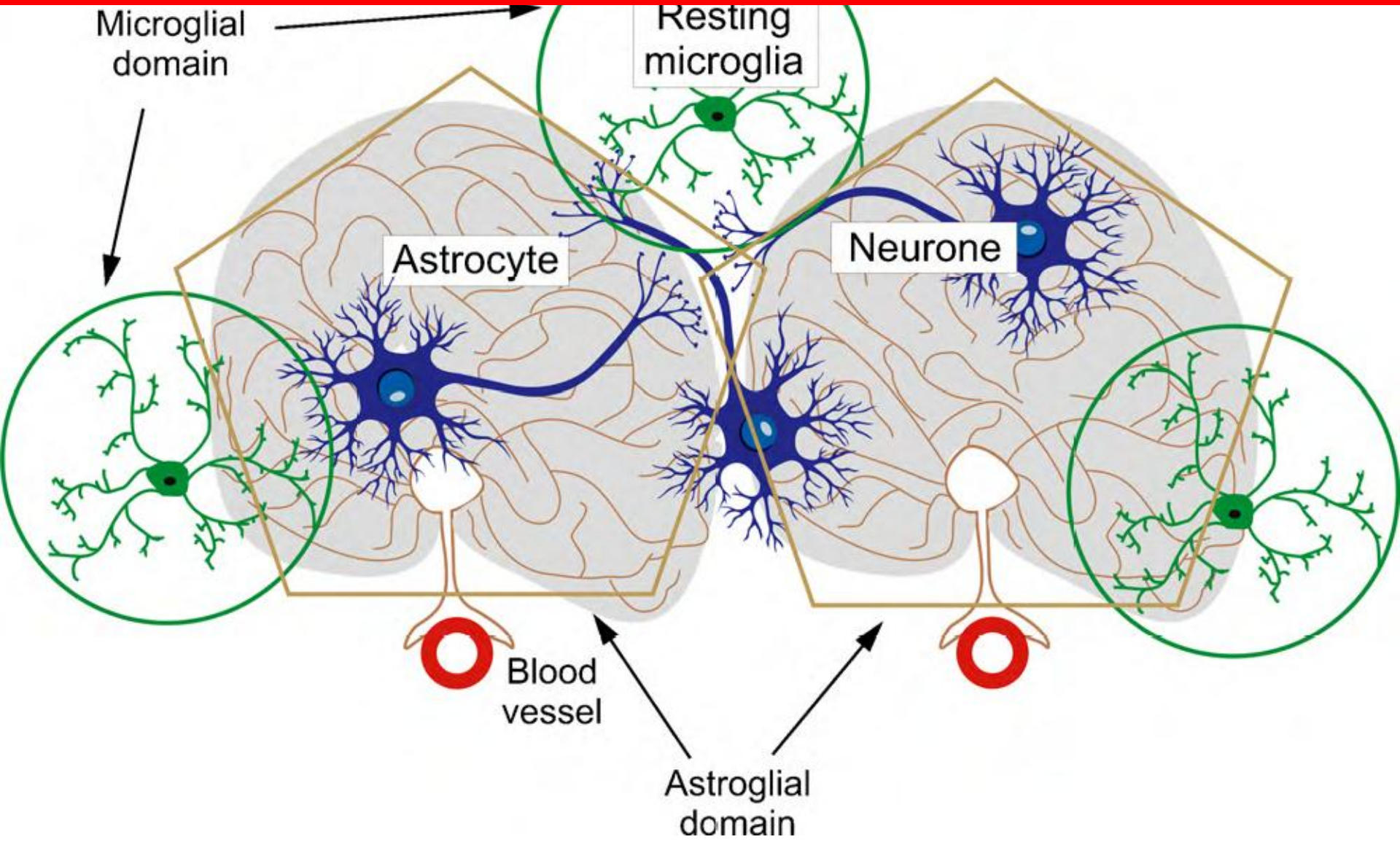


Descending Facilitatory

Glial Cell Activation

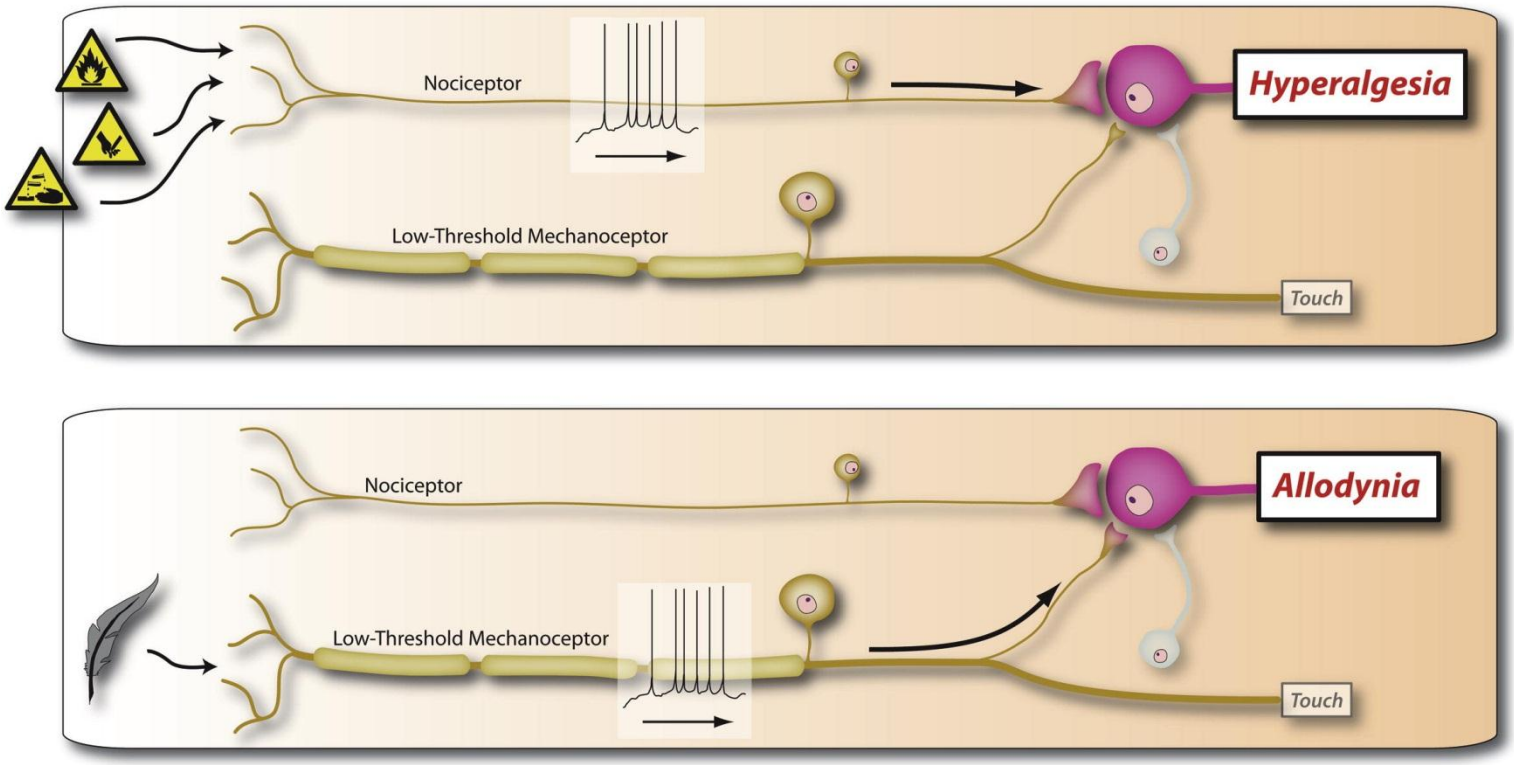
Na Channels In PSN	TTX sensitivity	Normal DRG Expressn	Growth factor Depend -ence	Inflammat-ion	Neuro-pathy
SNS2/NaN NaV 1,9	Resistant	Yes	GDNF	↑	↓
III NaV 1,4	Sensitive	No	?	X	↑
SNS/PN3 NaV 1.8	Resistant	Yes	NGF	↑	↓

C. Peripheral and Central Sensitisation -Neuroglial cells

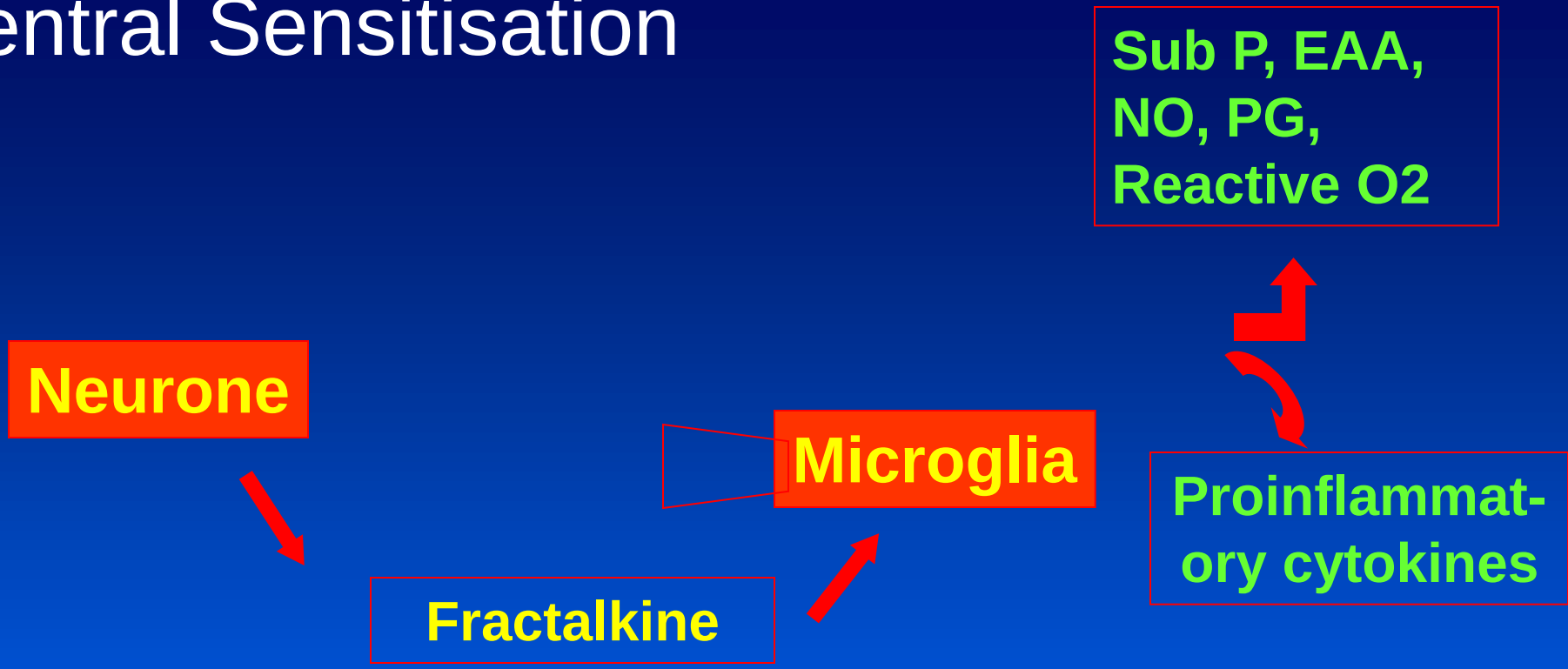


Verkhratsky A. Neurochem Int 2010 ;57(4):332-43

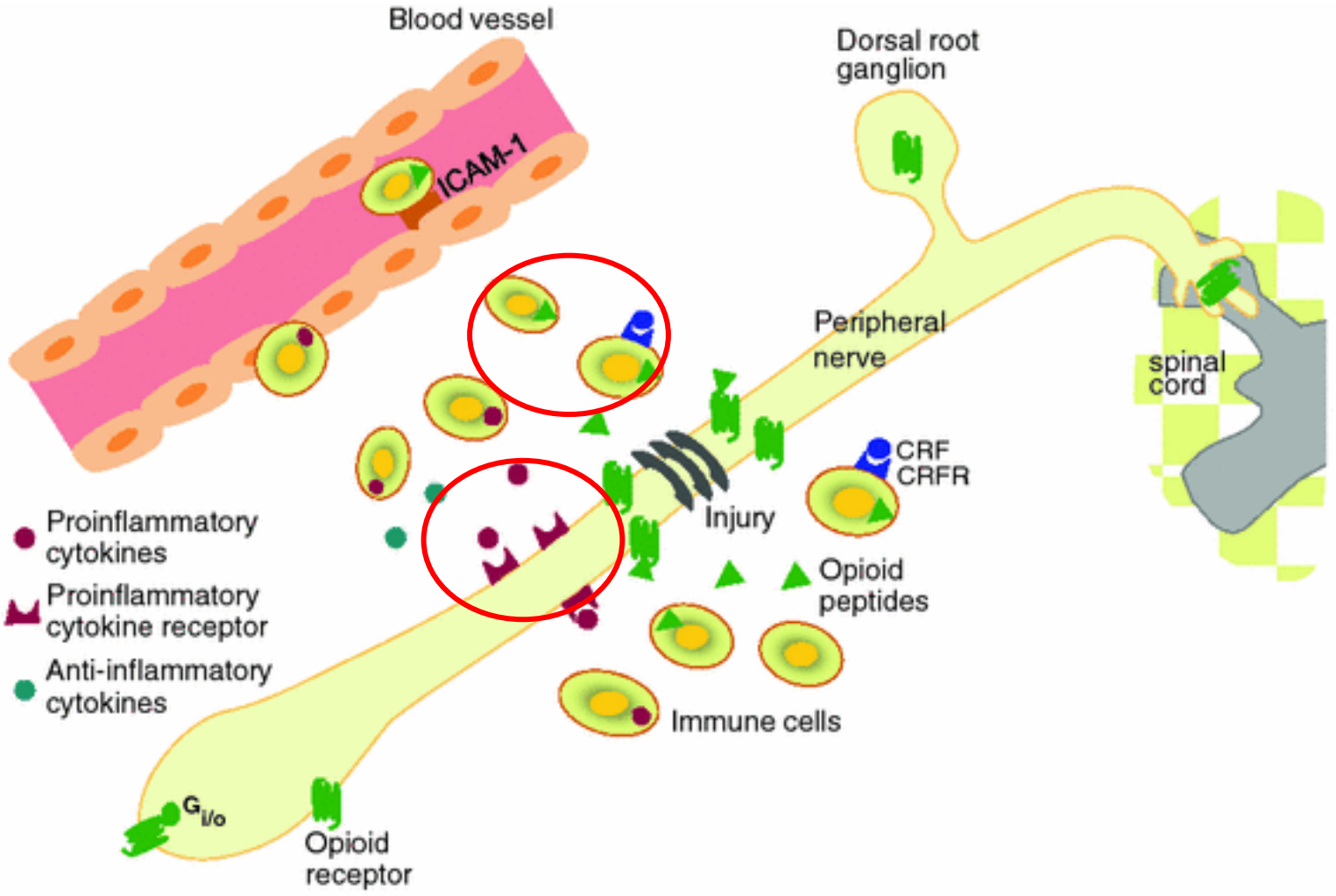
Central Sensitization



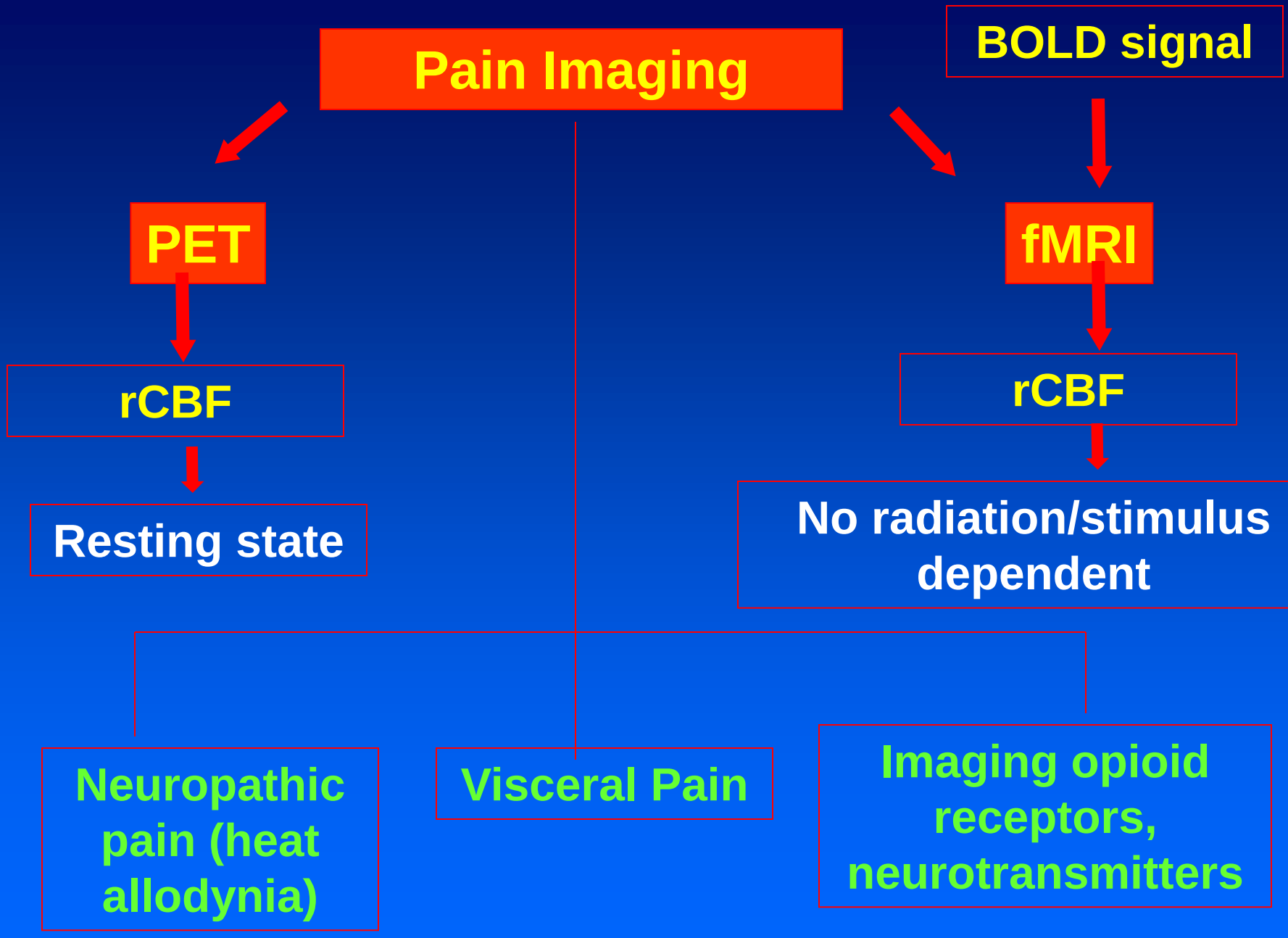
Central Sensitisation



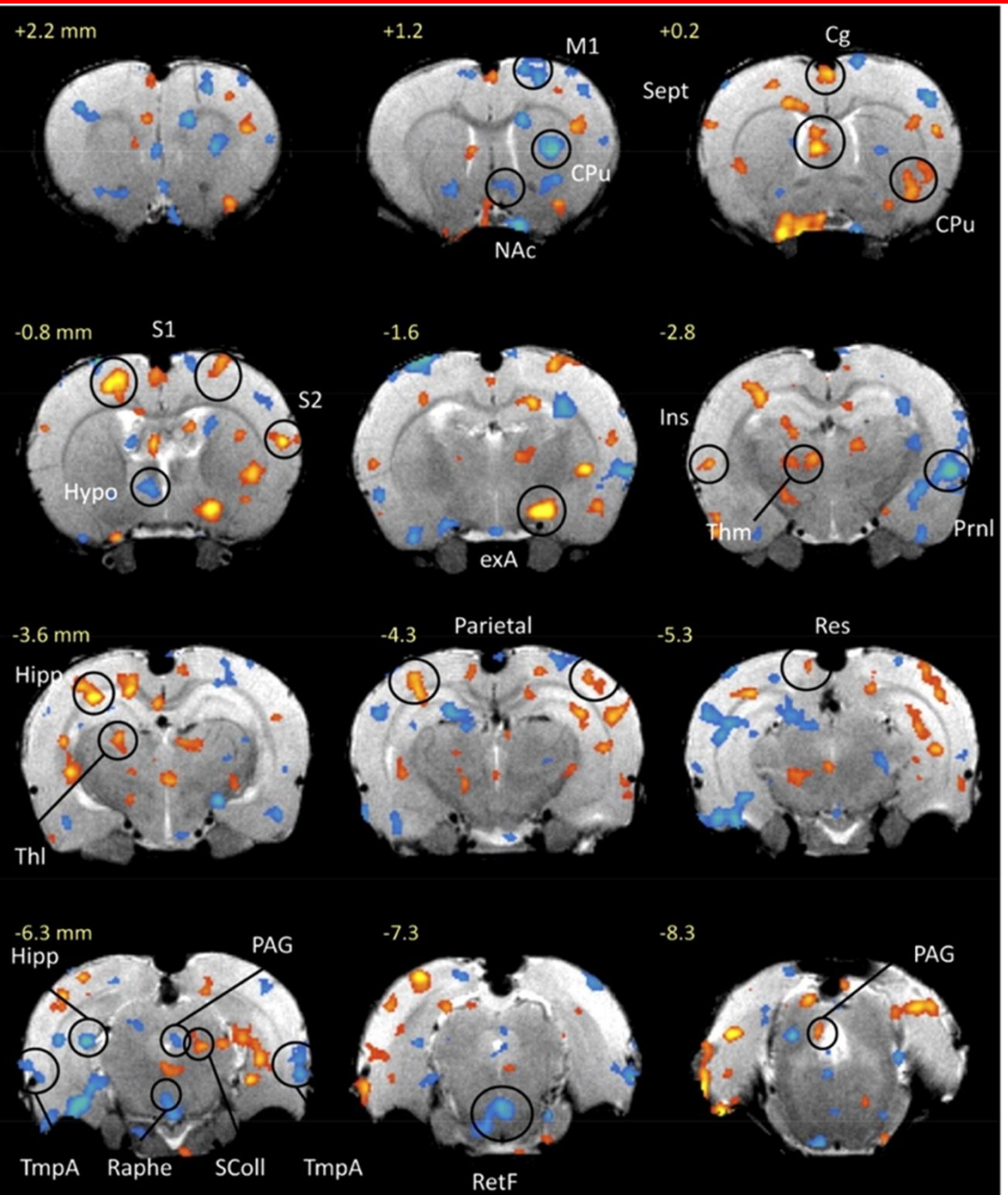
Central Sensitisation

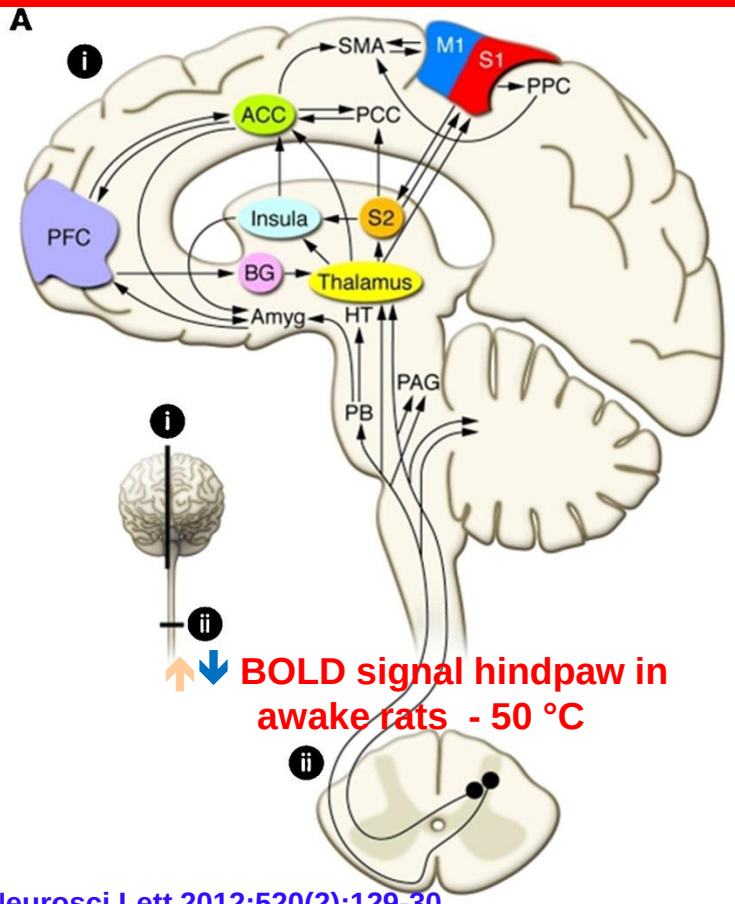

Blood vessel
ICAM-1
Dorsal root ganglion
Peripheral nerve
spinal cord
CRF
CRFR
Injury
Opioid peptides
Immune cells
Proinflammatory cytokines
Proinflammatory cytokine receptor
Anti-inflammatory cytokines
$G_{i/o}$
Opioid receptor

D. Brain Imaging


Pain Imaging
BOLD signal
PET
fMRI
rCBF
rCBF
Resting state
No radiation/stimulus dependent
Neuropathic pain (heat allodynia)
Visceral Pain
Imaging opioid receptors, neurotransmitters

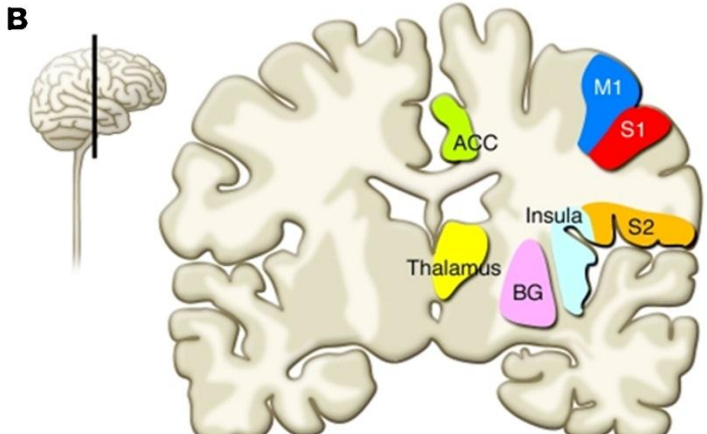
Graphic depiction of brain regions receiving nociceptive input and activated in MRI studies

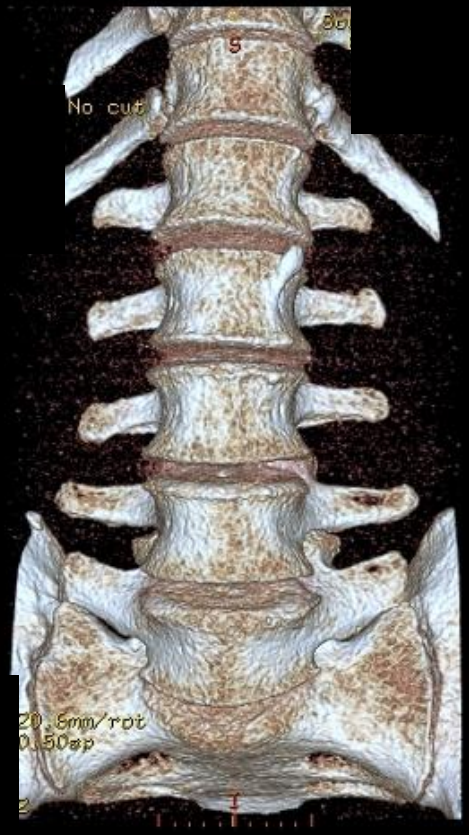




BOLD signal hindpaw in awake rats - 50 °C

Neurosci Lett 2012;520(2):129-30

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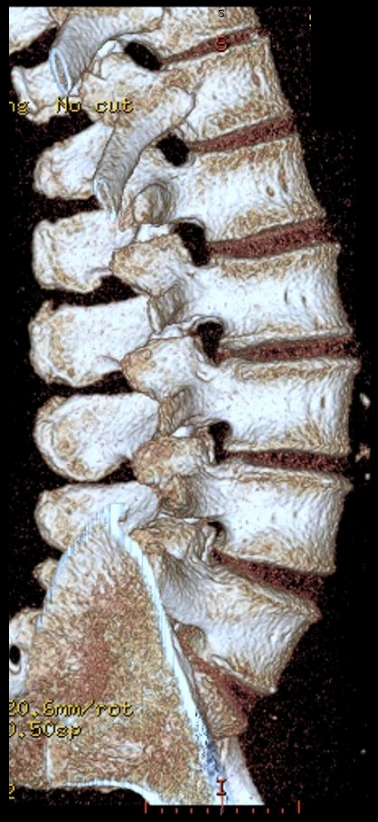
No cut
20.8mm/rot
0.50sp
I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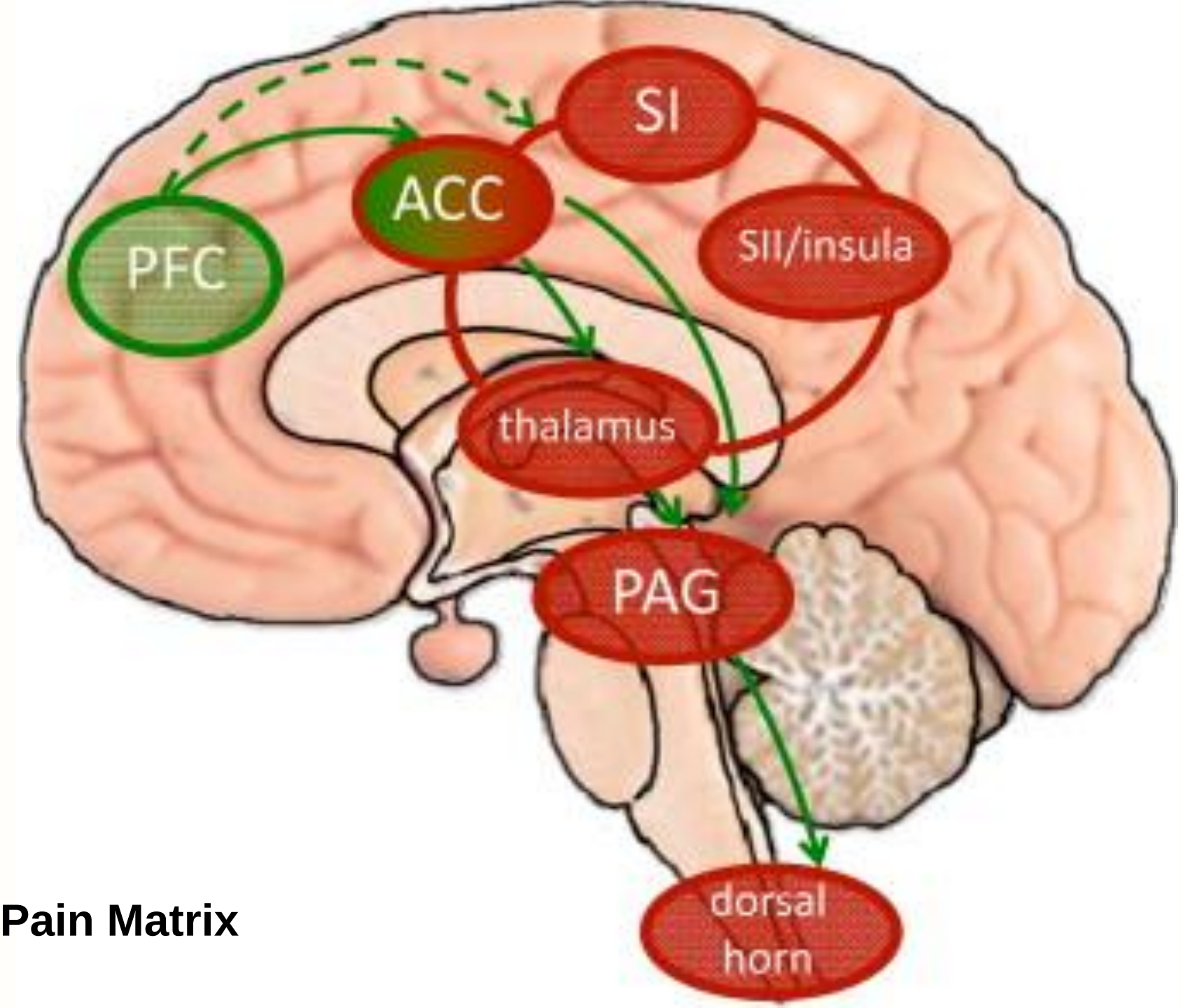
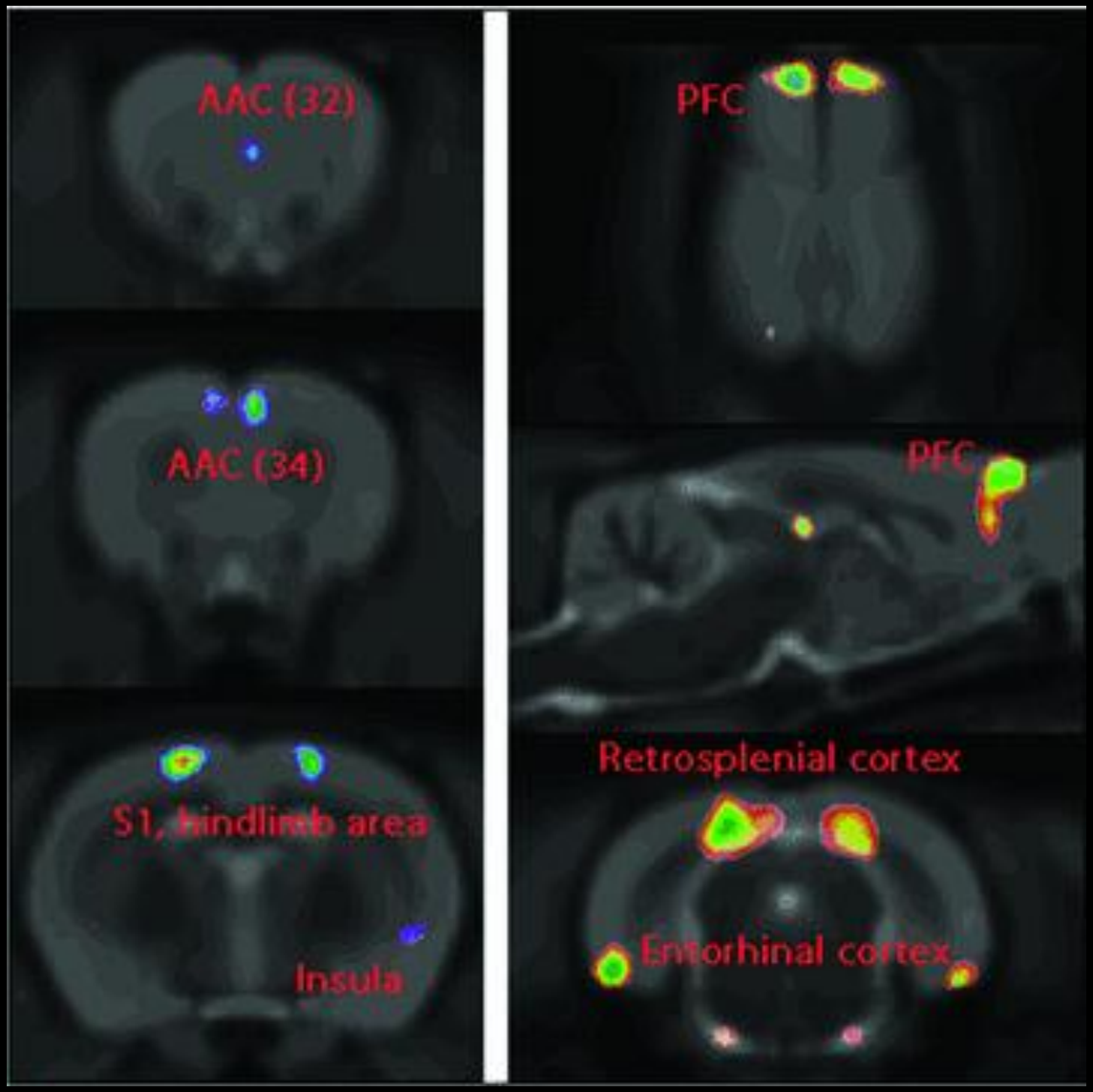


Pain Matrix

Understanding chronic inflammatory and neuropathic pain

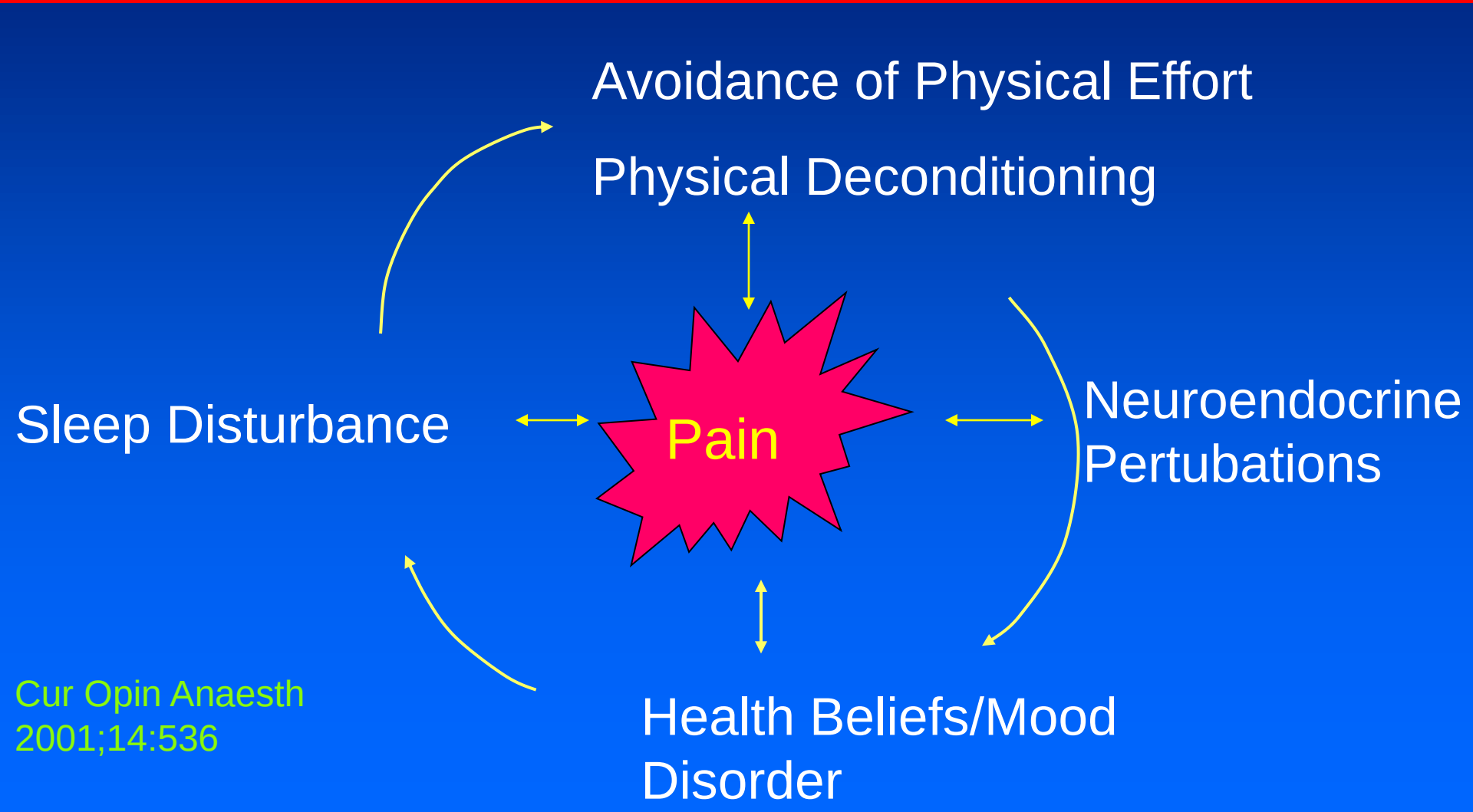
(Anals NY Acad Sc 2012 May:30-44) Chronic pain gives reduced gray matter volume; it reshapes the brain

Sensory-related areas: volume decreases in areas correlated with increased mechanical sensitivity



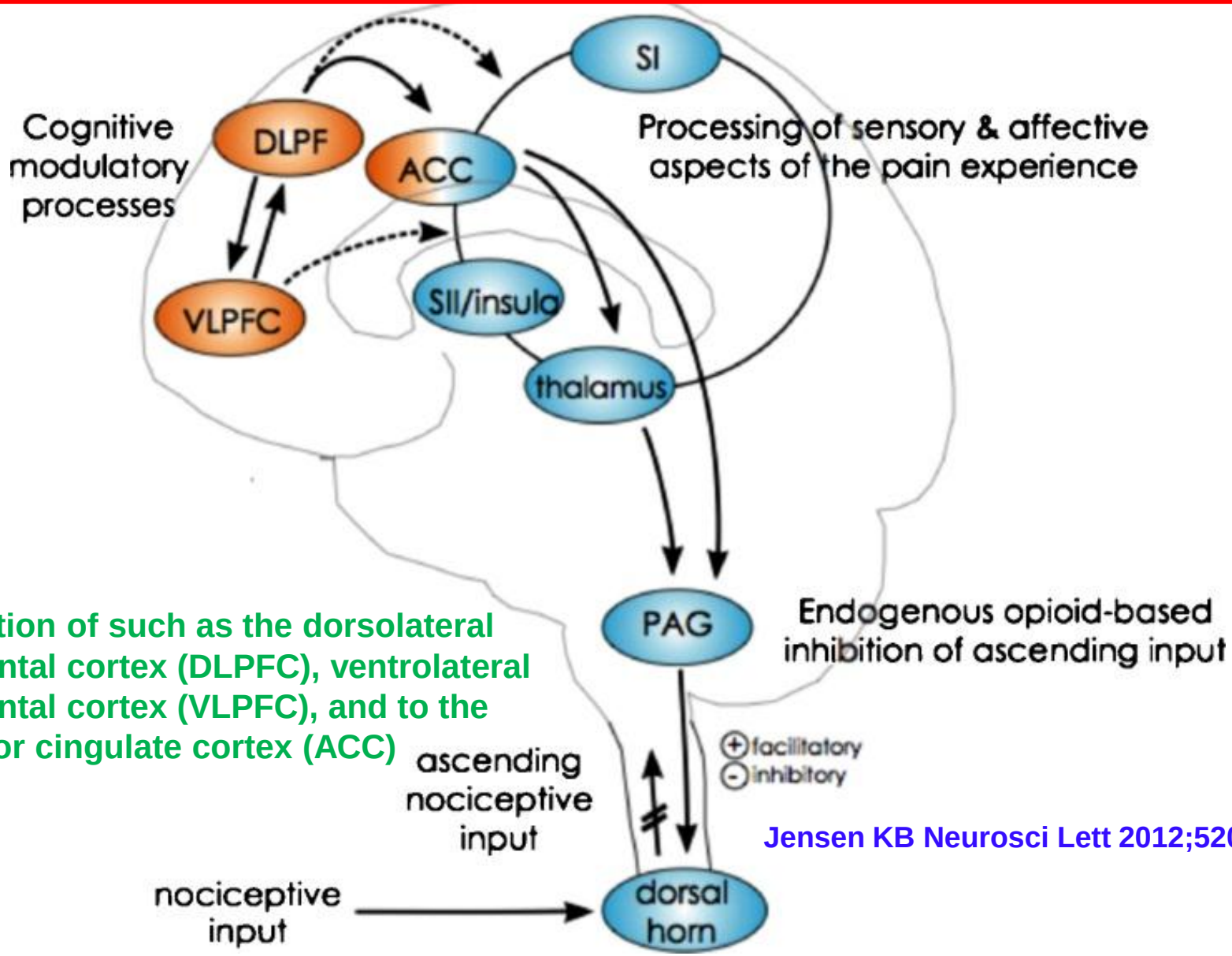
Affect-related areas: volume decreases in regions with the onset of anxiety-like behaviour

Psychological Effects



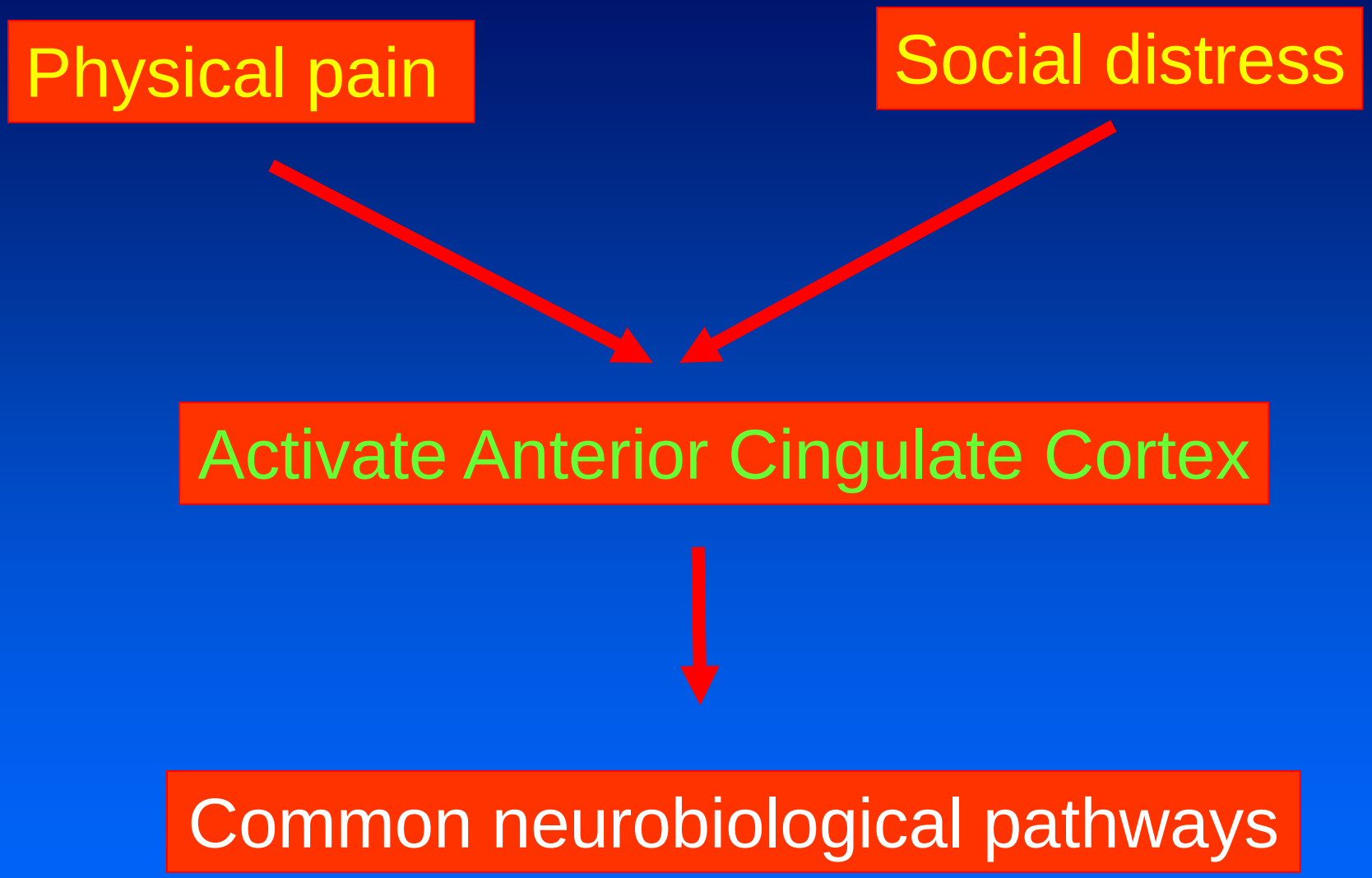
Cur Opin Anaesth 2001;14:536

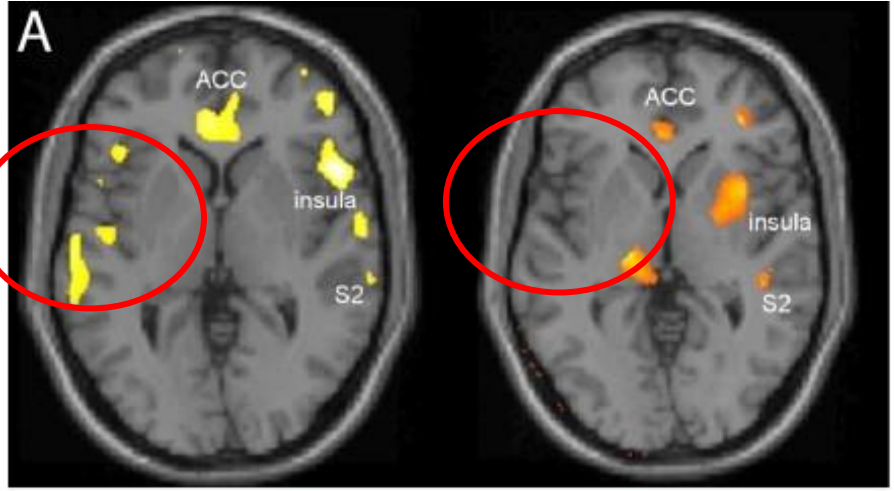
E - Cognitive Modulation of Pain



activation of such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and to the anterior cingulate cortex (ACC)

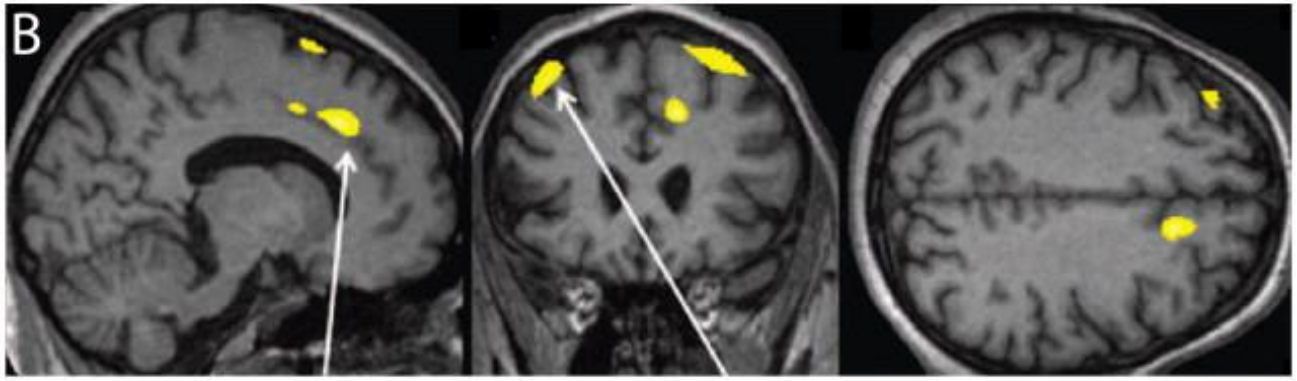
Jensen KB Neurosci Lett 2012;520(2):156-64

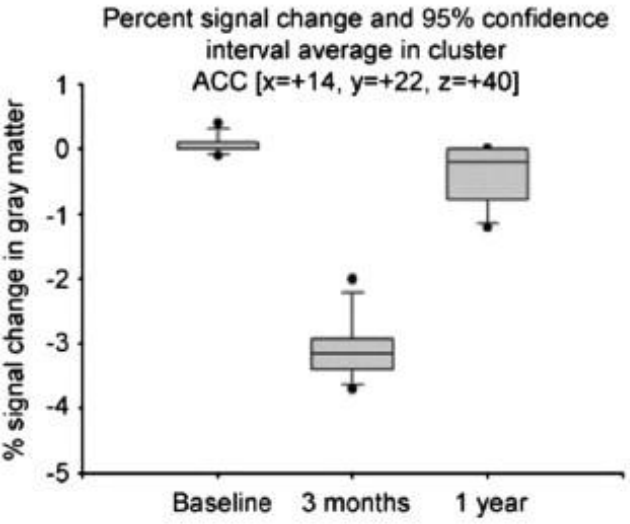

Physical pain
Social distress
Activate Anterior Cingulate Cortex
Common neurobiological pathways

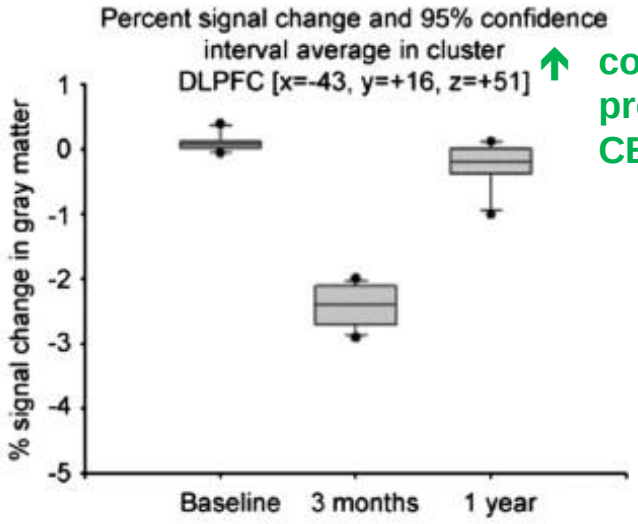


Evaluation of CBT in FM patients
Jensen KB Neurosci Lett 2012;520(2):156-64

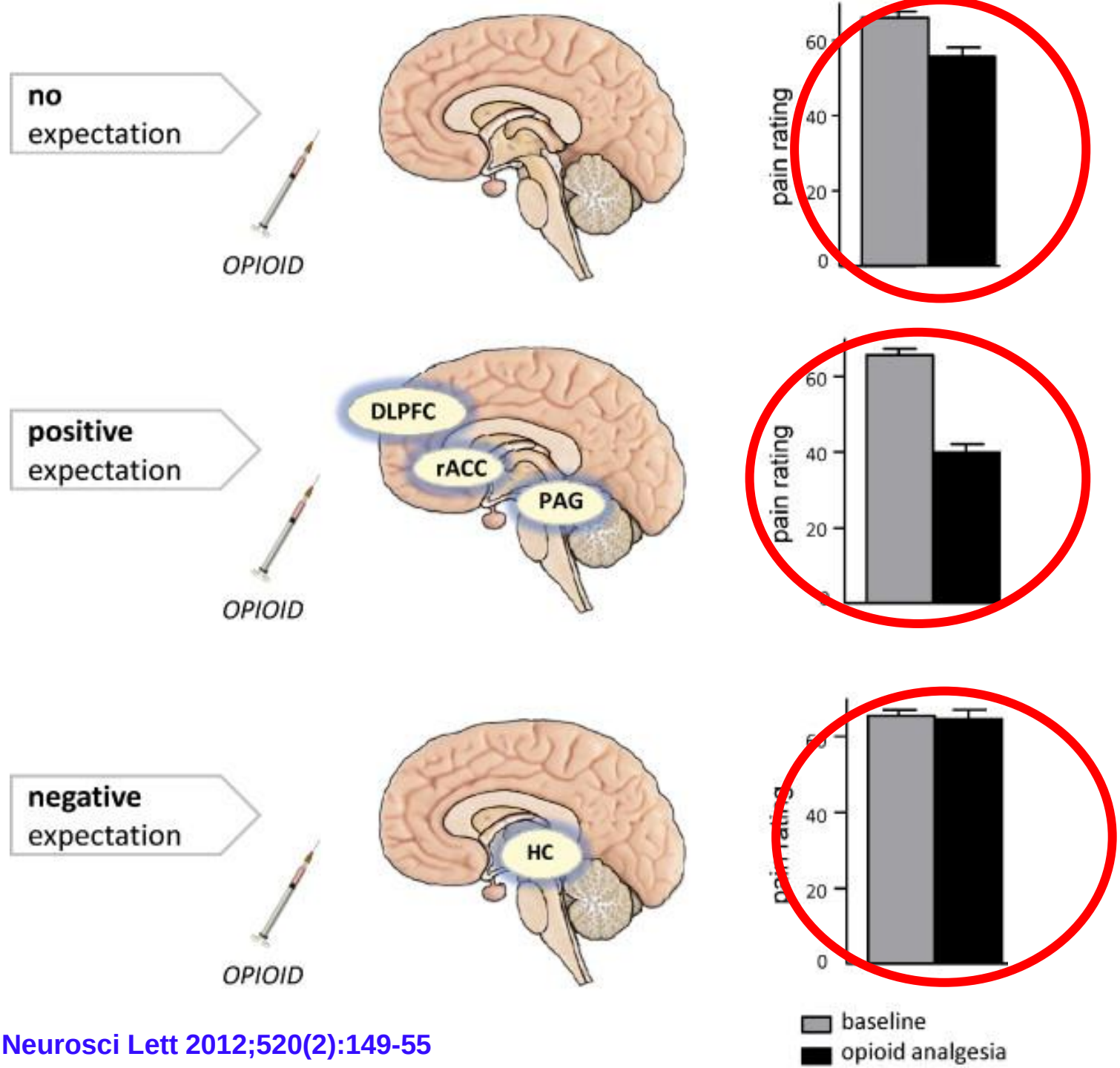
↑ pain-evoked brain activity in the left lateral prefrontal cortex in CBT group after treatment, compared to controls





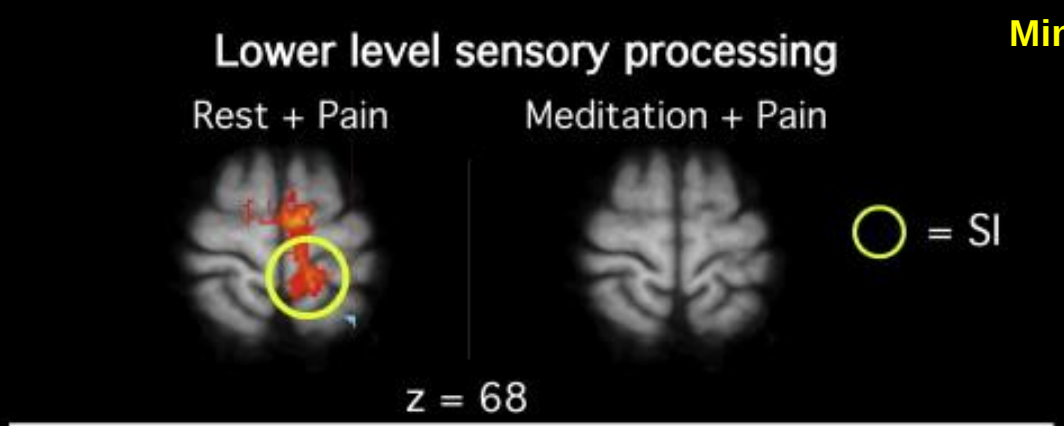


↑ connectivity between the left lateral prefrontal cortex and the thalamus in CBT group, compared to controls

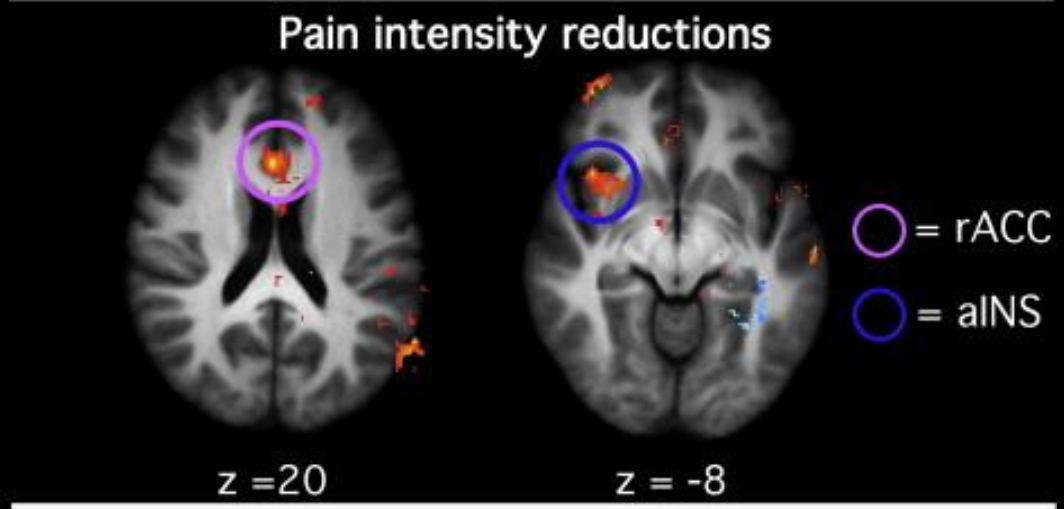


Bingel U. Neurosci Lett 2012;520(2):149-55

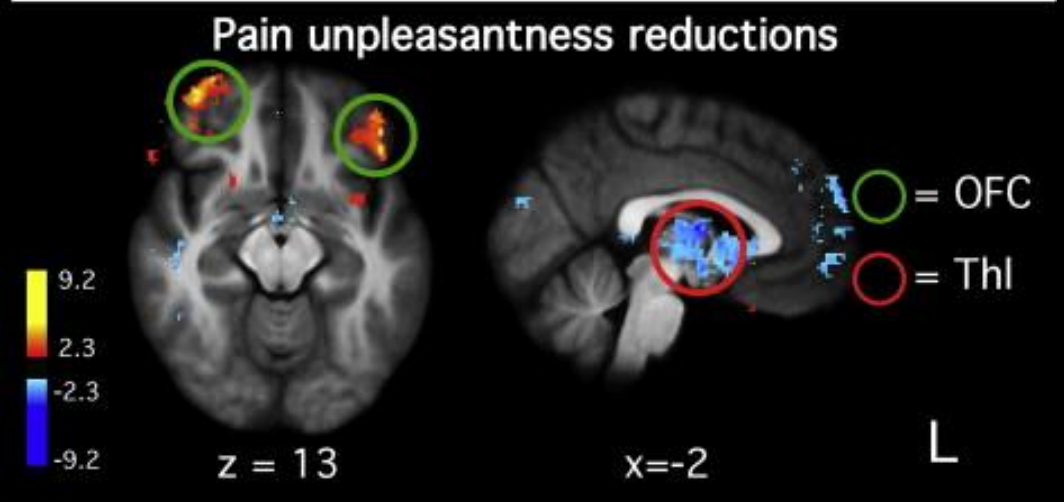
Mindfulness meditation significantly reduced pain (Zeidan F. Neurosci Lett 2012;520(2):165-73)



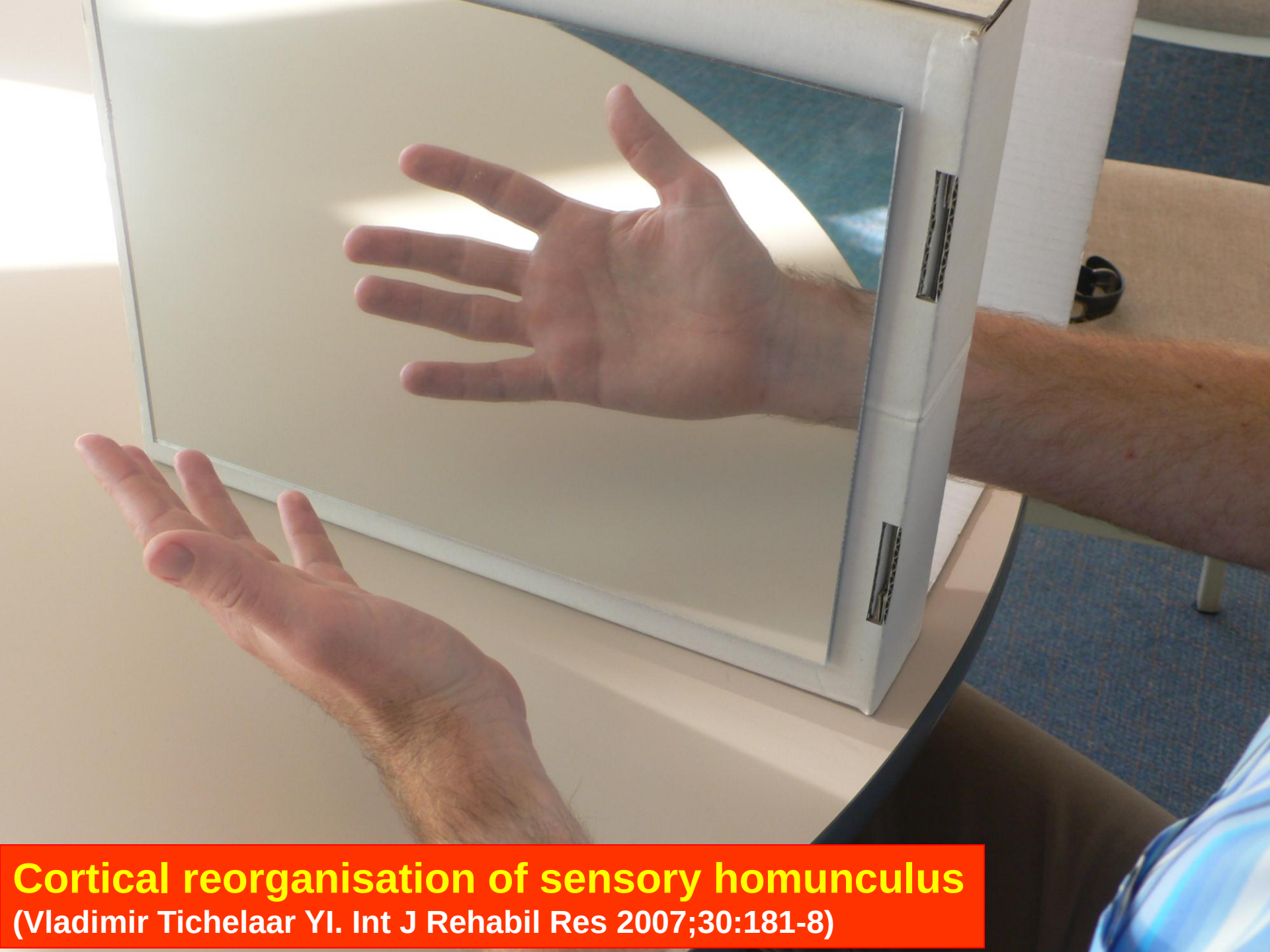
noxious heat, meditation significantly ⬇ lower level afferent processing in primary somatosensory cortex (SI)



meditation-related pain intensity reductions were associated with greater activity in rostral anterior cingulate cortex (rACC), an area involved in cognitive control



Greater orbitofrontal cortex (OFC) activity was associated with greater decreases in pain unpleasantness ratings. Moreover, thalamic (Thl) deactivation was associated with reductions in pain unpleasantness

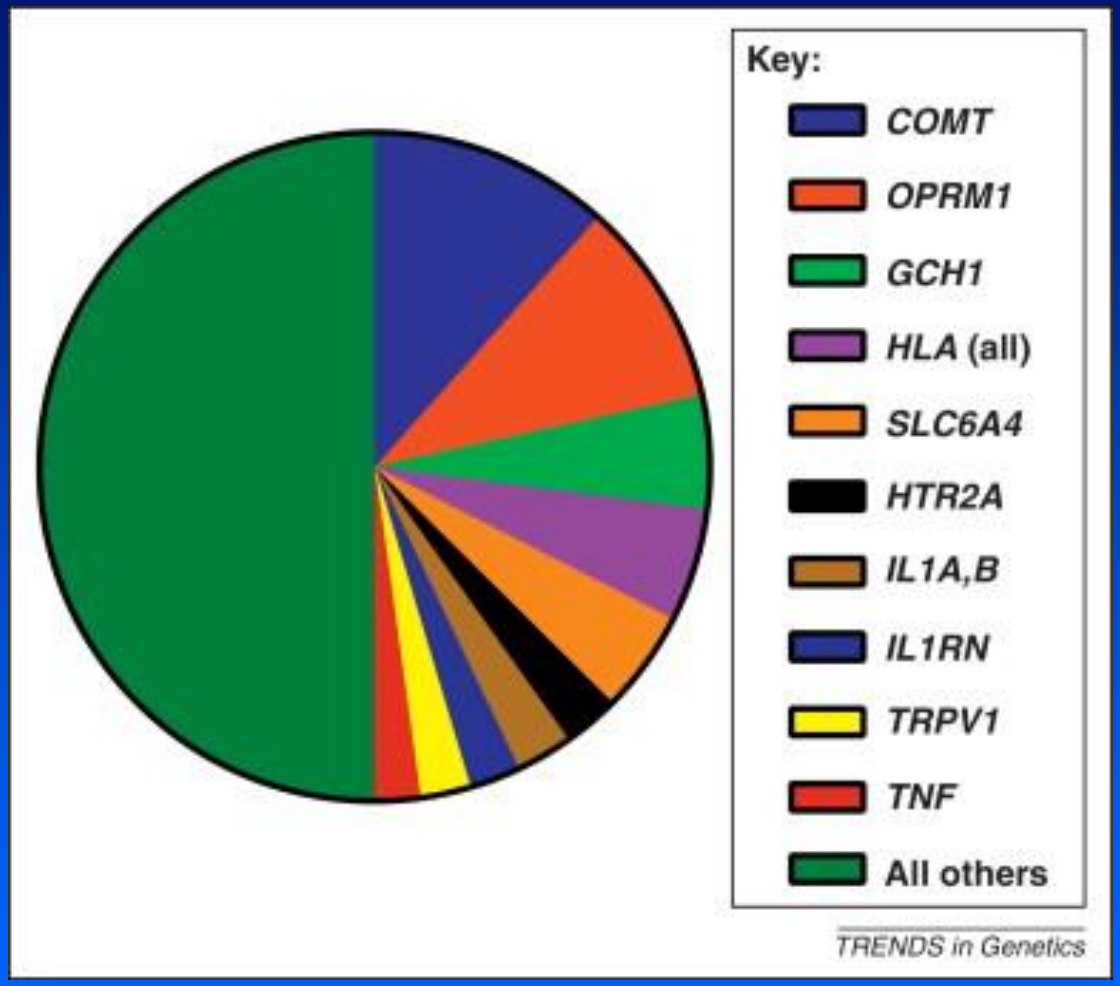


Cortical reorganisation of sensory homunculus
(Vladimir Tichelaar YI. Int J Rehabil Res 2007;30:181-8)

F- Genetics and Pain

Knock-Out Mice + Gene Array Studies

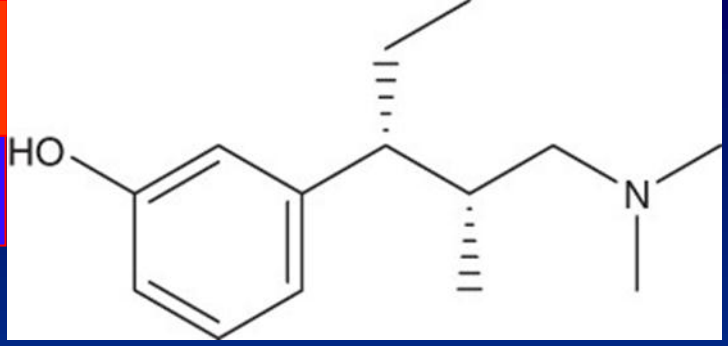
Mogil JS. Trends Genet 2012;28(6):258-66



G. New Drugs - Tapentadol

MOR-NRI

open-chain structure



strong μ-opioid receptor agonism
noradrenaline reuptake inhibition

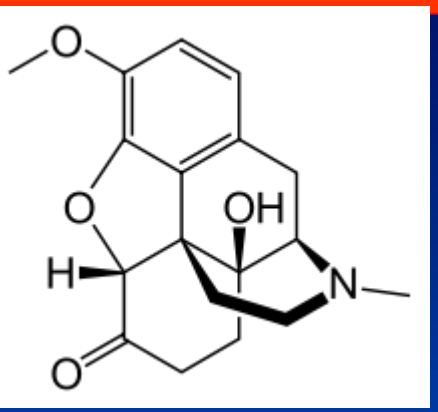
undergoes phase II metabolism (glucuronidation)

controlled substance with reduced gastrointestinal adverse effects

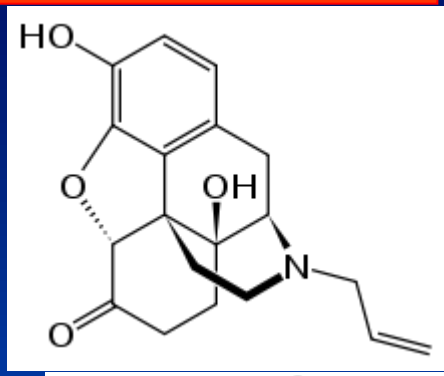
potency/ efficacy comparable to strong opioids

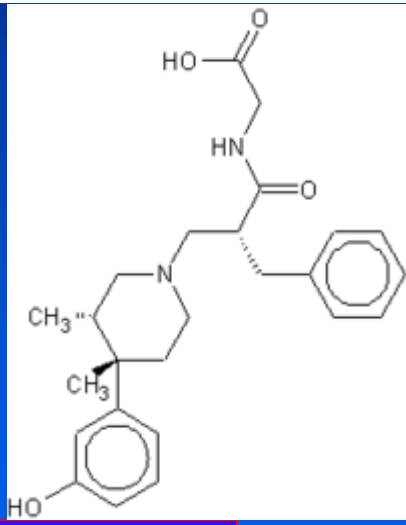
no analgesically active metabolite

Opioid Antagonists



Oral Oxycodone with Naloxone (Targin) in ratio of 2:1





Methylnaltrexone
does not pass blood–brain barrier; analgesic effect of opioids is unaffected; 0.15 mg/kg SC

Alvimopan
peripherally acting
μ-opioid receptor antagonist
accelerates GI recovery
12mg bd po

G. – New Drugs

Ampakines

obtund opioid-induced side-effects

Opiorphin

inhibits breakdown of endogenous opioids (targets endocannabinoid system)

Tanezumab

humanised monoclonal antibody that sequesters NGF - effective analgesic in lumbar osteoarthritis

CB2 modulators

H. Neuropathic Pain – small fibre neuropathies

decreased intra-epidermal nerve fibre density after skin punch biopsy

I - New Delivery Systems

transdermal buccal, intra-articular intravesical routes

↓ toxicity of local anaesthetics and opioids

Transdermal drug delivery limited by stratum corneum

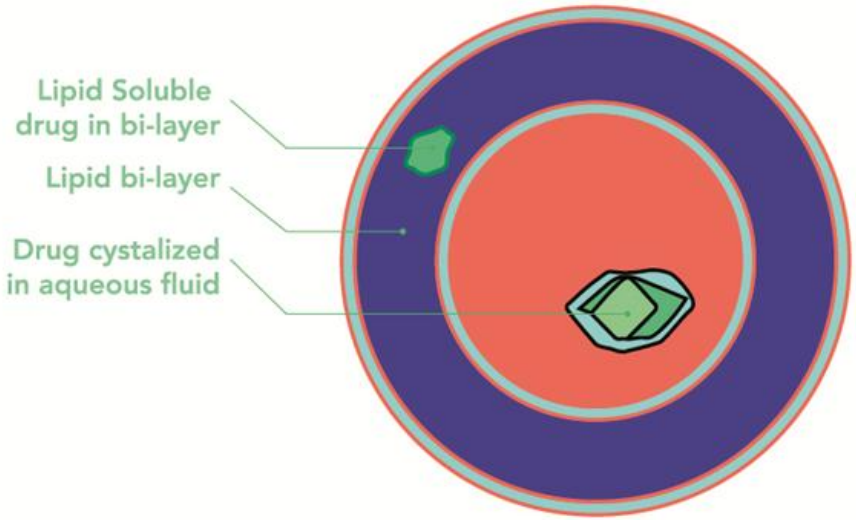
iontophoresis
electroporation
microporation
phonophoresis

Lipid-based nanocarriers (liposomes, lipid-core micelles, and lipid nanocapsules)

Vesicular systems

(ethosomes, transfersomes and niosomes)

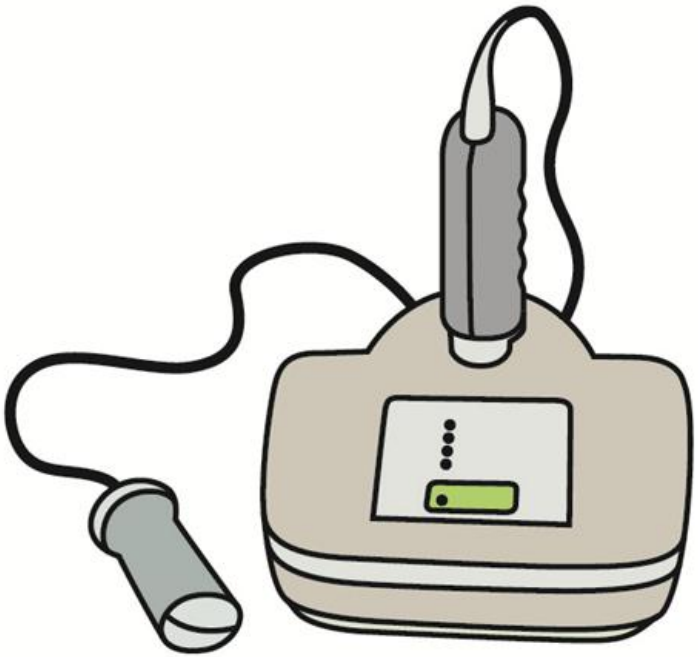
Liposome for Drug Delivery



Liposome for Drug Delivery

(Shipton EA. Anesthesiol Res Pract 2012;2012:546409)

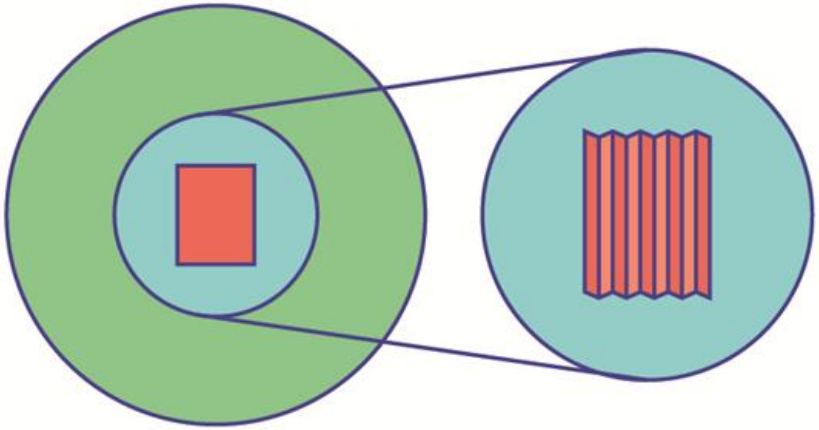
Sonophoresis



Sonophoresis

(Shipton EA. TACC 2012: in press)

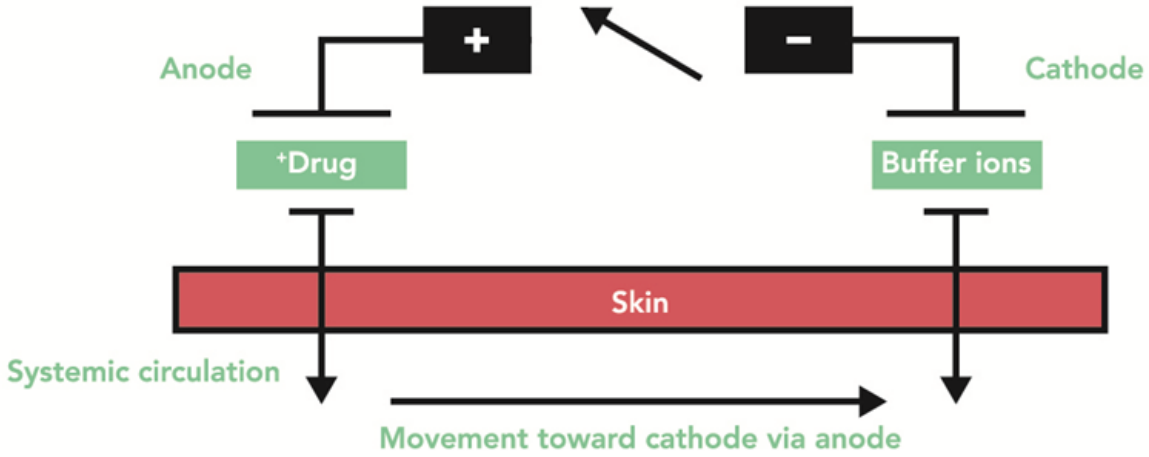
Magnetophoresis



(Shipton EA. TACC 2012: in press)

Iontophoresis

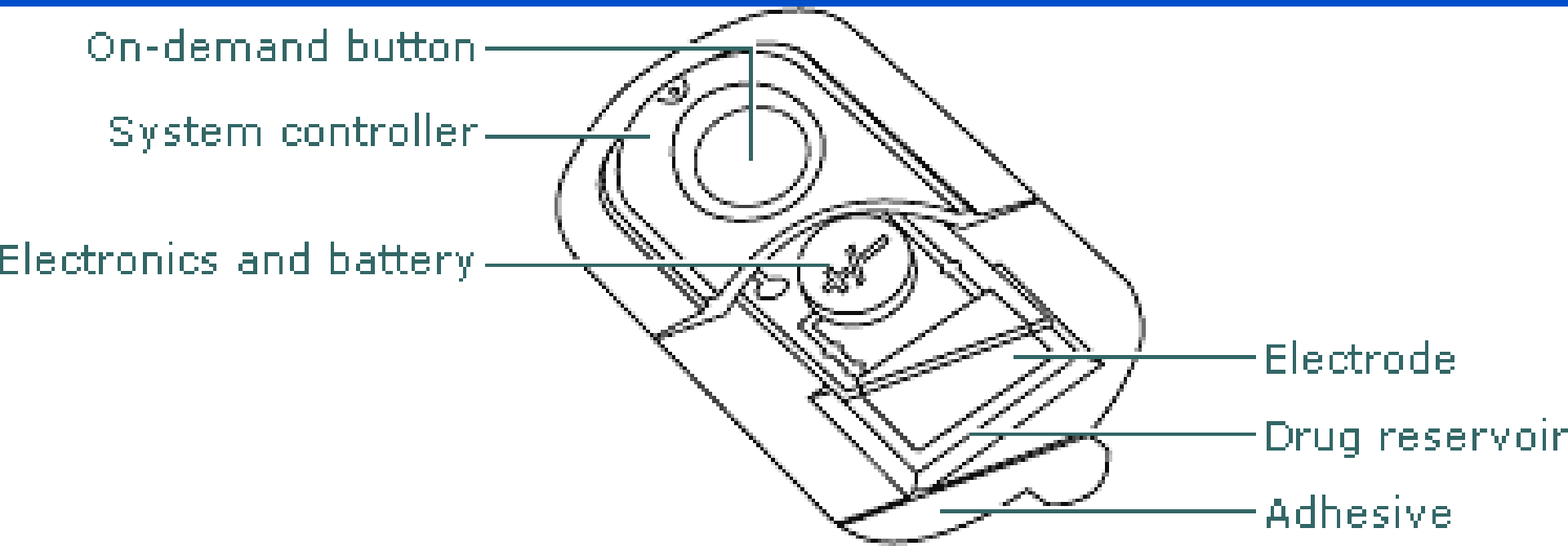
when current is applied drug cations are repelled; they move through skin, and absorbed into systemic circulation

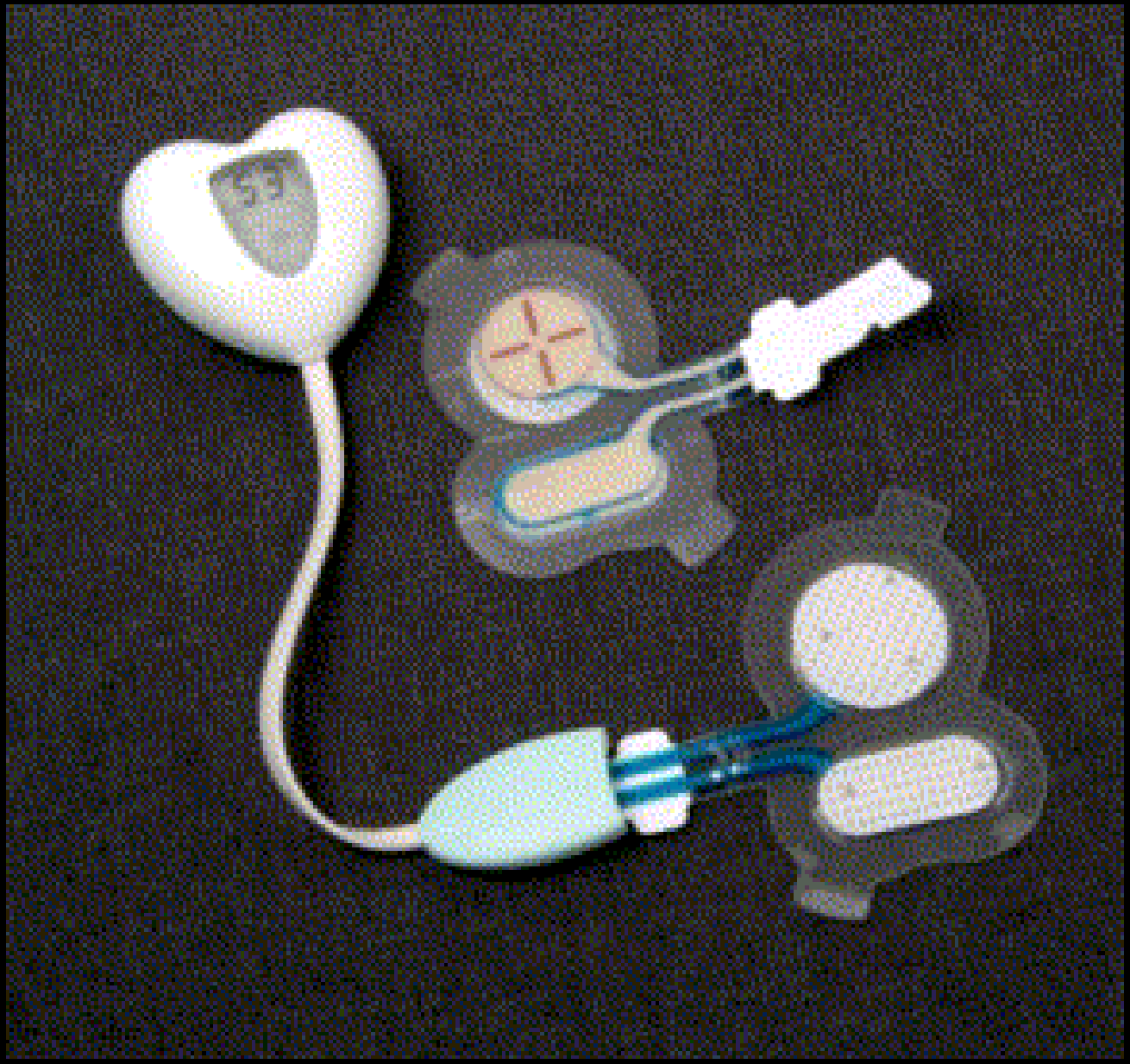


(Shipton EA. TACC 2012: in press)

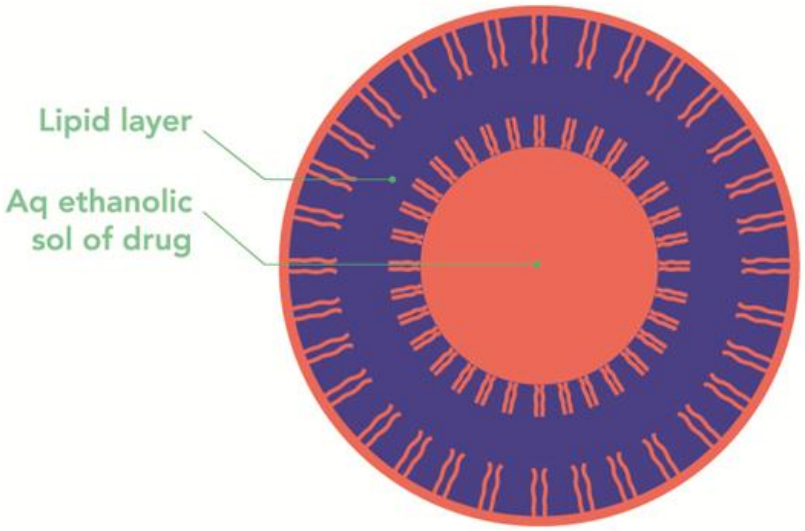
Fentanyl HCl PCTS is preprogrammed, needle free, self-contained drug-delivery system that uses electrotransport technology (iontophoresis) to deliver 40 µg of fentanyl per on-demand dose

On-demand fentanyl HCl patient-controlled transdermal system (PCTS) - superior to placebo, well tolerated for the control of moderate to severe postoperative pain for up to 24 h after major surgery (Anesth Analg 2004;98:427-433)





Ethosomes



(Shipton EA. TACC 2012: in press)

J- Neuromodulation

Spinal cord stimulation used for pain failed back surgery CRPS, angina, peripheral vascular disease

electrodes implanted in epidural space, feels paraesthesias in areas of pain that reduces pain

improved quality of life and function, many returning to work

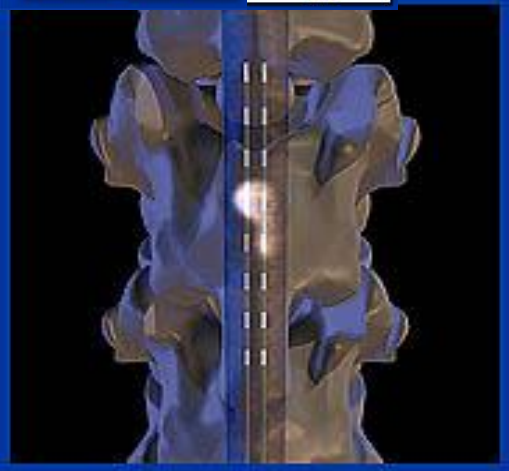
new perspective in cerebral ischaemia and vasospasm

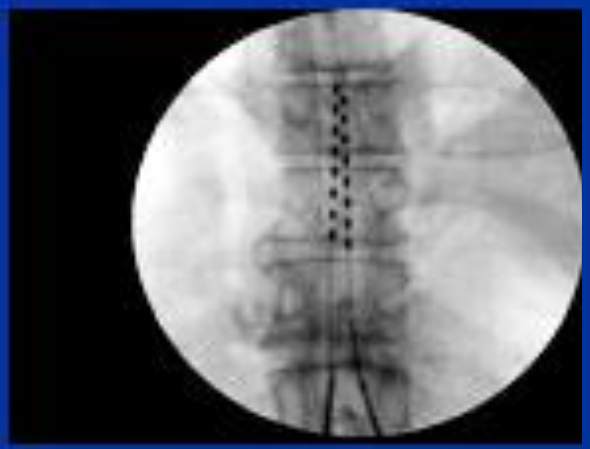
Nevro-Senza technology
high frequency signal, no paraesthesia

Peripheral nerve stimulation
neuropathic pain disorders, occipital neuralgia, migraine, subcutaneous leads

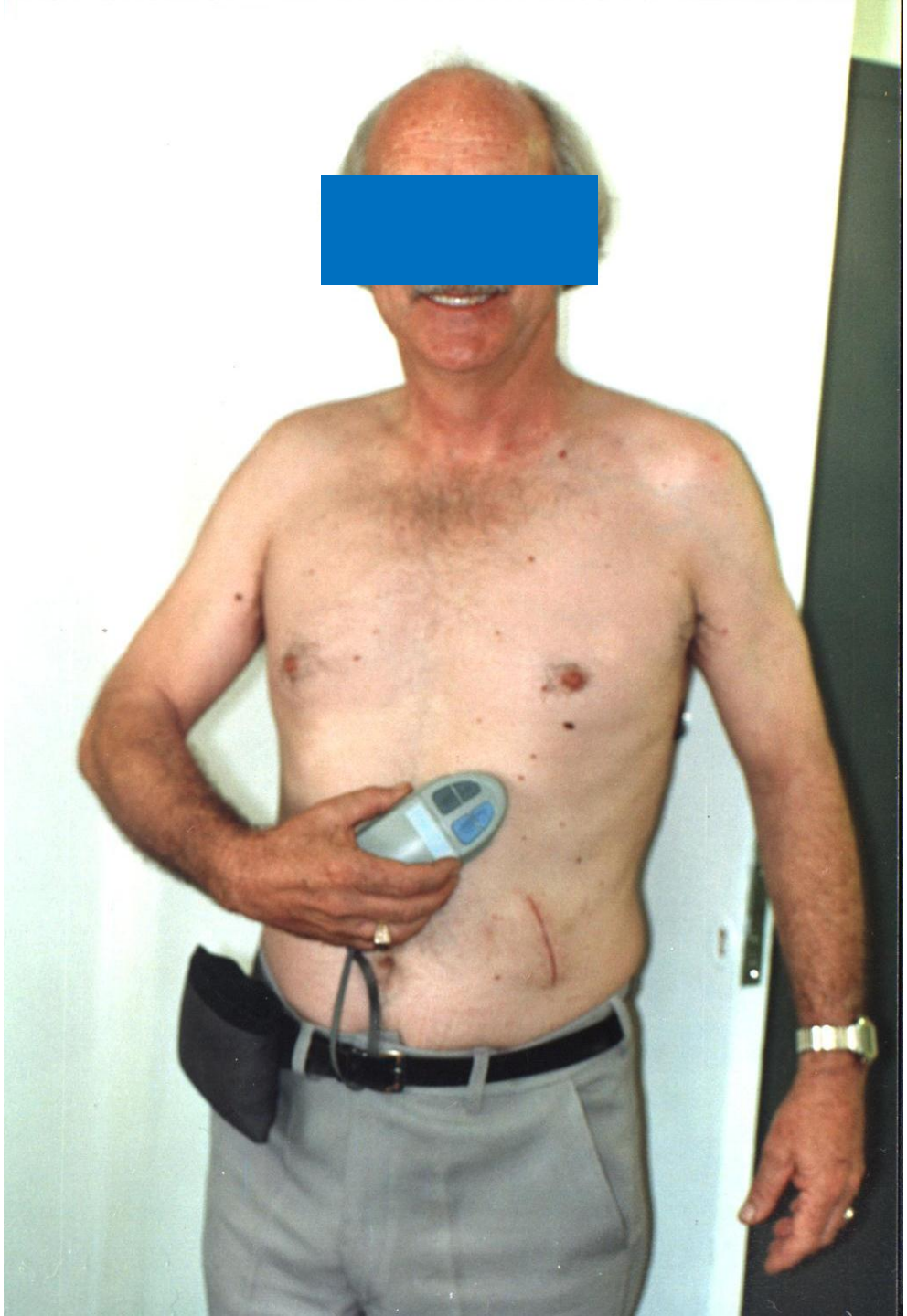
Deep brain stimulation
technique for painful dystonia (CRPS); use in pain and cluster headache

Spinal Cord Stimulation



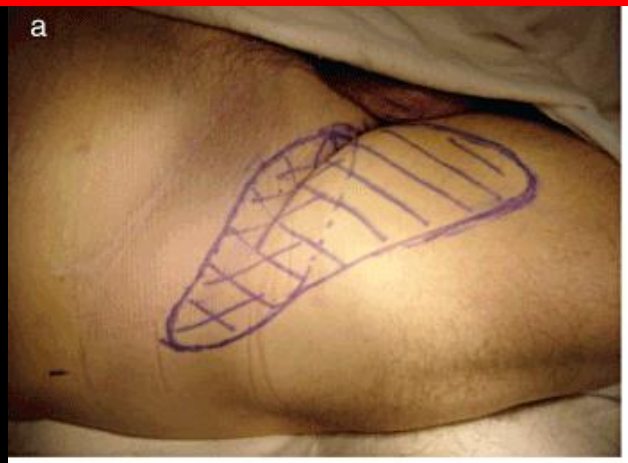


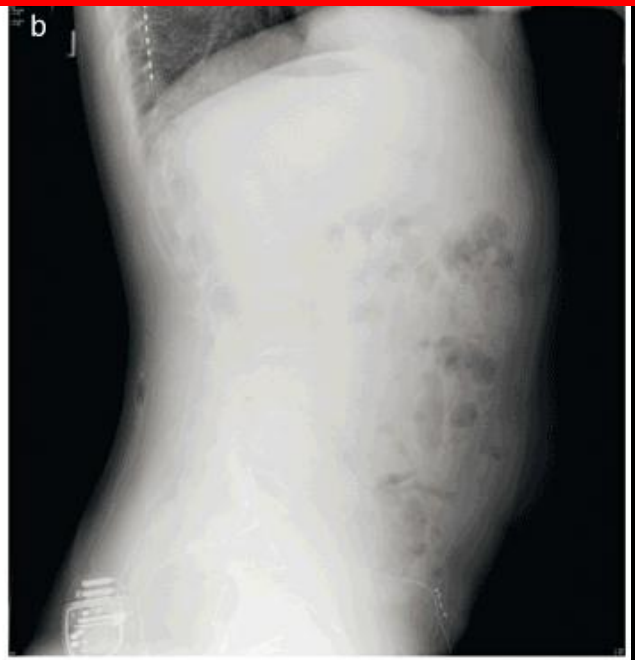

16.....9
8.....1
NIPG1000
SN 001066
nevro
senza™
THIS SIDE UP

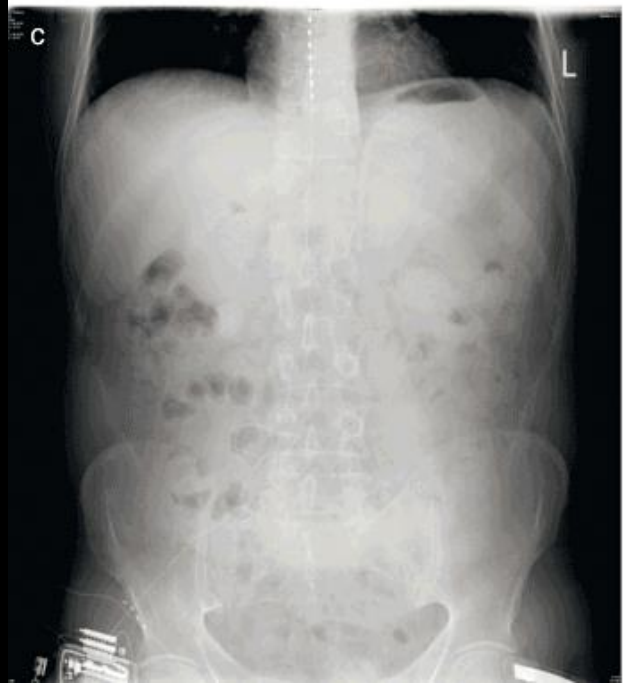


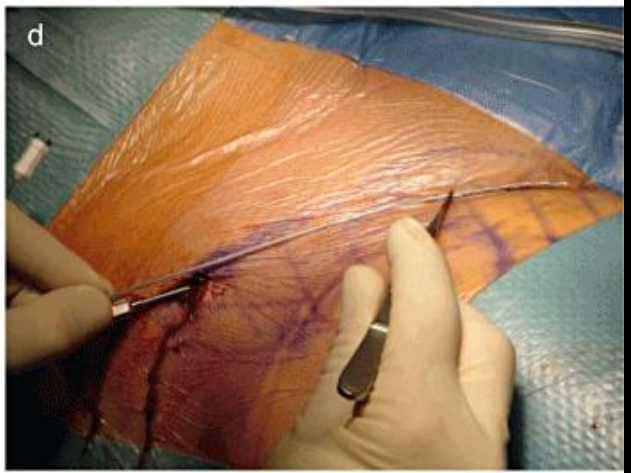
Combined Spinal Cord and Peripheral Nerve Field Stimulation for Persistent Post-Herniorrhaphy Pain

(Neuromodulation June 2012: in press)



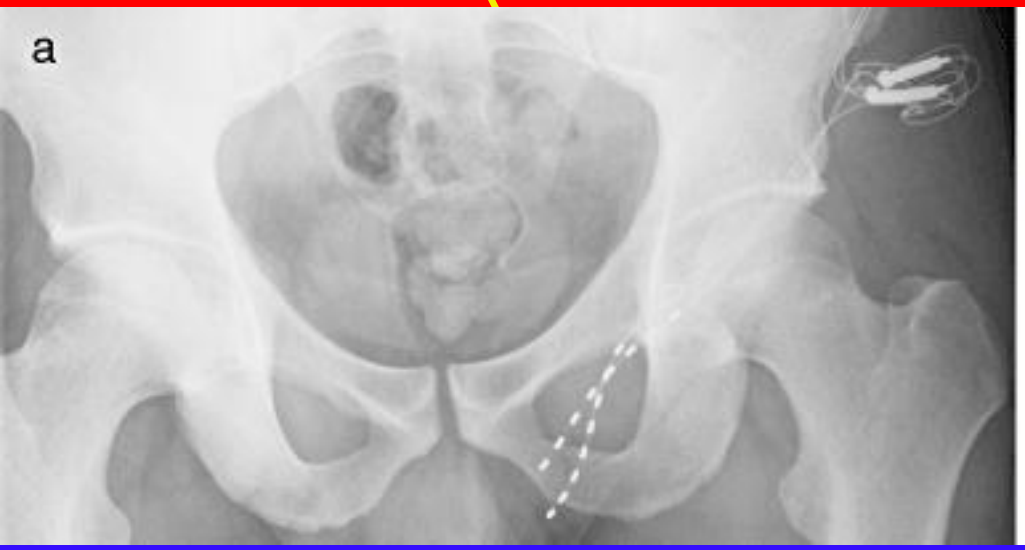


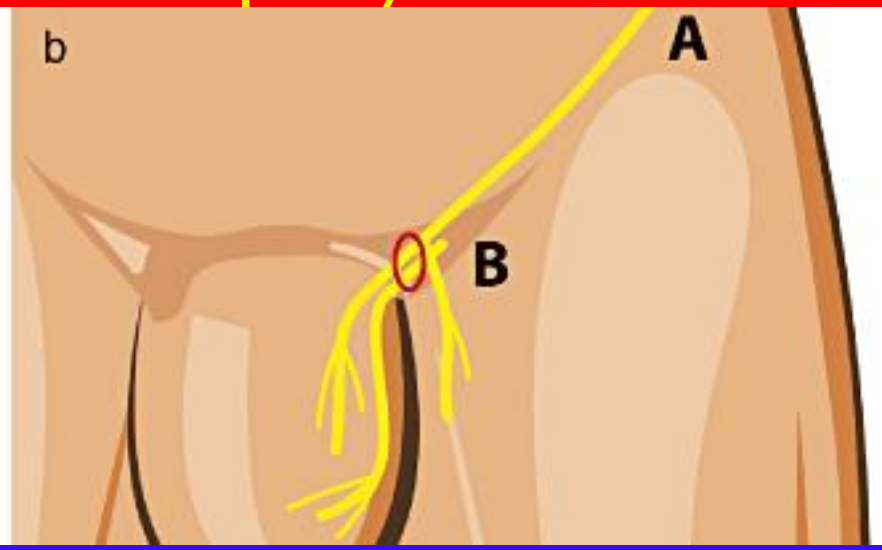


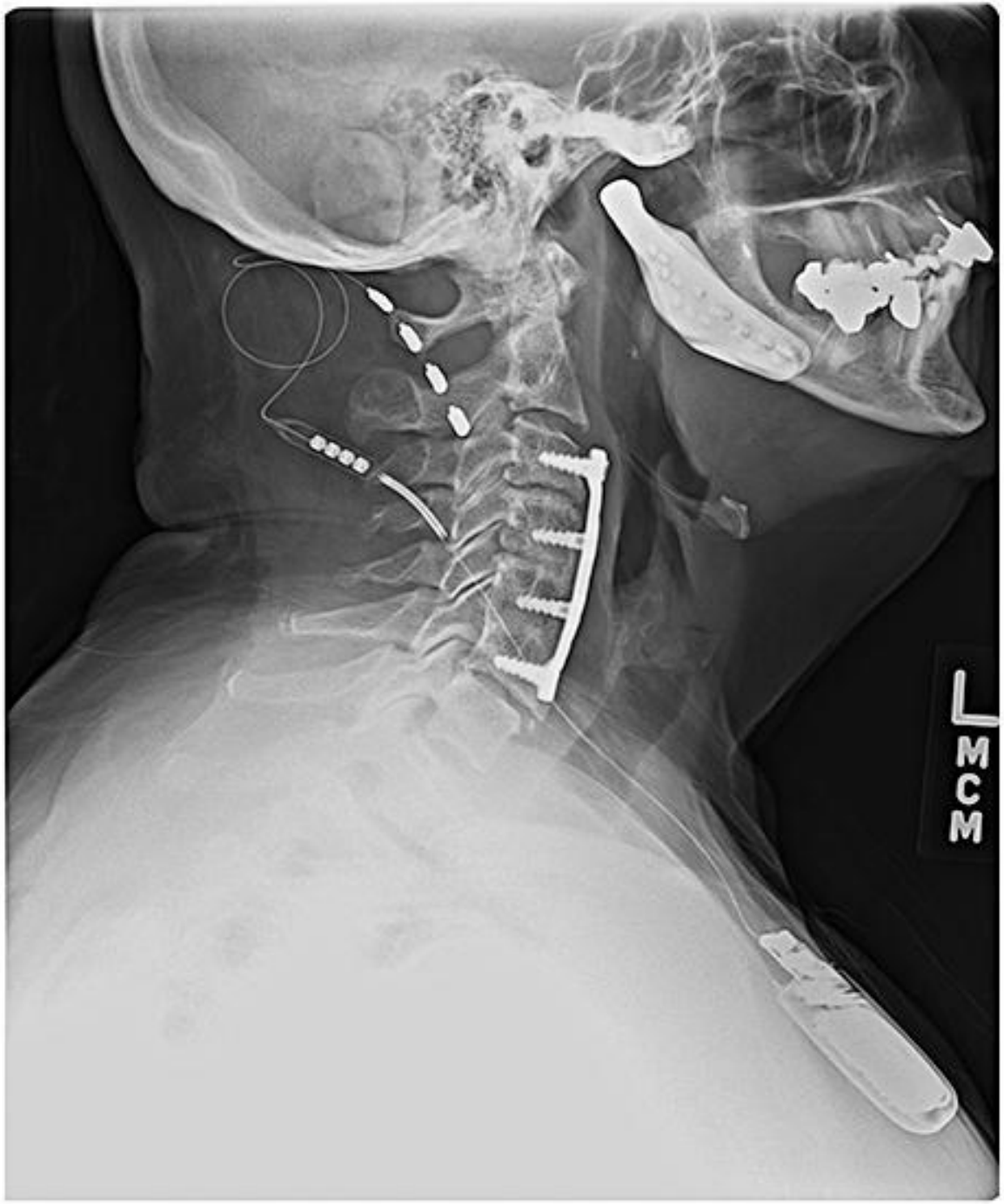


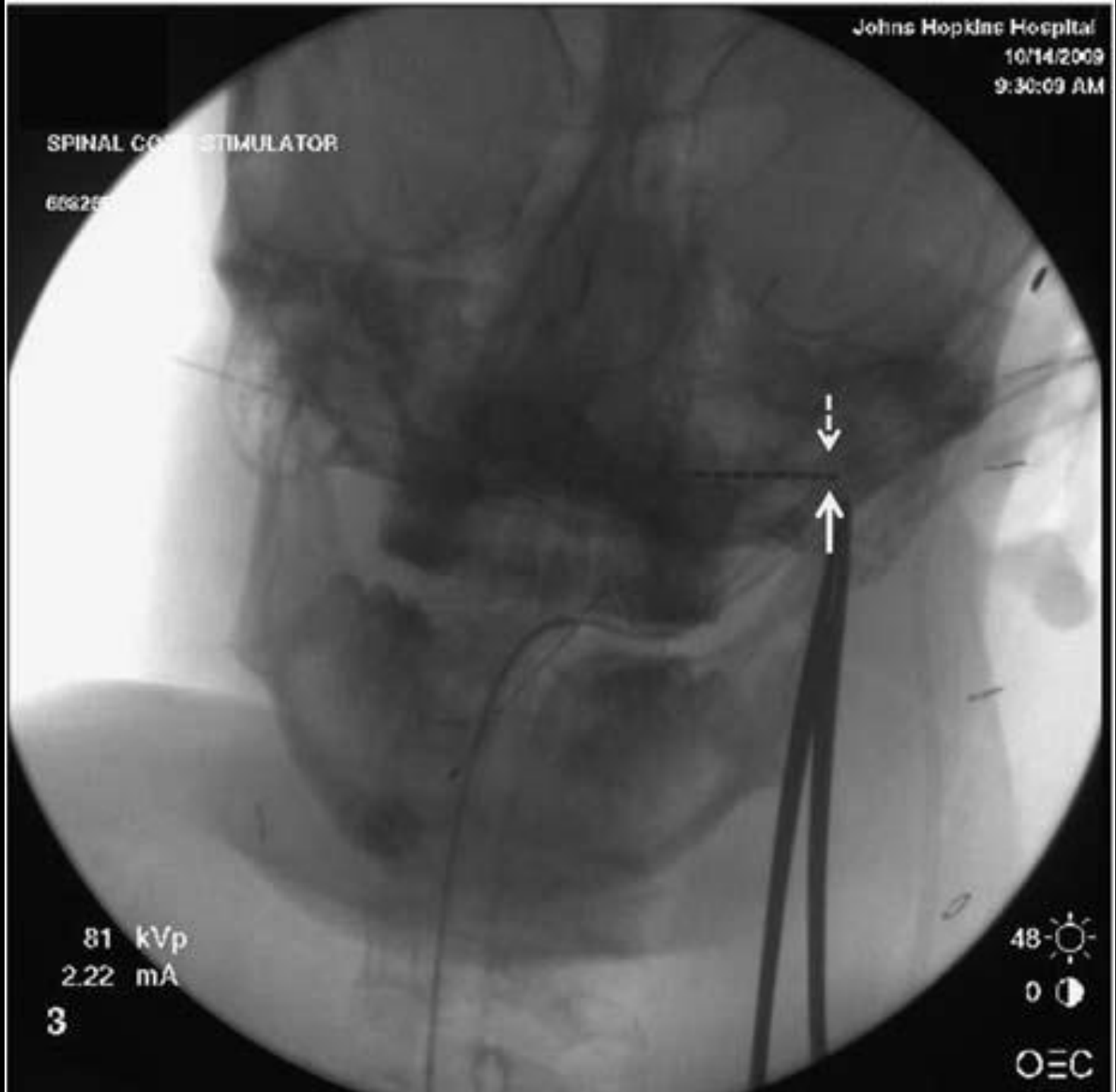
Successful Treatment of Testicular Pain With Peripheral Nerve Stimulation of the Cutaneous Branch of the Ilioinguinal and Genital Branch of the Genitofemoral Nerves

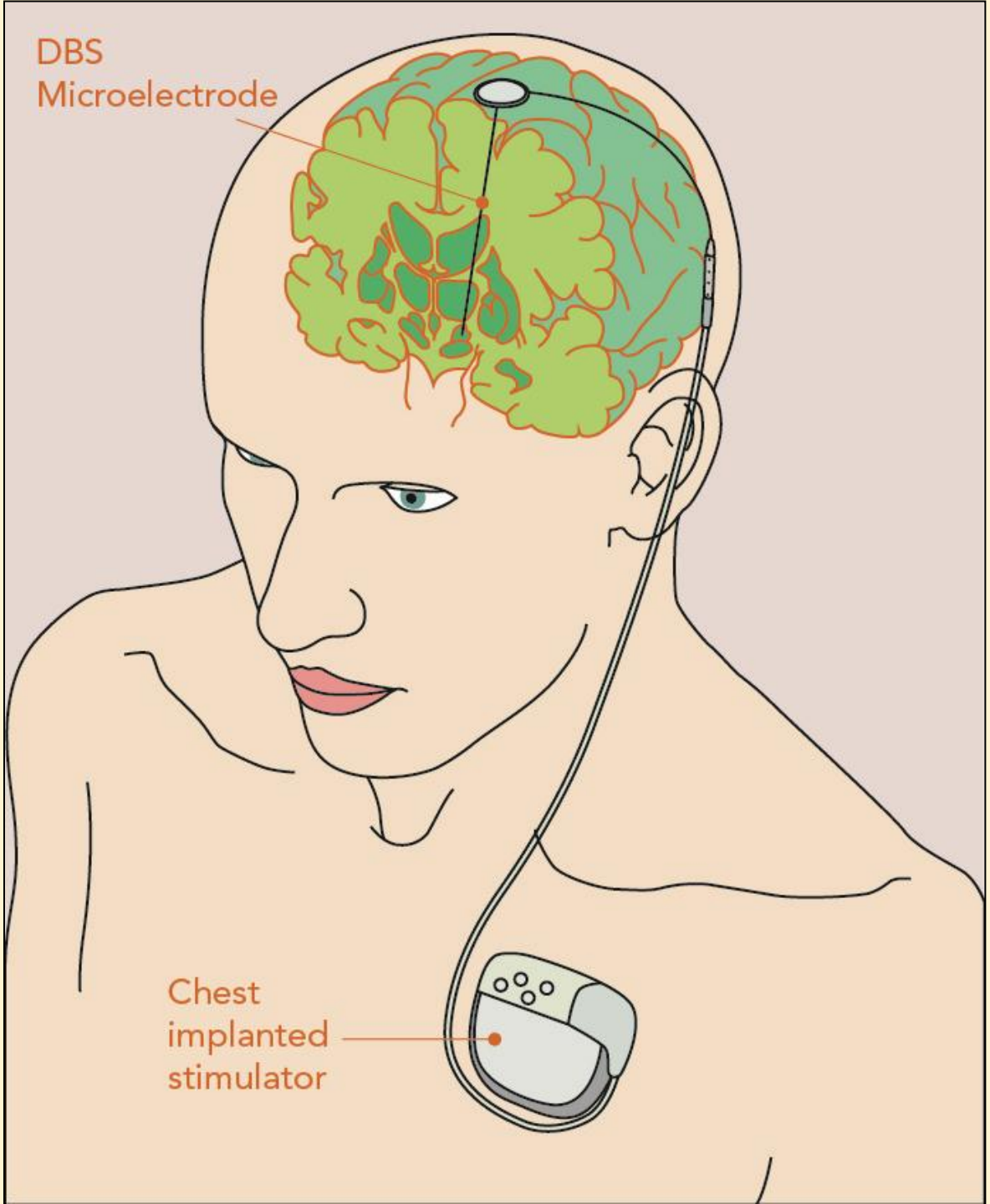
(Neuromodulation Jan 2012: in press)





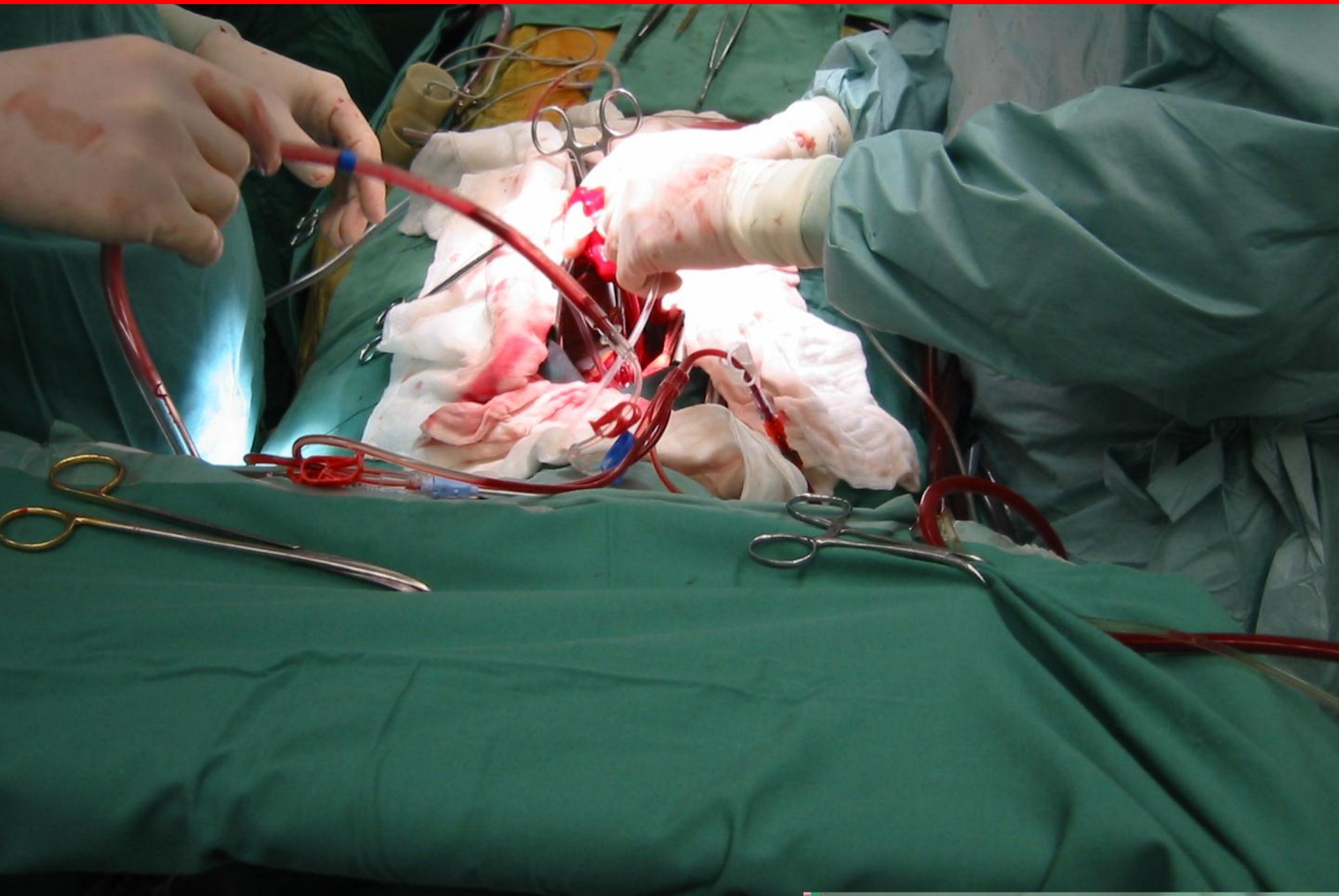

L
MCM


Johns Hopkins Hospital
10/14/2009
9:30:09 AM
SPINAL CO STIMULATOR
81 kVp
2.22 mA
3
48
0
OEC



Shipton EA
Neurol Res Int 2012: in press.

K - Perioperative Pain



Types of surgery	Estimated incidence of chronic postoperative pain (%)
Hysterectomy	15
Hip Surgery	10 – 20
Amputation	30 – 50
Breast surgery	20 – 30
Thoracotomy	30 – 40
Inguinal hernia repair	10
Coronary artery bypass	30 – 50
Caesarean section	10

K - Perioperative Pain

transition of acute postoperative pain to chronic post-surgical pain - complex and poorly understood

involves altered pain processing

intraoperative postoperative surgical, psychosocial, socio-environmental patient-related factors

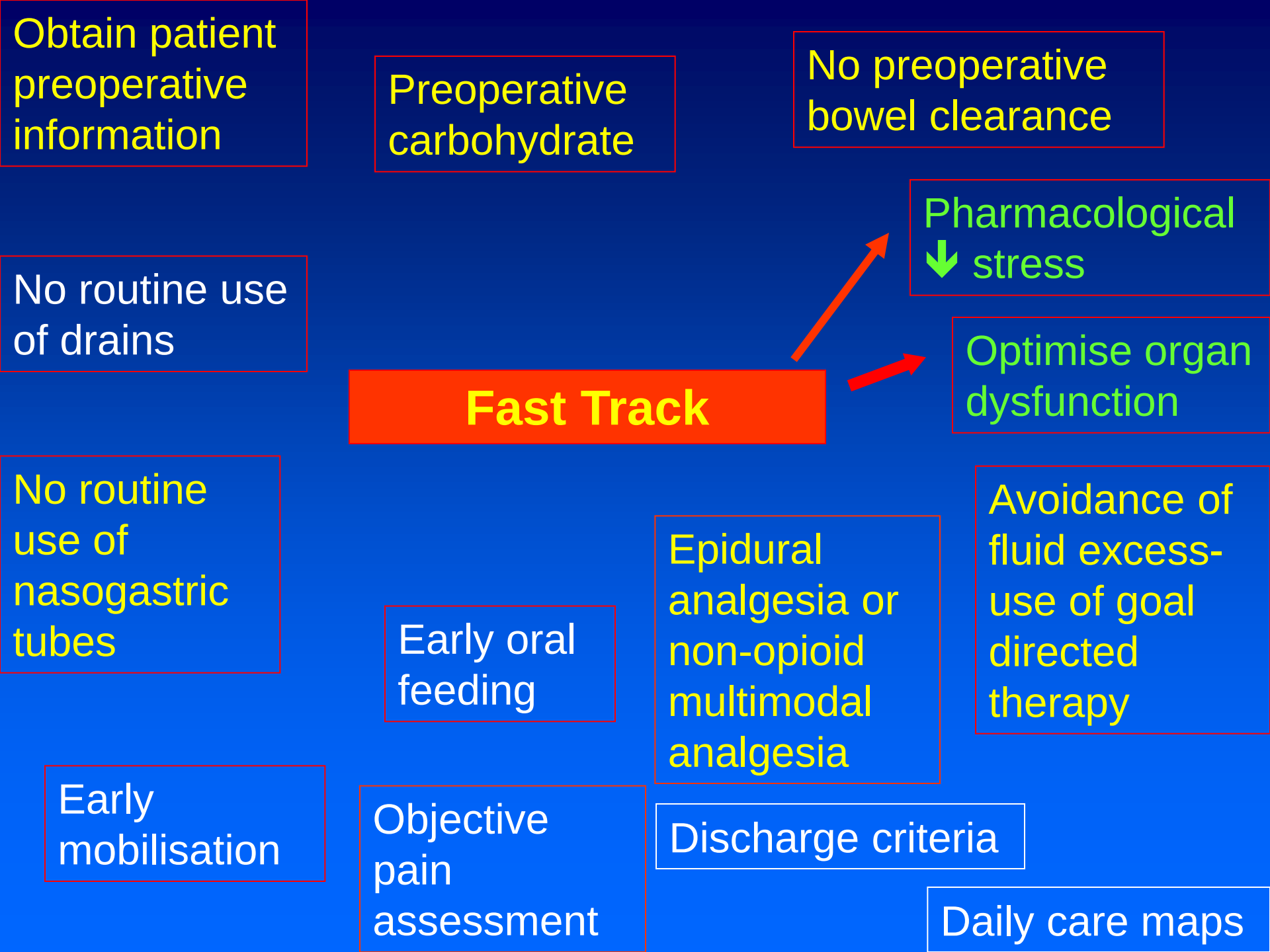
multimodal analgesic drug combinations

fast tracking multidisciplinary teams

Risk Factors – Mark patients with high risk factors for developing persisting post surgical pain and follow up after discharge	
Preoperative	
	Address patient attitudes and concerns Provide education (patient, physician) Identify operative procedures that cause severe pain
Intraoperative	
	Use least painful surgical approach (e.g. keyhole) with acceptable exposure Use multimodal pharmacological analgesia in addition to afferent neural blockade
Postoperative	
	Continue analgesia well into the postoperative period Measure pain levels (the 'fifth vital sign') Bedside neurological examination if neuropathic pain is suspected
Discharge	
	Individualise discharge analgesic packages and home follow-up Use antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin) as first-line co-analgesics if needed

Prevention and Management of Risk factors in Acute Perioperative pain for developing Chronic pain

(Shipton EA. Anaesth Intensive Care. 2011 Sep;39(5):824-36)


Obtain patient preoperative information
Preoperative carbohydrate
No preoperative bowel clearance
Pharmacological ↓ stress
No routine use of drains
Optimise organ dysfunction
Fast Track
No routine use of nasogastric tubes
Avoidance of fluid excess- use of goal directed therapy
Epidural analgesia or non-opioid multimodal analgesia
Early oral feeding
Early mobilisation
Objective pain assessment
Discharge criteria
Daily care maps

L. - Cancer Therapy

Intrathecal analgesia

Radiofrequency techniques (for tumour ablation, neurotomies)

Imaging Thoracoscopy give safer coeliac plexus and splanchnic nerve blocks

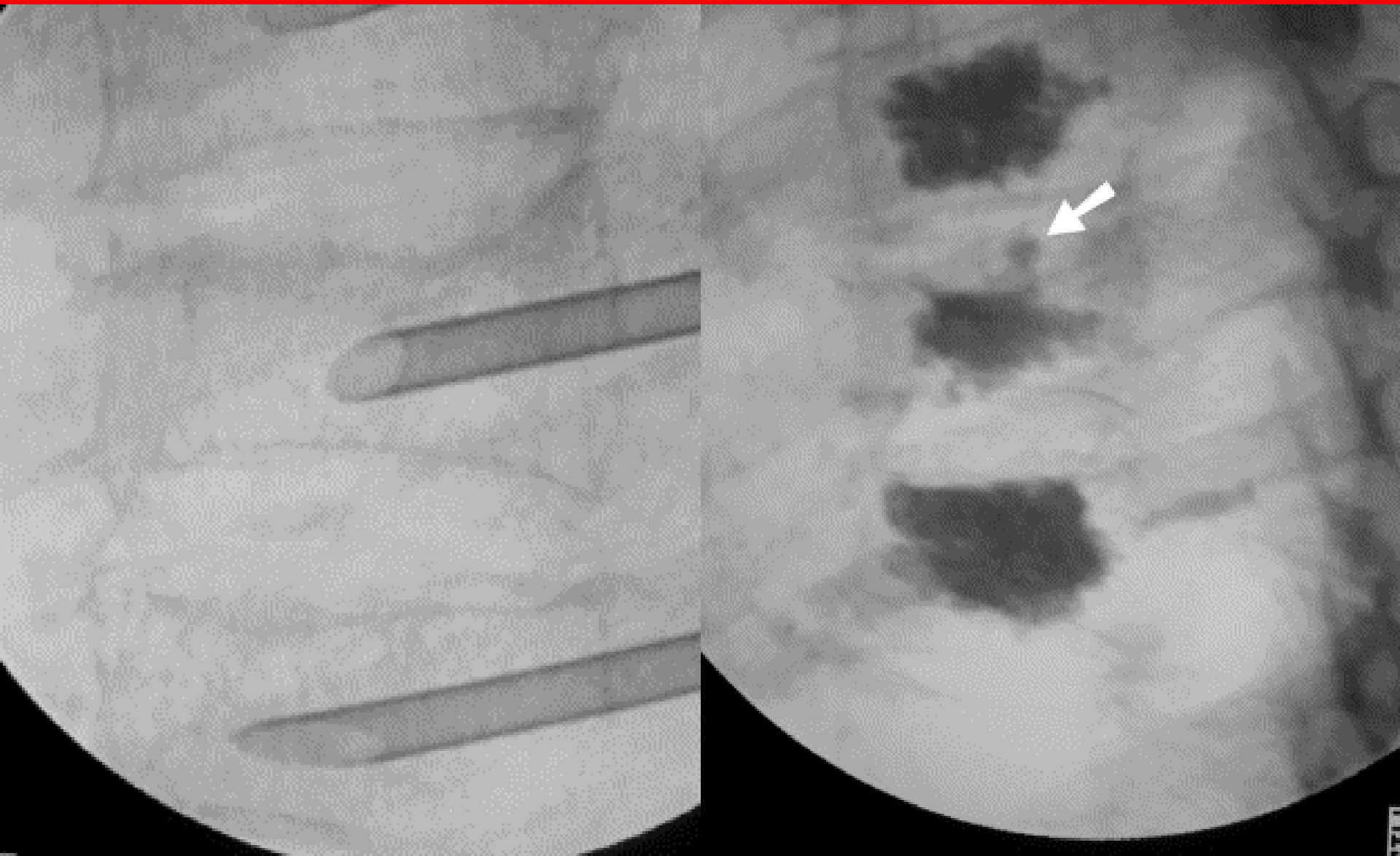
Vertebroplasty techniques for pain relief, stabilisation

Percutaneous cordotomy aided by computed tomography/MRI and endoscopy guidance

Percutaneous electrical nerve stimulation, 8% capsaicin patches used for neuropathic pain

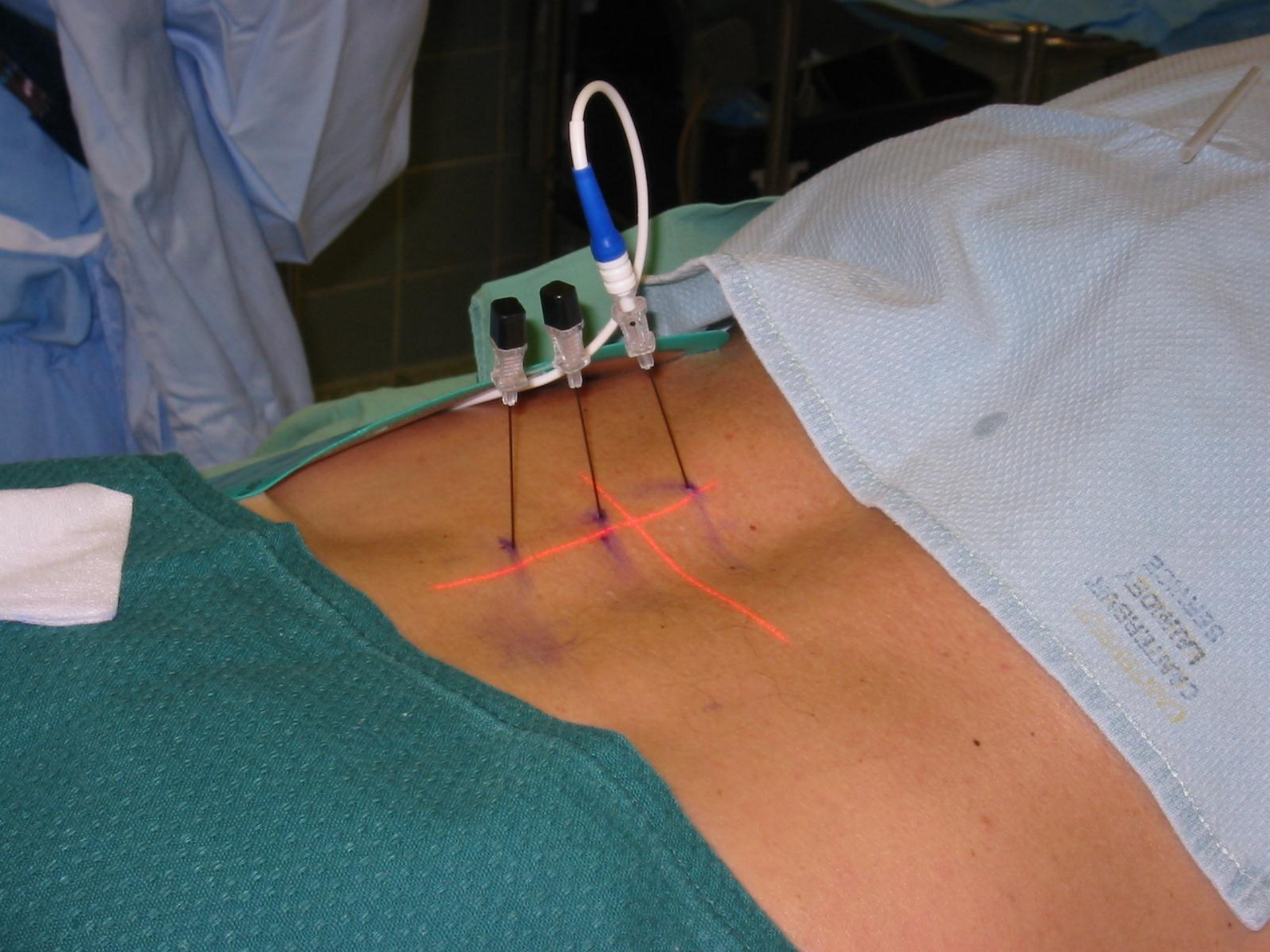
Radiofrequency Machine

Percutaneous Vertebroplasty

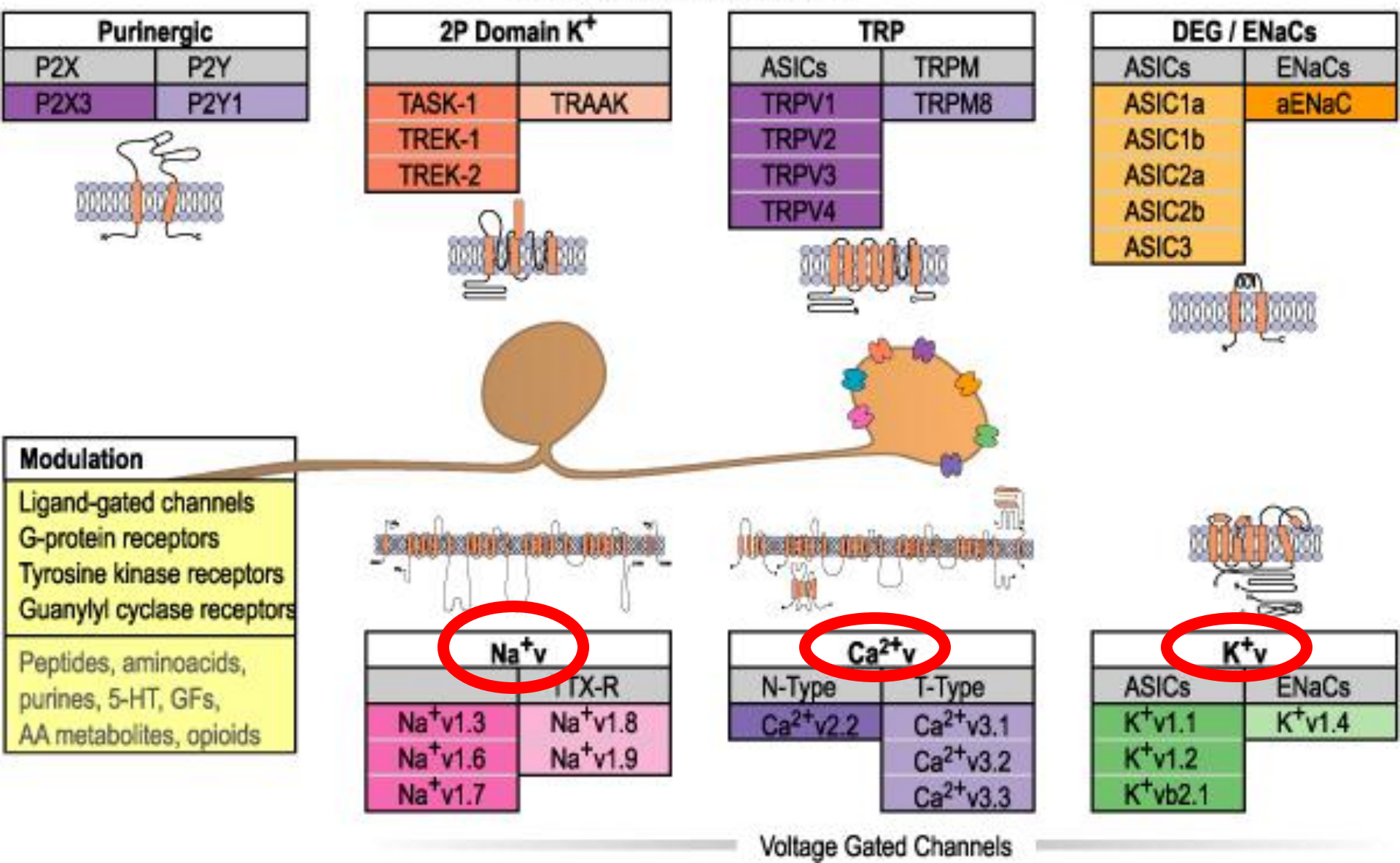


M. Conclusion - Take Home Points

- Patterns of chronic pain in New Zealand are similar to international patterns
- Chronic pain represents a major health issue in New Zealand
- Optimal management of acute and chronic pain start with assessment of patients' expectations, with weighing the pros and cons of potential drug therapies, and to determine an individualised treatment strategy
- Thorough patient assessment with regular review and pharmacovigilance ensure optimal efficacy and safety in prescribing
- Future therapies include focal therapy with sustained analgesic efficacy (capsaicin patches, botulinum toxin)
- Treatments acting on new targets, such as cytokine inhibitors, metabotropic glutamate inhibitors, and TRPV1 antagonists
- Early referral with acute persistent pain



Na^+, Ca^{++}, and K^+ Channels



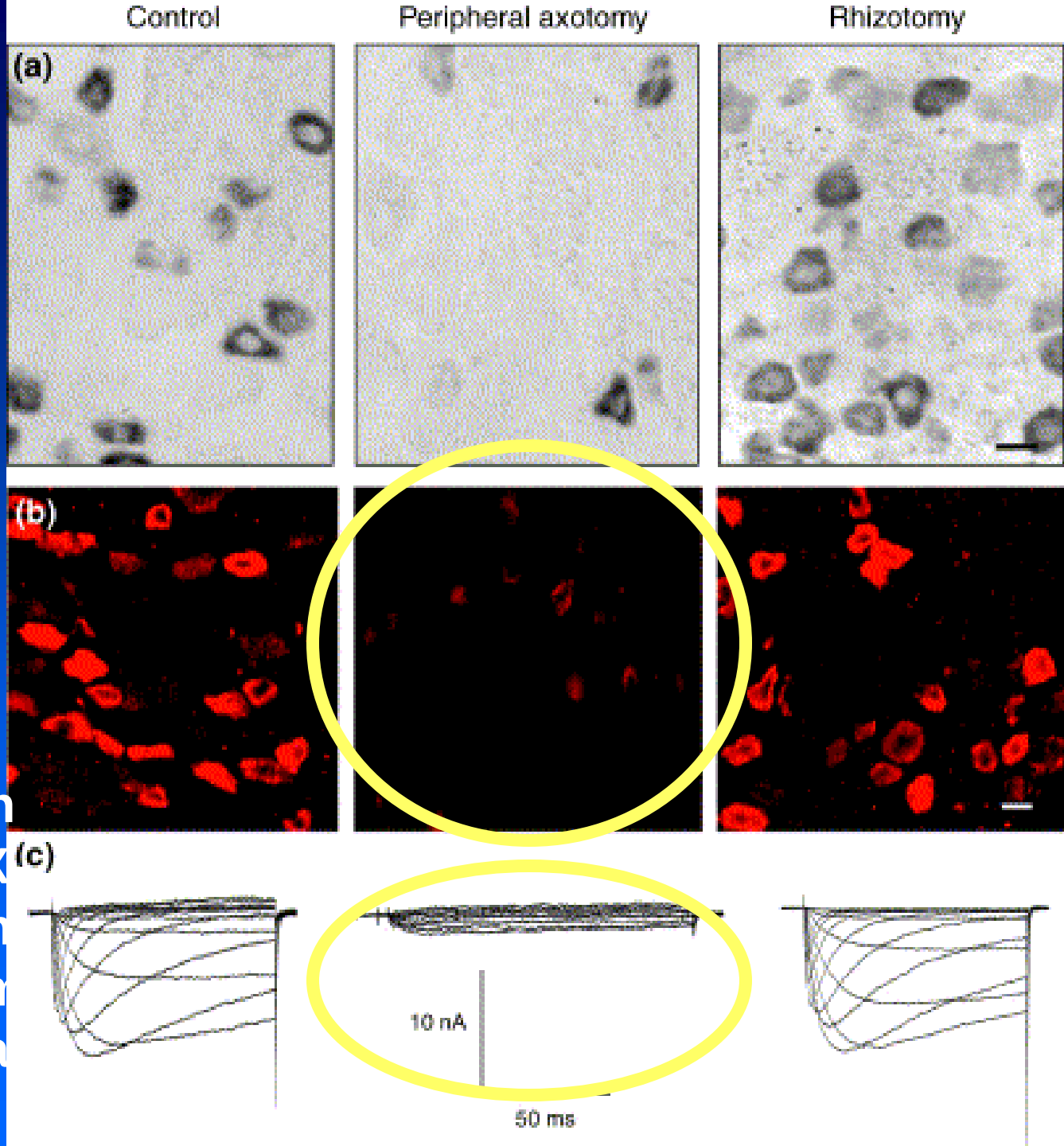
$Na_v1.9$ following nerve injury

(a) *In situ* hybridization

(b) immuno-cytochemistry

(c) whole-cell patch-clamp studies

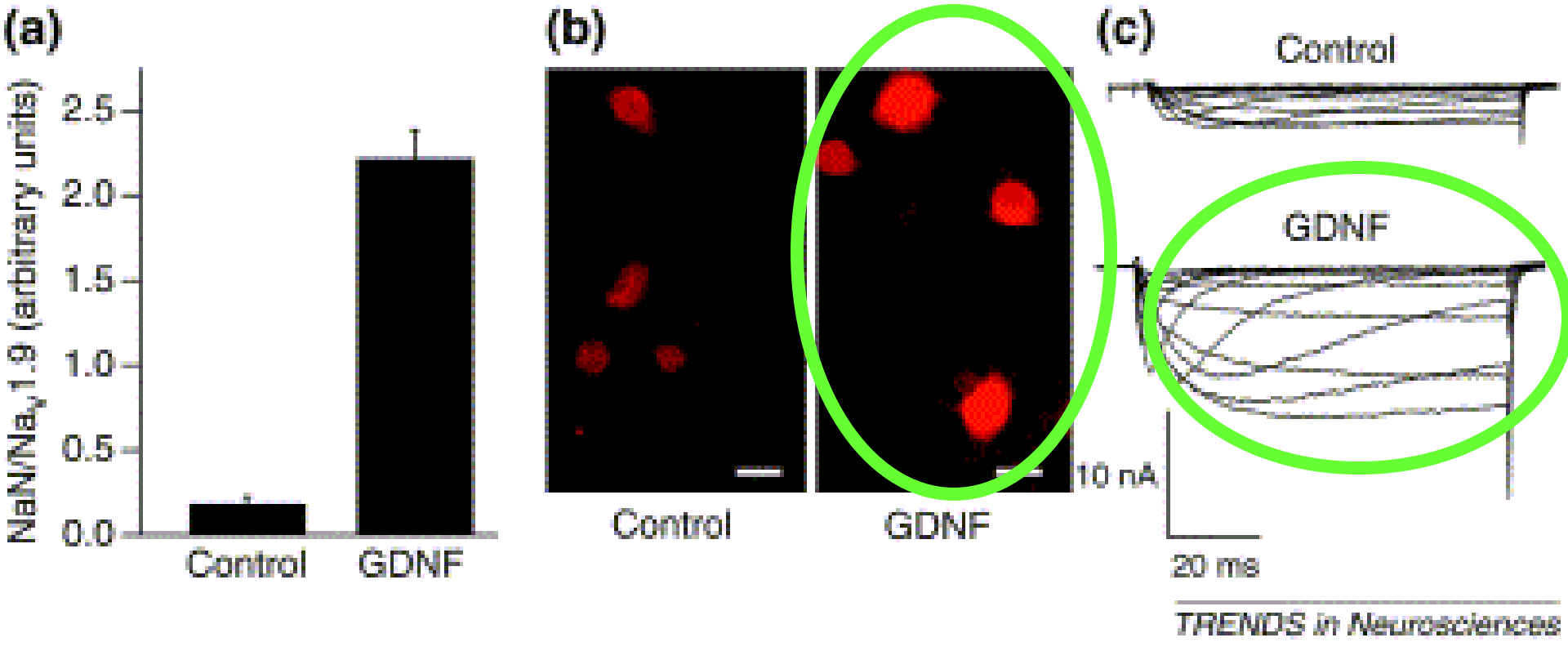
⬇ in $Na_v1.9$ transcripts, protein and persistent TTX resistant current in small neurons from dorsal root ganglia following axotomy



Rescue of *Scn11a* gene expression by glial-cell-derived neurotrophic factor (GDNF)

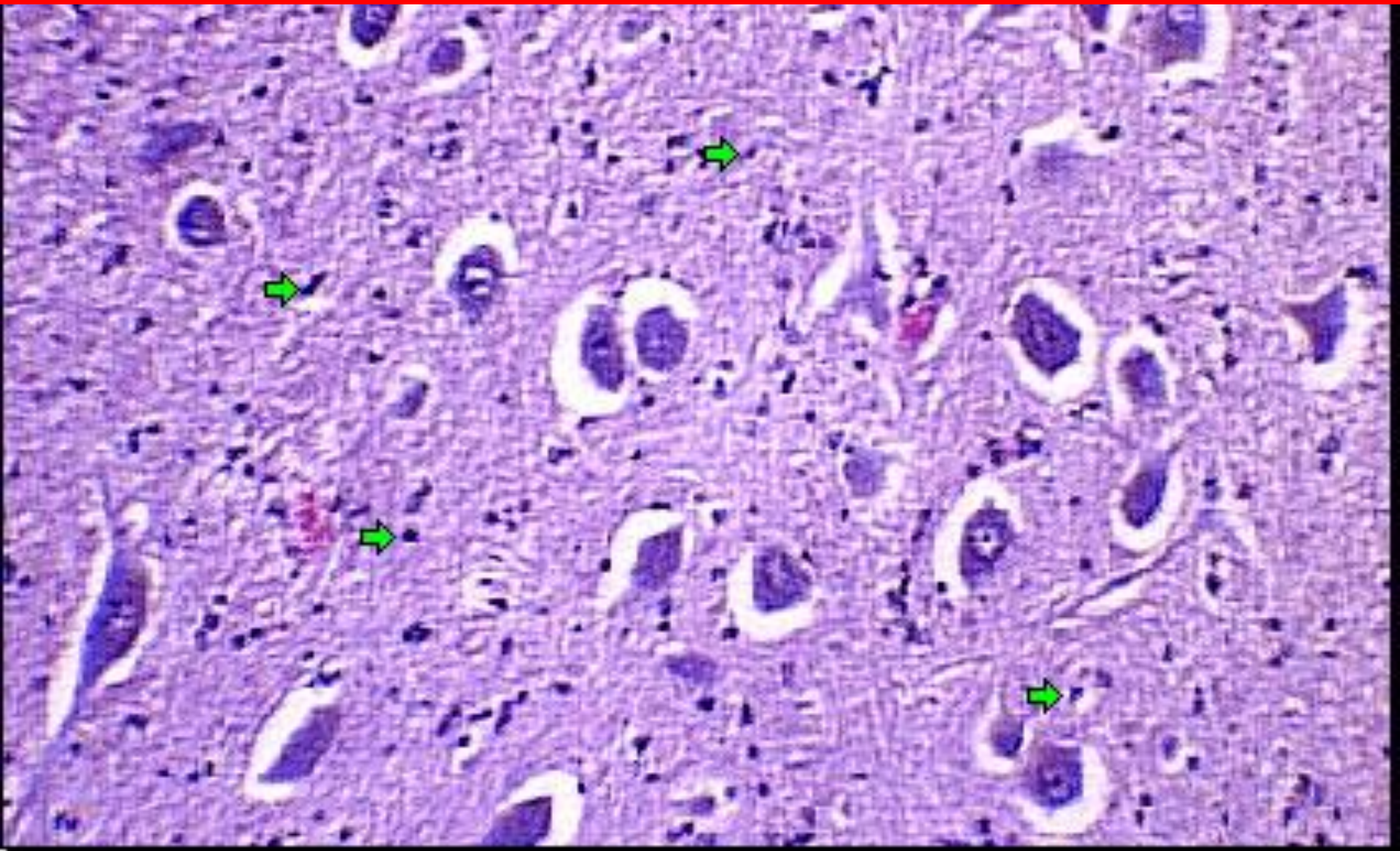
Addition of GDNF to cultures of dorsal root ganglia (DRG) maintained *in vitro* for seven days significantly upregulates (a) $Na_v1.9$ transcripts, (b) protein and (c) persistent TTX-resistant current compared to control cultures. Scale bars, 25 m.

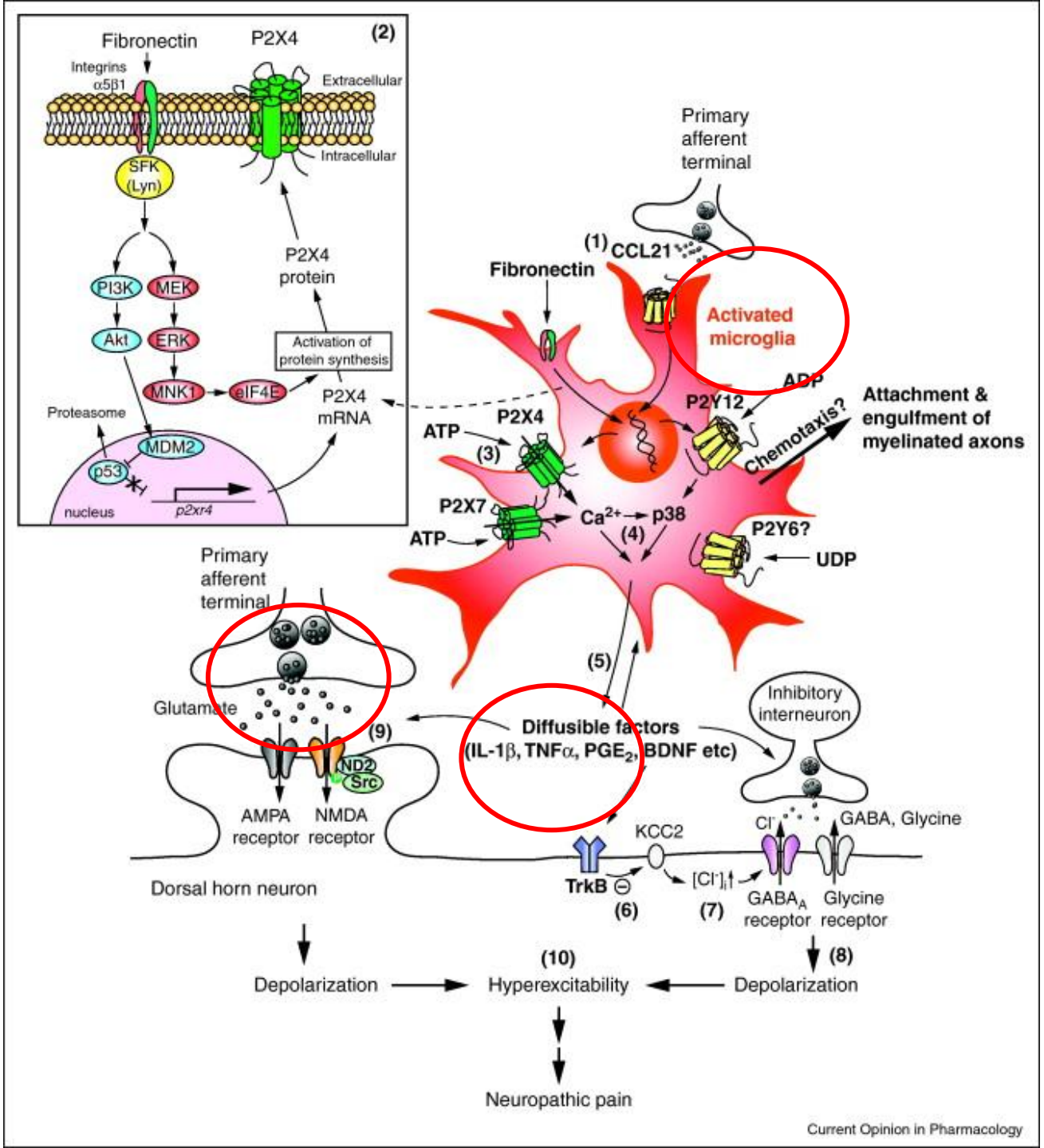
(Trends in Neursciences 2004)



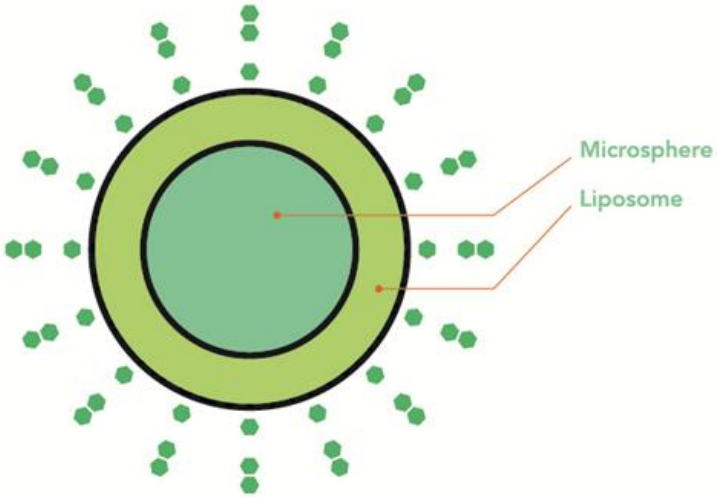
C. Peripheral and Central Sensitisation

Neuroglial cells



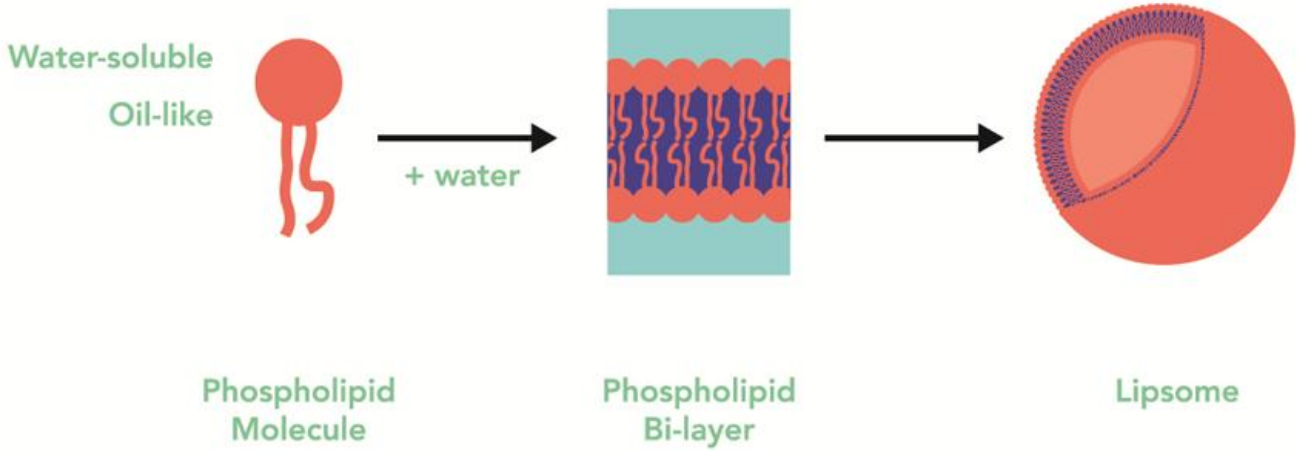

Fibronectin
P2X4
(2)
Integrins
α5β1
Extracellular
Intracellular
SFK
(Lyn)
PI3K
MEK
Akt
ERK
MNK1
eIF4E
P2X4
protein
Activation of
protein synthesis
P2X4
mRNA
Proteasome
MDM2
p53
nucleus
p2xr4
Primary
afferent
terminal
(1) CCL21
Fibronectin
Activated
microglia
ADP
P2Y12
Attachment &
engulfment of
myelinated axons
Chemotaxis?
ATP
P2X4
(3)
P2X7
ATP
Ca2+
p38
(4)
P2Y6?
UDP
Primary
afferent
terminal
Glutamate
(9)
ND2
Src
AMPA
receptor
NMDA
receptor
(5)
Diffusible factors
(IL-1β, TNFα, PGE2, BDNF etc)
Inhibitory
interneuron
KCC2
Cl-
GABA, Glycine
Dorsal horn neuron
TrkB
(6)
[Cl-]i
(7)
GABAA
receptor
Glycine
receptor
(8)
Depolarization
(10)
Hyperexcitability
Depolarization
Neuropathic pain
Current Opinion in Pharmacology

Microspheres (or nanospheres) within a liposome



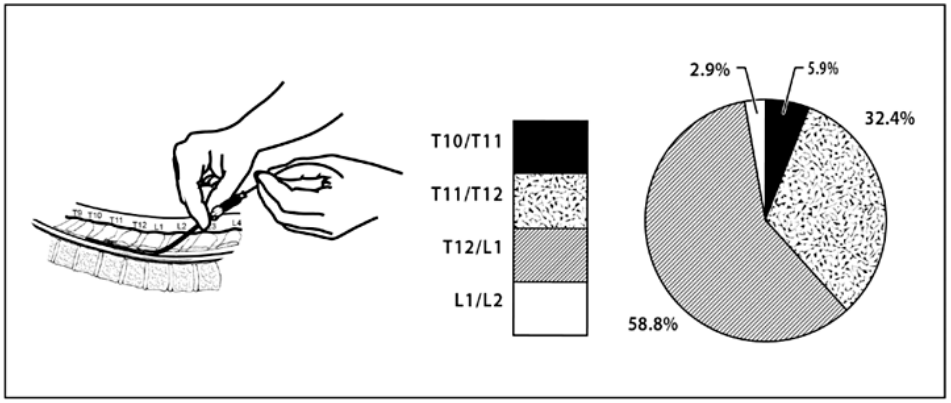
(Shipton EA. Anesthesiol Res Pract 2012;2012:546409)

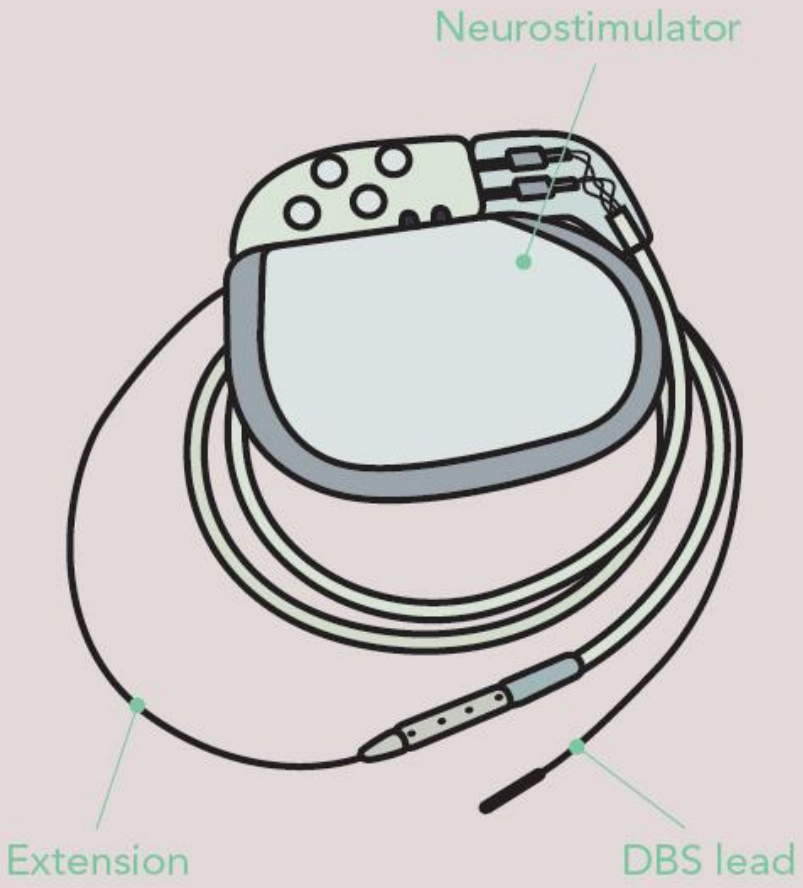
A liposomal structure assembled from phospholipid molecules



(Shipton EA. TACC 2012: in press)

Technological Innovation in Spinal Cord Stimulation: use of a New Delivery Device for Introduction of Spinal Cord Stimulation Leads





Shipton EA
Neurol Res Int 2012: in press.

New Millennium

- A - Introduction
- B – Pain Conduction
- C – Peripheral and Central Sensitisation
- D – Brain Imaging
- E – Cognitive Modulations of Pain
- F – Genetics
- G – New Drugs
- H – Neuropathic Pain
- I - New Delivery Systems
- J – Neuromodulation
- K – Perioperative Pain
- L – Cancer Therapy
- M - Conclusion