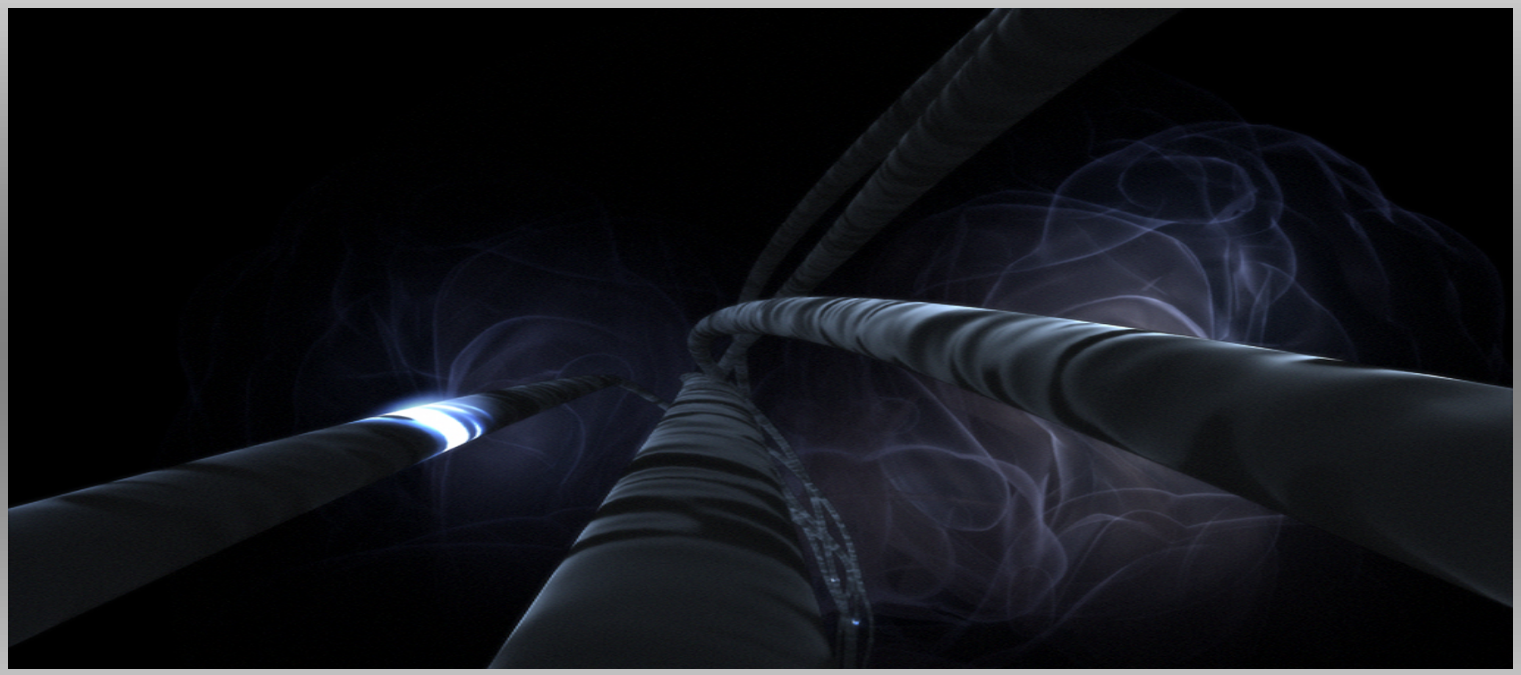
Targeting the CNS for drug discovery for pain



The London Pain Consortium

Tony Dickenson
University College London

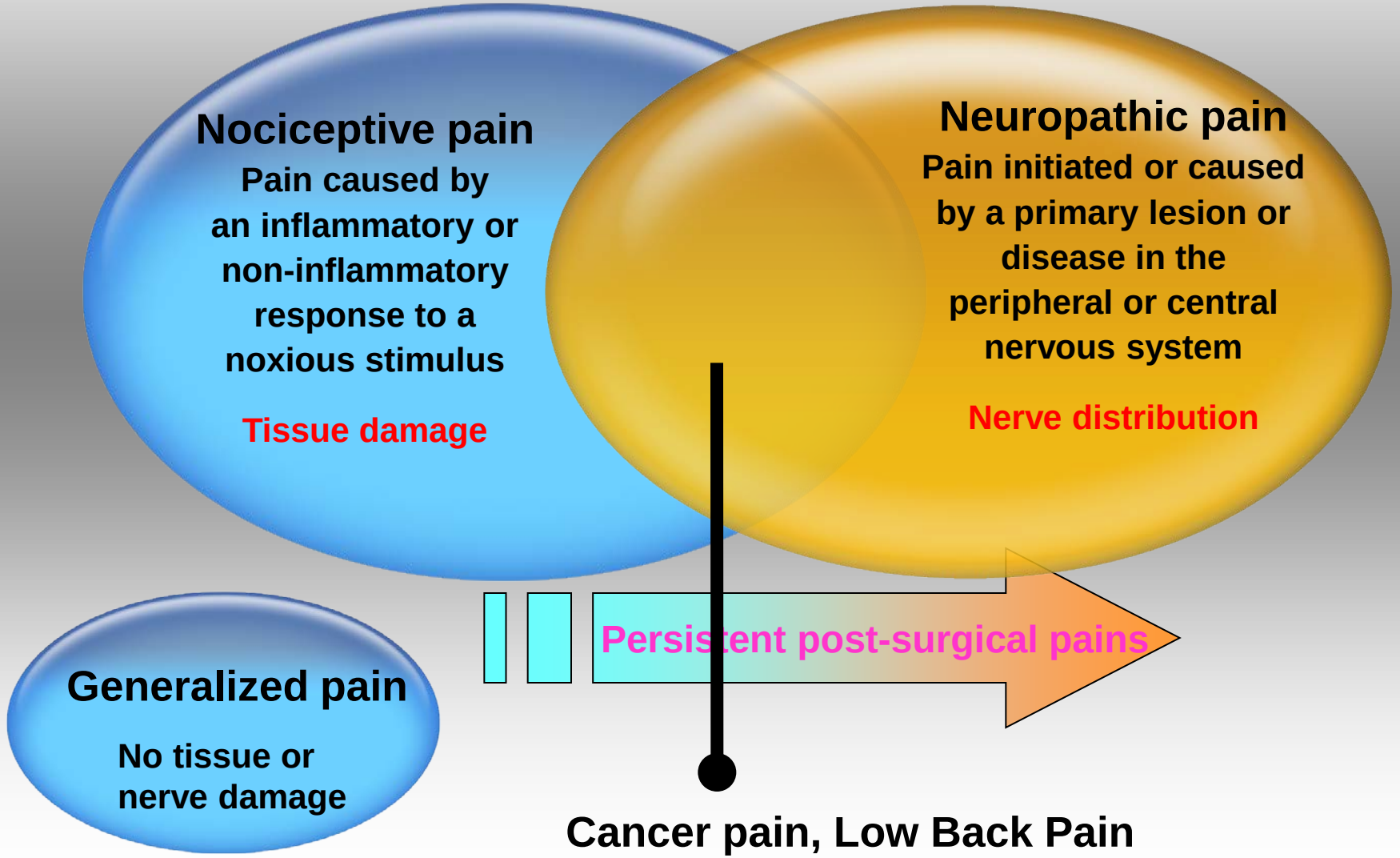
Jean-Joseph-Xavier Bidaud (1758-1846) Vien: Siege of a City(1795)

Central targets

- Avoid potential redundancy of peripheral targets
- Potentially blunt pain co-morbidities
- Broader actions
- Increase inhibitions and decrease excitations

- Tolerability
- Multiple roles - GABA, AMPA-R etc
- Compensations
- Dependence issues

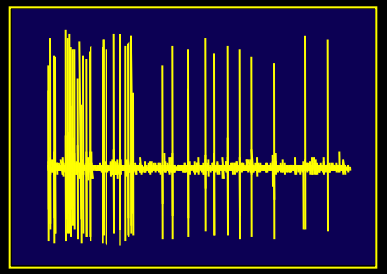
Understanding key types of pain



Activity generated within CNS pain circuits

Higher centres

Brain stem mechanisms and descending controls



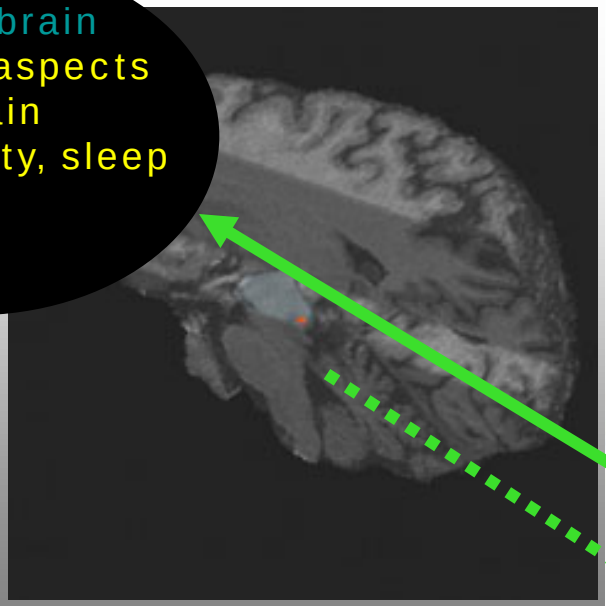
Inflammation

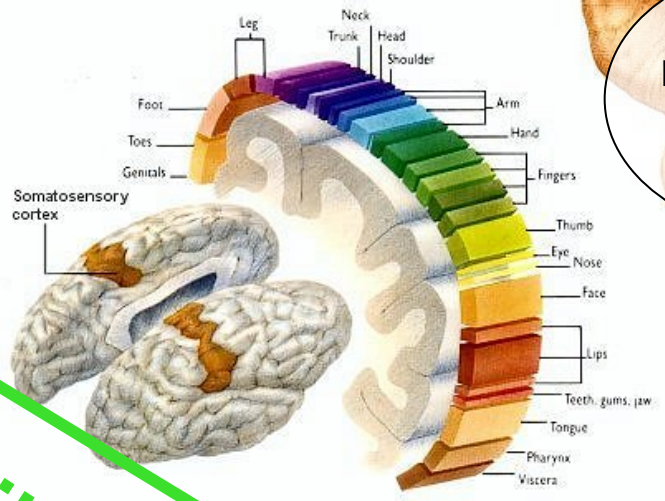
Spinal events

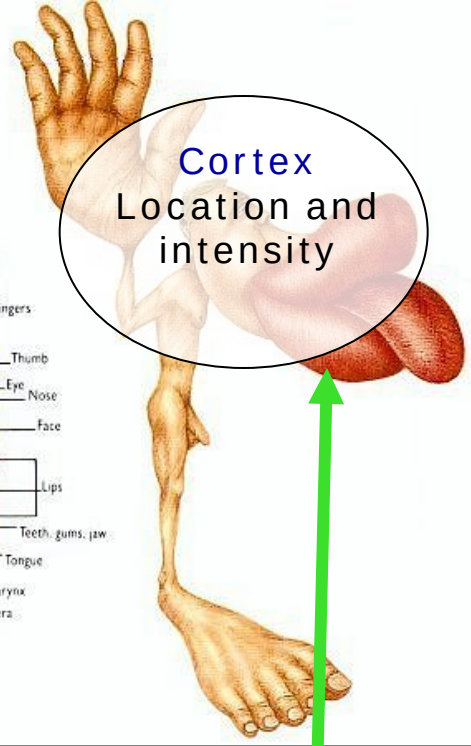
Peripheral events

Neuropathy

Limbic brain
Affective aspects of pain
Fear, anxiety, sleep





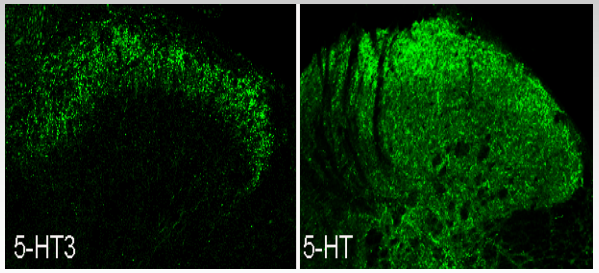


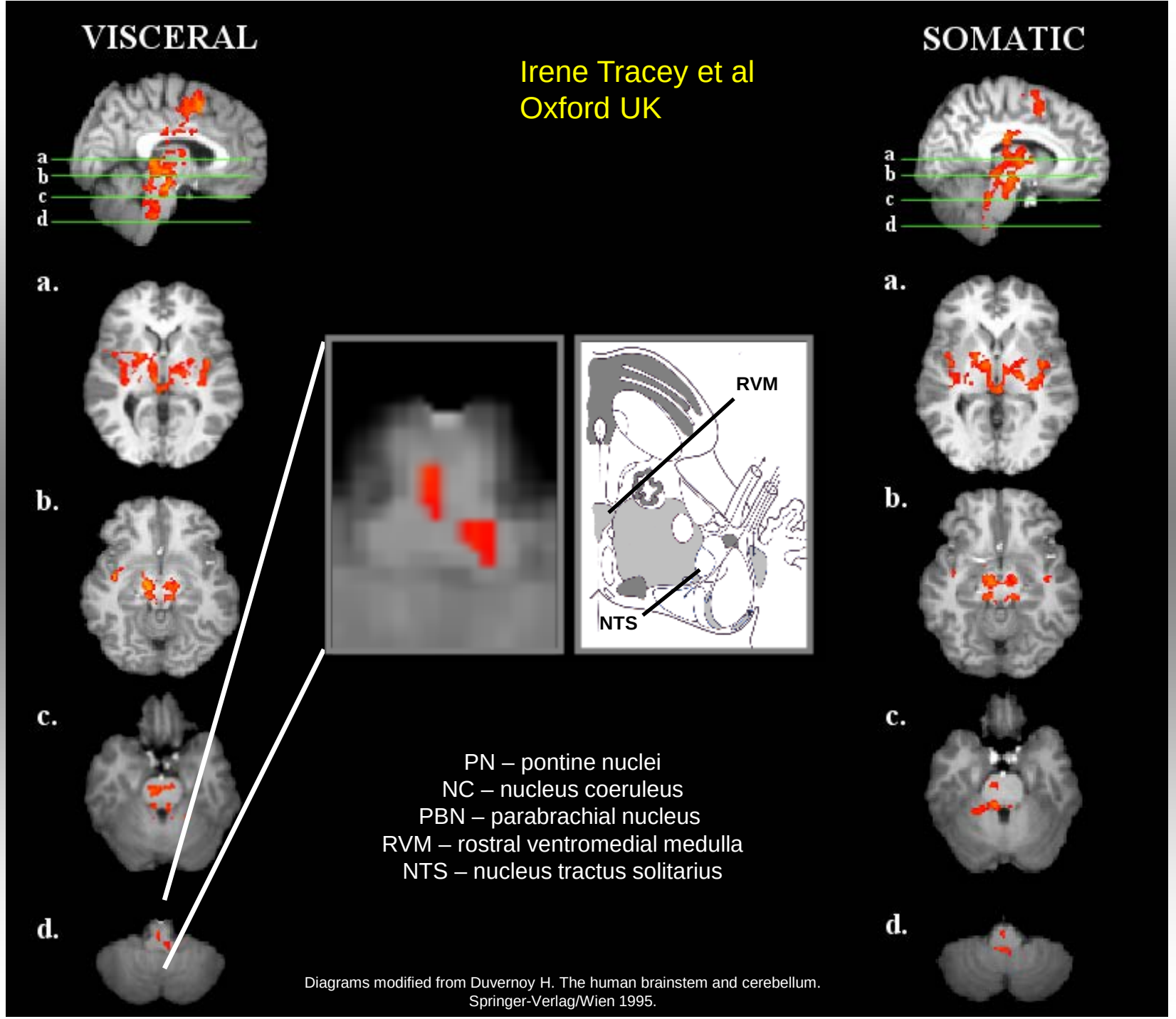
Cortex
Location and intensity

Descending controls
Allow top-down processes to alter pain - link mood, sleep and pain

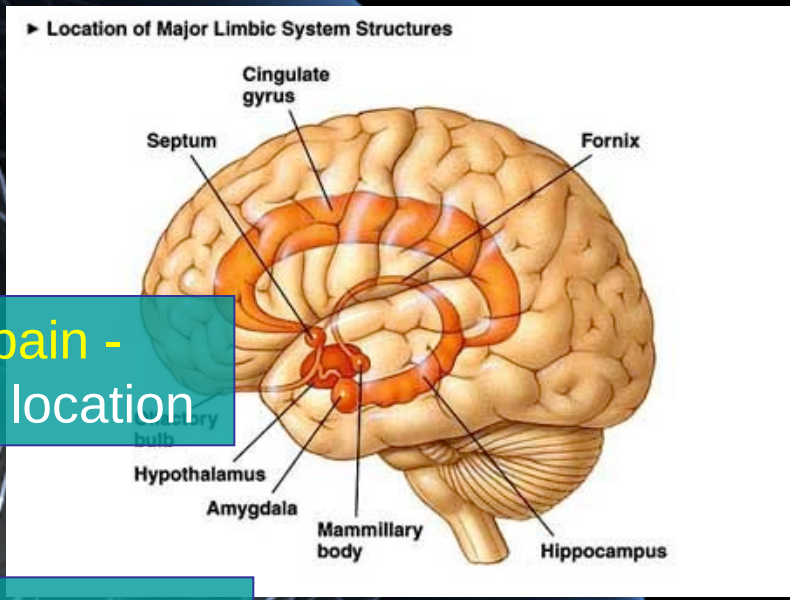
Spinal cord
Integrates, amplifies and modifies incoming messages
Output to brain

Incoming peripheral nerves
- Convey touch, temperature
- Convey painful messages - heat, mechanical, chemical
- Are altered by tissue and nerve damage




VISCERAL
SOMATIC
Irene Tracey et al
Oxford UK
a
b
c
d
a.
b.
c.
d.
RVM
NTS
PN – pontine nuclei
NC – nucleus coeruleus
PBN – parabrachial nucleus
RVM – rostral ventromedial medulla
NTS – nucleus tractus solitarius
5.4
2.6
Diagrams modified from Duvernoy H. The human brainstem and cerebellum.
Springer-Verlag/Wien 1995.

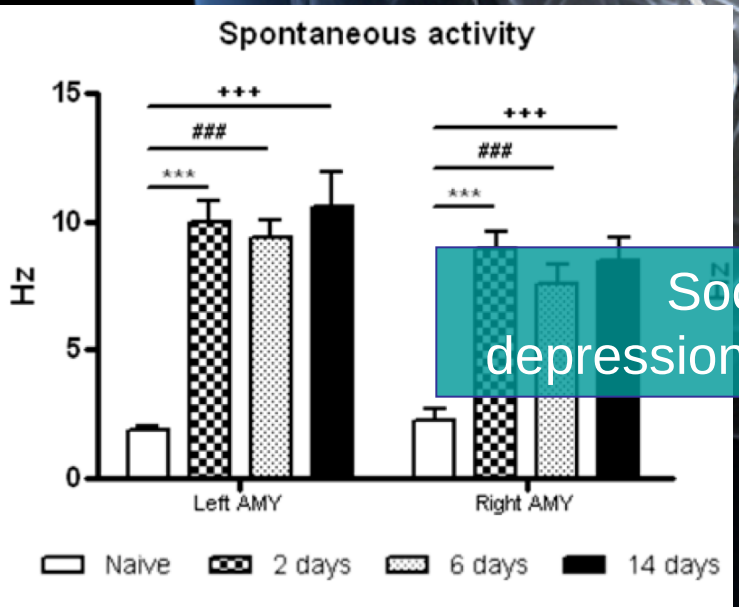
Pain is unique



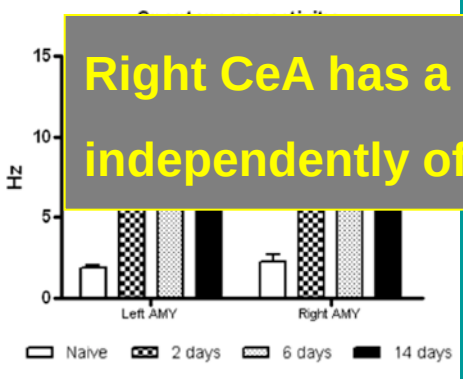
Sensory aspects of pain - threshold, intensity and location

Psychological aspects of pain - unpleasant, threatening, aversive

Social, economic issues
depression, anxiety, sleep disorders *etc*

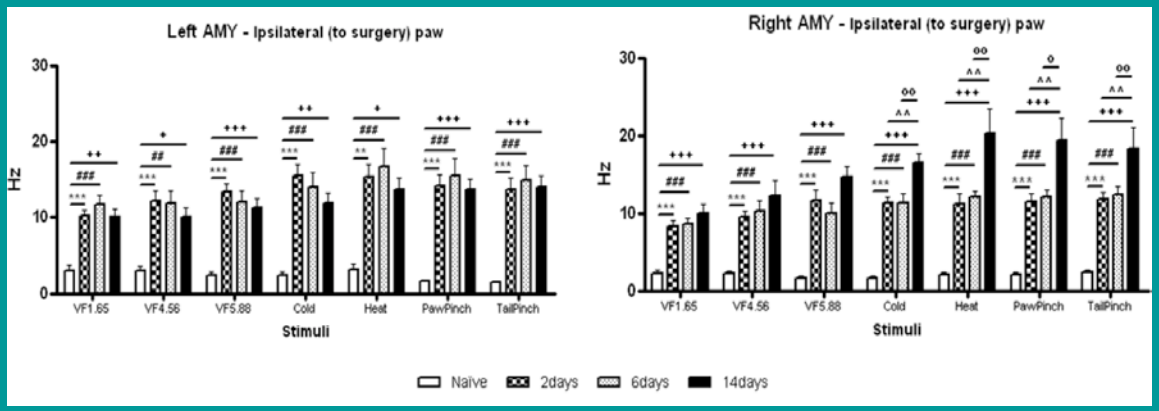


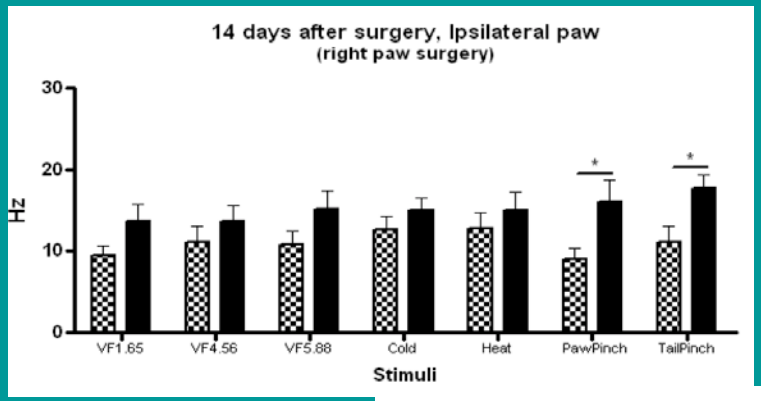
Right CeA has a higher response to stimuli in late SNL animals, independently of the side of surgery.

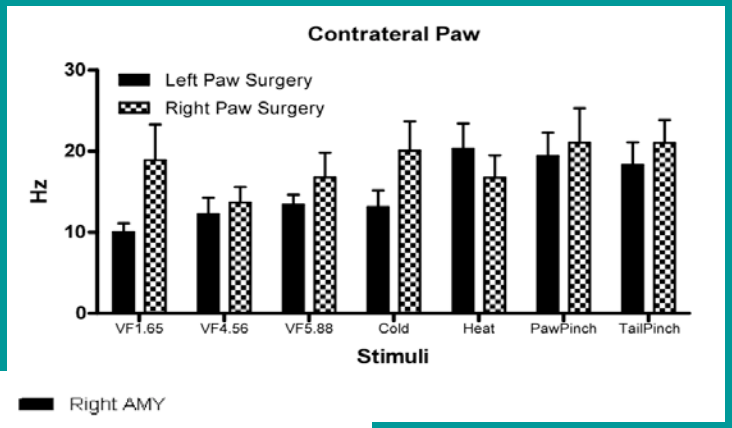


animals

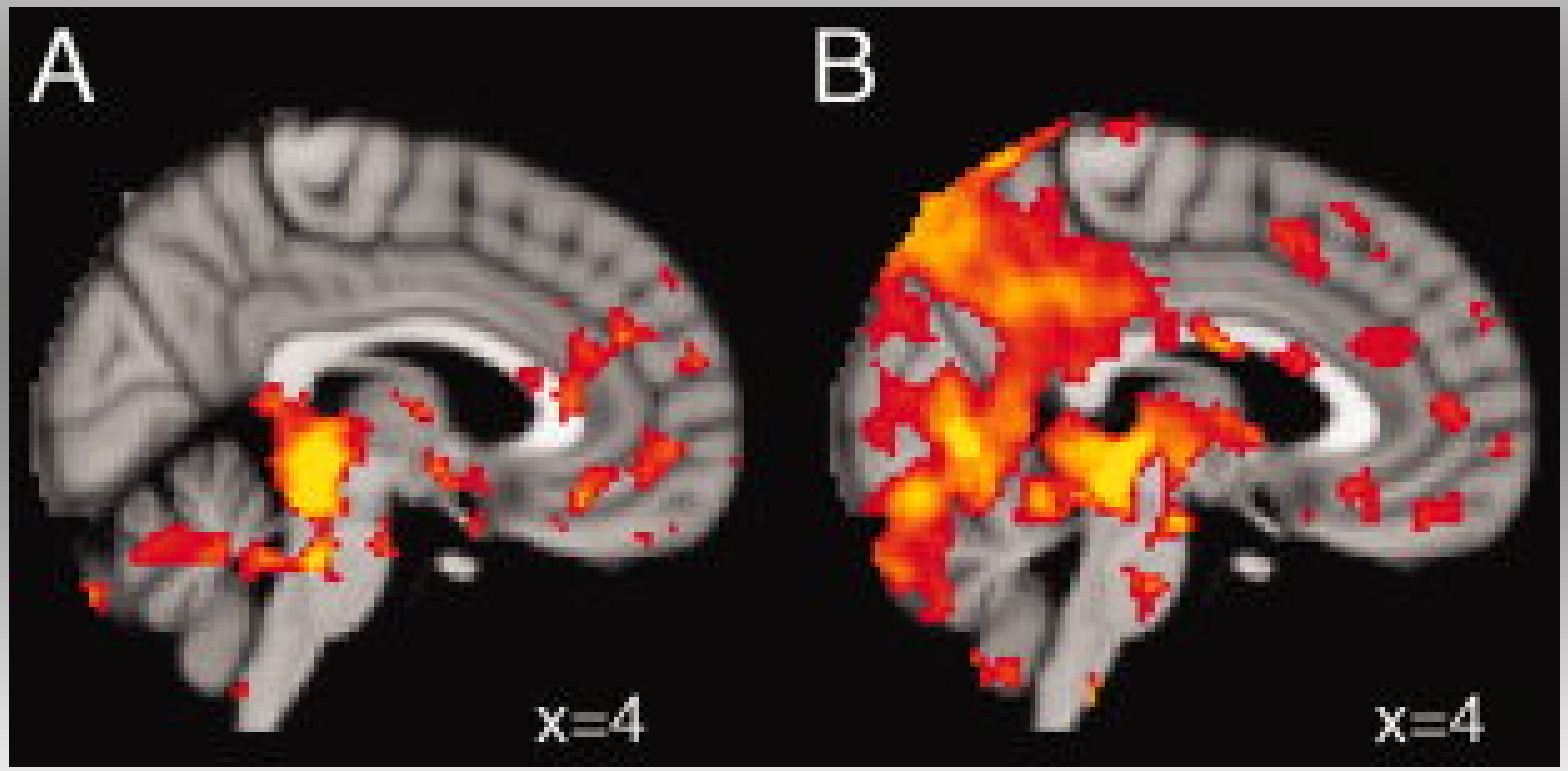
SNL animals increase evoked activity changes throughout post surgery time – higher in the right CeA, 14 days after.

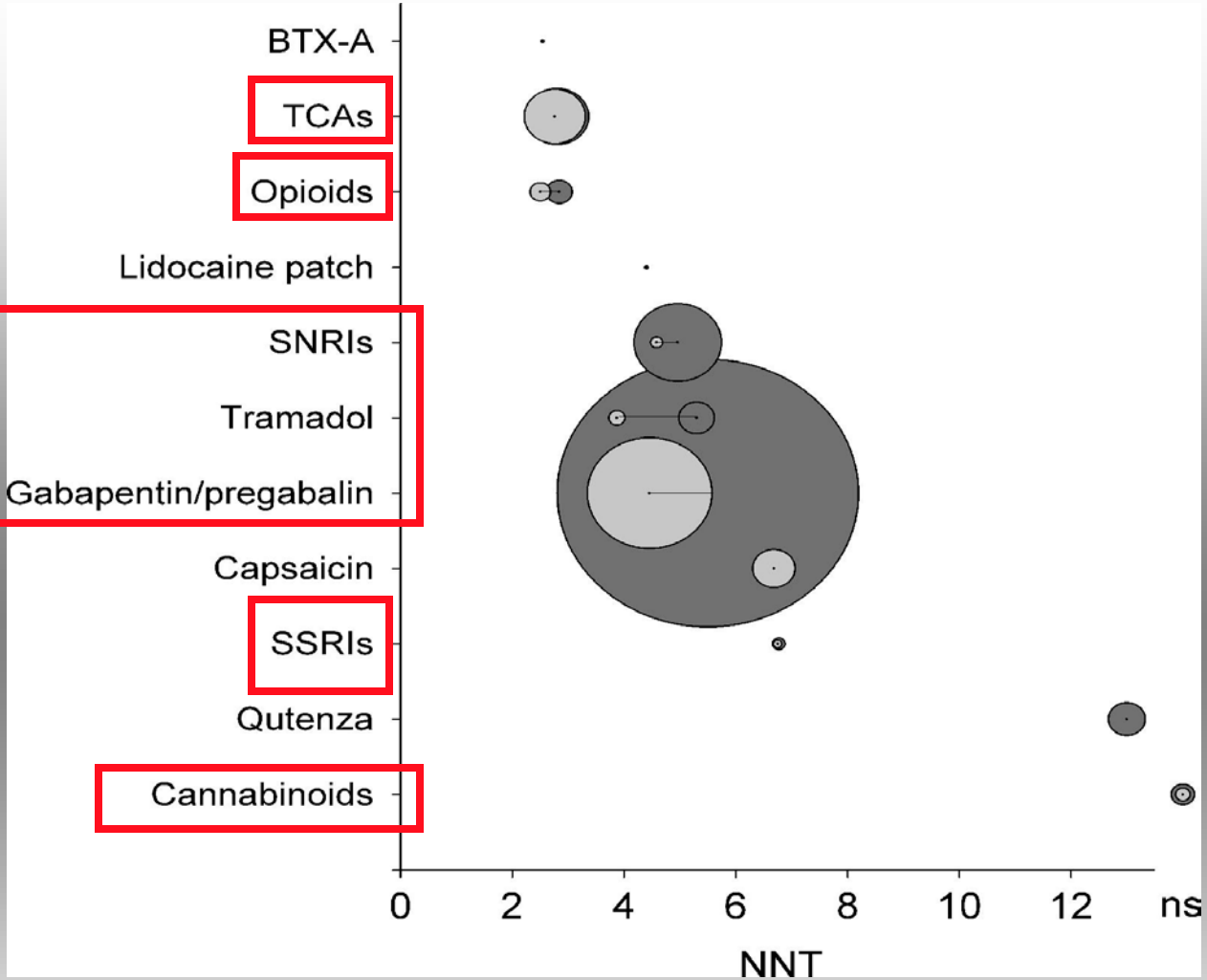


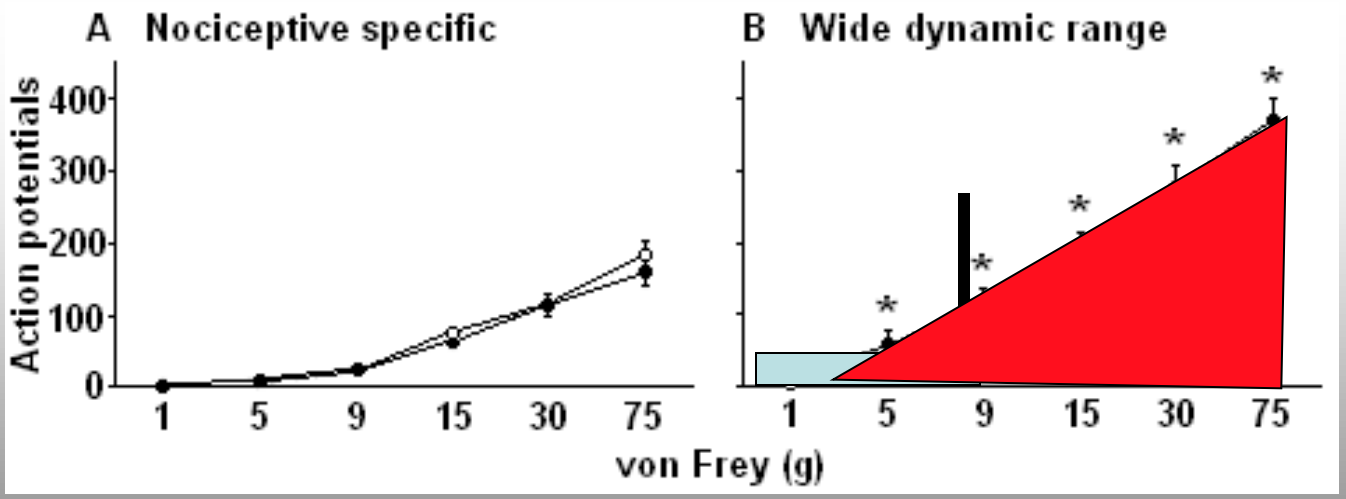


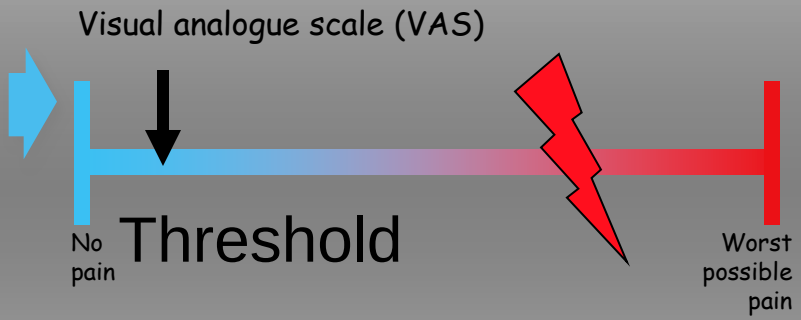


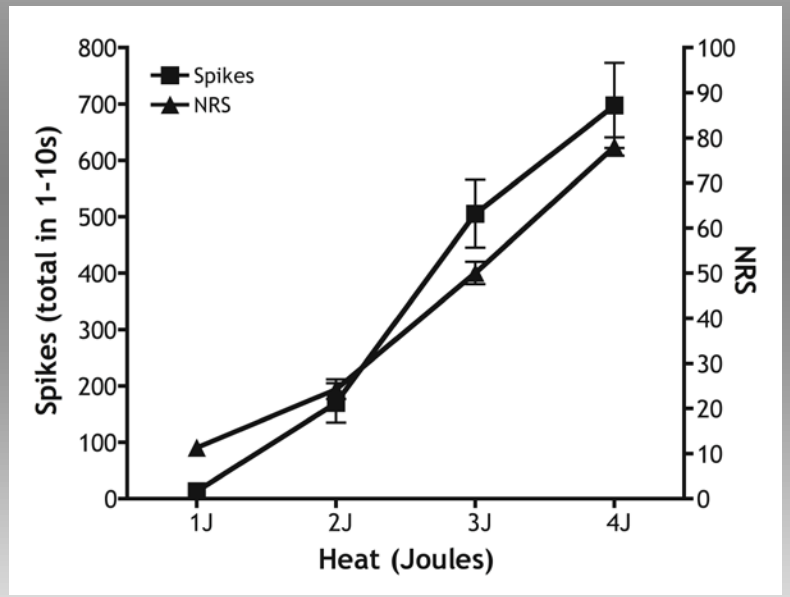
Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine.Caterina Mainero MD, PhD[1], Jasmine Boshyan BS[1], Nouchine Hadjikhani MD, PhD[1,2,*]

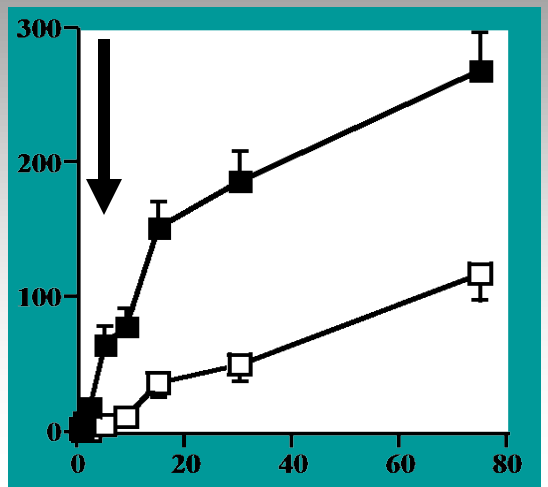


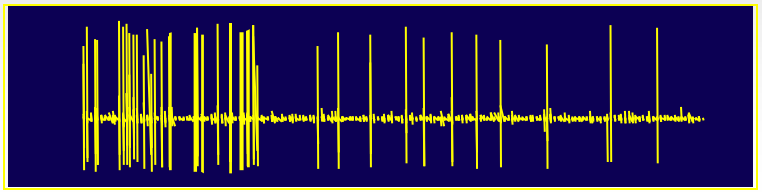

BTX-A
TCAs
Opioids
Lidocaine patch
SNRIs
Tramadol
Gabapentin/pregabalin
Capsaicin
SSRIs
Qutenza
Cannabinoids
0
2
4
6
8
10
12
ns
NNT


A Nociceptive specific
B Wide dynamic range
Action potentials
400
300
200
100
0
1
5
9
15
30
75
von Frey (g)

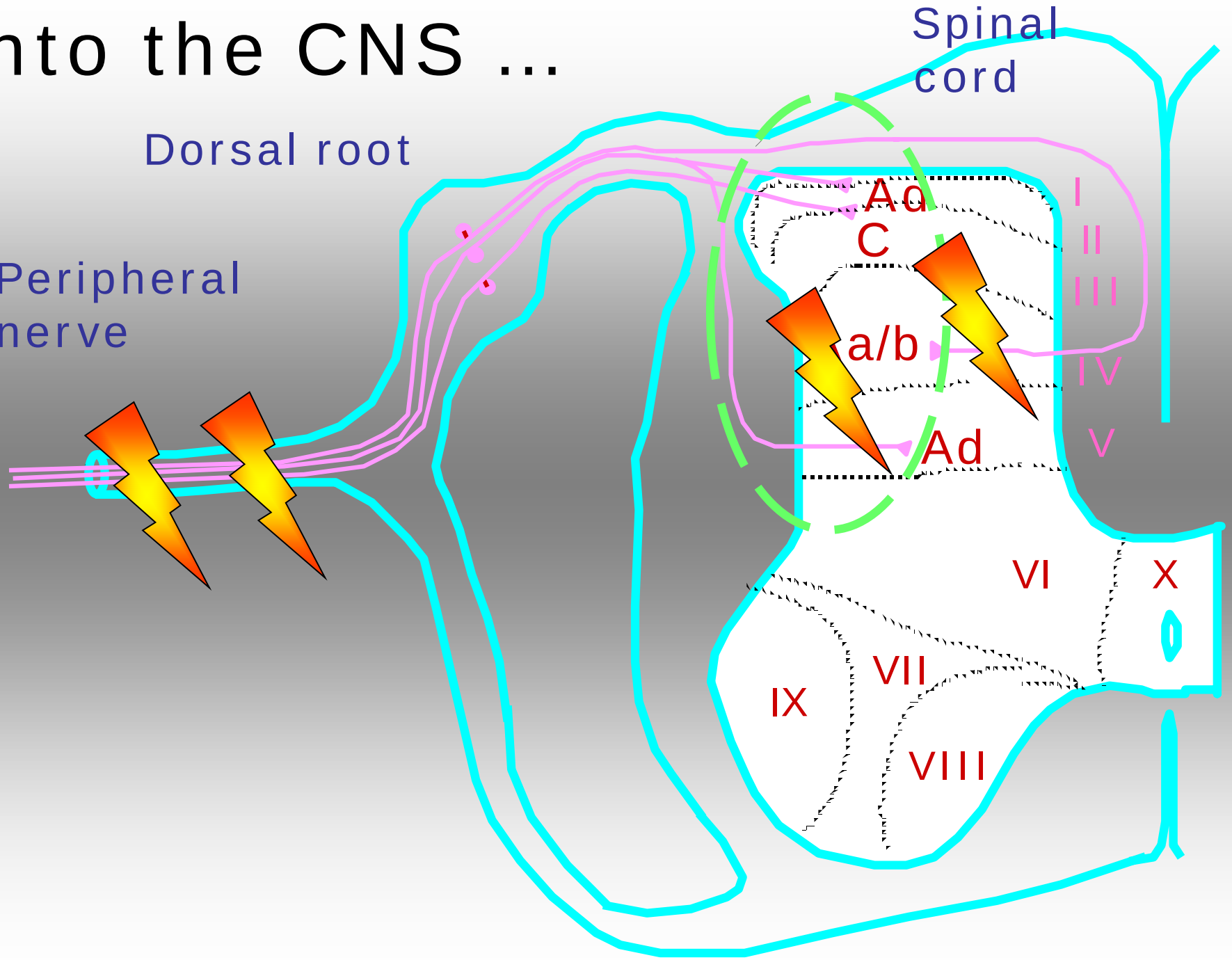

Visual analogue scale (VAS)
No pain
Threshold
Worst possible pain


Spikes
NRS
Spikes (total in 1-10s)
NRS
800
700
600
500
400
300
200
100
0
100
90
80
70
60
50
40
30
20
10
0
1J
2J
3J
4J
Heat (Joules)

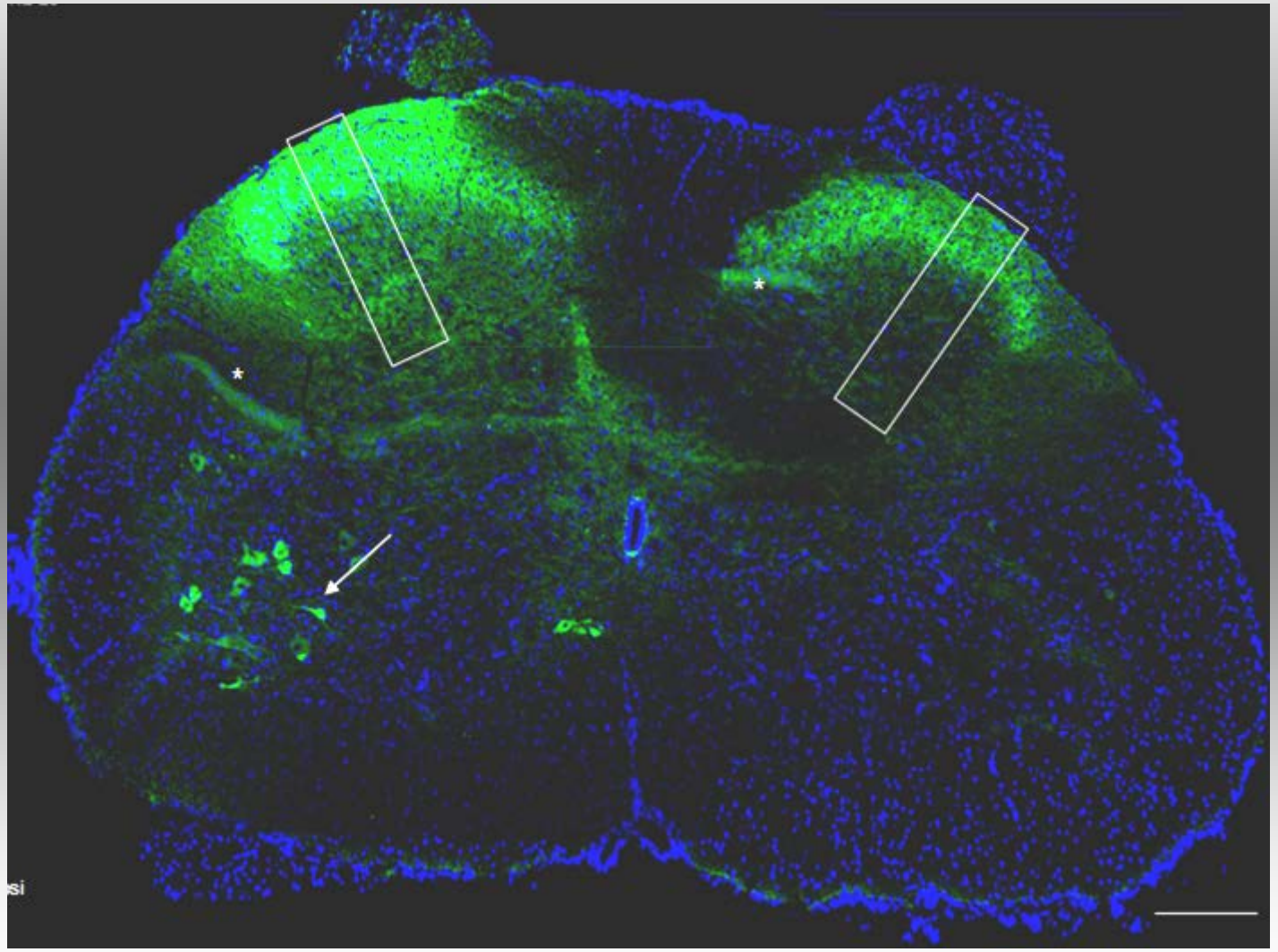

300
200
100
0
0
20
40
60
80



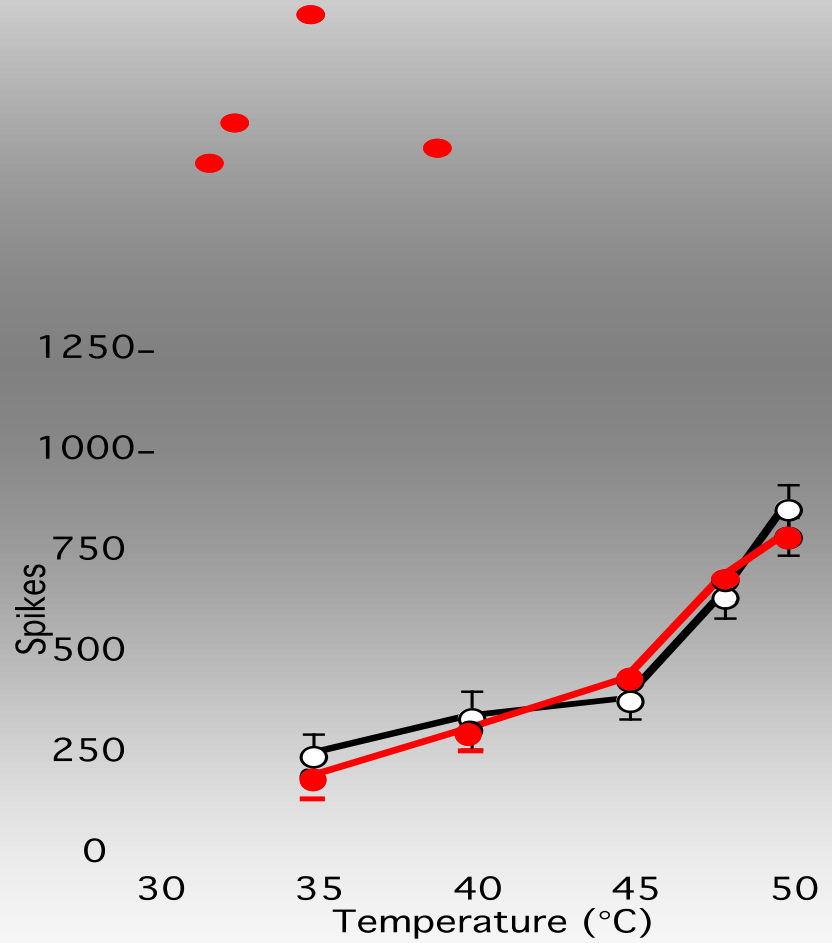
Into the CNS ...


Spinal cord
Dorsal root
Peripheral nerve
Aδ
C
a/b
Aδ
I
II
III
IV
V
VI
X
VII
IX
VIII

Marked changes in calcium channel function

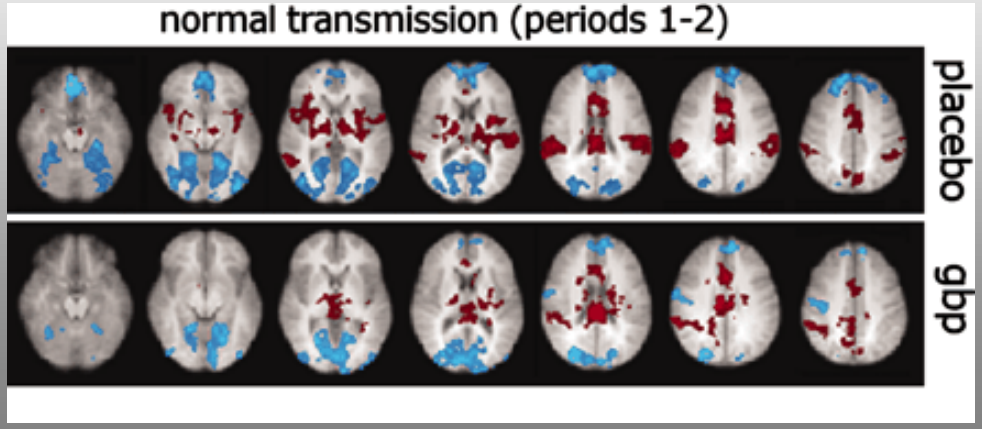


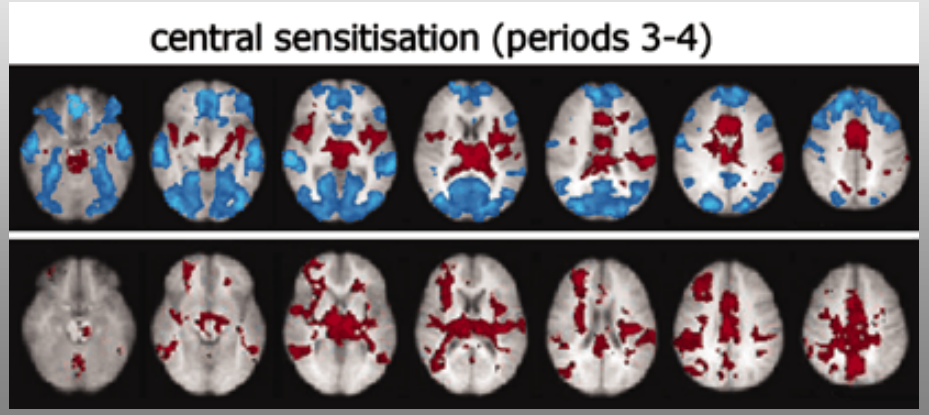
Bauer CS et al. *J Neurosci* 2009;29:4076-88

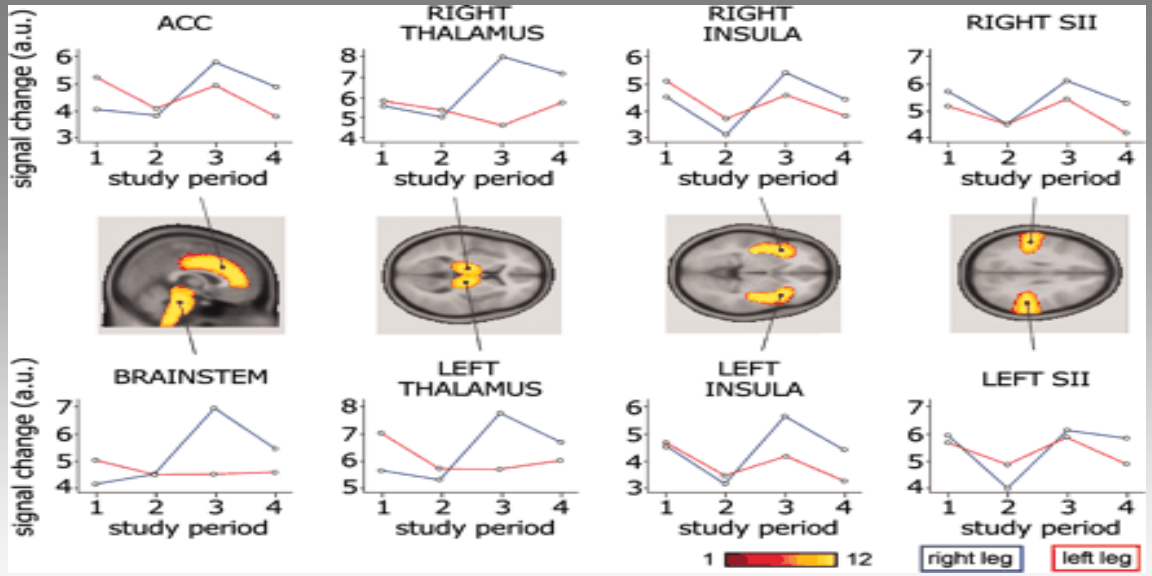


Pregabalin on spinal neurones - partial reduction - state dependent

GBP reduces hyperalgesic signals in human brainstem etc

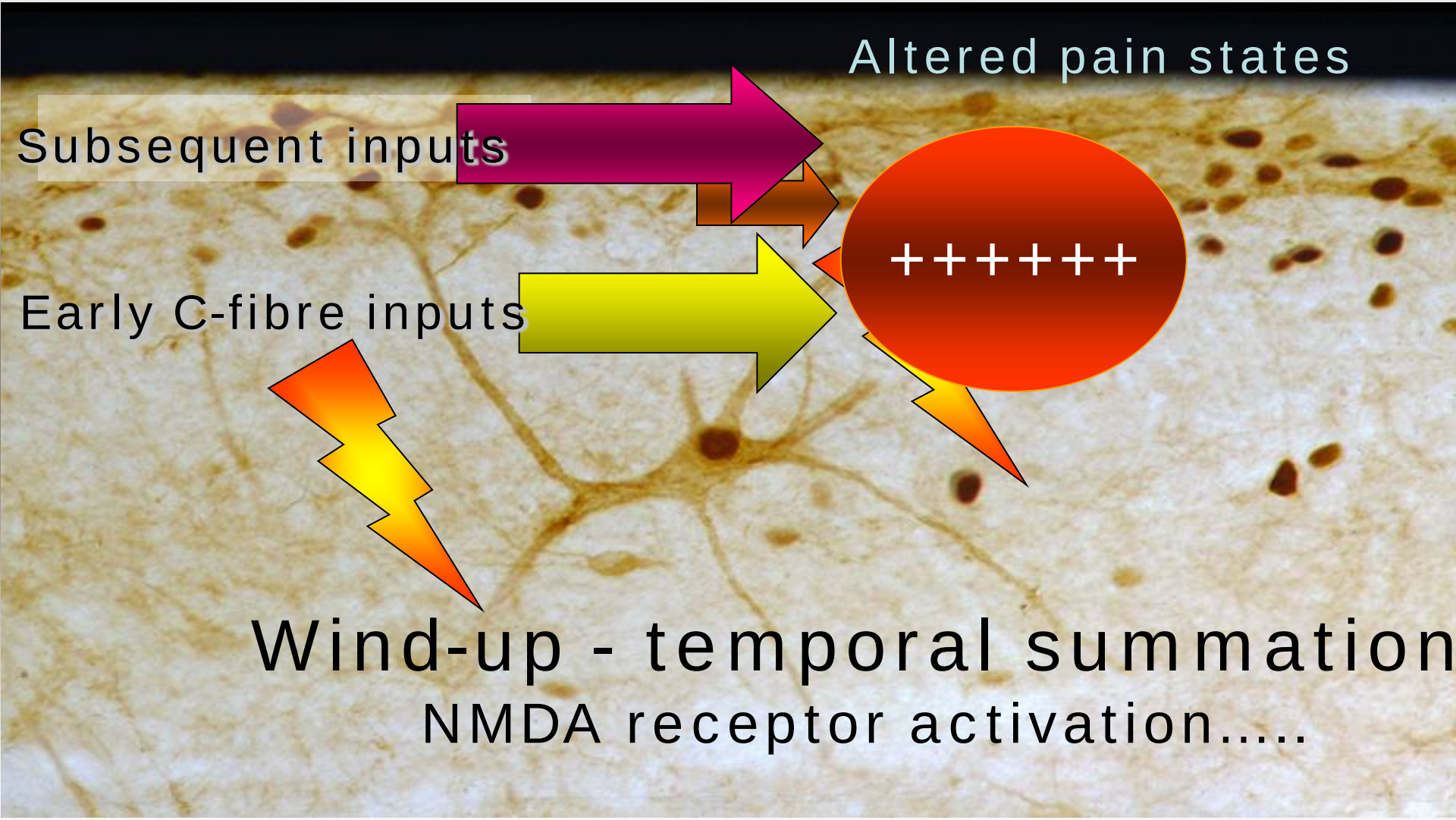




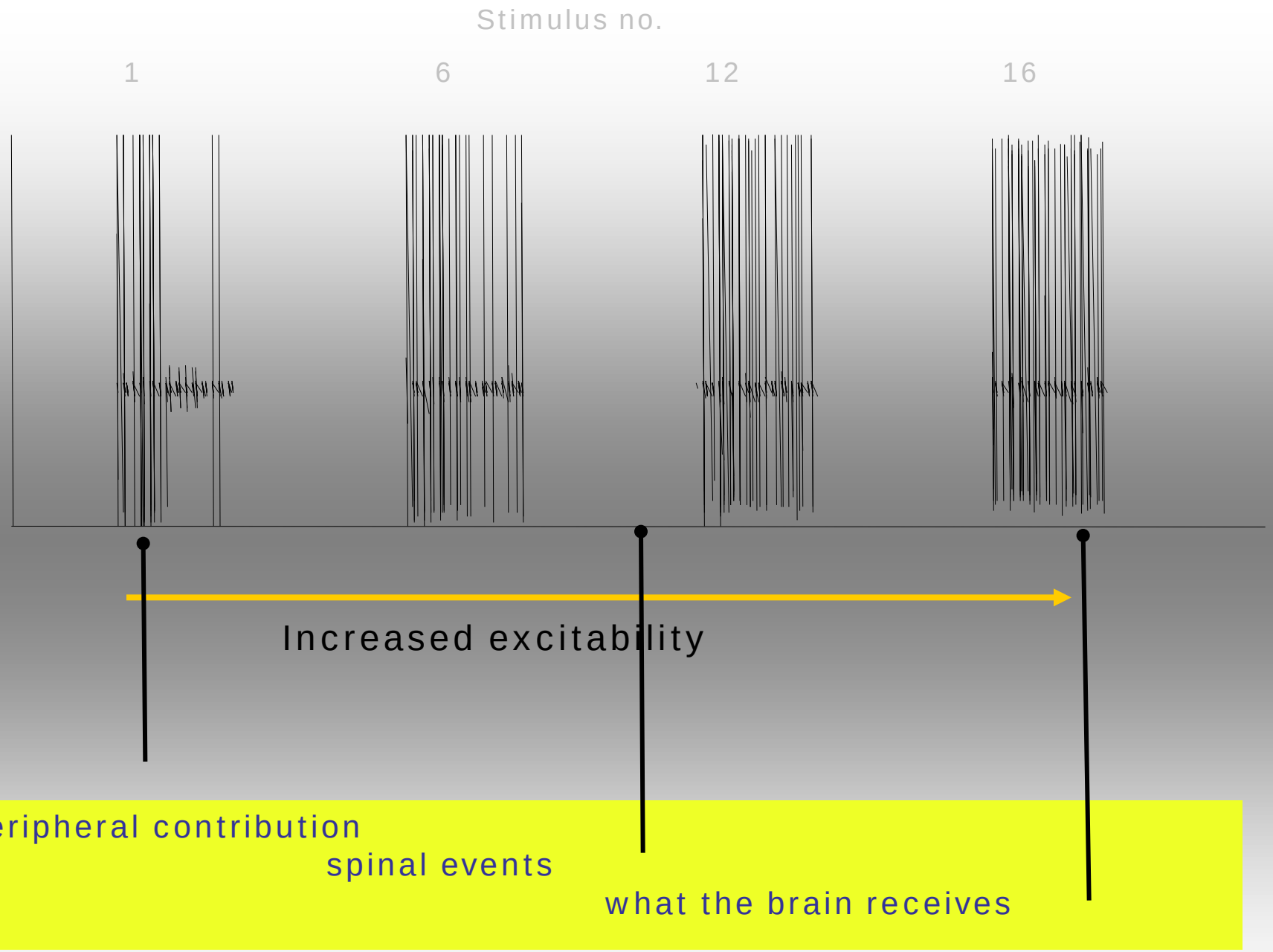


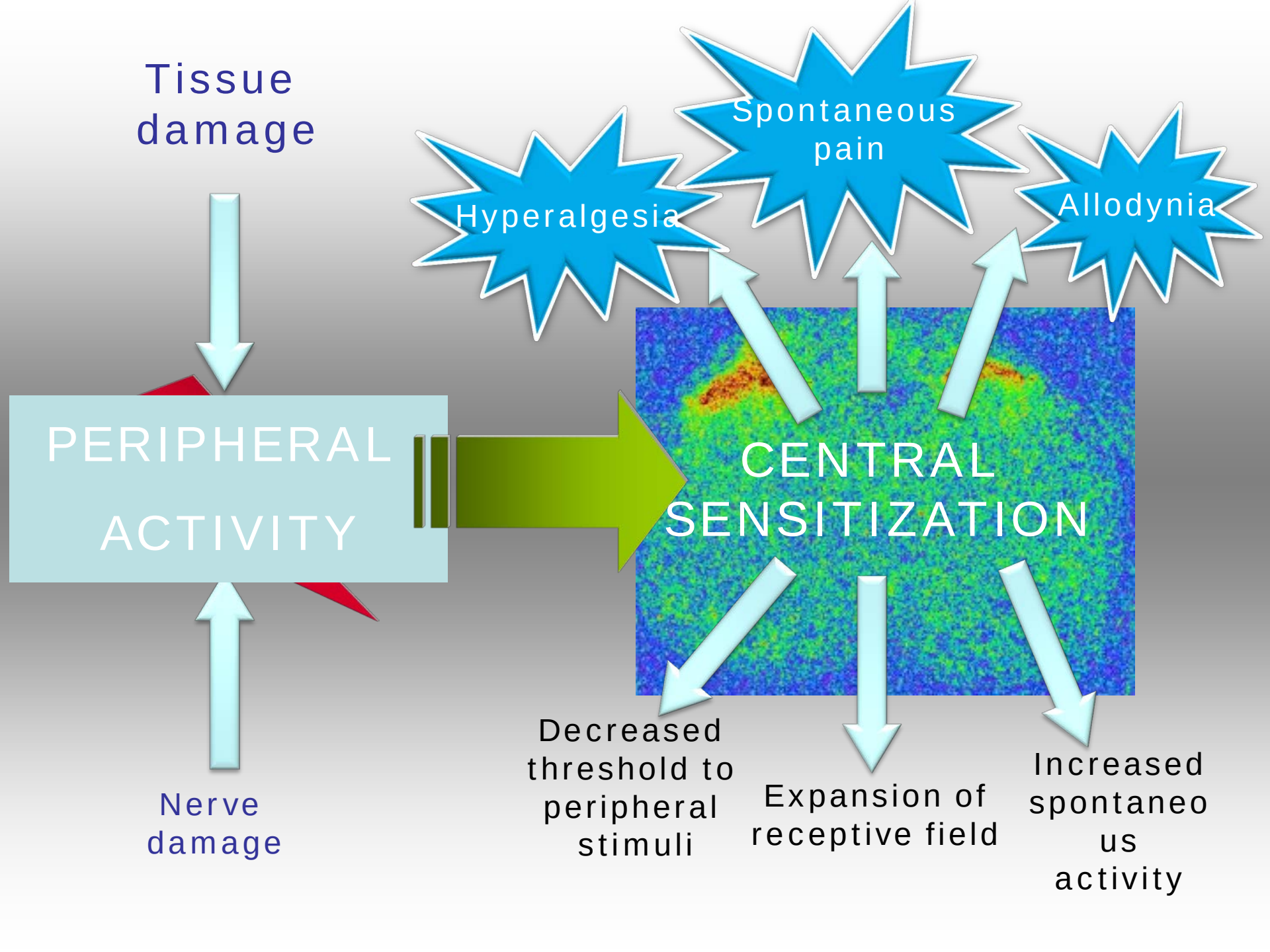
Iannetti et al. PNAS 2008

Spinal Mechanisms - Central Hypersensitivity



Peripheral and descending pathways converge ...

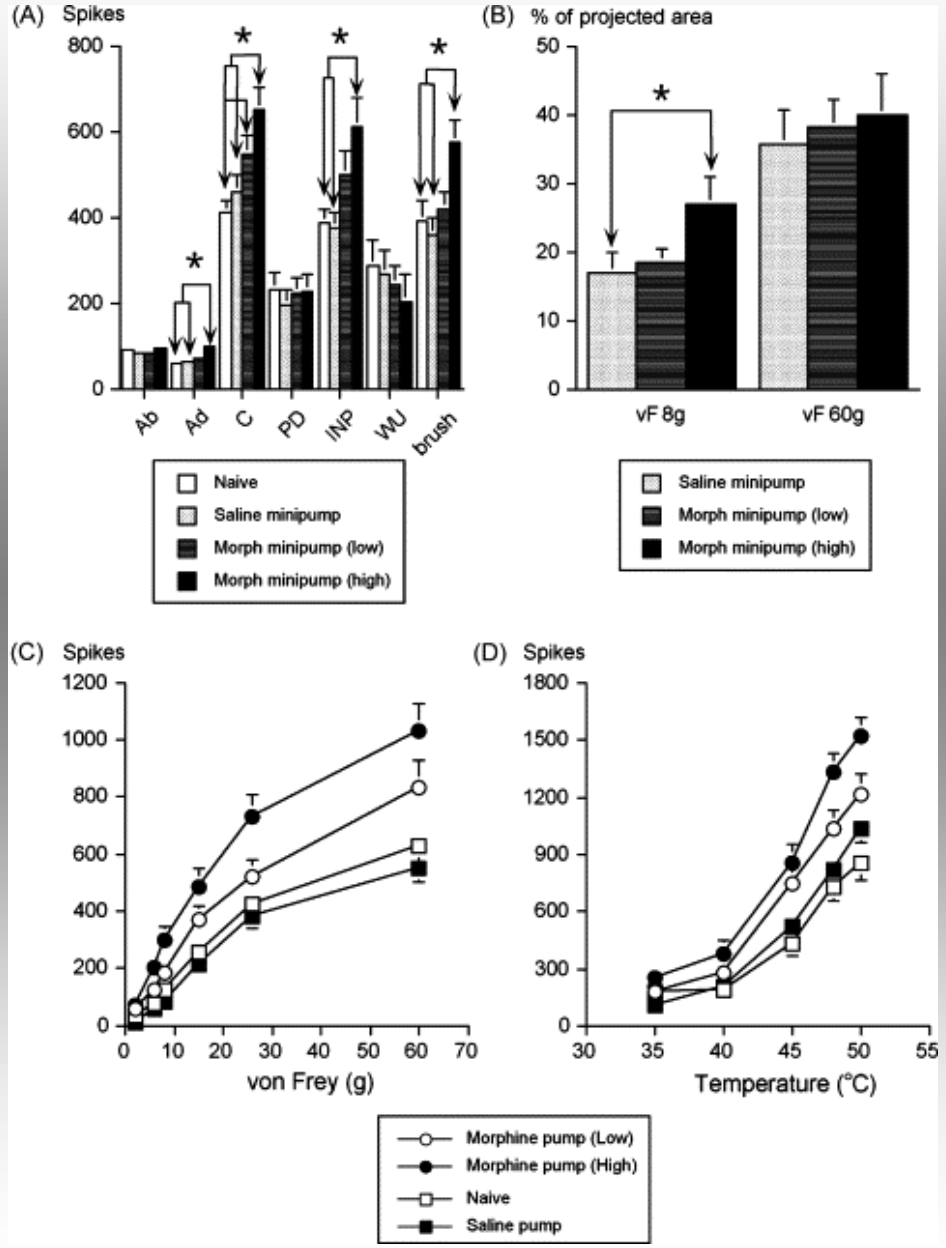

Stimulus no.
1
6
12
16
Increased excitability
Peripheral contribution
spinal events
what the brain receives
Ketamine modulates

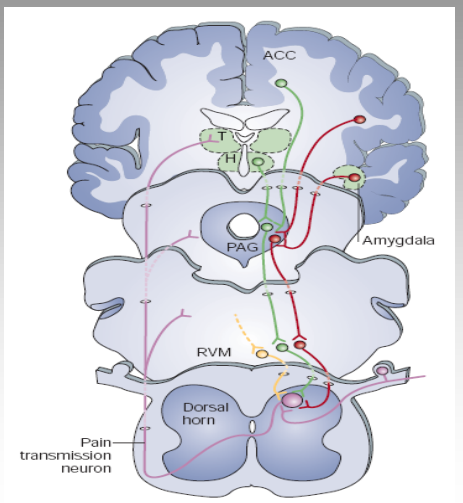

Tissue damage
Spontaneous pain
Hyperalgesia
Allodynia
PERIPHERAL ACTIVITY
CENTRAL SENSITIZATION
Nerve damage
Decreased threshold to peripheral stimuli
Expansion of receptive field
Increased spontaneo us activity

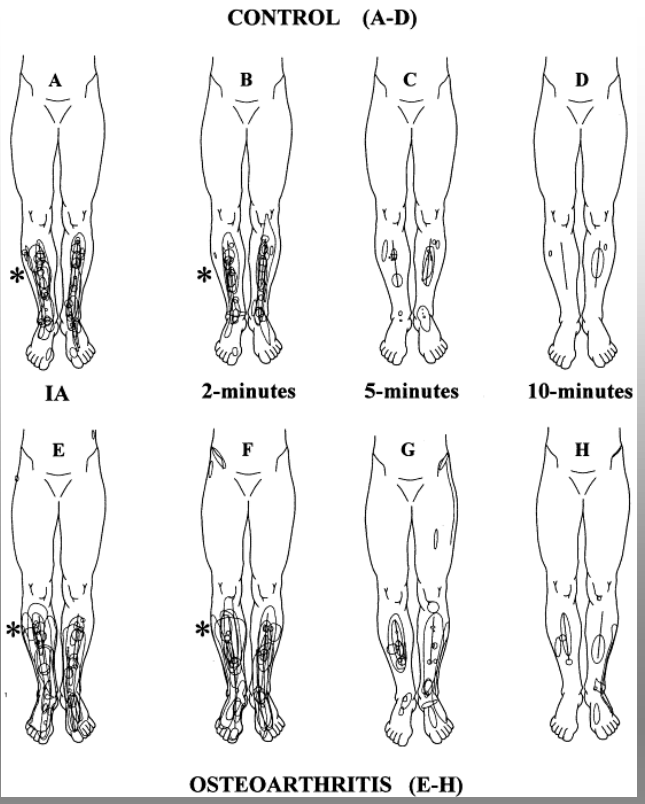
OIH with morphine 7 days

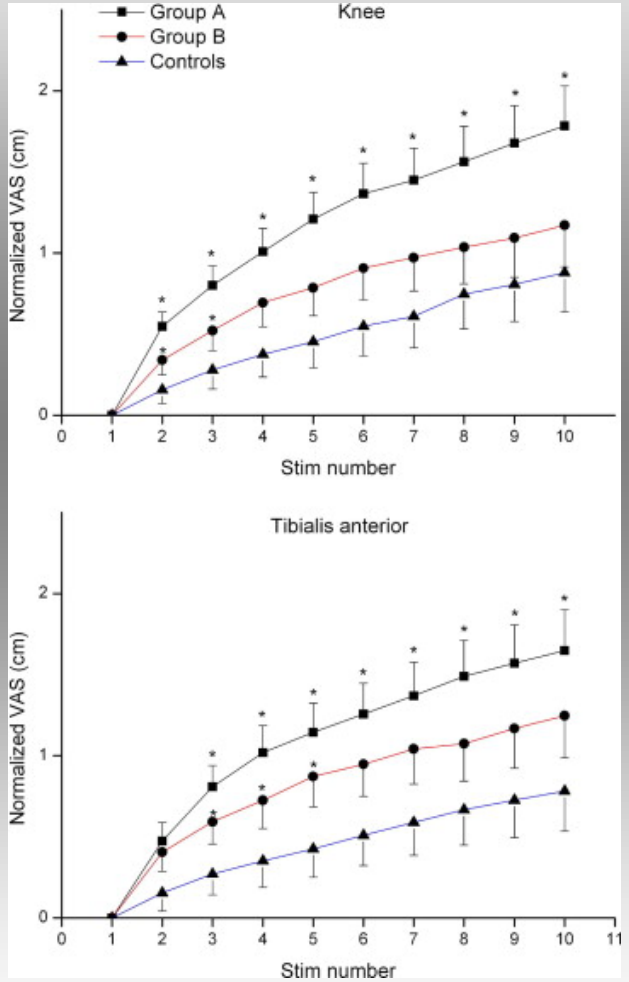
Enhanced mechanical and thermal coding - spinal neurones

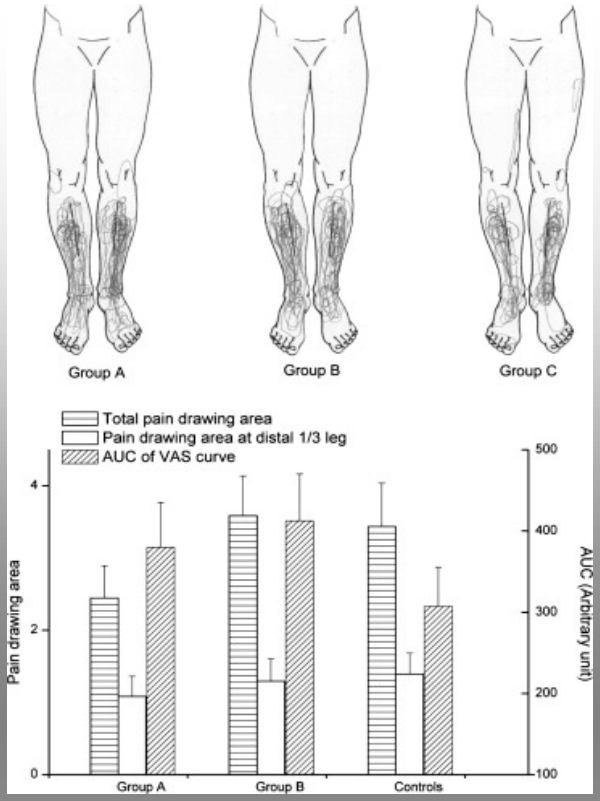
Completely normal periphery



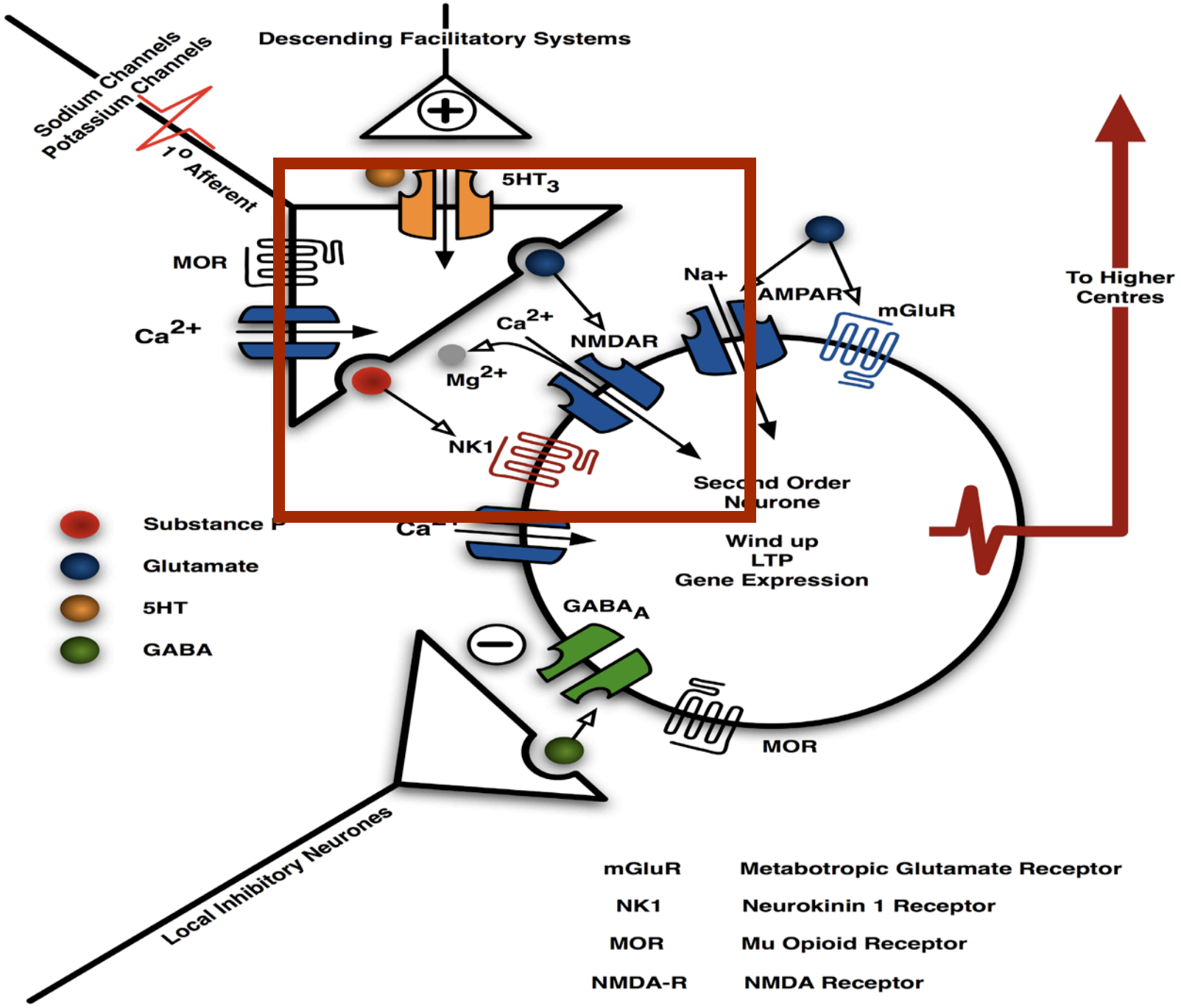






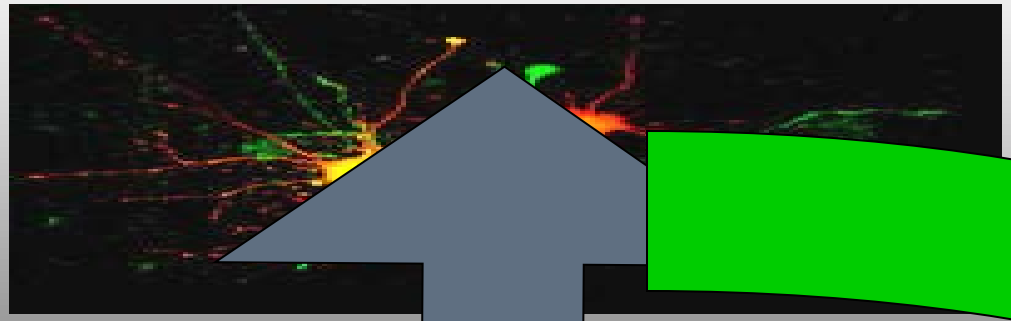


Increased wind-up and spread of pain in knee OA patients



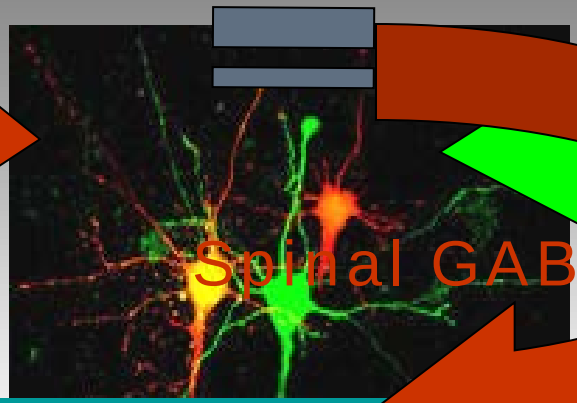
mGluR	Metabotropic Glutamate Receptor
NK1	Neurokinin 1 Receptor
MOR	Mu Opioid Receptor
NMDA-R	NMDA Receptor
AMPA-R	AMPA Receptor

Midbrain and brainstem



Descending NA - Alpha- 2 R

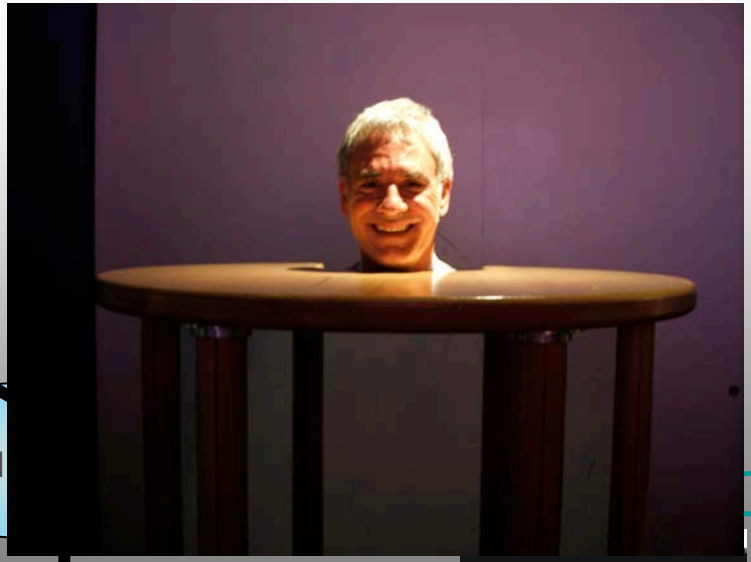
Descending 5HT3 facilitation



Spinal GABA inhibition

A small group of spinal
NK1 R neurones...required for wind-up via spinal mechanisms

Noradrenaline and 5



PAIN

Limbic System
Amygdala
Hypothalamus

Periaqu

Cell

Locus coeruleus

Off-Cell

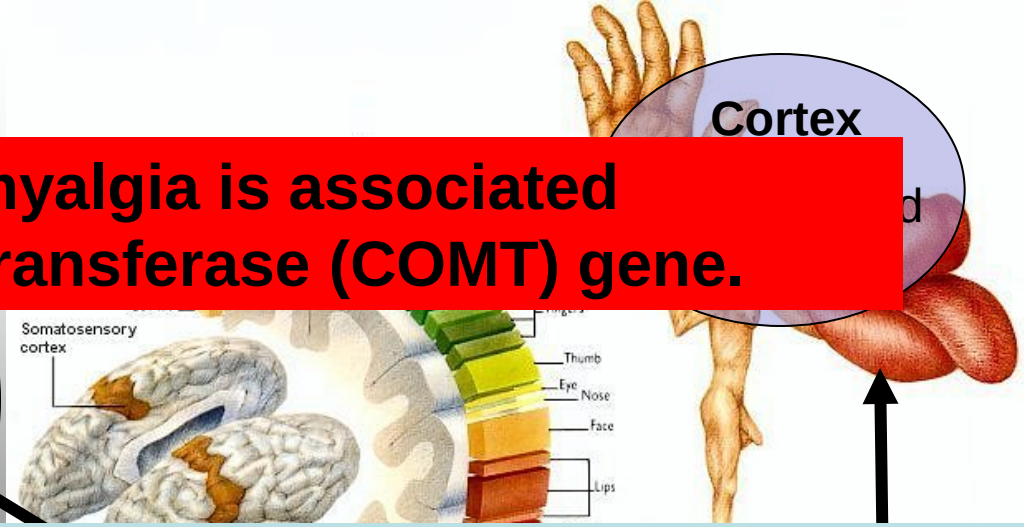
Rostroventral medial medulla

On-Cell

Noradrenaline and 5HT

Inhibitory and excitatory controls

Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene.



Affective aspects of pain

Fear, anxiety, sleep, hunger

Serotonin transporter gene (SLC6A4) polymorphism in patients with irritable bowel syndrome and healthy controls.

Descending controls
Allow top-down processes to alter pain - link mood, sleep and pain

Spinal cord
Integrates, amplifies and modifies incoming messages
Output to brain

Incoming peripheral nerves
- Convey touch, temperature
- Convey painful messages - heat, mechanical, chemical
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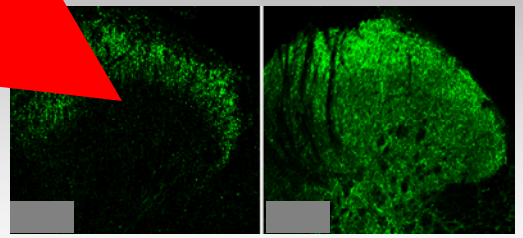


Descending inhibitions in humans…….

Neuron

Article

Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

Falk Eippert,1,* Ulrike Bingel,2 Esther D. Schoell,1 Juliana Yacubian,1 Regine Klinger,3 Ju _ rgen Lorenz,4 and Christian Bu _ chel1

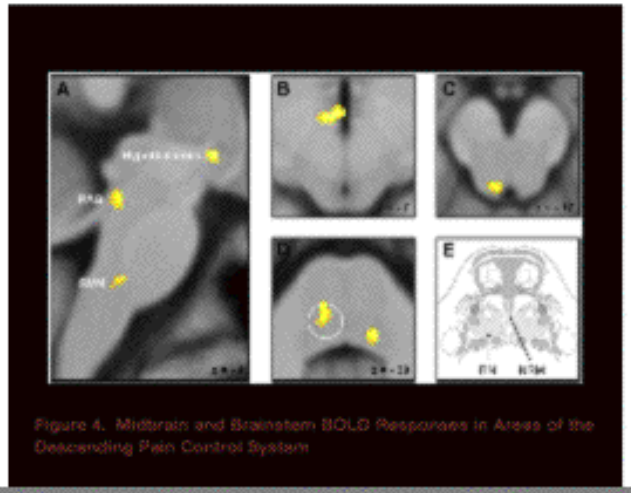


Figure 4. Midbrain and Brainstem BOLD Responses in Areas of the Descending Pain Control System

Science 16 October 2009:
Vol. 326 no. 5951 p. 404
DOI: 10.1126/science.1180142

BREVIA

Direct Evidence for Spinal Cord Involvement in Placebo Analgesia

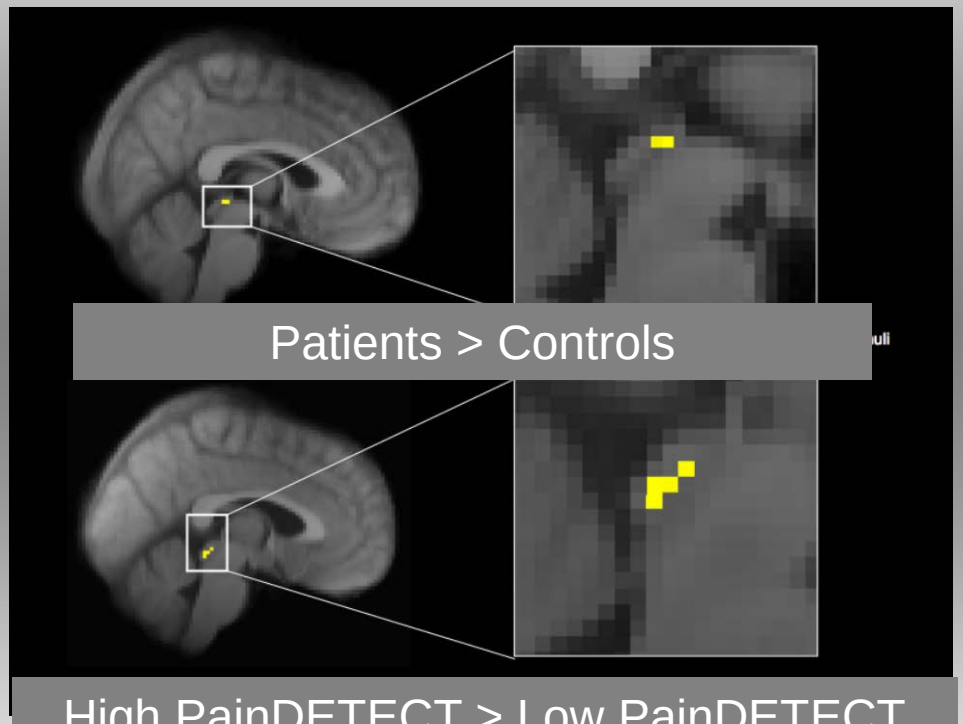
Falk Eippert *, Jürgen Finsterbusch, Ulrike Bingel and Christian Büchel

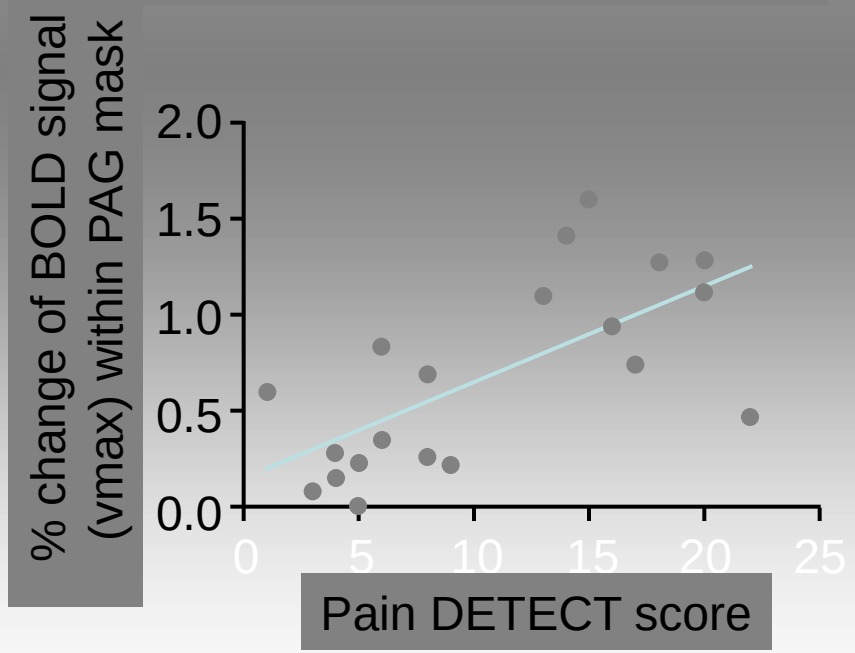
Descending facilitations in humans…….

Translation to patients

Psychophysical and Functional Imaging Evidence Supporting Presence of Central Sensitisation in a Cohort of Osteoarthritis Patients

PAG activation

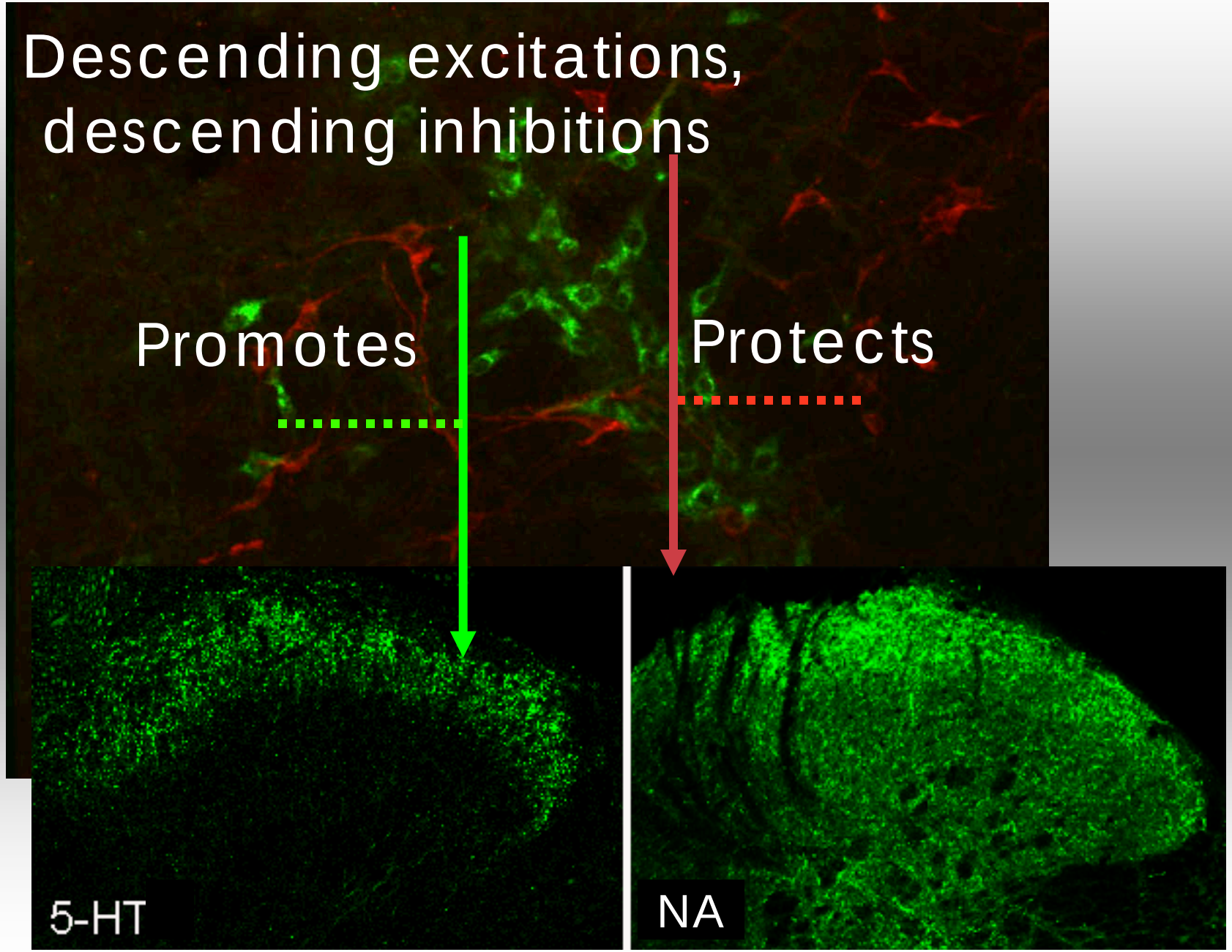




Gwilym SE et al. Arthritis Rheum 2009; 61(9):1226-34

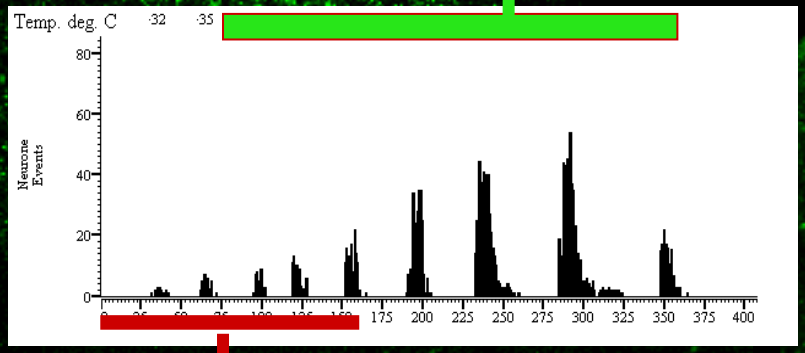
Diffuse noxious inhibitory controls (DNIC)

- *Extra-segmental inhibitions - via brain*
- Maximal in primary insomnia
- Slowed in chronic fatigue disorder
- Reduction relates to chronic post-op pain
- Reduced in fibromyalgia
- Altered by gender, age....
- Reduced in opioid hyperalgesia


Descending excitations,
descending inhibitions
Promotes
Protects
5-HT
NA

Excitations up – Inhibitions down

Reduced NA function - mood and sleep change
Increased 5HT function - anxiety, fear, sleep change

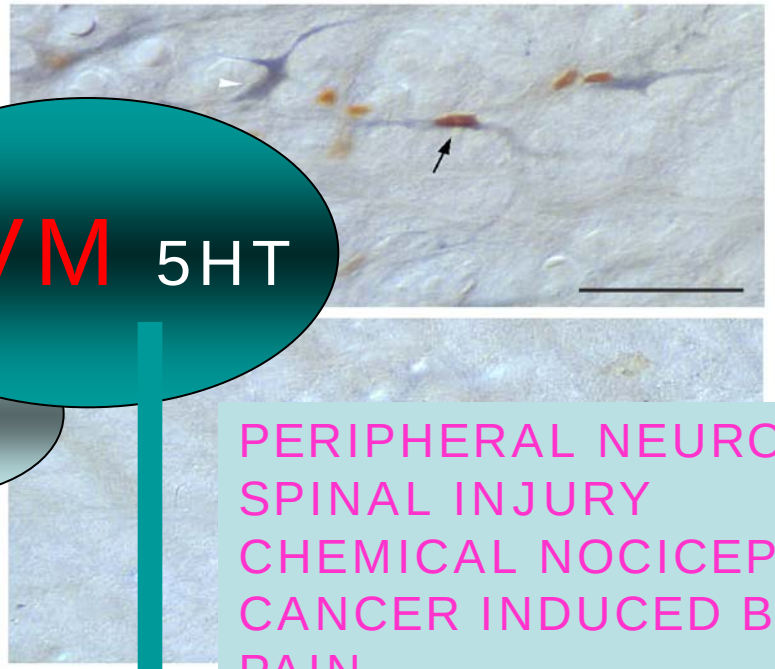


Spinal - brainstem - spinal loops - increase - 5HT promotes pai

Affective areas

PB

RVM 5HT



PERIPHERAL NEUROPATHY
SPINAL INJURY
CHEMICAL NOCICEPTION
CANCER INDUCED BONE PAIN
OPIOID HYPERALGESIA
FMS, IBS etc ???

Inhibitions

NOXIOUS
innocuous

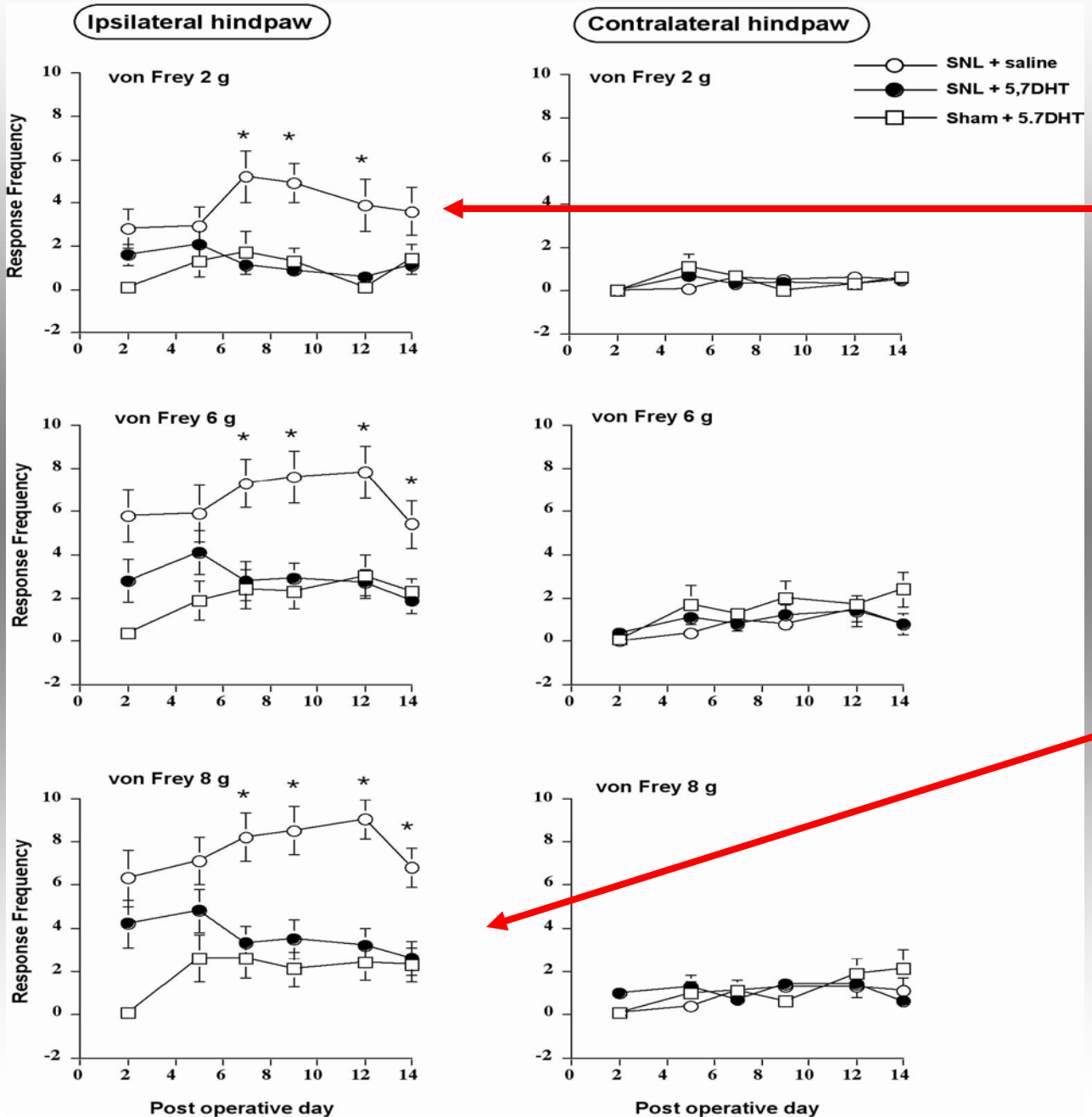
5HT3 Facilitations

Hyperalgesia

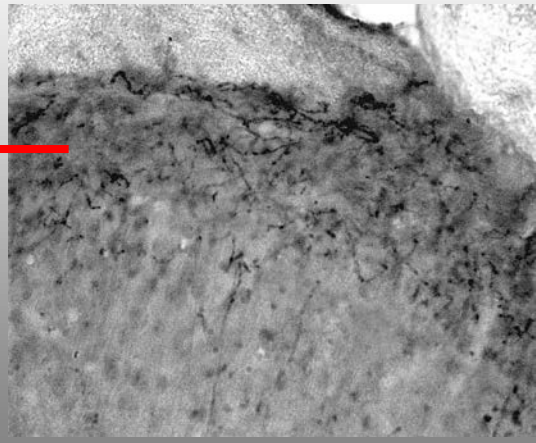
Spinal SP neurones

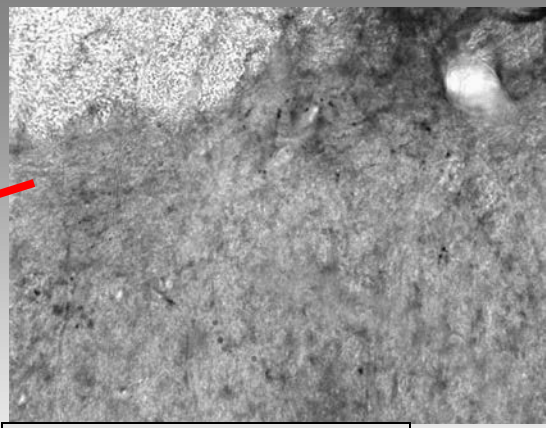
Spinal neurones II

Neuropathy - endogenous 5HT promotes pain



Normal 5HT innervation

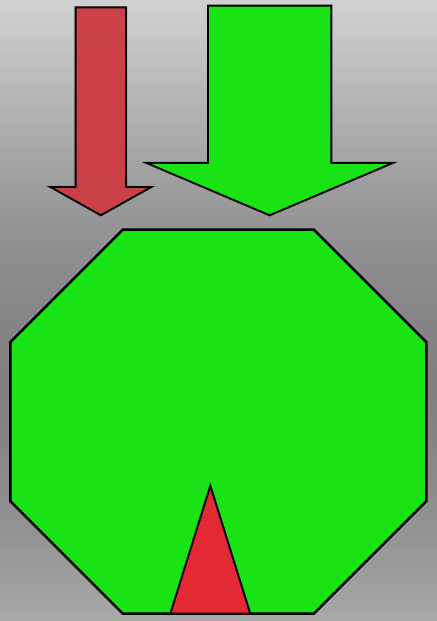




Deplete 5HT
Reduce allodynia

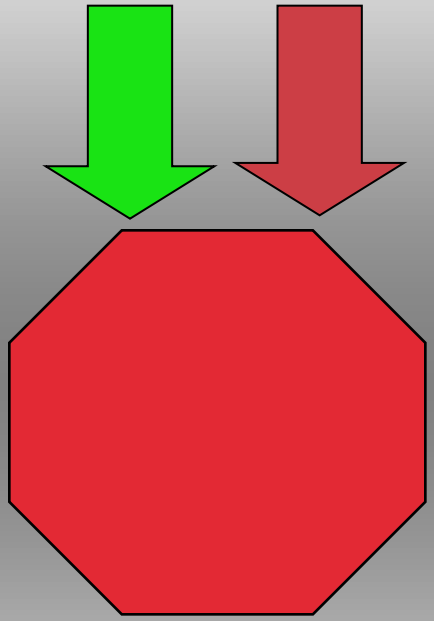
Descending facilitations allow hypersensitivity
Descending inhibitions protect….

Partly NA controls



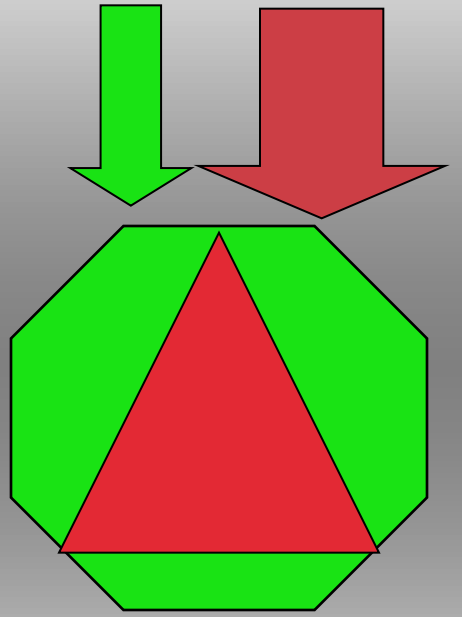
Nerve injury

Strain 1
SNL Surgery
85% mechanical hypersensitvity



Normal

Normal
No Surgery (from Strain 1)

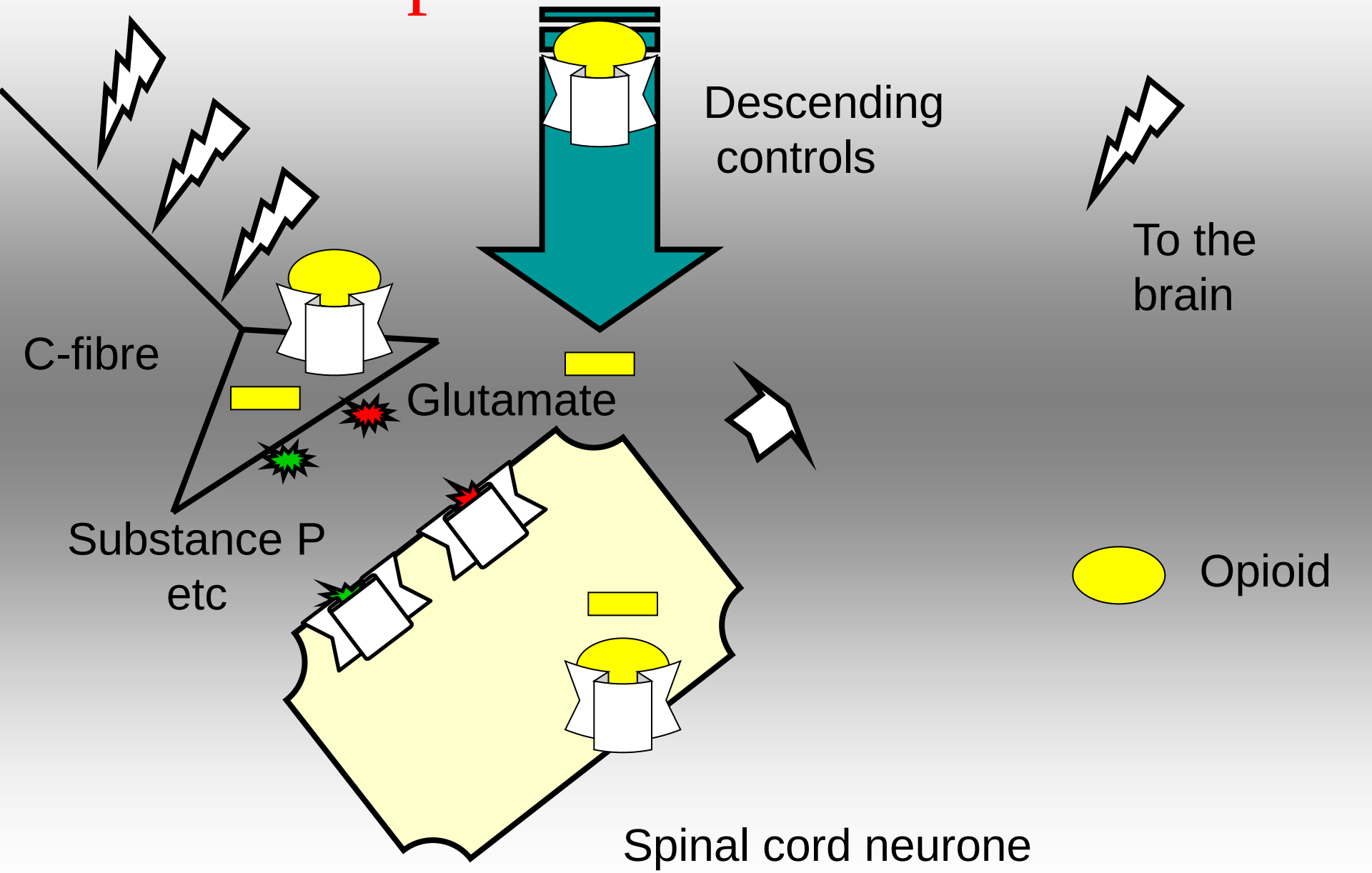


Nerve injury

Strain 2
SNL Surgery
50% mechanical hypersensitvity

De Felice M, et al. Pain. 2011 Jul

Opioid mechanisms



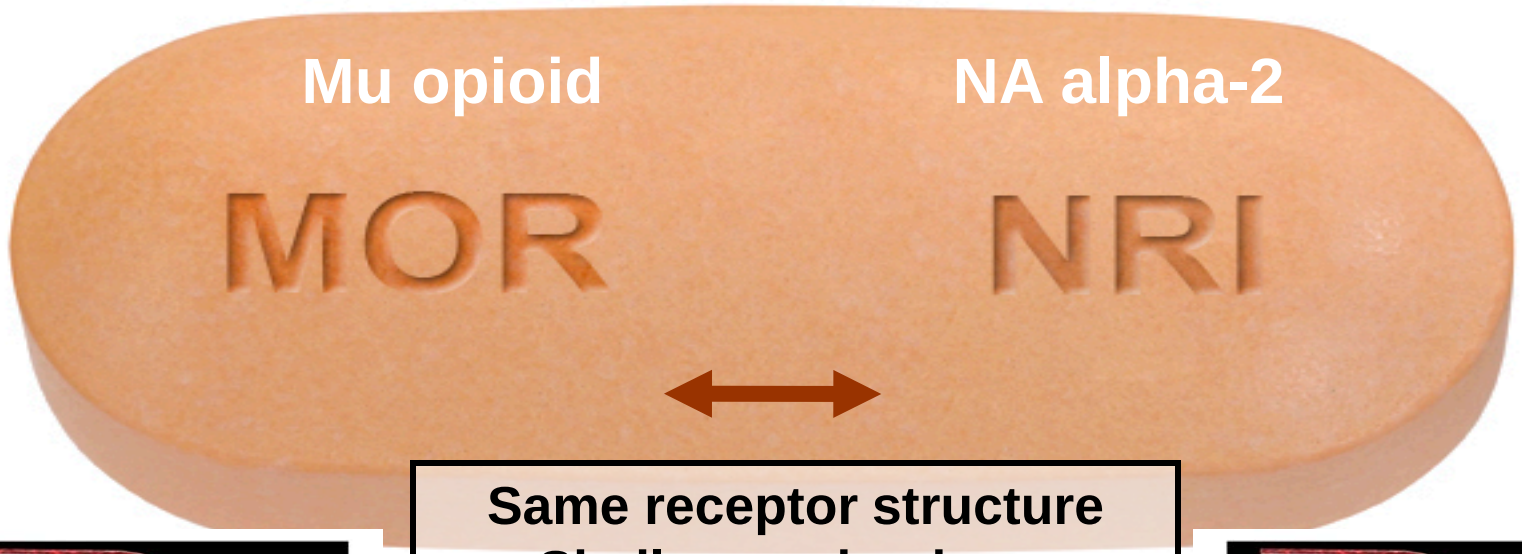
Bench to bedside

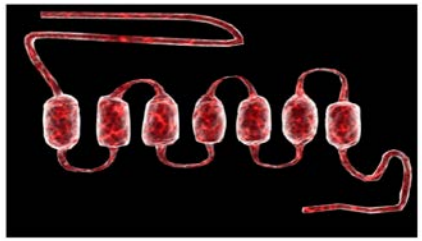
- Triptans
- COX-2 inhibitors
- CGRP blockers
- ABT - nACR
- GBP in pain
- Ketamine analgesia
- TCA, SNRI etc analgesia
- Sodium and TRP channel subtypes - inherited pain syndromes
- (Lacosomide)
- NGF ab

- NK1 antagonists
- NMDA antagonists
- Channel blockers

Tapentadol – Two mechanisms on neurones

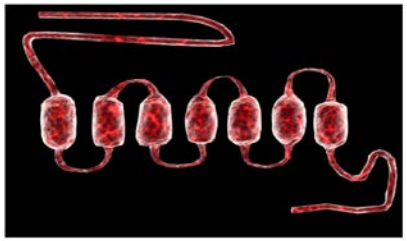
Naloxone Yohimbine/Atipamezole





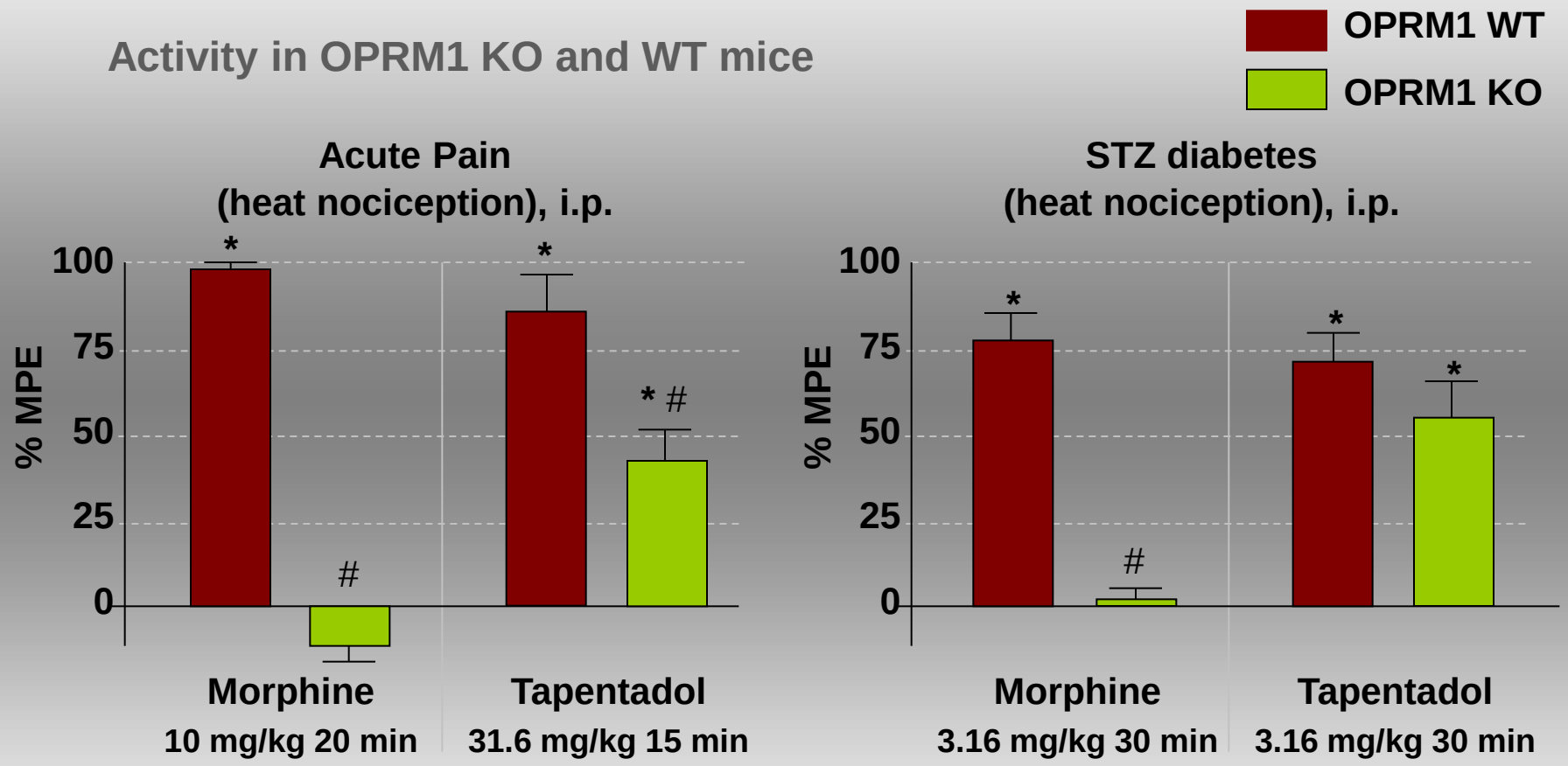
Same receptor structure
Similar mechanisms

Similar potassium channels



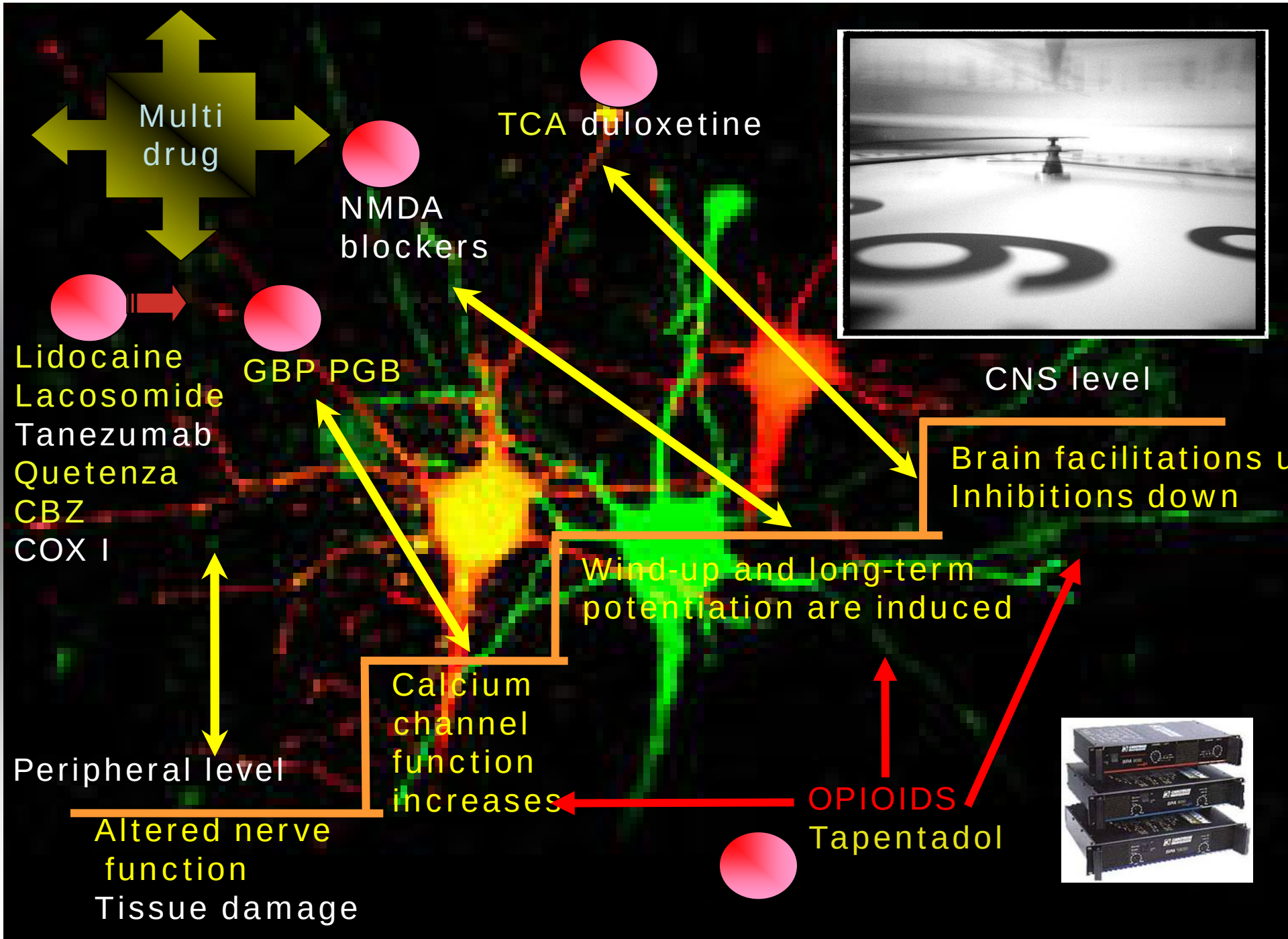
Mechanical SNL

Tapentadol: Analgesia and Antihyperalgesia in Opioid Receptor Knock-Out Mice



Antinociceptive and antihyperalgesic efficacy of Tapentadol partially retained in MOR knock-out mice

Koegel B, Neuroscience Letters 2011


Multi drug
NMDA blockers
TCA duloxetine
Lidocaine
Lacosomide
Tanezumab
Quetenza
CBZ
COX I
GBP PGB
CNS level
Brain facilitations u
Inhibitions down
Wind-up and long-term potentiation are induced
Calcium channel function increases
Peripheral level
Altered nerve function
Tissue damage
OPIOIDS
Tapentadol