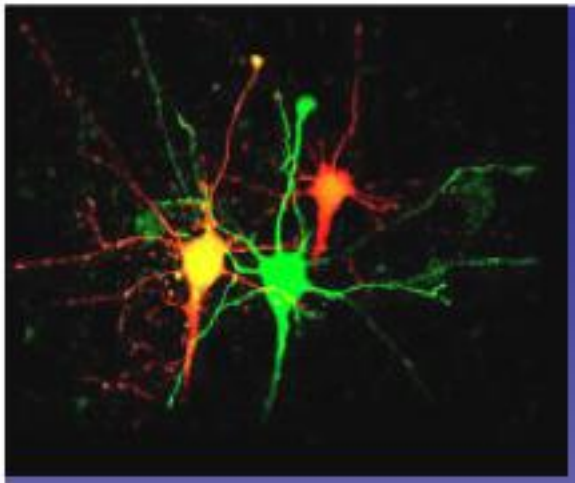
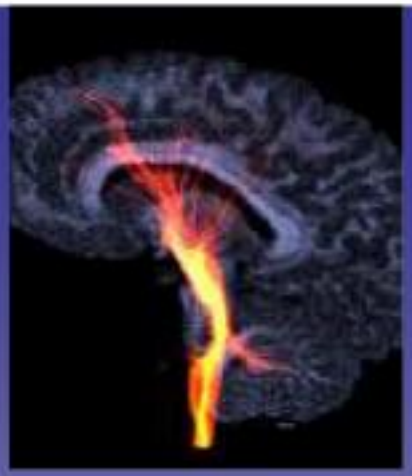
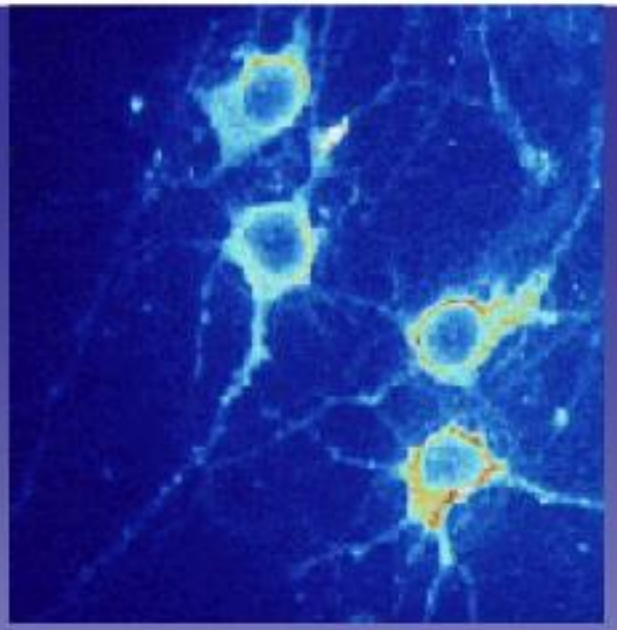




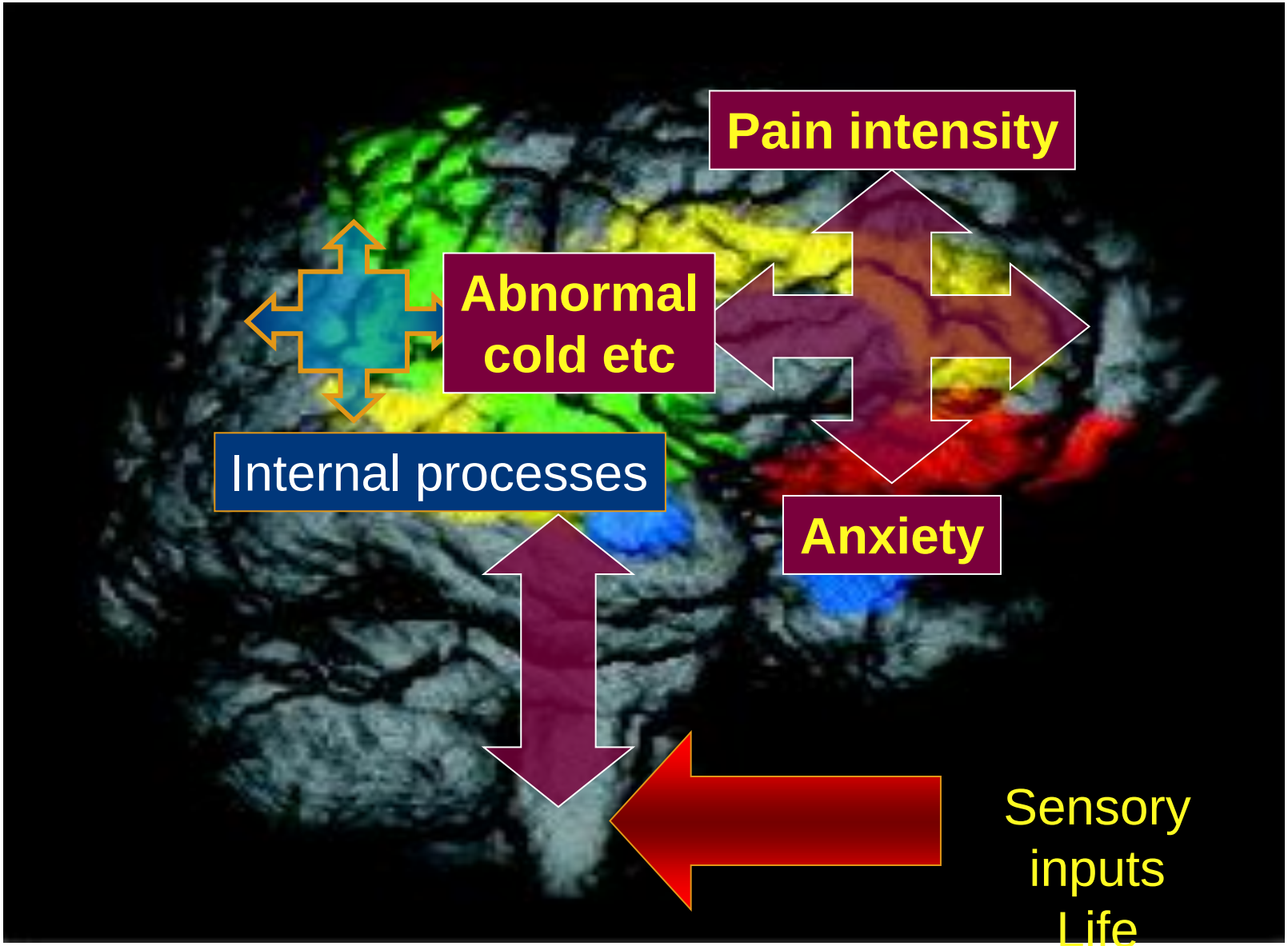


Recent advances in neuropharmacology related to acute pain

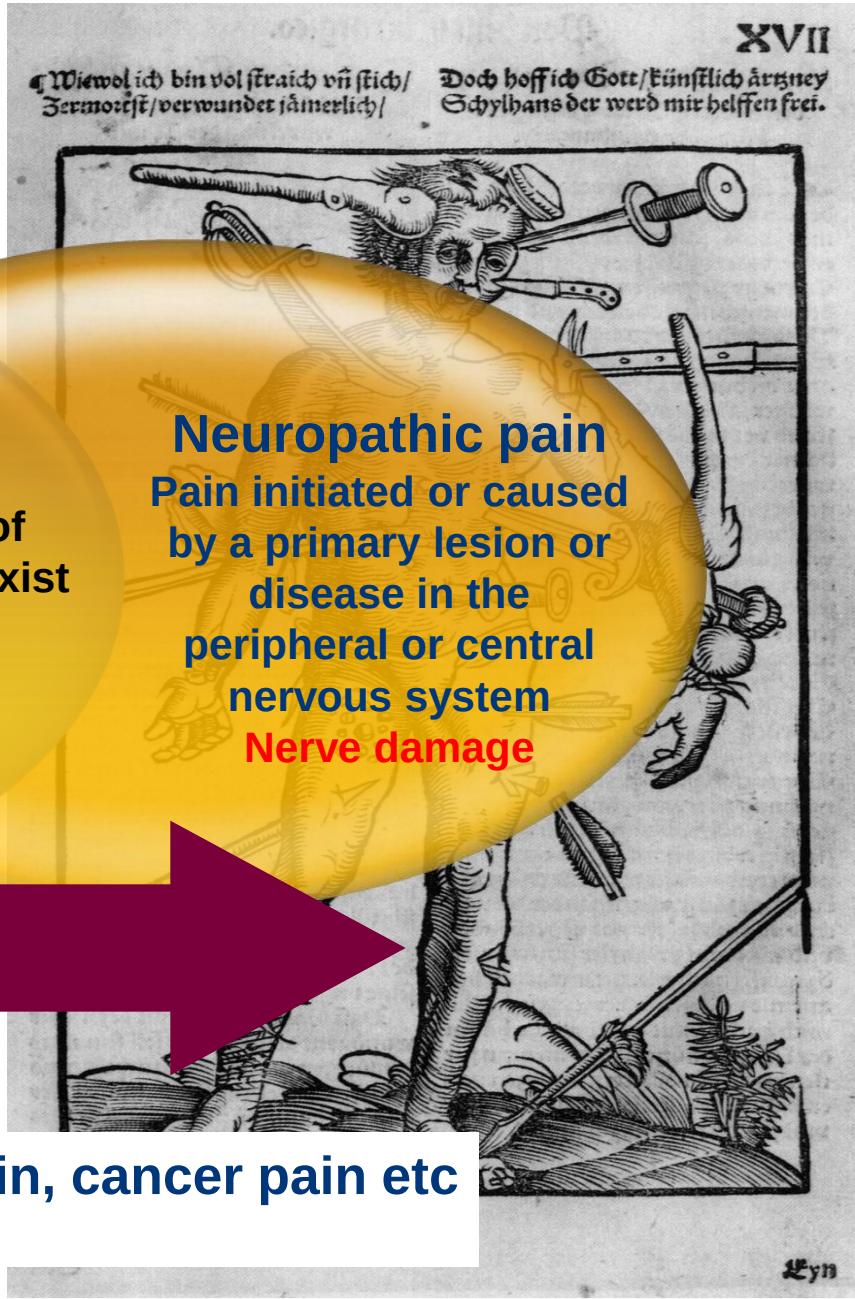
Tony Dickenson
NPP Pharmacology
University College London

The London Pain Consortium

A struggle between the outer and inner worlds



Key types of pain



Nociceptive pain

Pain caused by an inflammatory or non-inflammatory response to a noxious stimulus

Tissue damage

Both types of pain can co-exist

Neuropathic pain

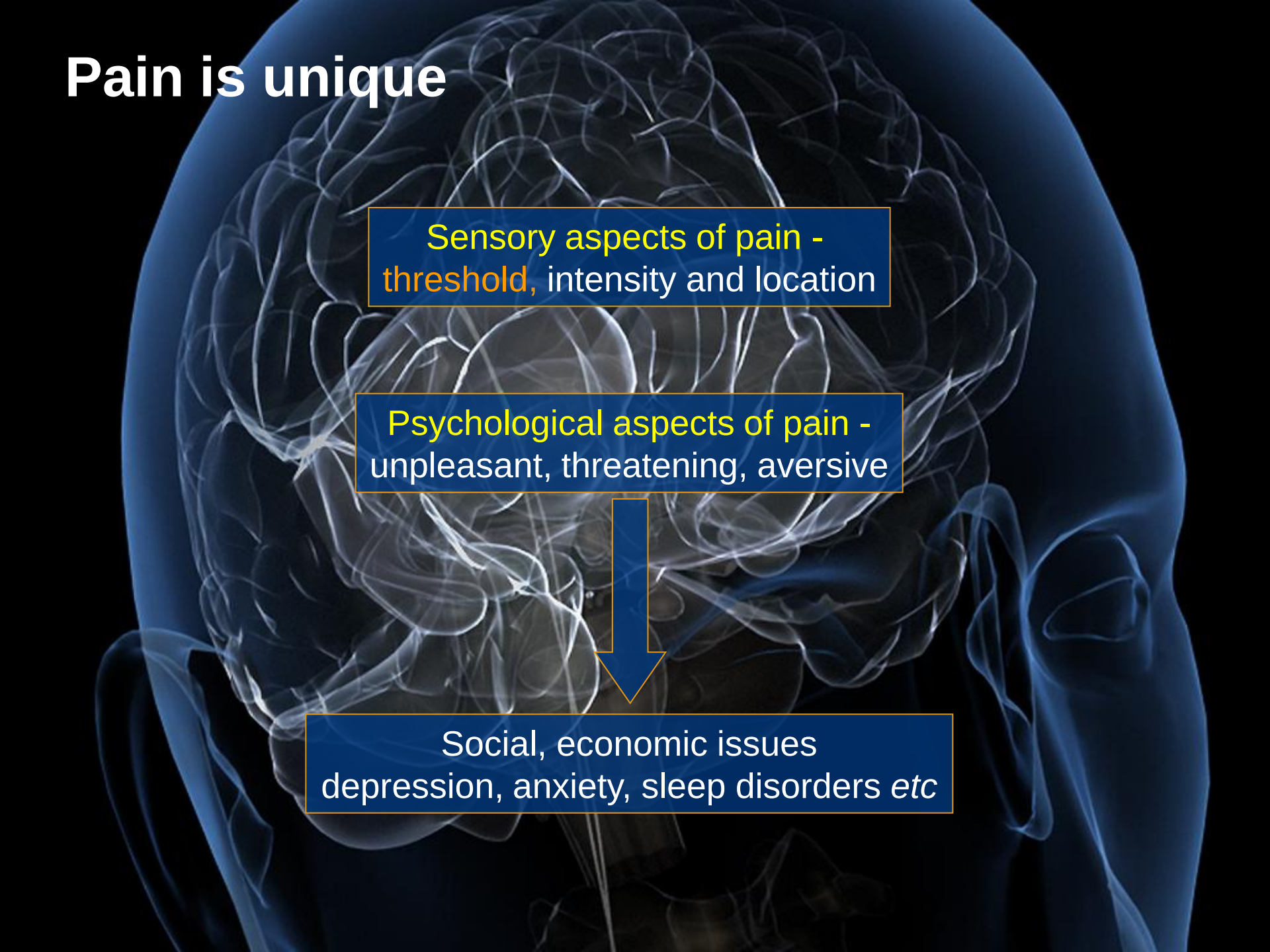
Pain initiated or caused by a primary lesion or disease in the peripheral or central nervous system

Nerve damage

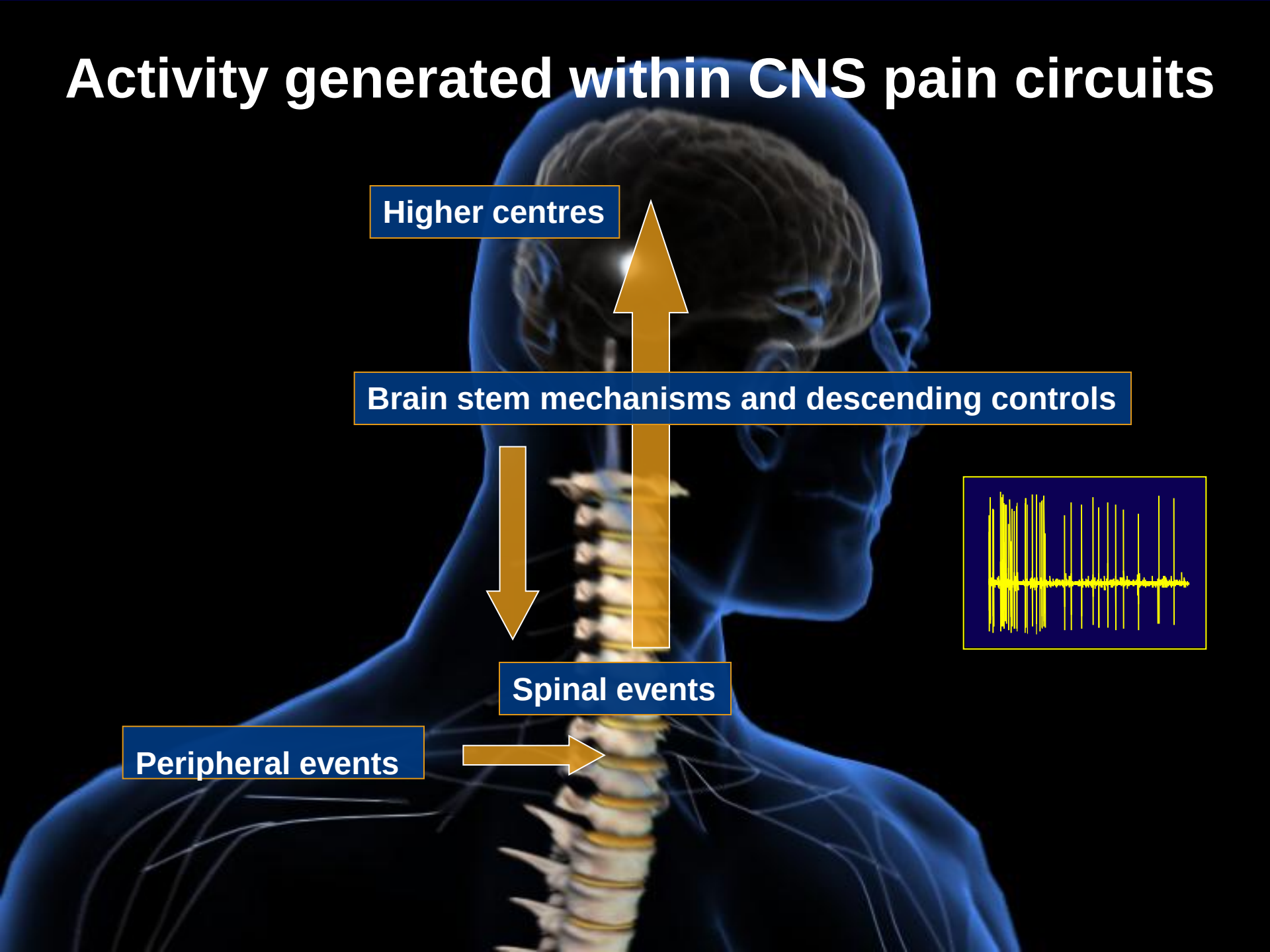
Mild
Moderate
Severe

Low back pain, cancer pain etc

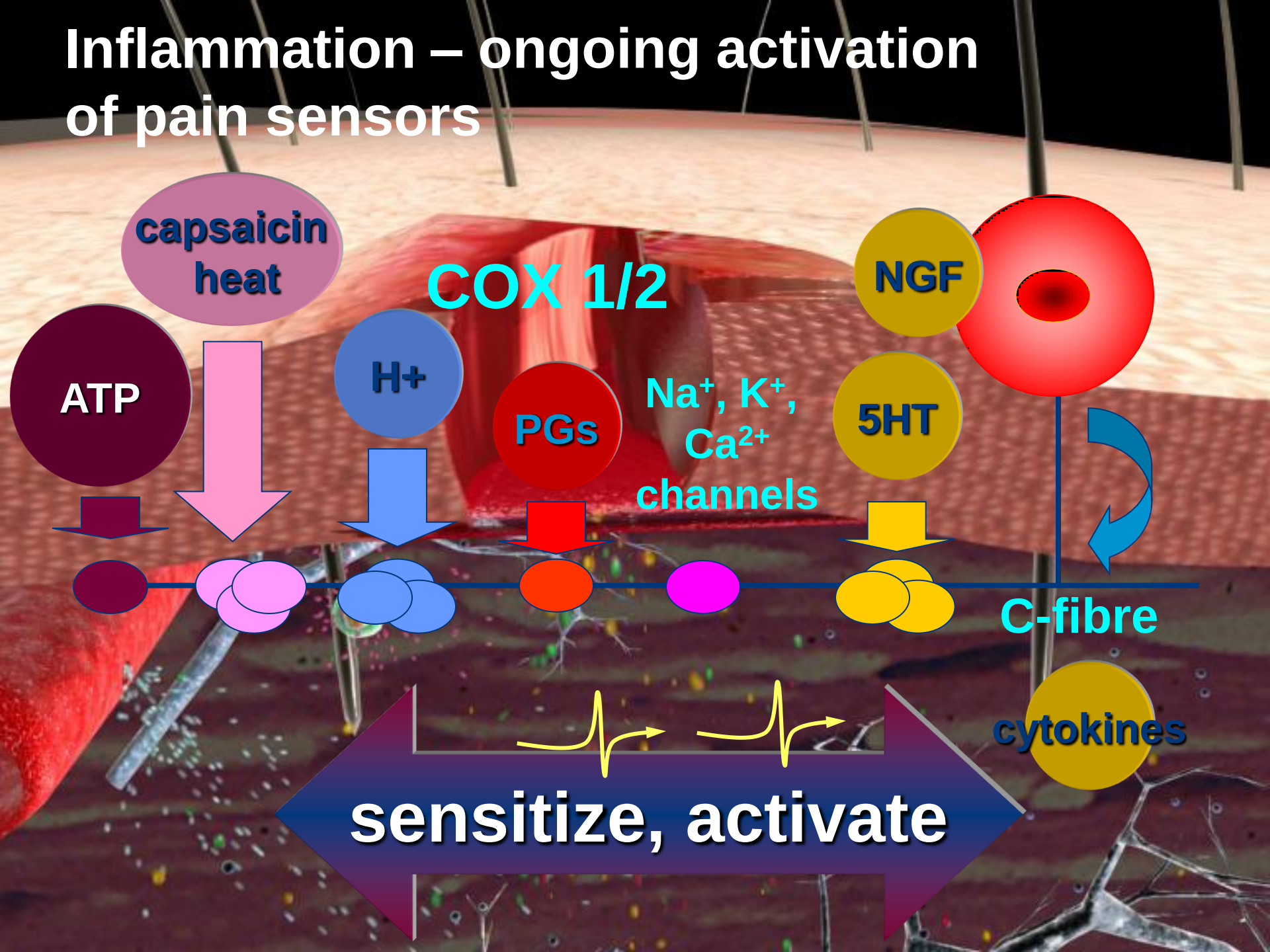
Pain is unique



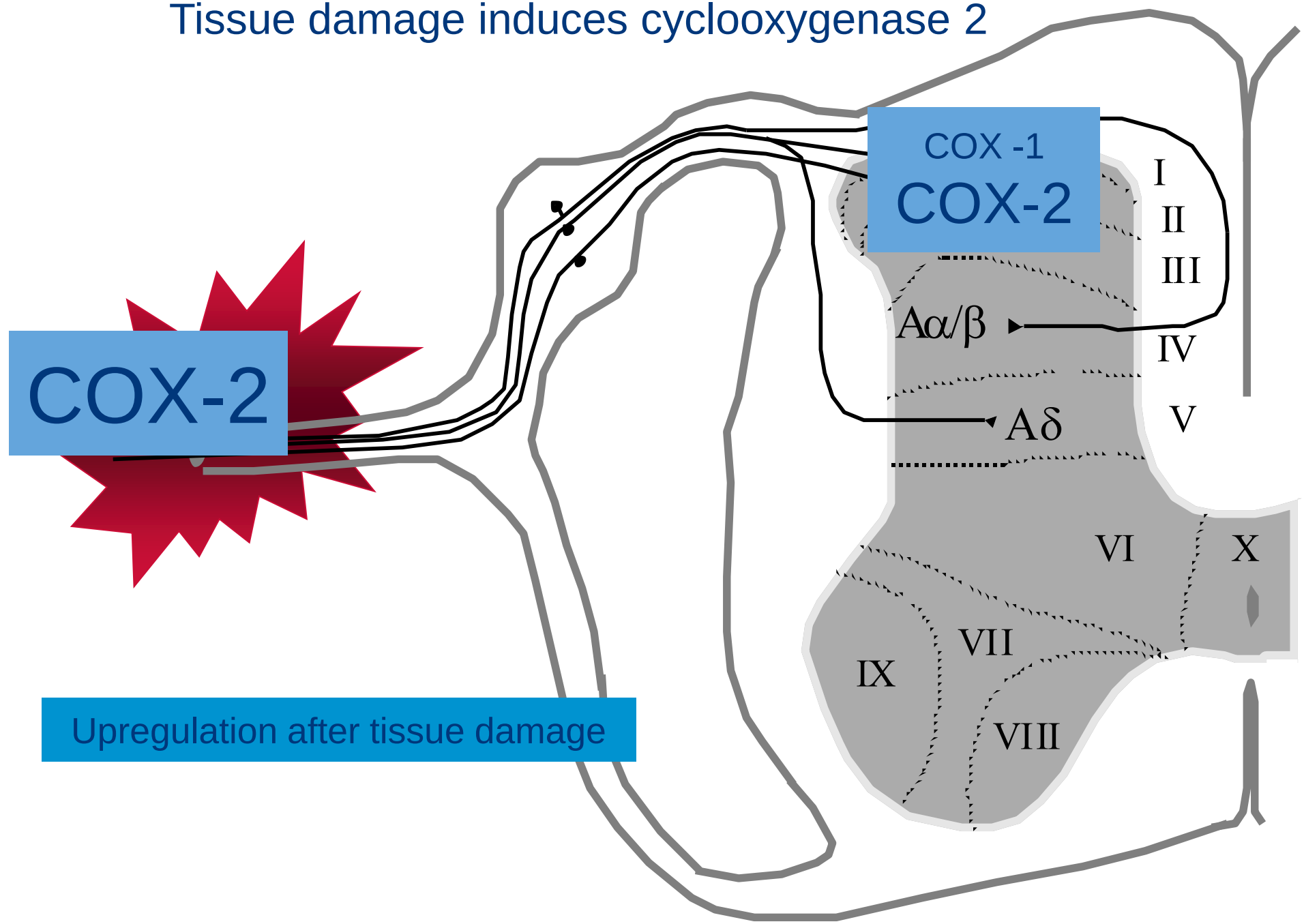
Activity generated within CNS pain circuits



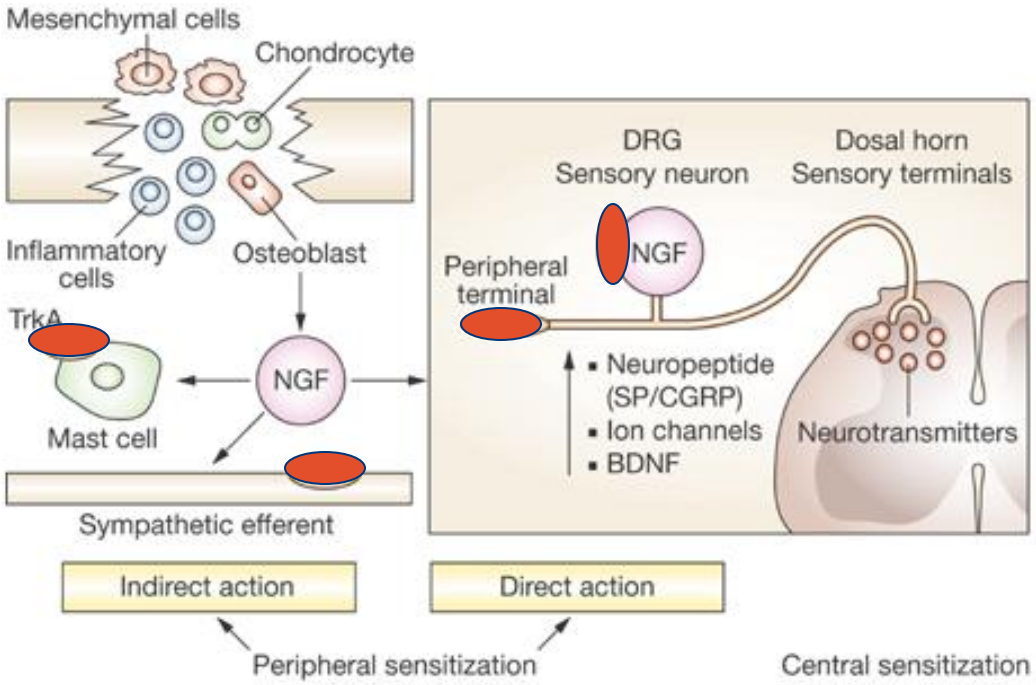
Inflammation – ongoing activation of pain sensors



Tissue damage induces cyclooxygenase 2

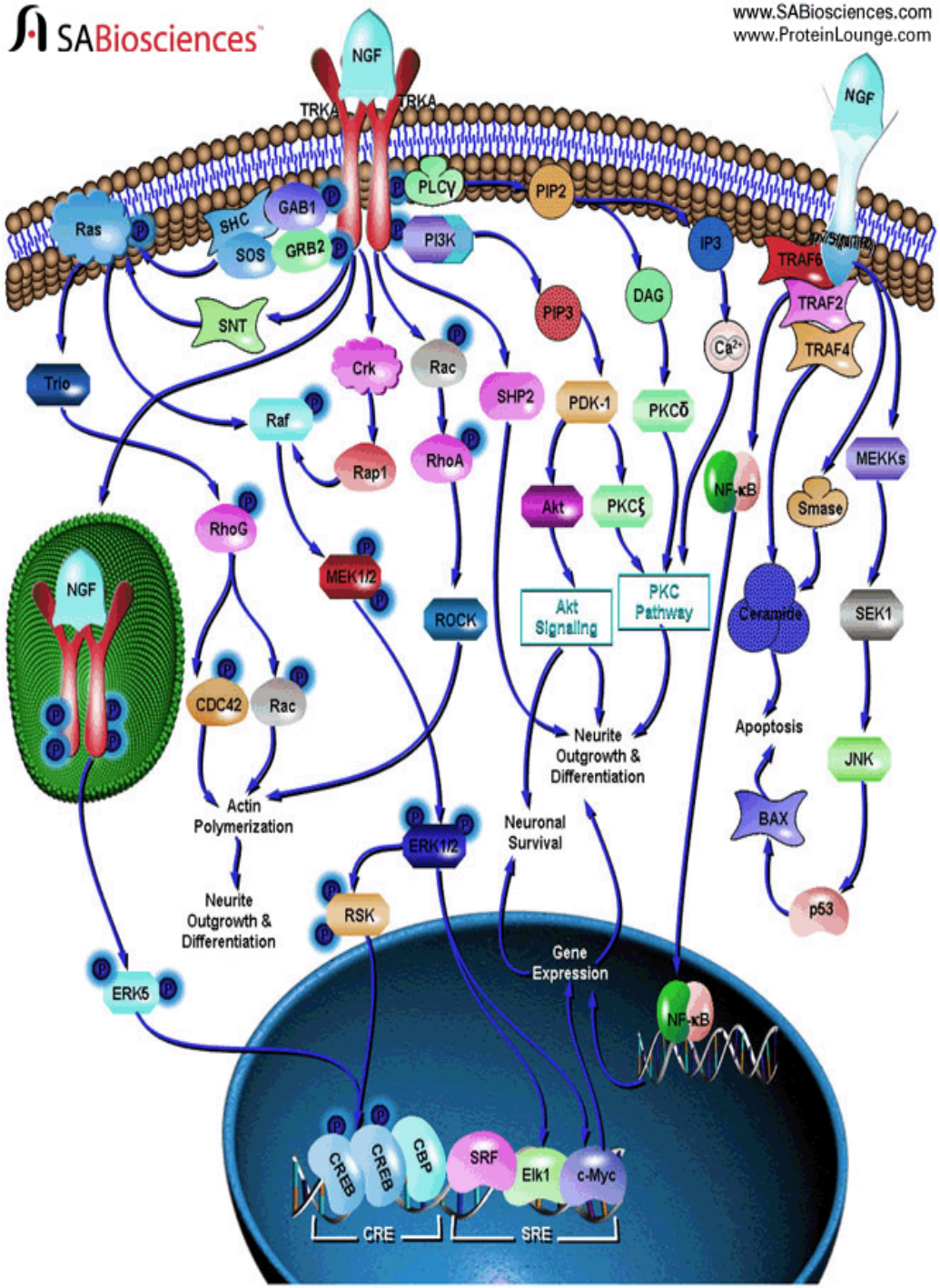


Nerve Growth Factor -Direct peripheral, direct gene effects and indirect…



Xian CJ and Zhou X-F *et al.* (2009) Treating skeletal pain: limitations of conventional anti-inflammatory drugs, and anti-neurotrophic factor as a possible alternative
Nat Clin Pract Rheumatol doi:10.1038/ncprheum0982

nature CLINICAL PRACTICE
RHEUMATOLOGY



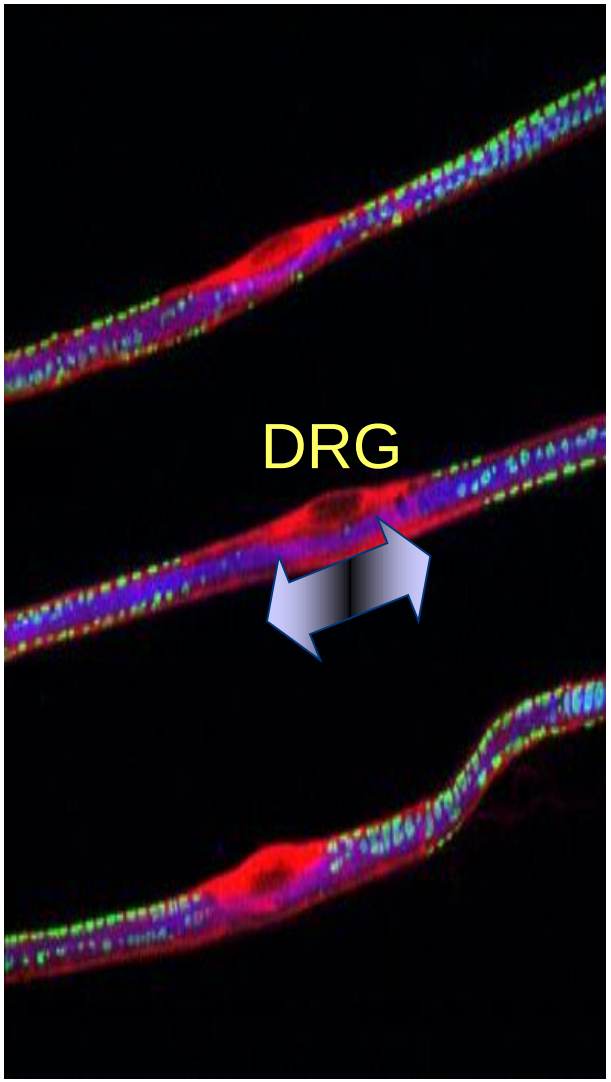
Tanezumab - humanized Monoclonal Antibody

10pM >100 hr stable binding
Prevents TrkA action

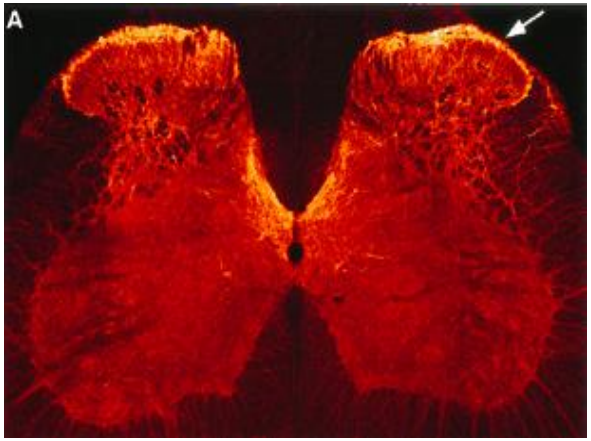
Excess of NGF in states of inflammation

Loss of NGF role
in neuropathy

Neuropathy - nerves tend not to heal…



A -beta fibres
Non-noxious
A -delta fibres
Some noxious
C- fibres
Noxious

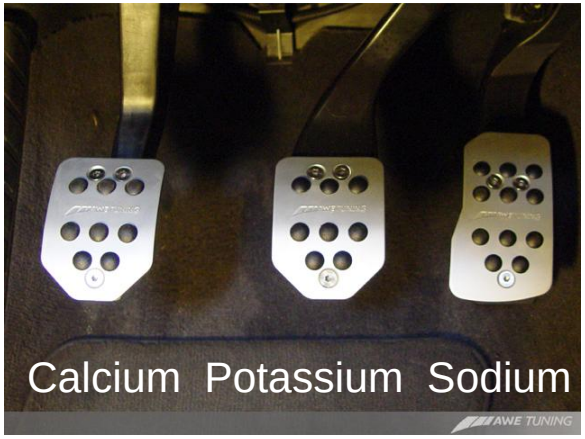


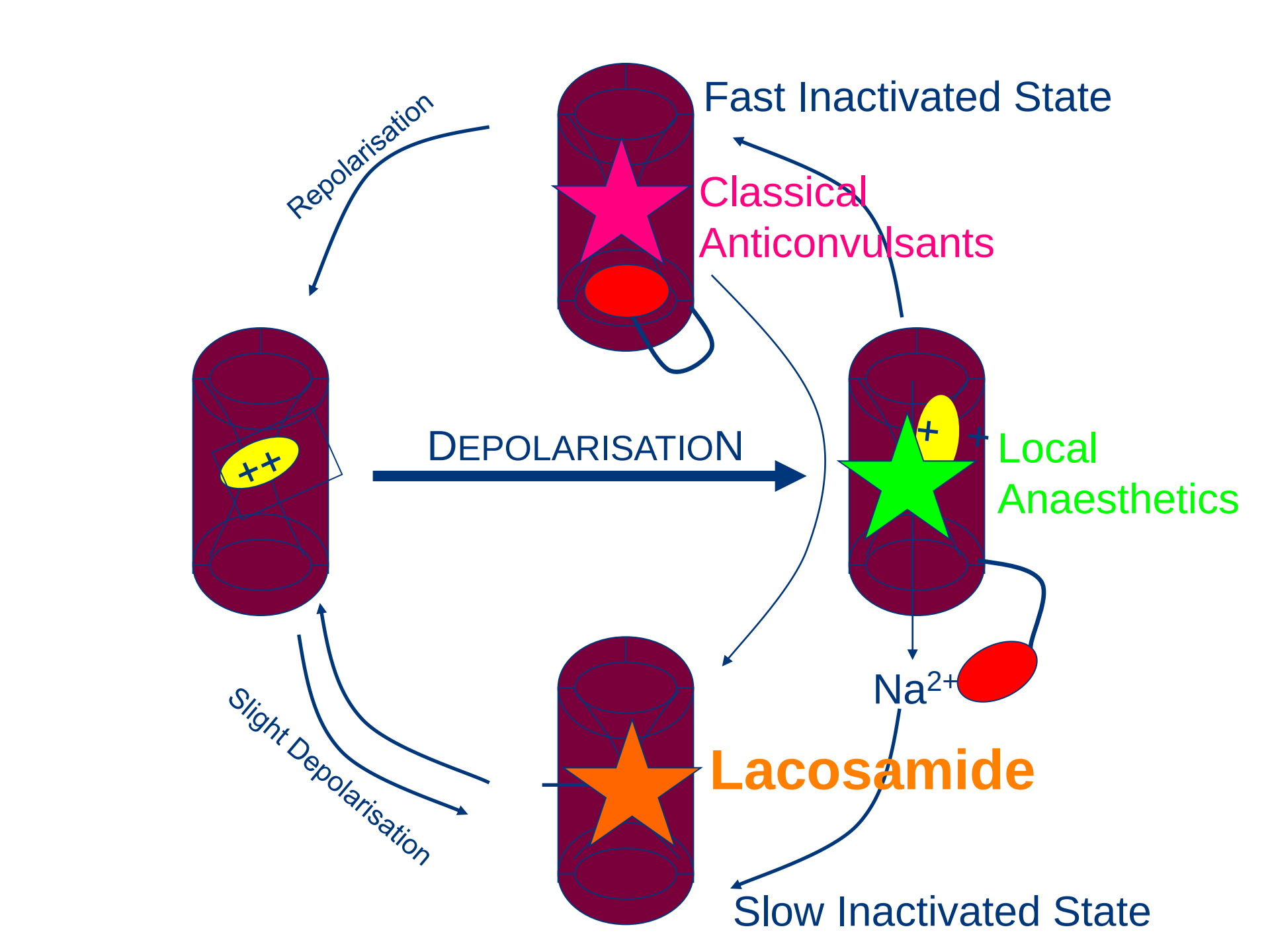
Disordered conduction

Accumulations of channels

Ectopic and ephatic activity

De-novo channels




Fast Inactivated State
Classical
Anticonvulsants
Repolarisation
DEPOLARISATION
++
+
+
Local
Anaesthetics
Na2+
Lacosamide
Slight Depolarisation
Slow Inactivated State

Sodium channels

Nav 1,7

Expressed in fine fibres
Mutations cause sensory and autonomic changes in erythermyalgia - analgesia

Nav 1,8

Unique to fine fibres
Roles in pain in animals and esp mechanical

Nav 1,3

cord after nerve injury - also in brain after

Nav 1,5

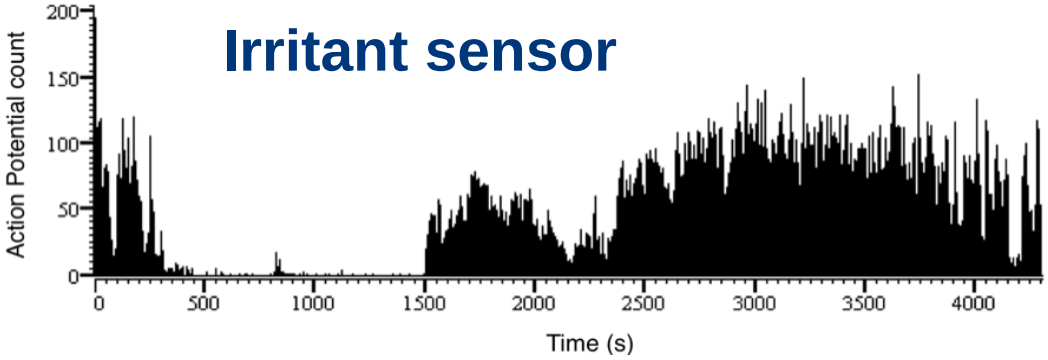
d in visceral pain

Block multiple channels - TTX and 1.5?

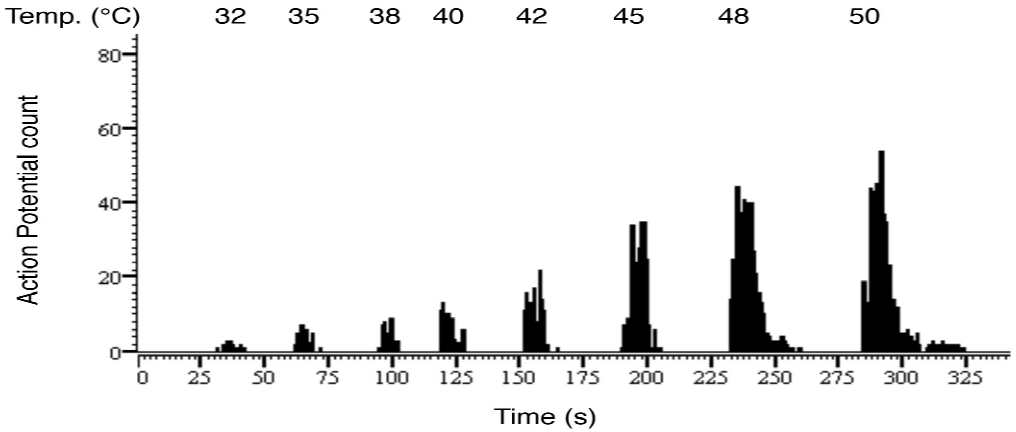
Channelopathic pain syndromes

Inherited erythromyalgia	Nav 1.7	Lower threshold, enhanced responses	Attacks of burning pain and redness in extremities
Paroxysmal extreme pain disorder	Nav 1.7	Impaired inactivation Enhanced response	Episodic lower body ocular, jaw pain
Channelopathy associated insensitivity to pain	Nav 1.7	Loss of function	Inability to sense pain
Familial episodic pain syndrome	TRPA1	Enhanced response	Episodic upper body pain, triggered by fasting, cold, fatigue

A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome



Prodermal……pain 1.5 hrs…..sleep



Normal acute pain

Upper body pain

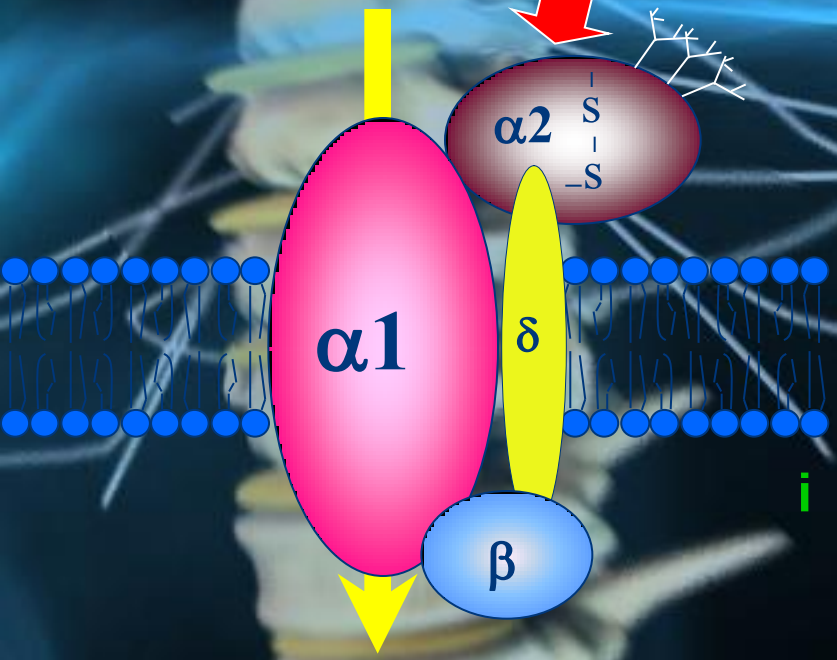
Triggered by
- cold
- hunger
- fatigue
- exertion

Kremeyer B et al.
Neuron 2010;66(5):671-80

Channels are key to neuropathic pain

Major spinal increases in excitability

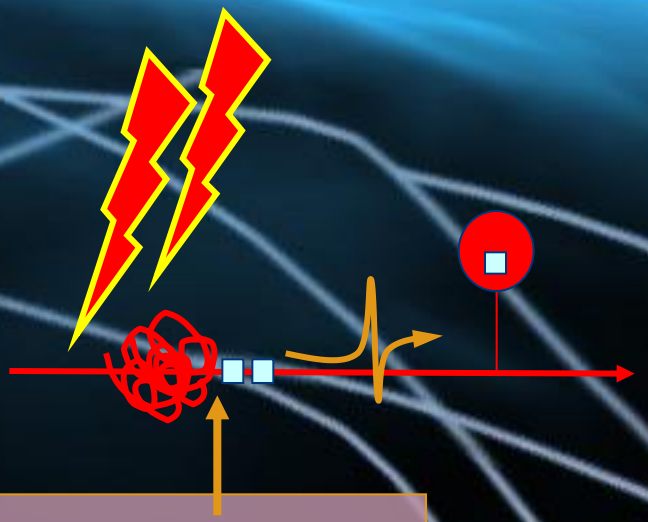
$\alpha_2\delta$ ligands



Release of transmitters

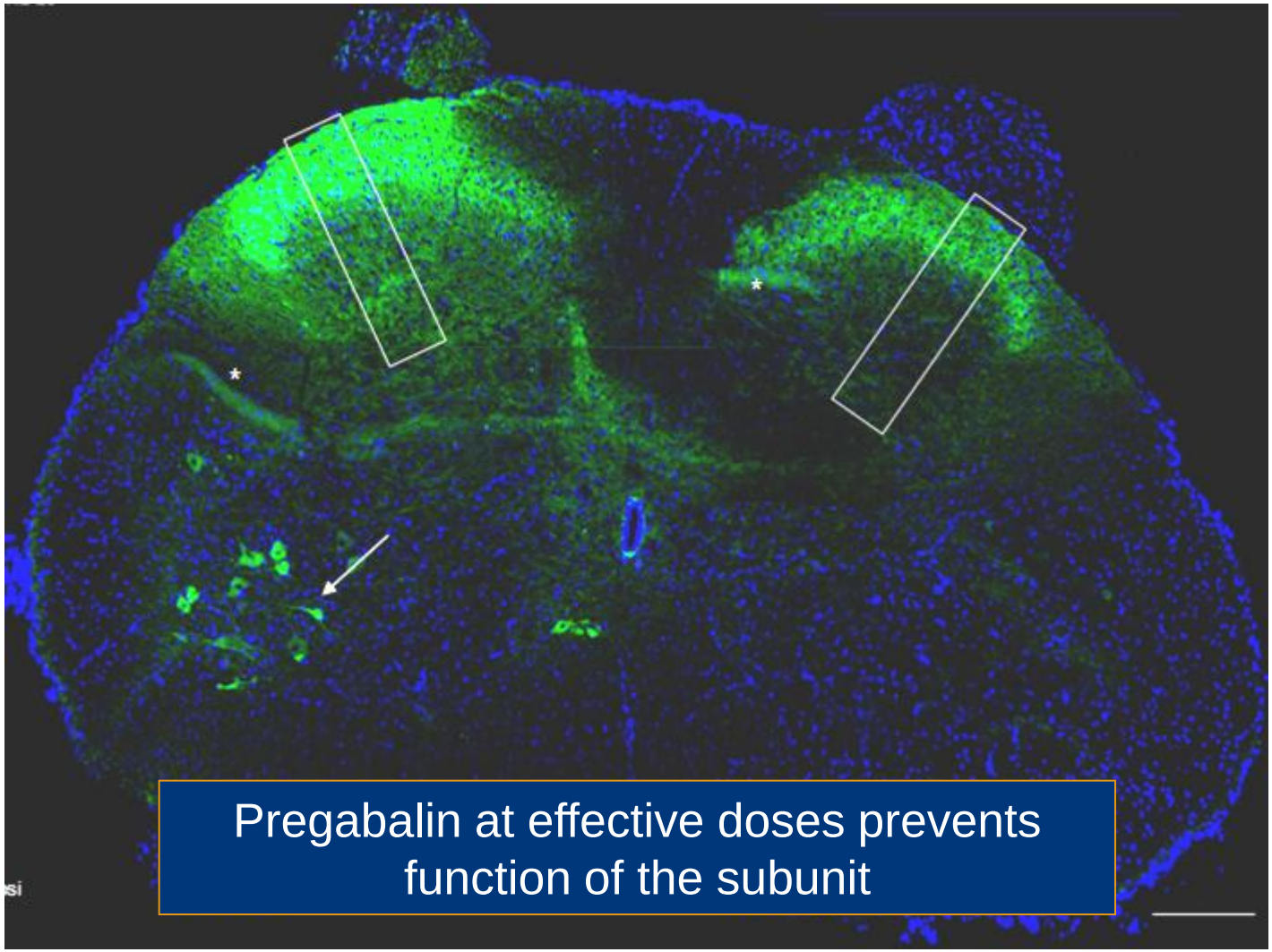
Damaged Zone

Electrical activity



Carbamazepine
Lidocaine

Upregulated alpha-2 delta subunits in the spinal cord on the side of nerve injury



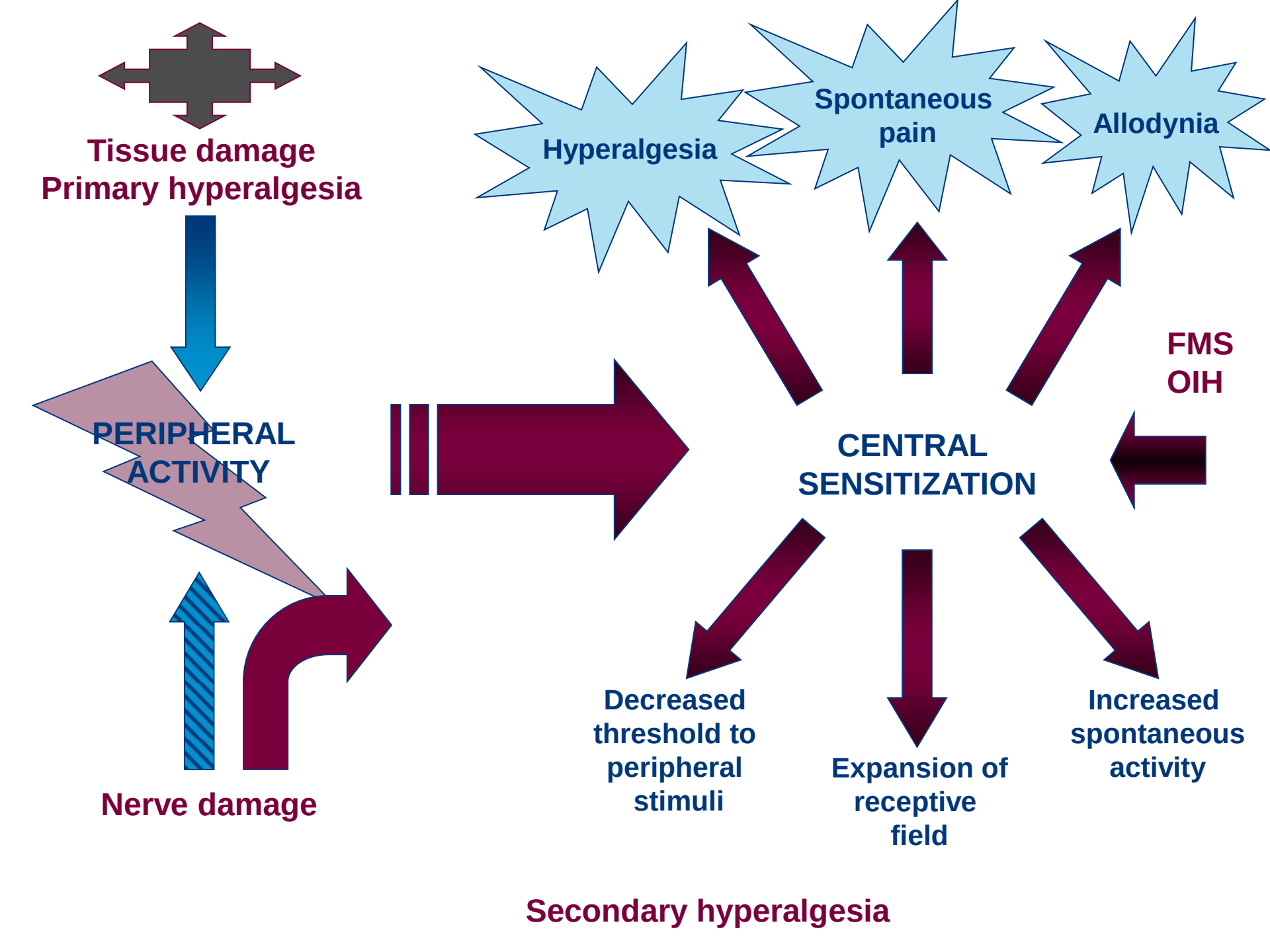
Bauer CS et al. *J Neurosci* 2009;29:4076-88

Pregabalin and Alpha-2 Delta 1

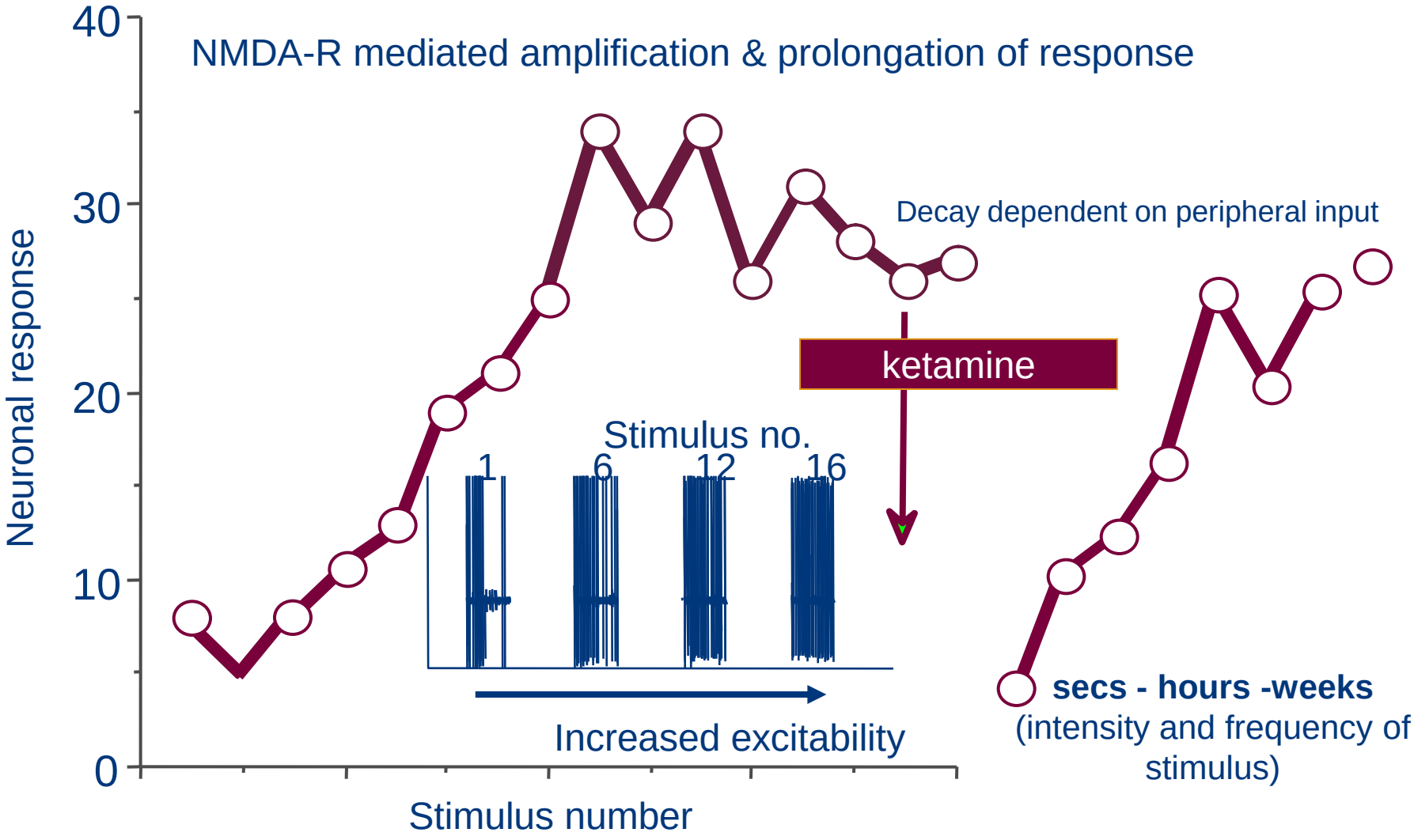
- Traumatic neuropa
- In all peripheral fibr
- Corresponds to ner

- Pregabalin has no e effect
- Pregabalin at beha nt of alpha-2 delta 1 to the membrane - tra

  If the channel is no ot function normally…..state-d

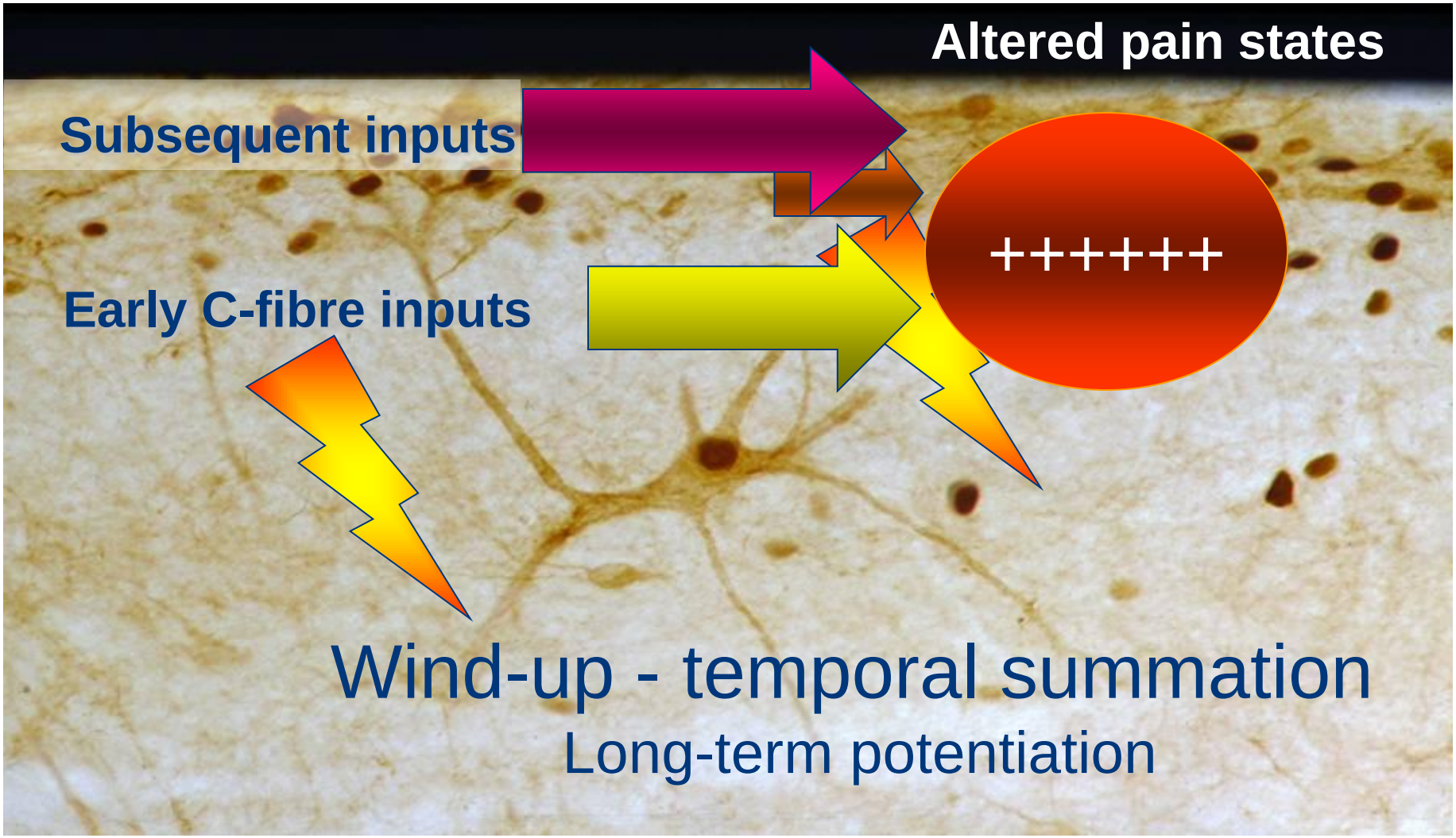

Tissue damage
Primary hyperalgesia
Hyperalgesia
Spontaneous pain
Allodynia
FMS
OIH
PERIPHERAL ACTIVITY
CENTRAL SENSITIZATION
Decreased threshold to peripheral stimuli
Expansion of receptive field
Increased spontaneous activity
Nerve damage
Secondary hyperalgesia

NMDA receptors and wind-up

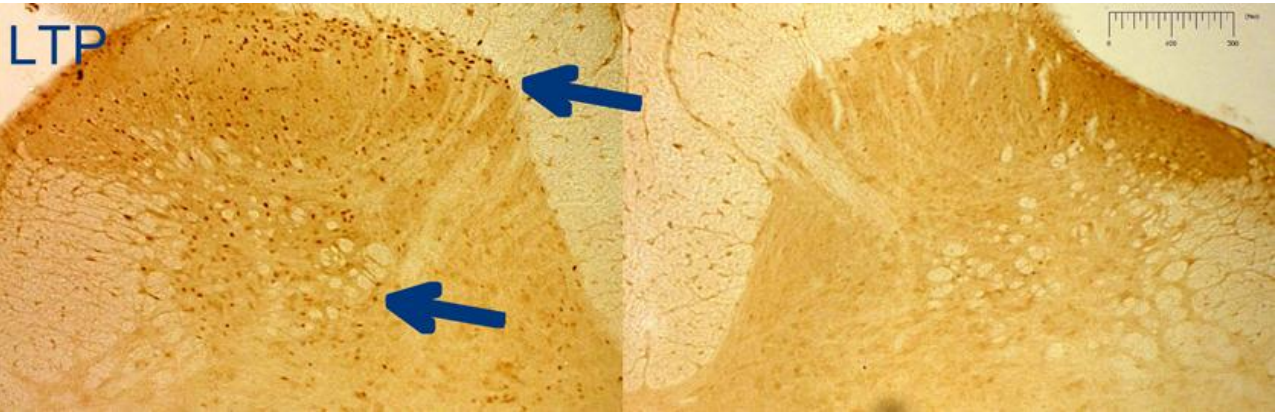


D'Mello RD, Dickenson AH. *Br J Anaesthesia* 2008;101:8-16

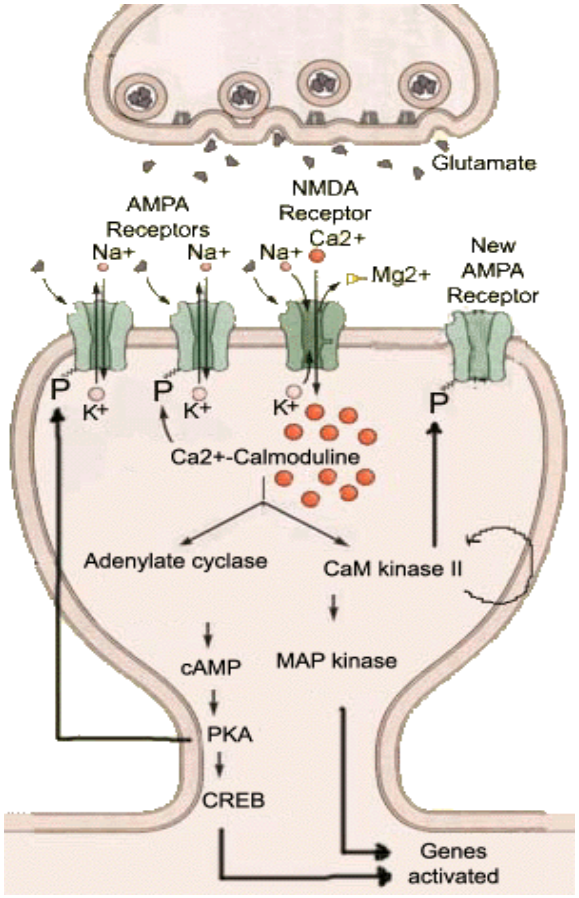
Spinal mechanisms - central hypersensitivity

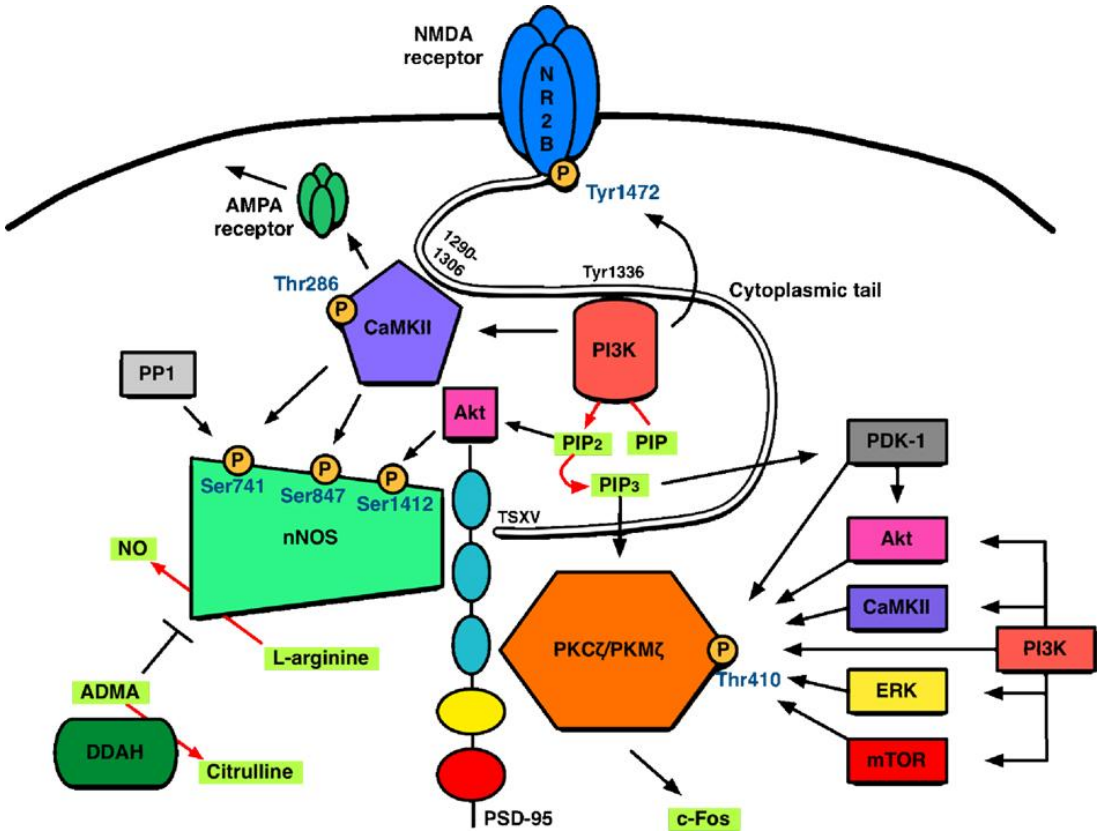


Peripheral and descending pathways converge …

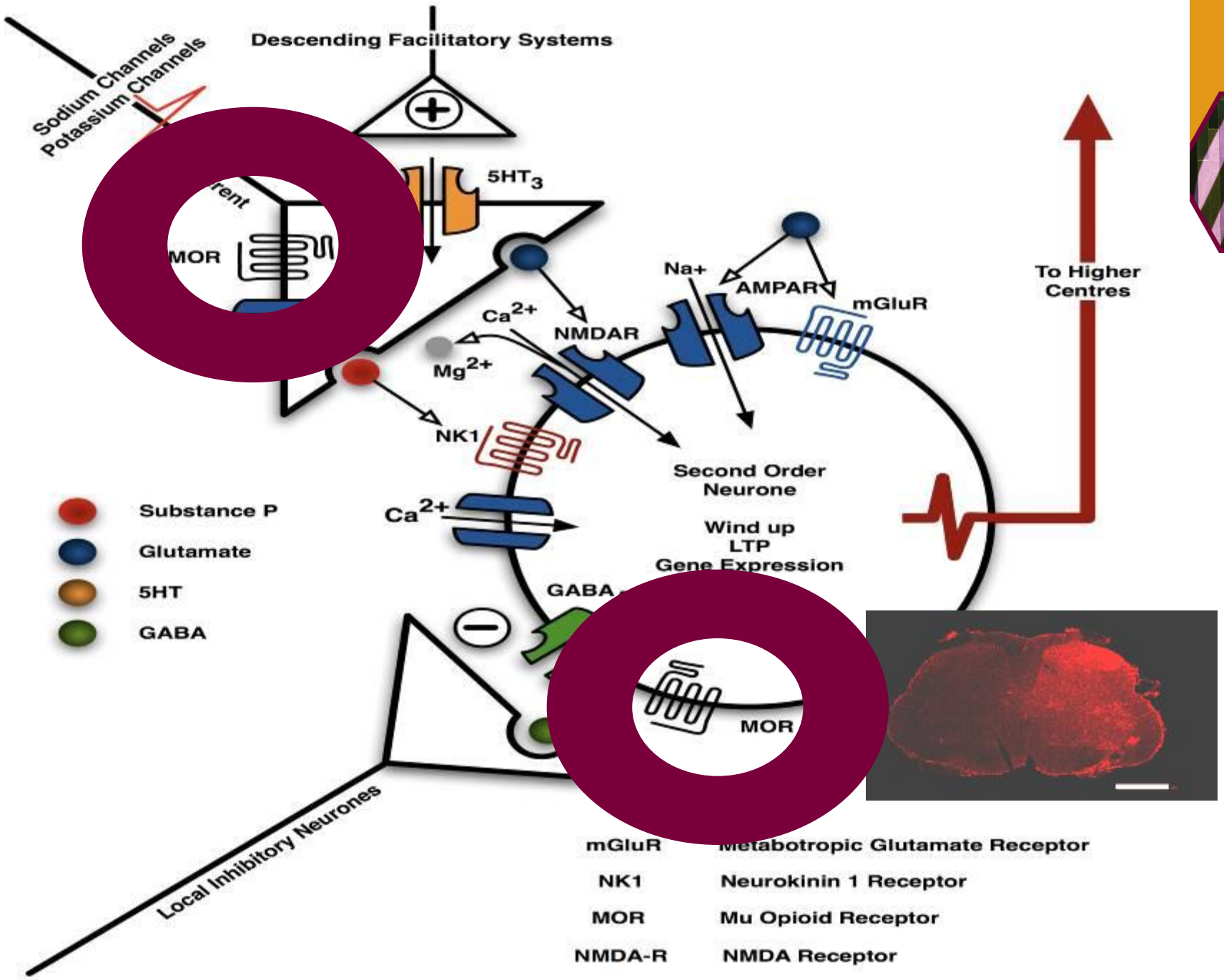


Genes related to memory processes, responses to the outside world *etc*.

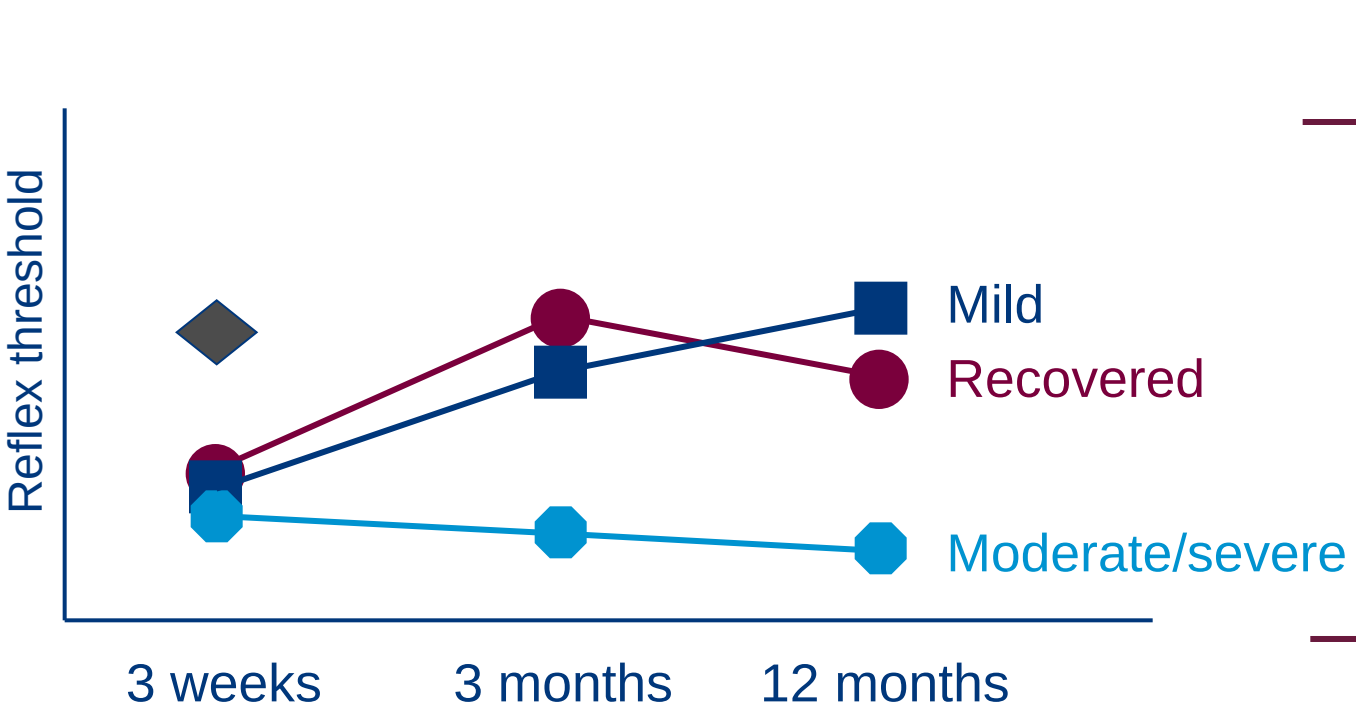


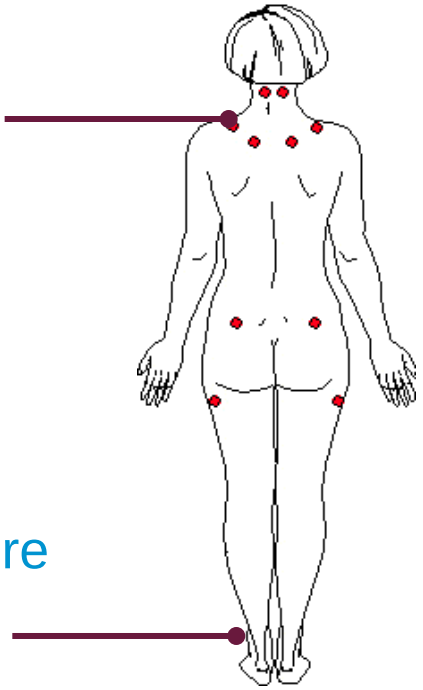


Rygh LJ et al. *Eur J Neurosci* 2006; 761-72

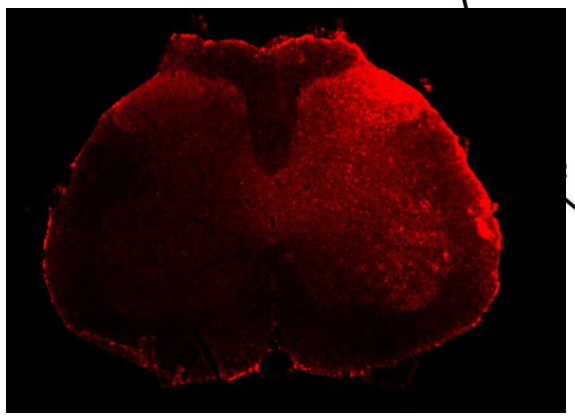

Descending Facilitatory Systems
Sodium Channels
Potassium Channels
5HT3
MOR
Na+
AMPAR
mGluR
To Higher Centres
Ca2+
NMDAR
Mg2+
NK1
Second Order Neurone
Ca2+
Wind up
LTP
Gene Expression
GABA
Substance P
Glutamate
5HT
GABA
MOR
Local Inhibitory Neurones
mGluR Metabotropic Glutamate Receptor
NK1 Neurokinin 1 Receptor
MOR Mu Opioid Receptor
NMDA-R NMDA Receptor
AMPA-R AMPA Receptor

Differential development of central hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury



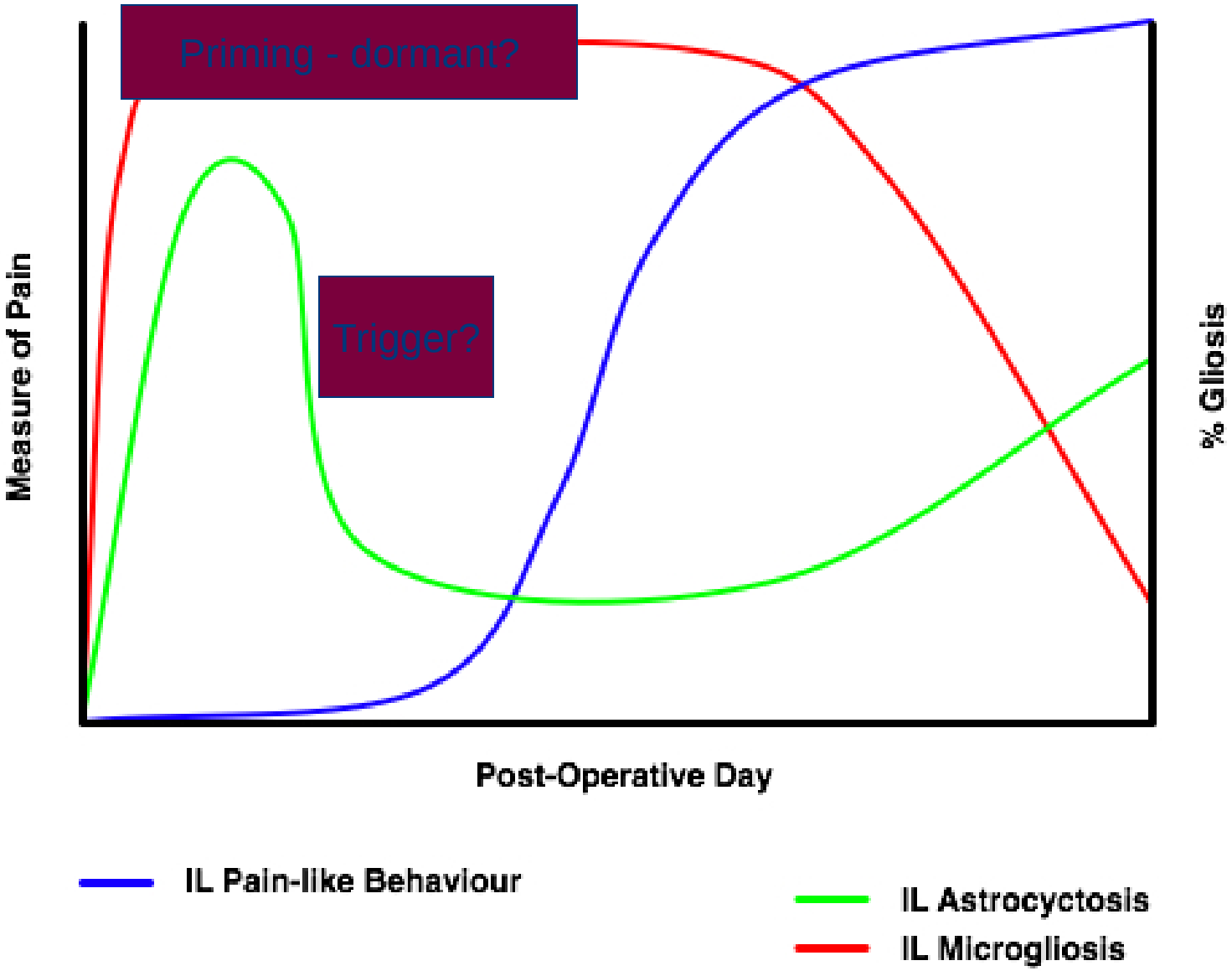


Sterling M. *Pain* 2010 in press

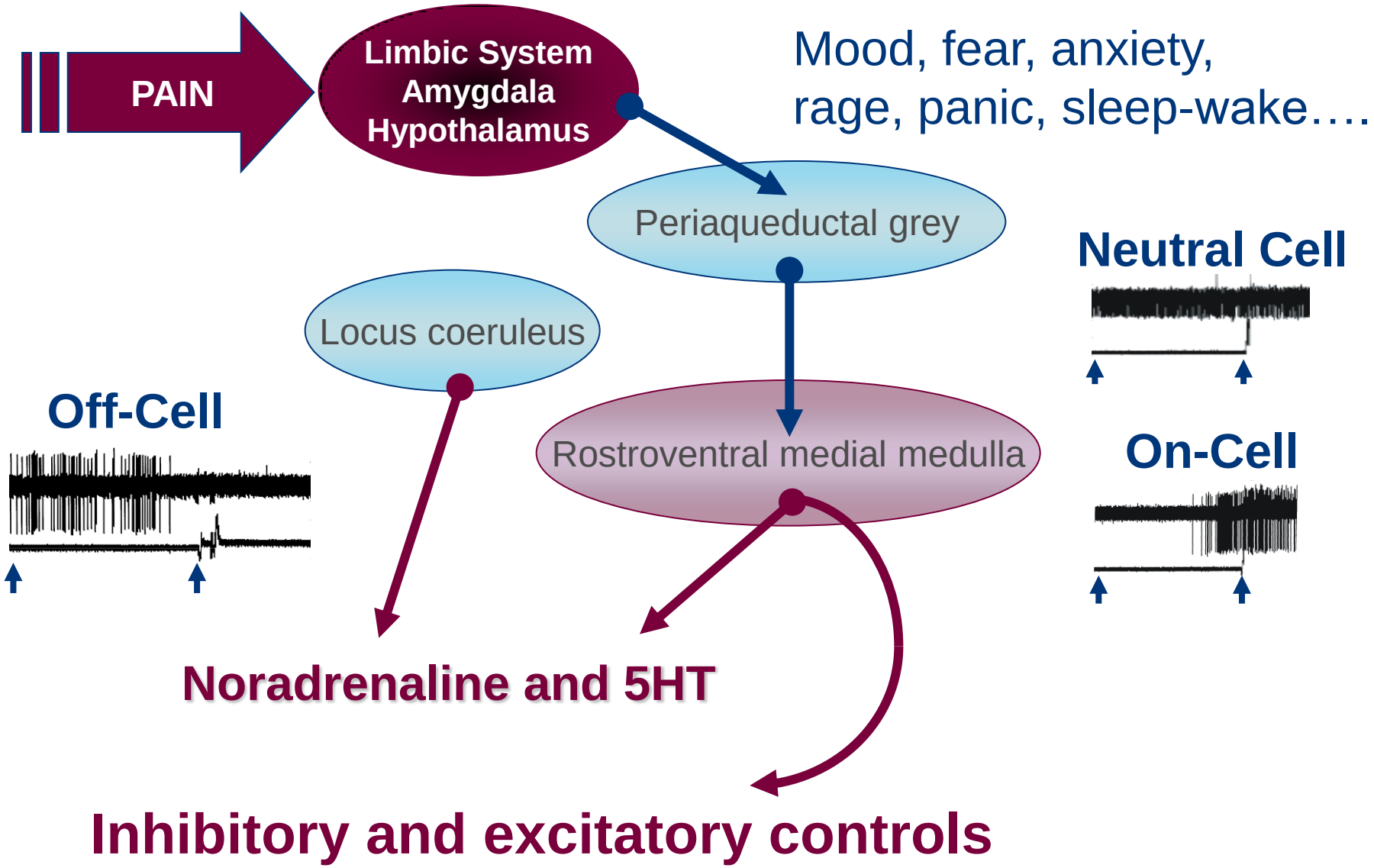


A Beta Input Revealed
Descending Neurone
5HT
5HT3
Glutamate
NGF
trkA
VDKC
VDSC
Na^+
K^+
PRIMARY AFFERENT NOCICEPTOR
SP
CATHEPSIN S
FRACTALKINE
CCL2
CX3CR
CCR2
Resident Microglia
ACTIVATION
NK1
AMPA
Ca^{2+} NMDAR
Phosphorylation
IL1
IL1R
TNFα
TNF
PG
EP
KCC2
CL^-
DORSAL HORN NEURONE
Wind up
LTP
Gene Expression
To Higher Centres
BDNF
trk B
$GABA_A$
GABAergic Inhibitory interneurone
ATP
P2X4
Ca^{2+}
SNARE
MIGRATION
CCR2
CIRCULATING MICROGLIA PRECUSORS

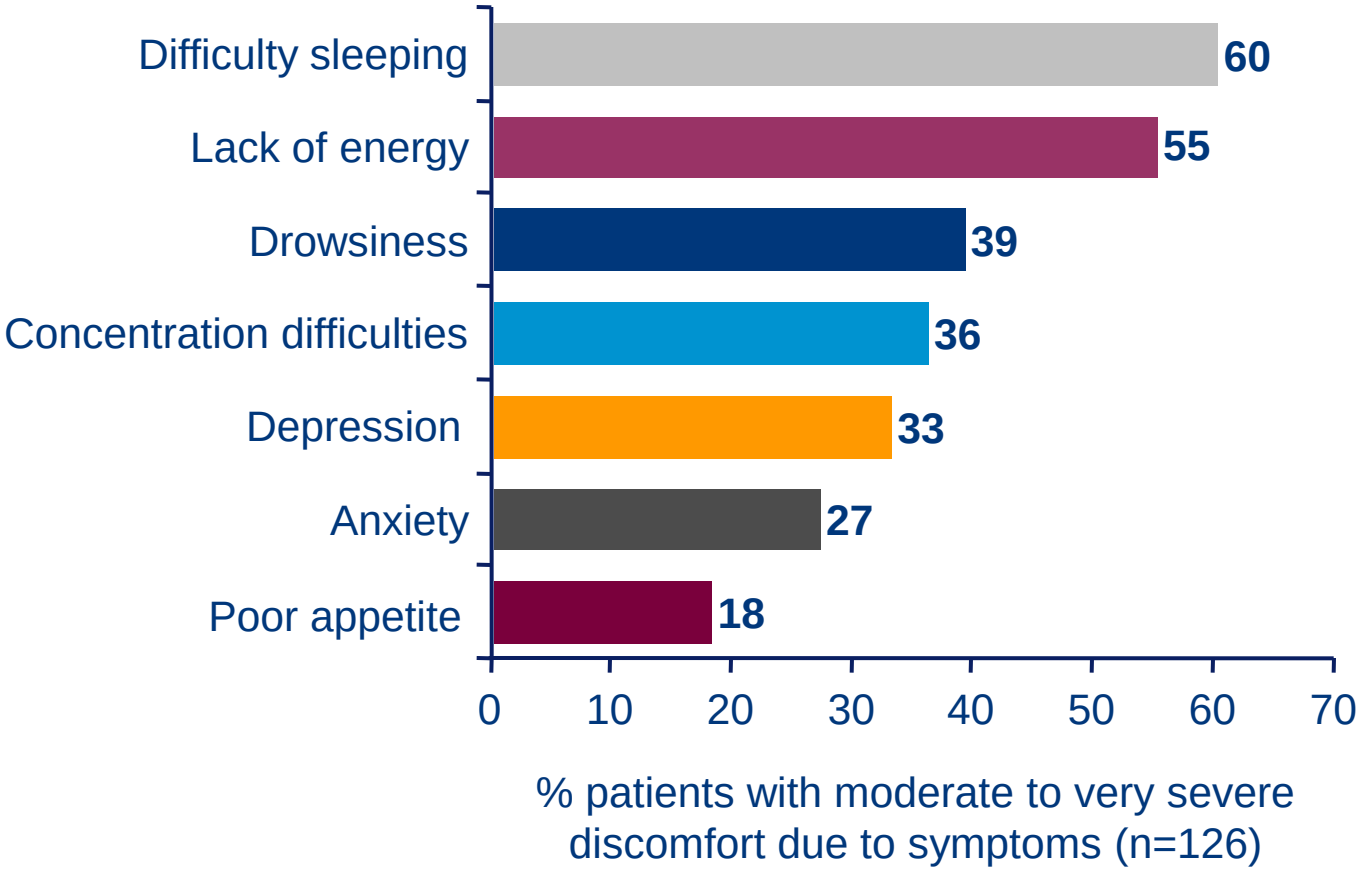
Non-neuronal cell changes - the issue of timing…..



Noradrenaline and 5HT



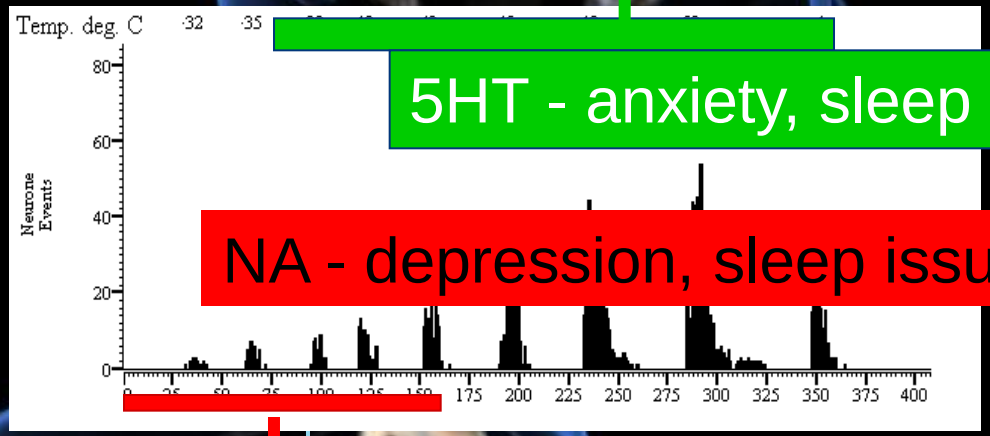
Pain changes our brain functions



Meyer-Rosberg K et al. *Eur J Pain* 2001;5:379–89

Neuropathy - loss of NA inhibition - gain of 5HT facilitation

Brain stem mechanisms and descending controls



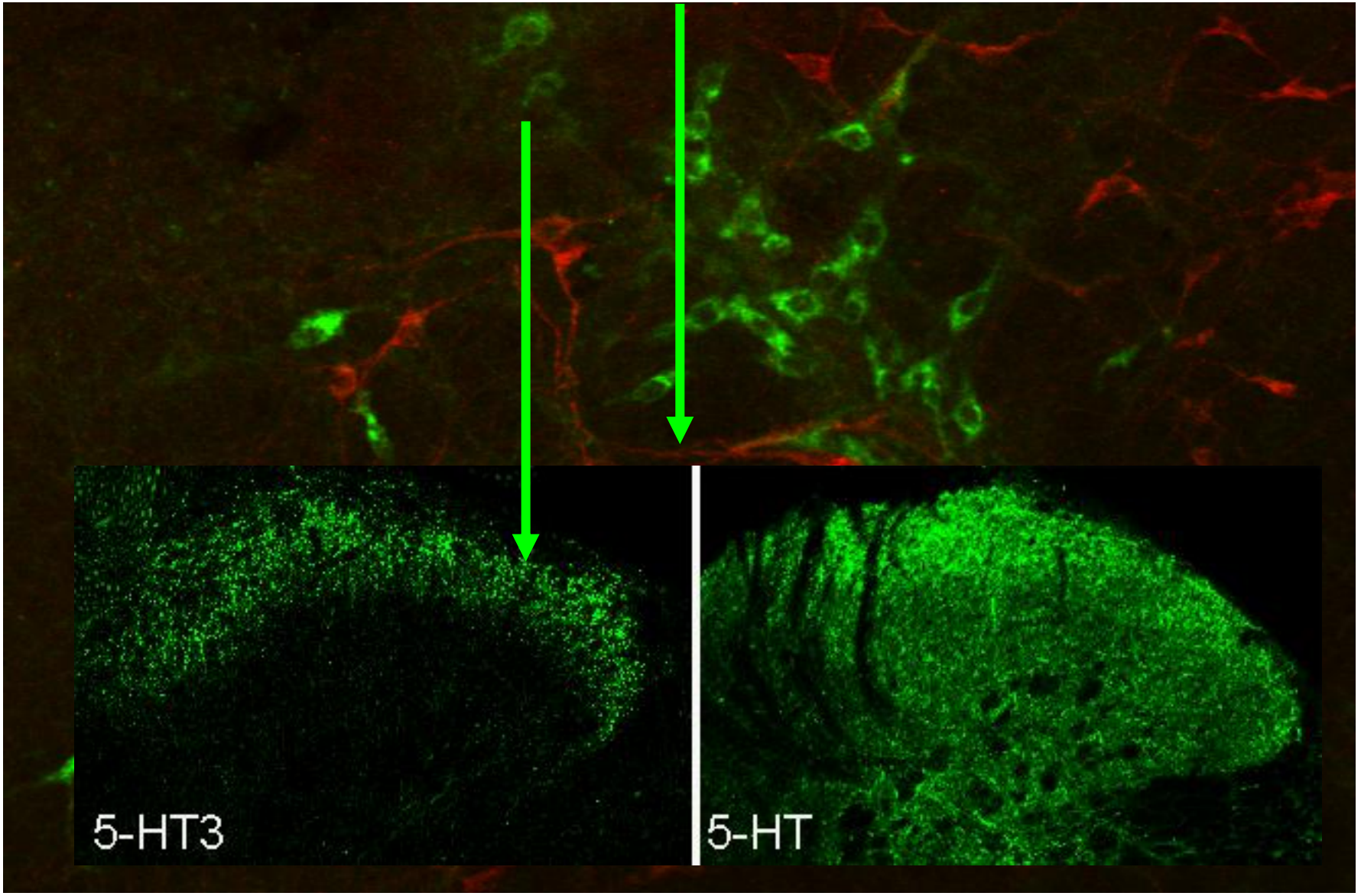
5HT - anxiety, sleep issues

NA - depression, sleep issues

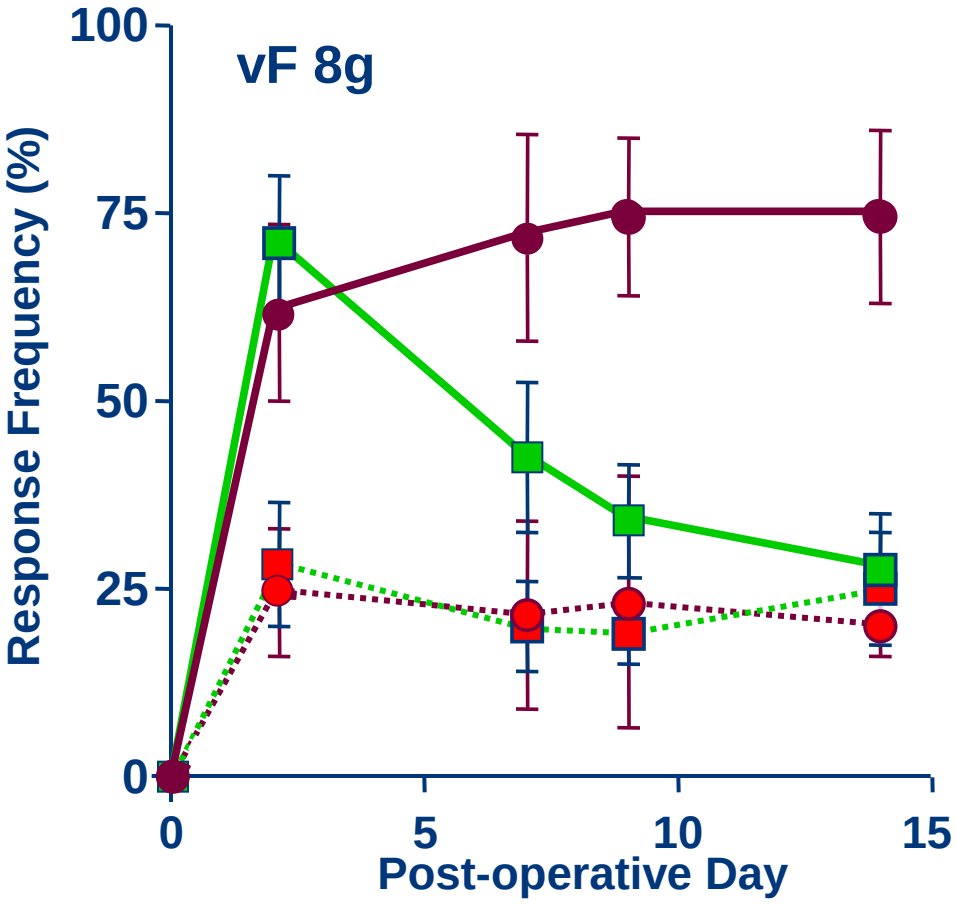
Hyperexcitability through spinal events

Peripheral transduction

Excitations up – Inhibitions down



Time ….. The pain moves….



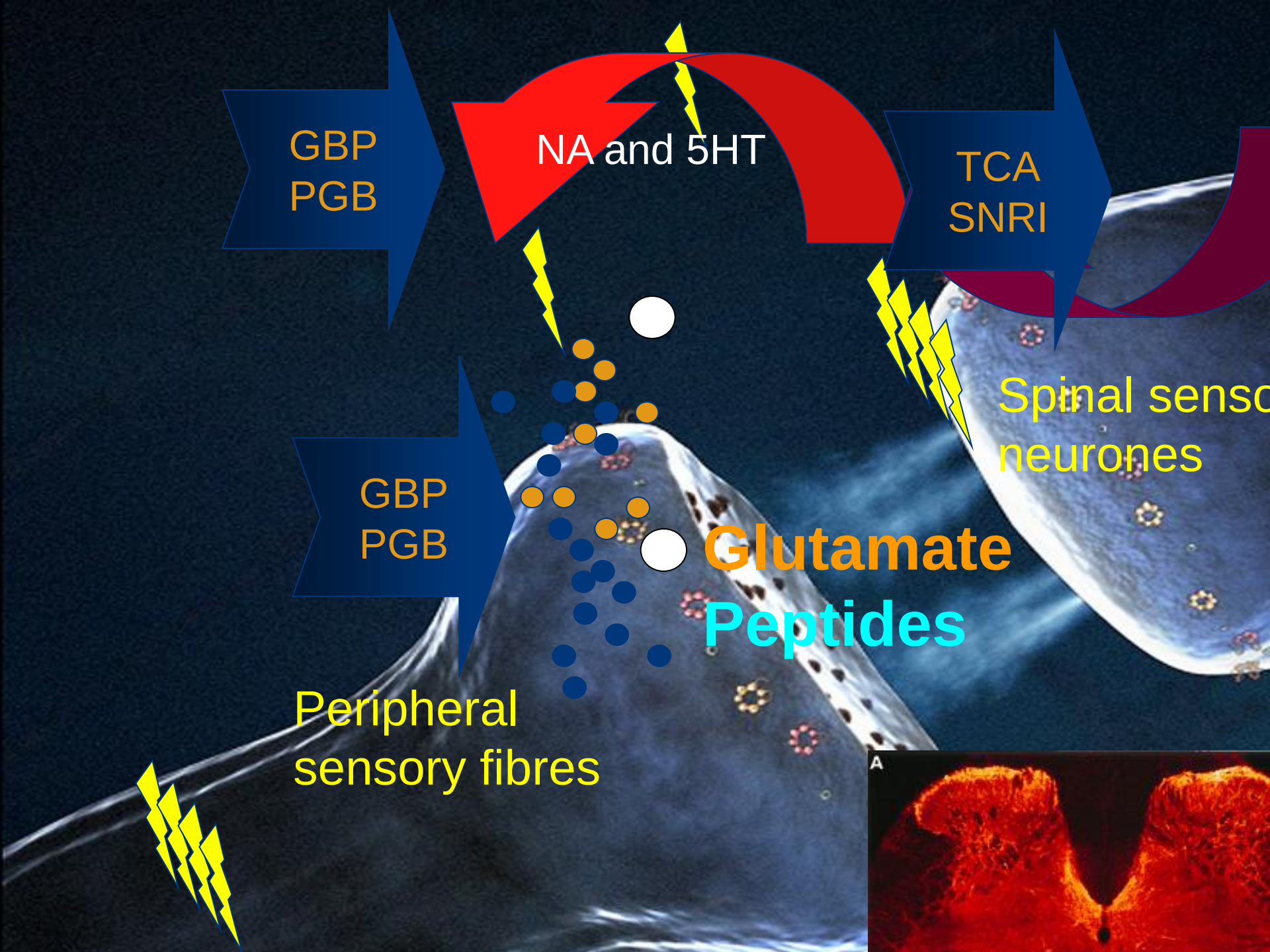
Maintained hypersensitivity after peripheral neuropathy
and abnormal cold…

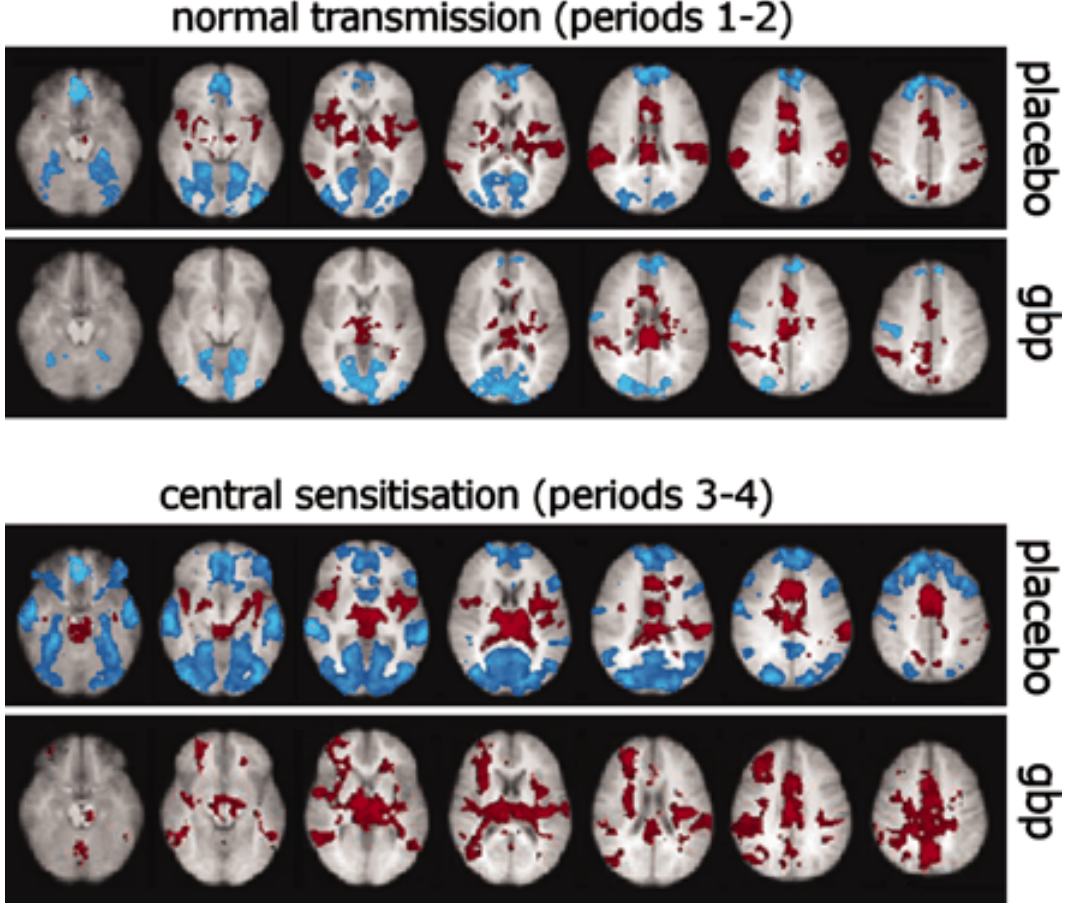
Ablation of RVM descending facilitations

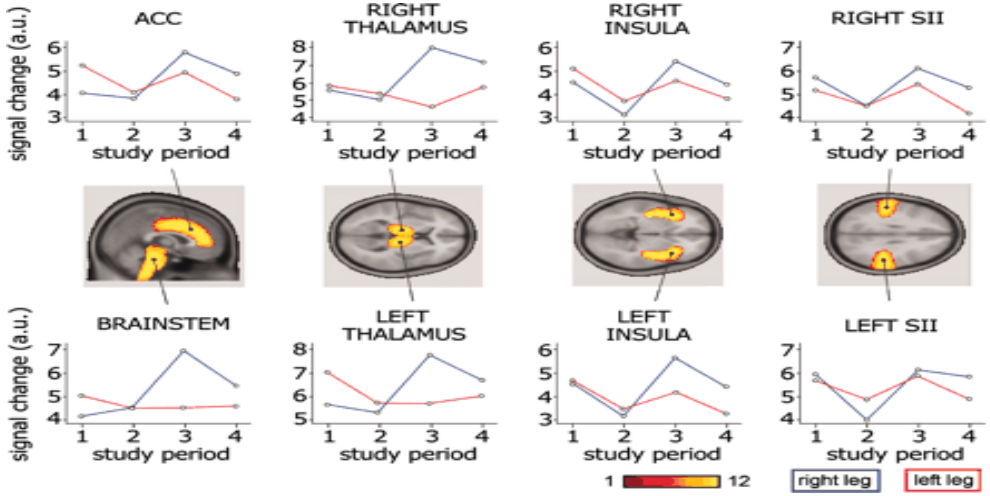
Control values

Could there be time-related events in neuropathic pain?

Bee LA, Dickenson AH. *Pain* 2008;140:209-23


GBP
PGB
NA and 5HT
TCA
SNRI
Spinal senso
neurones
GBP
PGB
Glutamate
Peptides
Peripheral
sensory fibres
A

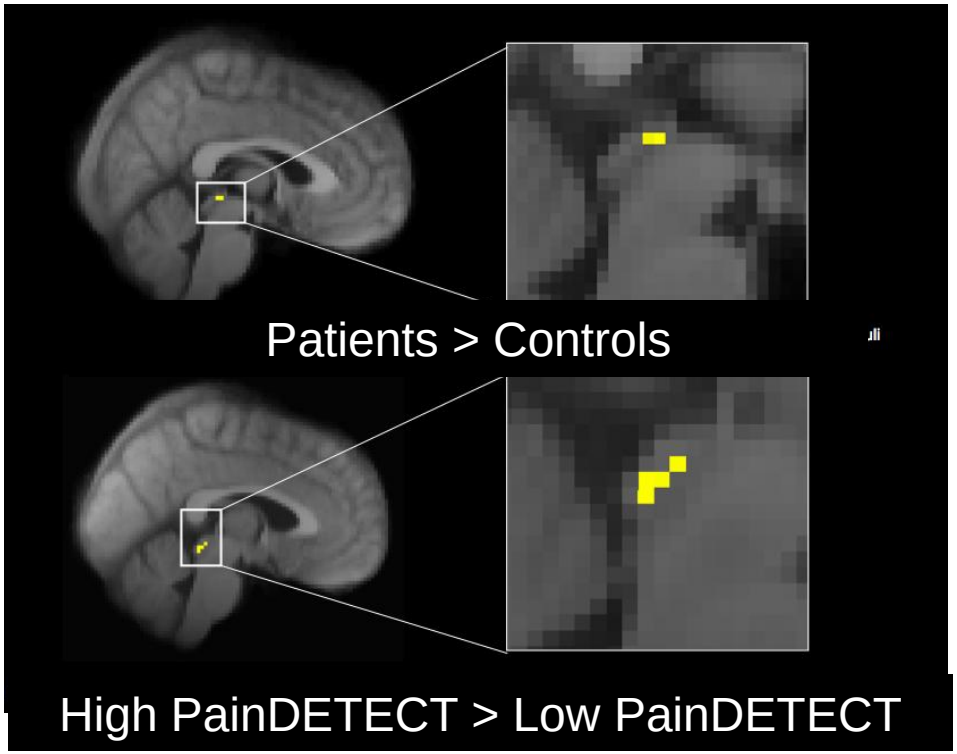




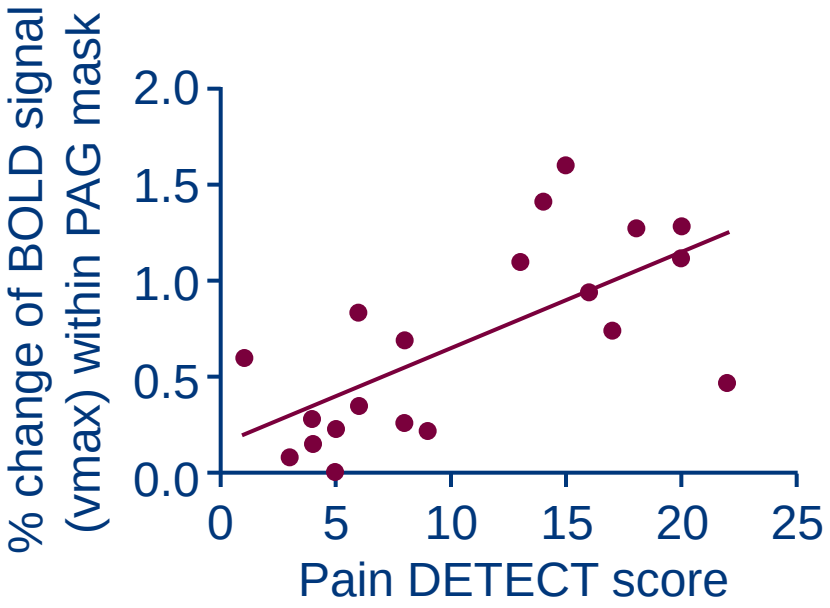
GBP reduces hyperalgesic signals in human brainstem etc Iannetti et al PNAS 2006

Translation to patients…..

PAG activation



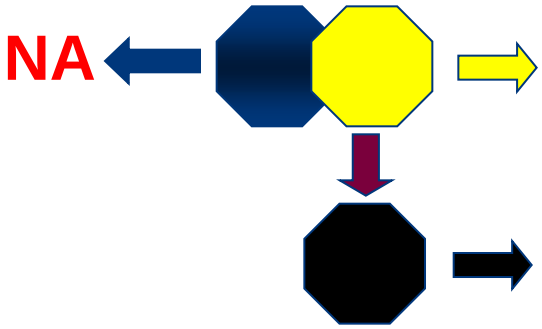
Psychophysical and Functional Imaging Evidence Supporting Presence of Central Sensitisation in a Cohort of Osteoarthritis Patients



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

Modes of action
Tapentadol vs. Tramadol

Tramadol - mu opioid binding/ NA and 5HT uptake block
Direct opioid receptor inhibition via metabolite
Isomers acting on monoamines



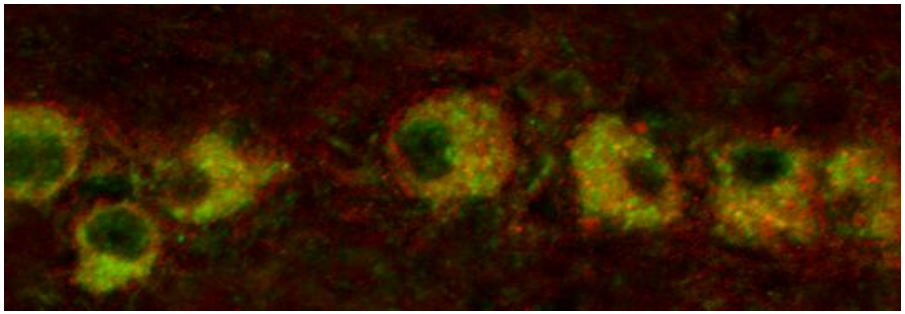
5HT - pain, nausea and GIT issues

Mu opioid

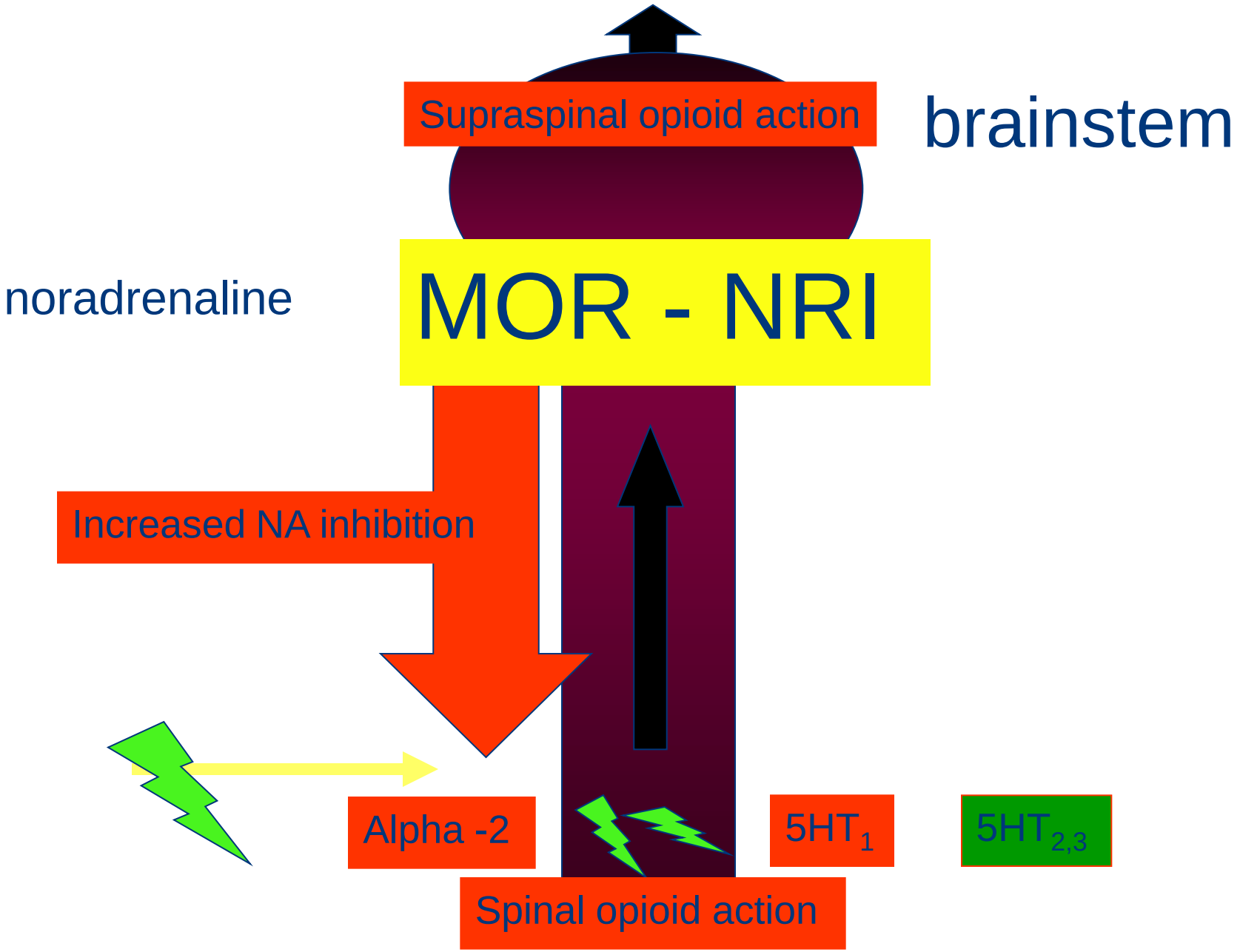
Tapentadol - mu opioid and NA only – removes pro-pain 5HT - single entity

Synergy

Mu opioid

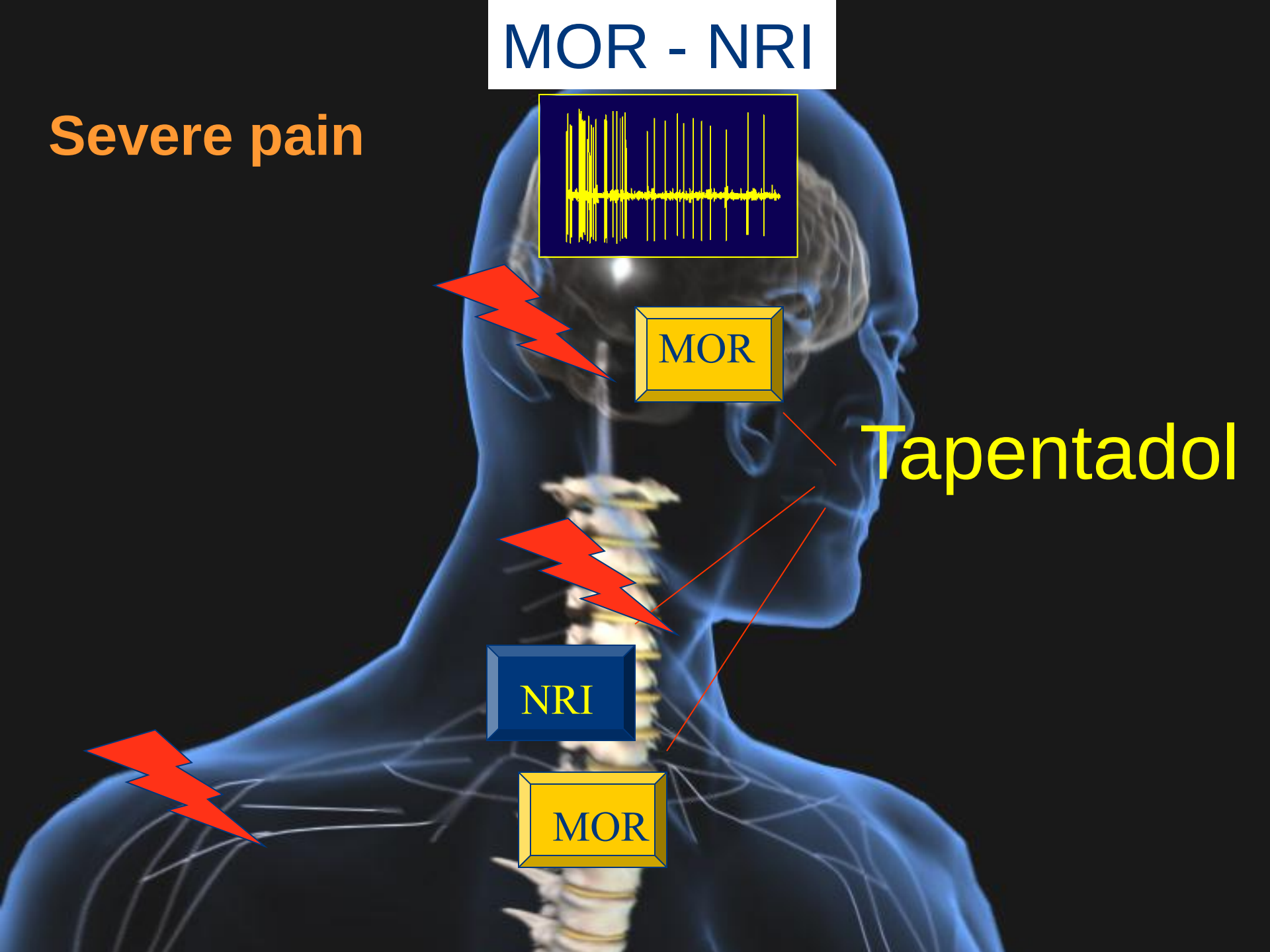


Tapentadol + Intense pain



MOR - NRI

Severe pain

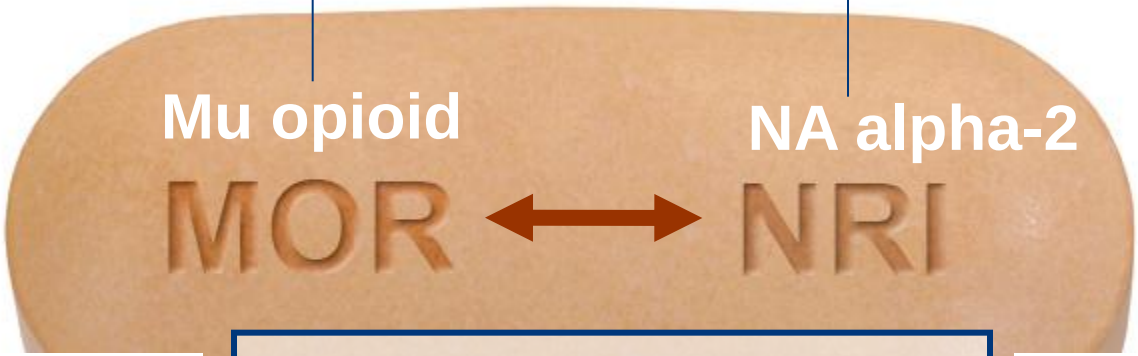


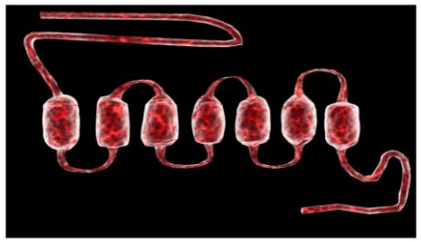
Tapentadol

Tapentadol – Two mechanisms on neurons

Naloxone

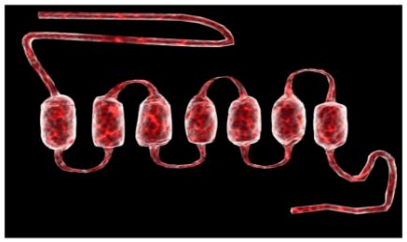
Atipamezole





Same receptor structure
Similar mechanisms

Similar potassium channels



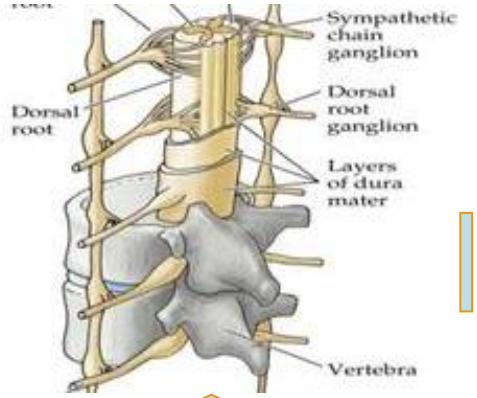
Mechanical SNL

- Increases in efficacy on spinal neuronal hypersensitivity after nerve injury
- Increased effects on brush and heat
- Equal potency, greater efficacy than morphine in nerve injury
- Opioid and alpha-2 adrenoceptor synergy
- Move to greater alpha-2 adrenoceptor actions after nerve injury

Systemic tapentadol modulates spinal opioid function and increases spinal NA

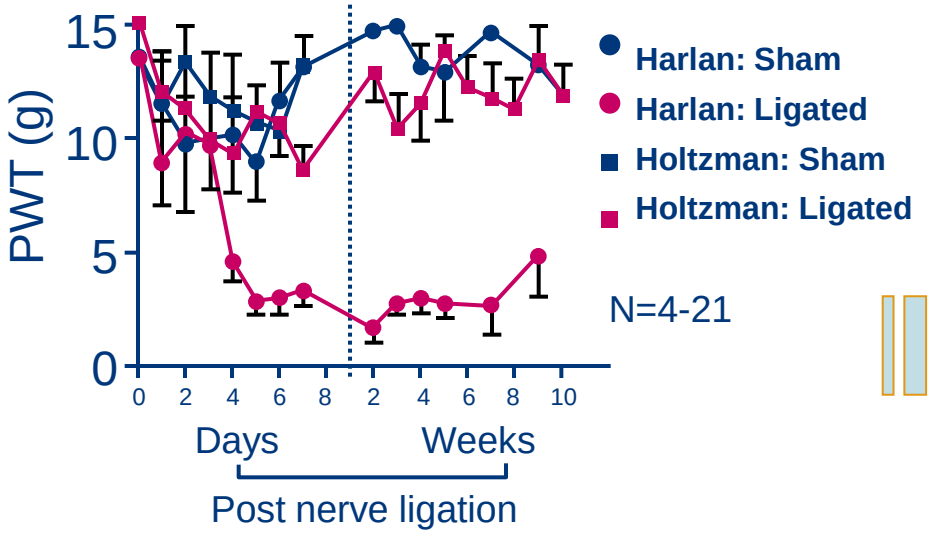
Targets for therapy

Trauma

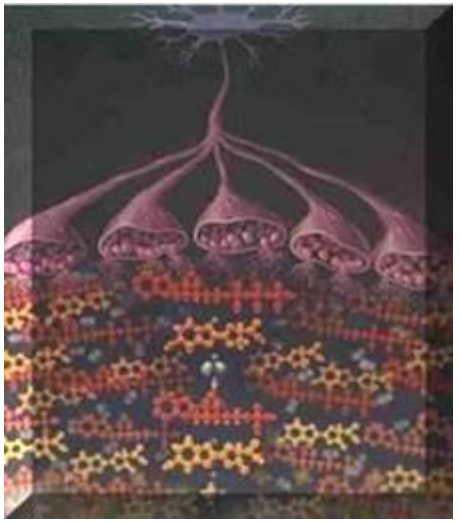


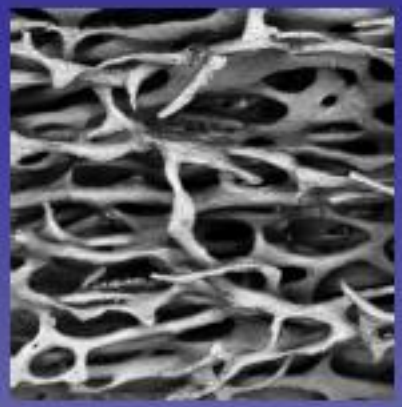
Multiple mechanisms

Genes may protect or predispose



Signs and symptoms

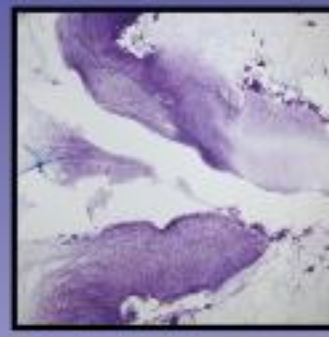




Visceral processes

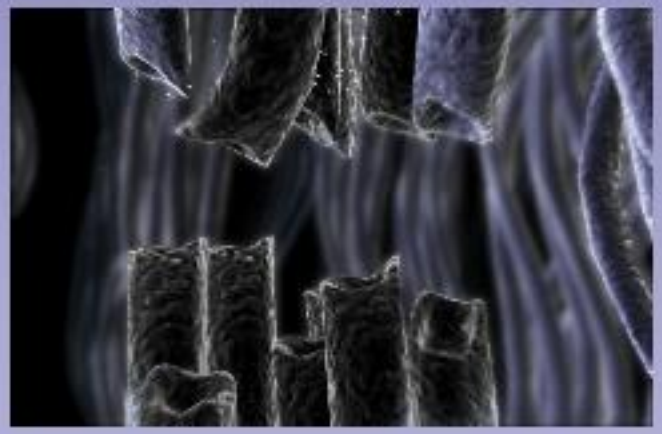
Cancer induced bone pain

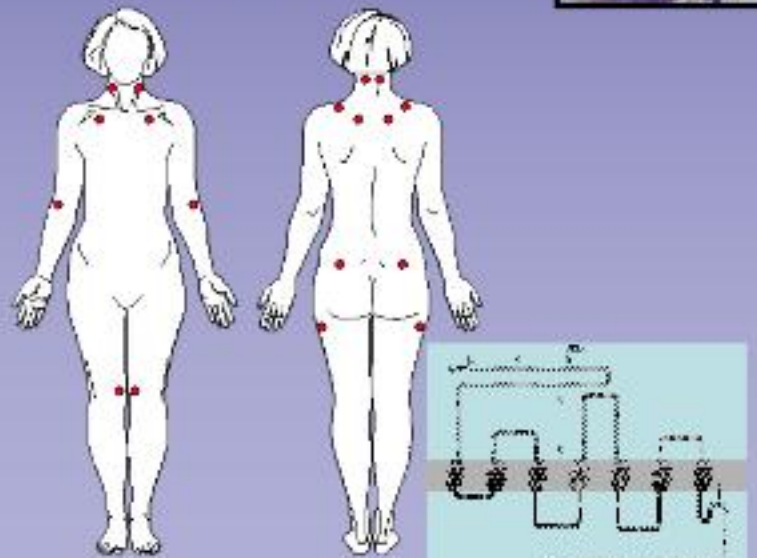
OA

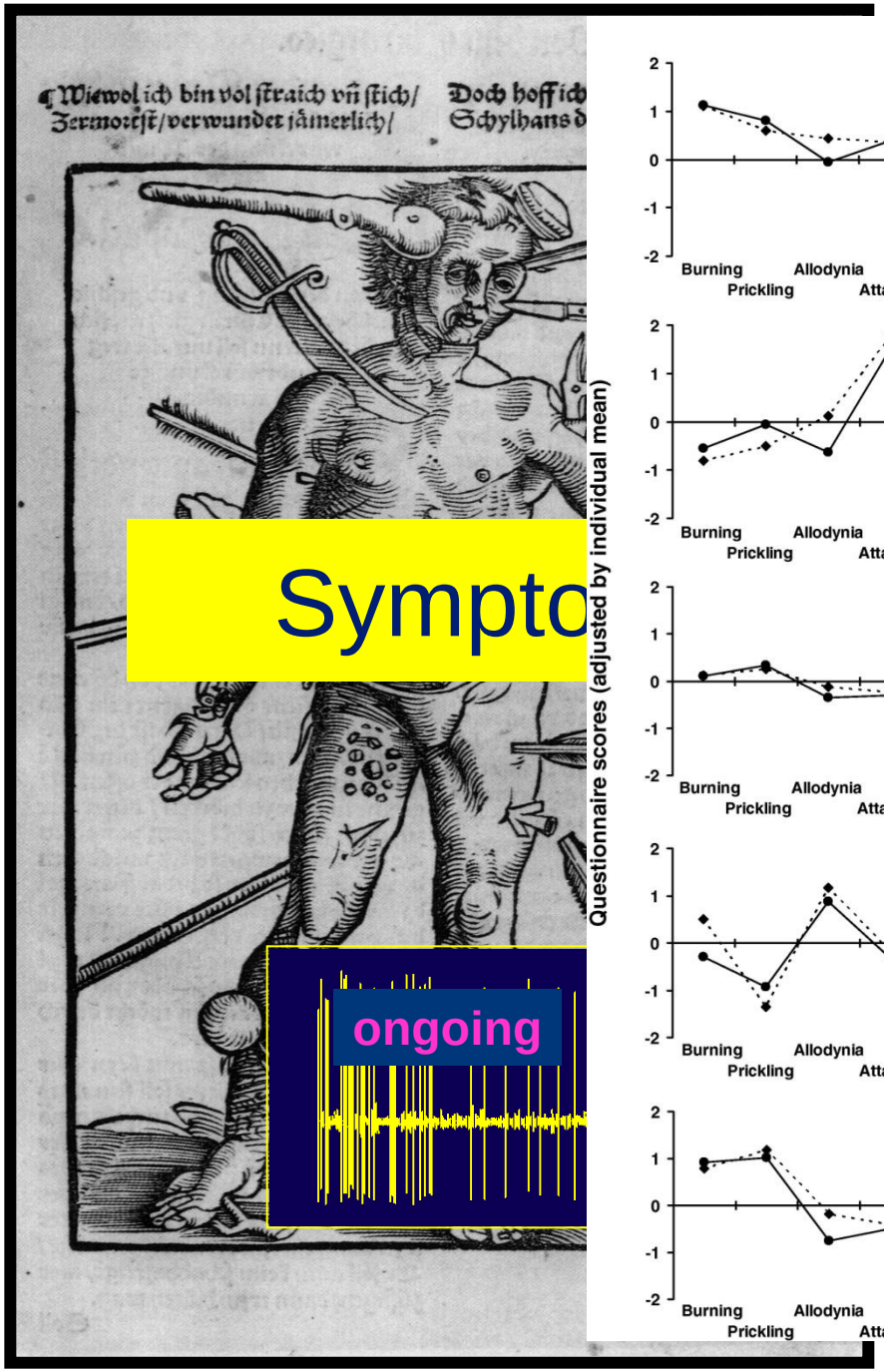


Neuropathy

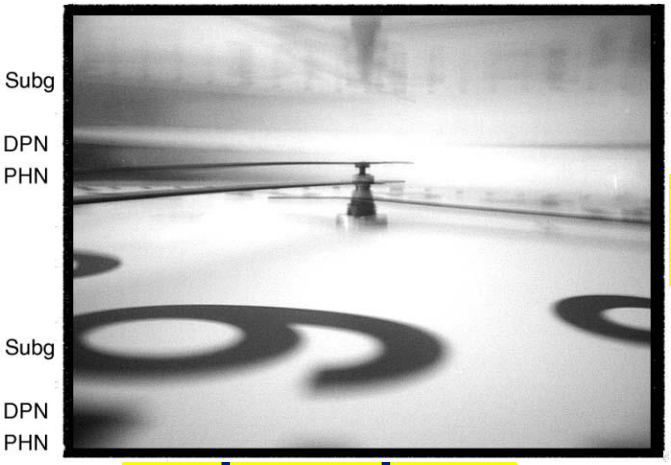
Opioid induced hyperalgesia







Sympto



echanism

Subgroup 3

DPN 37%
PHN 25%

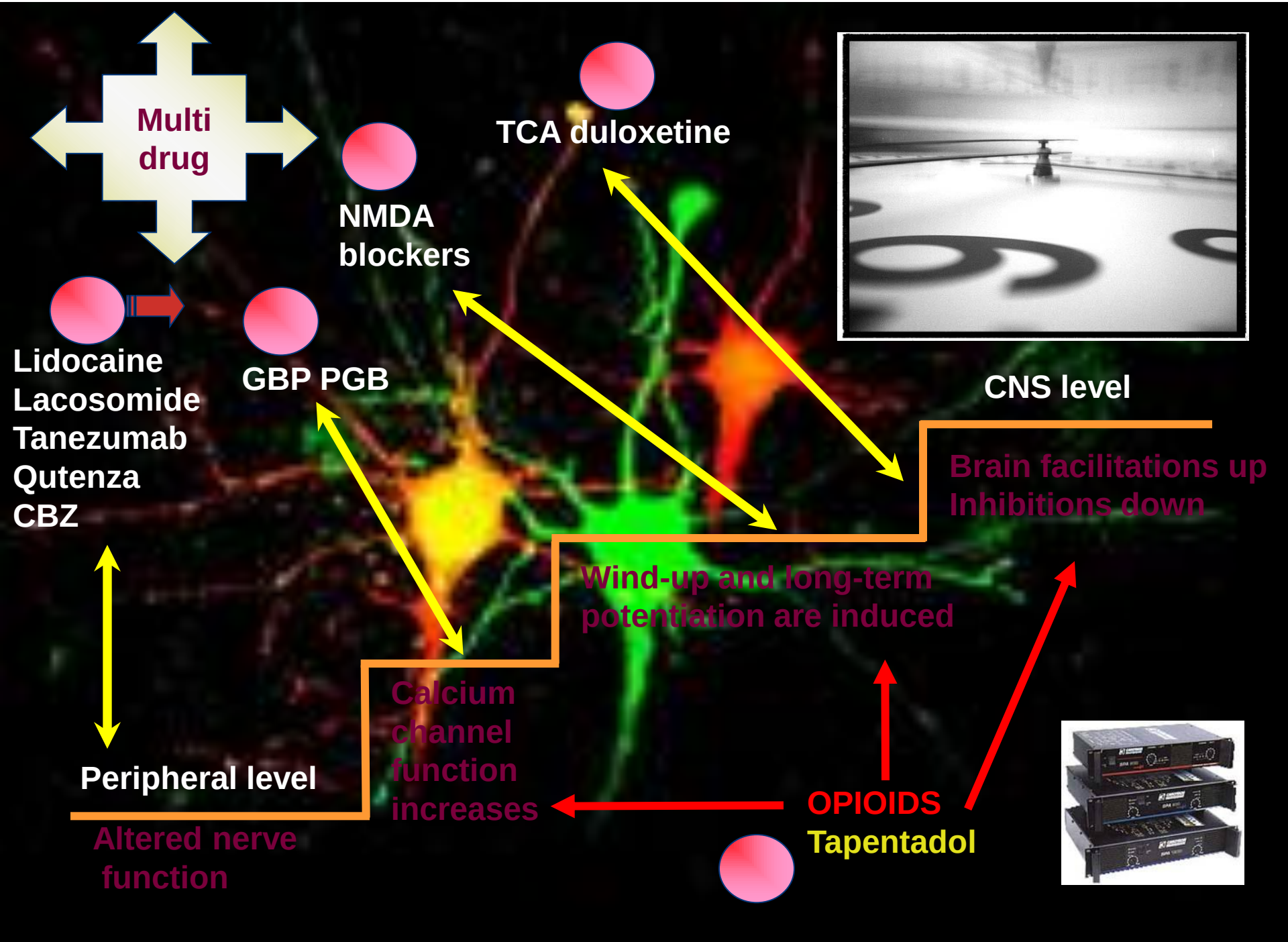
Subgroup 4

DPN 9%
PHN 24%

Mechanism

Subgroup 5

DPN 26%
PHN 5%


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