Towards a Better Understanding of Chronic Pain

Russell Raath
MBChB MMed FIPP
Anaesthesiologist and Chronic Pain Practitioner
Jakaranda Pain Clinic
Pretoria

The concept that

“pain is pain”

and that chronic pain is simply acute pain continuing for too long

is archaic and wrong

This misconception leads to:

1. General misunderstanding of what chronic pain is
2. Inadequate and inappropriate treatment of the pain
    a. incorrect medication –
    b. medication dose escalation
    c. overdosing of medication
    c. unnecessary special investigations
        radiology - cost!!
    d. unnecessary surgery or repeat surgery –
        especially spine surgery
3. General neglect of these patients:
    a. doctor doesn't know what to do anymore
    b. patients get told it's in their head – to
        psychologist or psychiatrist
    c. patients get told they must "learn to live with it"
    d. 'change behaviour'.

Chronic Pain:

IS NOT:

simply a symptom of another underlying condition

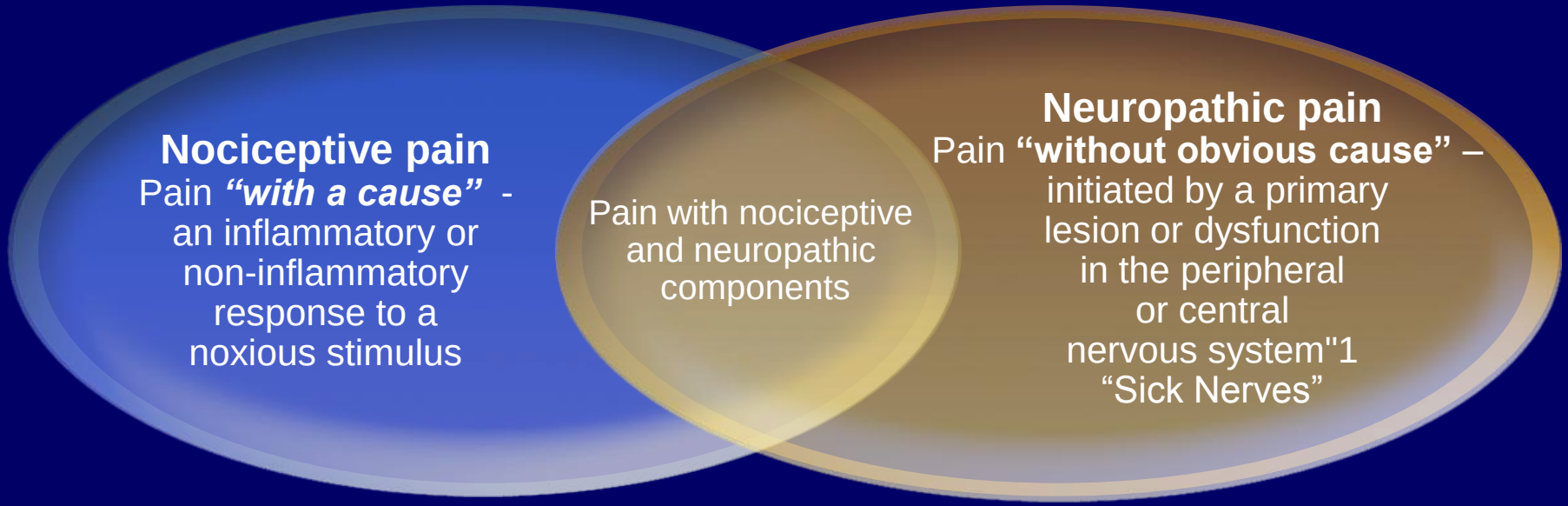
“protective” DOES NOT Serve as warning Of underlying condition

IS:

A medical entity, clinical condition And pathology in its own right

Destructive, Serving no purpose at all

Chronic Pain:



1. Merskey H, Bogduk N, eds. Classification of Chronic Pain. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.

Nociceptive Pain

→ Acute (mostly)

→ Chronic

Examples

- Pain due to inflammation
- Limb pain after a fracture
- Joint pain in osteoarthritis

Common Descriptors

- Aching
- Throbbing

Other characteristics

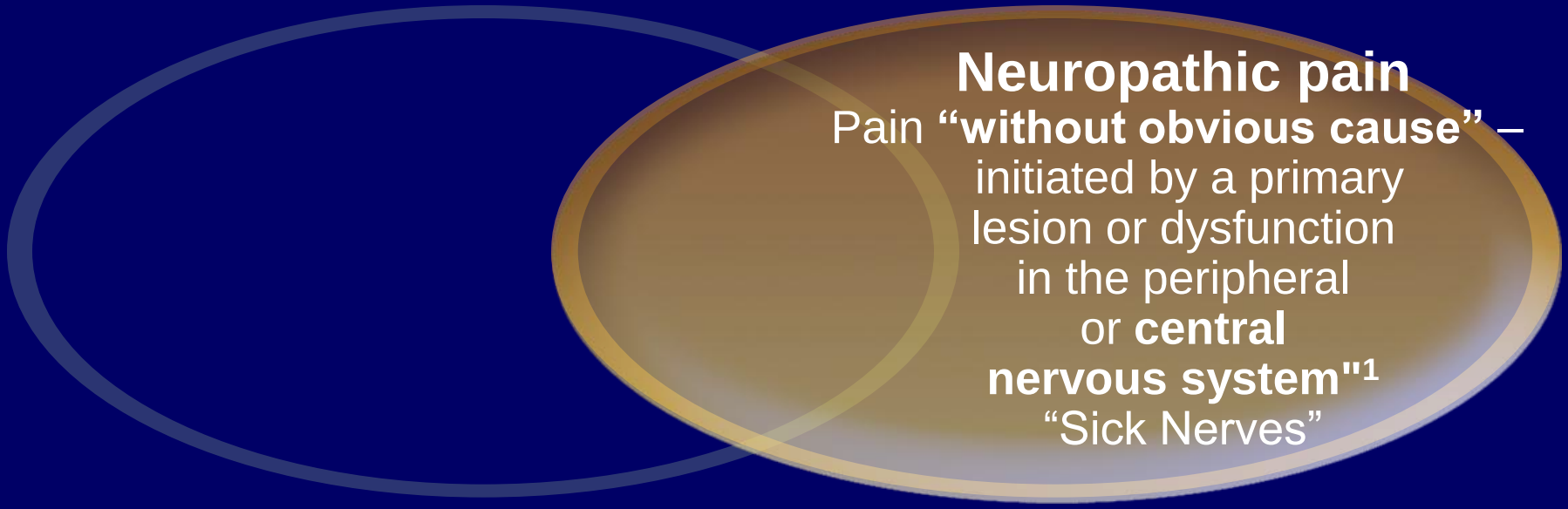
- Pain typically localised at site of injury
- Usually time limited, resolving when damaged tissue heals
- Responds to conventional analgesics

1. Merskey H, Bogduk N, eds. Classification of Chronic Pain. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.

Neuropathic Pain

Acute

Chronic (mostly)



When nerves becomes damaged or sick, they stop working properly.

They may send the wrong signal to the brain.

Injured nerves might tell the brain that your foot is burning even when:

you aren't stepping on something hot

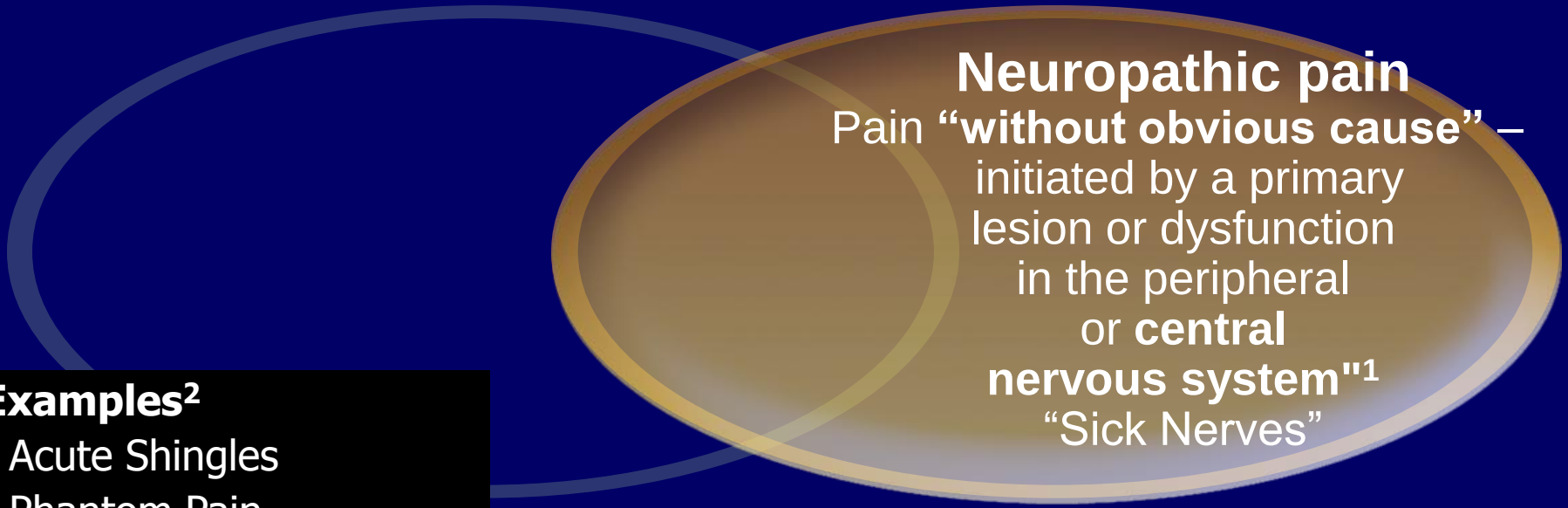
or there is no toe at all!

1. Merskey H, Bogduk N, eds. Classification of Chronic Pain. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214. .

Neuropathic Pain

Acute

Chronic (mostly)



Examples[2]

- Acute Shingles
- Phantom Pain
- Post-herpetic neuralgia
- Diabetic peripheral neuropathy
- Trigeminal neuralgia
- Postsurgical neuropathy
  Scarring, Fibrosis, Nerve Injury
- Central Pain
  Stroke, TBI, Cord Injury

Common descriptors[2]

- Burning
- Stabbing (lancinating)
- Tingling
- Radiating
- Hypersensitivity to touch or cold (allodynia)

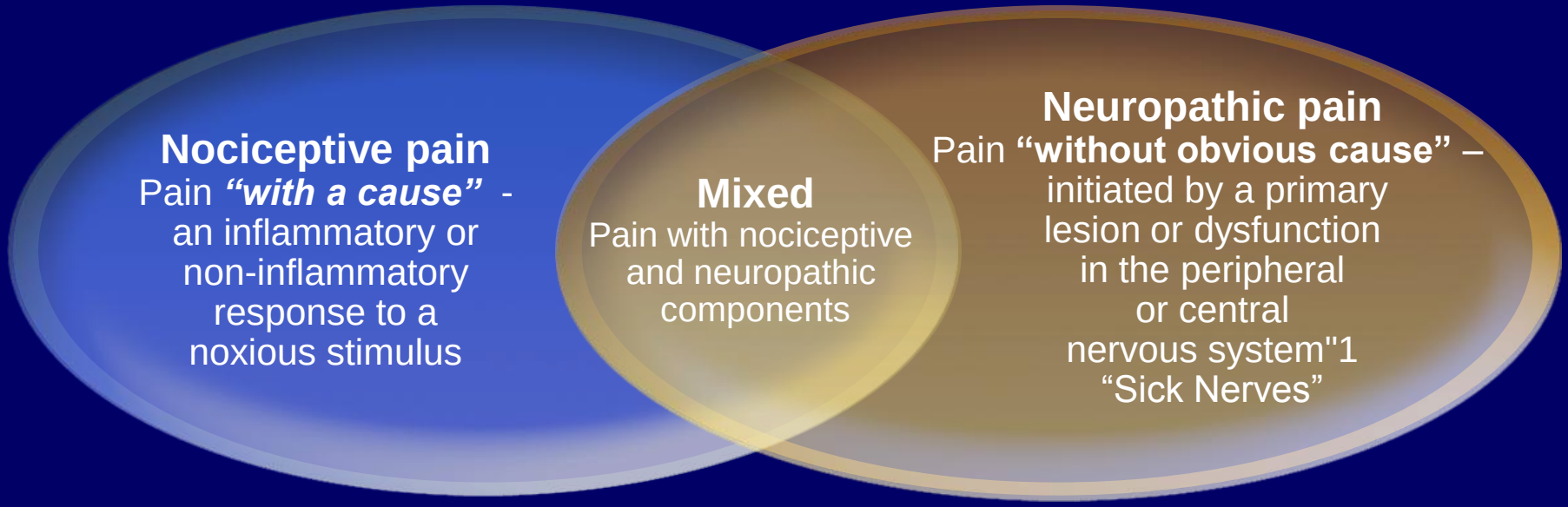
Other characteristics[2]

- Responds poorly to conventional analgesics.
- Often in distribution of a specific nerve....

EXCEPT...

1. Merskey H, Bogduk N, eds. Classification of Chronic Pain. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.
2. Clinical States: Neuropathic Pain. In: McMahon S, Koltzenburg M, editors. Wall and Melzack's Textbook of Pain. 5th ed.Edinburgh: Churchill-Livingstone; 2005.

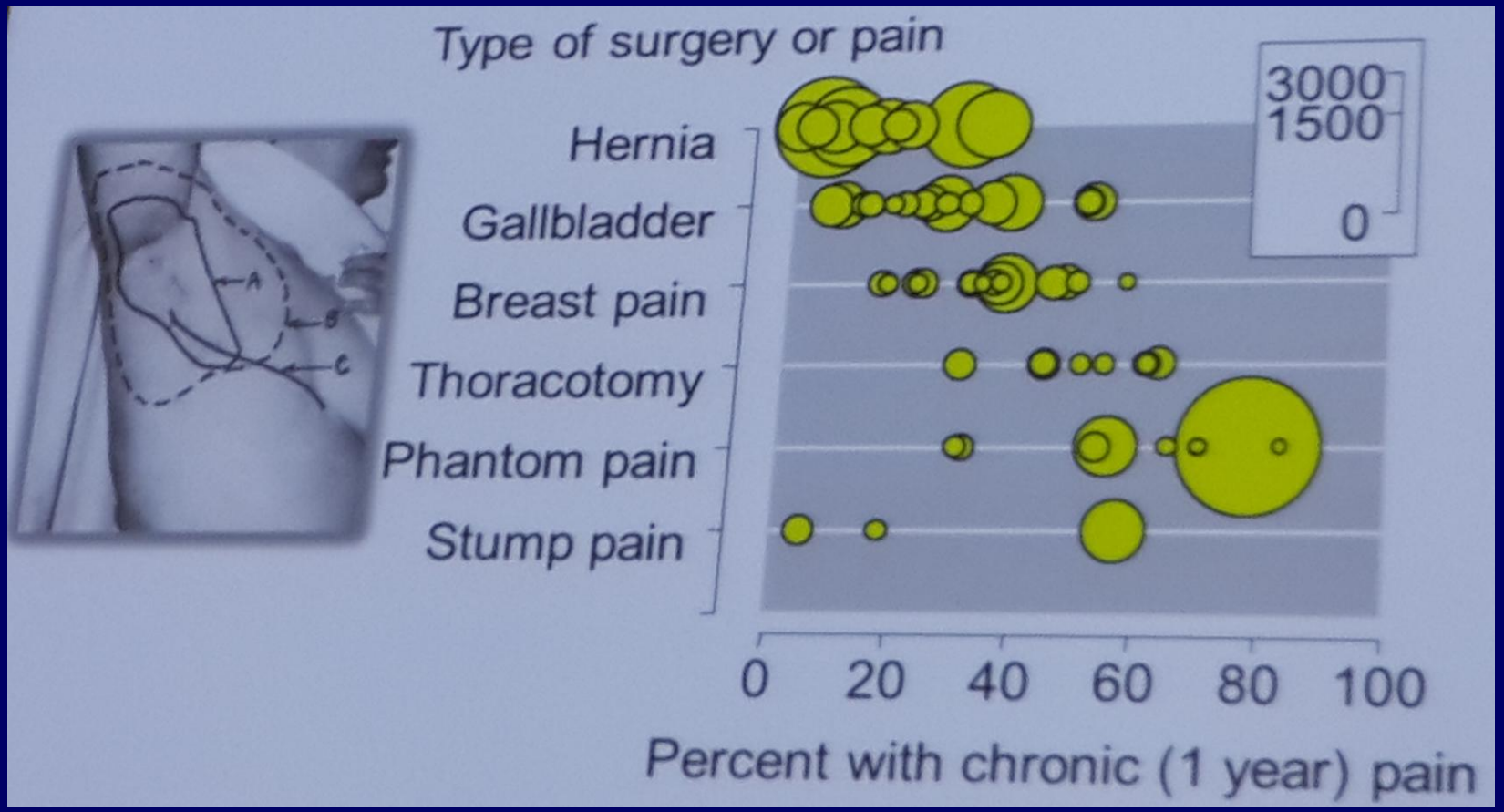
There are *Different* Types of Pain



Examples[2]
Osteo-arthritis pain
Fibro myalgia
Back and leg

1. Merskey H, Bogduk N, eds. Classification of Chronic Pain. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.

PPP = >25% of population in chronic pain clinics



Perkins and Kehlet Anesthesiology 2000, 93; 1123 - 1133

Persistent Postoperative Pain - aka PPP

Pain that develops after surgery
Pain of at least two months duration
Other causes of pain have been excluded

Macrae BJA 2008

Postoperative pain that persists for 3-6 months after surgery

Kehlet et al lancet 2006

Pain that persists after the time of healing

Bonica, The Management of Pain 1953

Franciscus Ziekenhuis
Roosendaal

Chronic neuropathic pain after breast cancer surgery

Pain Clinic
Roosendaal

Plony Stroo
Nurse Practitioner Pain Clinic, Franciscus Ziekenhuis Roosendaal, The Netherlands, e-mail: astroo@fzr.nl

Objectives:

- To evaluate prevalence of chronic neuropathic pain after breast cancer surgery at Franciscus Hospital Roosendaal.
- To have more information about:
  1. Influences of used surgical techniques.
  2. Usage of medicine.
  3. The influence of pain on sleep, mood and work experience

Material and methods:

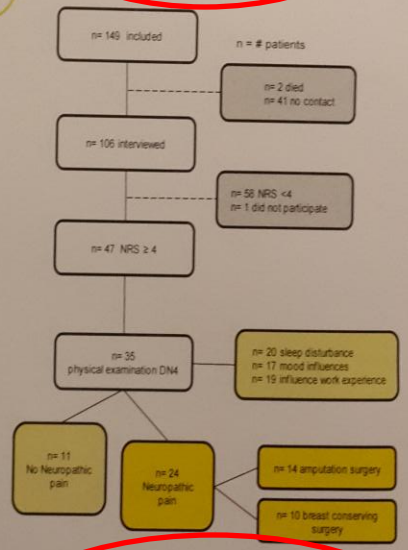
- A quantitative descriptive cohort of patients treated for breast cancer between July 1, 2011 and July 1, 2012.
- Patients were interviewed 8-20 months after surgery.
- Pain scores were measured using the 11- point numeric rating scale (NRS).
- Only patients with NRS ≥4 were invited for the physical examination.
- Extended information about pain was collected with the Brief Pain Inventory (BPI).
- Neuropathic pain was measured with the Douleur Neuropatic 4 Questions (DN4).

Results:

- The cohort consisted of 149 patients.
- 106 patients were succesfully interviewed by telephone.
- NRS ≥ 4 was measured in 47 patients (45% of the 106 patients).
- 35 patients were physicaly examined.
- Neuropathic pain was measured in 24 patients (23% of the 106 patients).
  - 10 patients were operated with breast-conserving surgery.
  - 14 patients were operated with amputation surgery.
  - 1 patient used neuropathic pain medication.
- Other results: (35 patients)
  - Sleep disturbance (20 patients).
  - Mood influences (17 patients).
  - Negative influence on work experience (19 patients).

Discussion:

- 23% of the patients report chronic neuropathic pain measured at DN4 ≥ 4.
- 45% of the patients developed chronic (neuropathic and non neuropathic) pain.



Conclusions:

Many patients suffer from chronic neuropathic pain after breast cancer surgery.

All healthcare professionals (medical doctors, nurses and others) need to pay attention to this pain and treat it properly.

Discussion:

- 23% of the patients report chronic neuropathic pain measured at DN4 ≥ 4.
- 45% of the patients developed chronic (neuropathic and non neuropathic) pain.

Conclusions:

Many patients suffer from chronic neuropathic pain after breast cancer surgery.

All healthcare professionals (medical doctors, nurses and others) need to pay attention to this pain and treat it properly.

Some incidences of PPP

Post-cesarean	12,3 %	Nikolajsen	2004
Knee replacement	19,0 %	Stanos	2001
Inguinal herniorraphy	28,0 %	Mikkelson	2004
Mastectomy	52,0 %	Macdonald	2005
Post thoracotomy	50 – 80 %	Senturk	2002

Chronic Post Traumatic Pain

Orthopaedic trauma	11-48% (77% in severe trauma)
Thoracic trauma	59%
Burn patients	30%
Spinal cord injuries	26-96% (86%)
Traumatic brain injuries	40-75%

Radresa O. et al. J Trauma Acute Care Surg Volume 76, Number 4, 2014

PPP – Risk factors and predictors

- Type of surgery
- Genetic predisposition
- Female gender
- Young age
- Preoperative anxiety
- Negative psychosocial factors
- Obesity
- Pre-existing pain
- Inflammatory state
- Severe/poorly controlled postoperative pain

Grosu and De Cock Anesthesiology Clinics 2011

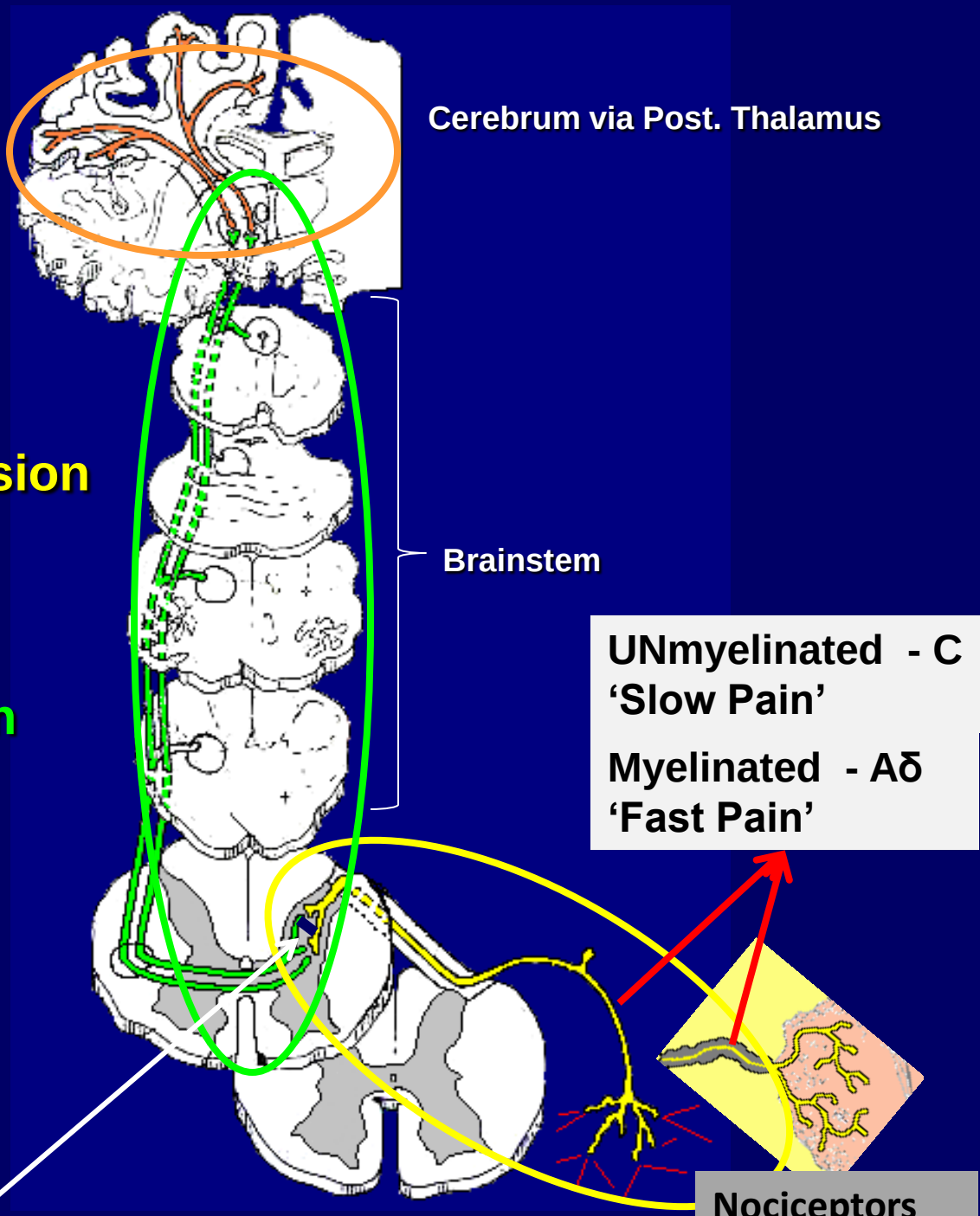
Pain Pathways

3 Neurons Involved in pain perception

1. Primary Neuron
- Transduction
- Peripheral Transmission

2. Secondary Neuron
- Central Transmission

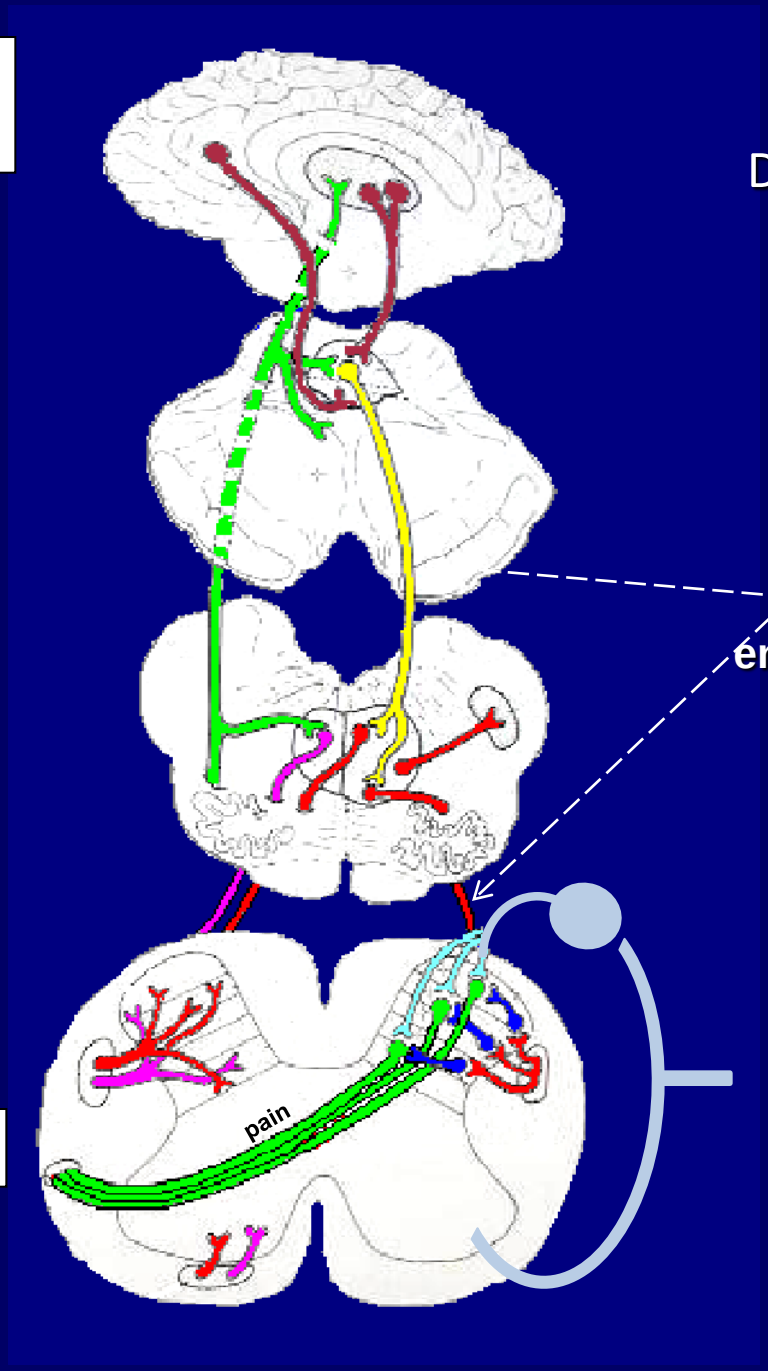
3. Tertiary Neuron
- Central Transmission
- Perception



Modulation

Descending modulatory fibres

"Bi-directional"



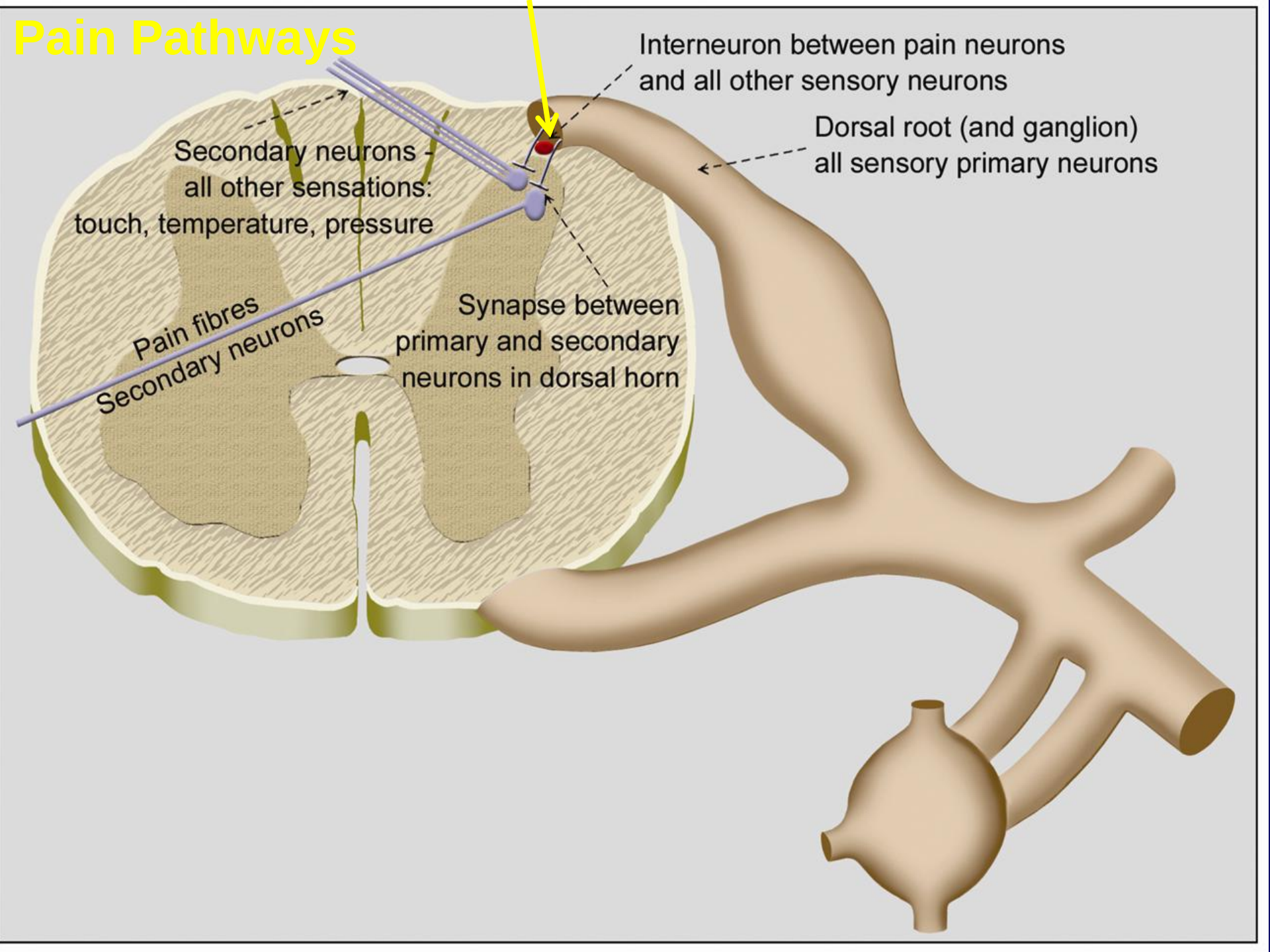
Ease

Opioids
endo- and exo-

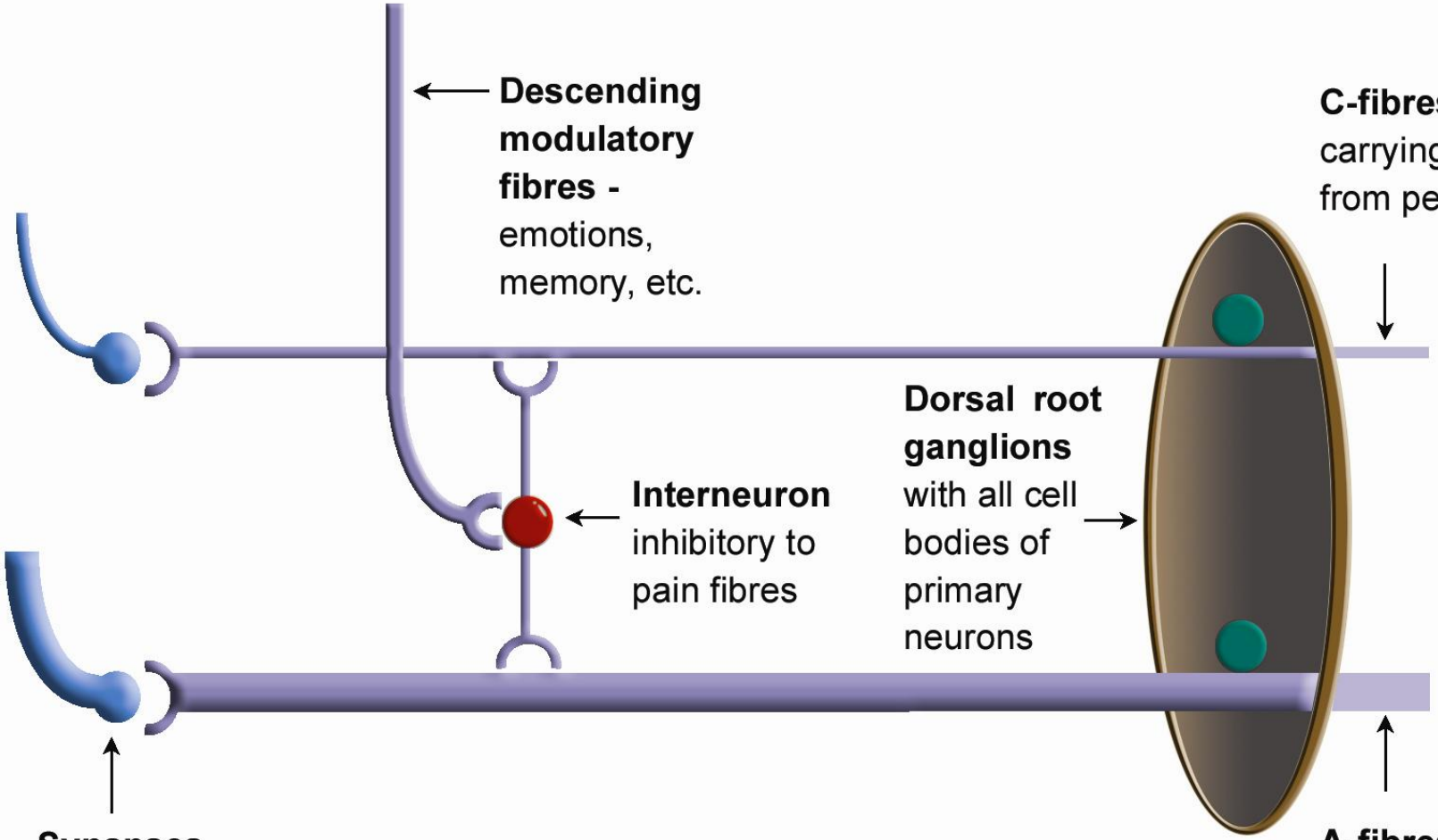
Worsen or Cause

Minor injuries
Expectation

Fear
Prolonged Pain


Pain Pathways
Interneuron between pain neurons and all other sensory neurons
Dorsal root (and ganglion) all sensory primary neurons
Secondary neurons - all other sensations: touch, temperature, pressure
Pain fibres
Secondary neurons
Synapse between primary and secondary neurons in dorsal horn

Pain Pathways



Chronic Pain:

Whatever the ORIGIN

NOCICEPTIVE **NEUROPATHIC**

ULTIMATELY
both lead to

altered pain processing
in dorsal horn of spinal cord
(or brain)
due to physical (neuroplastic) changes there

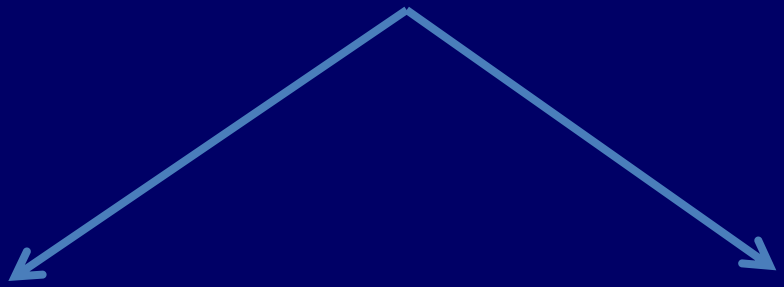
"Wind up
or
"Central
Sensitisation"
Chronic Pain

giving BOTH types of chronic pain
a neuropathic element -
Treatment!!!

Facilitated Pain Transmission

(gate open, central sensitization)

Mediated by two main mechanisms



NMDA Receptors

Interneurons

NMDA Receptors

N-methyl-D-aspartate

Where does NMDA occur physiologically in the body ?

Nowhere !

It is a synthetic substance !
Used only in research to identify the receptors!
The NMDA receptors is actually a glutamate (excitatory) receptor !!

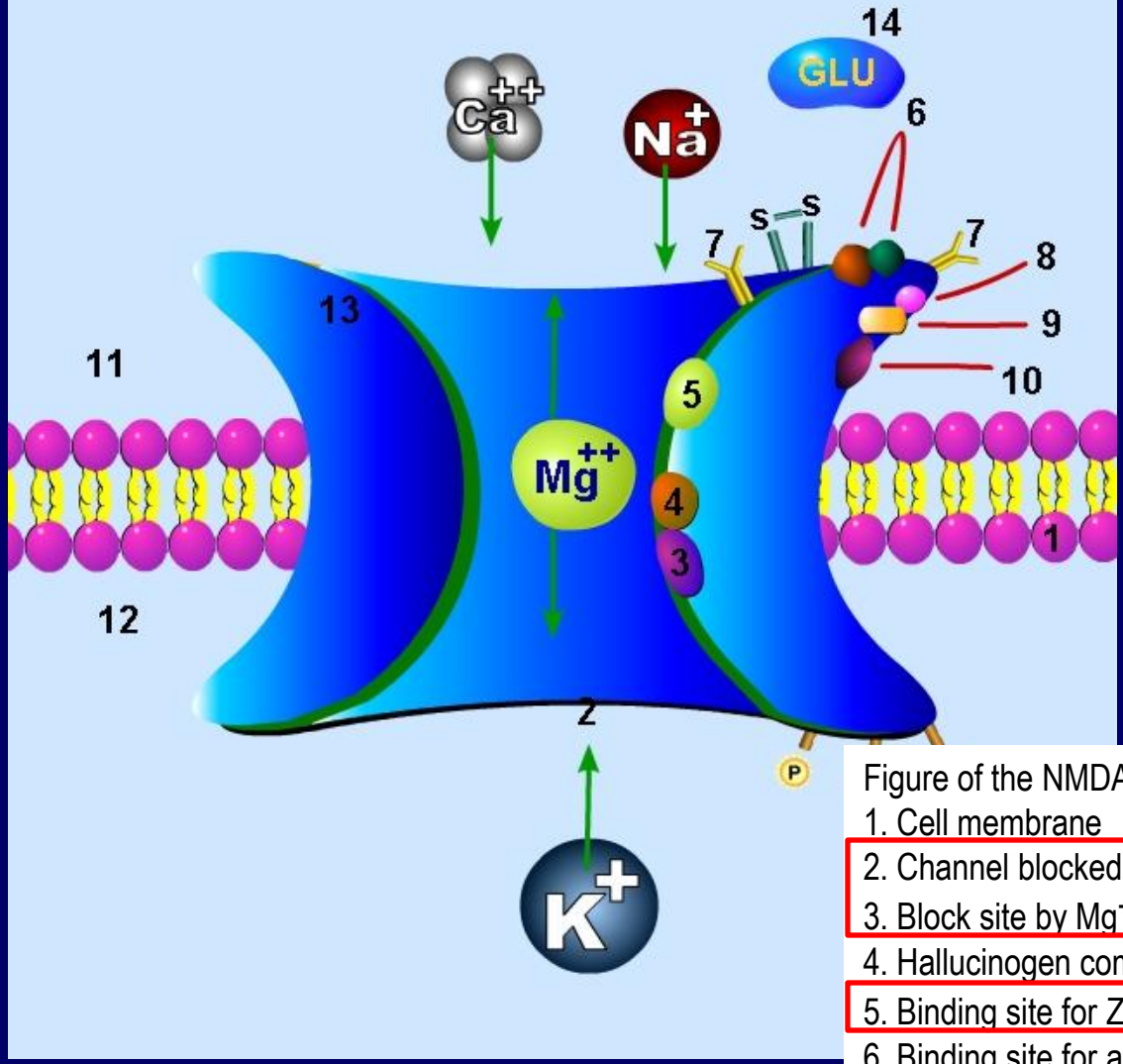


Figure of the NMDA receptor present the nervous system. Legend:

1. Cell membrane
2. Channel blocked by Mg^{++} at the block site (3)
3. Block site by Mg^{++}
4. Hallucinogen compounds binding site
5. Binding site for Zn^{++}
6. Binding site for agonists(glutamate) and/or antagonist ligands(APV)
7. Glycosilation sites
8. Proton biding sites
9. Glycine binding sites
10. Polyamines binding site
11. Extracellular space
12. Intracellular space

Peripheral NMDA Receptors

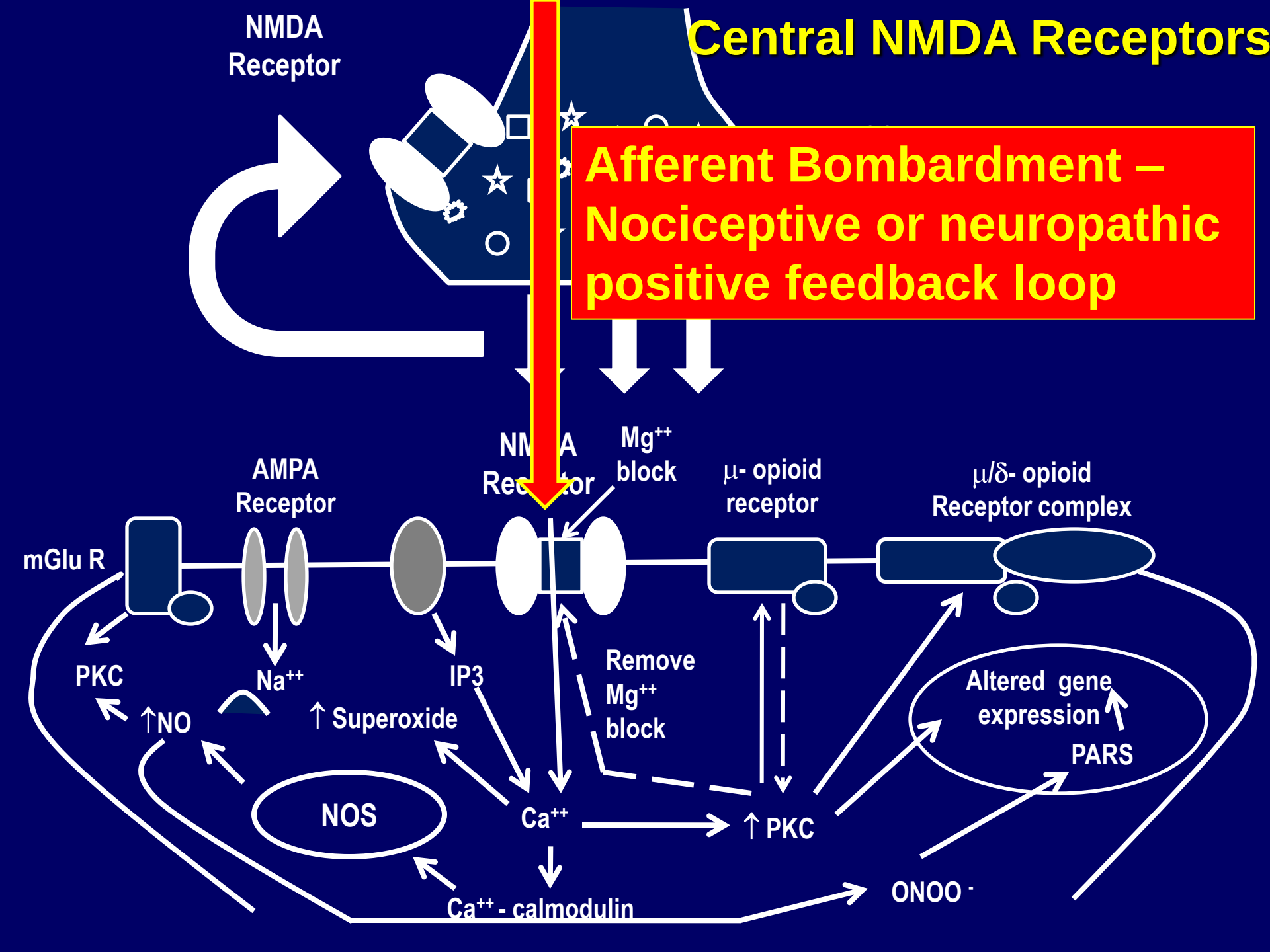
In inflammation:

The number of NMDA receptors on peripheral nerve fibres increases

Sensitisation and Hyperalgesia

Inhibited by NMDA receptors antagonists:
In development - EXCITING !

Central NMDA Receptors



So,

By afferent bombardment
(untreated acute pain),

BOTH noceptive and neuropathic pain,

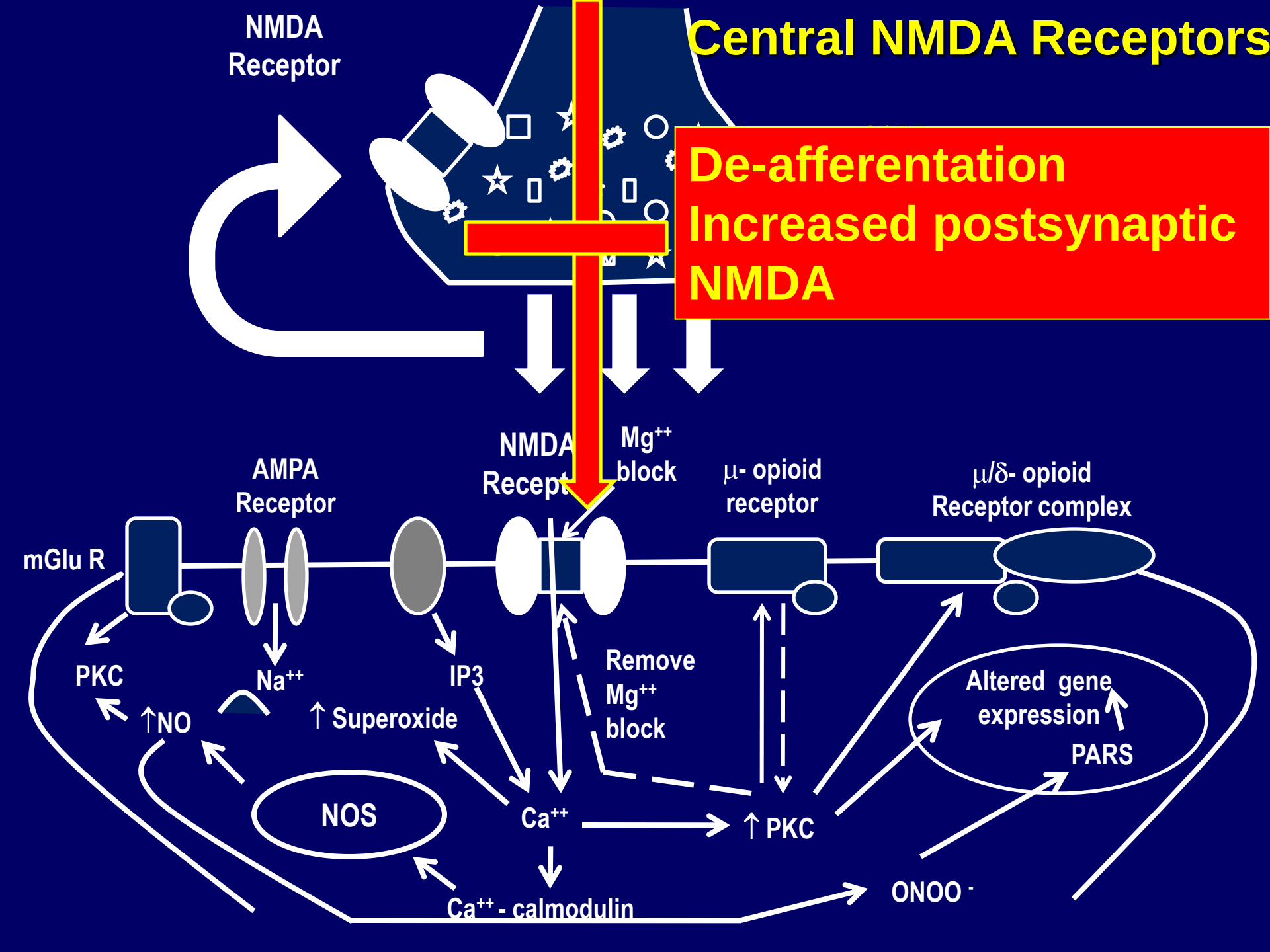
If inadequately treated,

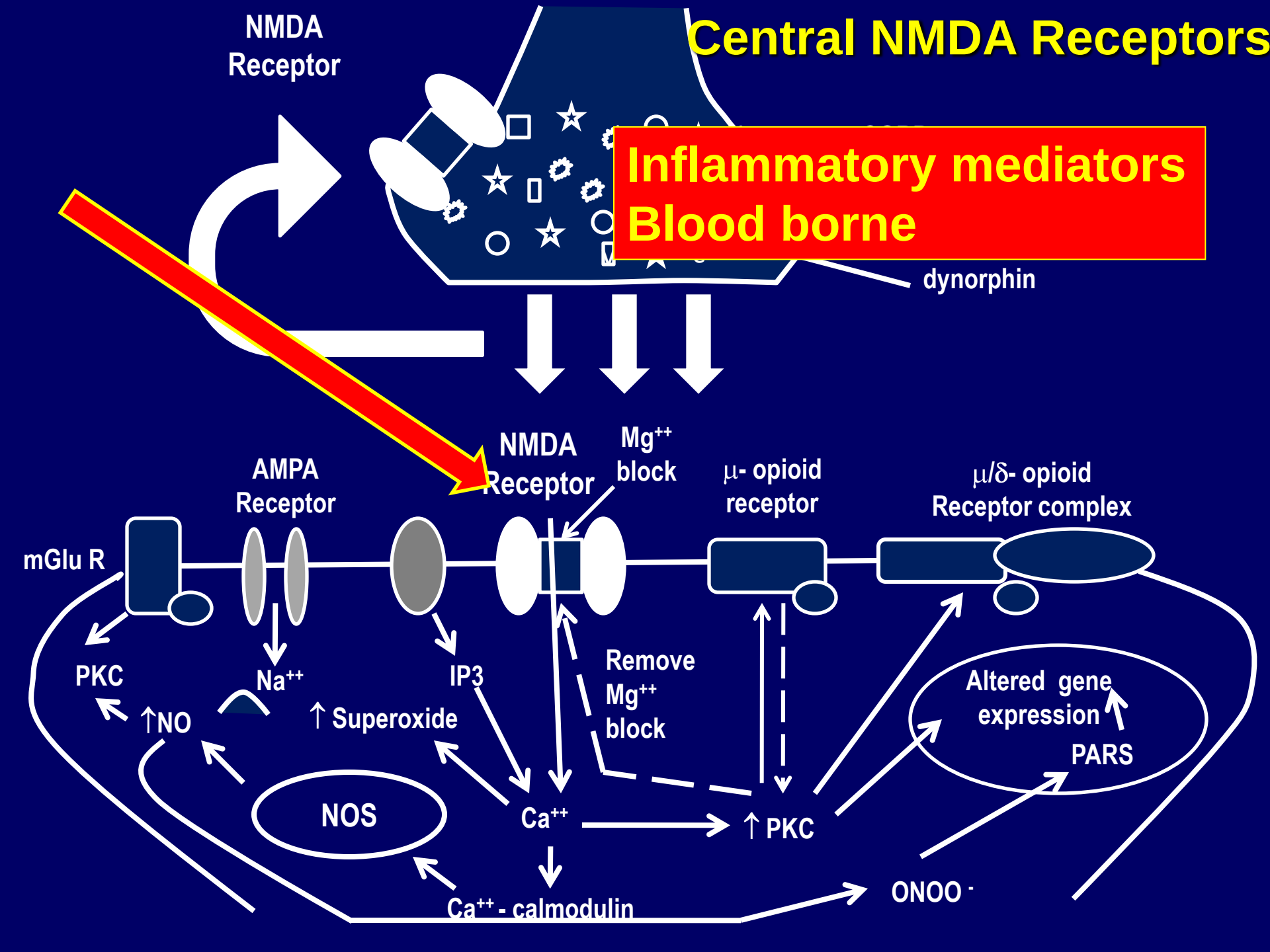
Lead to chronic pain
i.e changes in dorsal horn of spinal cord
(central sensitisation / wind up)

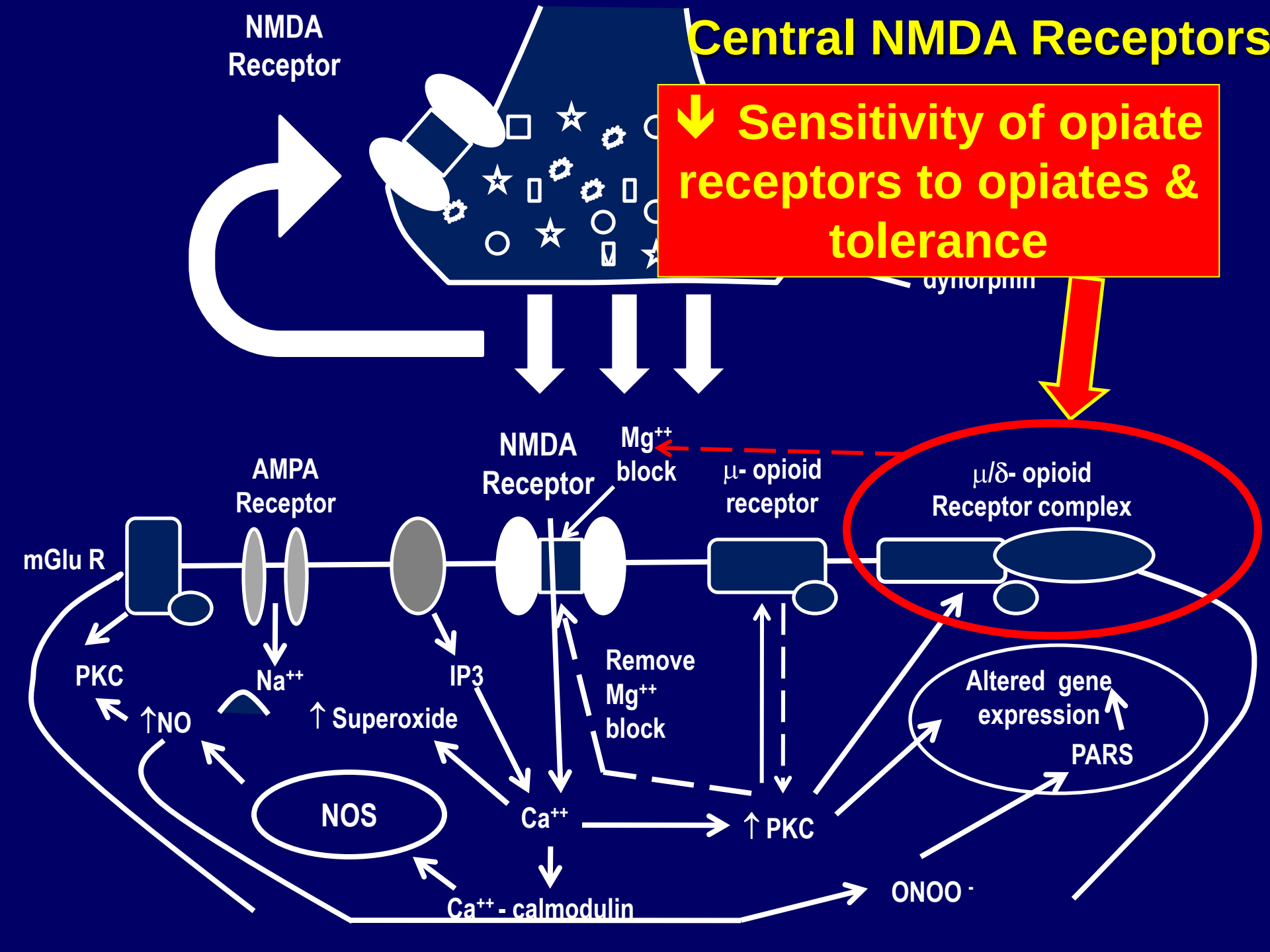
So both end up having a neuropathic element

See…. Duloxetine

Central NMDA Receptors




Central NMDA Receptors
NMDA Receptor
Inflammatory mediators
Blood borne
dynorphin
NMDA Receptor
Mg++ block
AMPA Receptor
μ- opioid receptor
μ/δ- opioid Receptor complex
mGlu R
PKC
Na++
IP3
Remove Mg++ block
Altered gene expression
PARS
↑NO
↑ Superoxide
NOS
Ca++
↑ PKC
Ca++ - calmodulin
ONOO -


NMDA Receptor
Central NMDA Receptors
↓ Sensitivity of opiate receptors to opiates & tolerance
dynorphin
AMPA Receptor
NMDA Receptor
Mg++ block
μ- opioid receptor
μ/δ- opioid Receptor complex
mGlu R
PKC
Na++
IP3
Remove Mg++ block
Altered gene expression
PARS
↑NO
↑ Superoxide
NOS
Ca++
↑ PKC
Ca++ - calmodulin
ONOO -

NMDA Receptors Antagonists

NMDA receptor antagonists inhibit hyperexcitability of spinal cord neurons induced by C-fiber stimulation.

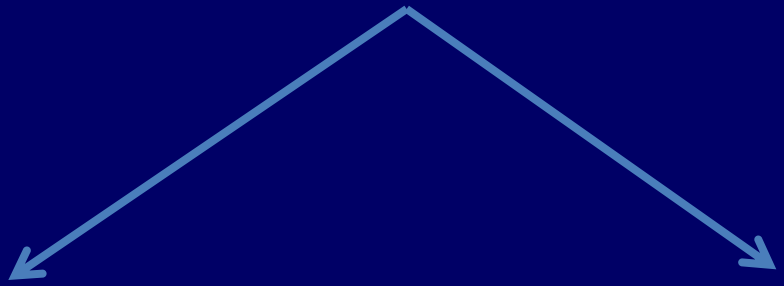
Inhibited by NMDA receptors antagonists:

Clinically available
- **MAGNESIUM**
- **Zinc**
- **ketamine**
- **dextromethophan**
- **dextro-methadone**
- **amantidine (symmetrel)**
- **memantine (Ebixa)**

Facilitated Pain Transmission

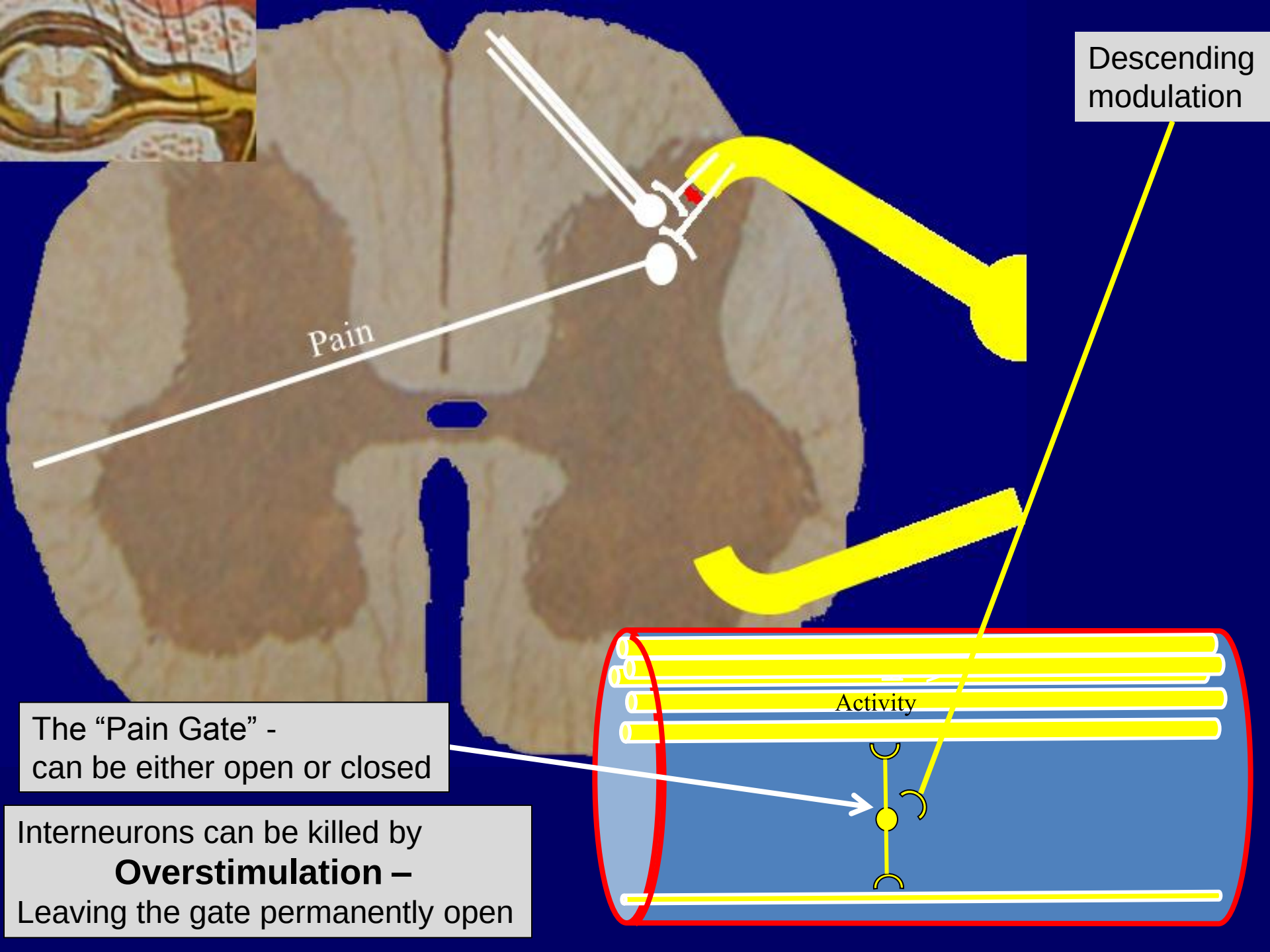
(gate open, central sensitization)

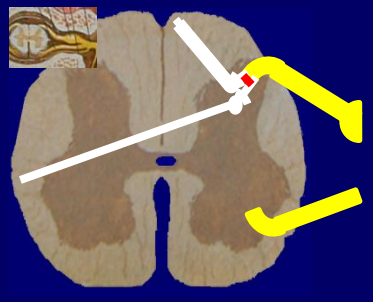
Mediated by two main mechanisms



NMDA Receptors

Interneurons


Descending modulation
Pain
Activity
The “Pain Gate” -
can be either open or closed
Interneurons can be killed by
Overstimulation –
Leaving the gate permanently open



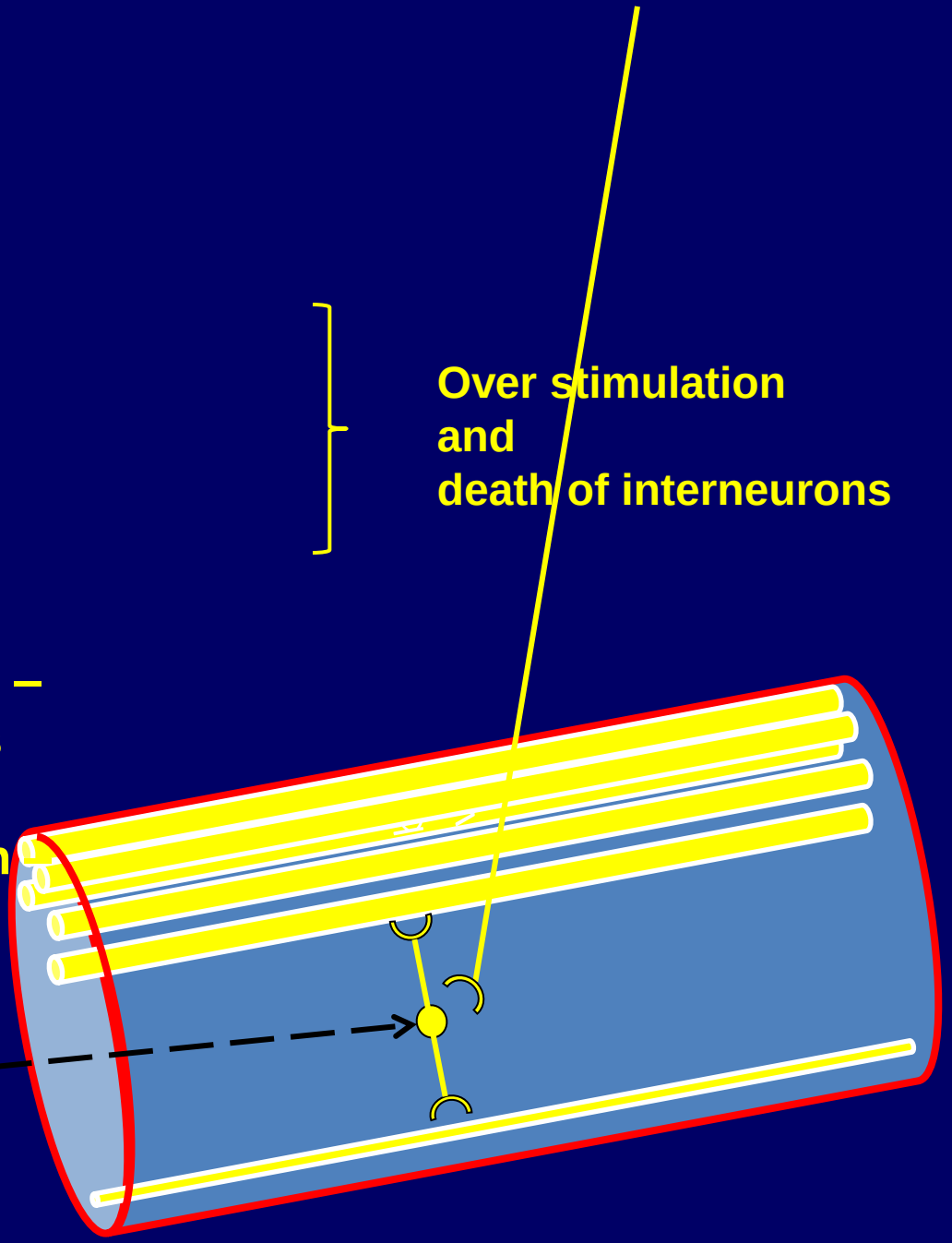
So,

Interneurons are killed by Afferent bombardment

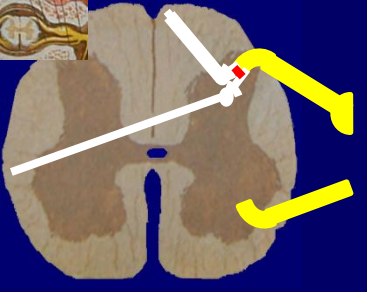
Over stimulation and death of interneurons

Body's own modulatory system – Stimulates interneurons

Constant, severe untreated pain



Interneurons can be killed by **Overstimulation –** Leaving the gate permanently open

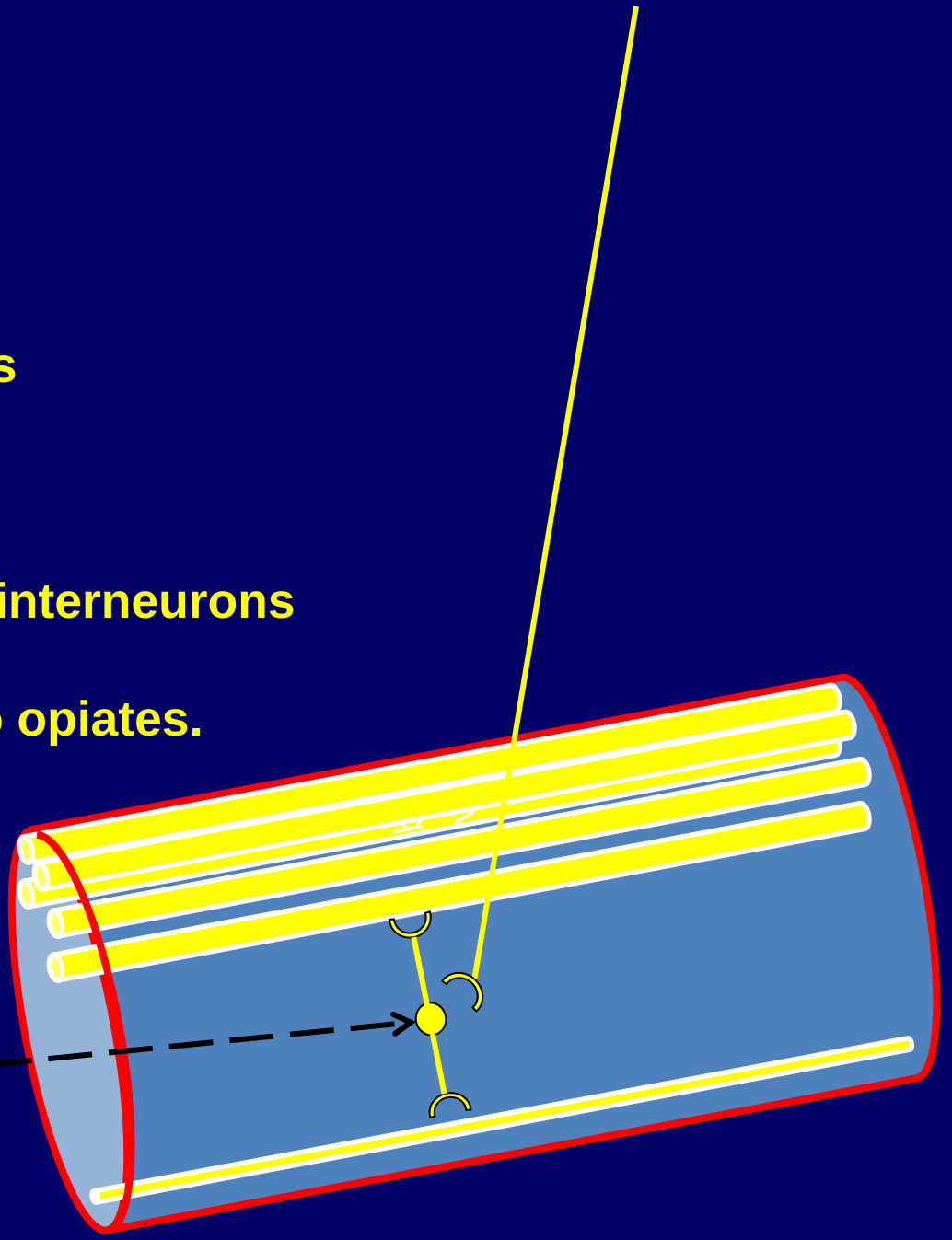


Opiates Stimulate interneurons

Ever increasing doses –

Over stimulation and death of interneurons

And hyperalgesia, tolerance to opiates.



Interneurons can be killed by
Overstimulation –
Leaving the gate permanently open

Prolonged central sensitisation - can lead to:

Permanent alterations in central nervous system –

1. **Death of inhibitory neurons**
2. **Replacement of them with new afferent *excitatory* neurons**
3. **Establishment of aberrant excitatory synaptic connections**

Making chronic pain VERY difficult to treat sometimes

Need to treat *acute pain* <u>adequately and appropriately</u>

NOT just for patient comfort

but to prevent or minimise chronic pain

Prolonged central sensitisation - can lead to:

Permanent alterations in central nervous system –

1. Death of inhibitory neurons

2. Replacement of them with new afferent *excitatory* neurons

3. Establishment of aberrant excitatory synaptic connections

Making chronic pain VERY difficult to treat sometimes

Need to treat *chronic pain* <u>differently</u>
as an entity on it's own
and NOT
simply apply acute pain therapy
for a long time!!

Need to treat *chronic pain (noc & neuro)* <u>differently</u>
as an entity on it's own
and NOT
simply apply acute pain therapy
for a long time!!

1. **NMDA Blockers**
2. **Neuropathic pain drugs**
    a. **Gabapentin**
    b. **Pregabalin**
    c. **Carbamazepine**
    d. **Amitryptaline**
    e. **etc.**
3. **? Opiates**
4. **Interventions**
5. **SCS and**

Regional anesthesia?

- outcome at 6 months
- epidural anaesthesia for the prevention of PPP after thoracotomy (n=250)
- paravertebral block for breast cancer surgery (n=89)

Study or subgroup	Favours regional Events	Total	Conventional pain control Events	Total	Weight	OR IV, Random, 95% CI
1.1.1 Thoracotomy (epidural analgesia)						
Ju 2008	26	48	31	43	43.4%	0.46 [0.19, 1.10]
Lu 2008	9	62	12	28	31.4%	0.23 [0.08, 0.63]
Senturk 2002	25	46	18	23	25.2%	0.33 [0.10, 1.04]
Subtotal (95% CI)		156		94	100.0%	0.34 [0.19, 0.60]
Total events	60		61			
Heterogeneity: τ^2=0.00; χ^2=1.04, df=2 (P=0.59); I^2=0%						
Test for overall effect: Z=3.69 (P=0.0002)						
1.1.2 Breast cancer surgery (paravertebral block)						
Ibarra 2011	5	15	7	14	39.3%	0.50 [0.11, 2.24]
Kairaluoma 2006	5	30	12	30	60.7%	0.30 [0.09, 1.00]
Subtotal (95% CI)		45		44	100.0%	0.37 [0.14, 0.94]
Total events	10		19			
Heterogeneity: τ^2=0.00; χ^2=0.27, df=1 (P=0.60); I^2=0%						
Test for overall effect: Z=2.09 (P=0.04)						

Andreae MH and Andreae DH. Br J Anaesth. 2013 Nov;111(5):711-20

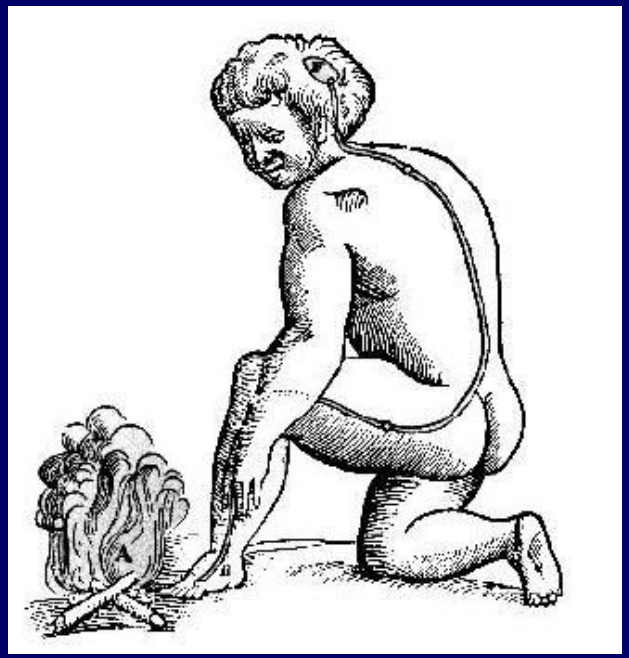
Thank you

Pain as a Clinical Entity

Traditionally:

Pain has been seen as a symptom of another underlying process / pathology which should go away once the underlying process / pathology has been eliminated.

This fits in with the definition of Acute Pain and has a protective function



Pain as a Clinical Entity

Traditionally:

Pain has been seen as a symptom of another underlying process / pathology which should go away once the underlying process / pathology has been eliminated.

BUT, clinically we have all seen:

1. **Bad pathology – no or little pain.**
2. **Mild pathology – 'uncontrollable' pain.**
3. **Pathology eliminated – pain still present.**
4. **Pathology eliminated – 'new' pain.**
5. **No apparent pathology at all – bad pain.**

Something else going on!!?

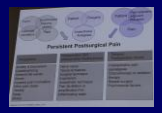
Sometimes the pain is chronic:

by definition

if it persists for longer than 3 months

‘time definition” is arbitrary

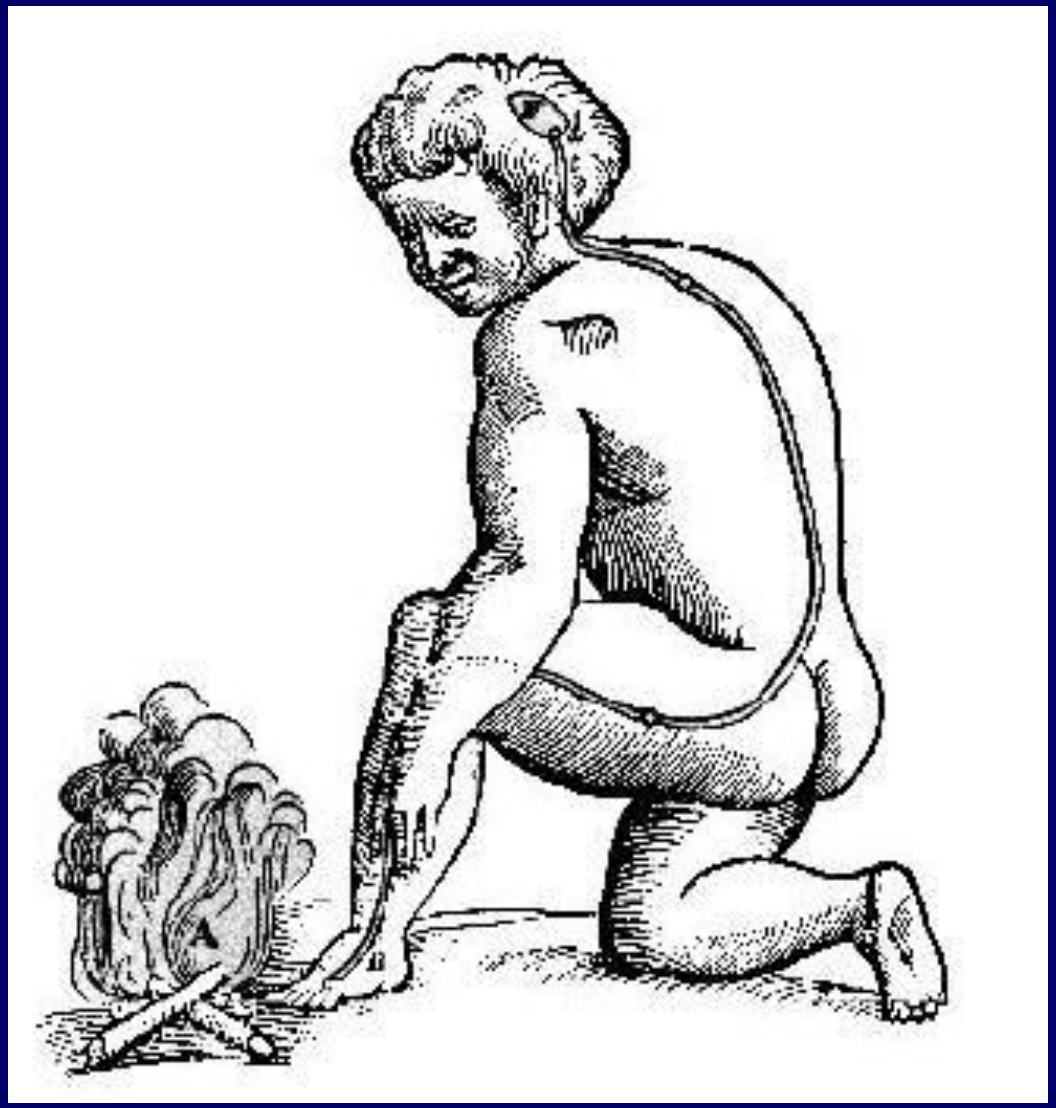
1. Sometimes chronic pain is present before 3 months have passed
2. Sometimes the mechanism for chronic pain is present form the outset.
3. Sometime the chronic pain happens “on its own” with no apparent causative factor



Preoperative	Intraoperative & post-operative healing period	Delayed Post-operative period
Anxiety and Depression Catastrophizing Stressful life events Genes Impaired Pain Modulation Other pain states Obesity Sleep Stress	Nerve injury Tissue ischaemia Surgical technique Experience Anaesthetic technique Pain facilitation or amplification Pro-inflammatory states	Postoperative pain Hyperalgesia Chemotherapy or radiation therapy Repeat surgery Psychosocial factors

Adapted form Wu and Raja, Lancet 2011

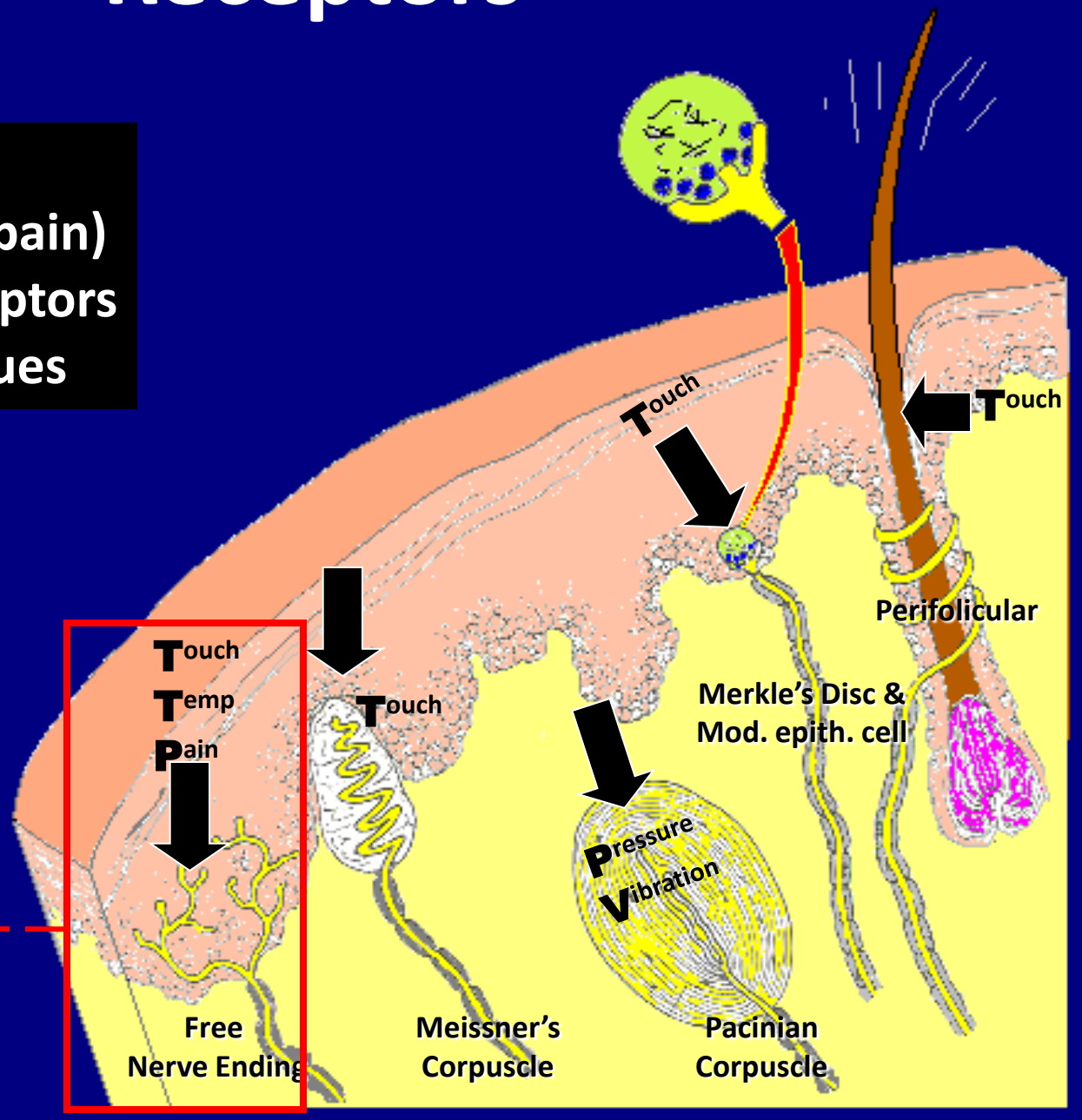
Pain Pathways



Pain Pathways

Receptors

All sensation (including acute pain) originates at receptors in skin and tissues



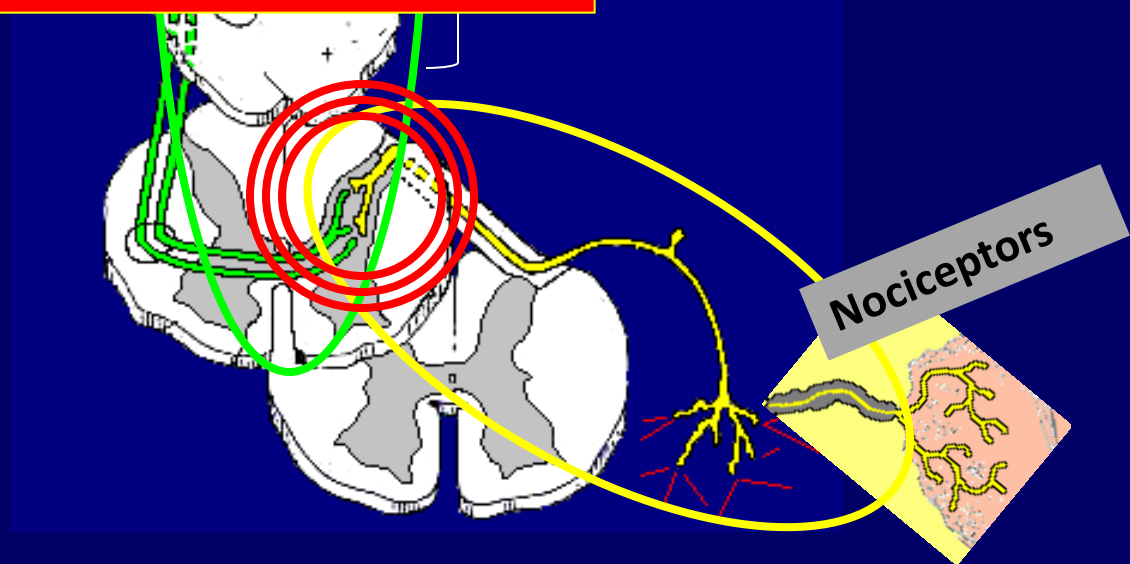
"Nociceptors"

“Wind up”
Central sensitisation
↓
Physical changes in dorsal horn
Altered Pain Processing
↓
Facilitated pain transmission (gate open)
Increased perception of pain – hyperalgesia
and, even,
origination of new pain impulses

rum via Post. Thalamus

nstem

3. Tertiary Neuron
Central Transmission
Perception



Pain Pathways

NMDA Receptors

New !

Late 1980's

↓

NMDA receptor antagonists inhibit hyperexcitability of spinal cord neurons induced by C-fiber stimulation.

Activation of NMDA receptors after tissue injury and inflammation enables facilitated processing in the spinal cord

Interneurons can be killed by
Overstimulation –
Leaving the gate permanently open