Neuropathic Pain

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Agenda

- Definitions and glossary
- Classification of pain
- Pathways of pain
- Neuropathic pain
    - Pathogenesis of neuropathic pain
    - Causes of neuropathic pain
    - Management of neuropathic pain

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Definitions and glossary

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Definitions and glossary

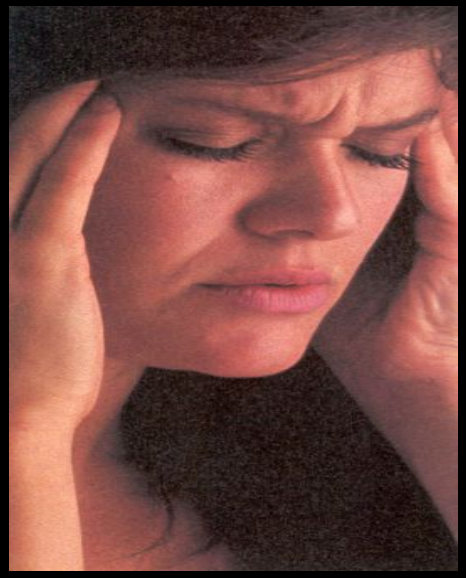
W h a t i s p a i n ?

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of s u c h d a m a g e ."

Merskey H et al, eds. In: *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 1994:209-212.

Components

- Motivational-Affective: Emotional
- Sensory-Discriminative



“Pain is a more terrible lord of mankind than death itself.”

Albert Schweitzer

Definitions and glossary

A L L O D Y N I A

Pain due to a stimulus which does not normally provoke pain.

A N A L G E S I A

Absence of pain in response to stimulation which would normally b e p a i n f u l .

A N E S T H E S I A D O L O R A S A

Pain in an area or region which is anesthetic.

Definitions and glossary

C A U S A L G I A

A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

C E N T R A L P A I N

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

D Y S E S T H E S I A

An unpleasant abnormal sensation, whether spontaneous or evoked.

Definitions and glossary

HYPERALGESIA

An increased response to a stimulus which is normally painful.

HYPERESTHESIA

Increased sensitivity to stimulation, excluding the special senses.

HYPERPATHIA

A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Definitions and glossary

HYPOALGESIA

Diminished pain in response to a normally painful stimulus.

NEURALGIA

Pain in the distribution of a nerve or nerves.
Note: Common usage, especially in Europe, often implies a paroxysmal quality, but neuralgia should not be reserved for paroxysmal pains.

NEURITIS

Inflammation of a nerve or nerves.
Note: Not to be used unless inflammation is thought to be present

Definitions and glossary

N E U R O P A T H Y

A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

N E U R O P A T H I C P A I N

Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

P A R E S T H E S I A

An abnormal sensation, whether spontaneous or evoked.

Definitions and glossary

Sign/Symptom	Description (example)
Spontaneous symptoms	
• Spontaneous pain	Persistent burning, intermittent shock-like or lancinating pain
• Dysesthesias	Abnormal unpleasant sensations e.g. shooting, lancinating, burning
• Parasthesias	Abnormal, not unpleasant sensations e.g. tingling
Stimulus-evoked symptoms	
• Allodynia	Painful response to a non-painful stimulus e.g. warmth, pressure, stroking
• Hyperalgesia	Heightened response to painful stimulus e.g. pinprick, cold, heat
• Hyperpathia	Delayed, explosive response to any painful stimulus

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Classification of pain

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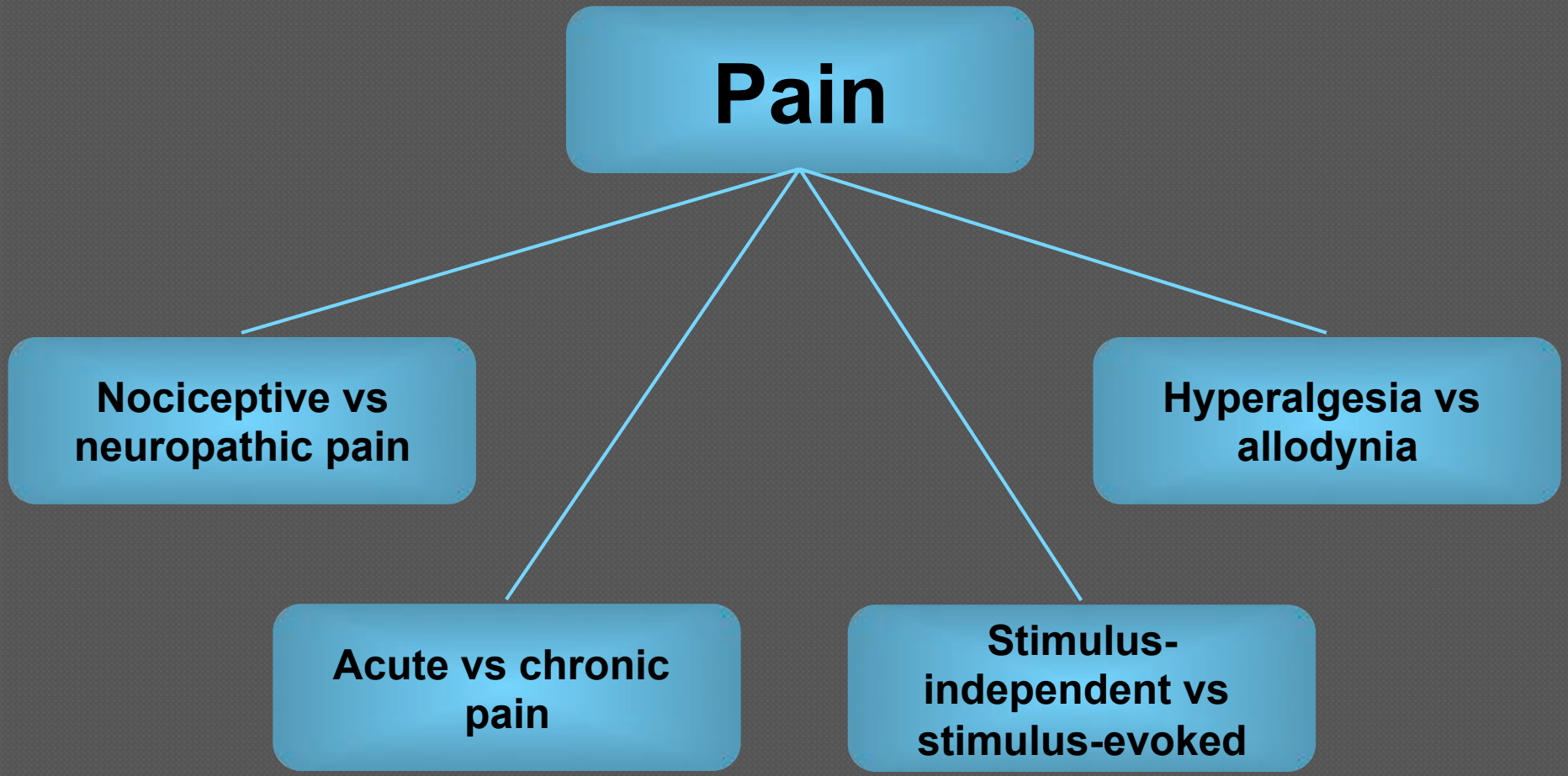
Classification of pain



Classification of pain

Nociceptive Pain

An appropriate physiologic response to painful stimuli

Neuropathic Pain

An inappropriate response caused by a primary lesion or dysfunction in the nervous system

Merskey H et al, eds. In: *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* 1994:209-212.

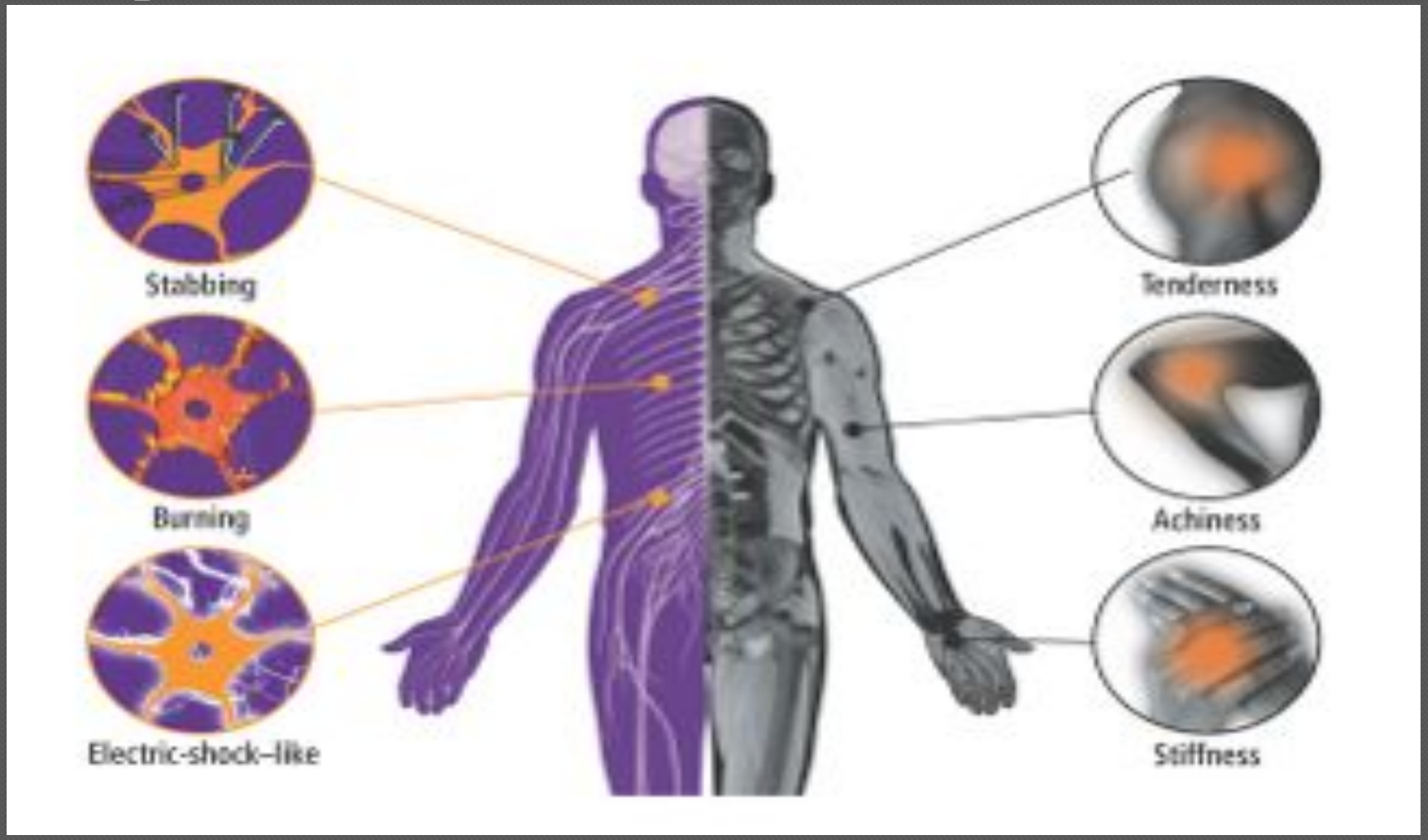
Classification of pain

Neuropathic Pain	Muscle/skeletal Pain (nociceptive pain)
Chronic pain (months/years)	Acute pain (hours or days)
Caused by injury or disease to nerves	Caused by injury or inflammation that affects both the muscles and joints
Mild to excruciating pain that can last indefinitely	Moderate to severe pain that disappears when the injury heals
Causes extreme sensitivity to touch – simply wearing light clothing is painful	Causes sore, achy muscles
Sufferers can become depressed or socially withdrawn because they see no relief in sight and may experience sleep problems	Sufferers can become anxious and distressed but optimistic about relief from pain

Wall PD. *Textbook of Pain*. 4th ed; 1999; Jude EB. *Clin in Pod Med and Surg*.1999;16:81-97; Price SA. *Pathophysiology*: *Clinical Concepts of Disease Processes*. 5th ed; 1997: Goldman L. *Cecil Textbook of Medicine*. 21st ed; 2000

Classification of pain

Neuropathic Pain **Muscle/Skeletal Pain**



Price SA. Pathophysiology: *Clinical Concepts of Disease Processes*. 5th ed; 1997; Galer BS et al. *Diabetes Res Clin Pract.* 2000;47:123-128

Classification of pain

A time-based definition

Acute Pain

- **Time limited, <3 months**
- Results from injury to tissue
- Resolves with healing
- Example: herpes zoster

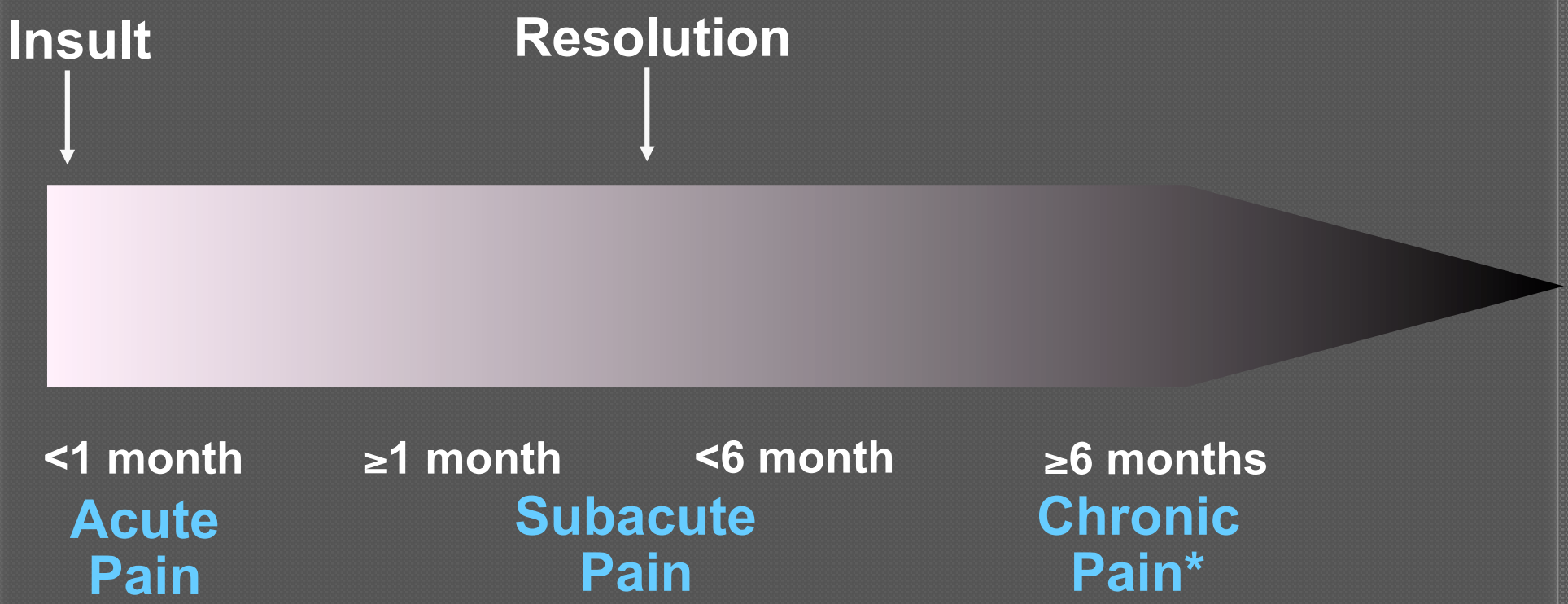
versus

Chronic Pain

- **Persistent, ≥3 to 6 months**
- Continues after initial injury heals
- Example: postherpetic neuralgia

Merskey H et al, eds. In: *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 1994:209-212.

Classification of pain



*Nociceptive; mixed nociceptive and neuropathic; or neuropathic.

Cole BE. *Hosp Physician.* 2002;38:23-30.

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Pathway of Pain

Physiology of Pain Perception(4 Basic processes)

Transduction☺

1. Noxious stimuli (thermal, mechanical, and chemical) - - - - - tissue damage
2. Traumatized tissues release inflam. mediators (PGs, Bradykinin, 5HT, SP, Histamine.
3. Nociceptive free nerve endings sensitized by opening Na + channels - - - - Depolarization
4. So; noxious stimuli are converted to impulse (in milliseconds)

Pathway of Pain

The 1st order neurone

- Is the cell of the **posterior root ganglion** & its axon.
- This axon is divided into a lateral & a medial branch.
- The lat. branch forms the afferent sensory nerve.
- The medial branch enters the spinal cord to ascend a few segments forming **Lissauer's tract,** and relays in the cells of **Substantia Gelatinosa of Rolandi (S.G.R.)** capping the post, horn of the gray matter.

Pathway of Pain

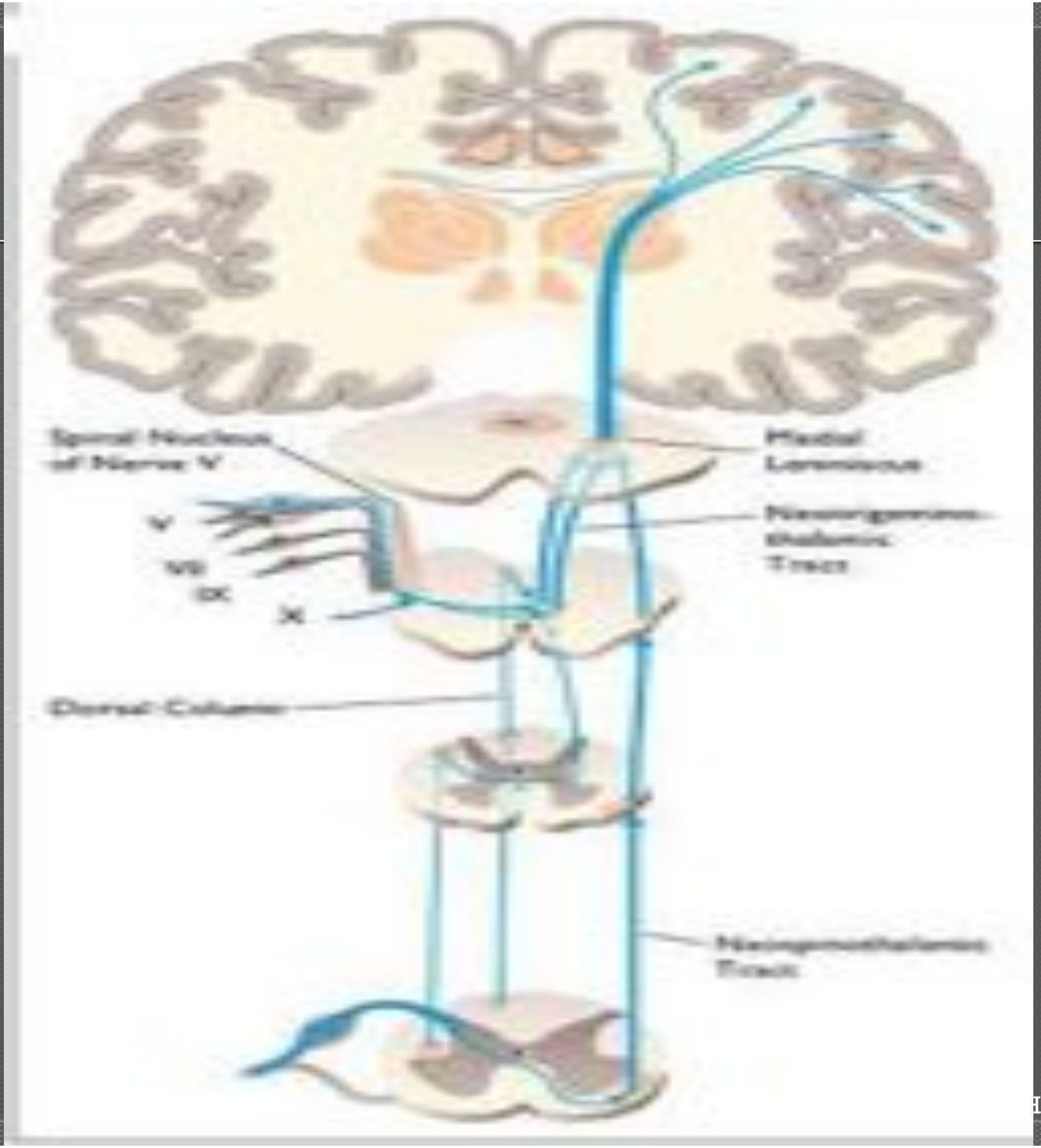
The 2nd order neurone

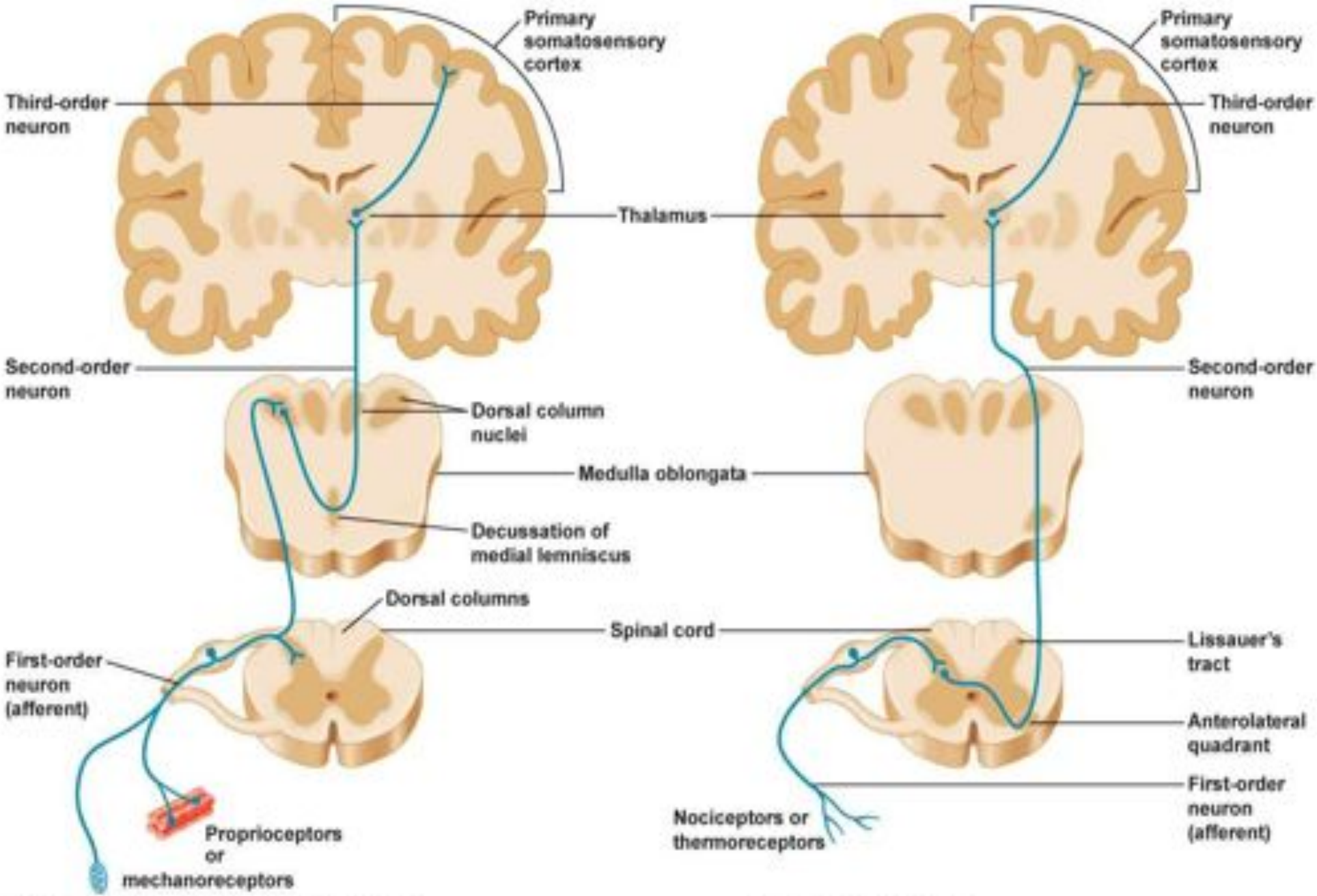
- Is the cell of **S.G.R.** & its axon.
- This axon crosses to the **OPPOSITE** side & ascends in the **Lateral Spinothalamic Tract** of the spinal cord then in the lateral lemniscus of the brain stem, to relay in the thalamus.

Pathway of Pain

The 3rd order neurone

- Starts in the cell of the **thalamus,** its axon ascends to pass through the posterior limb of the internal capsule conducting the impulse to the **cortical sensory area** in the parietal lobe.


Spinal Nucleus
of Nerve V
V
VII
IX
X
Dorsal Column

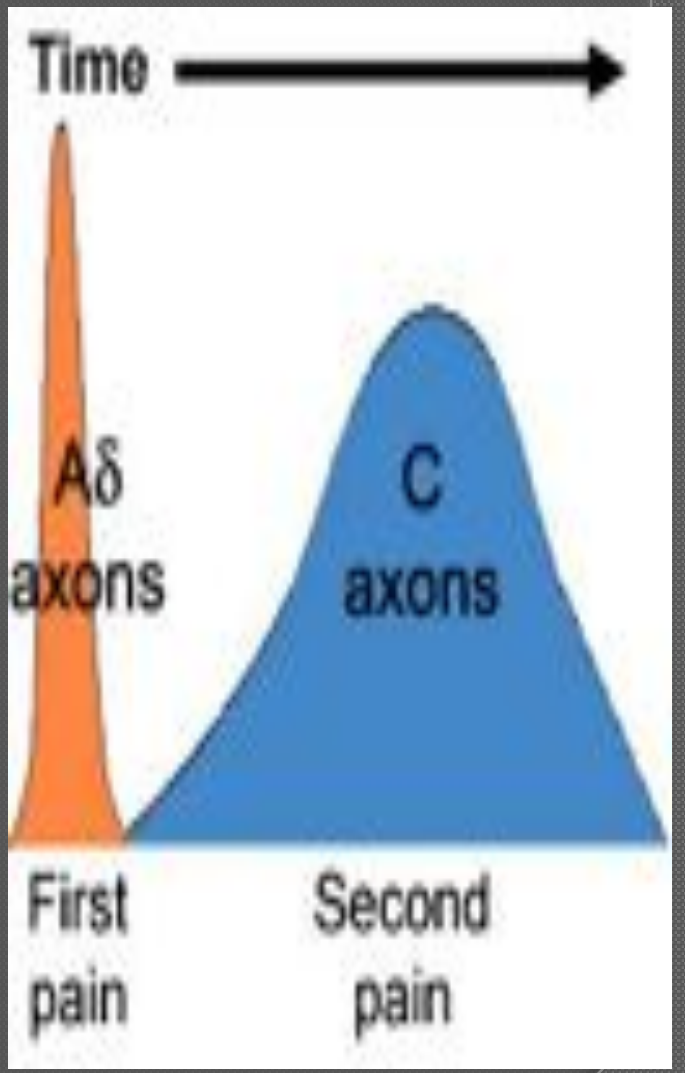


Pathway of Pain

- **Transmission**

- **Neural Pathway:**

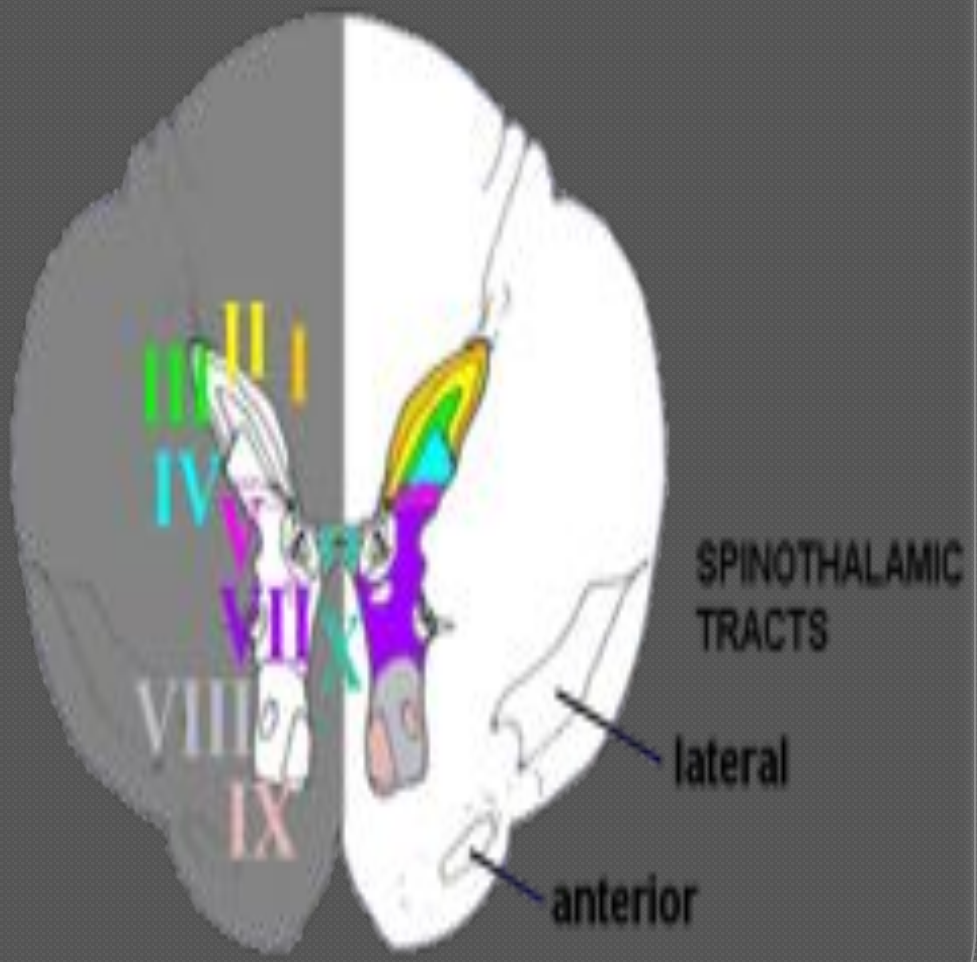
First Pain	Second Pain
Sharp	Dull (unpleasant)
Initial	Later
Brief	Long – lasting



Pathway of Pain

Spinal cord pathway:

- DRG (1st order)
- Dorsal horn (2nd order) (laminae I-V)
  - Wide Dynamic Range Cell (WDR): Glu (AMPA)
  - Nociceptive specific neurons
  - SGR (lamina II).



Pathway of Pain

Ascending Pathways:

- Spino-Reticulo-Diencephalic: connected to R.F (connected to hypothalamus and Cingulate gyrus “autonomic components”) and medial thalamus
- Spinothalamic: VLNT

The Thalamus:

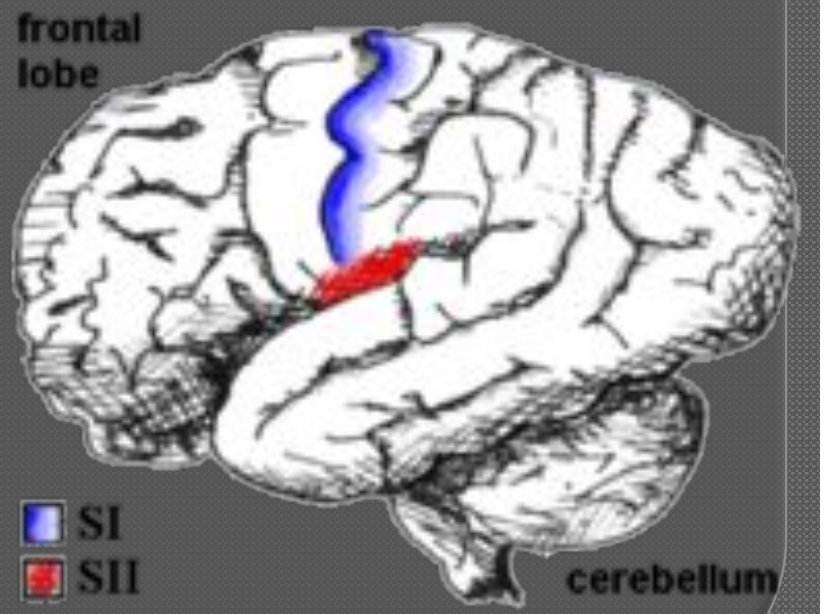
- The central switching station of the brain.
- The lateral nuclei deal with sensory / discriminative aspects.
- The medial ones with 'affective' pain.

Pathway of Pain

Cortical structures

Tangentially involved in the perception of pain !?!?!

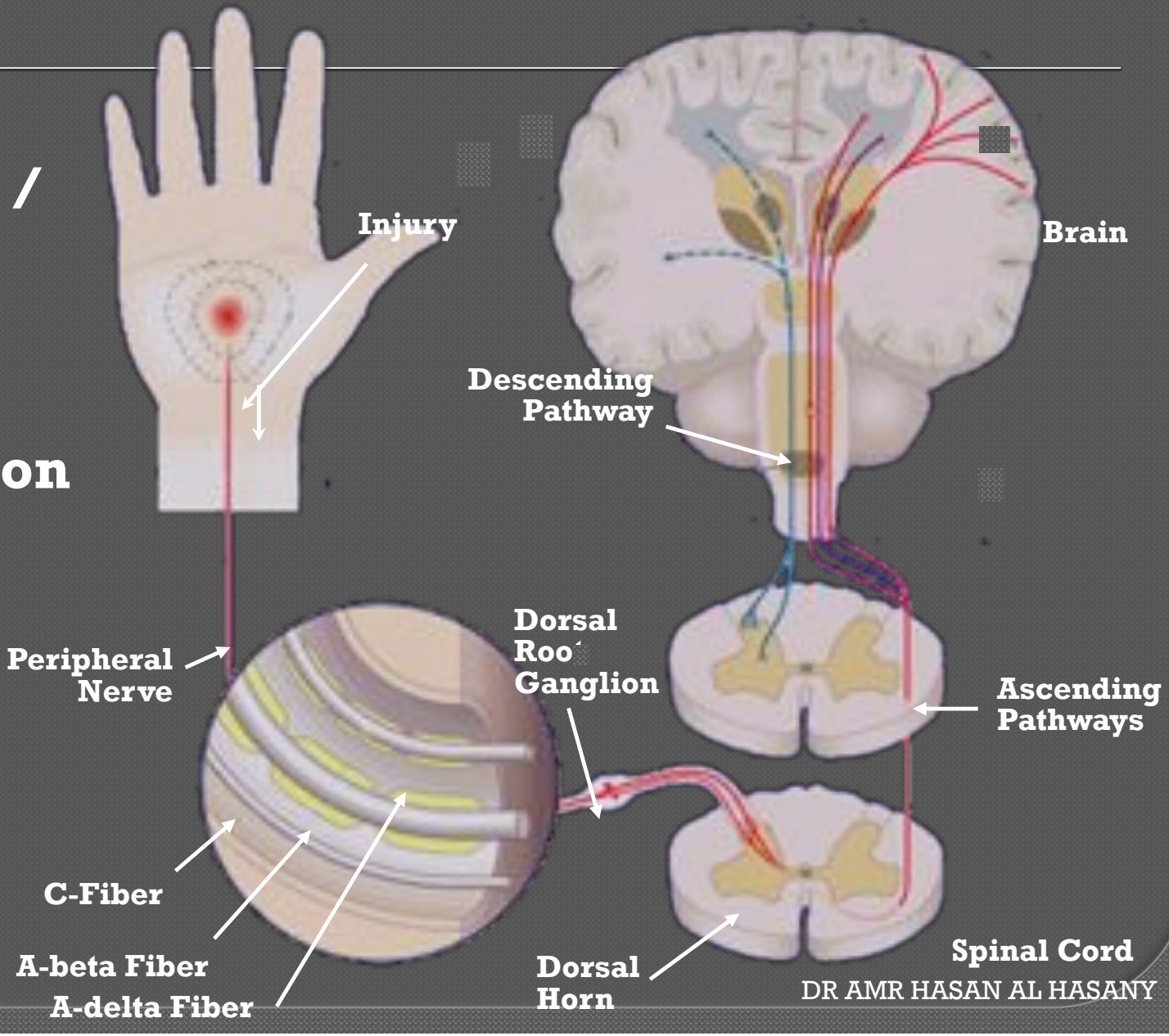
- Major cortical players are:
  - Primary sensory cortex, S I
  - Secondary sensory cortex, S II
  - Anterior part of the insula
  - Cingulate gyrus.



Pathway of Pain

Modulation / perception:
In cortex.

Interpretation



Pathway of Pain

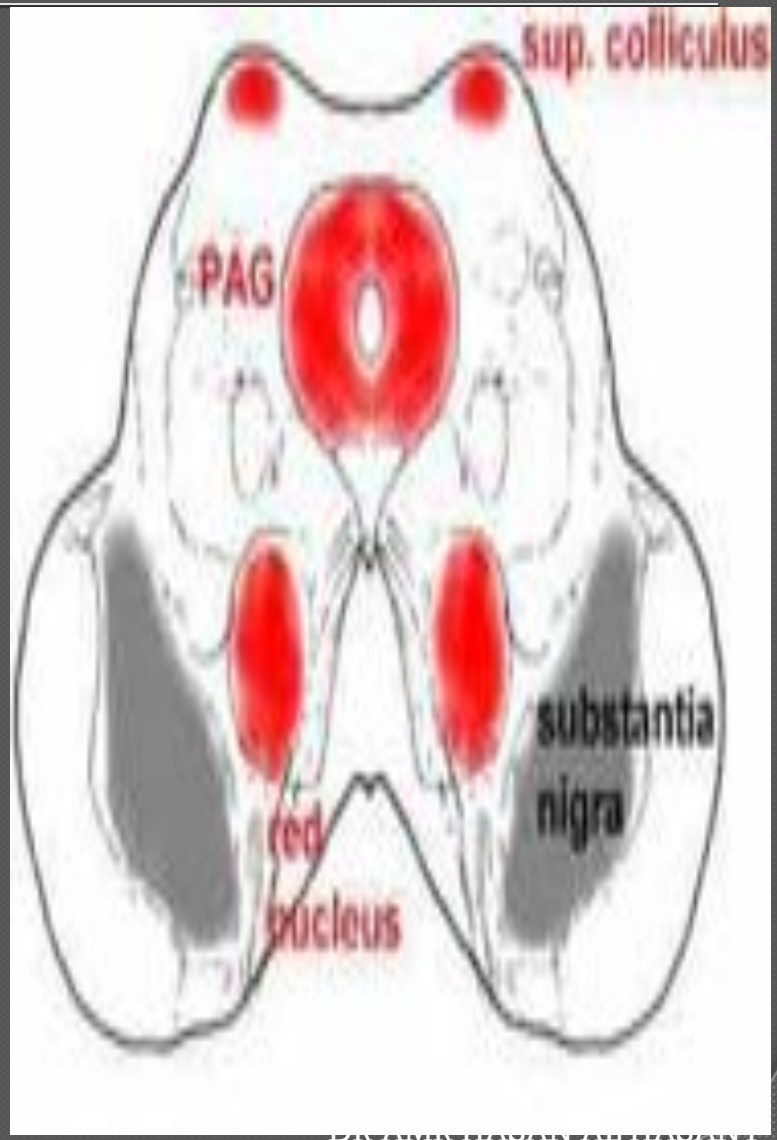
- **Descending pathways originate from three main areas:**
  - Cortex
  - Thalamus
  - Brainstem: *Periaqueductal grey matter* (PAG)

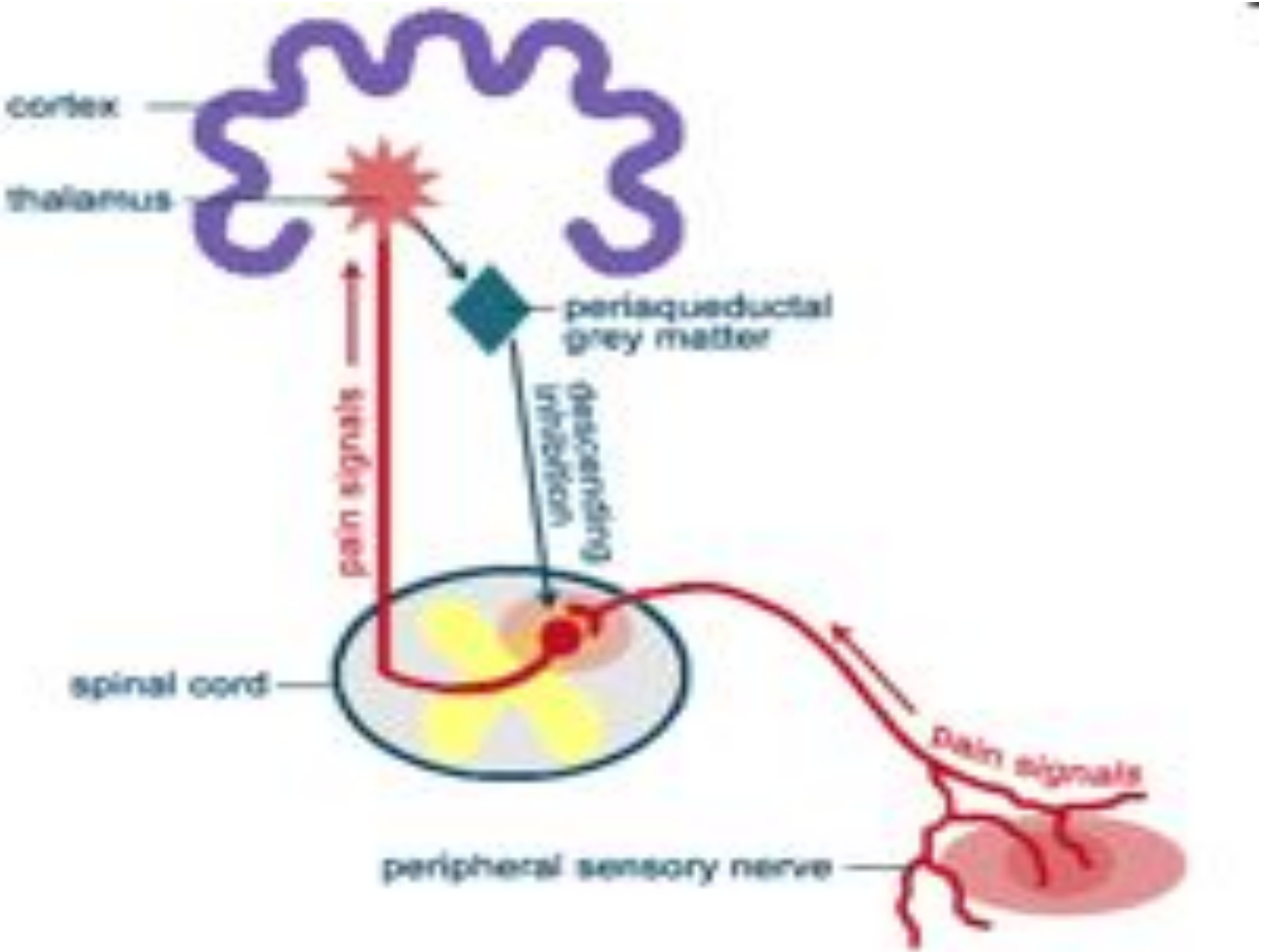
Pathway of Pain

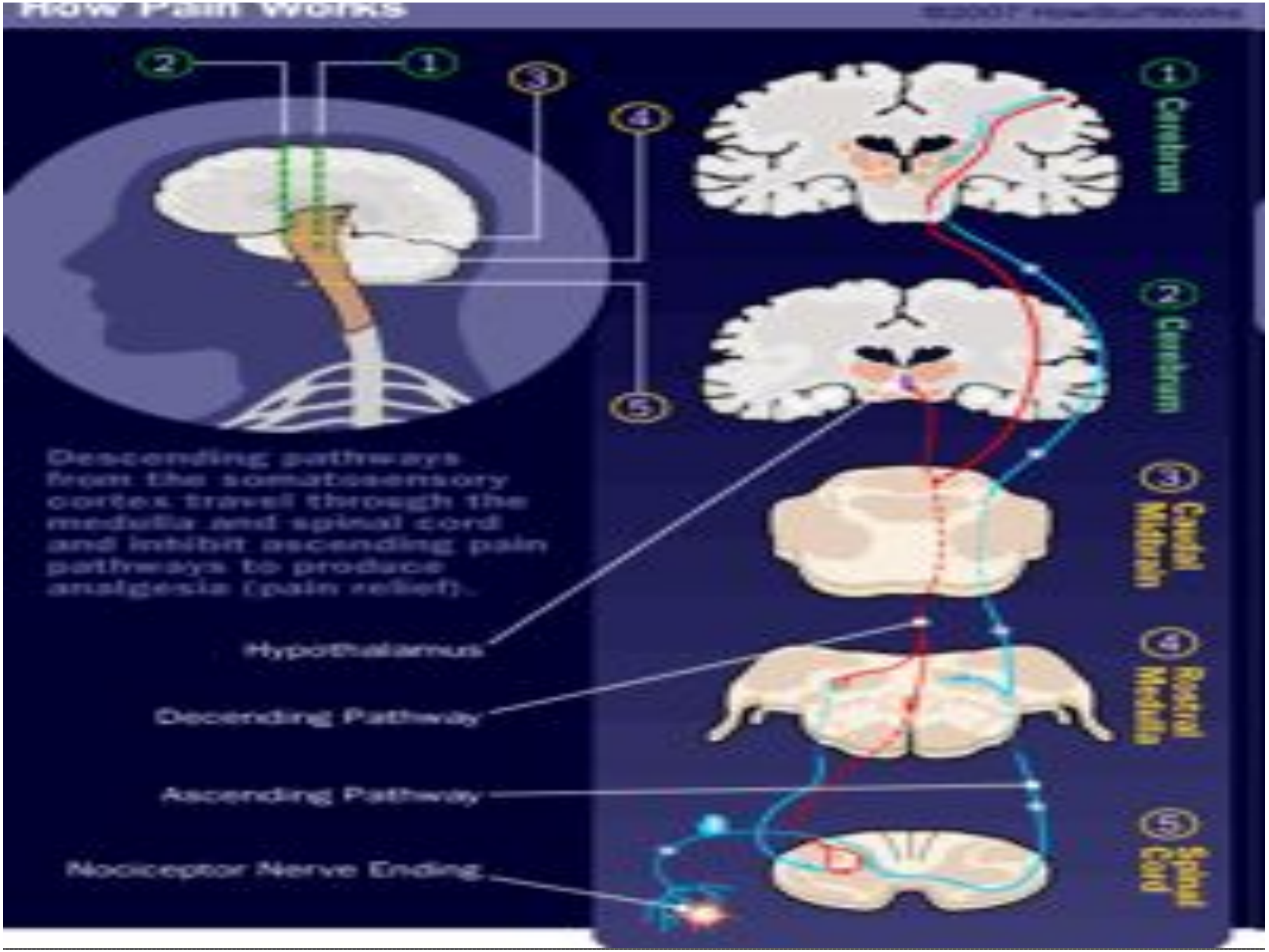
- **Descending pathways originate from three main areas:**

1. The somatosensory cortex
2. The periventricular nucleus of the hypothalamus
3. The pontine reticular formation
4. Raphe nuclei and adjacent medullary reticular formation

- From PAG →R.F of medulla (raphe nucleus) in ventromedian medulla (5HT) →Dorsolateral funiculus of the spinal cord, to end up in →Interneurones next to SGR (lamina II) (enkephalin) that inhibit incoming pain impulses.




cortex
thalamus
periaqueductal grey matter
descending inhibition
pain signals
spinal cord
pain signals
peripheral sensory nerve


How Pain Works
1
2
3
4
5
Descending pathways from the somatosensory cortex travel through the medulla and spinal cord and inhibit ascending pain pathways to produce analgesia (pain relief).
Hypothalamus
Decending Pathway
Ascending Pathway
Nociceptor Nerve Ending
1 Cerebrum
2 Cerebrum
3 Caudal Midbrain
4 Rostral Midbrain
5 Spinal Cord

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Neuropathic Pain

- Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

- Neuropathic pain is usually chronic, difficult to treat, and often resistant to standard analgesic management.

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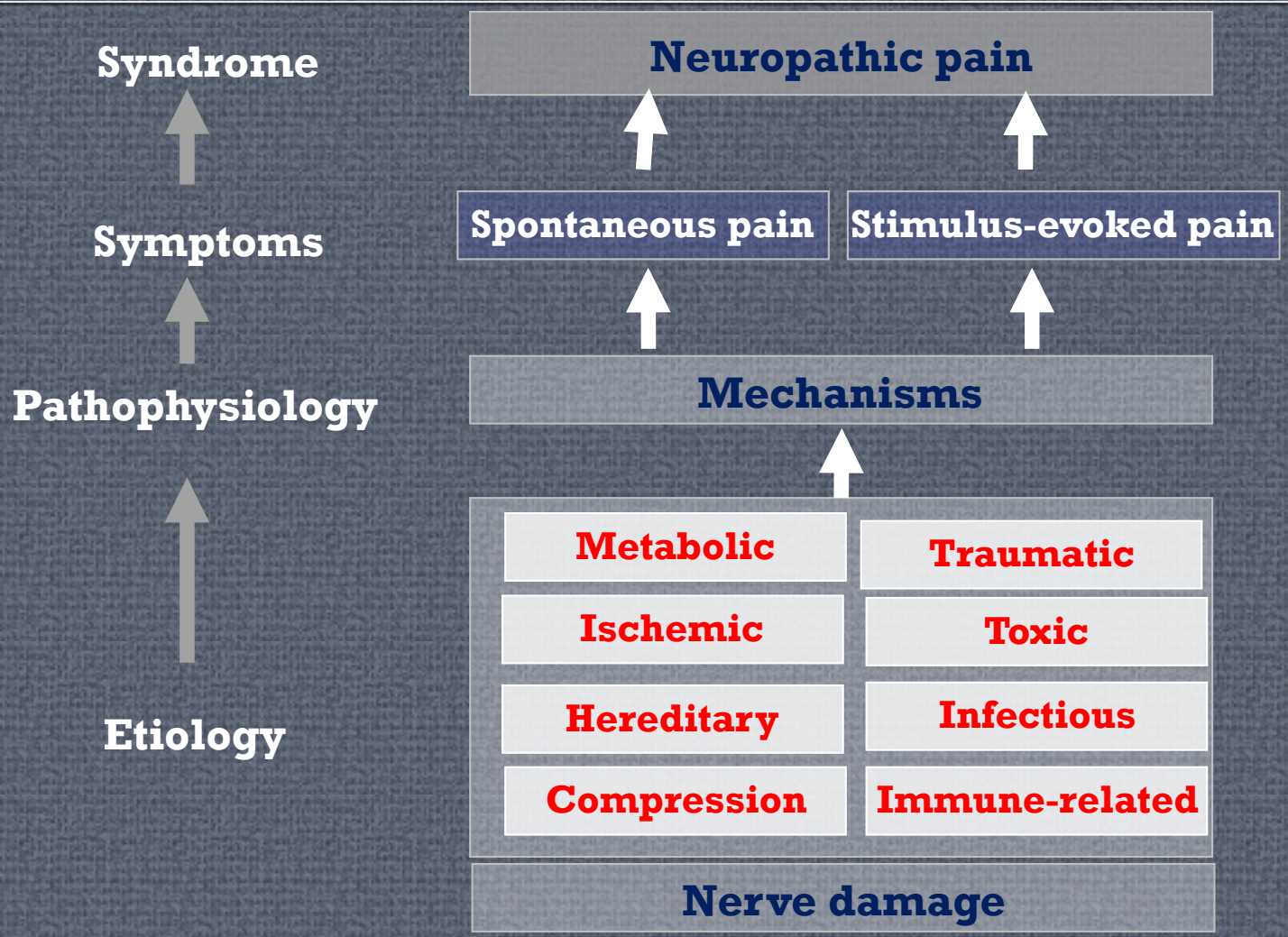
Neuropathic pain



Woolf and Mannion. Lancet 1999;353:1959-64

Pathogenesis of neuropathic pain

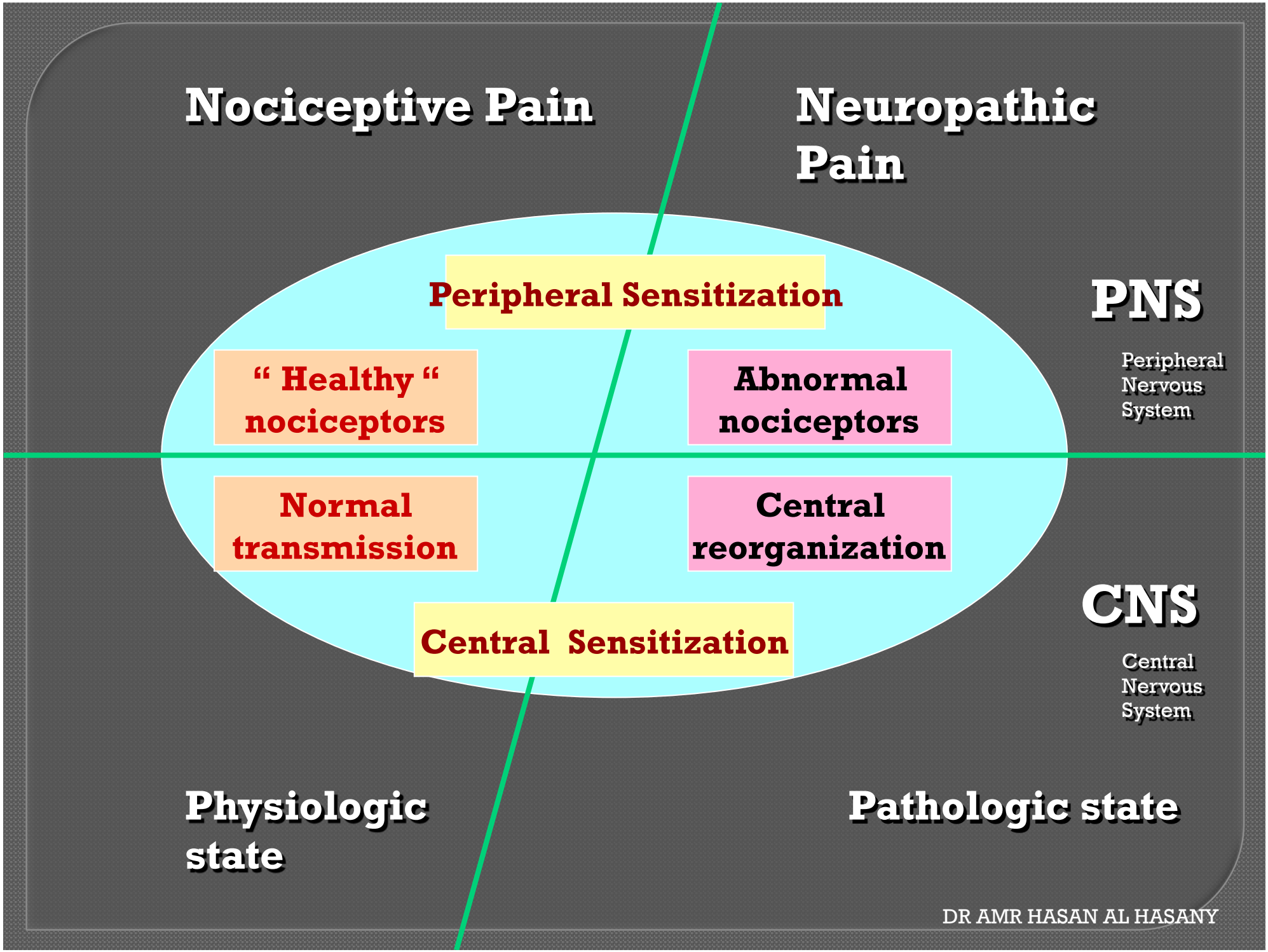
- **Peripheral Mechanisms**

  After a peripheral nerve lesion, neurons become more sensitive and develop abnormal excitability and elevated sensitivity to stimuli [peripheral sensitization] .

Pathogenesis of neuropathic pain

Central Mechanisms

- As a consequence of ongoing spontaneous activity arising in the periphery, STT neurons develop an increased background activity, enlarged receptive field and increased responses to afferent impulses, including normal tactile stimuli [central sensitization].


Nociceptive Pain
Neuropathic Pain
Peripheral Sensitization
PNS
Peripheral Nervous System
" Healthy " nociceptors
Abnormal nociceptors
Normal transmission
Central reorganization
Central Sensitization
CNS
Central Nervous System
Physiologic state
Pathologic state
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Pathogenesis of neuropathic pain

Peripheral Mechanisms

- Membrane hyperexcitability
- Ectopic discharges
- Peripheral sensitization

Central Mechanisms

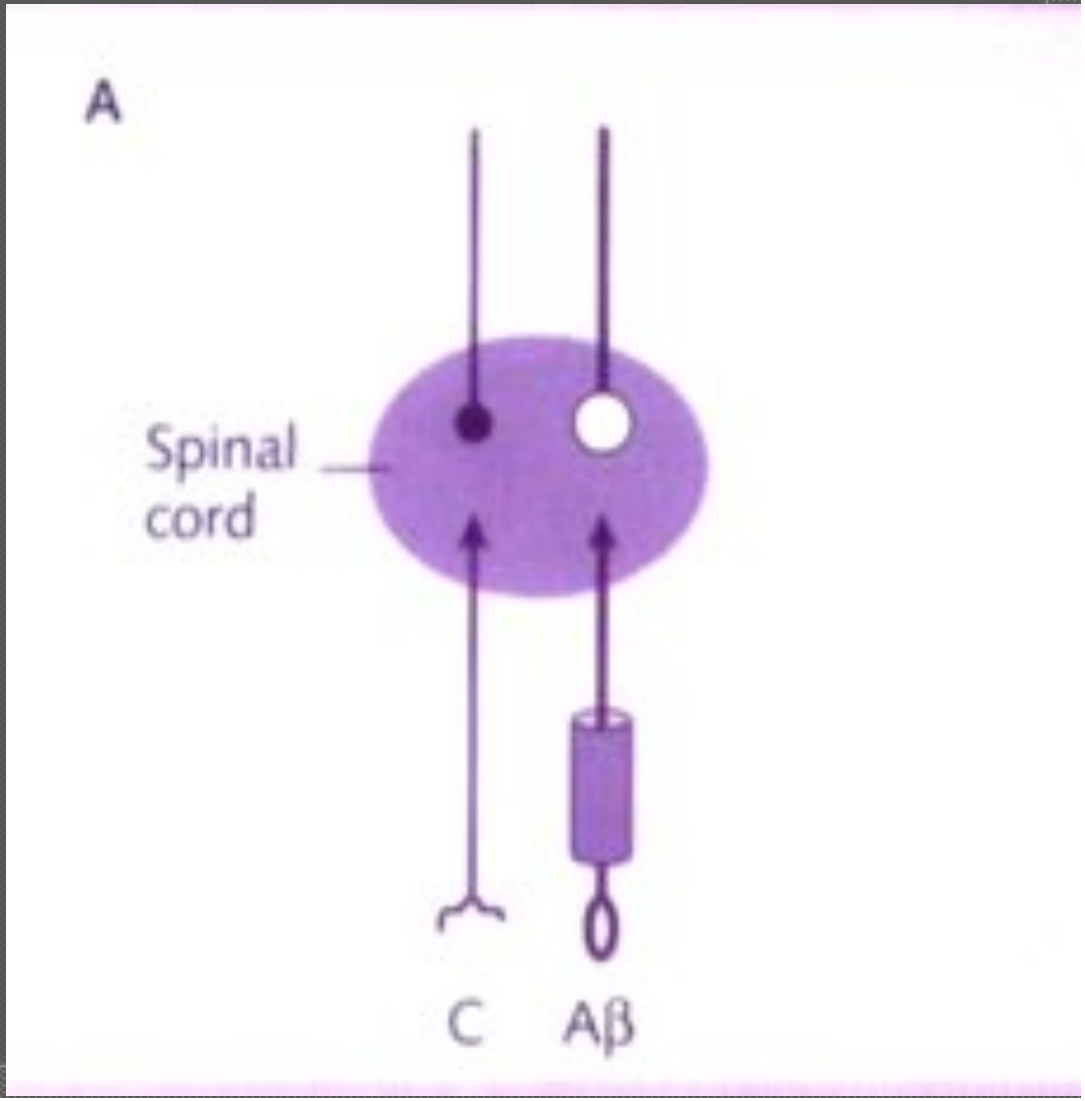
- Wind up
- Central sensitization
- Central reorganization of Aβ fibers
- Loss of inhibitory controls

Attal N et al. *Acta Neurol Scand.* 1999;100(suppl):12-24; Woolf CJ et al. *Lancet*. 1999;353:1959-1964.

Neuropathic Pain

NEUROPATHIC PAIN

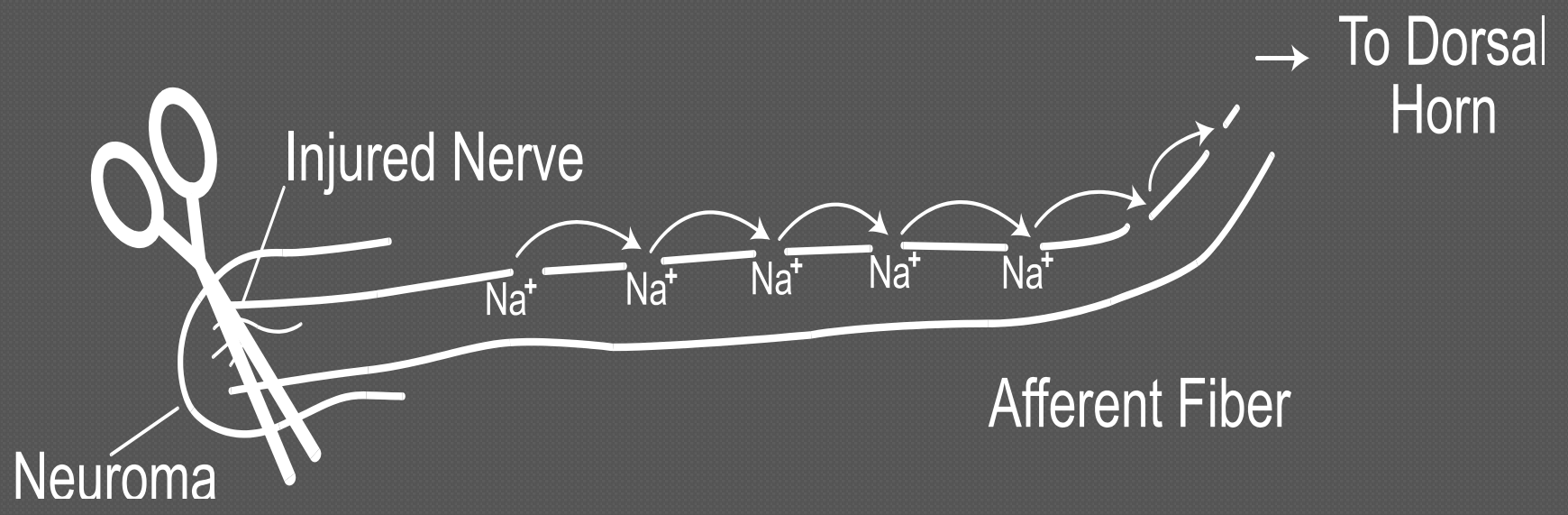
- Abnormal sensations are transmitted along myelinated Aβ or Aδ fibers or unmyelinated C fibers



Pathogenesis of neuropathic pain

1-Ectopic Discharges

Injured nerves develop higher number of Na^+ channels



Na^+ = sodium ion channels.

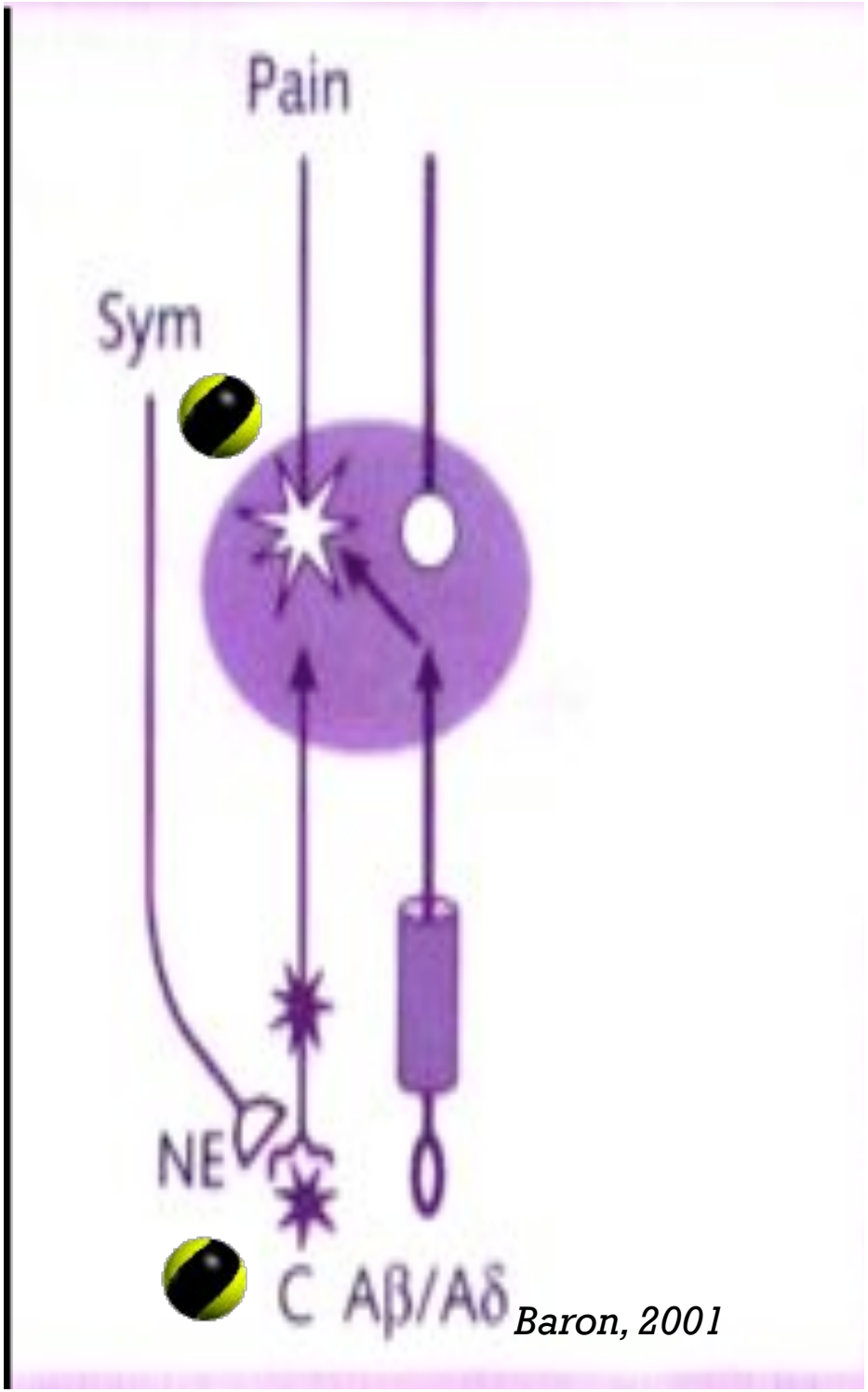
2. Peripheral Sensitization

- Nociceptive C-afferents→

- Spont. Pain (burning)

- **evoked pain (allodynia, hyperalgesia).**

- Non-nociceptive Aβ afferents → parasthesias & dysthesia.



Baron, 2001

Peripheral Sensitization

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Pathogenesis of neuropathic pain

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Pathogenesis of neuropathic pain

1-wind up

•Sensitization of DHC resulting from high frequency stimulation by nociceptive thus → DHC continue to discharge despite cessation of C fiber stimulation.

Pathogenesis of neuropathic pain

1-wind up

•Wind-up is a frequency-dependent increase in the excitability of spinal cord neurones, evoked by electrical stimulation of afferent C - f i b r e s .

•Glutamate (NMDA) and tachykinin NK1 receptors are required to generate wind-up and therefore a positive modulation between these two receptor types has been suggested by some authors.

Central Mechanisms: Windup

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Pathogenesis of neuropathic pain

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Pathogenesis of neuropathic pain

2-Central sensitization involves:

- Prolonged depolarization of dorsal horn neurons and changes in postsynaptic membrane receptors

- **Changes in postsynaptic dorsal horn membrane receptors manifest as:**
  - Reduced activation threshold
  - Increased receptive field
  - Increased response to suprathreshold stimulus

Central Sensitization

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Pathogenesis of neuropathic pain

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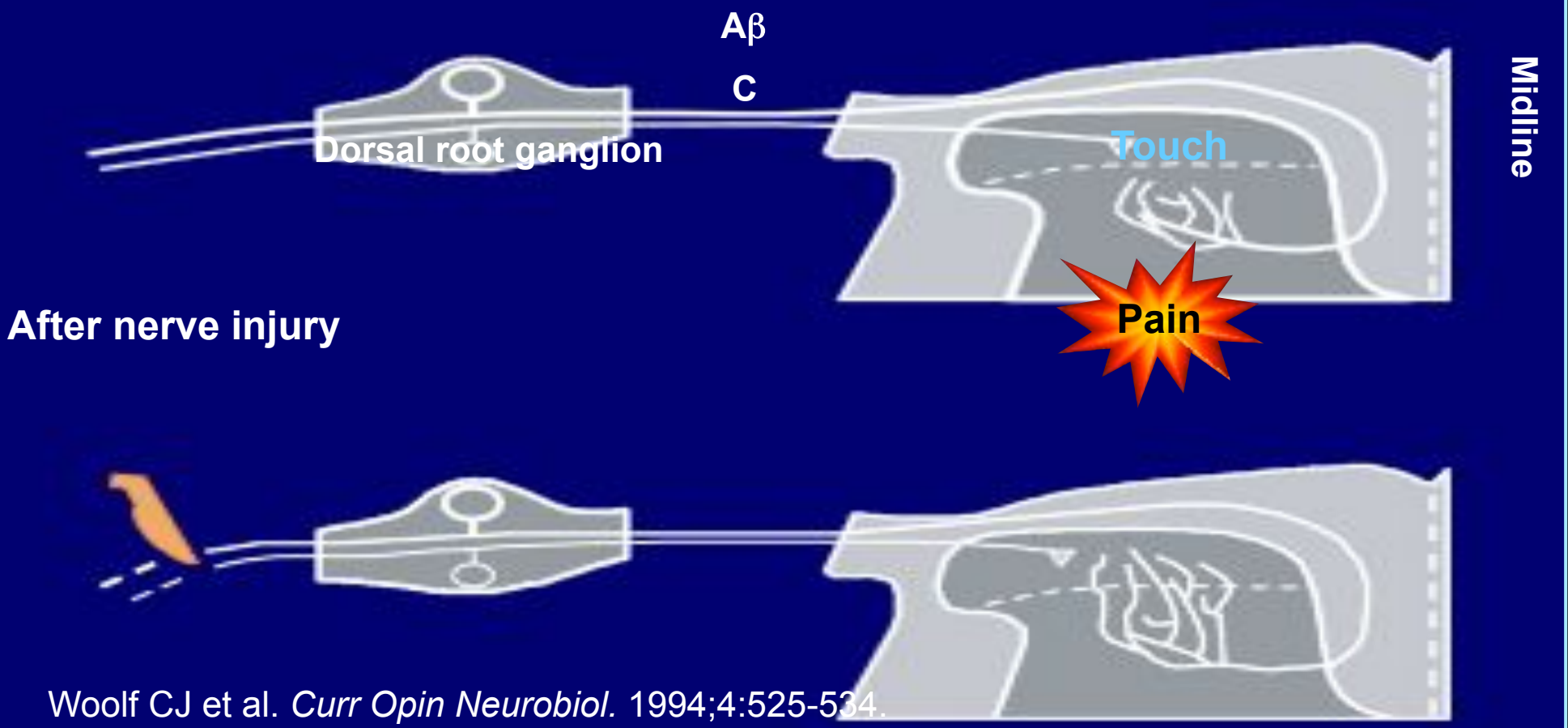
Pathogenesis of neuropathic pain

3.Central Reorganization

Normal terminations of primary afferents in the dorsal horn



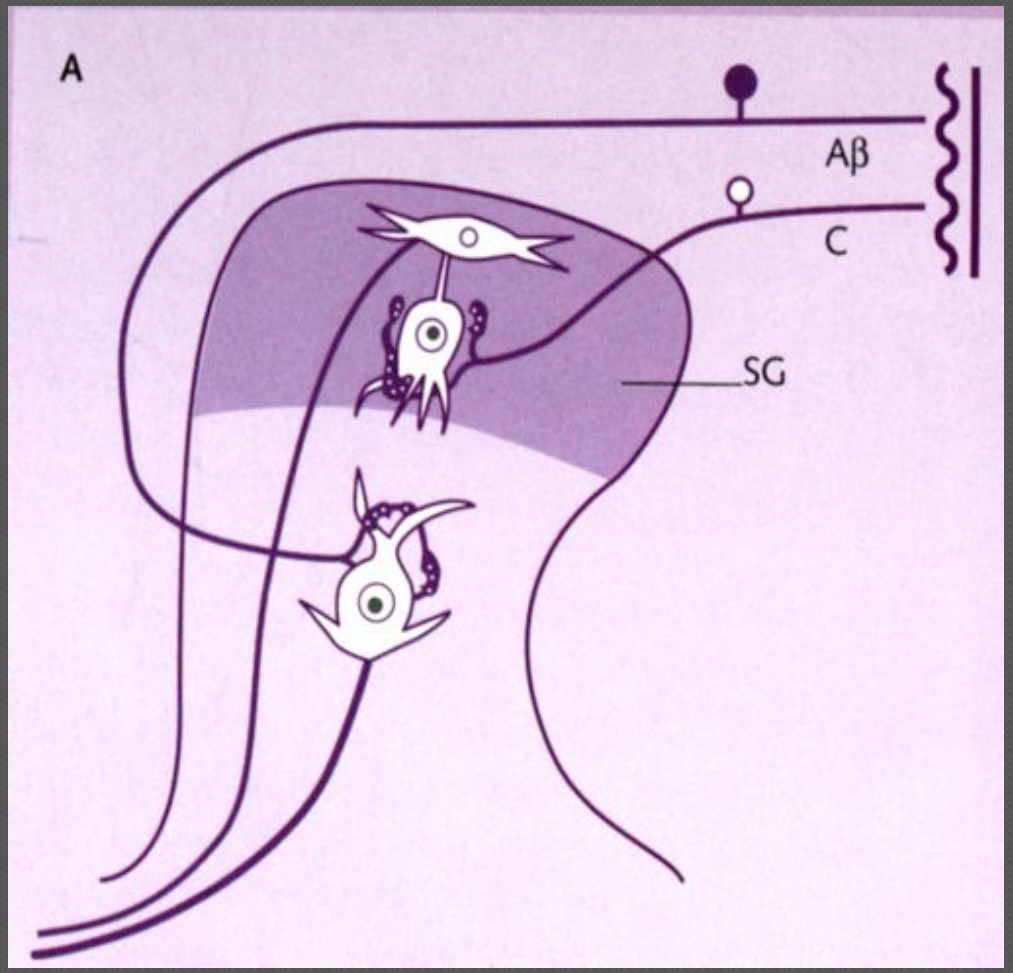
Woolf CJ et al. *Curr Opin Neurobiol.* 1994;4:525-534.

Pathogenesis of neuropathic pain

3-Central Organization

Under physiologic circumstances: central terminals of AB low threshold mechanosensetive afferent proeject to

dorsal horn laminae ventral to substania gelatinosa (SG)

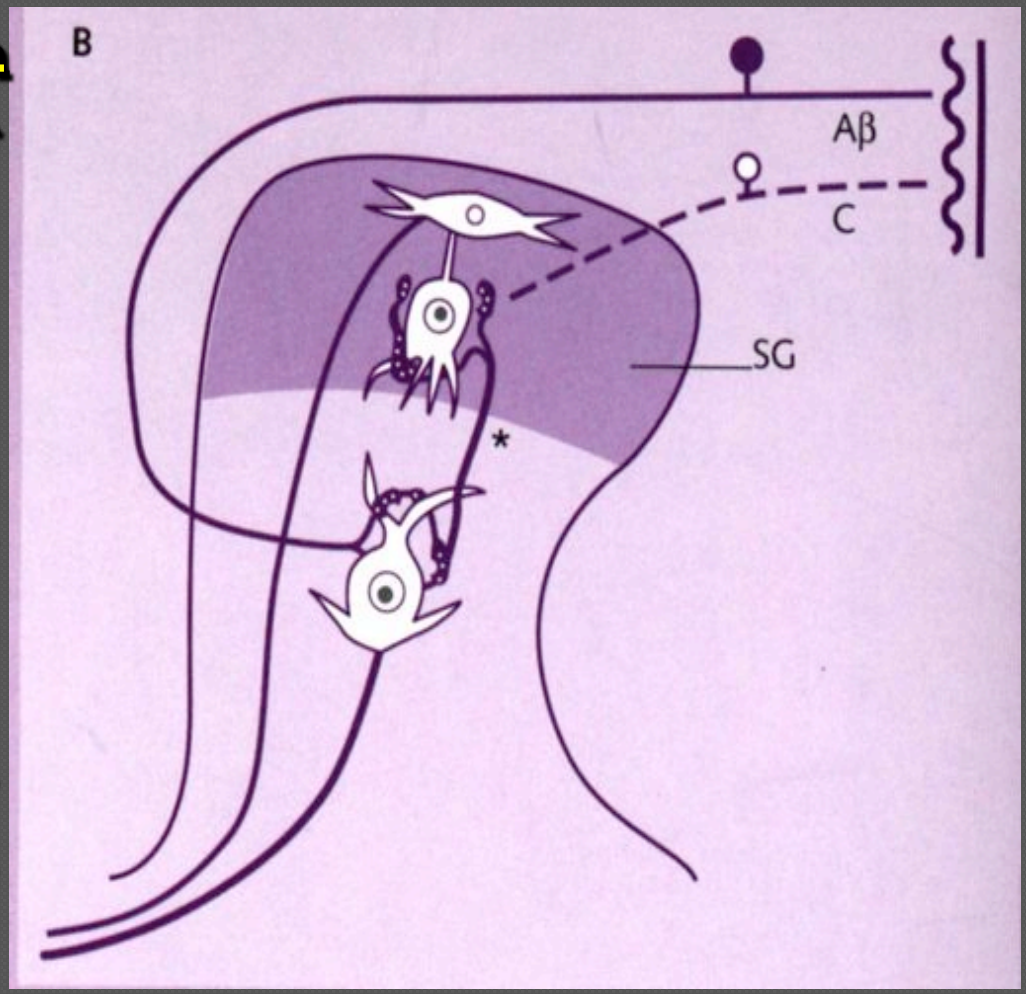


Baron, 2001

Pathogenesis of neuropathic pain

3-Central Reorganization

Partial degeneration of nociceptive C- fibers: central terminals of AB low threshold mechanosensetive afferent sprout dorsally into (SG) Functional contact with differentiated 2nd order neurone



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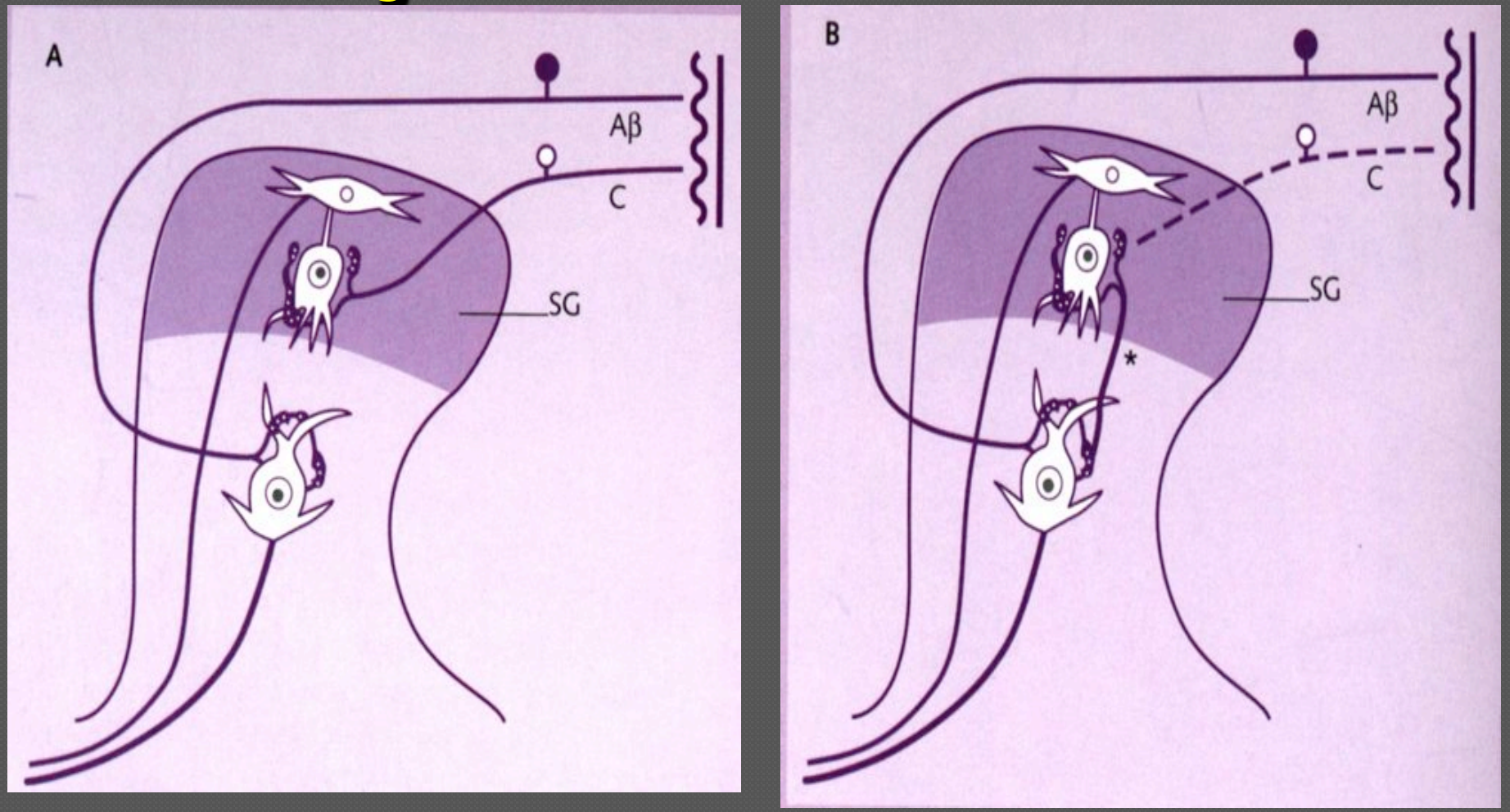
Pathogenesis of neuropathic pain

3-Central Reorganization



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Pathogenesis of neuropathic pain

4- Loss of Inhibitory Controls

- Neurons in the dorsal horn can facilitate or inhibit transmission of sensation
  - *Inhibition is mediated by GABA and glycine*
- Experimental peripheral nerve injury in animals decreases GABA and glycine levels and downregulates GABA and opioid receptors
- Inhibition is lost and excitatory mechanisms dominate, resulting in the propagation of pain impulses.

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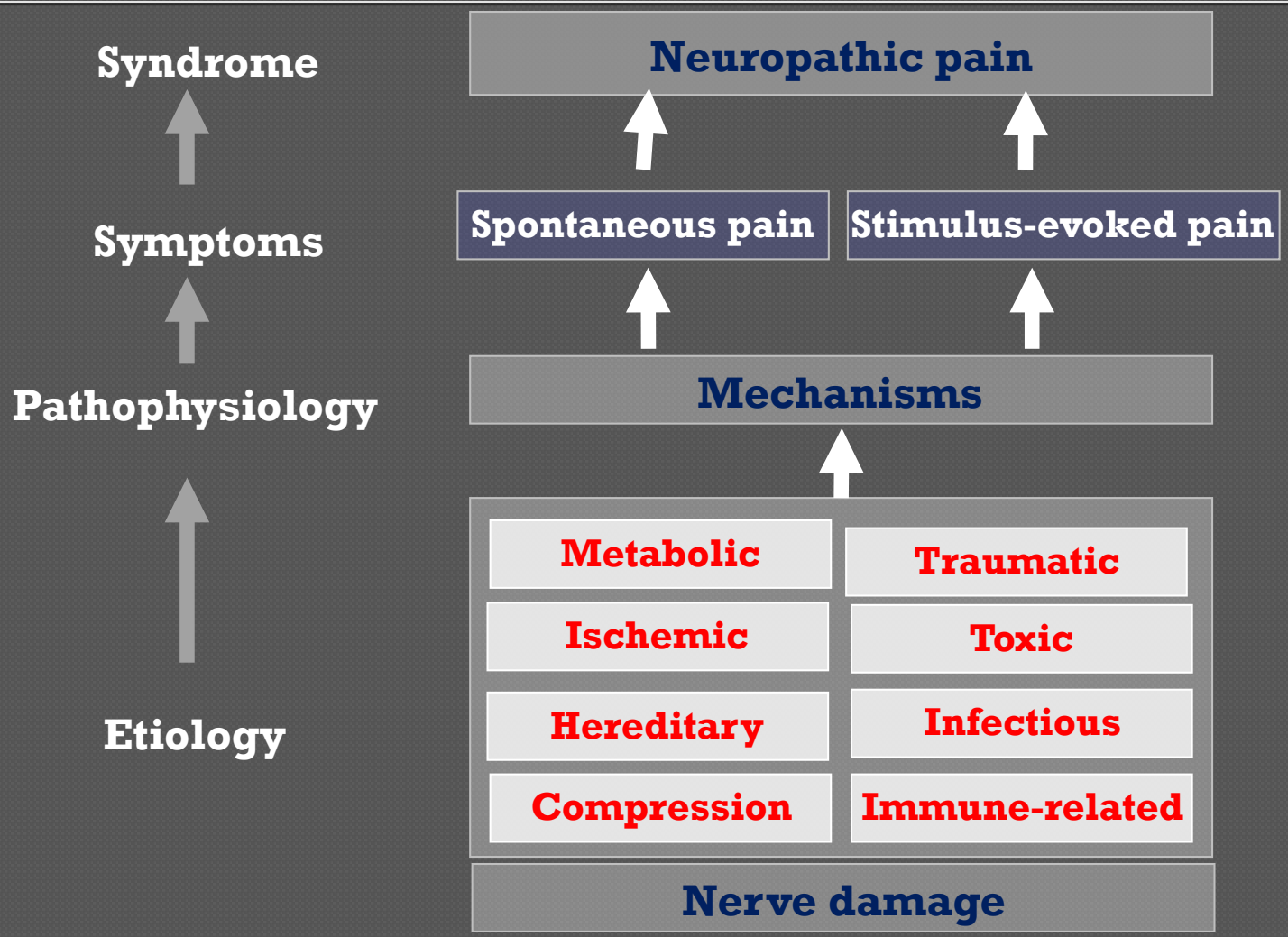
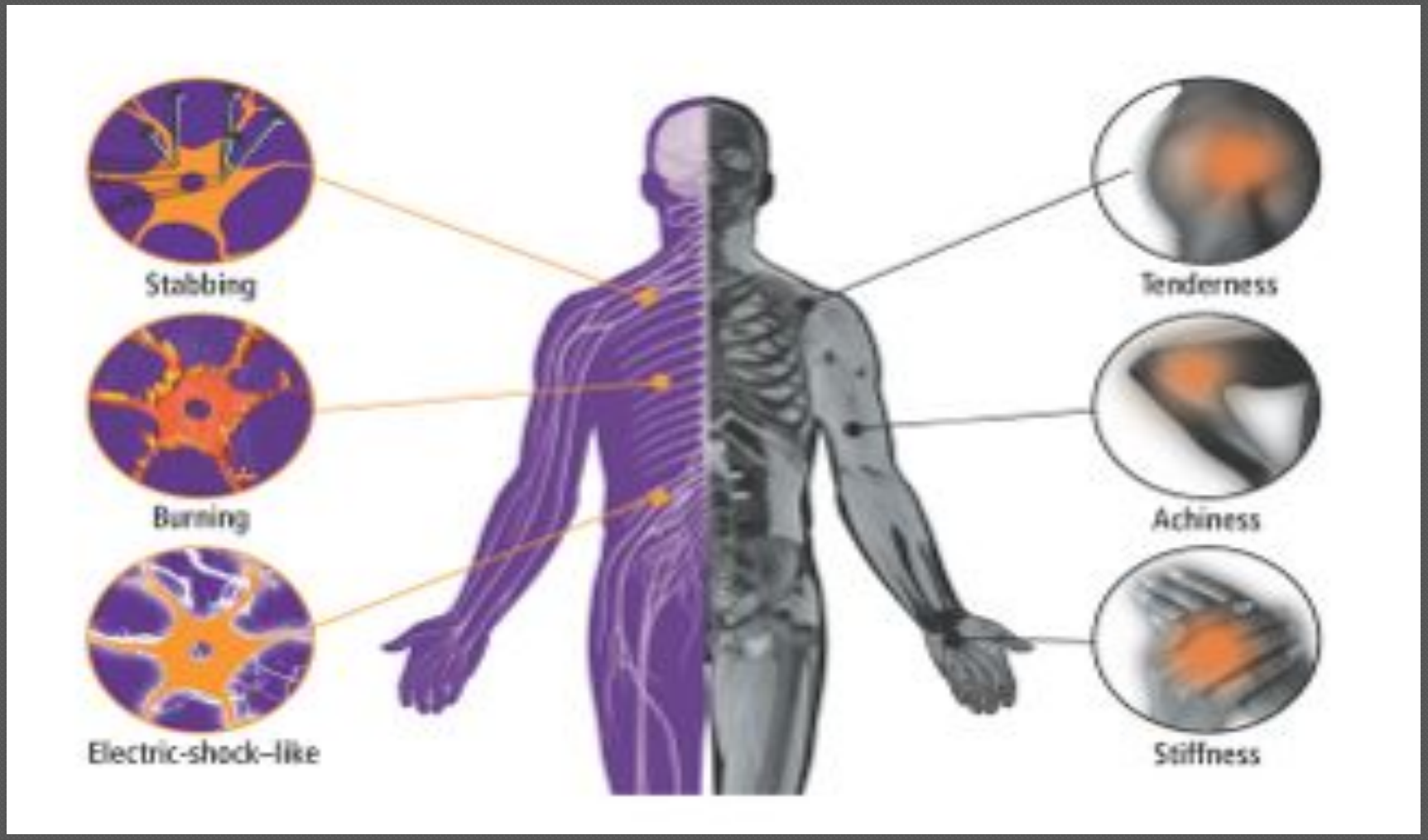
Neuropathic pain



Woolf and Mannion. Lancet 1999;353:1959-64

Neuropathic Pain : Clinical Characteristics



Neuropathic Pain : Clinical Characteristics

Positive sensory signs and symptoms

- Dysesthesias
- Paresthesias
- Spontaneous pain*
- Stimulus-evoked pain

Negative sensory signs and symptoms

- Loss / impairment of sensory quality
- Numbness and reduced sensation

Sensory changes and pain may coexist

*Also known as stimulus-independent pain

Baron R. Clin J Pain. 2000;16:S12-S20.

Definitions and glossary

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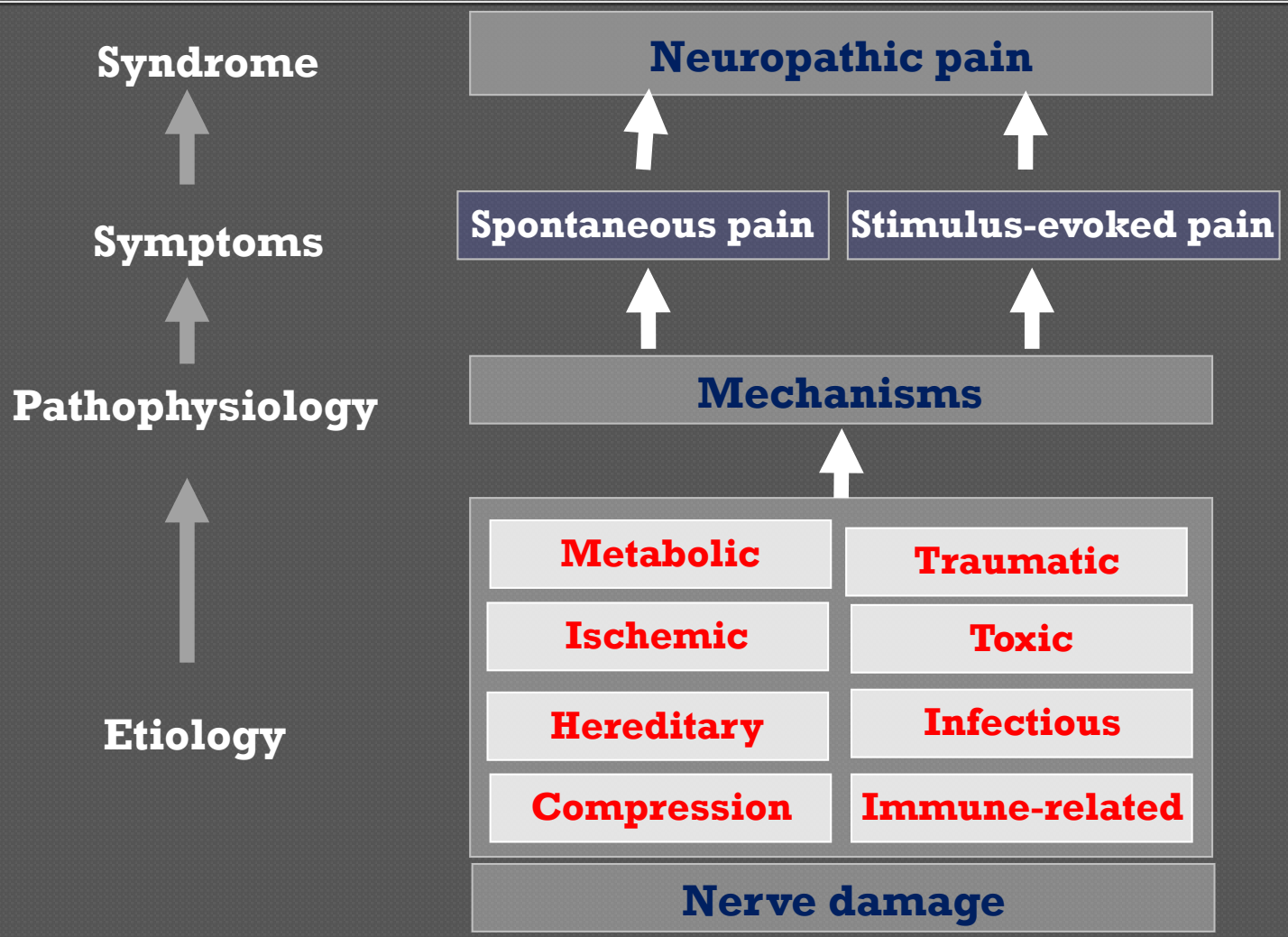
A N A L G E S I A

Absence of pain in response to stimulation which would normally b e p a i n f u l .

A N E S T H E S I A D O L O R A S A

Pain in an area or region which is anesthetic.

Neuropathic pain



Woolf and Mannion. Lancet 1999;353:1959-64

Agenda

- Definitions and glossary
- Classification of pain
- Pathways of pain
- Neuropathic pain
  - Pathogenesis of neuropathic pain
  - Causes of neuropathic pain
  - Management of neuropathic pain

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Neuropathic pain

Neuropathic pain

Pain initiated or caused by a primary lesion or dysfunction in the nervous system

Peripheral neuropathic pain

Central neuropathic pain

Merskey H et al. (Eds) In: Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 1994:209-212.

Neuropathic Pain – Causes

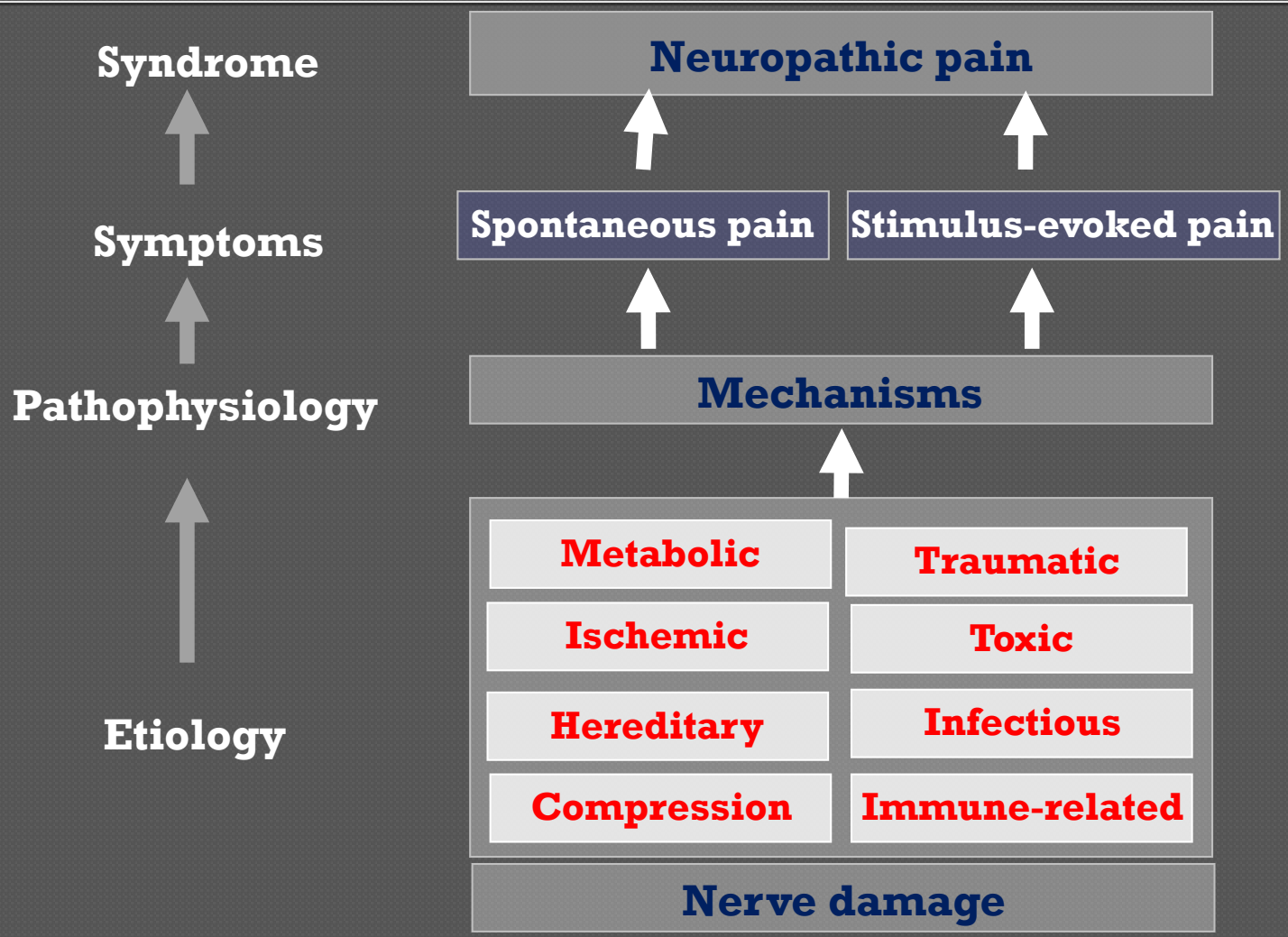
- **Peripheral causes of neuropathic pain**
  - Trauma
    - e.g. surgery, nerve entrapment, amputation
  - Metabolic disturbances
    - e.g. diabetes mellitus
  - Infections
    - e.g. herpes zoster (shingles), HIV
  - Toxins
    - e.g. chemotherapeutic agents, alcohol
  - Vascular disorders
    - e.g. polyarteritis nodosa
  - Nutritional deficiencies
    - e.g. niacin, thyamine, pyridoxine
  - Direct effects of cancer
    - e.g. metastasis, infiltrative
- **Central causes of neuropathic pain**
  - Stroke.
  - Spinal cord lesions.
  - Multiple sclerosis.
  - Tumors.

Wall PD, Melzack R (Eds). Textbook of pain. 4th Ed. 1999; Galer BS, Dworkin RH (Eds) A clinical guide to neuropathic pain. 2000: Woolf CJ et al. Lancet. 1999;353:1959-1964.

Neuropathic Pain is highly prevalent among a number of different patients

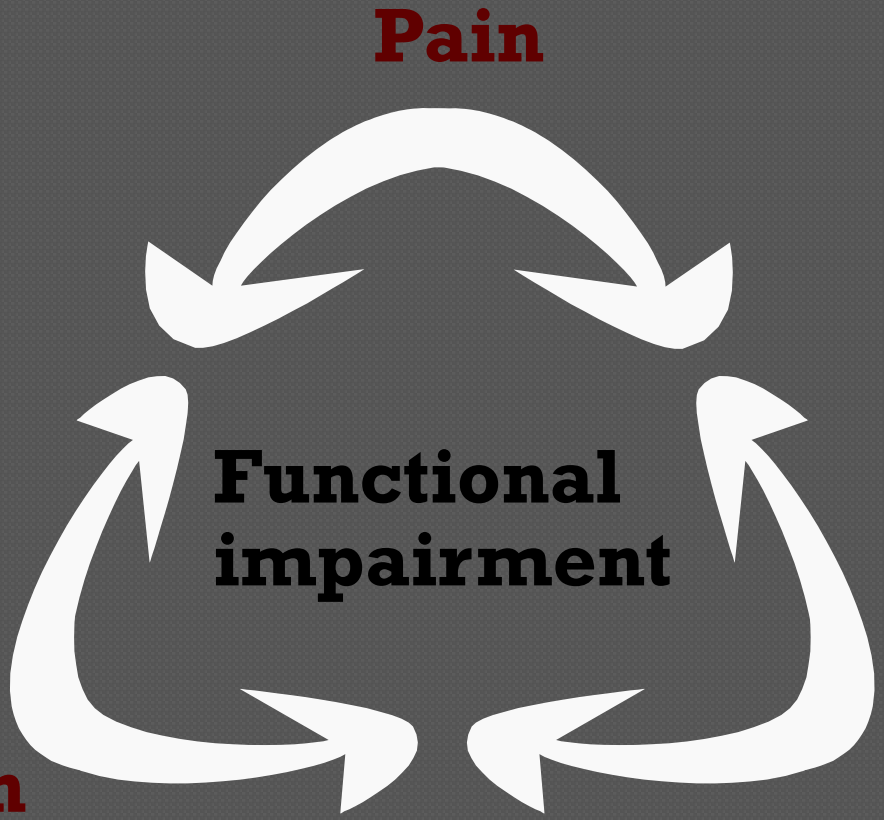
- ***Painful Diabetic Neuropathy (PDN)***
- ***Low back pain*** Neuropathic pain affects up to 55% of patients with chronic low back pain.
- ***Postherpetic Neuralgia (PHN)*** Neuropathic pain affects 25 to 50% of people over 50 who have had herpes zoster.
- ***Cancer*** Neuropathic pain affects about 33% of cancer patients.
- ***Spinal cord injury*** Neuropathic pain affects 75% of patients with spinal cord injury.
- ***Stroke*** Neuropathic pain affects 8% of post-stroke patients.
- ***Multiple sclerosis*** Neuropathic pain affects approximately 55% of patients with multiple sclerosis.

Neuropathic pain



Woolf and Mannion. Lancet 1999;353:1959-64

Neuropathic pain: syndrome



Nicholson and Verma. Pain Med. 2004;5 (suppl. 1):S9-S27

Neuropathic pain: syndrome

Quality of Life
Physical functioning
Ability to perform activities of daily living
Work
Recreation

Psychological Morbidity
Depression
Anxiety, anger
Sleep disturbances
Loss of self-esteem

Social Consequences
- Marital/family relations
- Intimacy/sexual activity
- Social isolation

Socioeconomic Consequences
- Healthcare costs
- Disability
- Lost workdays

1.U.S. News & World Report. Washington, DC: U.S. News & World Report L.P.; March 17, 1997:55-57, 60-62, 65, 67.

2.Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomized controlled trial. Pain. 2000;84:203-211.

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Neuropathic Pain – Assessment History

Identify the following:[1]

- Type, distribution and location of pain
  - Character of complaints
    - e.g. burning, shock-like, pins and needles etc.
  - Based on anatomic drawing
    - Dermatomal
    - Non-dermatomal
- Duration of complaints
- Average intensity of pain in the last day/week (0-10)
- Extent of interference with daily activity (0-10)

Areas of further exploration

- Previous medical history
- Exposure to toxins or other drug treatment
  e.g. radiation
- Use of pain medications
- Associated psychological and mood disturbance

1. Jensen and Baron. Pain. 2003;102:1-8

Diagnostic Workup : Electrophysiologic Studies

EMG-NCV

- To localise pain-generator/nerve or root lesion
- To rule out :

- Axonal Vs focal segmental demyelination
- Underlying small-fiber or mixed polyneuropathy

Biopsies

- **Nerve (eg, sural nerve) : to diagnose vasculitis, amyloidosis, sarcoidosis, etc.**
- **Skin : to evaluate density of unmyelinated fibers within dermis and epidermis**

LANSS Scale

THE LANSS PAIN SCALE

Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____ DATE_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

a) NO - My pain doesn't really feel like this..... (0)

b) YES - I get these sensations quite a lot..... (5)

2) Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO - My pain doesn't affect the colour of my skin..... (0)

b) YES - I've noticed that the pain does make my skin look different from normal .... (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO - My pain doesn't make my skin abnormally sensitive in that area..... (0)

b) YES - My skin seems abnormally sensitive to touch in that area..... (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

a) NO - My pain doesn't really feel like this ..... (0)

b) YES - I get these sensations quite a lot ..... (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

a) NO - I don't really get these sensations..... (0)

b) YES - I get these sensations quite a lot ..... (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO, normal sensation in both areas ..... (0)

b) YES, allodynia in painful area only ..... (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas ..... (0)

b) YES, altered PPT in painful area ..... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) .....

If score < 12, neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain

- completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 5 pain questions and 2 skin sensitivity tests
- Validated

DN4 Diagnostic Questionnaire

- Completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 2 pain questions (7 items)
- 2 skin sensitivity tests (3 items)
- Validated

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes		no
1 - **Burning**			
2 - **Painful cold**			
3 - **Electric Shocks**			

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes		no
4 - **Tingling**			
5 - **Pins and Needles**			
6 - **Numbness**			
7 - **Itching**			

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

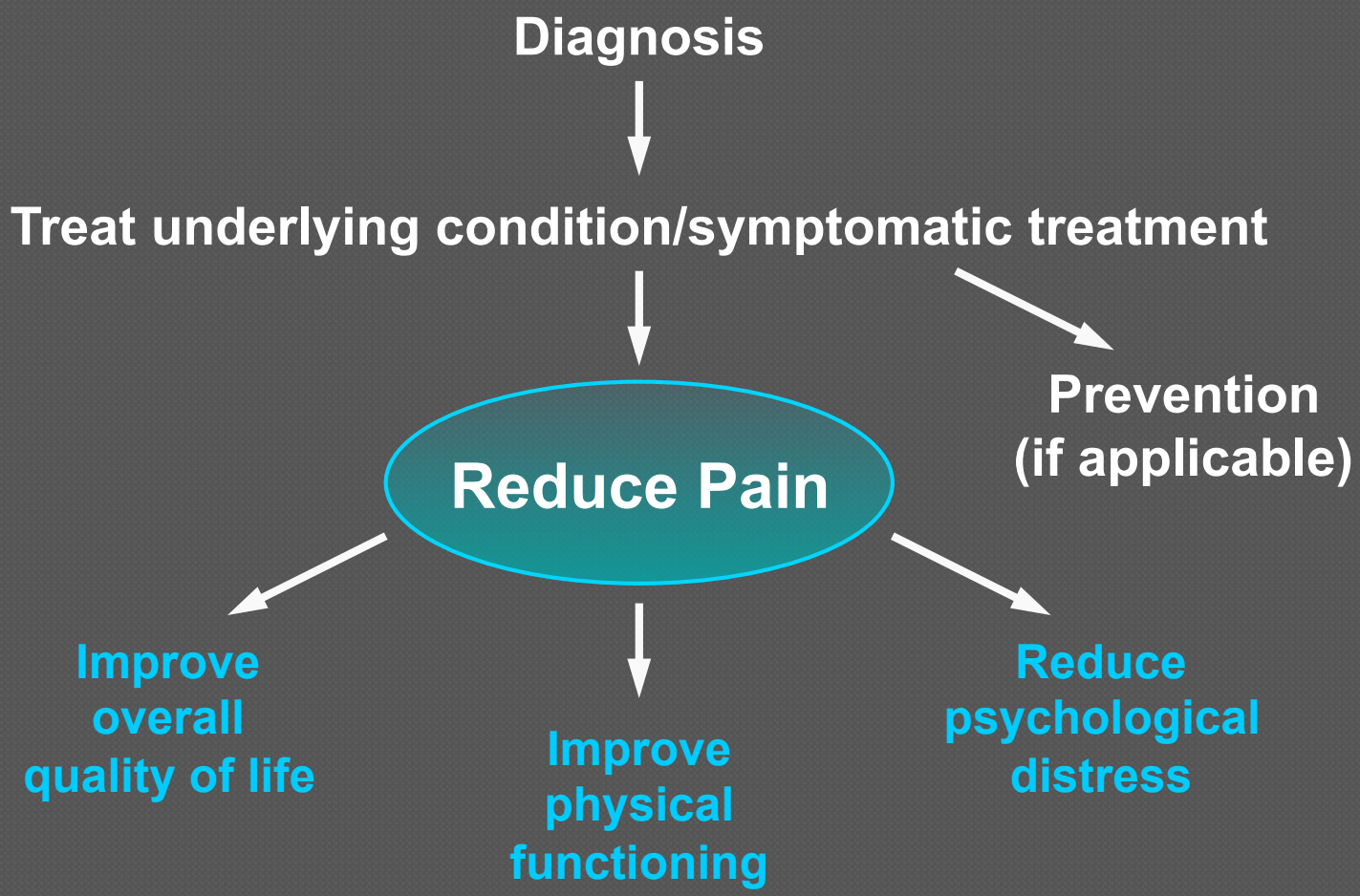
	yes		no
8 - **Hypoesthesia to touch**			
9 - **Hypoesthesia to prick**			

Question 4: In the painful area, can the pain be caused or increased by:

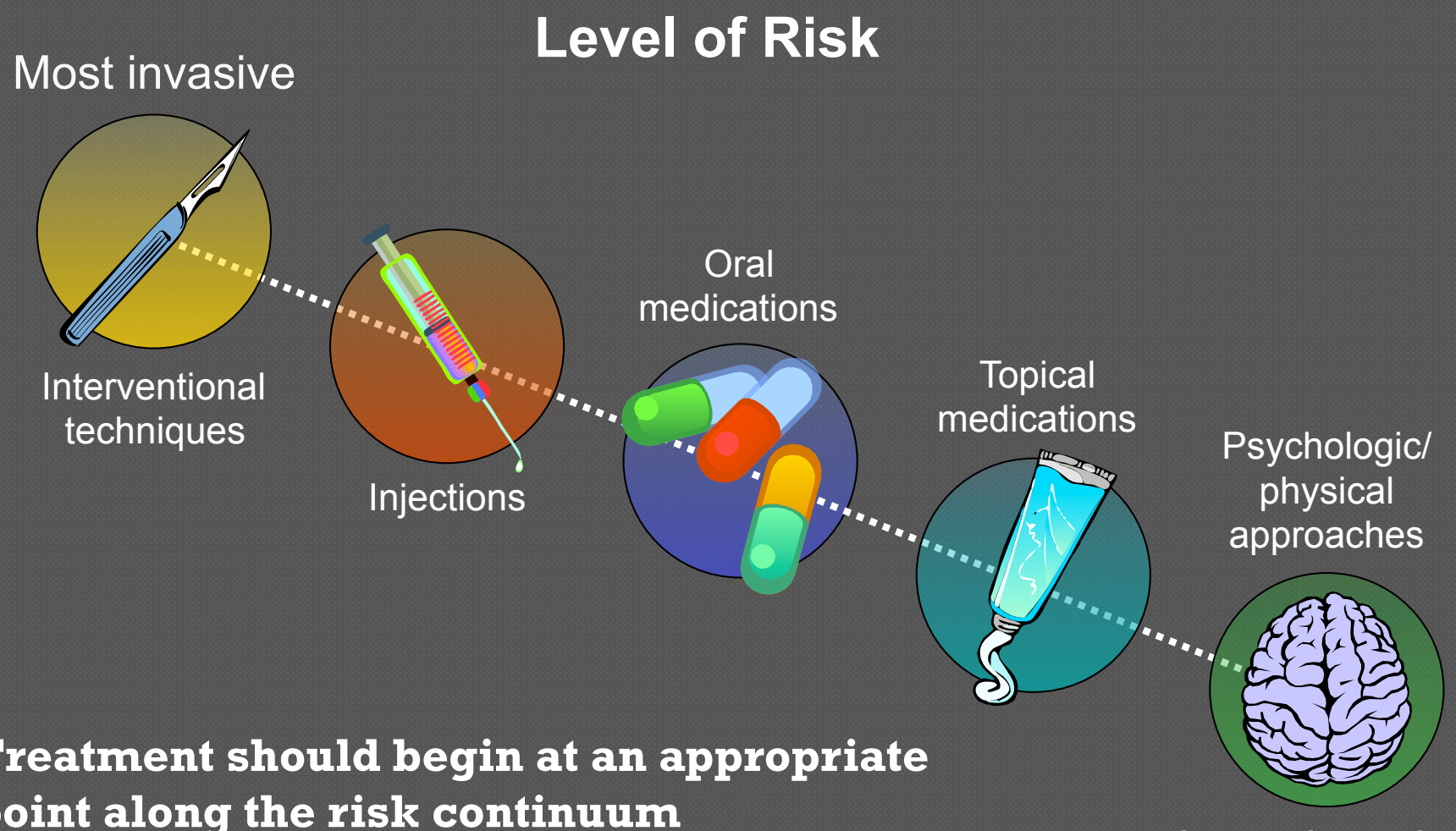
	yes		no
10 - **Brushing**			

DN4: Douleur Neuropathique en 4 questions
Bouhassira et al. Pain. 2005;114:29-36

Goals of Management



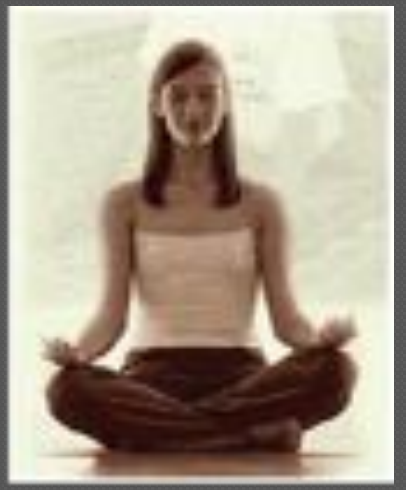
Risk Continuum of Pain Therapy



Treatment should begin at an appropriate point along the risk continuum

Non-pharmacologic Options

- Cognitive-behavioral strategies
  - Meditation
  - Biofeedback
  - Relaxation therapy
- Physical rehabilitation
- Acupuncture
- TENS



Pharmacologic Treatments

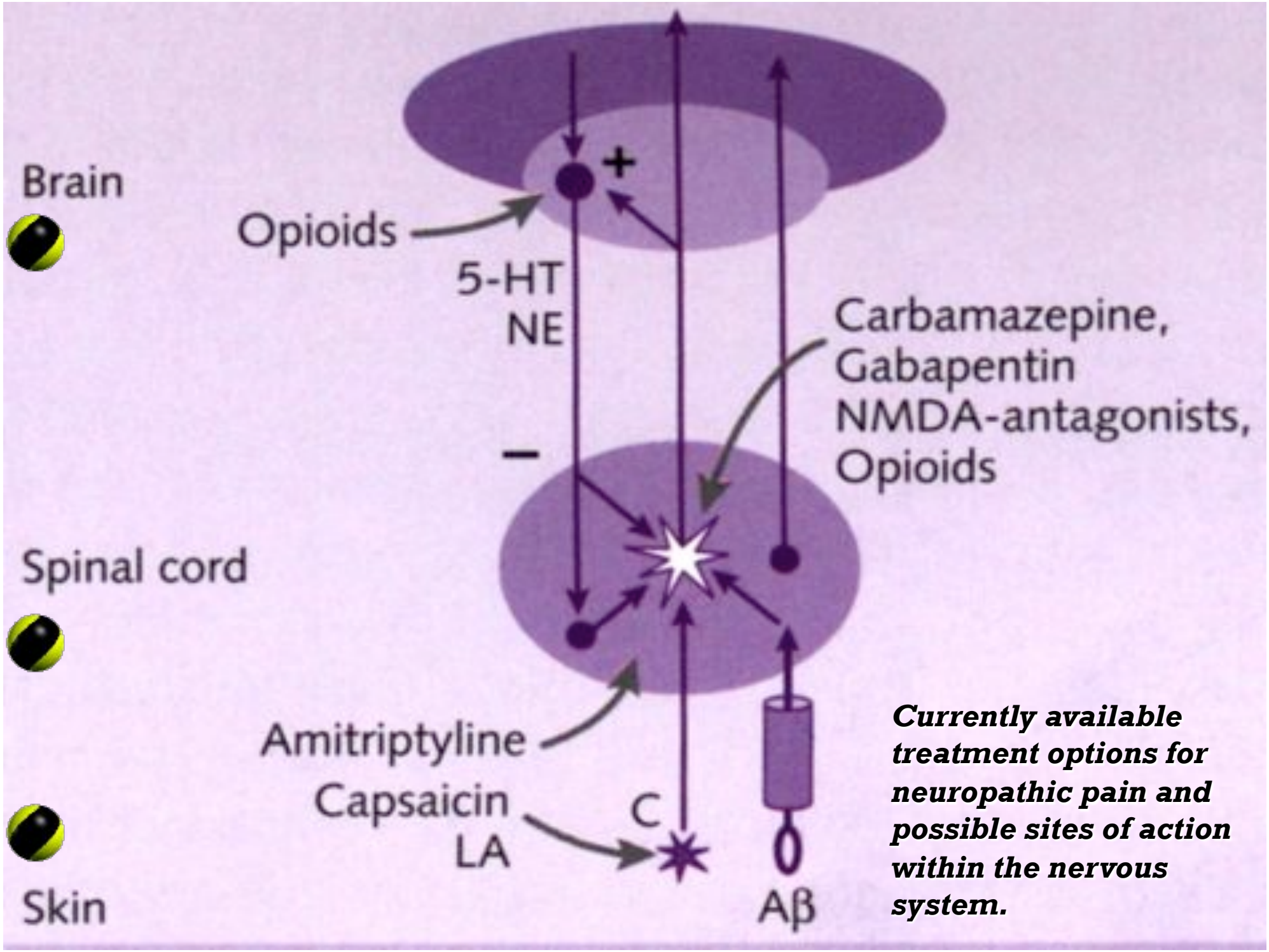
- Anticonvulsants: GBP, CBZ, OXC, LTG
- Lidocaine patch 5%
- Opioid analgesics
- Tramadol
- Tricyclic antidepressants, SSRIs, SNRIs
- Recently approved agents
  - Duloxetine
  - ***Pregabalin***

Pharmacological Treatments

Topical Agents	Lidocaine patch 5%,* capsaicin
Opioids	Oxycodone, tramadol, fentanyl, morphine, hydrocodone
Antidepressants TCAs SNRIs	 Amitriptyline, nortriptyline, desipramine, imipramine, doxepin Duloxetine,* venlafaxine
Anticonvulsants	Carbamazepine,* valproate, lamotrigine, topiramate, oxcarbazepine, gabapentin,* pregabalin*
Intrathecal	Ziconotide†, opioids

*: FDA approved in various neuropathic pain disease

+: FDA approved for use in severe chronic pain



Currently available treatment options for neuropathic pain and possible sites of action within the nervous system.

Drug treatment of pain: Principles

Mechanism	*Symptom*	*Molecular targets*	*Drugs*
Na+ channels Accumulation Redistribution Altered expression	**Spontaneous pain** **Paresthesias** **Neuroma sign**	**Na+ channels** **TTX-sensitive** **TTX-resistant**	**Carbamazepine** **Lamotrigine** **Mexilitine** **Tricyclic antidepressants**
Central sensitization	**Hyperalgesia** Tactile Cold Pin-prick	**NMDA receptors** **Neurokinin-1 receptors** **nNOS** **Protein kinase γ**	***antagonists* NMDA** **Ketamine** **Dextramethorphan** **Amantidine**

Drug treatment of pain: Principles (cont.,)

Mechanism	Symptom	Molecular targets	Drugs
Peripheral sensitization	**Hyperalgesia** Pressure Thermal **Spontaneous pain** **Neurogenic inflammation**	Vanilloid receptor-1-desensitization Neurokinin 1 Na+ channels: TTX-resistant Nerve growth factor	**Capsaicin**
Sympathetic stimulation	**Spontaneous pain**	α-receptor antagonists Nerve growth factor/trKA	**Phentolamine** **Guanethidine**

Drug treatment of pain: Principles (cont.,)

Mechanism	*Symptom*	*Molecular targets*	*Drugs*
Increased transmission **Reduced inhibition**	Spontaneous pain Hyperalgesia	Calcium channels, N-type Receptors	Conotoxin Opiates Gabapentin Clonidine Tricyclic antidepressants SNRIs

Pharmacological Treatments

First Step Consider nonpharmacologic treatments

Second Step Initiate first-line drug monotherapy
(Pregabalin or Gabapentin or TCA or SNRI)

Third Step Partial response: add
No response: Switch to alternate first-line

Forth Step Partial response: add
No response: Switch to tramadol/oxycodone

Fifth Step Ineffective/not-tolerated: pain specialty clinic

Pregabalin

The new generation of Gabapentin in the treatment of Neuropathic Pain

Pregabalin is a centrally acting neuromodulating agent

Pregabalin binding affinity for α2-δ -subunit, and potency, is six times more than that of gabapentin.

Pregabalin is a centrally acting neuromodulating agent

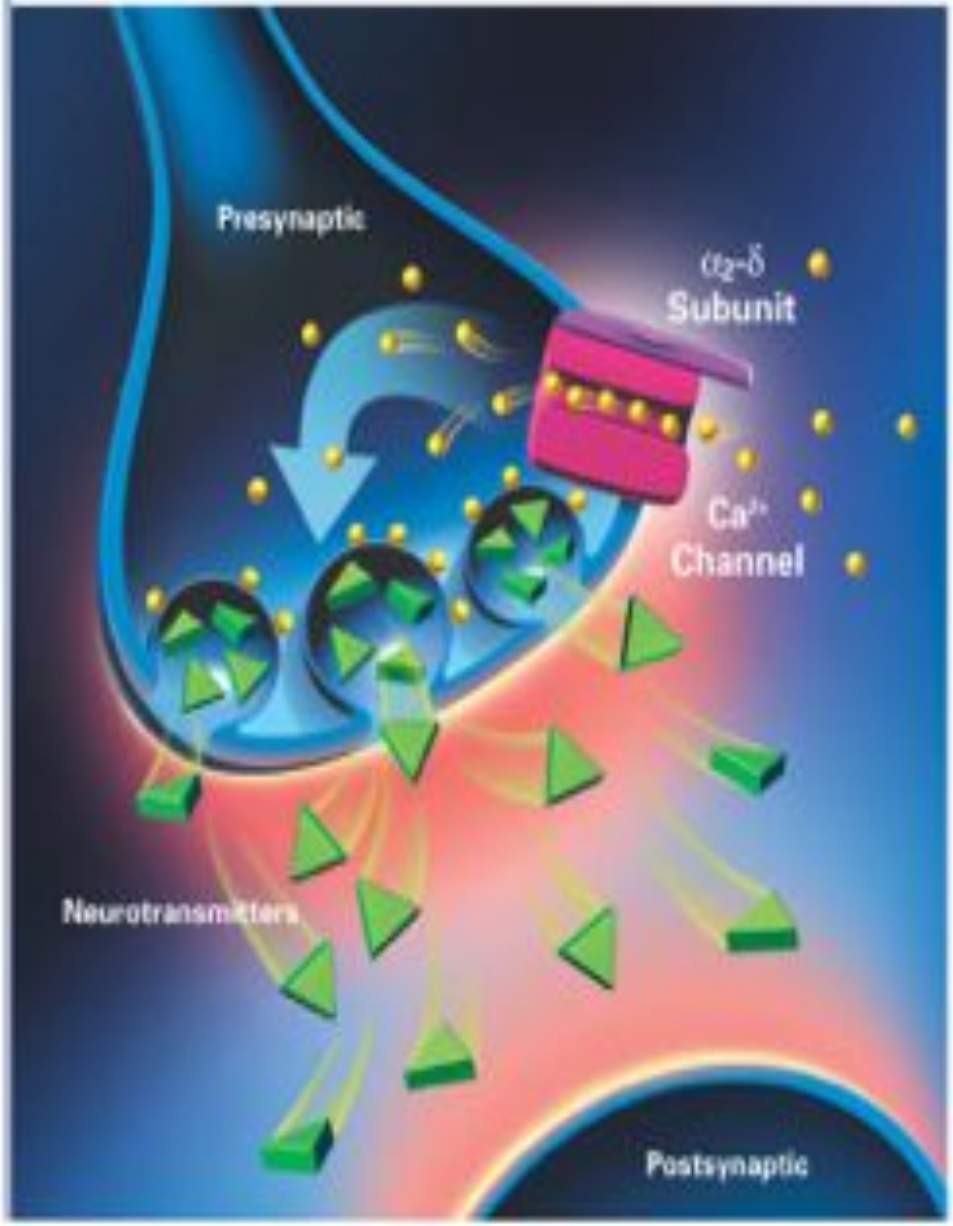
- **Pregabalin modulates the hyperexcited neuron by:**

-High affinity binding the α2-δ subunit of voltage-gated calcium channels.

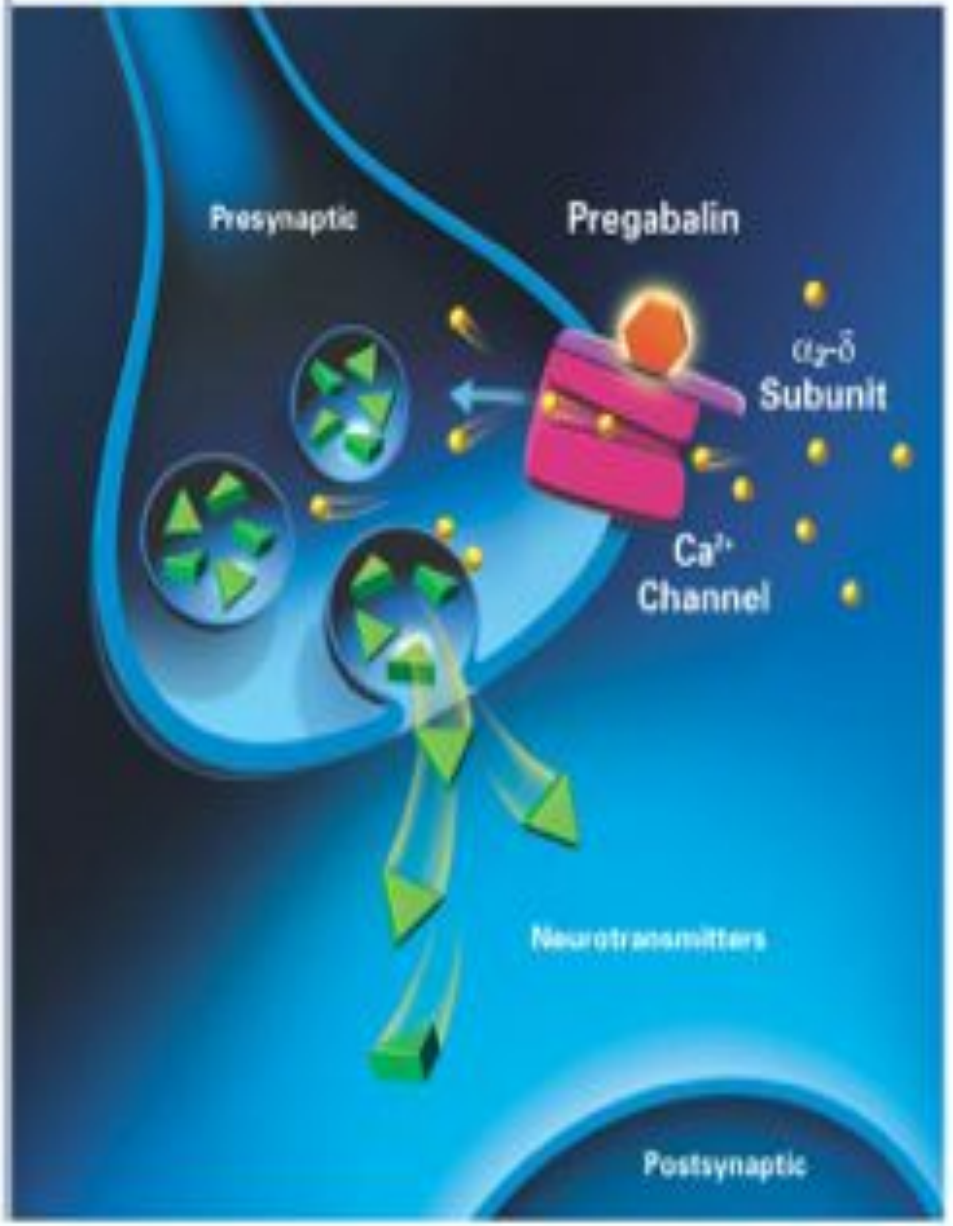
-Attenuating calcium influx into presynaptic terminals.

-Reducing excessive release of excitatory neurotransmitters.

Hyperexcited Neuron[1]



Modulation of Hyperexcited Neuron With Pregabalin[1]



Pregabalin Pharmacokinetic

- **Pregabalin has linear pharmacokinetics**

Bioavailability exceeds 90% and is independent of dose, which produces a more predictable patient response.

	Pregabalin	Gabapentin
Time to the effective dose	**1 day**	**9 days**

- Bockbrader H, Hunt T, Strand J, Posvar E, Sedman A. Pregabalin pharmacokinetics and safety in healthy volunteers: results from two phase 1 studies. Neurology 2000; 54:A421
- Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45:13–8
- Pregabalin monograph.

Pregabalin has broad FDA approved therapeutic indications compared with Gabapentin

FDA approved indications for Pregabalin and Gabapentin

Indications	Pregabalin	Gabapentin
Neuropathic pain associated with diabetic peripheral neuropathy	√	
Neuropathic pain associated with postherpetic neuralgia	√	√
Fibromyalgia	√	

- Pregabalin monograph.

Pregabalin Dosage and Administration:

- *The recommended dosage scheme*

- Dosing should begin at 50 mg three times / day increased to 100 mg three times / day, based on efficacy and tolerability.

- The recommended dosage in the treatment of Fibromyalgia 300 – 450 mg / day.

Pregabalin has no clinically significant drug interactions

- Since Pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement.

- In vitro and in vivo studies showed that Pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

Whenever You get
Pain in your life
Just think about
the full form of PAIN !

(Positive Attitude In
Negative Situation)

THANK YOU