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ACUTE PAIN SENSATIONS AND NOCICEPTOR ACTIVITY – OLD ANSWERES, NEW DILEMMAS

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Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

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U narodu je posebna pažnja poklanjana psihološkoj pripremi na bol, koja je eksplicitno izražena u pesmi *Stari Vujadin*:

"O sinovi, moji sokolovi,
Onđe će nas biti i mučiti,
Prebijati i noge i ruke,
I vaditi naše oči čarne.
O sinovi moji sokolovi,
Ne budite srca udovička,
No budite srca junačkoga."

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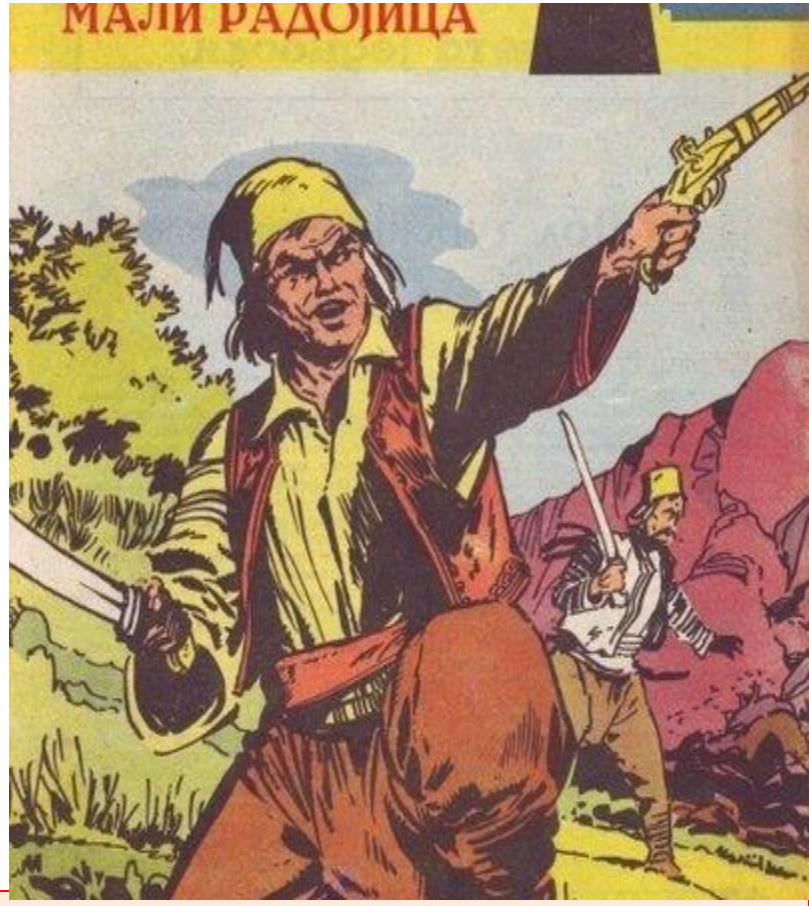
Gradacija trpljenja bola najbolje je opisana u pesmi *Mali Radojica*:

"Lože njemu vatru na prsima.
Al' je Rade srca junačkoga,
Ni' se miče, ni' pomiče Rade.
Uvatiše zmiju prisojkinju,
Pa turaju Radu u njedarca,
Al' je Rade srca junačkoga,
Ni' se miče, ni' se od nje plaši.
I uzeše dvadeset klinaca,
Udaraju pod noktove Radu,
I tu junak tvrda srca bio,
Ni' se miče, ni' dušicom diše."



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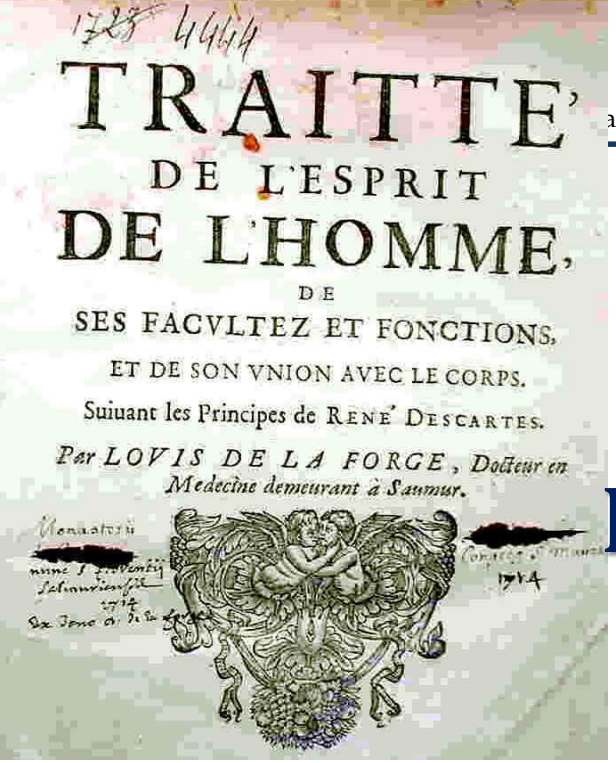
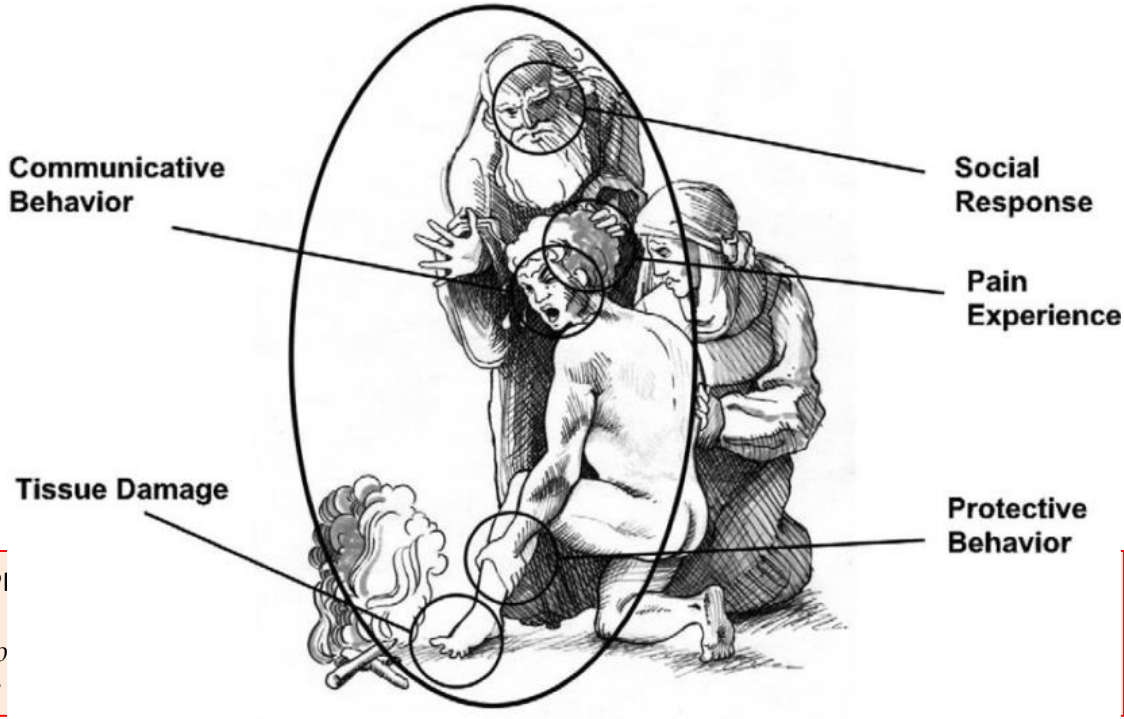

TRAITTE'
DE L'ESPRIT
DE L'HOMME,
DE
SES FACVLTEZ ET FONCTIONS,
ET DE SON VNION AVEC LE CORPS.
Suiuant les Principes de RENE' DESCARTES.
Par LOVIS DE LA FORGE, Docteur en Medecine demeurant à Saumur.

Louis de la Forge (1632-1666)



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“La Fontaine de Bakhtchisaraï” **Karl Pavlovitch Brullov (1799–1852)**

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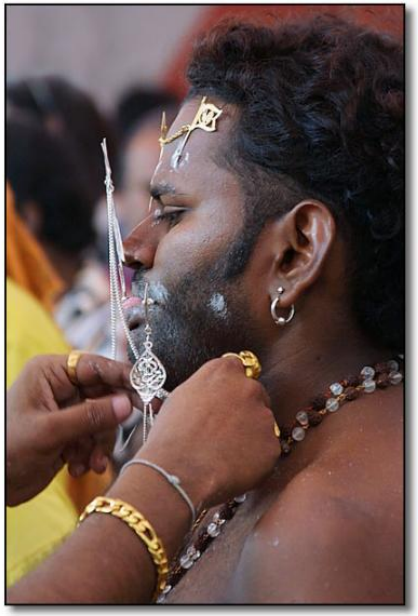
THAIPUSAN FESTIVAL



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JUDGING BY FEAR

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CHRONIC PAIN IN EUROPE

- Affects 20% of European citizens
- Disrupts the lives of millions of European citizens and their families
- More common in women
- More common with increasing age
- Negative impact on quality of life, physical and psychological well-being
- Major economic cost:
  - Indirect (inability to work)
  - Direct (treatment-related costs)
- Grossly under-recognised and under-treated
- Major public health concern
- Access to comprehensive pain assessment and management is a basic human right
- Coordinated and collaborative approach is urgently required, particularly in patients whose pain does not respond to standard therapeutic interventions

POSITION PAPER

European Pain Federation position paper on appropriate opioid use in chronic pain management

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Common Causes of Pain

- Low back pain and arthritis account for half of all musculoskeletal disease diagnoses[1]

- Low back pain is most commonly reported type of pain[2]
  - Leading cause of disability among Americans <45 years of age[2,3]
  - >26 million adults experience frequent back pain2
  - ~15% of Americans experience back pain lasting >2 weeks[1]

- Arthritis and chronic joint problems affect ~70 million individuals[1]
  - ~18 million affected by osteoarthritis
  - ~2 million suffer from rheumatoid arthritis

1. Emons MF. *Manag Care.* 2003;12(8 suppl):2-7.
2. Pain facts and figures. American Pain Foundation Web site. http://www.painfoundation.org/print.asp?file=Newsroom/PainFacts.htm. Accessed September 12, 2007.
3. Pai S et al. Orthop Clin North Am. 2004;35:1-5

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Congenital insensitivity to pain

- Some people are born without a sense of pain.
- Some people may feel pain but lack the affective response accompanying pain.
- This may lead to multiple traumas and injuries and even to early death.

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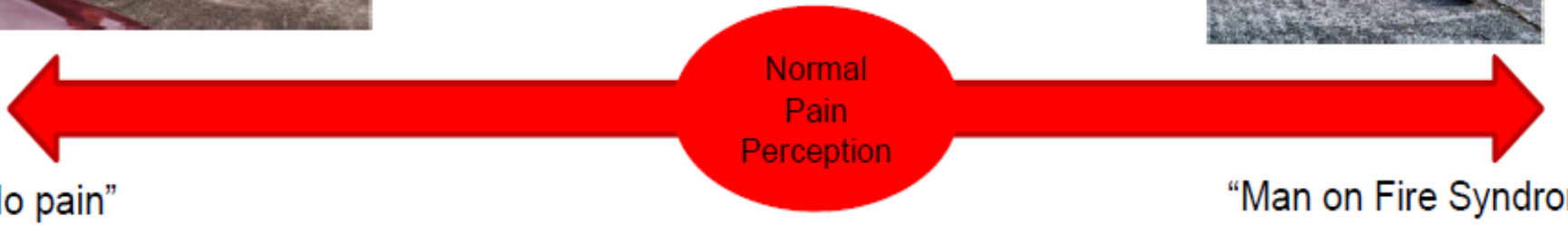
Genetic polymorphisms result in altered nociception

Genetics may explain 70% of variability in experiencing pain

SCN9A Gene: Nav1.7



"No pain"

"Man on Fire Syndrome"

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Qin W, Liu B, Deng A, Liu Y, Zhang X, Zhang L. J Pain Res. 2018;20;11:1355-1357
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What is pain?

Definitions

Pain is the psychical adjunct to an imperative protective reflex.

- Sherrington CS Cutaneous sensations. In Schafer EA (ed): Textbook of Physiology. London, Pentland, 1900
- Sherrington CS The Integrative Action of the Nervous System. New Haven, Yale University Press, 1906

Sir Charles Scott Sherrington
1857-1952

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Pitcher MH, Von Korff M, Bushnell MC, Porter L. J Pain. 2018;(18):30358-4.

Pain Is Like An Alarm Clock
It Lets Us Know, When There Is Something Wrong

What is Pain?

- Aversive sensation
- Intensity ranges from unpleasant to horrible
- Various classes of pain
  - pricking, stabbing, pinching (*mechanical*)
  - burning, freezing (*thermal*)
  - aching, stinging, soreness (*chemical*)
  - visceral (*mechanical, chemical*)
- Emotional component (pain tolerance)
- Protective function
  - Warn of injury that should be avoided or treated

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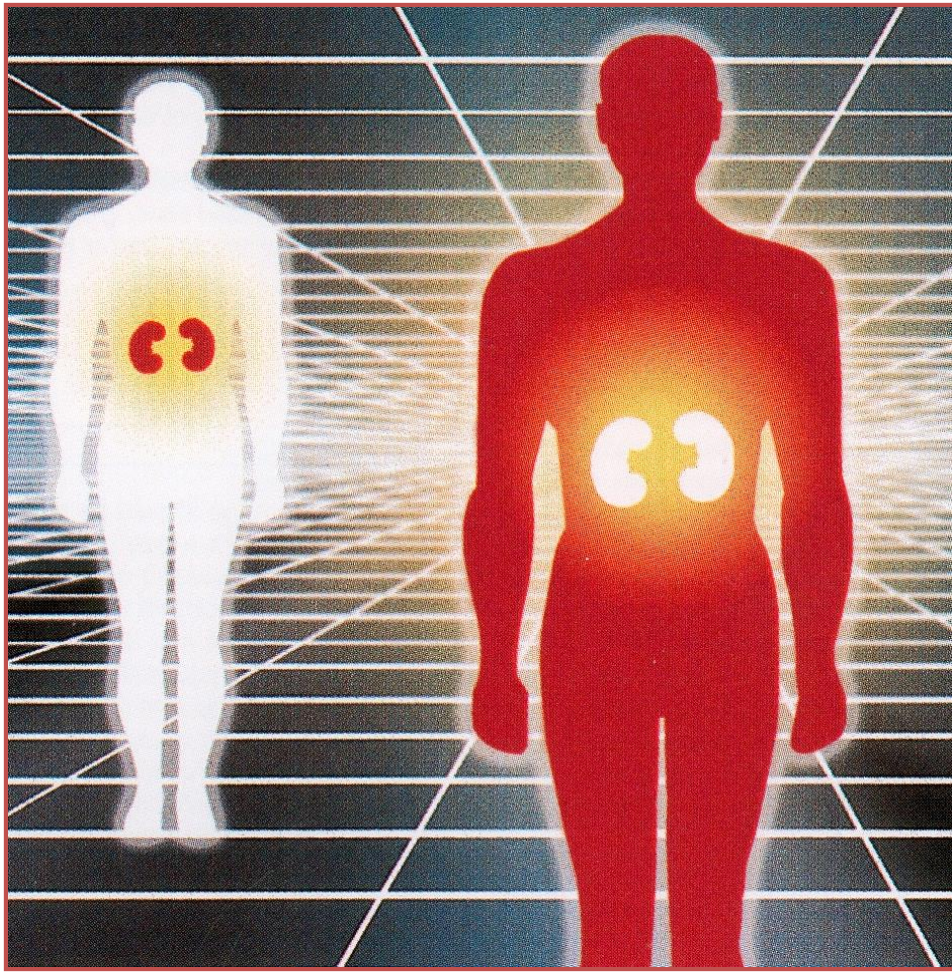
THE BIOMEDICAL MODEL OF PAIN

- **Pain as a sensory event reflecting underlying disease or tissue damage.**



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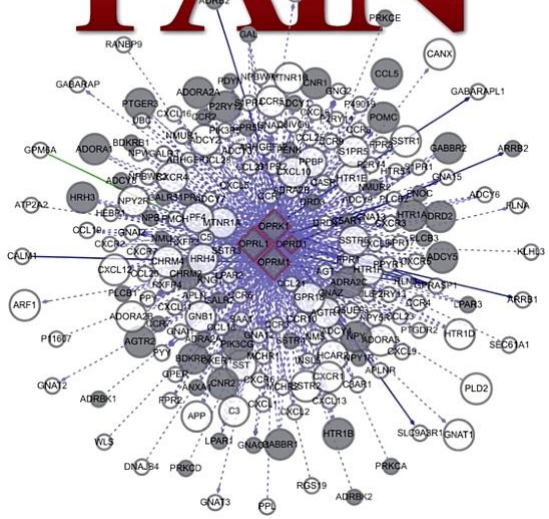
What is pain?

Definitions

An unpleasant sensory and emotional experience associated with actual or potential tissue damage.

PAIN®



IASP
International Association for the Study of Pain

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MULTI DIMENSIONAL CONCEPT OF PAIN

ence. (IASP Taxonomy 2012) The individual experience and manifestation of pain is influenced by a complex series of interactions involving sensory, pathophysiological, affective, socio-cultural, behavioural and cognitive elements (Fig. 1; Dalal and Bruera 2012).

PKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Brien TO, EJP 2017; 21: 3-19.

ACUTE PAIN TURNS TO CHRONIC

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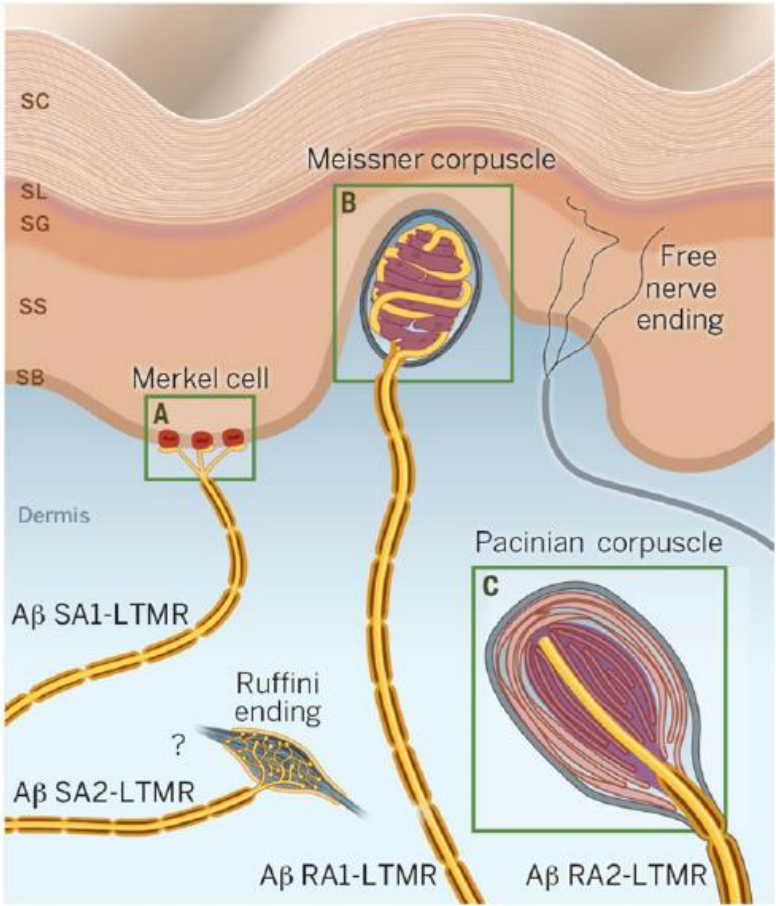
STIMULUS AND RESPONSE

Stimulus An external environmental trigger

Response An internal reaction to the stimulus

Huges D., Bioinspiration & Biomimetics 2015,



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Nociceptors

- peripheral receptors sensitive to painful mechanical and chemical stimuli, extreme heat or cold
- free nerve endings with small receptive fields
- specific for pain
- do not adapt to repeated stimulation as do low-threshold mechano/thermoreceptors
- are capable of differentiating between innocuous and noxious stimuli
- can be sensitized by tissue injury

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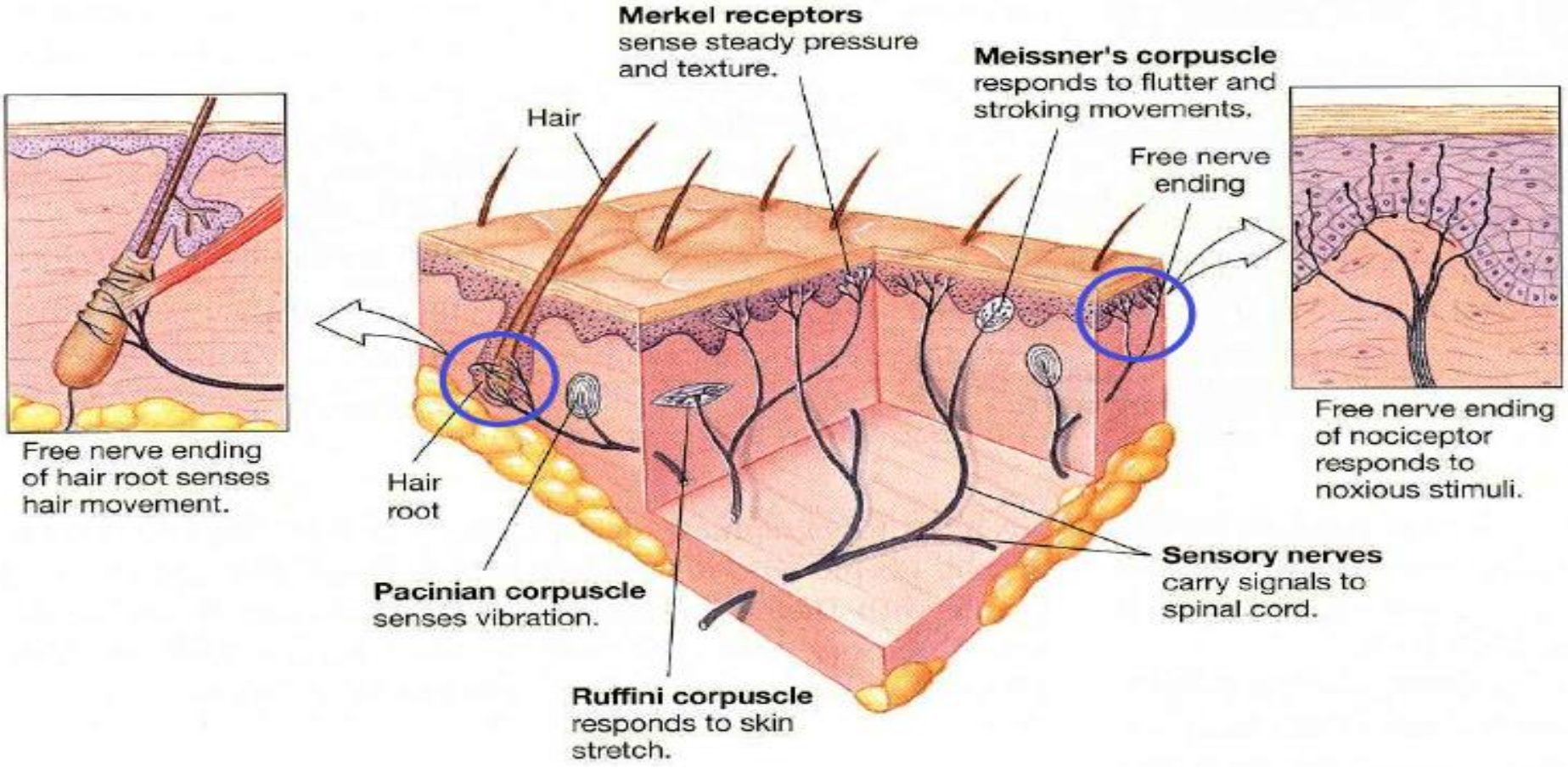
PAIN RECEPTORS – FREE NERVE ENDINGS



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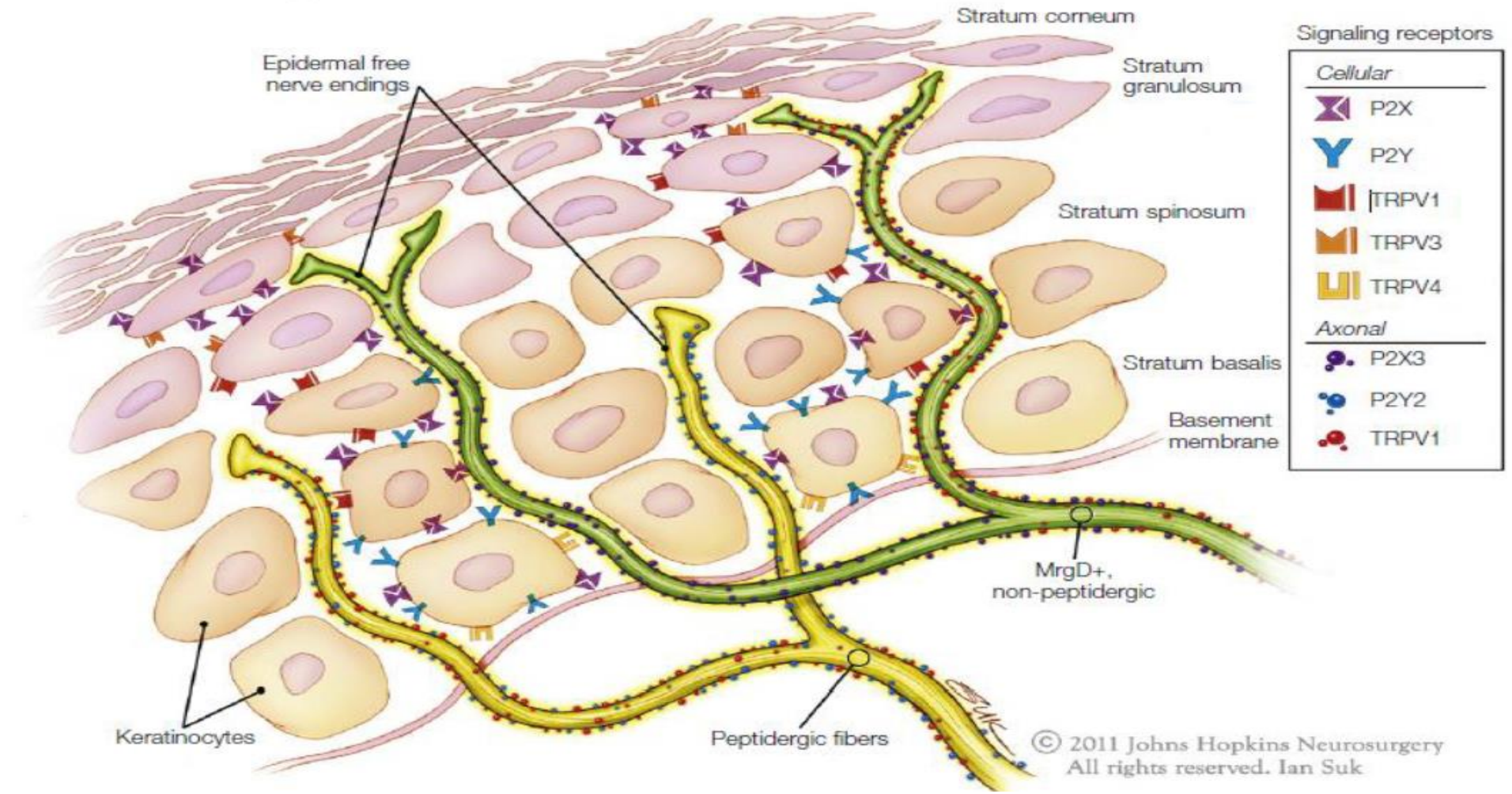
Nociceptors



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Classification of Nerve Fibres

Motor nerve fibres

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity	Associated muscle fibers
α	Aα	13-20 μm	Yes	80–120 m/s	Extrafusal muscle fibers
γ	Aγ	5-8 μm	Yes	4–24 m/s [2][3]	Intrafusal muscle fibers

Sensor nerve fibres

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity	Associated sensory receptors
Ia	Aα	13-20 μm	Yes	80–120 m/s[4]	Responsible for proprioception
Ib	Aα	13-20 μm	Yes	80–120 m/s	Golgi tendon organ
II	Aβ	6-12 μm	Yes	33–75 m/s	Secondary receptors of muscle spindle All cutaneous mechanoreceptors
III	Aδ	1-5 μm	Thin	3–30 m/s	Free nerve endings of touch and pressure Nociceptors of neospinothalamic tract Cold thermoreceptors
IV	C	0.2-1.5 μm	No	0.5-2.0 m/s	Nociceptors of paleospinothalamic tract Warmth receptors

Type	Erlanger-Gasser Classification	Diameter	Myelin	Conduction velocity
preganglionic fibers	B	1-5 μm	Yes	3–15 m/s
postganglionic fibers	C	0.2-1.5 μm	No	0.5-2.0 m/s

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Receptors

- Neurotrophin receptors
  - tyrosine kinase (trKA) receptor
  - transient receptor potential (vanilloid) receptors
    - TRPV I receptors
    - TRPV3 receptors
- Tachykinin receptors
- Purinergic receptors
- Adenosine triphosphate receptors
- Opioid receptors
- Cannabinoid receptors

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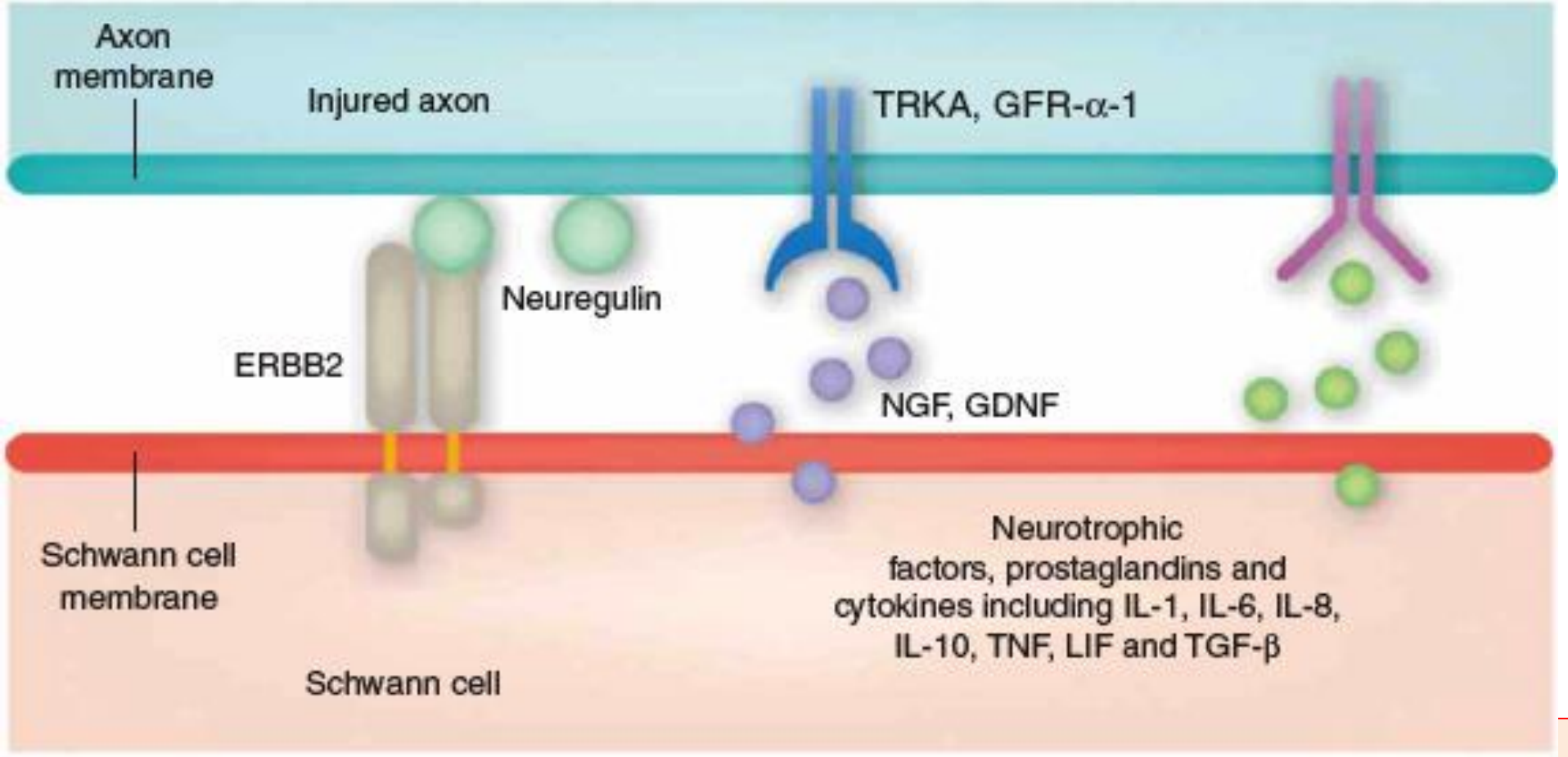
INJURED SCHWANN CELLS SENSITIZE NOCICEPTORS



Khodorova A, Zhang Y, Nicol G, Strichartz G. Physiol Res. 2018; 67 (Supplementum 1): S215-S225.

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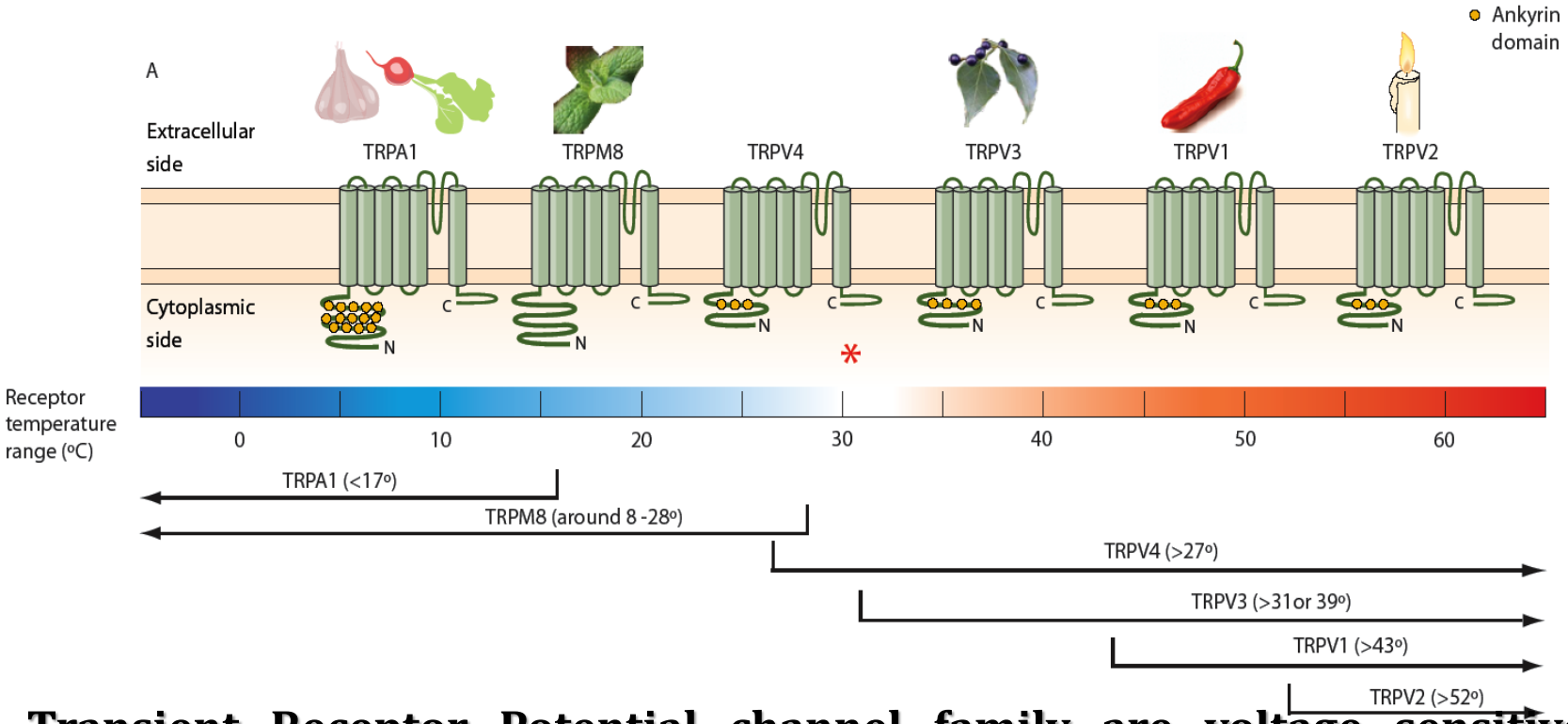
THERMO - TRANSIENT RECEPTOR POTENTIAL RECEPTORS RESPOND TO SPECIFIC TEMPERATURE RANGES



Six Transient Receptor Potential channel family are voltage sensitive and reciprocally modulated by temperature, Three family of six Transient Receptor Potential channel are found on cells and free nervous afferent endings in the skin. TrpV1, also known as the capsaicin receptor and the vanilloid receptor

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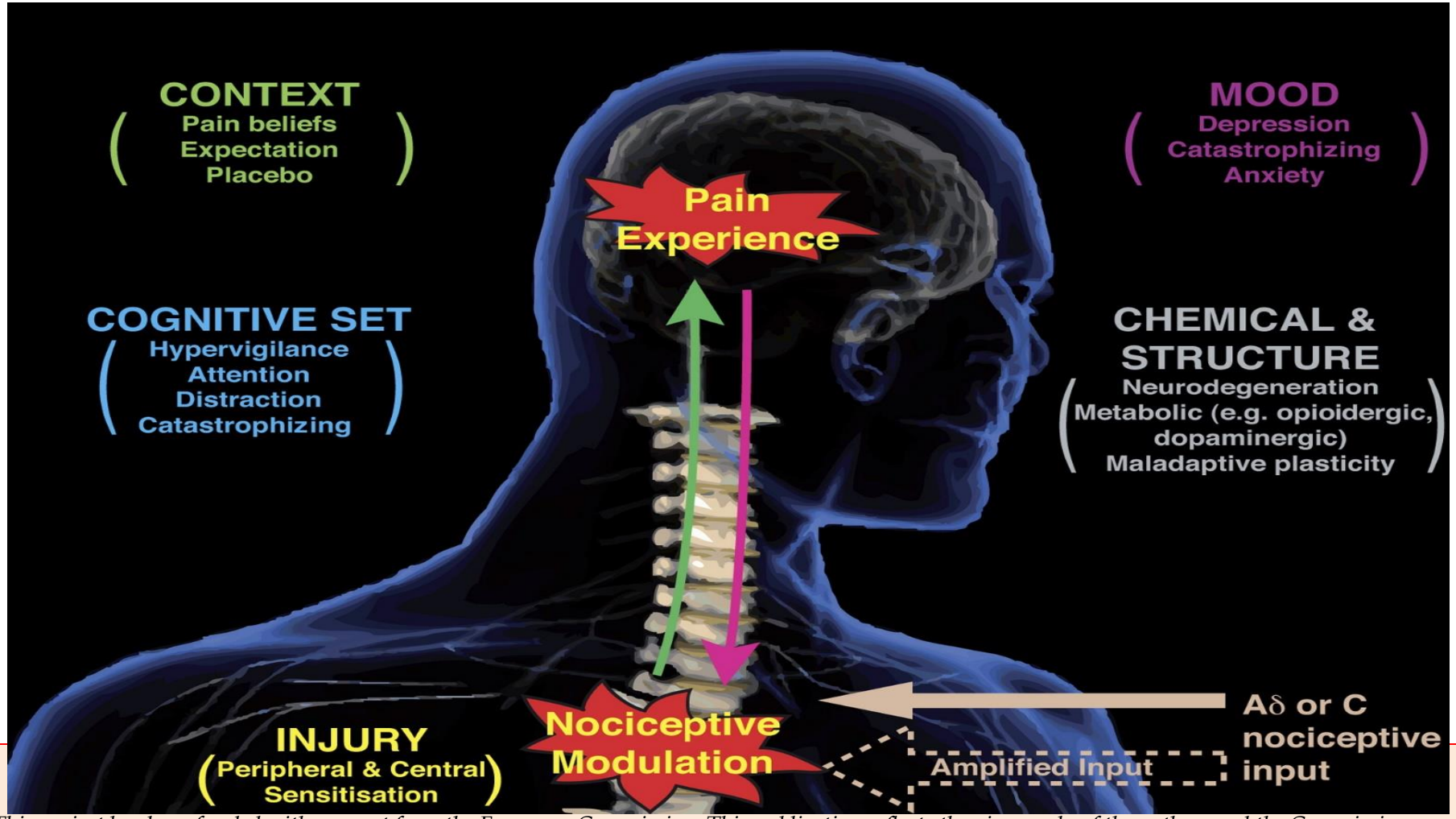
NOCICEPTIONS LEADS TO PAIN. HOW MUCH PAIN IS EXPERIENCED DEPENDS ON:



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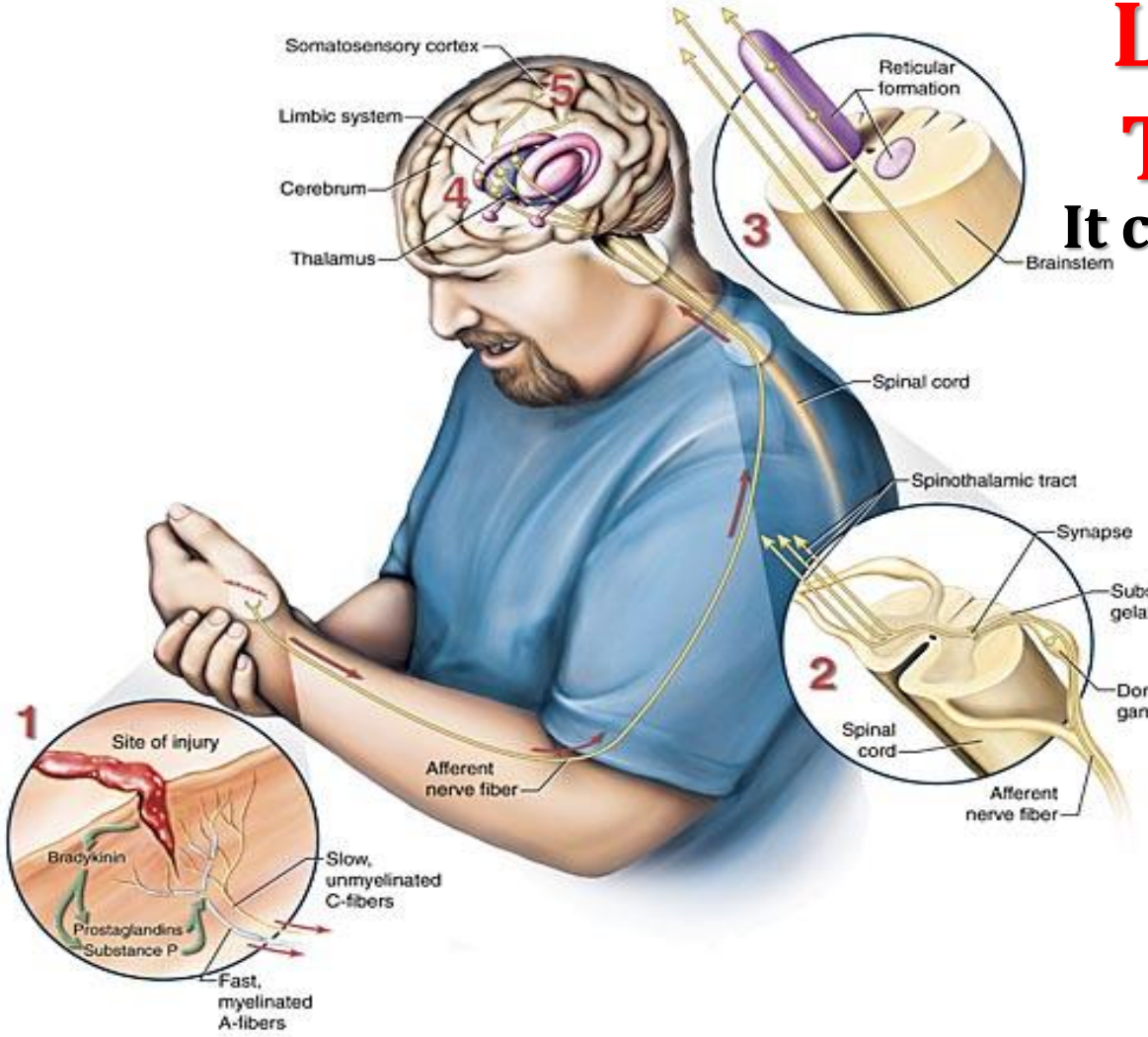
LEVELS OF PAIN TRANSMISSION

It consists of four processes:

1. TRANSDUCTION
2. TRANSMISSION
3. MODULATION
4. PERCEPTION



Neuroplastic changes

Sensitisation

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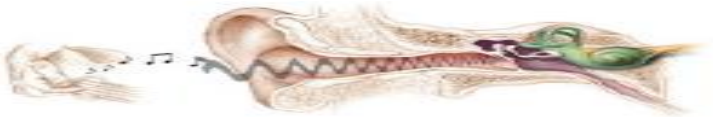
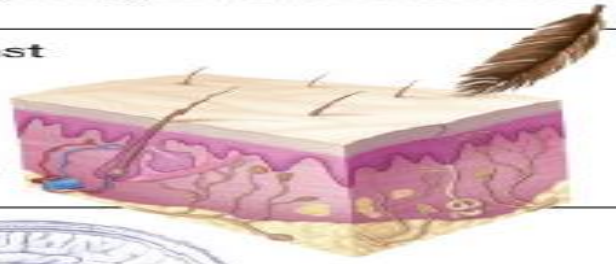
Transduction

The five senses convert physical energy from the world into neural energy, which is sent to the brain.

Sense	Sensory Input	Conversion into Neural Energy
Vision	Light reflected from surfaces, for example from a leaf, provides the eyes with information about the shape, color, and positions of objects.	 (See Figure 4.4 for a more detailed view.)
Audition (hearing)	Vibrations (from a guitar string, perhaps) cause changes in air pressure that move through space to the listener's ears.	 (See Figure 4.27 for a more detailed view.)
Touch	Pressure of a surface against the skin signals its shape, texture, and temperature. (See Figure 4.30 for a more detailed view.)	
Taste and Smell	Molecules dispersed in the air or dissolved in saliva reveal the identity of substances that we may or may not want to eat.	 (See Figures 4.31 and 4.33 for more detailed views.) 

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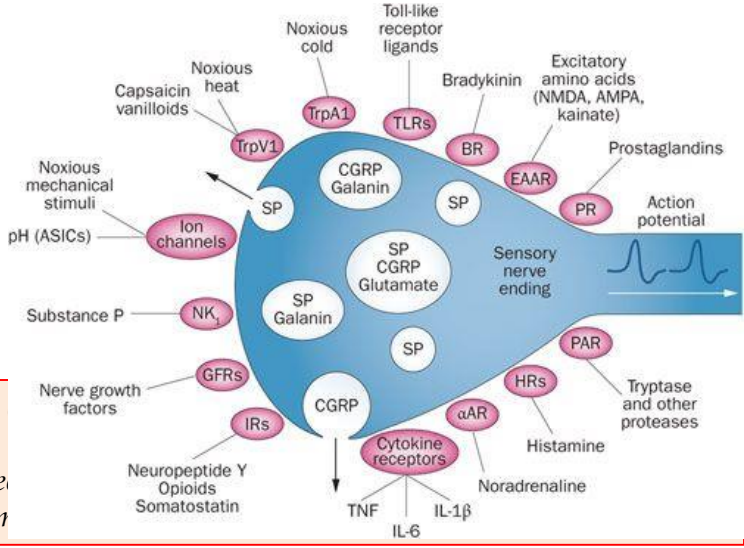
POLYMODAL NOCICEPTORS

- C fibers (unmyelinated free nerve endings)
- Respond to heat, pinch and cold (HPC receptors)
- Express TRPV1, TRPA1 and other TRP receptors
- Respond to irritant chemicals
  - Capsaicin (chili peppers): TRPV1 receptors
  - Mustard oil, garlic, horseradish: TRPA1 receptor
  - Low pH (acids)
  - Endogenous peptides: Bradykinin, NGF
  - Environmental irritants and pollutants



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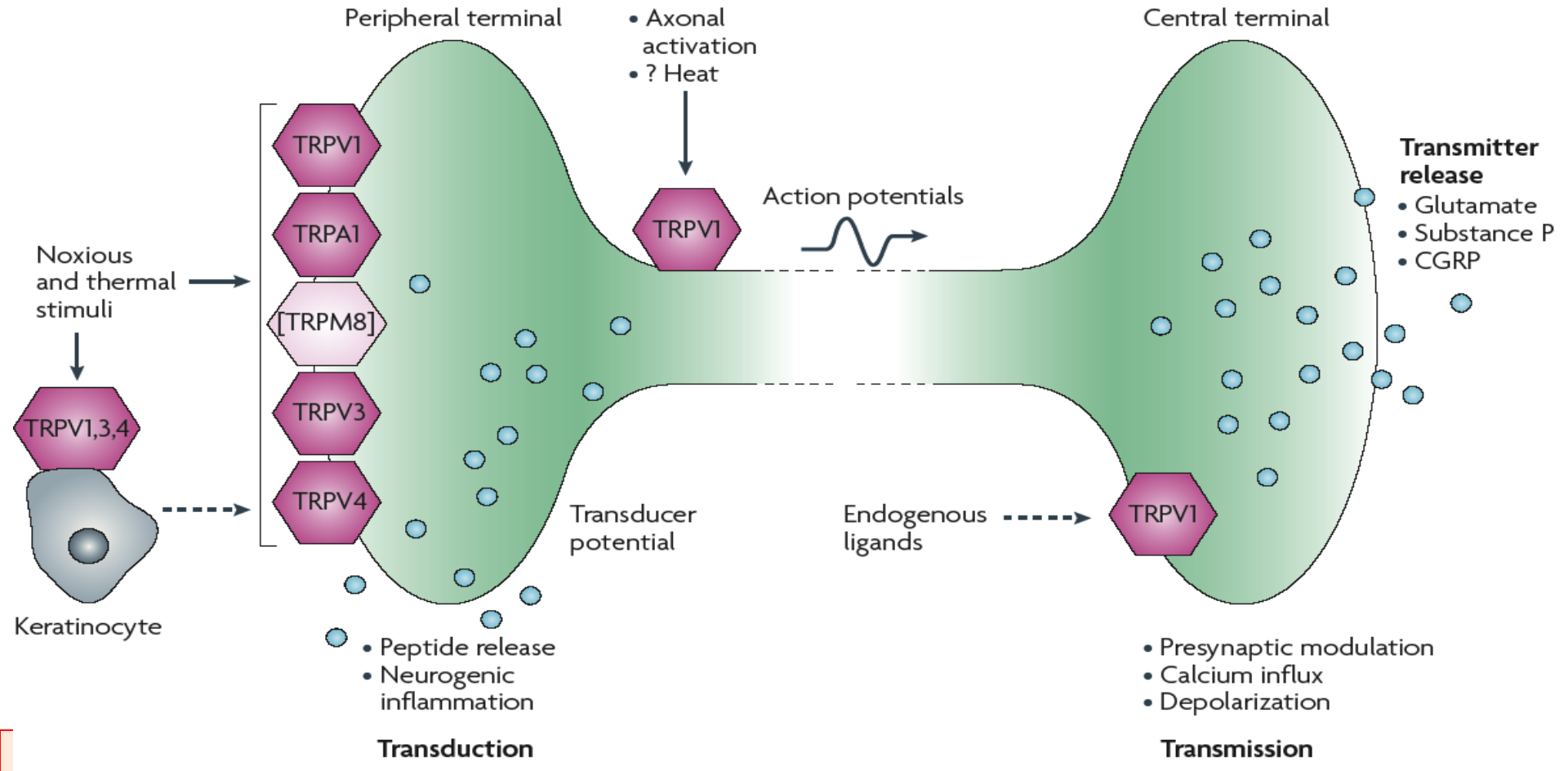
POLYMODAL NOCICEPTORS EXPRESS MULTIPLE RECEPTORS



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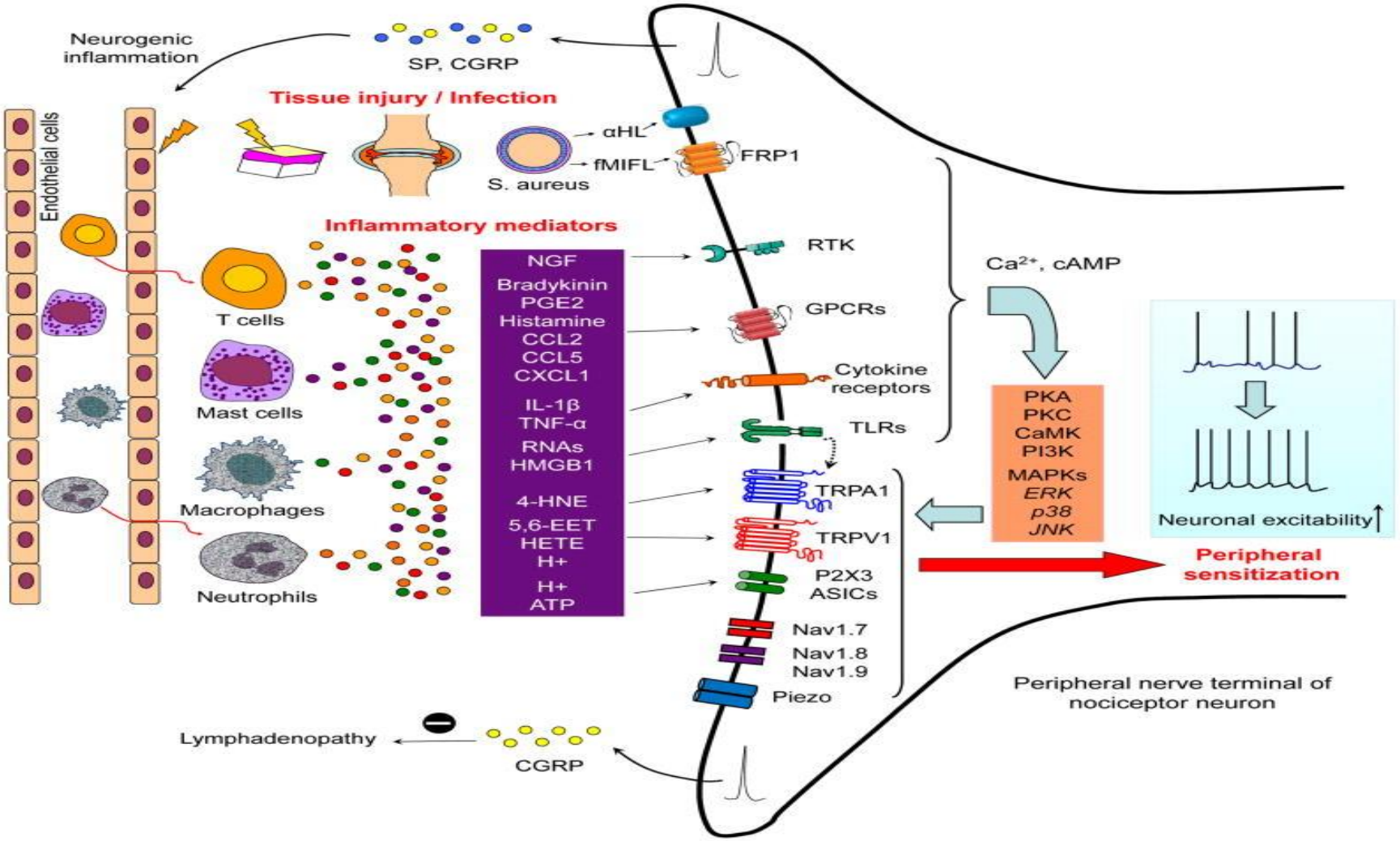
INFLAMMATION EVOKE PAIN VIA INFLAMMATORY MEDIATORS AND PERIPHERAL SENSITIZATION



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Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13(7): 533–548.

ALGOGENIC (INFLAMMATORY MEDIATORS) SUBSTANCES

Substance	Main effects
Kinins: • bradykinin (in blood) • kallidin (in tissues)	nociceptor activation
Serotonin	
Histamine	vasodilation, oedema, itching, nociceptor sensitization
Prostaglandins	nociceptor sensitization
Leukotrienes	
H^+	hyperalgesia
Cytokines	nociceptor sensitization and stimulations
Adenosine	hyperalgesia

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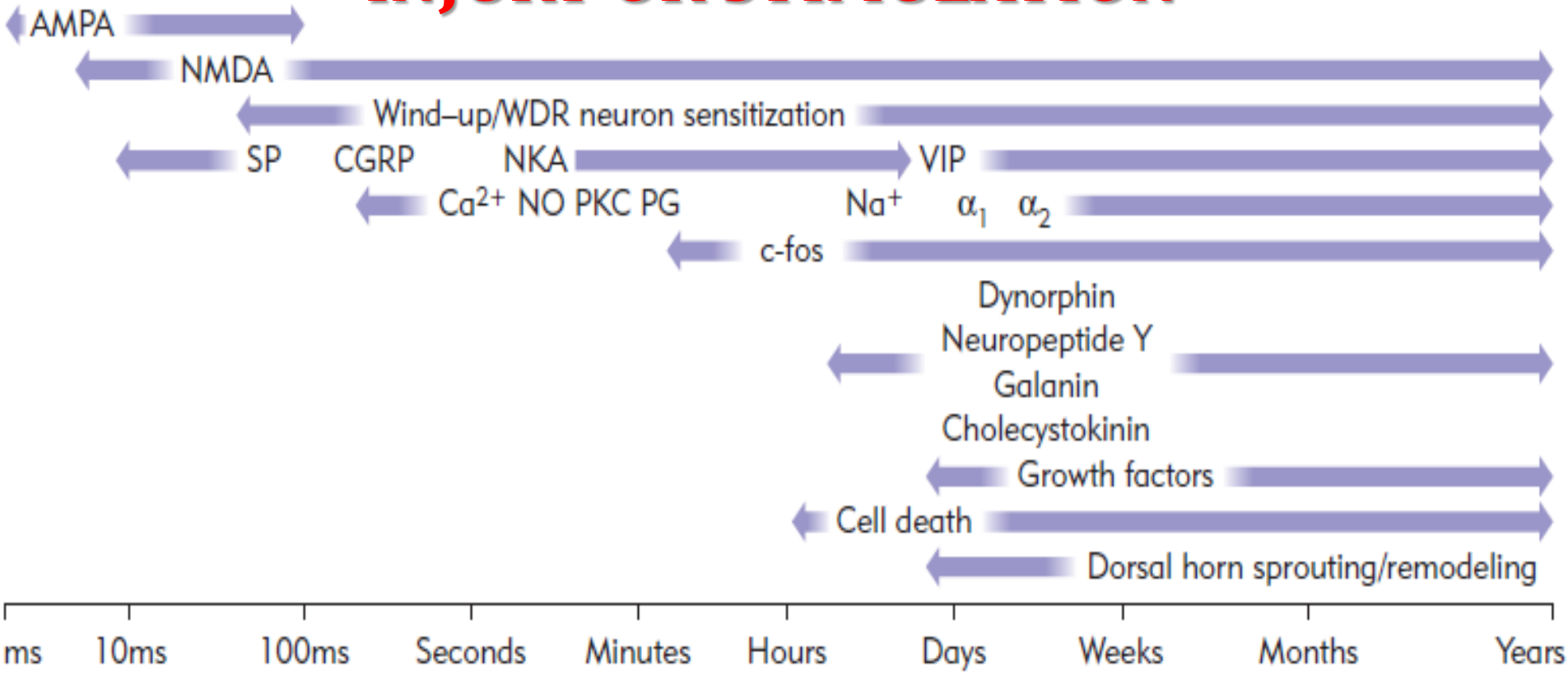
EVENTS FOLLOWING PERIPHERAL NERVE INJURY OR STIMULATION



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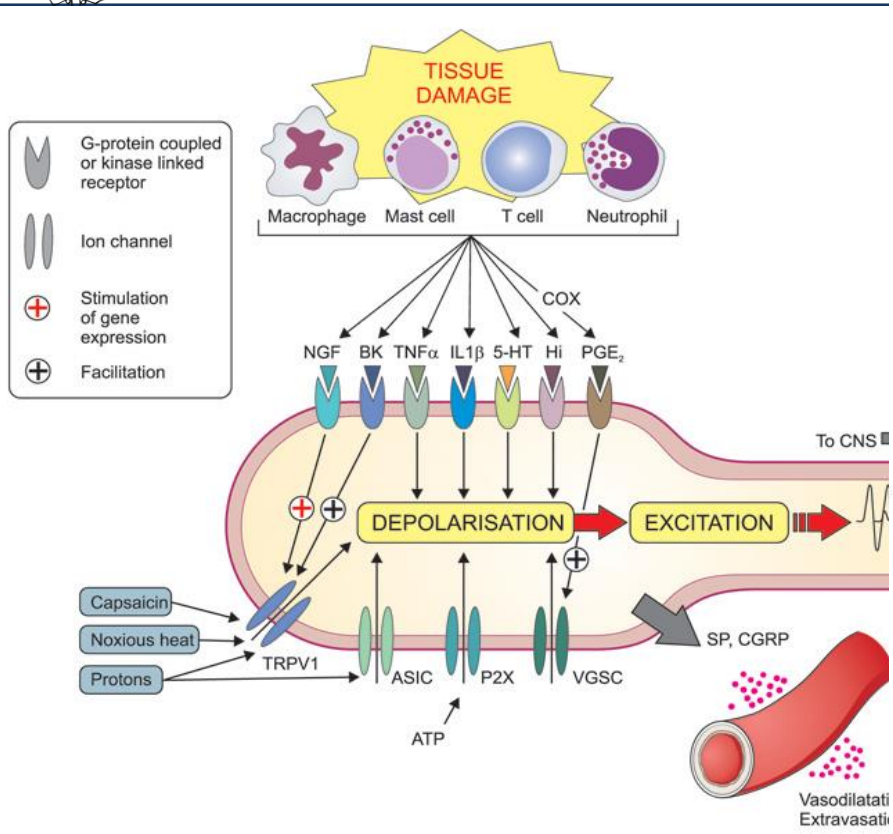
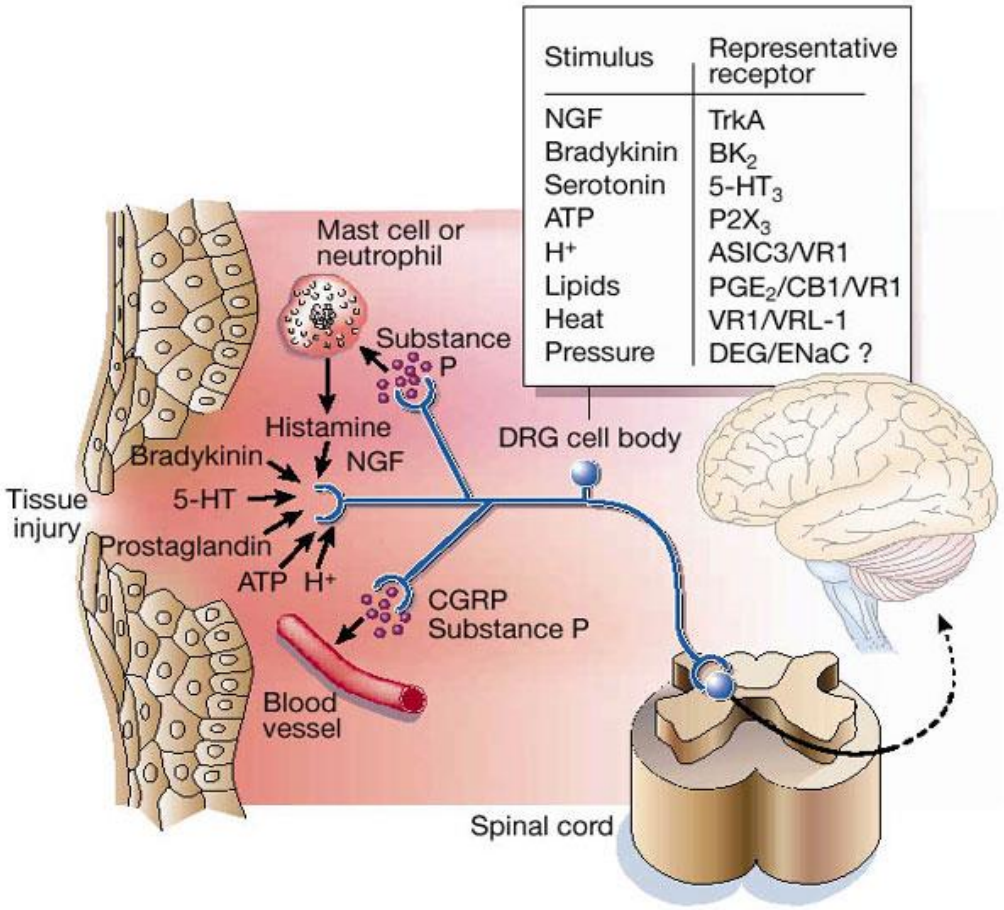
Sneddon UE, Physiology, 33: 63–73, 2018





↓ threshold
↑ firing rate
→
Nerve impulses ↑↑
→
Primary HYPERALGESIA
ALLODYNIA

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

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WHAT CAUSES CENTRAL SENSITIZATION ?

- Potential mechanisms implicated in central sensitization:
  - NMDA receptor activation1
  - Altered gene expression in dorsal horn neurons1
  - Decreased inhibition2
  - Microglial activation3
  - Thalamic and somatosensory cortex changes4

1. Mannion RJ, Woolf CJ: Clin J Pain.2000;16(3):S151-S153.
2. Ossipov MH, et al. Ann NY Acad Sci.2000;909:12-24.
3. Wieseler-Frank J, et al. Neurosignals.2005;14:166-174.
4. Guilbaud G, et al. Exp Brain Res.1992;92:227-245.

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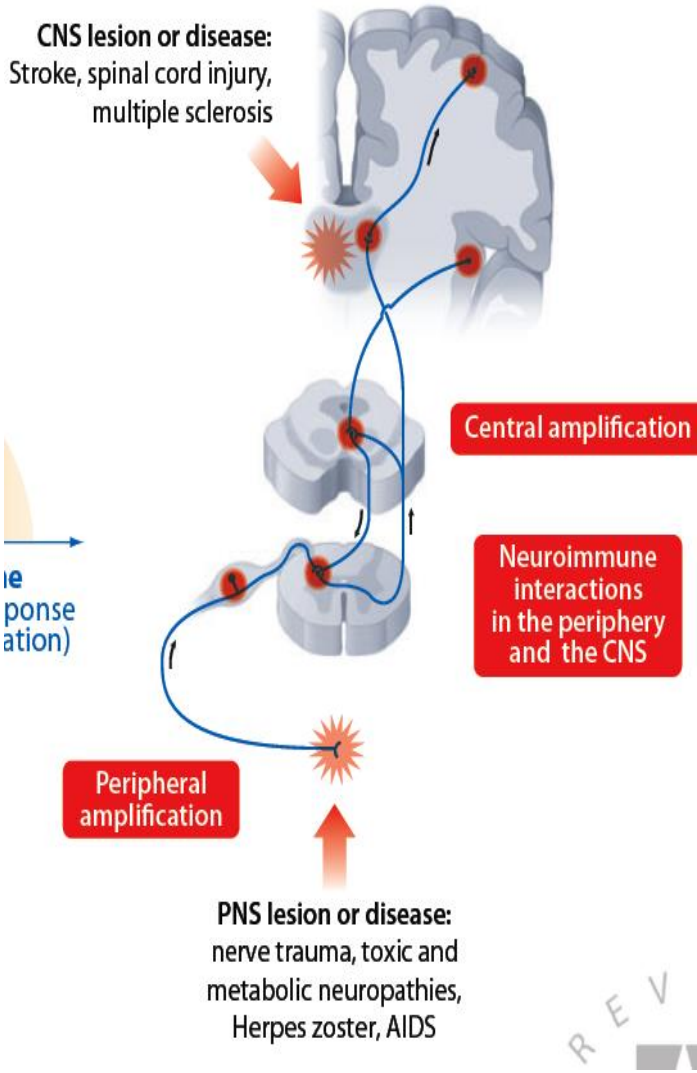
- The primary hyperalgesia has specific mechanisms very complex and include:
- 1.Direct stimulation of nociceptive primary afferents by
- 2. Antidromic activation of nociceptive primary afferents further enhance the activity of the nociceptors by a positive feedback mechanism and elicit vascular effects.
- 3. Synergistic actions and sensitization of nociceptors by the engagement of intracellular transduction systems. Previously“silent” nociceptors are recruited by this mechanism.
- 4.Modulatory events interactions amongst primary afferents, glial cells, immunocompetent cells, sympathetic terminals, etc.
- 5.Altered phenotype of primary afferents. Increase in primary afferent levels of sP,CGRP, nitric oxide and glutamate, and other changes.



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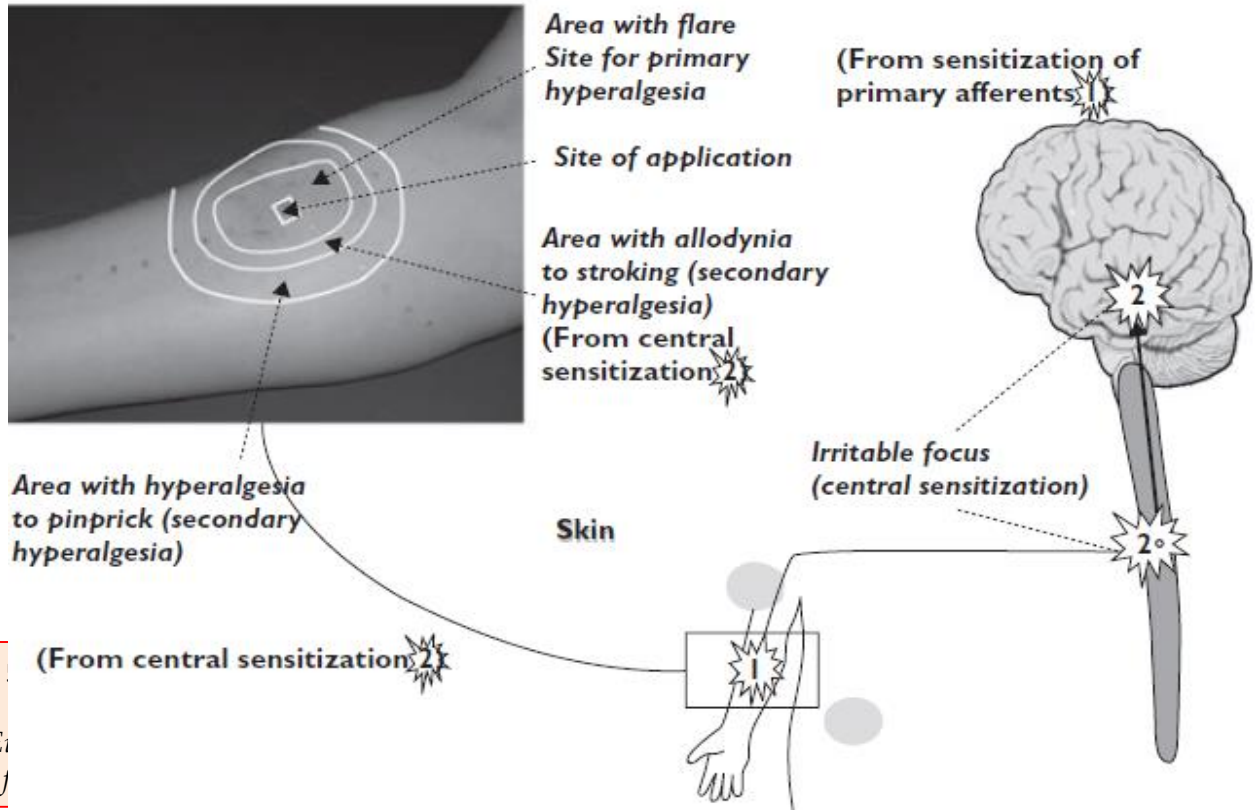
Three general electrophysiological characteristics at the cellular level:

- A stimulus provokes a response with greater number of generated action potentials (hyperalgesia).
- Receptive fields expand previously ineffective in eliciting firing (area of secondary hyperalgesia).
- There is also appearance of novel responses to Aβ fibers (allodynia).

CENTRAL SENSITISATIZATION



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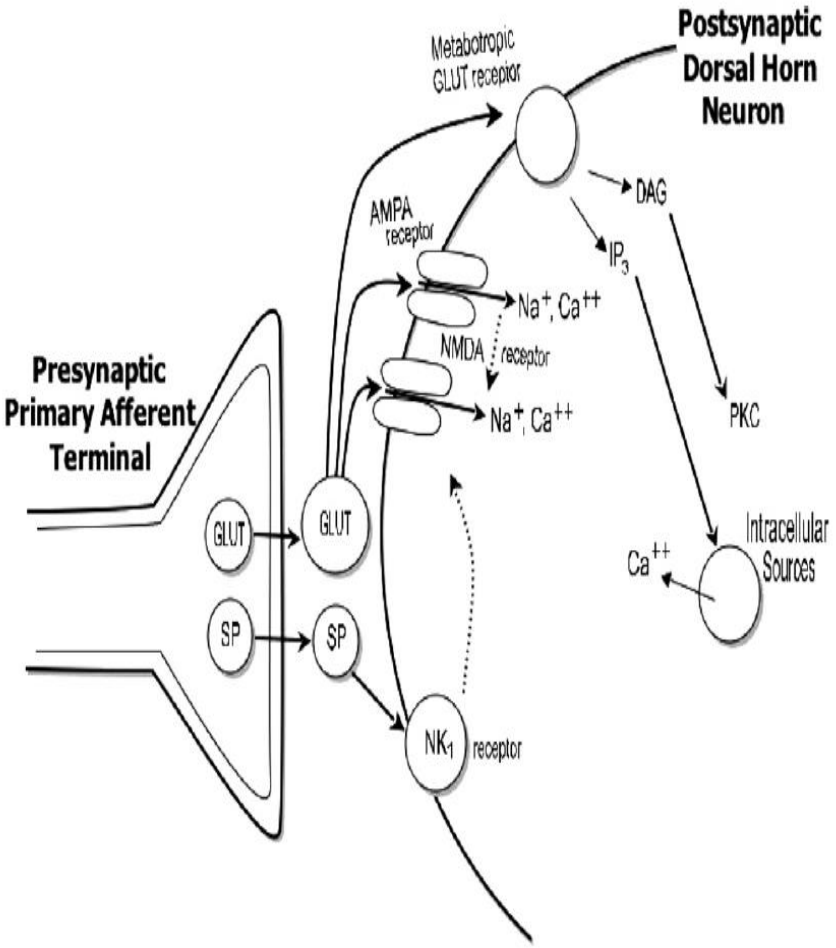
CENTRAL SENSITISATION

- 1. Progressive increase in the number of the action potentials generated by dorsal horn cells. This phenomenon is called wind-up and constitutes model of pain sensitization at the CNS level.
- 2. Heterosynaptic facilitation

  Progressive increase in neuronal excitability leads to an increased responsiveness to other inputs, specifically Aβ fibers.

- There is role of excitatory Amino Acids and tachykinins in the sensitization of dorsal horn neurons.
- Activation of NMDA receptors and increases in intracellular Ca++ level play role in triggering and maintaining neuronal sensitization in the dorsal horns.
- NMDA receptor antagonists (ketamine) potentiate the analgesic effect of opioids and may play a role in preventing central hypersensitive states.



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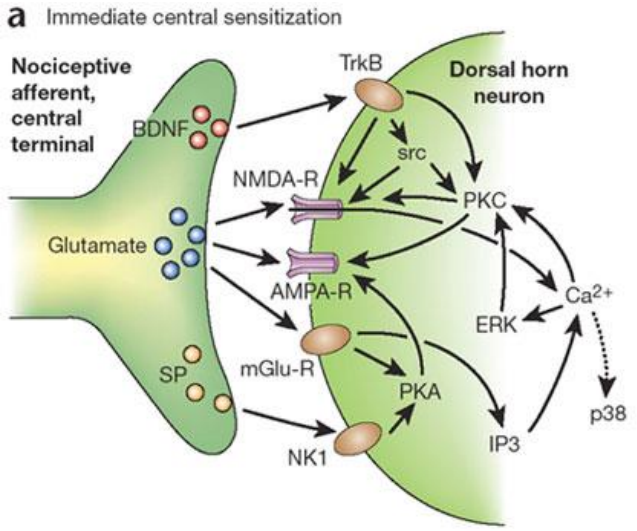
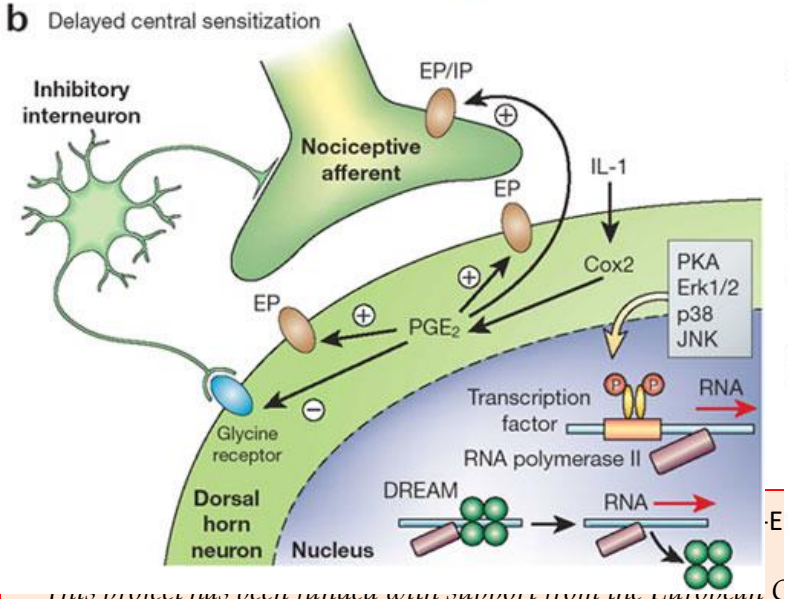
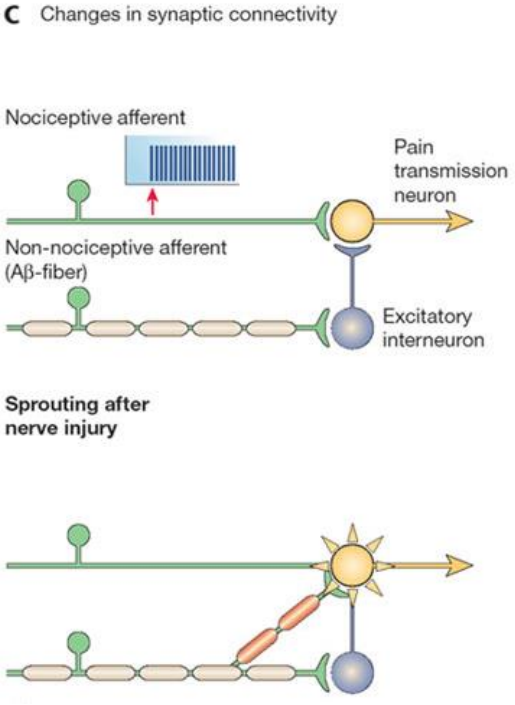
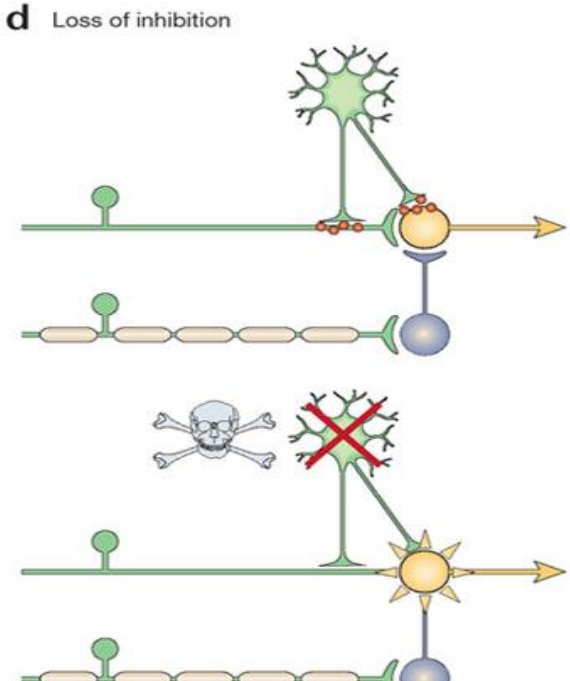
MECHANISM OF CENTRAL SENSITISATIZATION





- Another way is associated with the relatively slower transport of chemical substances called neurotrophins.
- Transient, functional reduction of the tonic GABA-ergic and glycinergic inhibitory interneuronal activity can accentuate processes of dorsal horn sensitization, contributing to the allodynia and hyperalgesia





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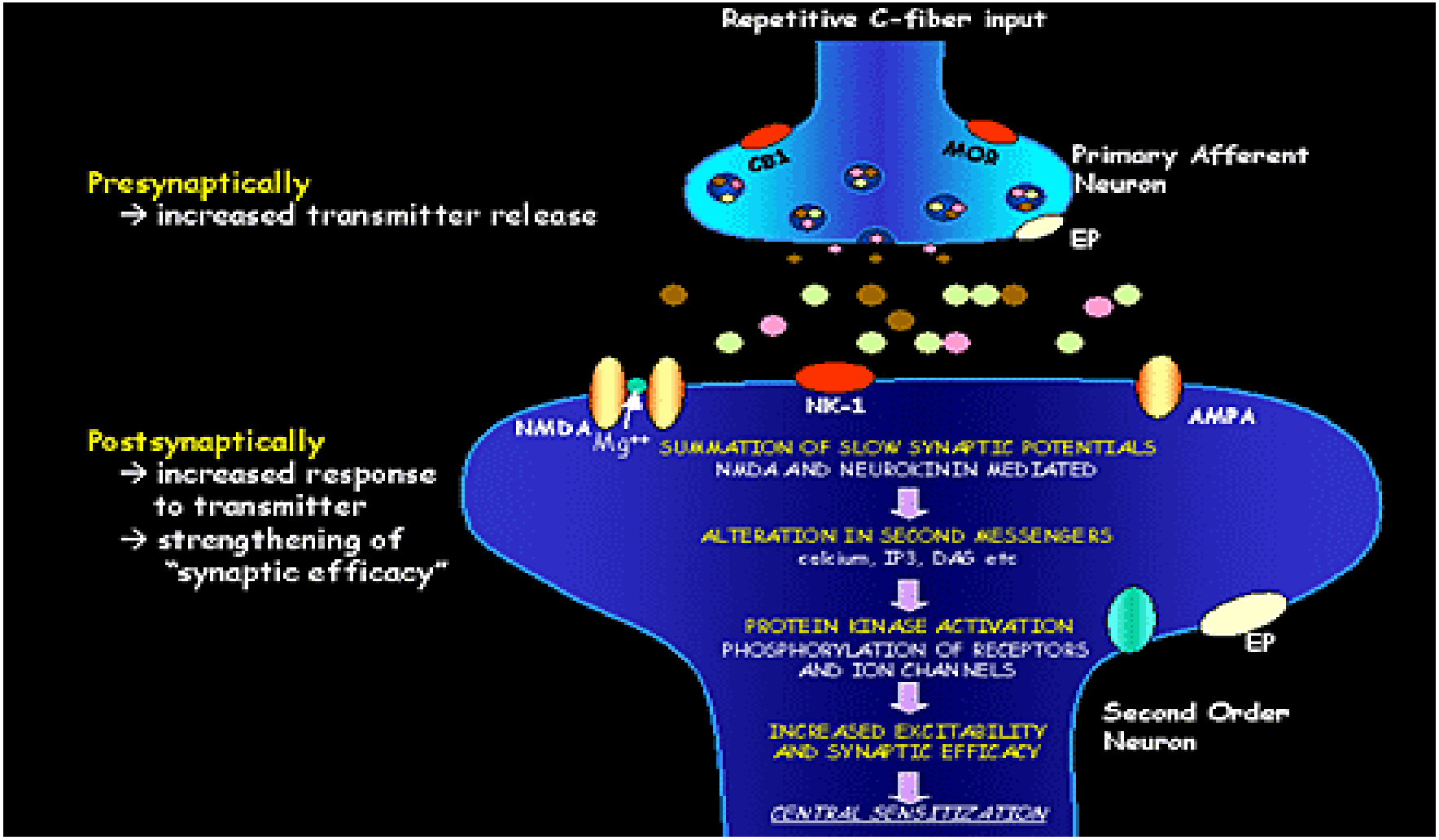
MECHANISM OF CENTRAL SENSITISATIZATION



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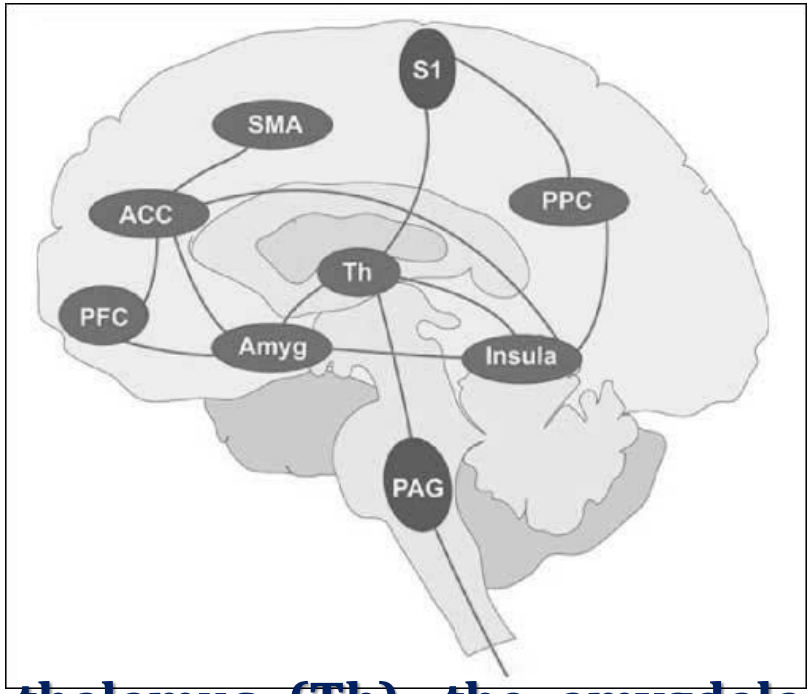
CENTRAL SENSITISATIZATION – PAIN MATRIX

- Increased responsiveness of the spinal cord after prolonged, intense nociceptive input.
- This includes the dorsal horn neurons, interneurons, and ventral horn neurons.
- The thalamus, cortex, and other brain areas also develop relevant changes.
- As a consequence of the central sensitization, low intensity or normal input of stimuli can produce an inappropriately greater response



The pain matrix mainly consists of the thalamus (Th), the amygdala (Amyg), the insula cortex (Insula), the supplementary motor area (SMA), the posterior parietal cortex (PPC), the prefrontal cortex (PFC), the cingulate cortex (ACC), the periaqueductal grey (PAG), the basal ganglia and cerebellar cortex and the primary (S1) and secondary (S2) sensory cortex.

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IS THIS ALL THE WAY THAT WE SAYING ?

Sensory-discriminative aspects of pain perception are often thought to be independently and specifically represented in S1 and S2, constituting the so-called "LATERAL PAIN SYSTEM" or "SOMATOSENSORY NODE", while affective aspects of pain perception would be represented in medial brain structures such as the ACC, constituting the "MEDIAL PAIN SYSTEM" or "AFFECTIVE NODE". Long-term elevated neurons for pain transmission can create a MEMORIZED PAINFUL MATRIX, or a neuronal lowered subacute, as the basis for the emergence of a chronic neuropathic pain.

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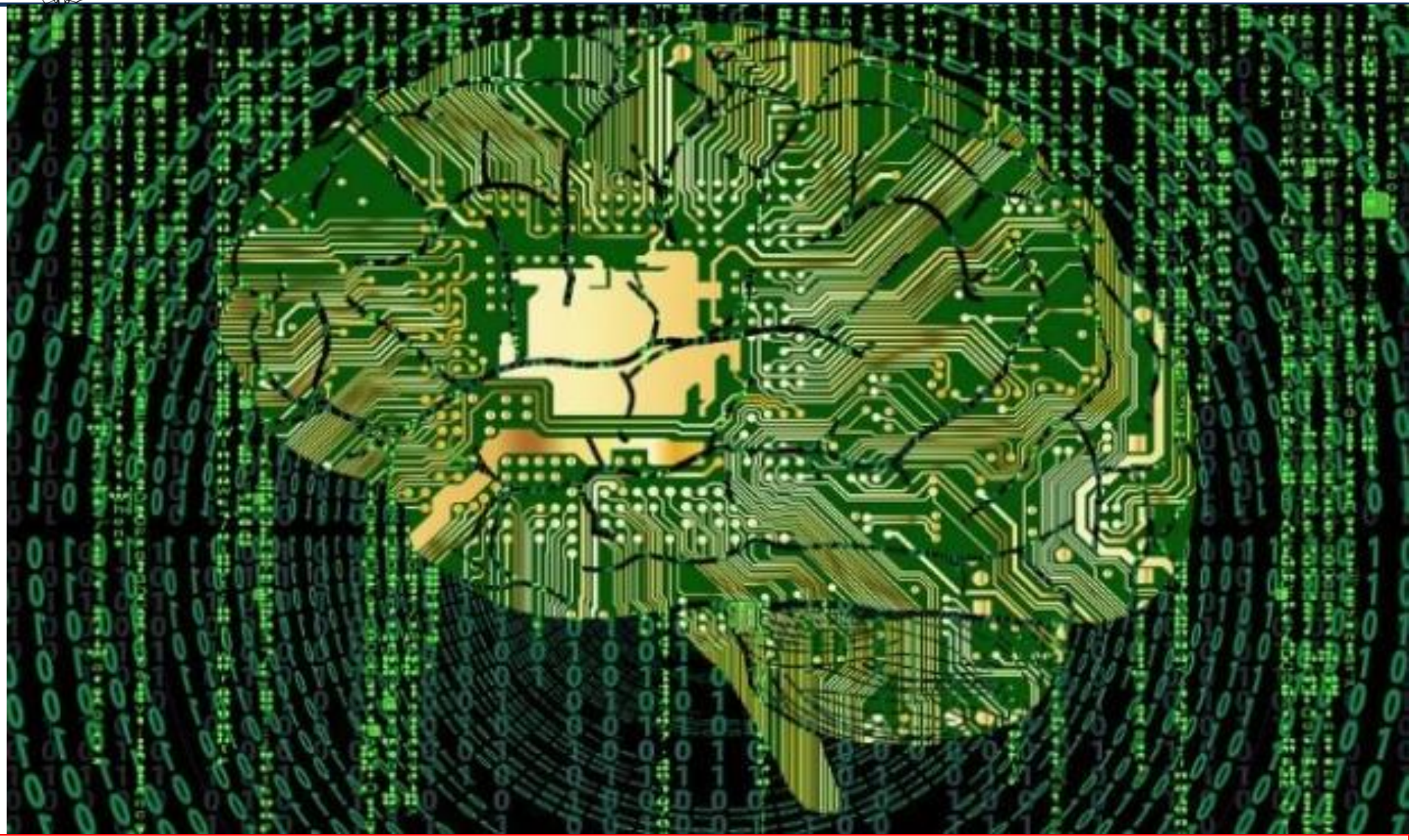
Neuroimage. 2018 May 15;172:562-574



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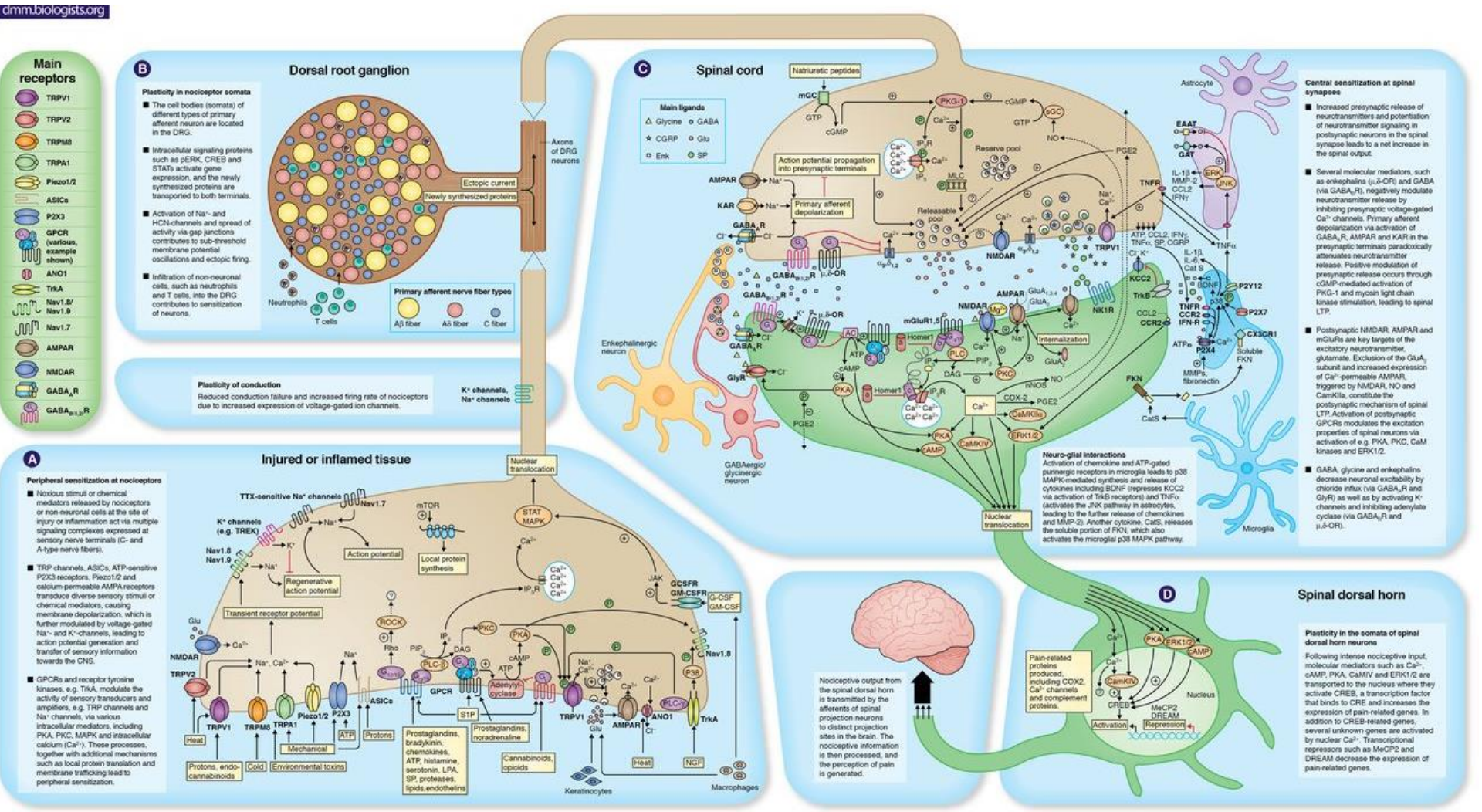

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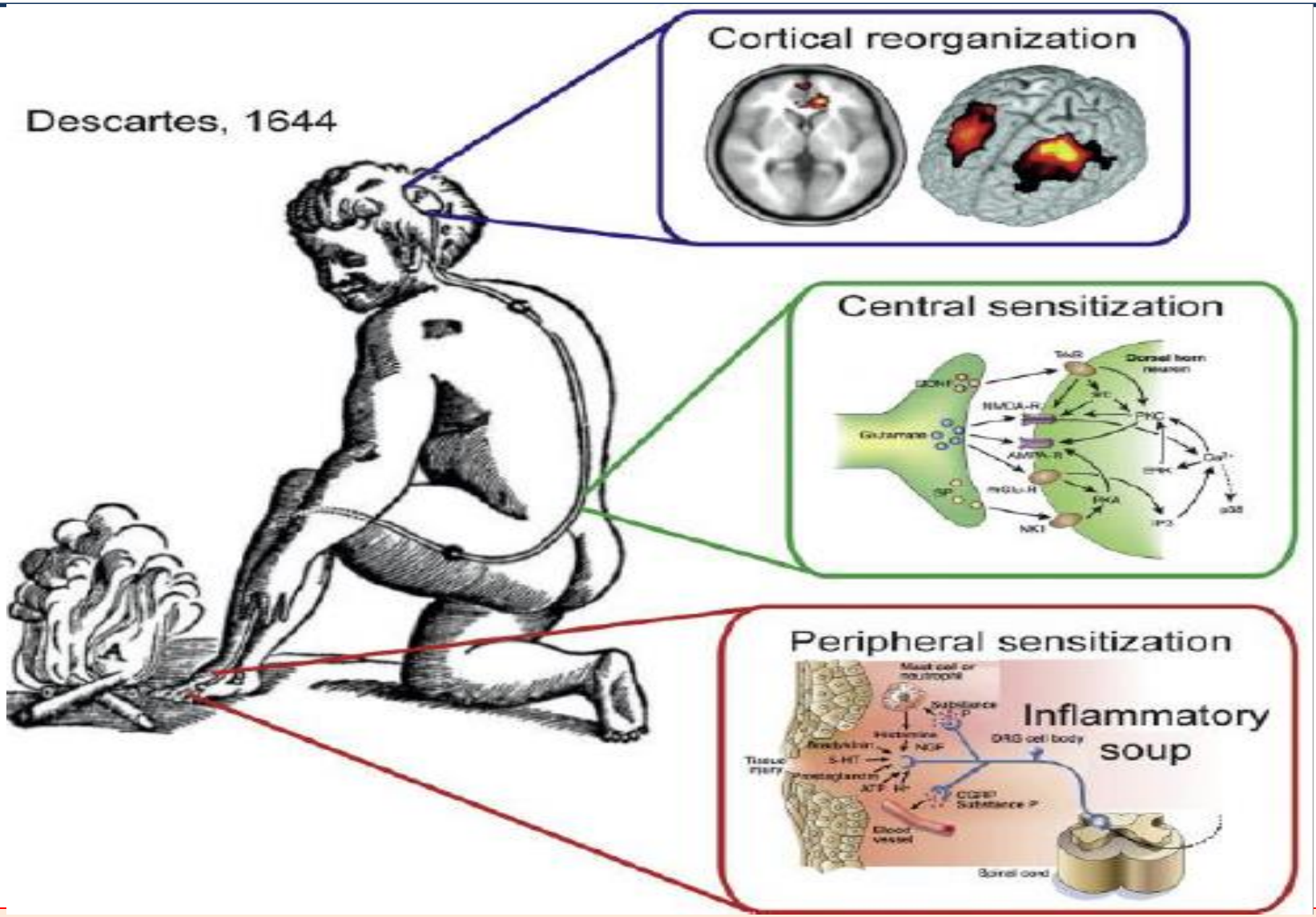

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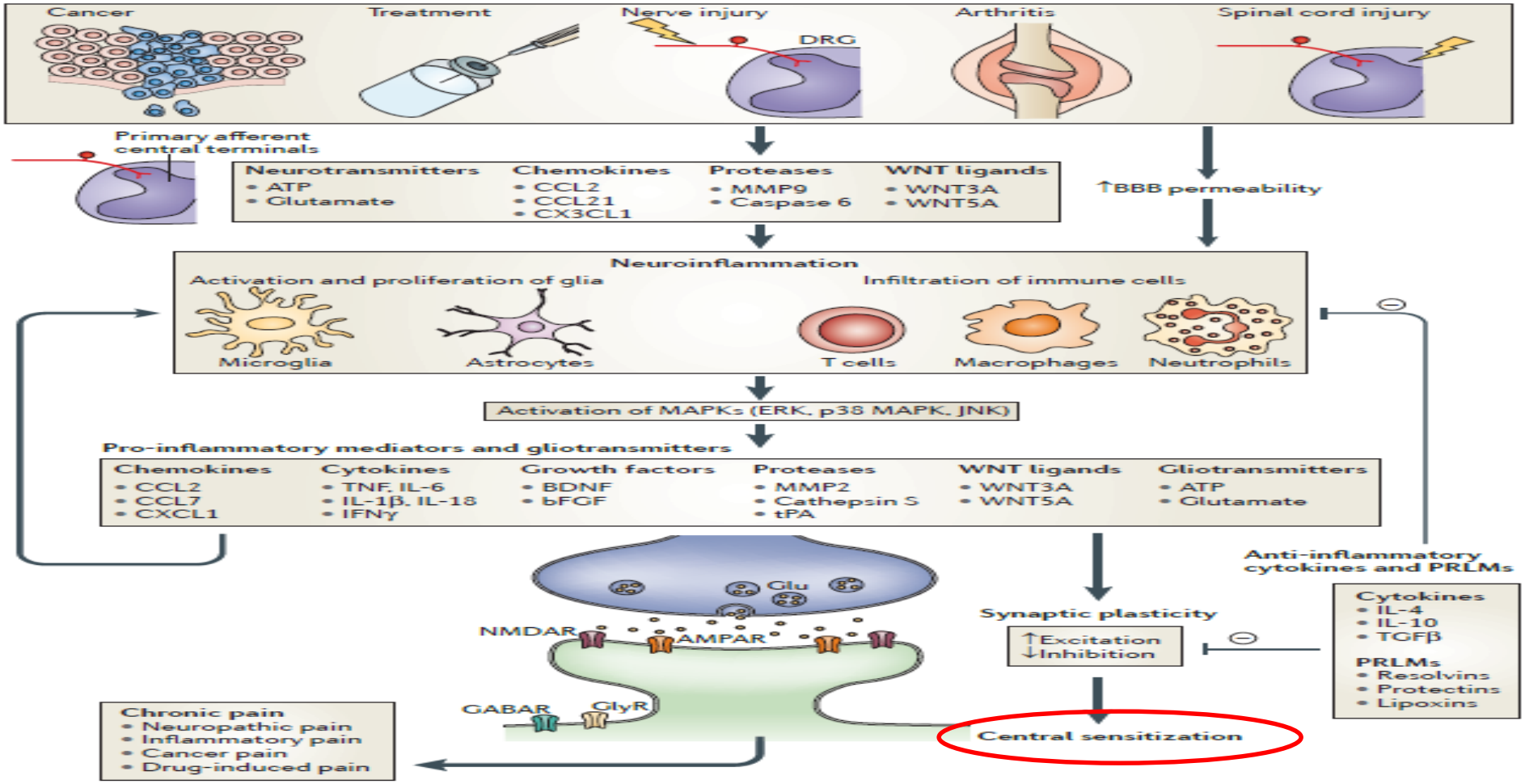
NEUROINFLAMMATION IN THE SPINAL CORD DRIVES CHRONIC PAIN VIA NEURON–GLIAL INTERACTIONS AND CENTRAL SENSITIZATION



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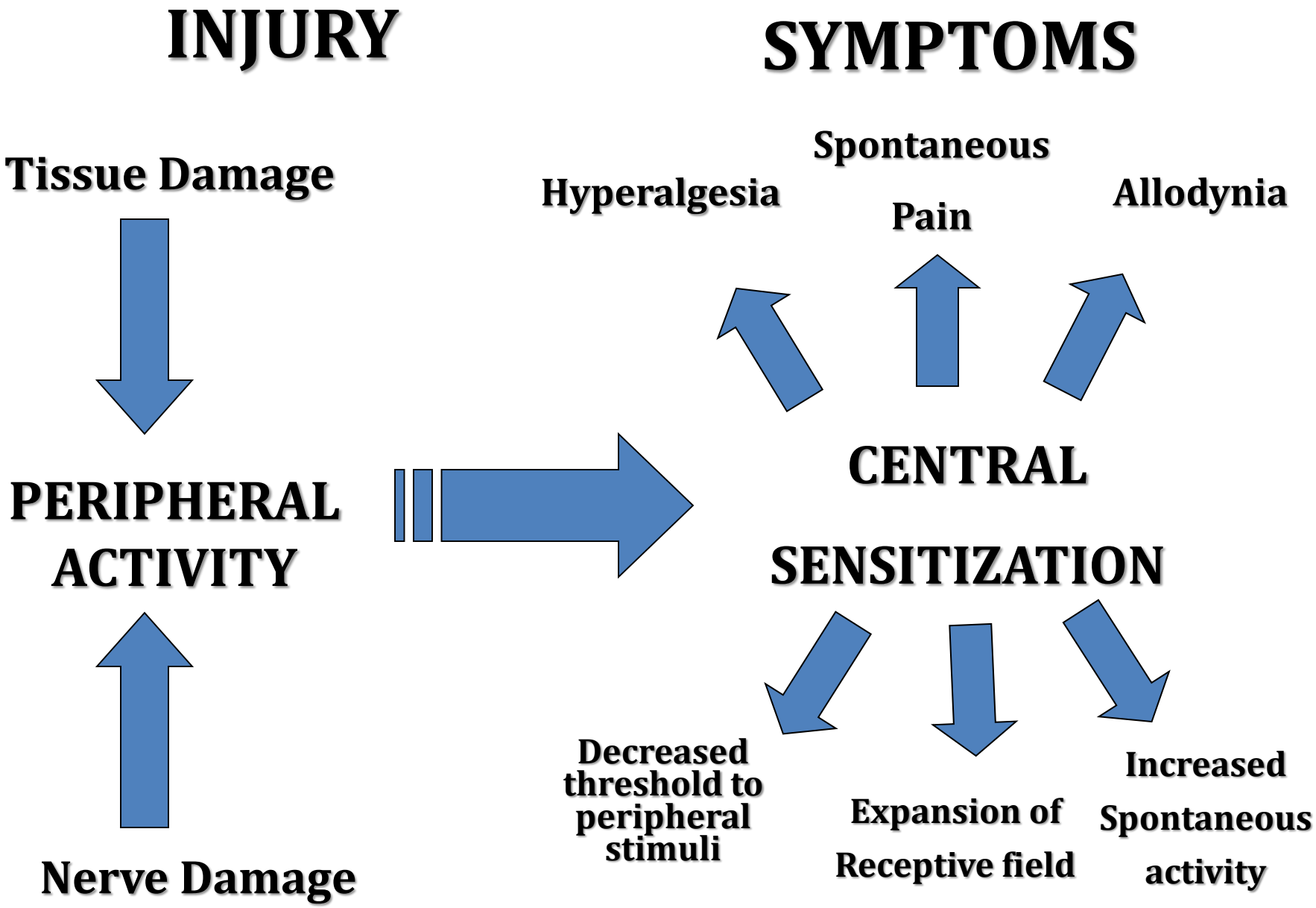
Ru-Rong J., Zhen-Zhong X., Yong-Jing G. Nature reviews , Drug discovery, 2018.


INJURY
SYMPTOMS
Tissue Damage
Spontaneous
Pain
Hyperalgesia
Allodynia
PERIPHERAL
ACTIVITY
CENTRAL
SENSITIZATION
Decreased
threshold to
peripheral
stimuli
Expansion of
Receptive field
Increased
Spontaneous
activity
Nerve Damage

Прва страна докторске дисертације Михаила Петровића Аласа

HEPMP
HIGHER EDUCATION PAIN MEDICINE PROJECT
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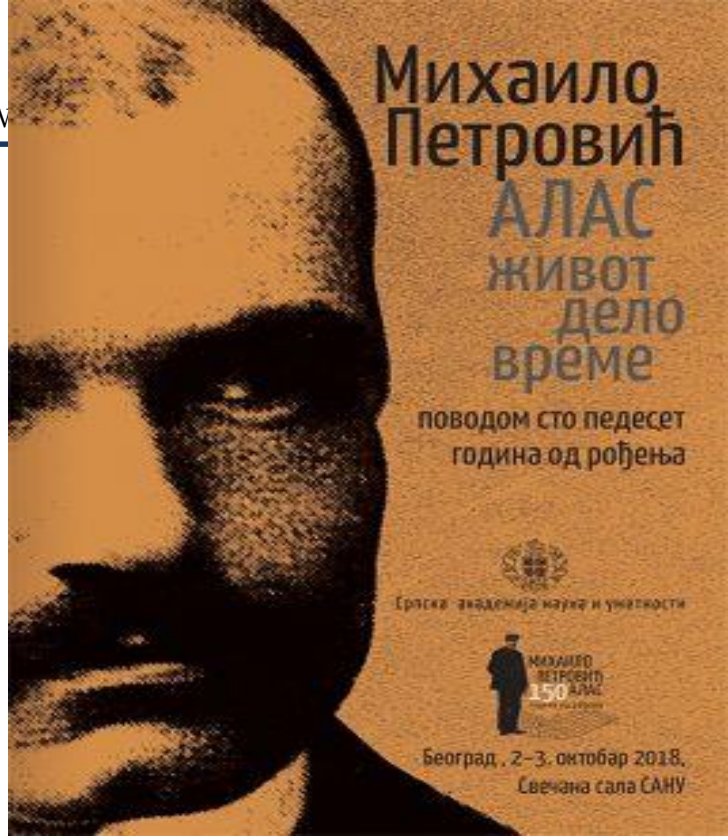

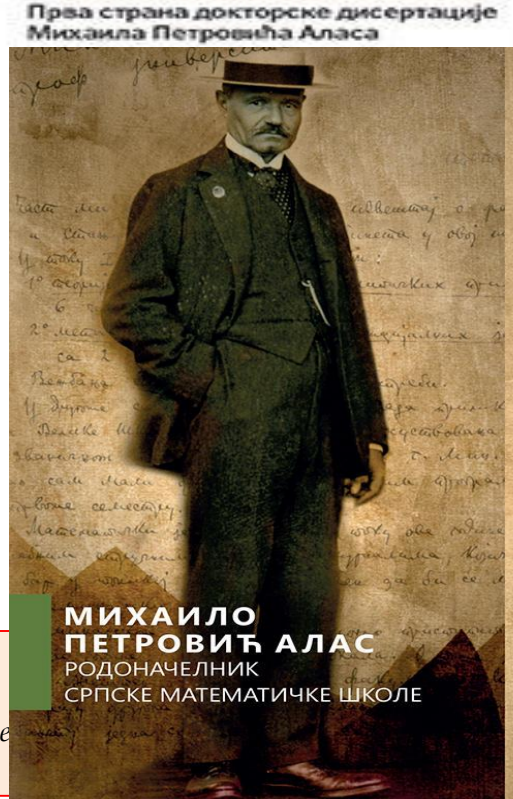

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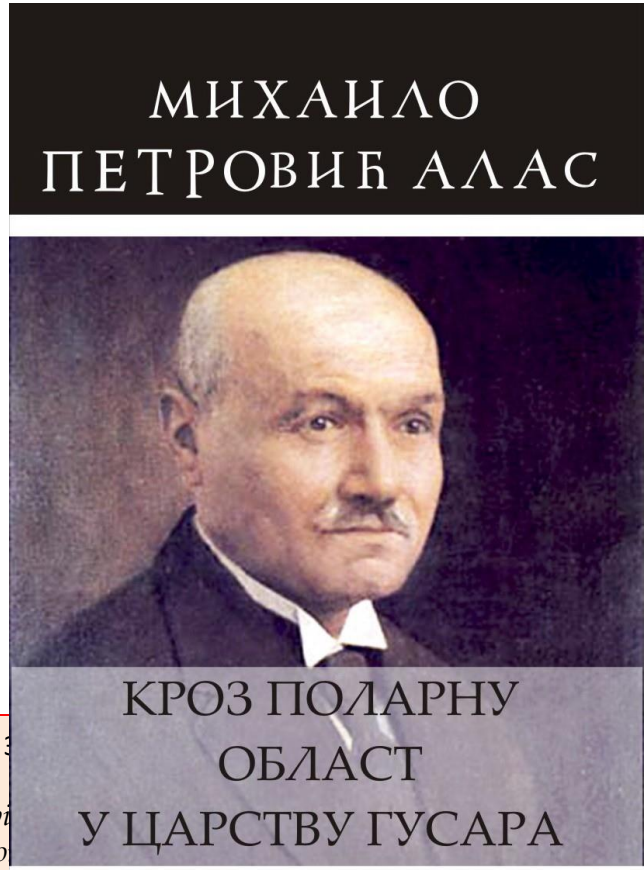
Mihailo Petrović Alas (6. maj 1868 - 8. jun 1943)



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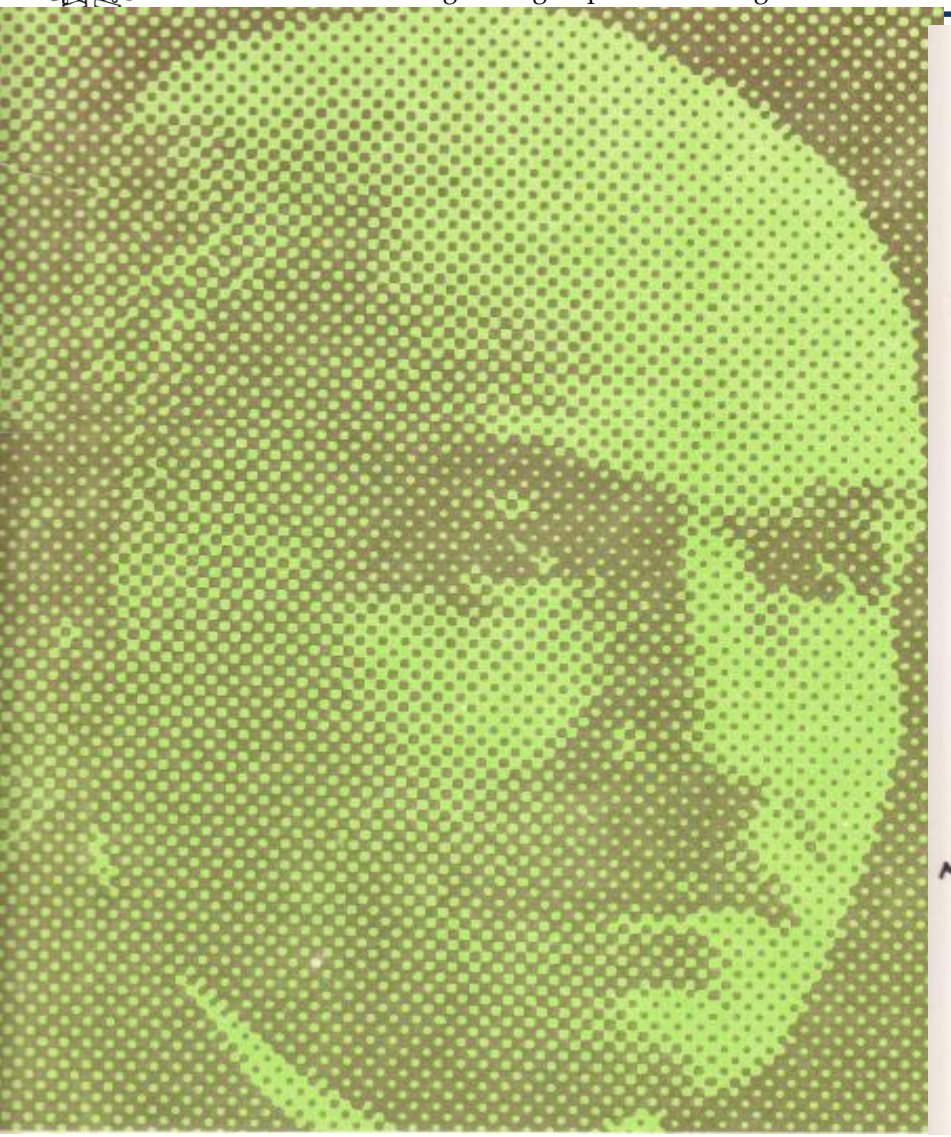

СОЦИЈАЛИСТИЧКА РЕПУБЛИКА СРБИЈА

ОСНОВНА ШКОЛА „ПОПИНСКИ БОРЦИ" у ВРЊАЧКОЈ БАЊИ
(НАЗИВ ОСНОВНЕ ШКОЛЕ)

ДОДЕЉУЈЕ

ДИПЛОМУ

„МИХАИЛО ПЕТРОВИЋ-АЛАС"

НЕШИЋ М. ДЕЈАНУ
(ПРЕЗИМЕ, СРЕДЊЕ СЛОВО И ИМЕ)

ЗА ИЗУЗЕТАН УСПЕХ У САВЛАЂИВАЊУ НАСТАВНОГ ГРАДИВА ИЗ ОБЛАСТИ ПРИРОДНО-МАТЕМАТИЧКИХ НАУКА — ПРЕДМЕТА МАТЕМАТ. БИОЛОГ. И ХЕМИЈЕ ЧИМЕ ЈЕ СТЕКАО СВА ПРАВА КОЈА МУ ПО ЗАКОНУ ПРИПАДАЈУ

Деловодни број 1054
у Врњ. Бањи 1987. године

М. П.

Директор школе

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

Academician Prof. dr Dragan Micić, MD, PhD

Strengthening Capacities for Higher Education of Pain Medicine in Western Balkan countries – HEPMP

Number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP

(Jačanje kapaciteta visokog obrazovanja u oblasti Medicine bola u zemljama zapadnog Balkana)

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HEPMP
Higher Education Pain Medicine Project

Prof. Predrag Stevanović, MD, PhD

Project coordinator

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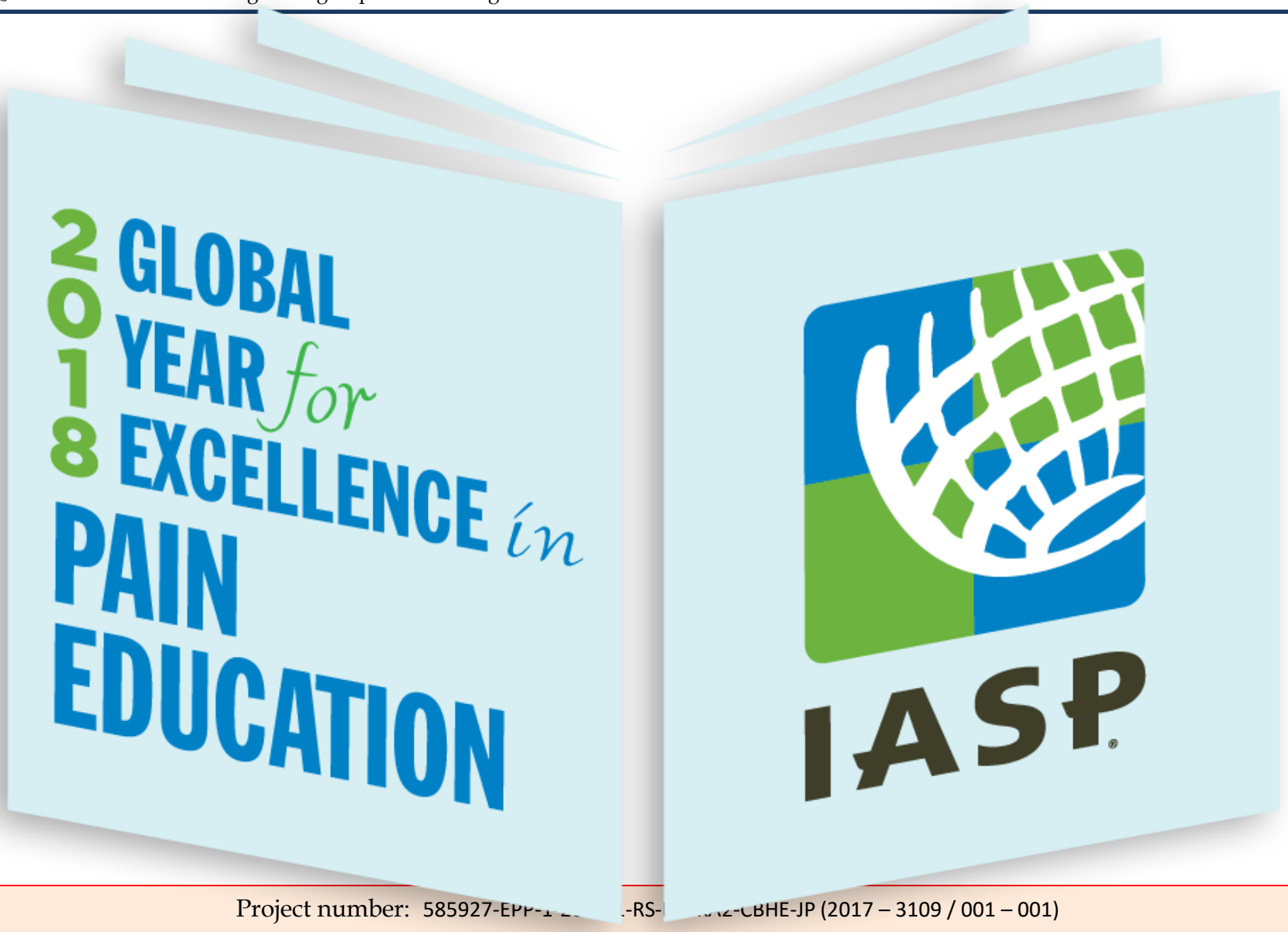

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"IF YOU ARE PLANNING FOR A YEAR, SOW RICE; IF YOU ARE PLANNING FOR A DECADE, PLANT TREES; IF YOU ARE PLANNING FOR A LIFETIME, EDUCATE PEOPLE."

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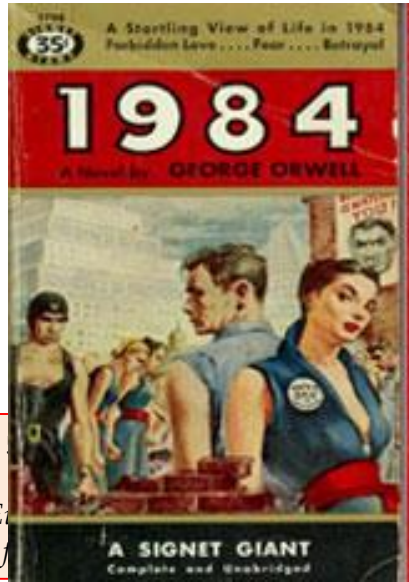
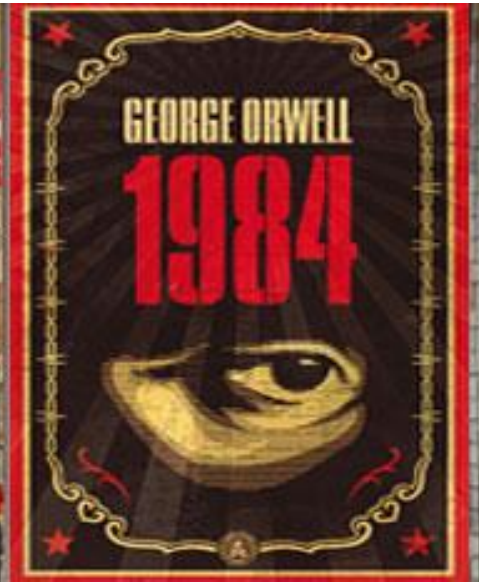
„Of pain you could wish only one thing: that it should stop. Nothing in the world was so bad as physical pain. In the face of pain there are no heroes...“

George Orvell (1903-1950)





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