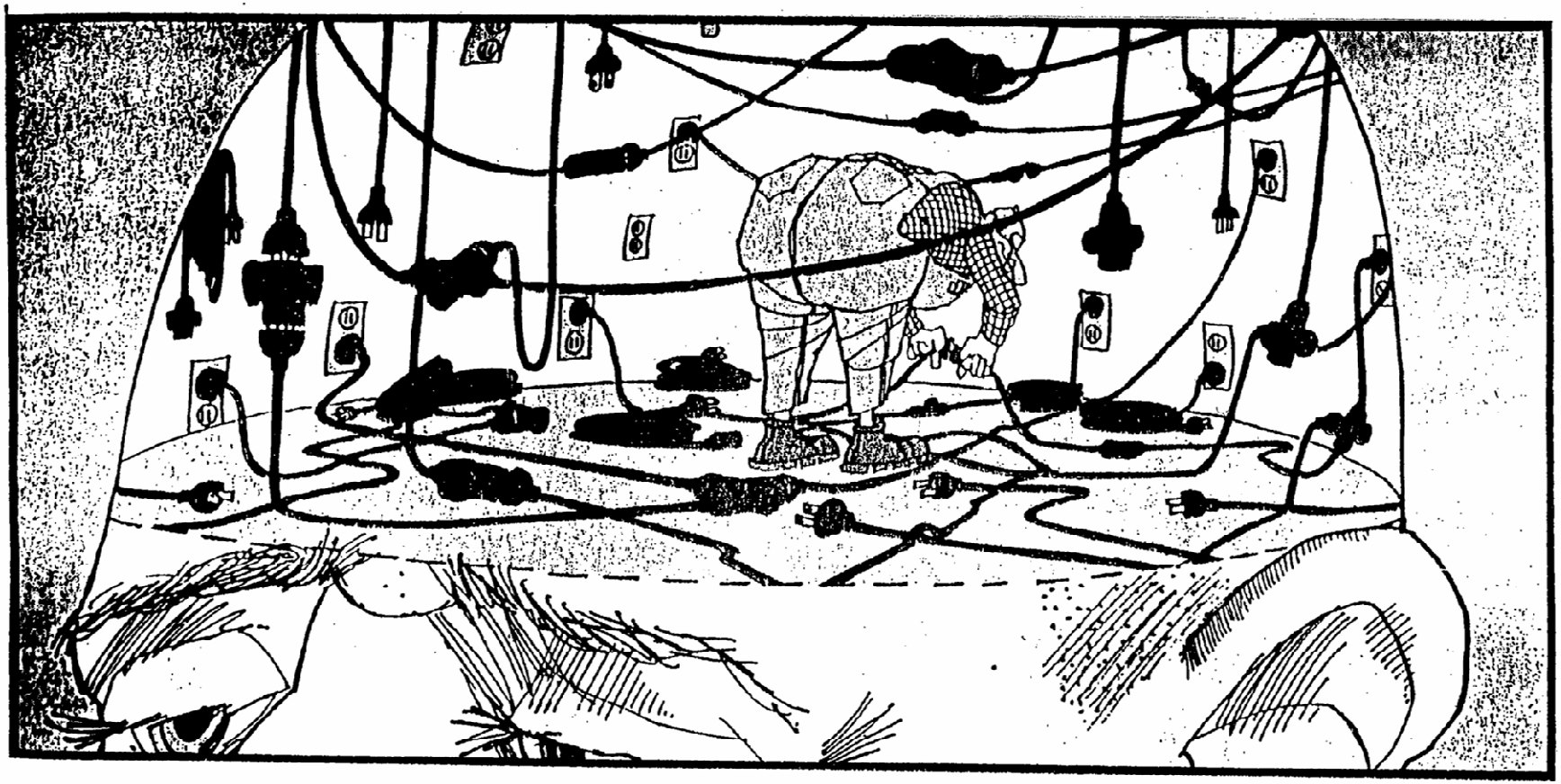
Patho-physiology of Nervous System Talk 1 – Pain and Motor disorders

Petr Marsalek

Department of pathological physiology

1.Med. F. CUNI



How the brain works.

Talks on NS

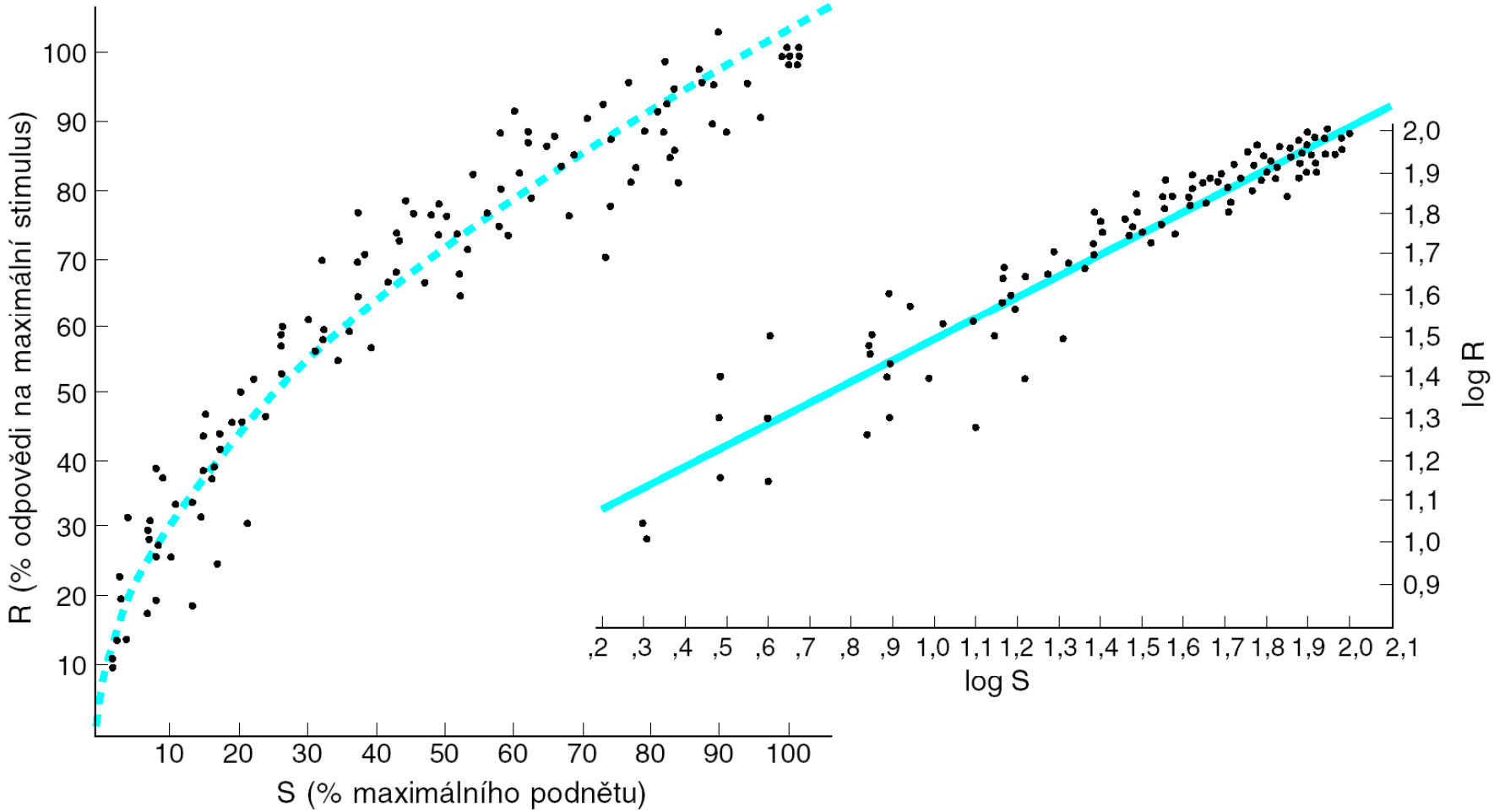
Talk 1 - This - Pain and Motor disorders

Talk 2 - Syndromes in neurosciences

Talk 3 - Disorders of special senses

Talk 4 - Cognitive functions, dementias, etc.

Response (R) is function of stimulus intensity (S), R=f(S)



Obr. 5-5. Vztah mezi intenzitou dotykového podnětu (S) a frekvencí akčních potenciálů v senzorických nervových vláknech (R). Tečky znázorňují jednotlivé hodnoty u koček; jsou vyneseny do souřadnic lineárních **(vlevo)** a logaritmických **(vpravo)**. Rovnice vyjadřuje vypočítaný exponenciální vztah mezi R a S. (Reprodukováno se souhlasem z WERNER, G., MOUNTCASTLE, VB. *Neural activity in mechanoreceptive cutaneous afferents. Stimulus-response relations, Weber functions, and information transmission*. J Neurophysiol, 1965, 28, 359.)

Golden age of psychophysics

Gustav Theodor Fechner,

(see: Weber-Fechner law, Ernst Heinrich Weber, 1795–1878)

*1801, Poland,

+1887, Leipzig, Germany,

1850 – one day G.T.F. arrived to an “instant enlightenment” and knew, how to describe sensory perception in general. It took him another 10 year to formulate everything in a definitive book:

Elemente der Psychophysik (1860),

1878 – definition of median (= this is the value, dividing the cumulative distribution function in two halves)

Aside: on One Psychophysics Application, or On the Scoville Scale of Hot Chili Peppers…

Who was W. Scoville ?

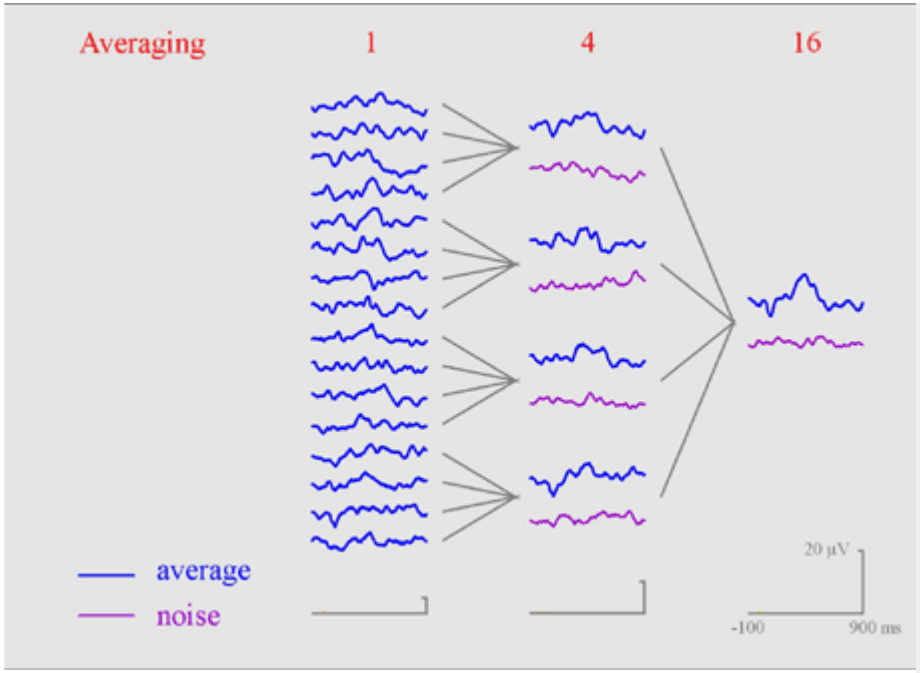
1. **Wilbur Lincoln Scoville, american pharmacist, (1865 – 1942)**
2. **William Beecher Scoville, american neurosurgeon, (1906 - 1984)**
3. **Brenda Milner, canadian psychologist, (1918 – present, age 97, born on the same day as Vernon Benjamin Mountcastle, 1918-2015)**
4. **William Beecher Scoville and Brenda Milner (1957). "Loss of recent memory after bilateral hippocampal lesions". Journal of Neurology, Neurosurgery and Psychiatry 20, (1): 11–21.**
5. **Patient H.M. - Henry Gustav Molaison (1926 – 2008)**

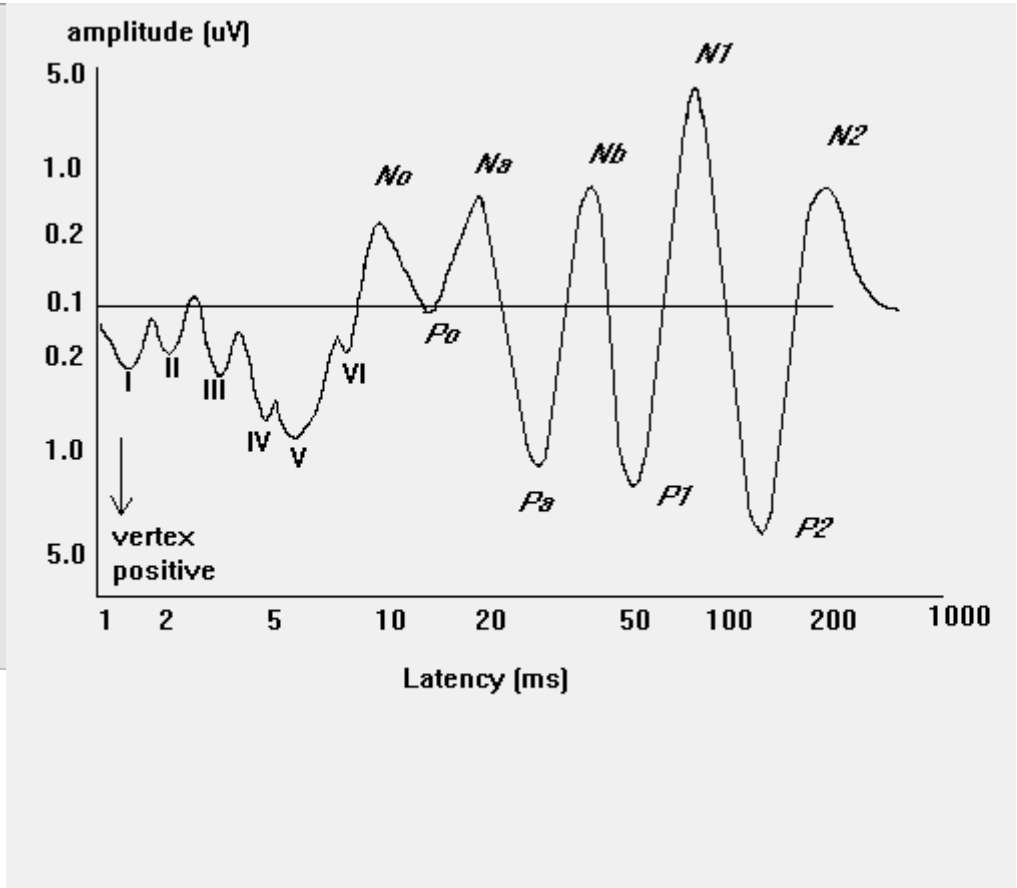
Scoville ratings of chemicals (Scoville heat units)	substance examples
16,000,000,000	Resiniferatoxin
5,300,000,000	Tinyatoxin
16,000,000	Capsaicin
15,000,000	Dihydrocapsaicin
9,200,000	Nonivamide
9,100,000	Nordihydrocapsaicin
8,600,000	Homocapsaicin
160,000	Shogaol (dehydr. ginger oil)
100,000	Piperine (black pepper alkaloid)
60,000	Gingerol (ginger oil)
16,000	Capsiate

Scoville ratings of hot peppers

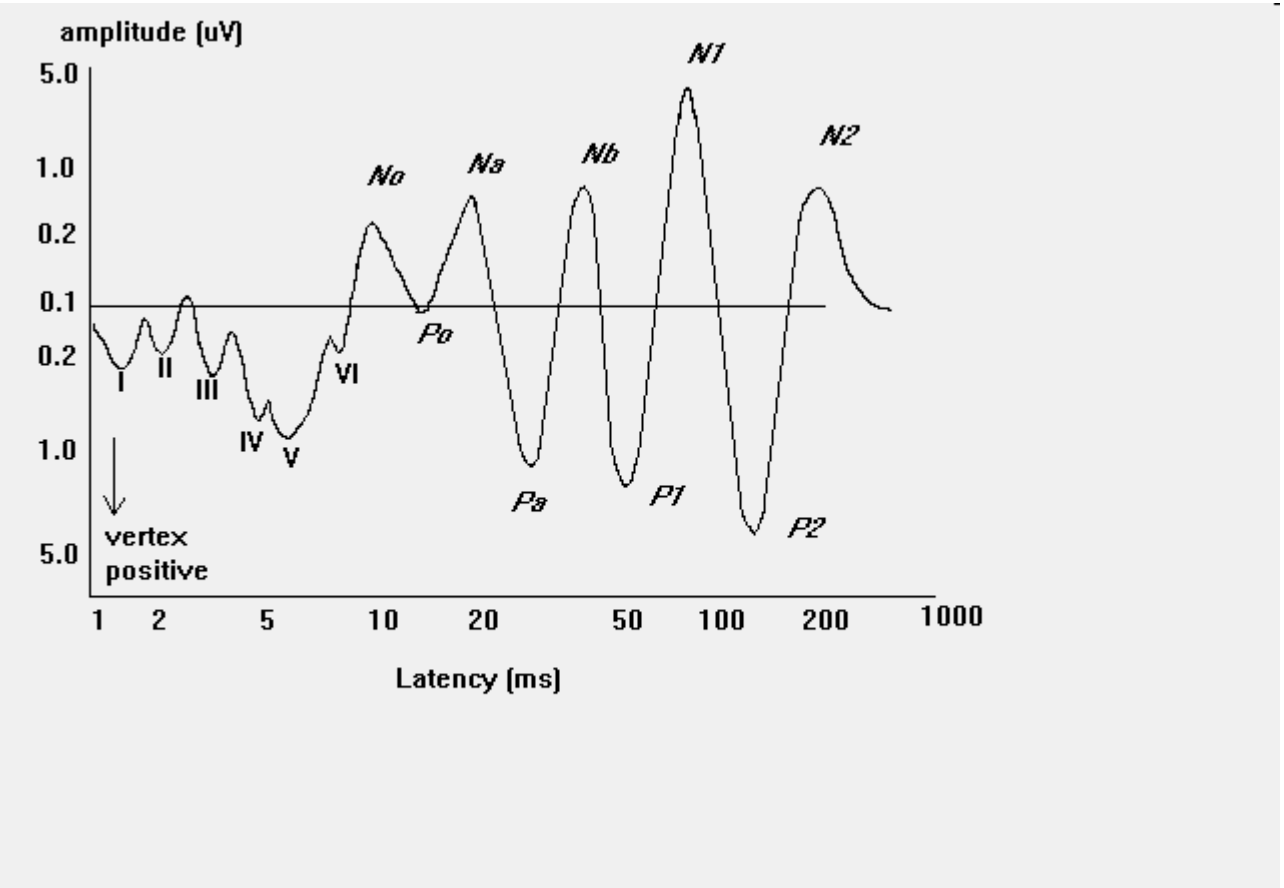
	examples
3 000 000-6 000 000	Pepper spray
2 000 000	Trinidad Moruga Scorpion
1 850 000	Chocolate 7-Pot
1 600 000	Dorset Naga
1 450 000	Trinidad Scorpion Butch Taylor
1 200 000	Naga Viper, Trinidad 7 Pot Jonah
1 200 000	Satan's Strain Trinidad Scorpion Moruga
1 100 000	Naga Morich, Infinity Chili
1 050 000	Bhut Jolokia
850 000	Trinidad 7 Pot CARDI Strain
350 000 – 580 000	Red Savina Habanero
100 000 – 350 000	Habanero
50 000 – 100 000	Pepper Birds Eye, Piri Piri
30 000 – 50 000	Tabasco pepper
5 000 – 23 000	Serrano
5 000 – 10 000	Chipotle
2 500 – 8 000	Jalapeño, Tabasco sauce
1 000 – 2 000	Poblano
100 – 500	Pimento

Evoked potentials





Evoked potentials – auditory as example

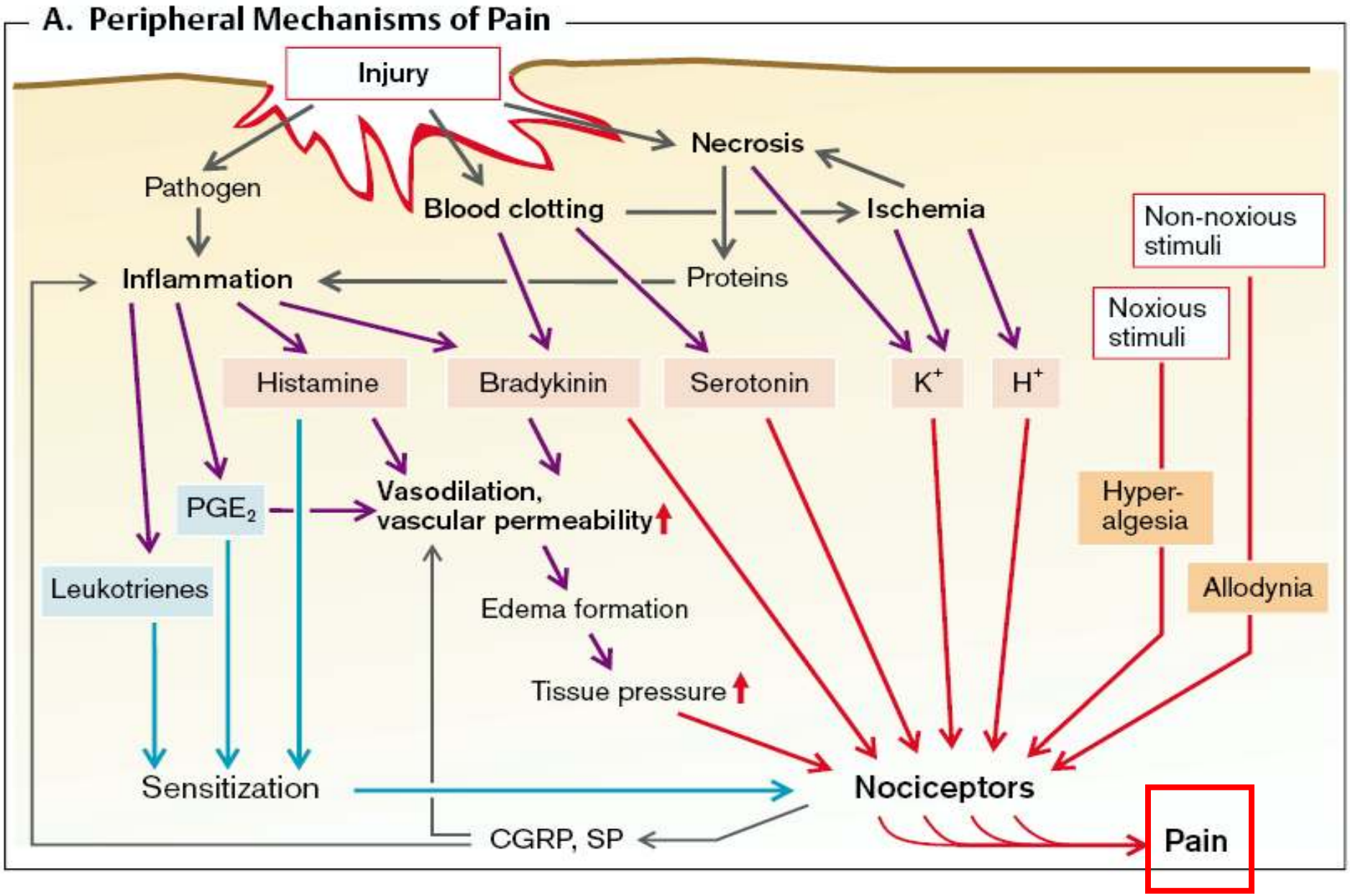


Objective Audiometry:
Brainstem or cortical evoked response audiometry BERA (CERA)

Outline

- Pain
- Motor disorders

Pain



CGRP (Calcitonin-gene related peptide), SP (Peptide substance)

Tissue injury leads to painful sensation

Pain:
1 is a warning that something goes wrong
2 helpful to diagnostics and localization pathologies
3 can be pathologic, anoying beyond the purpose

Psychological pain components
Algothymic component is its emotional context
Algognostic component says, where, what and how much it gets wrong

Pains, which lose the warning purpose are **…neuralgic pains**
neurologic investigation shows no deviation from norm.

Psychophysics: - no relation between stimulus intensity and percept intensity
- there is continuous transition between various touch and pain sensations
tickling, sharp point touch, warm, cold vs.
itching, puncture, scalding (opaření), congelation
what itches, we scrub (scrape) (?), [Fenistil – antihistaminic, antipruriginous drug]

Pain is modified by…

- previous experience, expectations
- instruction, suggestion
- emotions, especially fear and anxiety
- concurrent activation of other sensory inputs
- diversion/ redirection of attention

Pain leads to activation of…

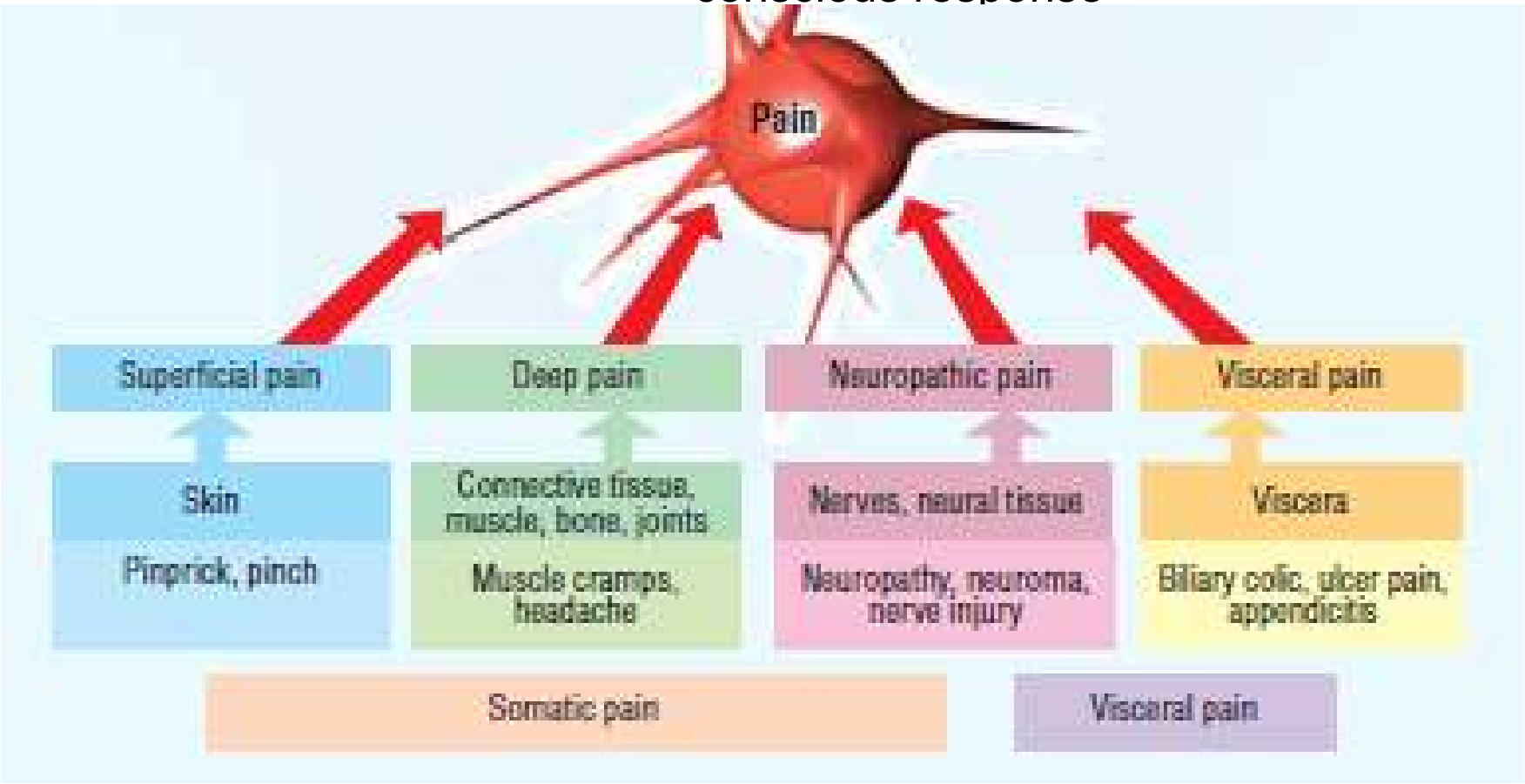
- sympathetic n.s.

vasoconstriction, hypertension, tachycardia, sweating, paleness, goose flesh, mydriasis

- parasympathetic n.s.

hypotension, bradycardia, nausea/ vomiting

- motor response
- conscious response



Types of pain, phenomenology

Patho-genetic classification of pain

- •receptive (nociceptive)
- •peripheral neurogenous (neuropathy)
- •central neurogenous
- •originating in autonomous nervous system (Sympathetic n.s.)
- •visceral
- •pain of psychical origin

Acute pain

-cause can be identified

-short term

-disappears when the original cause is cured

-usually does not recurr

Chronic pain

-longer than 6 months

-cause may not be identified

-intensity higher than expected to known stimulus

-causes high physical and psychical stress

-annoying in daily life

Nociceptors, pain receptors = dedicated receptors, ion channels and free nerve endings

- They are sensitive on the **pH changes** (pH in acute abscess, phlegmona reaches 5,8 = pain, pH in chronic abscess is normal, without pain)

- Nociceptors register the **ratio K^+:Ca^{2+}**
  (treshold for pain is lower in the lower Ca^{2+} level in ECV)
- evoking inflammation are (permeability of vessel wall, oedema) histamin, bradykinin, serotonin

- direct influence of free-nerve endings:
  potassium, histamin, bradykinin serotonin

- sensitisation of nociceptors:
  prostaglandins, esp. PgE_2, interleukin-1, interleukin-6, cyclooxygenases (COX-1, COX-2)

- From activated free nerve endings P-substance is released.
  It influences vessel wall (vasodilation, permeability of vessel wall, oedema) and mast cells (release of histamin after degranulation).

Fibres conducting nociceptive stimuli

- **C-fibres** – without myelin sheets, action potentials are convected slowly, fibres convect deep, nonaccurate localized, diffuse pain

- **Aδ-fibres** – with thin myelin sheet, fibres mediate fast conduction of sharp, accurate localized pain

- **Aα/Aβ-fibres** – large myelinated. Fibres do not convect nociceptive stimuli, they mediate tactile stimuli

- Afferent fibres enter dorsal spinal roots. In this region exist excitatory and inhibitory interneurons. Inhibitory interneurons gate the passage of information into thalamus and cortex.

Painful stimuli

-chemical

-endogenous inflammation mediators (bradykinin, prostaglandins, serotonin, histamin, K+, H+, Il-1)

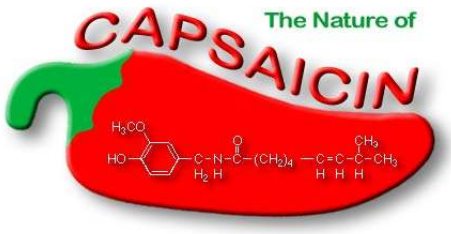
-exogenous substances (capsaicin, formalin = formaldehyde)

-low/ high temperatures

-temperature above 42°C is damaging

-mechanical

During painful stimuli…



- are activated tetrodotoxin resistant (TTX-R) channels
- ATP is relased from damaged cells and acts as pain mediator. ATP receptors are purin receptors (P_2X)
- vaniloid receptors (VR_1) are receptors for capsaicin, also activated above 42°C, pH < 6.5
- activated acid sensing ion channels (ASIC), when pH < 6.5
- Up-regulation of post-synaptic receptors of excitation neuro-transmitters - glutamate (NMDA) and substance P (NK_1)

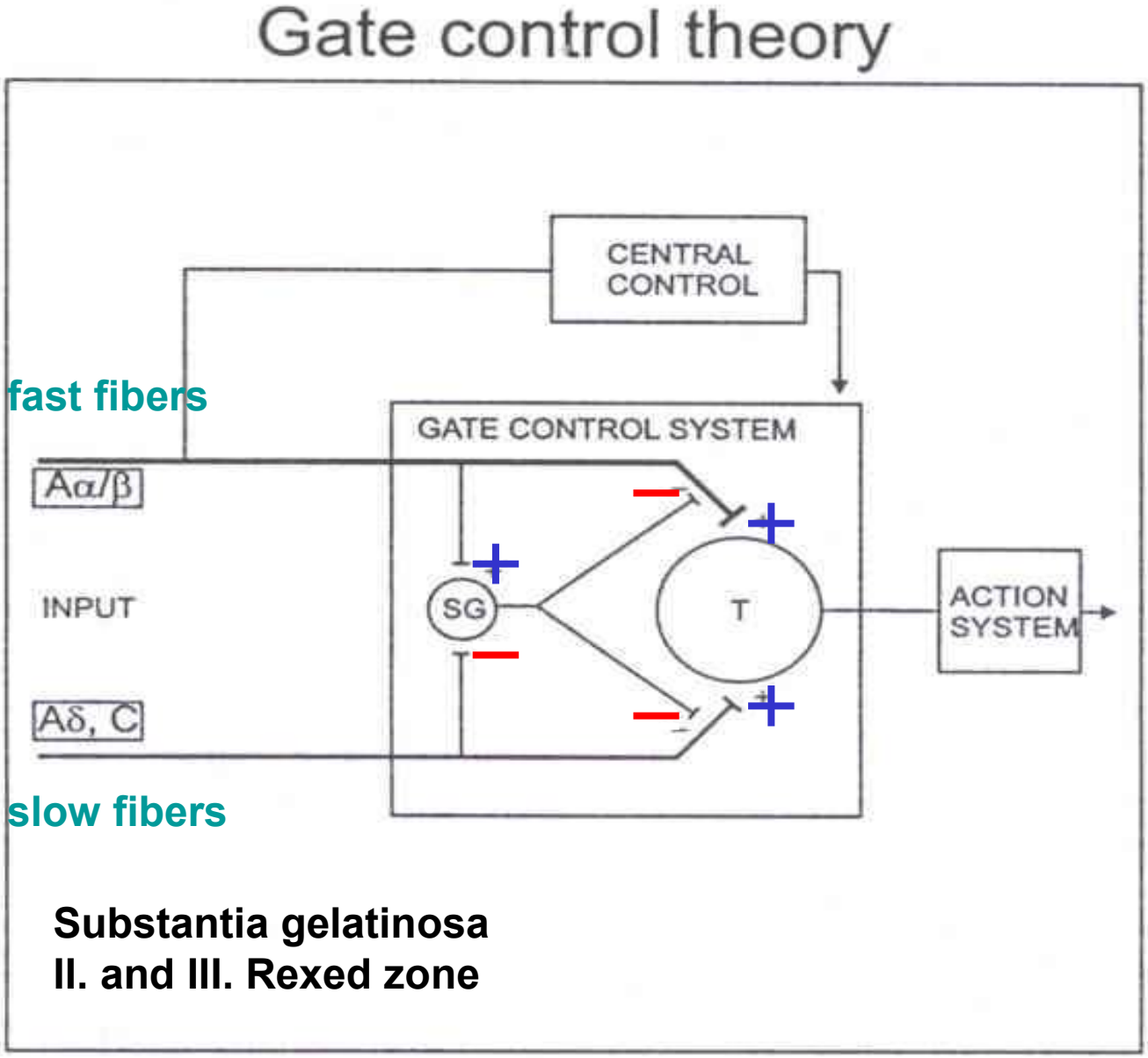
Vaniloid Receptors and Pain

Birds versus mammals...

(Versus insects...)

Eating hot peppers can be beneficial to rise the individual pain threshold…

Pain gating control – spinal cord



Opioid system and others

- nigro-striatal and meso-limbic, dopaminergic
  - motor systems and reward pathways
- hypothalamo-hypophyseous
  - central hormone modulation
- ascendent and descendent pathways
  - modulation
  - ascendent – spinal cord, talamus
  - descendent – peri-aquaeductal grey, nuclei raphe

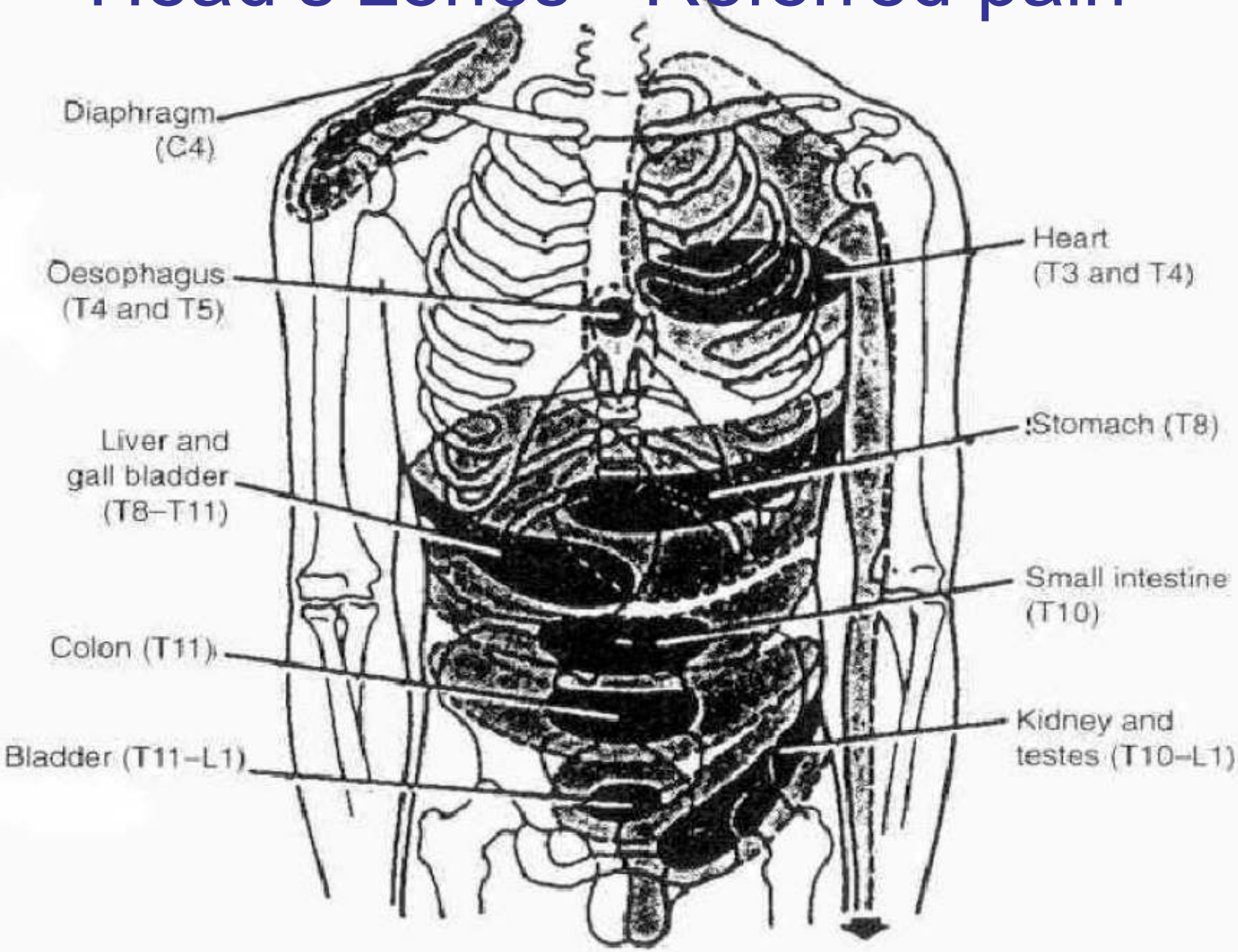
Endogenous opioids

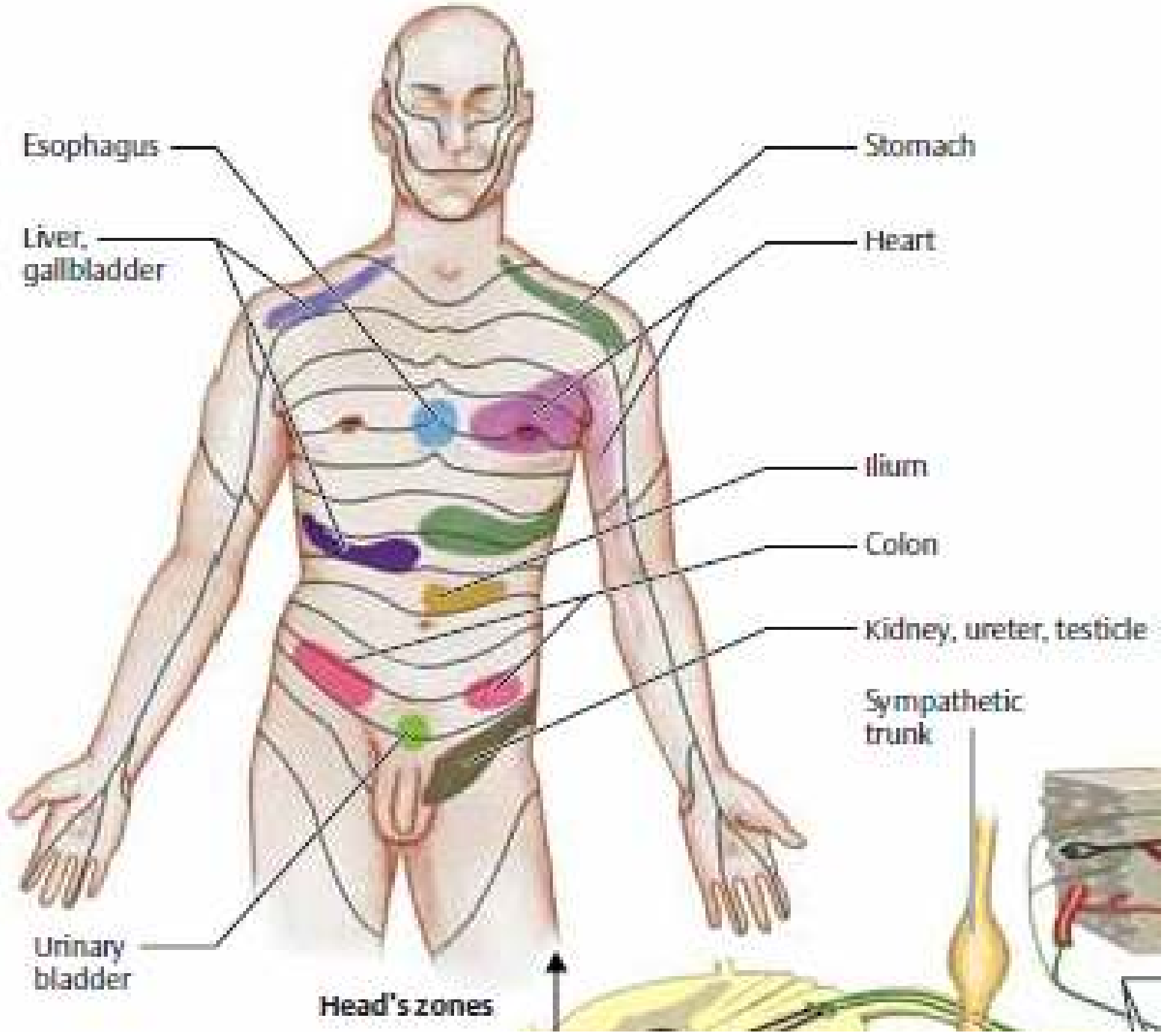
- β-endorphine (31 AA) - μ
- Endomorphine (4 AA) - μ
- Leu-enkefalin (5 AA) - δ
- Met-enkefalin (5 AA) - δ
- Dynorphine(A:AA 1-8, B:AA1-17) - κ
- nociceptin/ orphanin
- nocistatin
- pre-synaptic receptors
  - Inhibiting neuro-transmitter release
  - ⇓ Ca^{2+}
- post-synaptic receptors
  - ⇑ K^{+} conductance – hyperpolarization

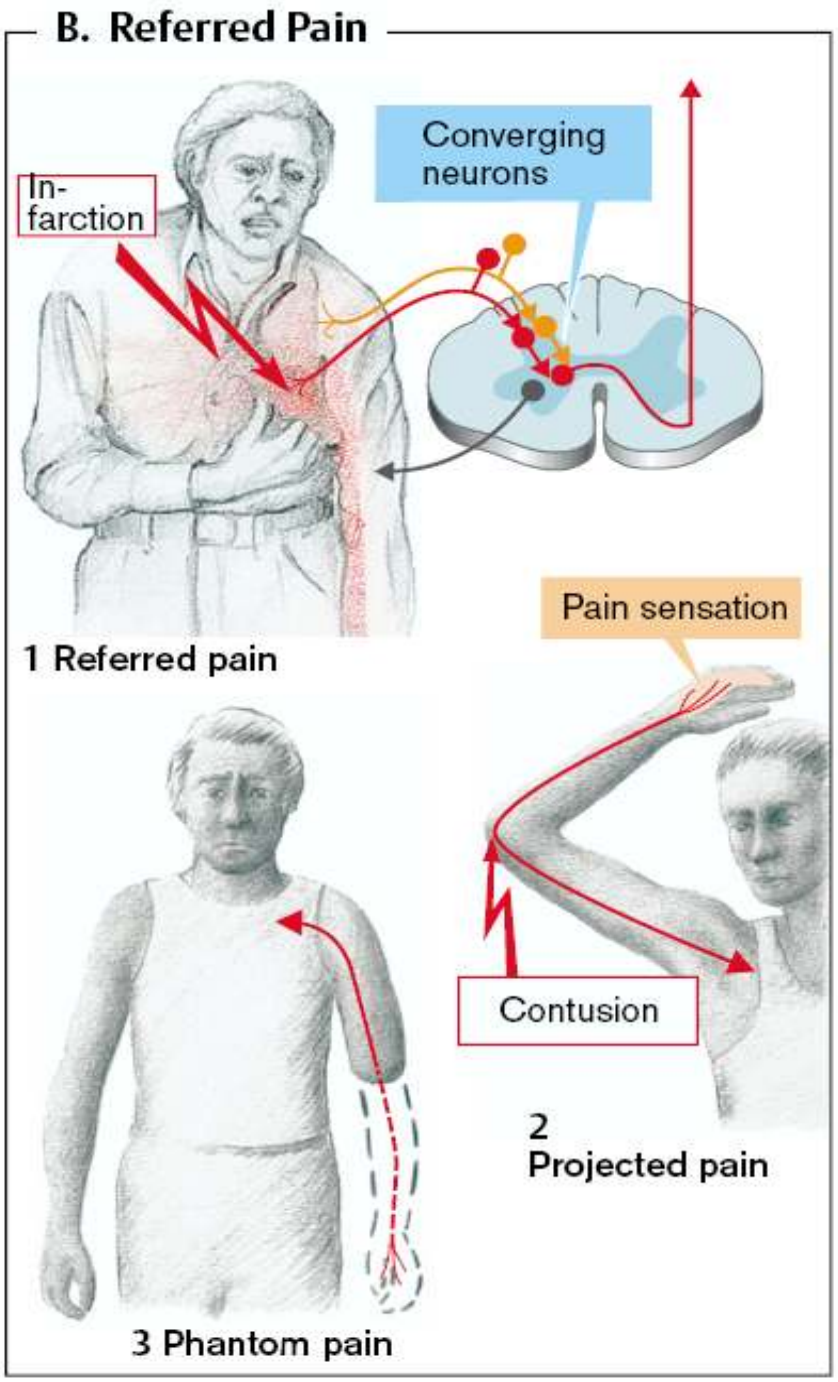
Endogenous cannabinoids

- amids and esthers of fatty acids
- anandamid
- palmitoyl-etanolamid (PEA)
- receptors CB1 a CB2
- CB1 in PAG and RVM, sensory neuron
- CB2 in structures of immune system
- FAAH – hydrolasis of FA amids
- In the inner ear and auditory pathway as well

Head's zones - Referred pain



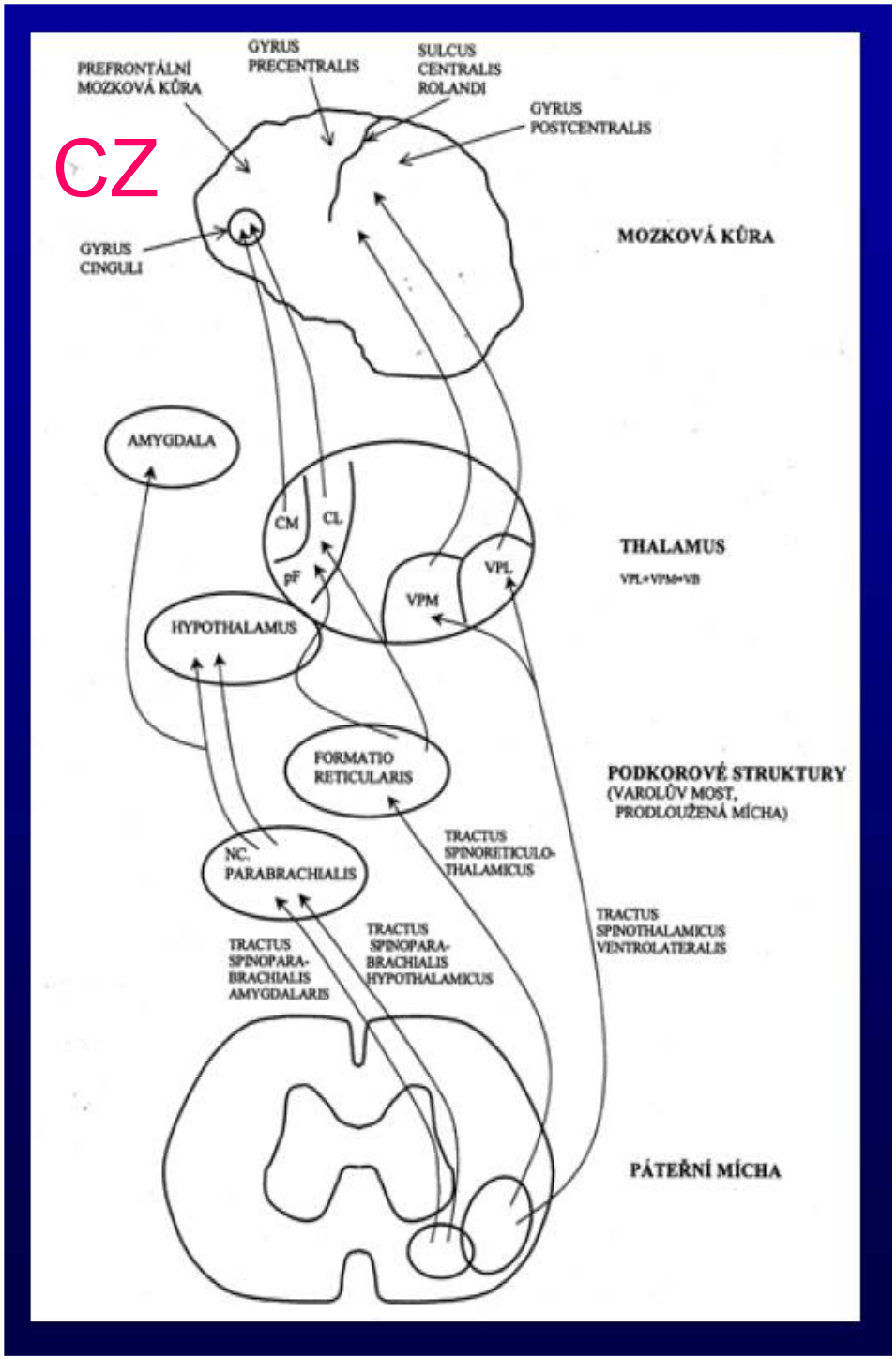

Esophagus
Liver, gallbladder
Stomach
Heart
Ilium
Colon
Kidney, ureter, testicle
Sympathetic trunk
Urinary bladder
Head's zones



Referred and pathologic pain

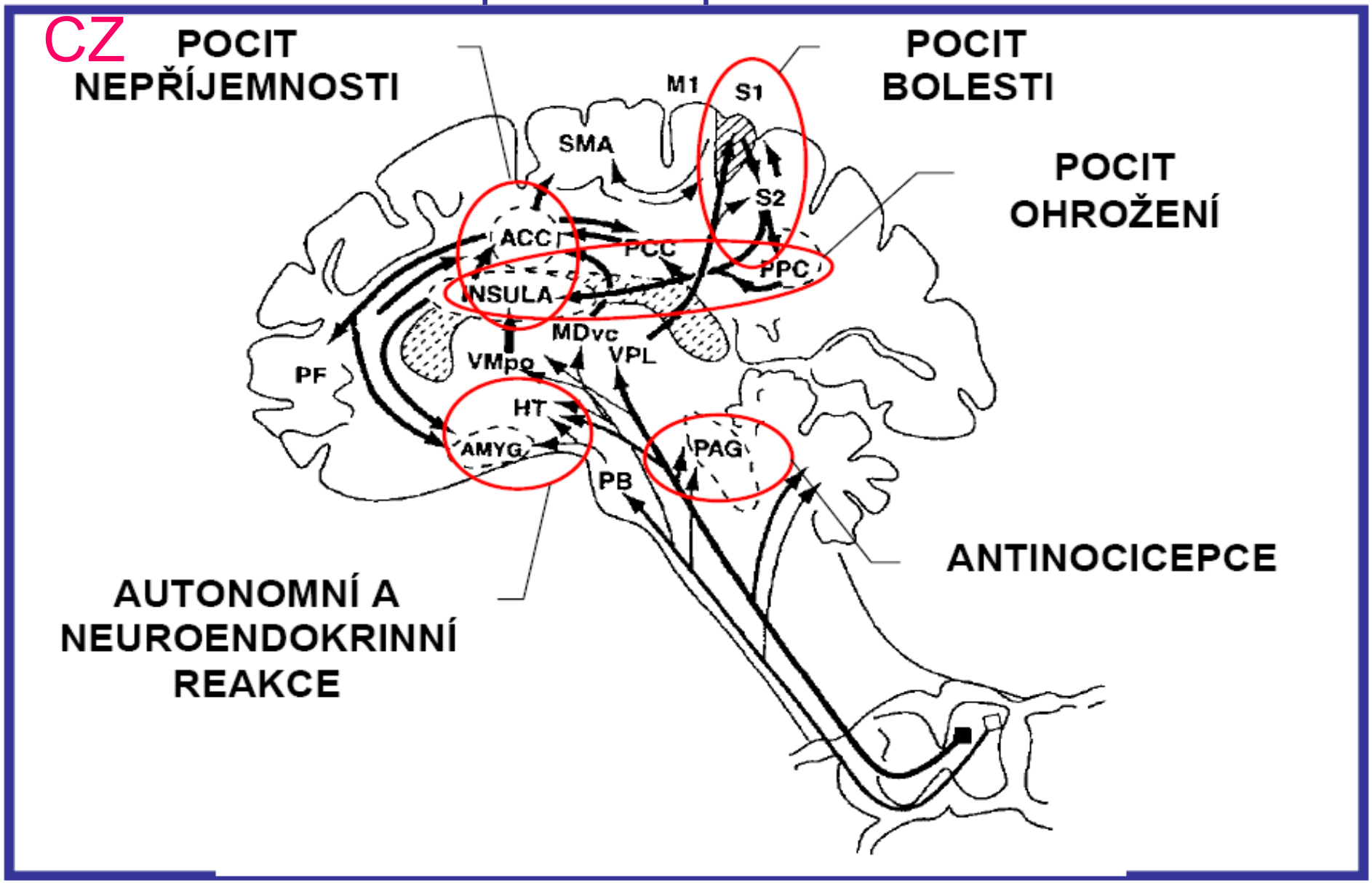
Other pathologic painful sensations:

…,
headache,
n. trigeminus,
Migraine,…

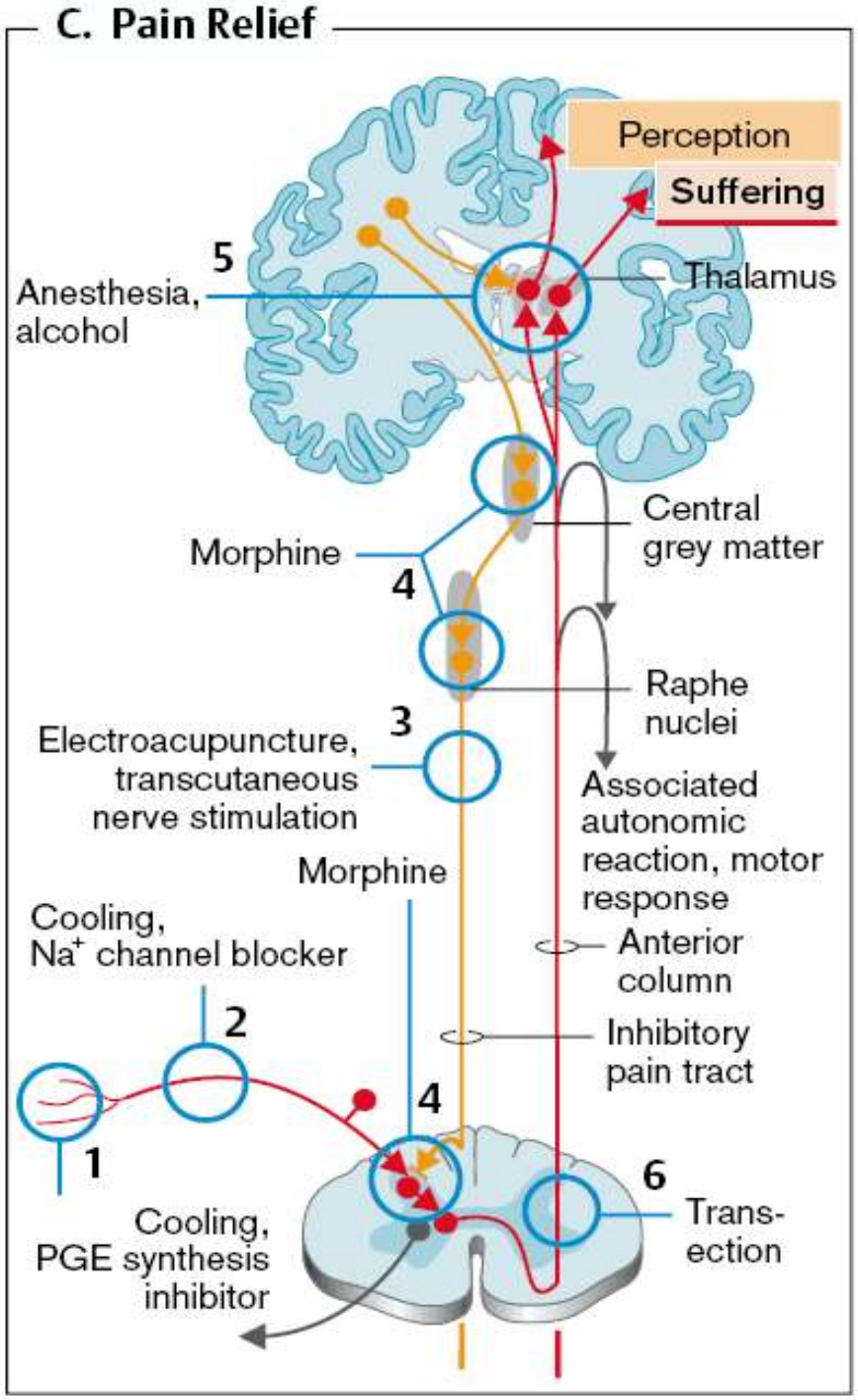


Localization of CNS pain pathways

Localization of sensory, affective and cognitive pain components



Pain Relief

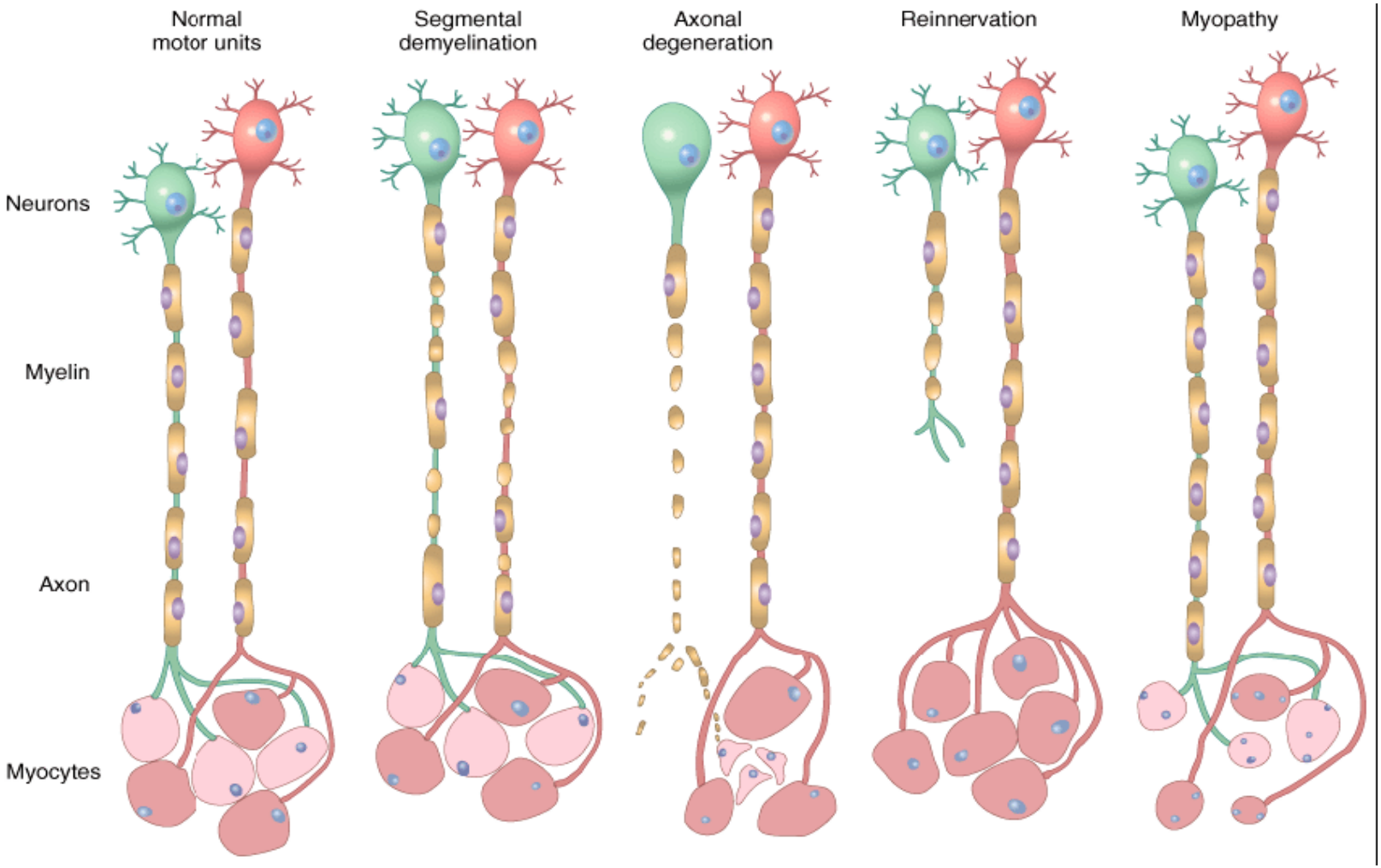

C. Pain Relief
Perception
Suffering
5
Anesthesia, alcohol
Thalamus
Central grey matter
Morphine
4
Raphe nuclei
3
Electroacupuncture, transcutaneous nerve stimulation
Associated autonomic reaction, motor response
Morphine
Cooling, Na+ channel blocker
Anterior column
2
Inhibitory pain tract
4
1
6
Trans-ection
Cooling, PGE synthesis inhibitor

Motor disorders/
Movement disorders

Movement disorders

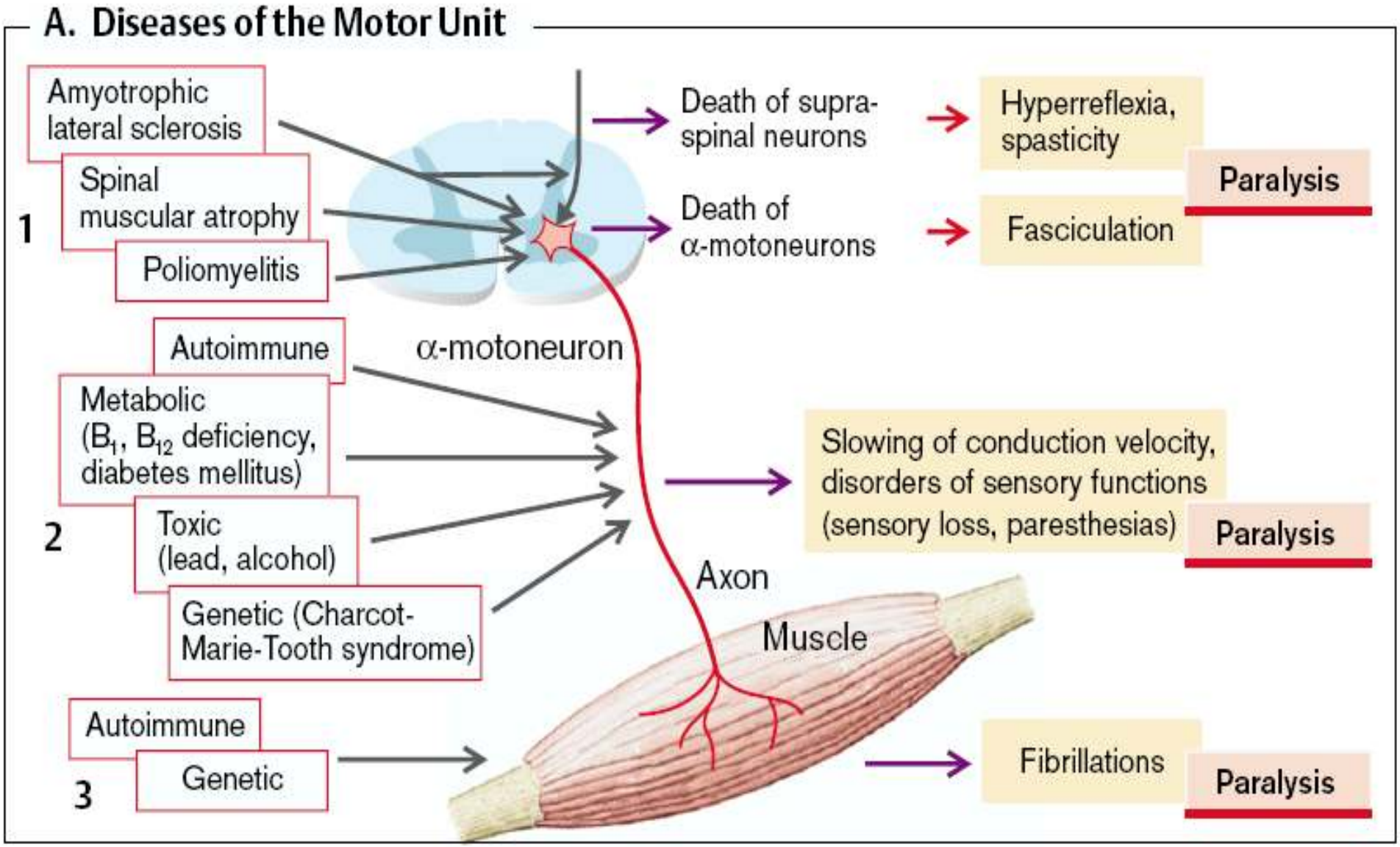
- Muscle disorders
- Lower motoneuron disorders
- Upper motoneuron disorders
- Basal ganglia disorders
- Cerebellum disorders
- Disorders of passive movement apparatus

Lower motoneuron - Neuromuscular unit disorders



norm neuropathy myopathy

Diseases of the motor unit-neuropathies



Neuropathies versus myopathies

Clinical findings	**Neuropathy**	**Myopathy**
Muscle weakness	**++**	**++**
Loss of reflexes	**+**	0
Fasciculations (twitchings)	**+**	0
Sensory deficit	**+**	0
Abnormal reflexes (Babinski)	**+**	0

Lower motoneuron disorders

- Peripheral nerve affected
  - Axonal degeneration; injury $\rightarrow$ Waller degeneration
  - Axonal demyelinization (Guillain Barre syndrome)

(Both motor and sensory disorder)

- α-motoneuron soma affected
  - Inflammation (example poliomyelitis)

Lower motoneuron disorders

- (phenomenology of sole motor disorders)
  - Motor unit (fasciculations)
  - atrophia of the whole motor unit
  - when denervated, first comes fibrillation, then atrophia

Upper motoneuron

Is it a

- Pyramidal pathway ?

or

- Extra-pyramidal system ?

Upper motoneuron, signs

- plegia, paralysis
- spasticity
- cogged wheel sign
- hyperreflexia
- clonus
- abnormal exteroceptive reflexes (Babinski)
- (no atrophy, no fasciculations)

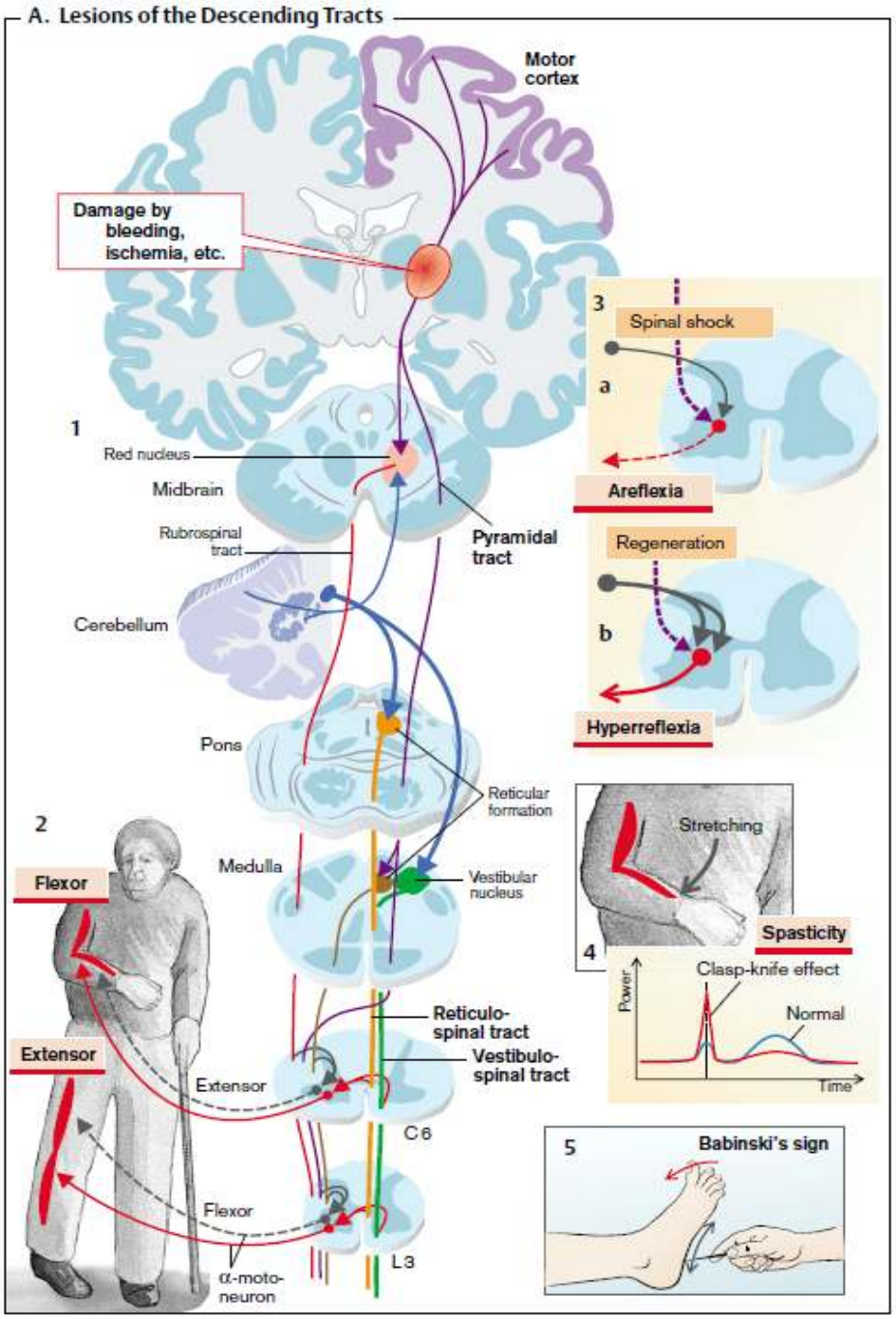
Upper motoneuron, point of view of general practice

"Upper motoneuron" means all descendent motor systems, not only tractus cortico-spinalis

Brain $\rightarrow$ lateral signs, hemiplegia

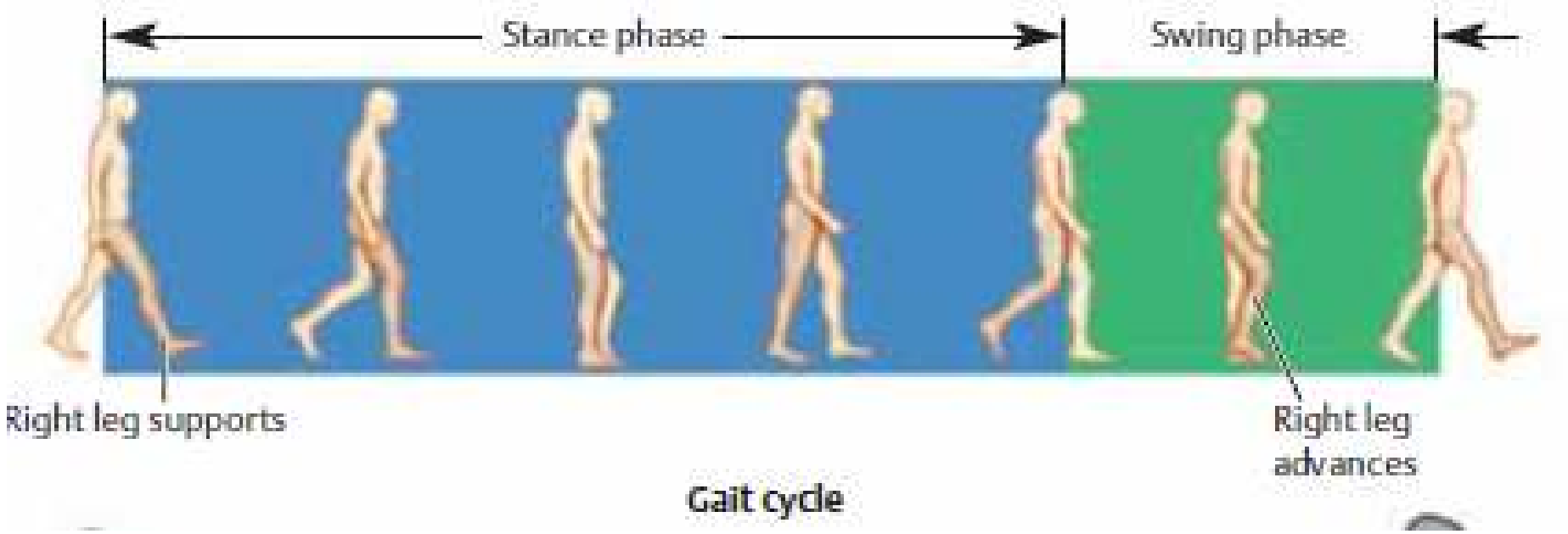
Spinal cord $\rightarrow$segmental signs, paraplegia, quadruplegia

Upper motoneuron disorders =descending tracts lesions



Spasticity

- Higher resistance towards passive movement, accented with higher velocity (scissor gait)
- Hyper-reflexivity
- Central spasticity (abnormal excitation)
- Spinal spasticity (interneurons)
  - Flexor reflexes
  - Extensor spasm (fragment of locomotion?)
  - Sensory neurons

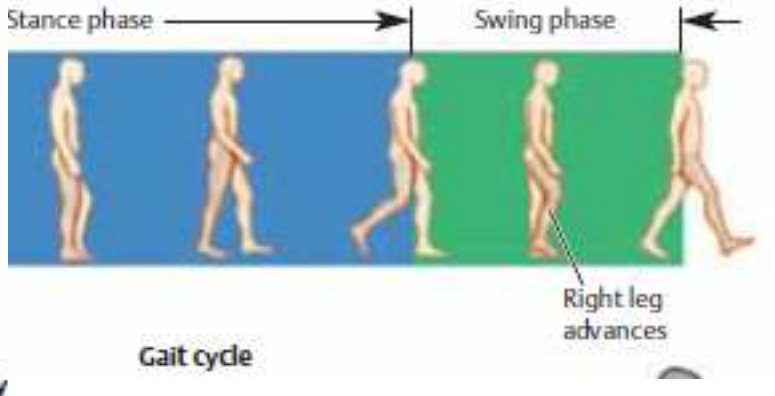

Stance phase
Swing phase
Right leg supports
Right leg advances
Gait cycle

Normal gait

Steppage gait

Posture and gait in youth (left) and old age (right)

Knee instability (quadriceps paresis, leg dorsally angulated)

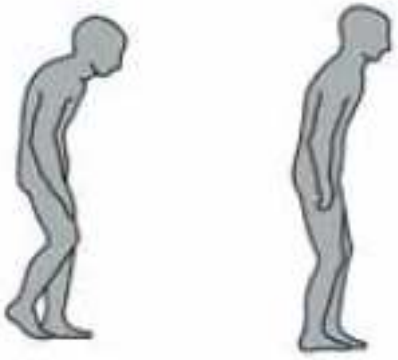


Gait cycle

Ataxic gait

Spastic gait (right hemiparesis)

Spastic gait (spastic paraparesis)



Hypokinetic-rigid gait (left, Parkinson disease; right, start delay/gait apraxia)

Psychogenic gait disturbances (histrionic movements)

Pathological gait

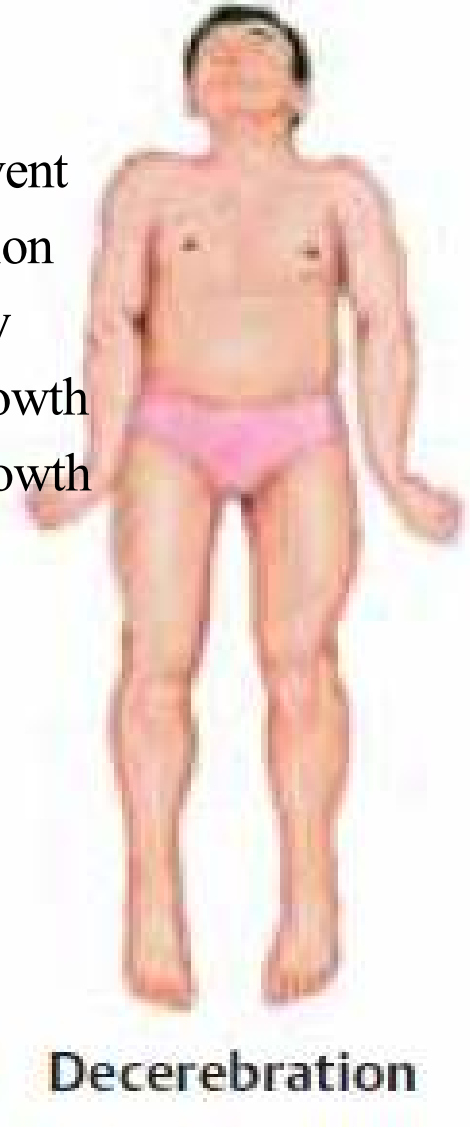
Central Nervous System (CNS) trauma. Spinal Cord Injury (SCI).

Spinal shock in man

Phase	Time	Physical exam finding	Underlying physiological event
1	0-1d	Areflexia/Hyporeflexia	Loss of descending facilitation
2	1-3d	Initial reflex return	Denervation supersensitivity
3	1-4w	Hyperreflexia (initial)	Axon-supported synapse growth
4	1-12m	Hyperreflexia, Spasticity	Soma-supported synapse growth

meningeal irritation position

In both
meningeal irritation
and spinal shock
extensor systems
take over
flexor systems

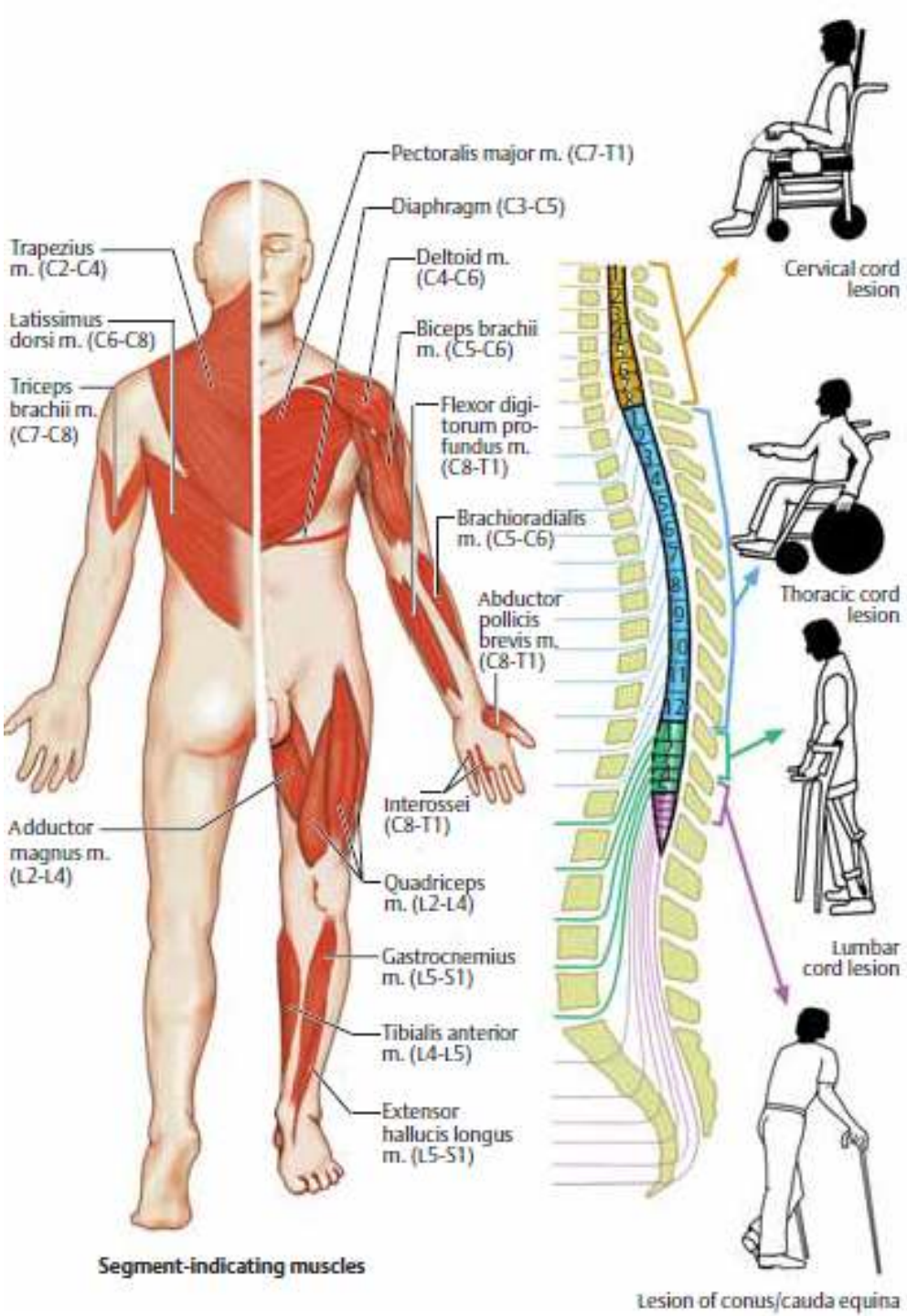


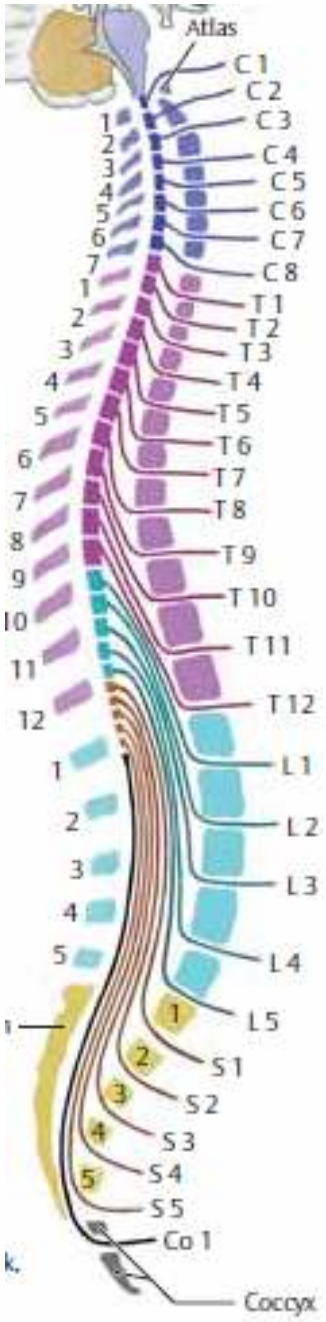
spinal shock position

Comparison of CNS to PNS (peripheral nervous system/ peripheral nerve) injury

Progression of CNS injury (Spinal cord as a model)

- local swelling at the site of injury which pinches off blood perfusion → ischemia
- Excessive release of glutamate and excitotoxicity of neurons and oligodendrocytes at the site of injury
- Infiltration by immune cells (microglia, neutrophiles)
- Free radical toxicity
- Apoptosis/ necrosis

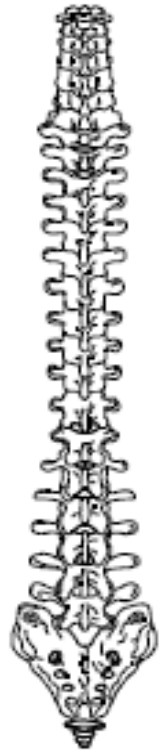

Pectoralis major m. (C7-T1)
Diaphragm (C3-C5)
Trapezius m. (C2-C4)
Deltoid m. (C4-C6)
Latissimus dorsi m. (C6-C8)
Biceps brachii m. (C5-C6)
Triceps brachii m. (C7-C8)
Flexor digitorum profundus m. (C8-T1)
Brachioradialis m. (C5-C6)
Abductor pollicis brevis m. (C8-T1)
Interossei (C8-T1)
Adductor magnus m. (L2-L4)
Quadriceps m. (L2-L4)
Gastrocnemius m. (L5-S1)
Tibialis anterior m. (L4-L5)
Extensor hallucis longus m. (L5-S1)
Cervical cord lesion
Thoracic cord lesion
Lumbar cord lesion
Segment-indicating muscles
Lesion of conus/cauda equina



Spinal nerves

Pathophysiology

- **Common Sites**
  - ☺ **C5-6 and T12 ---- L1**
- **higher the injury, the greater the motor/ sensory loss: refer to syllabi/dermatomes**
- **neuro dysfunction depends on the level of the injury**
  - ☺ **T1 or above QUAD (tetraplegia)**
  - ☺ **T2 or below PARA**
  - ☺ **Above C4 Resp. Paralysis**



Pathophysiology (Extent of Injury)

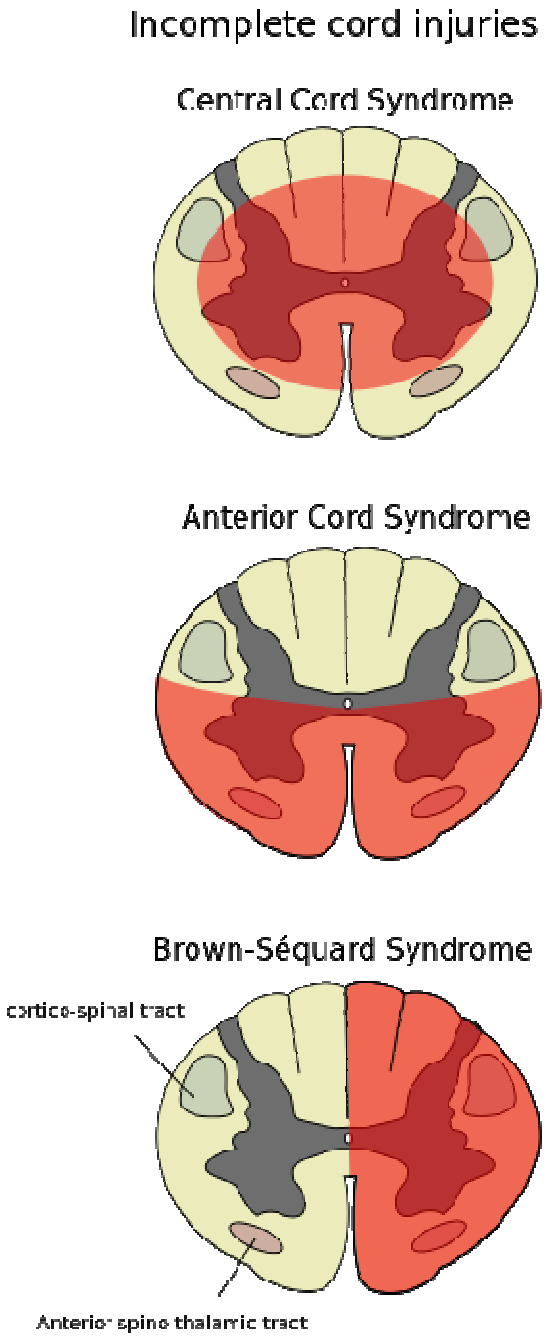
Complete

- Loss of voluntary movement/sensation below the injury
- reflex activity below level of lesion may return after spinal shock resolves
- worse prognosis for recovery--

Incomplete

- (1) Varying degrees of motor/sensory loss below the level of injury & (2) central, lateral, posterior injury
  - Three types
    - Central Cord
    - Brown-Sequard
    - Anterior Cord

Types of incomplete spinal cord injury



Central cord syndrome

Characterized by:

disproportionately greater motor impairment in upper compared to lower extremities, and variable degree of sensory loss below the level of injury in combination with bladder dysfunction and urinary retention.

Incomplete SCI ANTERIOR

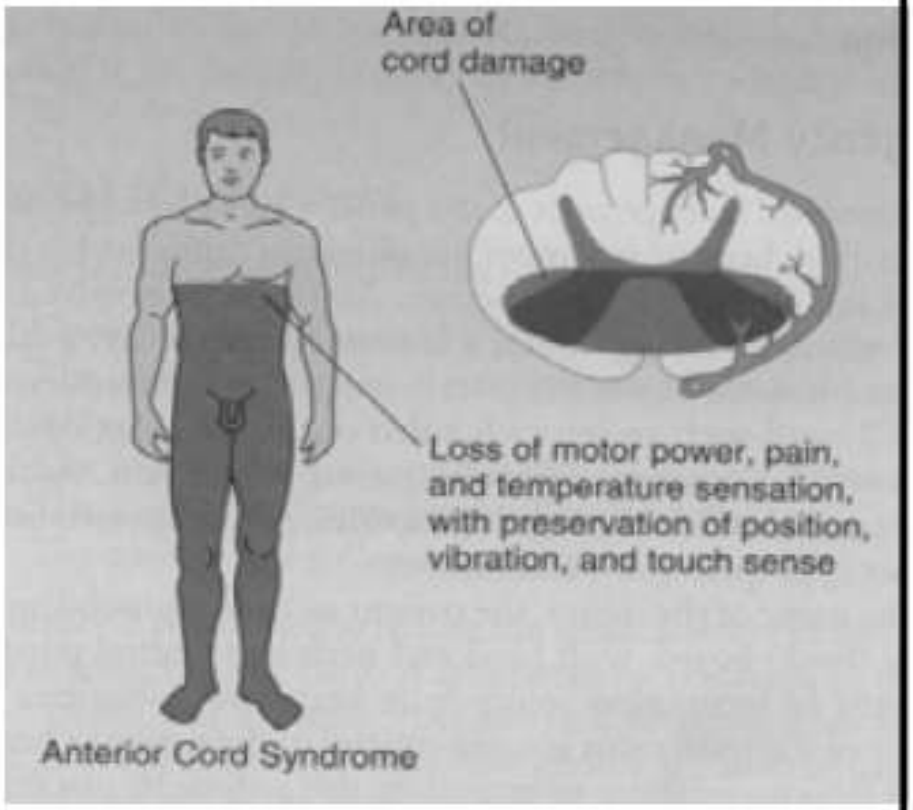
loss of motor, pain/temp

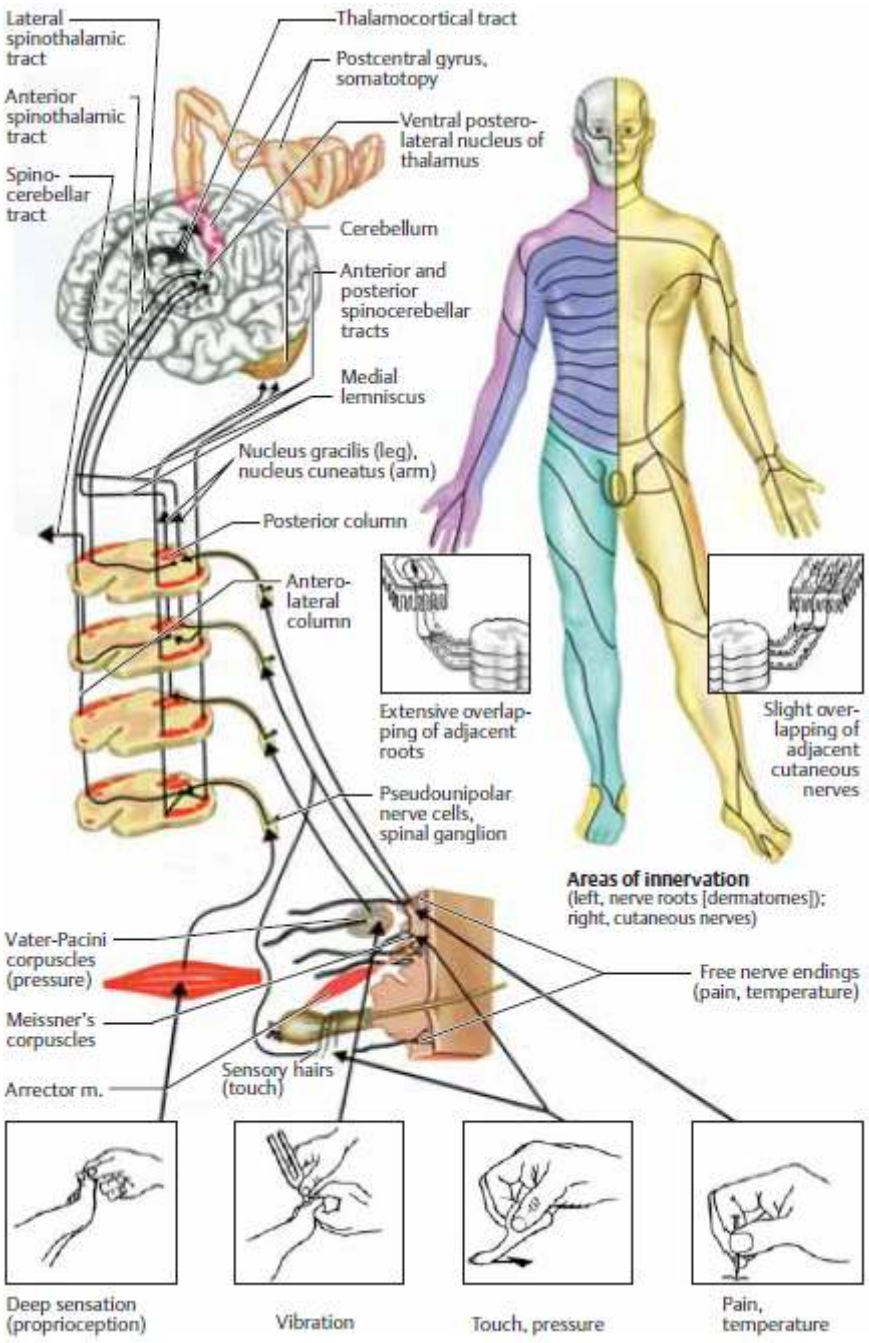
mixed sensory loss

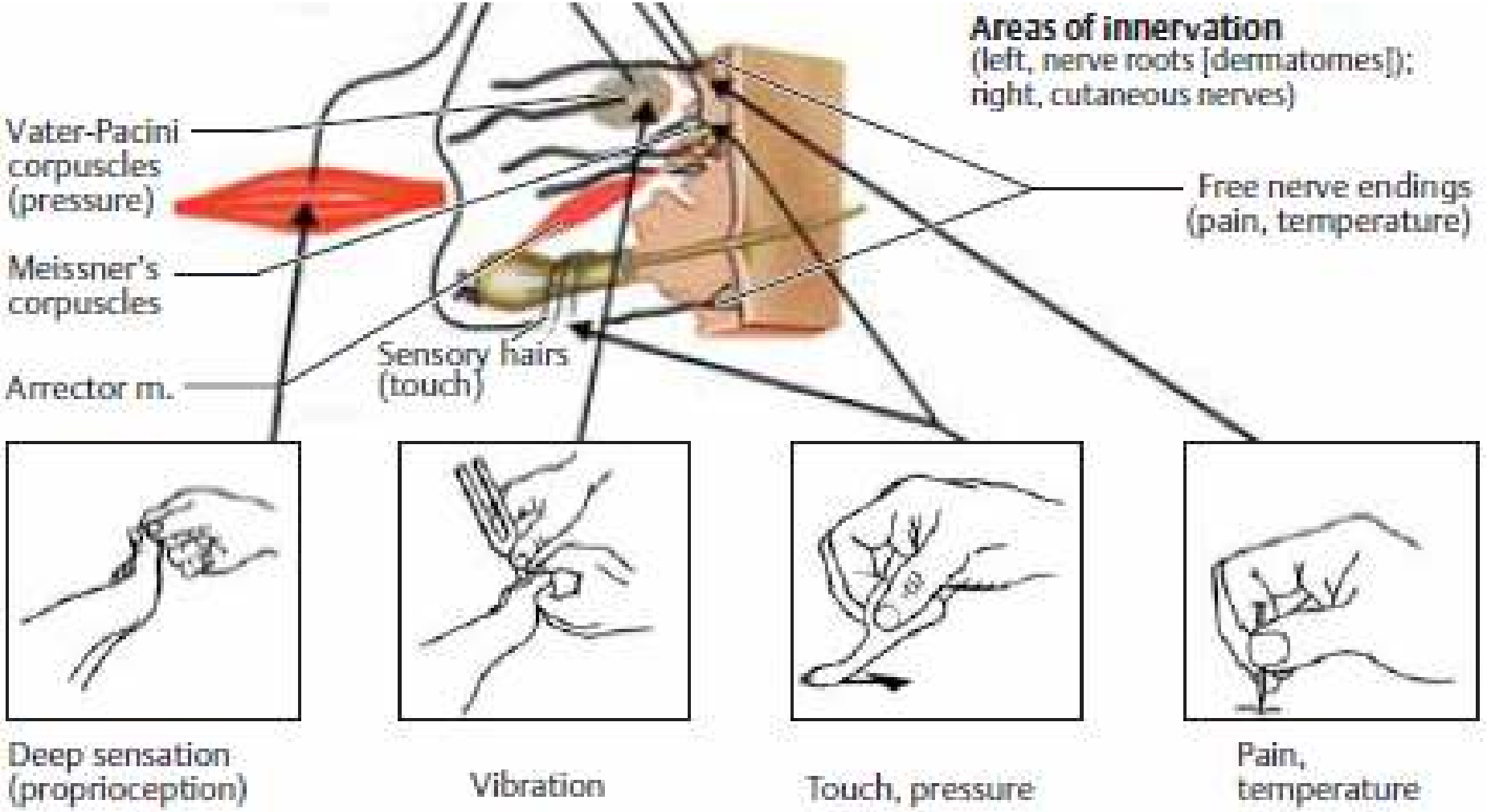
touch, proprioception, vibration remains intact

Cause: _____

_____




Lateral spinothalamic tract
Thalamocortical tract
Postcentral gyrus, somatotopy
Anterior spinothalamic tract
Ventral postero-lateral nucleus of thalamus
Spino-cerebellar tract
Cerebellum
Anterior and posterior spinocerebellar tracts
Medial lemniscus
Nucleus gracilis (leg), nucleus cuneatus (arm)
Posterior column
Antero-lateral column
Extensive overlapping of adjacent roots
Slight overlapping of adjacent cutaneous nerves
Pseudounipolar nerve cells, spinal ganglion
Areas of innervation
(left, nerve roots [dermatomes]; right, cutaneous nerves)
Vater-Pacini corpuscles (pressure)
Free nerve endings (pain, temperature)
Meissner's corpuscles
Sensory hairs (touch)
Arrector m.
Deep sensation (proprioception)
Vibration
Touch, pressure
Pain, temperature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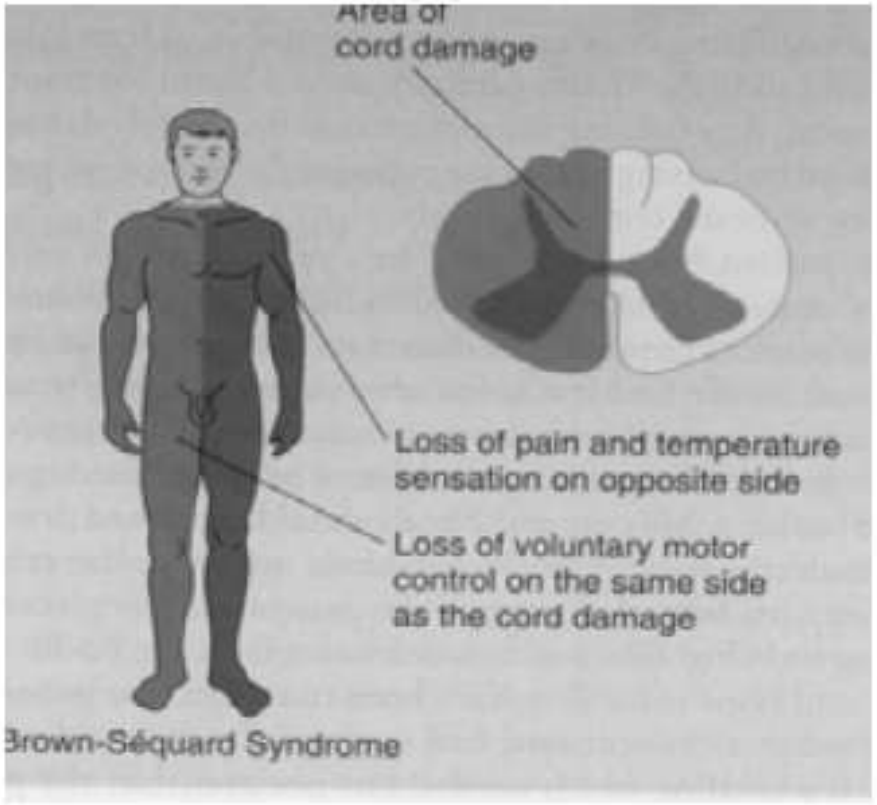
Sensory hairs (touch)
Free nerve endings (pain, temperature)
Deep sensation (proprioception)
Vibration
Touch, pressure
Pain, temperature

Incomplete SCI BROWN-SEQUARD
(cord hemi-section)



On same side as injury--loss of motor, touch, pressure, vibration BUT, pain/temp intact

On opposite side of injury--loss of pain/temp BUT, motor, touch, sensory vibration intact

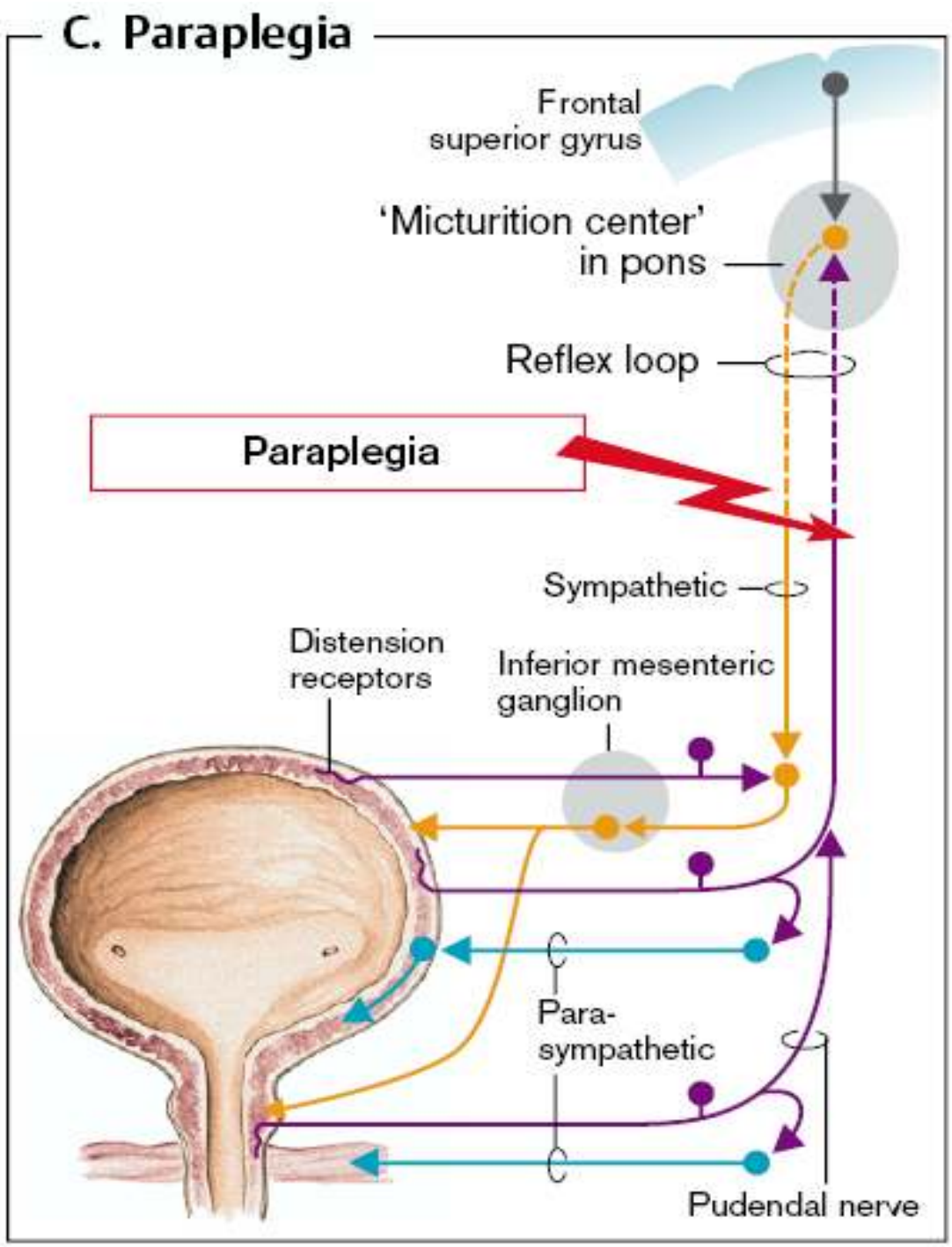
Cause: _____

_____

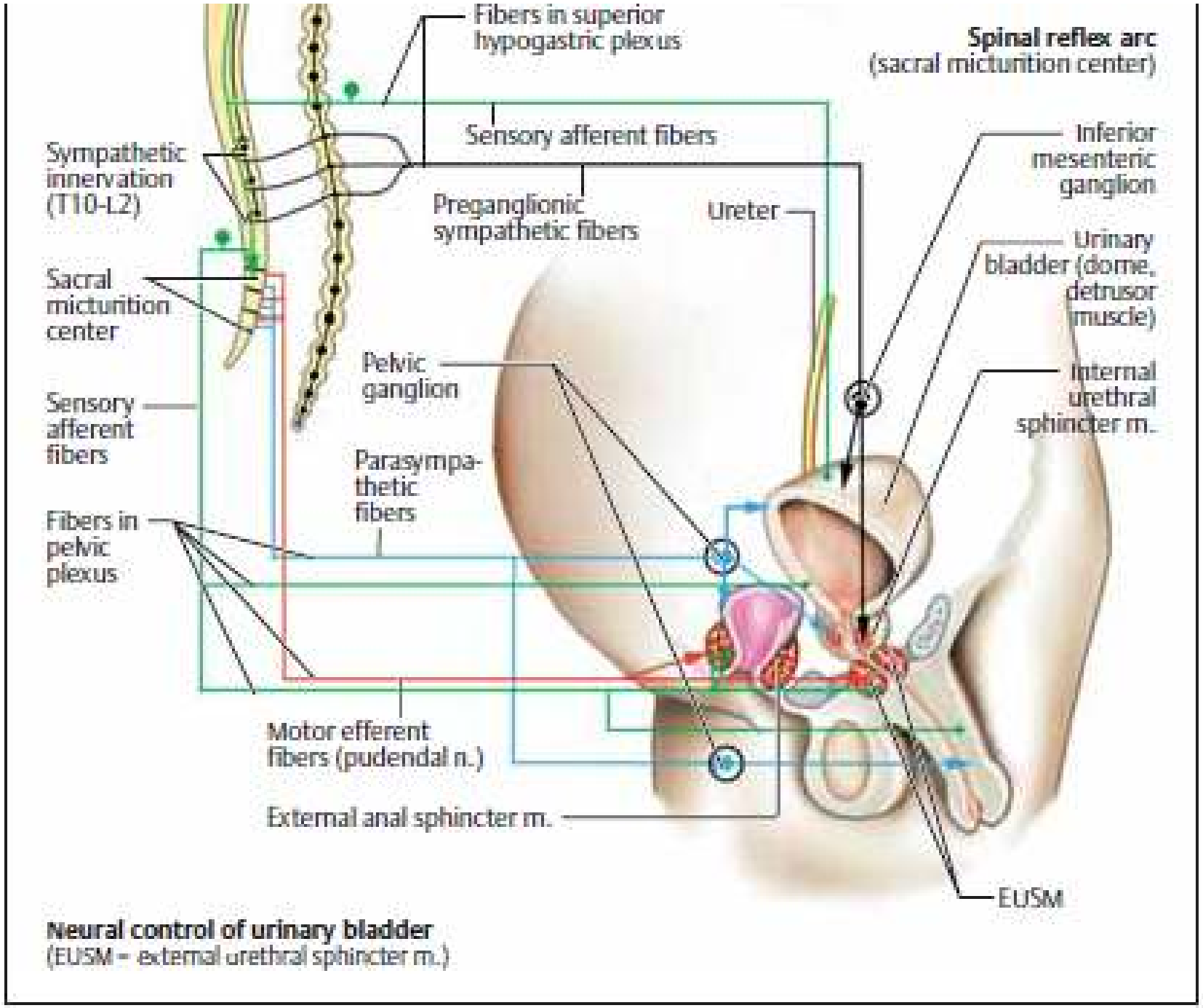
Incomplete SCI

conus medullaris/cauda equina

- Compression of lumbar-sacral area
  - **Conus T11-L1**
  - **Cauda L2-sacral**
- Better prognosis because injury in "horse tail" area
- Loss of motor is variable
- Sensory unimpaired
- Flaccid bowel and bladder
- Impaired sexual function

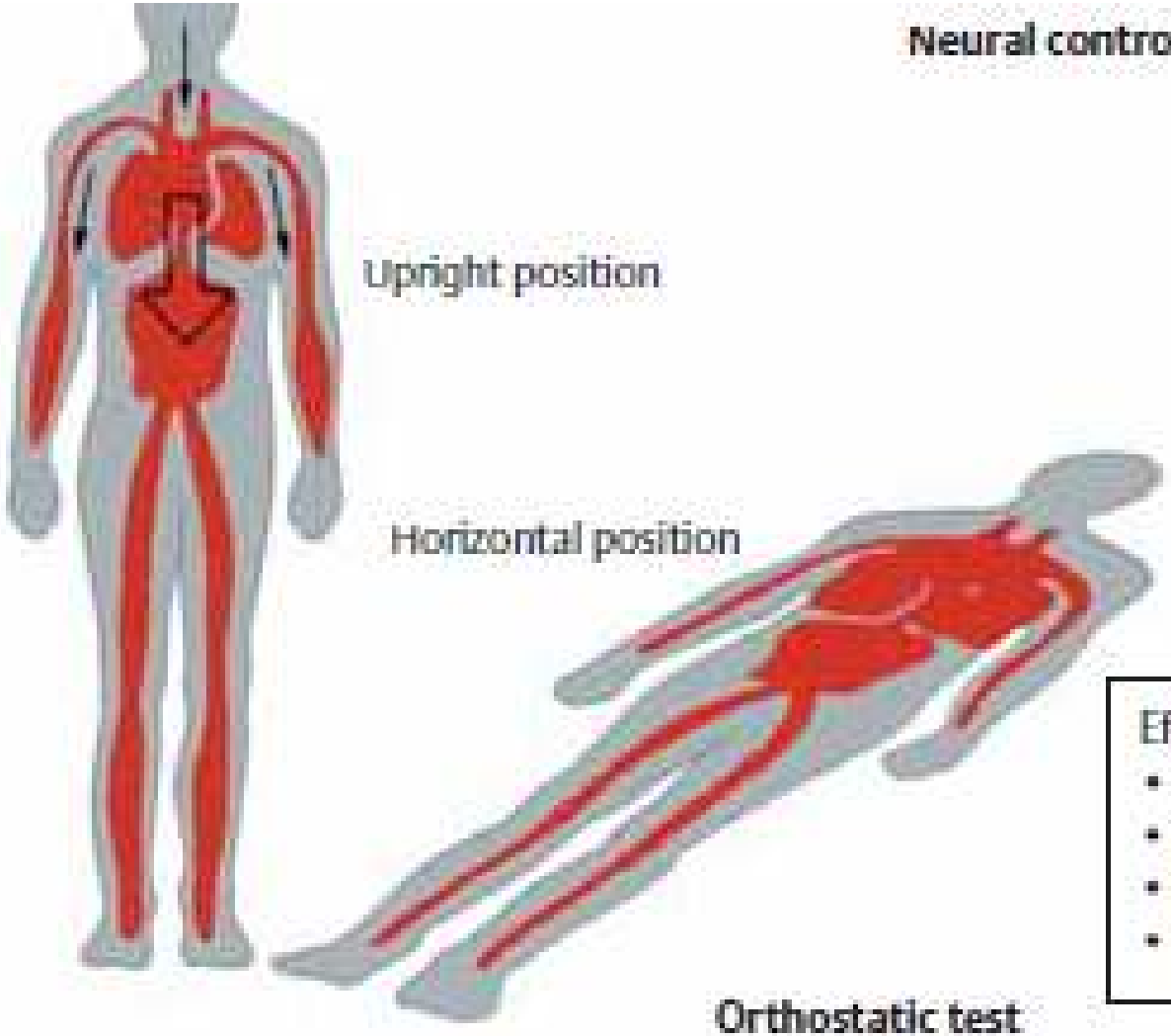


Autonomous urinary bladder



Neural control of urinary bladder
(EUSM = external urethral sphincter m.)

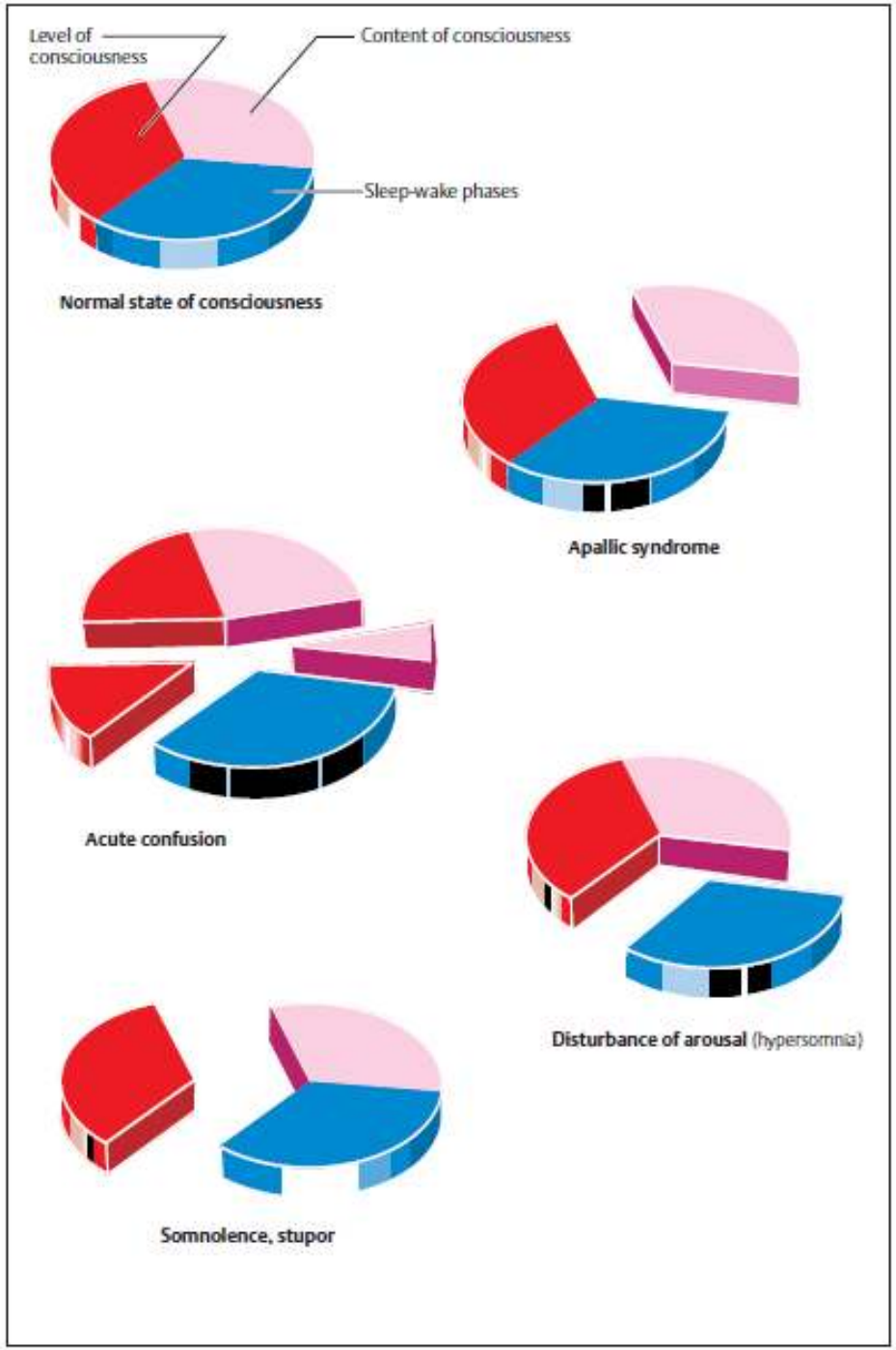
Neural control of circulatory system

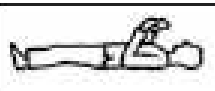
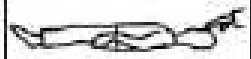
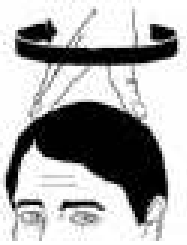


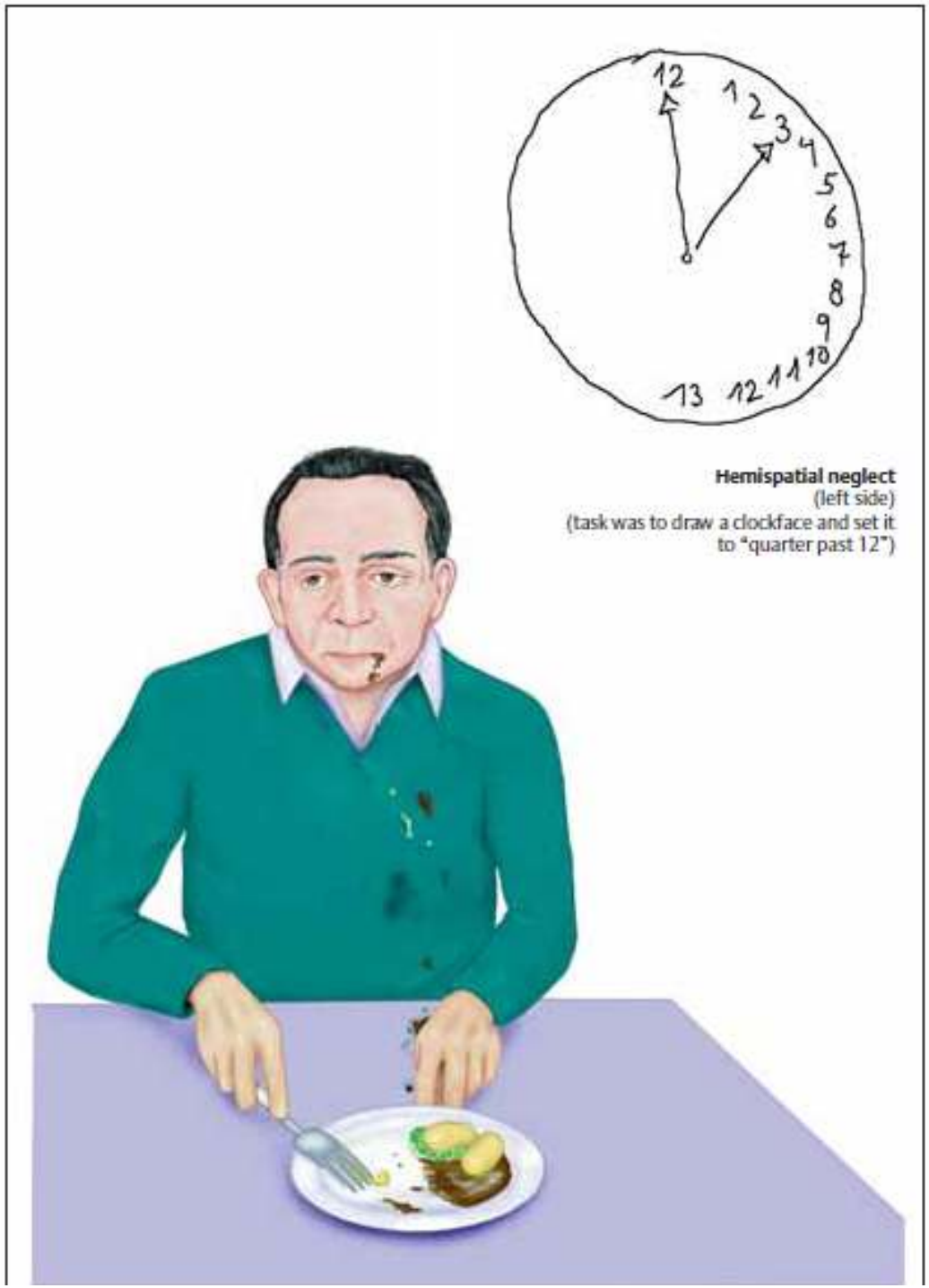
Orthostatic test

Effects of standing upright:

- Sympathetic activity ↑
- Vagal tone ↓
- Renin-angiotensin system ↑
- Blood flow to skin/fat/muscles ↓


Level of consciousness
Content of consciousness
Sleep-wake phases
Normal state of consciousness
Apallic syndrome
Acute confusion
Disturbance of arousal (hypersomnia)
Somnolence, stupor

Spontaneous movements						
Motor response (defensive response) to sensory stimulus	 Specifically localized	 Directed	 Decortication	 Decerebration	 Flexion/ extension	 Absent
Pupillary diameter						
Pupillary light reflex (direct and indirect)	 Immediate	 Delayed	 Sluggish	 Sluggish or absent	 Absent	 Absent
Vestibulo-ocular reflex (doll's -eyes reflex)						
Vestibulo-ocular reflex (cold water in either ear; test in left ear shown)						
	Normal	Diminishing responses and reflexes → Stages of coma				



Hemispatial neglect
(left side)
(task was to draw a clockface and set it to "quarter past 12")