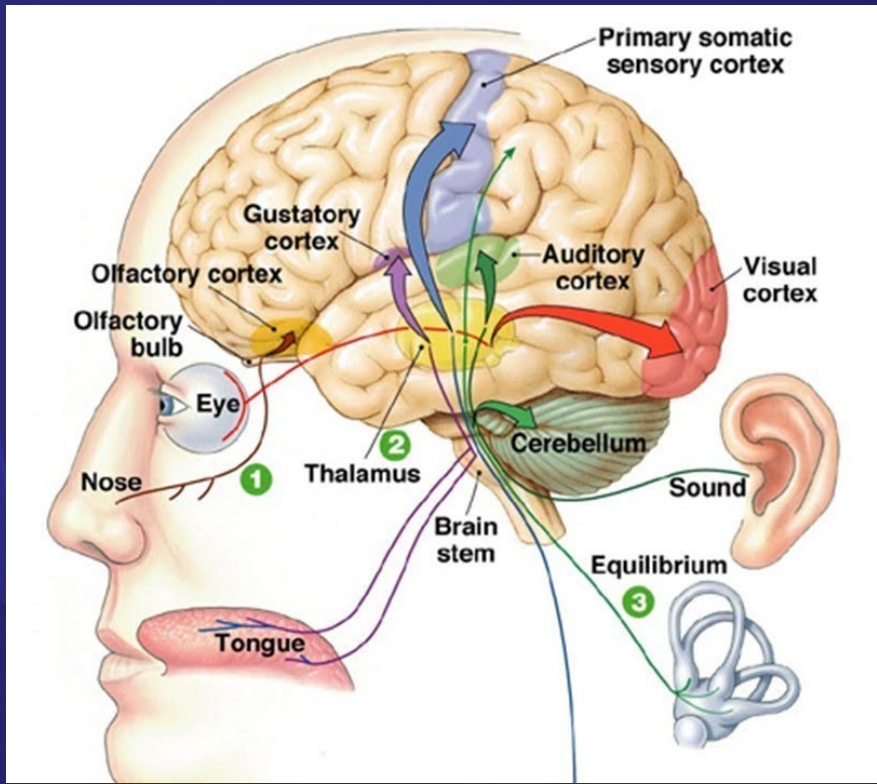
Volgograd State Medical University
Department of Normal Physiology

Special Physiology of Analyzers



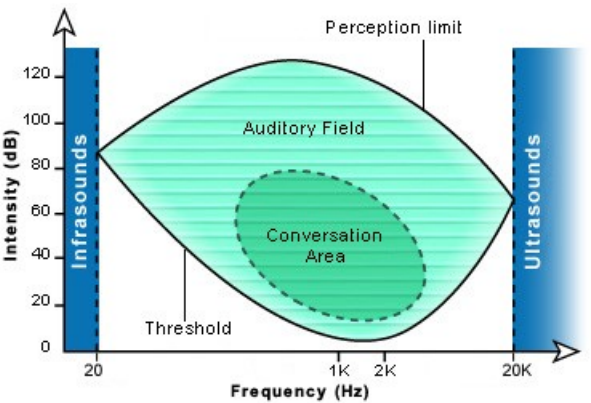
HEARING

Sounds at human level (frequencies)

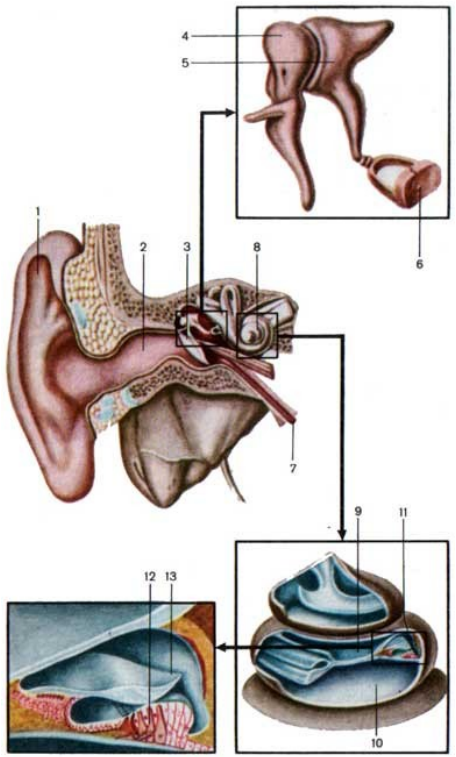
The human ear recognizes frequencies between 20 to 20,000 Hz as sounds. All frequencies below 20 Hz we call '*infrasounds*', and all frequencies above 20 kHz '*ultrasounds*'.
Not all animal ears work within the same frequency range. The mole rat ear perceives sounds 2 octaves below the lower limit of the human ear (below 10 Hz). On the other hand, a dog or a cat ear is able to perceive sounds 1 octave above the human frequency range (40 kHz), and a bat ear may react to sounds 3 octaves above that which we can hear (up to 160 kHz).

SOUND PRESSURE LEVEL

The tympanic membrane can respond to very low sound pressure as well as to massive sound pressure *without* any damage to the ear. This range, that is between minimum pressure, which is necessary to produce response in the ear drum to the maximum pressure *which can be tolerated without* damage, being very vast, *a logarithmic scale, Bel* or *decibel* (0.1 Bel) is used.



FUNCTIONAL ANATOMY OF THE EAR



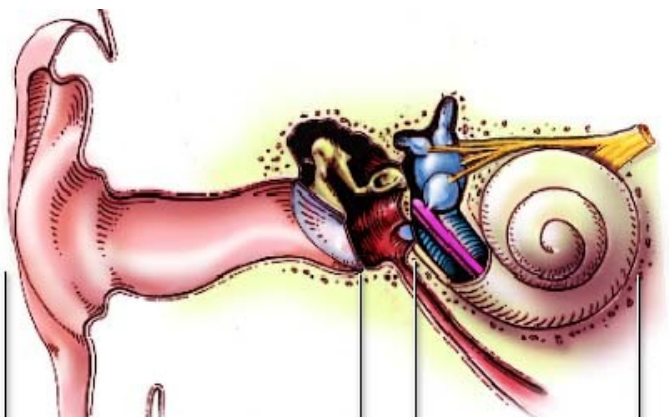
- **The ear has three cavities: (i) external ear, (ii) middle ear, (iii) internal ear.**
- **The internal ear houses two organs:**

  a) cochlea, meant for audition (hearing)

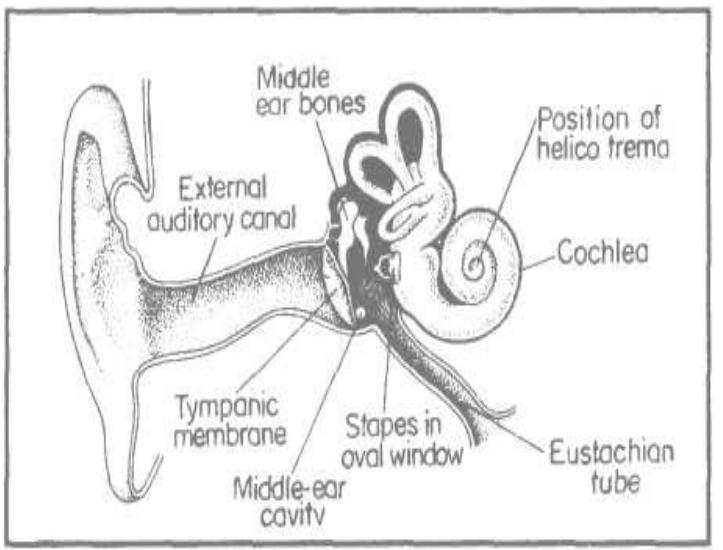
  b) vestibular apparatus, meant for maintenance of equilibrium and posture.

THE OUTER (EXTERNAL) EAR

- ***The auricle*** **is a concave cartilaginous structure, which collects and directs sound waves traveling in air into the ear canal or external auditory meatus.**
- ***The ear canal*** **directs airborne sound waves towards the tympanic membrane (eardrum). The ear canal resonates sound waves and increases the loudness of the tones in the 3000-4000 Hz range**



MIDDLE EAR



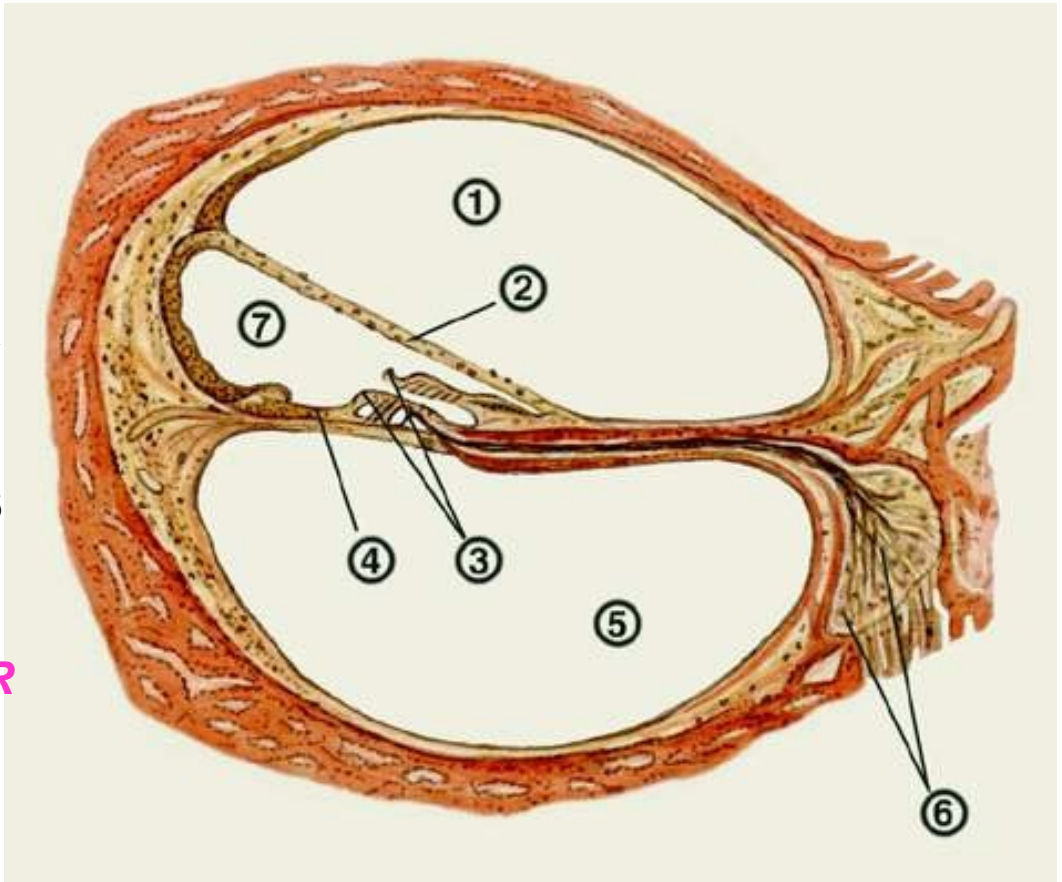
The tympanic membrane (*eardrum)* transmits the airborne vibrations from the outer to the middle ear and also assists in the protection of the delicate structures of the middle ear cavity and inner ear.

MIDDLE EAR

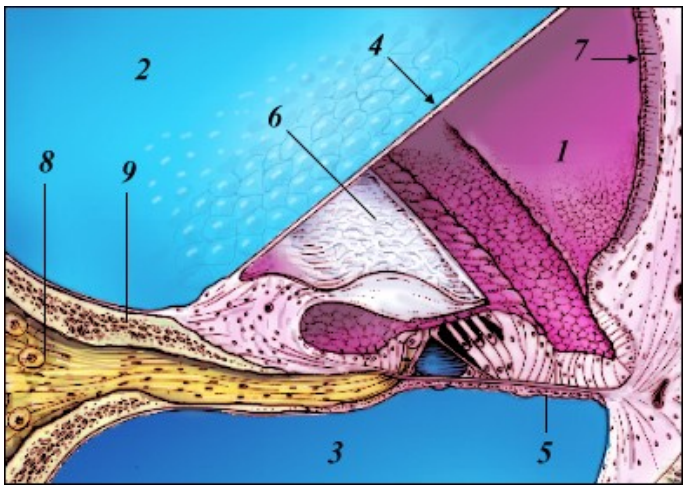
The middle ear is connected and transmits sound to the inner ear via the *ossicular chain*. The ossicular chain amplifies a signal approximately 25 decibels as it transfers signals from the tympanic membrane to the inner ear. The ossicular chain consists of the three smallest bones in the body: the *malleus, incus, and stapes*. The malleus is attached to the tympanic membrane. The footplate of the stapes inserts into the oval window of the inner ear.

THE INNER EAR (*COCHLEA*)

THE INNER EAR IS COMPOSED OF THE SENSORY ORGAN FOR HEARING - THE *COCHLEA*, AS WELL AS FOR BALANCE - THE *VESTIBULAR SYSTEM*.

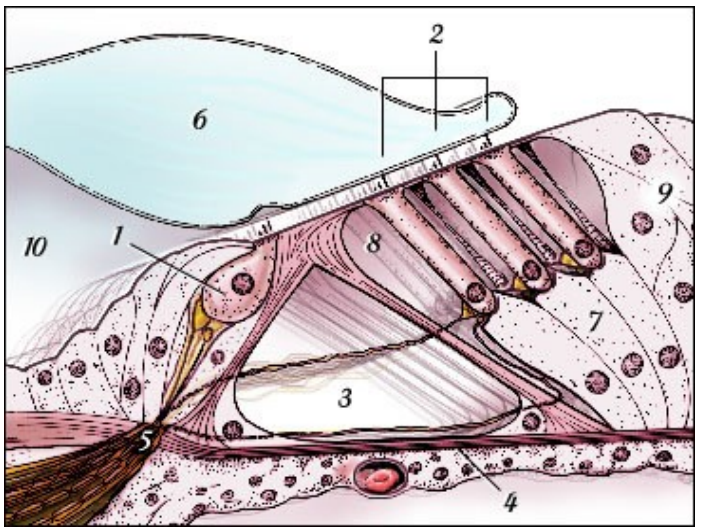


Cross section of one single turn of the cochlea



The cochlear duct (1) is isolated from the scala vestibuli (2) and scala tympani (3) by Reissner's (4) and basilar (5) membranes respectively. The organ of Corti is covered by the tectorial membrane (6) floating in the endolymph. The stria vascularis (7) and the fibres (8) going to the spiral ganglion through the bony spiral lamina (9) are also shown

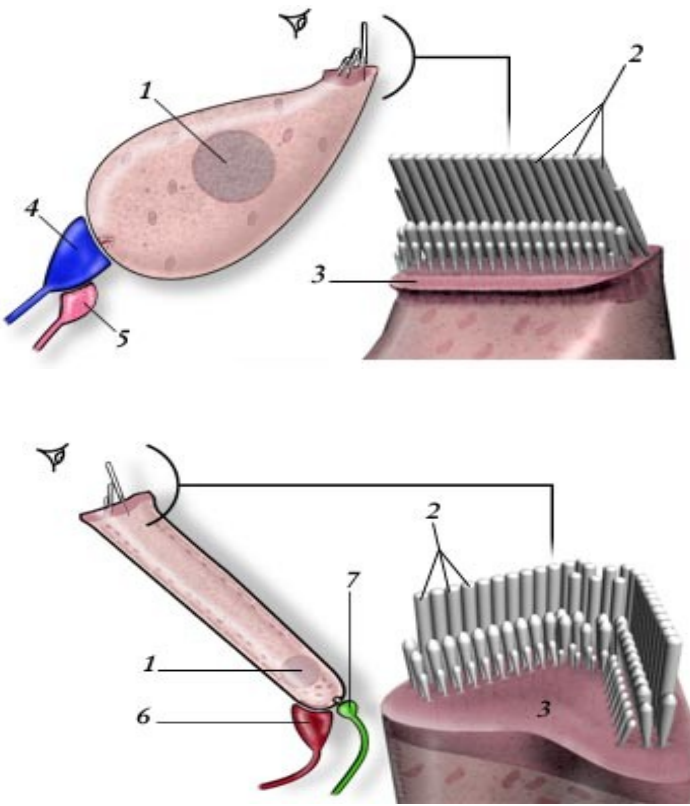
The organ of Corti



1-Inner hair cell
2-Outer hair cells
3-Tunnel of Corti
4-Basilar membrane
5-Habenula perforata
6-Tectorial membrane
7-Deiters' cells
8-Space of Nuel
9-Hensen's cells
10-Inner spiral sulcus

HAIR CELLS

Inner hair cells (IHCs) and outer hair cells (OHCs), differ by their shape and the pattern of their stereocilia



lower - higher frequency

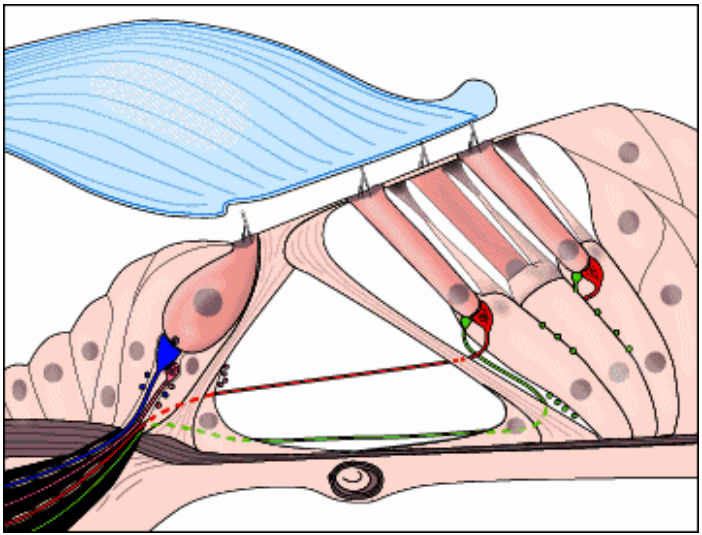
The *apical portion of the basilar membrane* (the most curled area of the cochlea) transfers lower frequency impulses. The *basal end* relays higher frequency impulses.

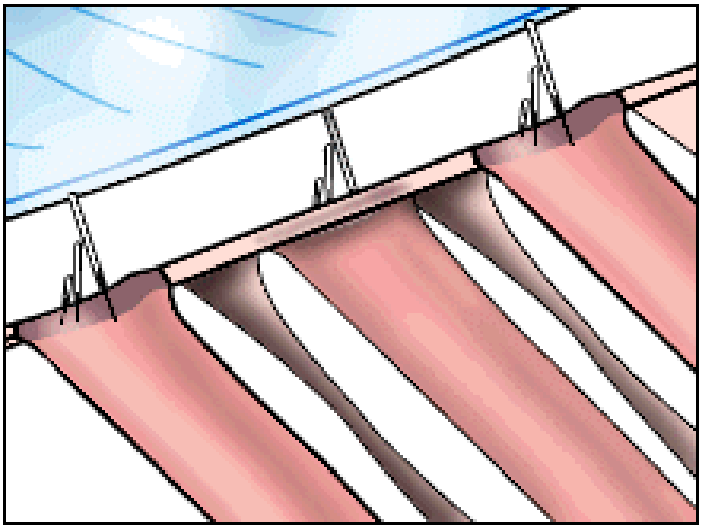
RECEPTOR POTENTIAL

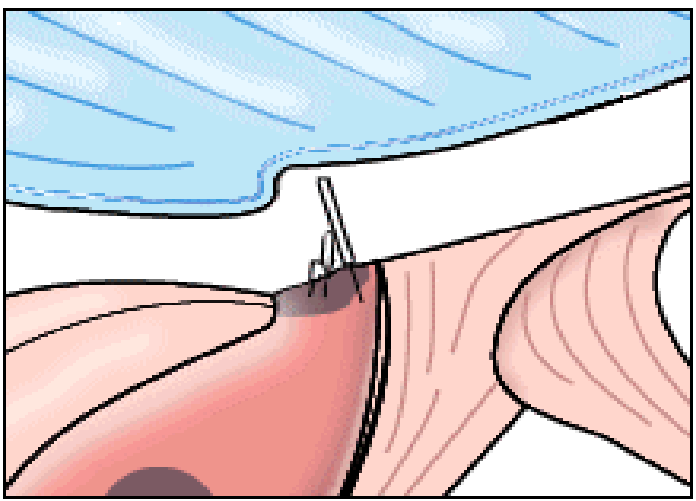
- **The hair cells are depolarized by the movement of K+ into the cell.**
- **The electrochemical gradient for K+ on the apical surface of the hair cells (where the stereocilia are located) favors the movement of K+ into the cell.**
- **The endolymph contains a high concentration of K+ and is electrically positive in comparison to the perilymph.**
- **Hair cells, like all other cells, contain a high concentration of K+ and are electrically negative in comparison to the perilymph. The high intracellular K+ concentration is maintained by Na-K pumps on the basal surface of the hair cell (i.e., the surface that faces the perilymph of the scala tympani).**

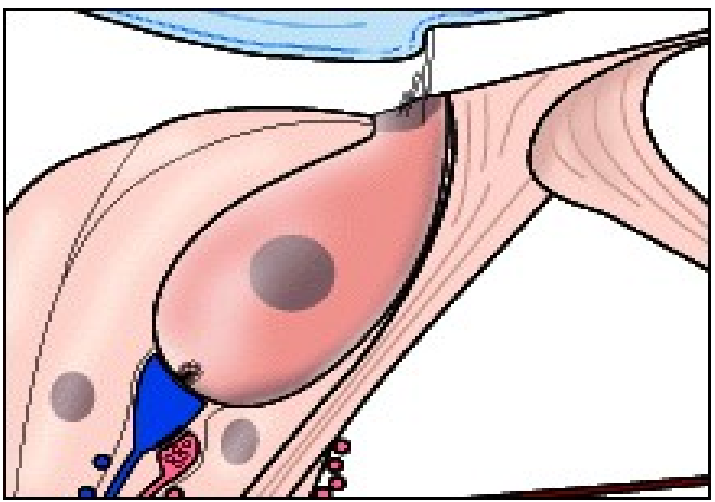
RECEPTOR POTENTIAL

- **Because the endolymph is electrically positive and the hair cell is electrically negative, a very large potential difference (-100 mV) exist across the hair cell membrane. All these create a driving force, pushing K+ into the cell.**
- **The gating of the K+ channels is controlled by the bending of the stereocilia. When the stereocilia bend away from the limbus, they cause K+ channels to open. K+ then flows into the cell and the hair cell depolarizes. When the stereocilia bend toward the limbus, they cause K+ channels to close and the hair cell hyperpolarizes.**



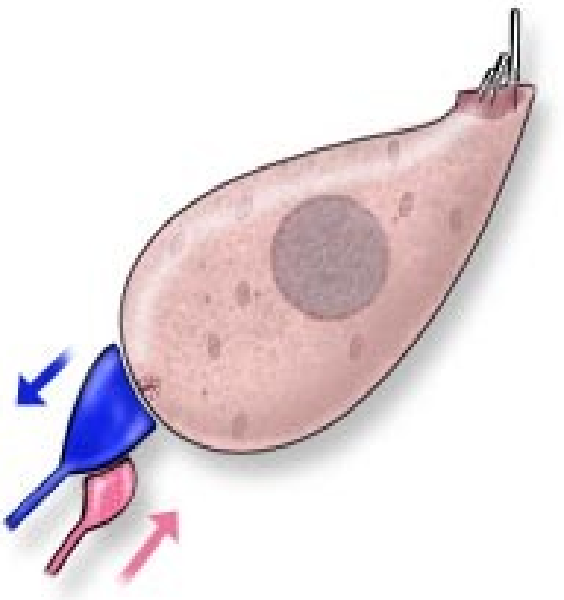




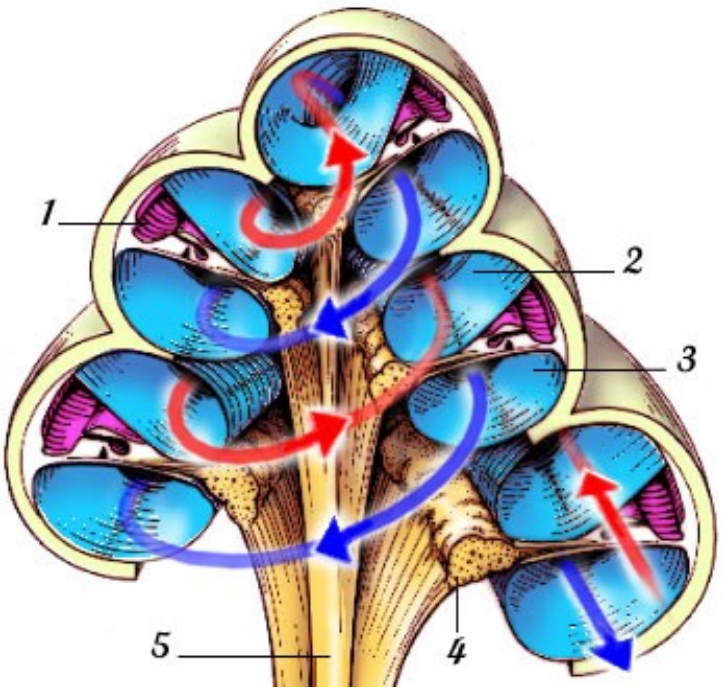


RELEASE OF SYNAPTIC TRANSMITTER

When the hair cell depolarizes, a Ca^{2+} channel opens, allowing Ca^{2+} to enter the cell. Ca^{2+} initiates the release of a synaptic transmitter (glutamate or aspartate), which stimulates the auditory nerve fiber.

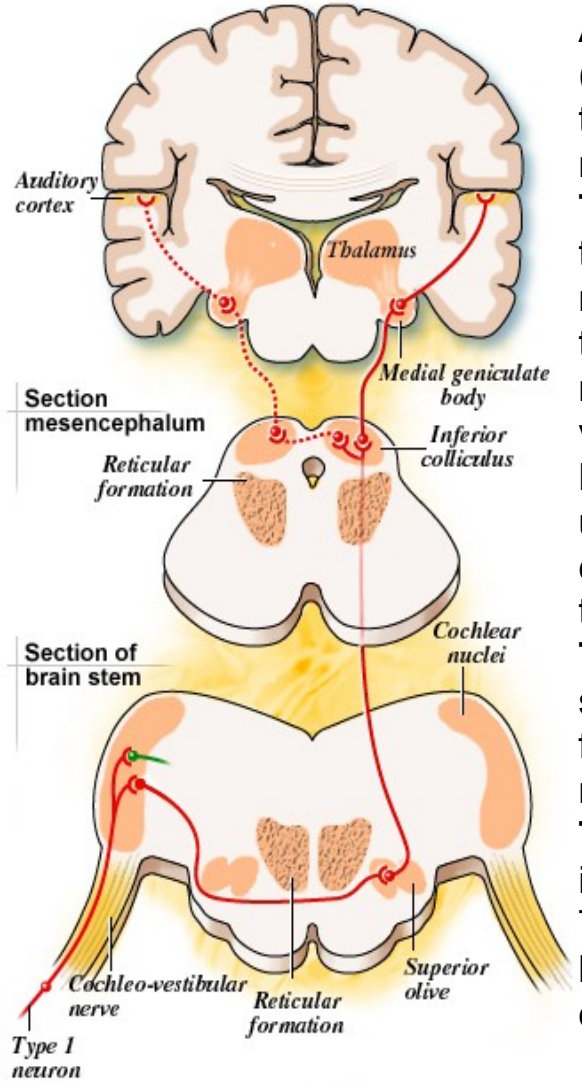


AUDITORY NERVE



The cell bodies of the auditory nerve fibers are located within the spiral ganglion (4). Their axons join those from the vestibular apparatus to form the vestibule-cochlear nerve.

PRIMARY AUDITORY PATHWAY



A final relay, before the cortex, occurs in the thalamus (median geniculate body); *genouillé* médian)it's here that an important integration occurs: preparation of a motor response (e.g. vocal response).

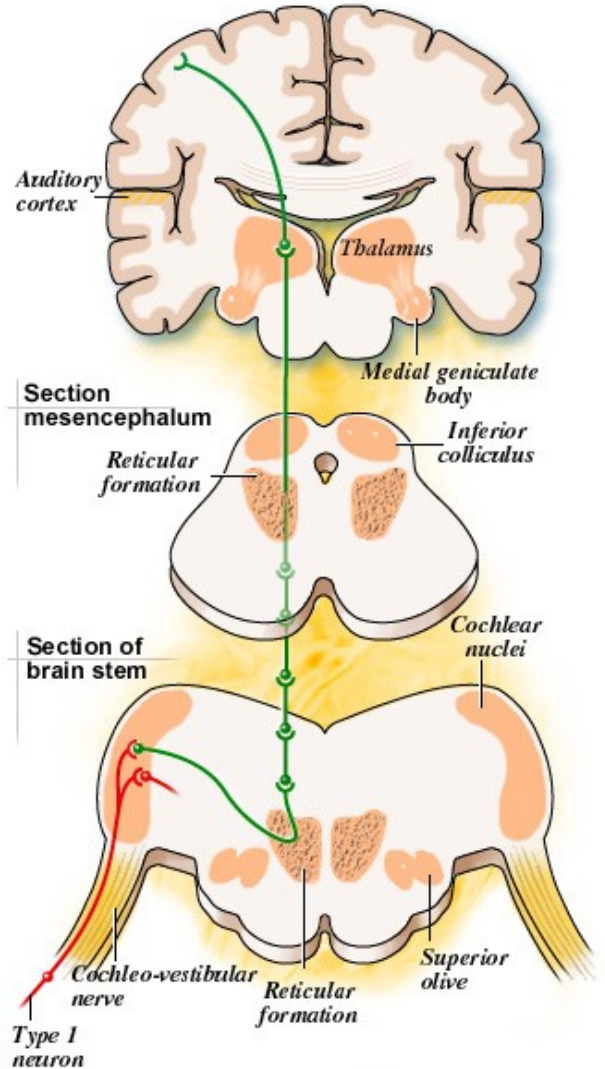
The final neuron of the primary auditory pathway links the thalamus to the auditory cortex, where the message, already largely decoded during its passage through the previous neurons in the pathway, is recognized, memorised and perhaps integrated into a voluntary response.

Leaving **this relay,** a third neuron carries the message up to the level of the mesencephalus (inferior colliculus). These two relays play an essential rôle in the localisation of sound.

The second major relay in the brain stem is in the superior olivary complex: the majority of the auditory fibres synapse there having already crossed the midline.

The first relay of the primary auditory pathway occurs in the cochlear nuclei in the brain stem, which receive Type I spiral ganglion axons (auditory nerve); at this level an important decoding of the basic signal occurs: duration, intensity and frequency.

NON-PRIMARY OR RETICULAR AUDITORY PATHWAYS

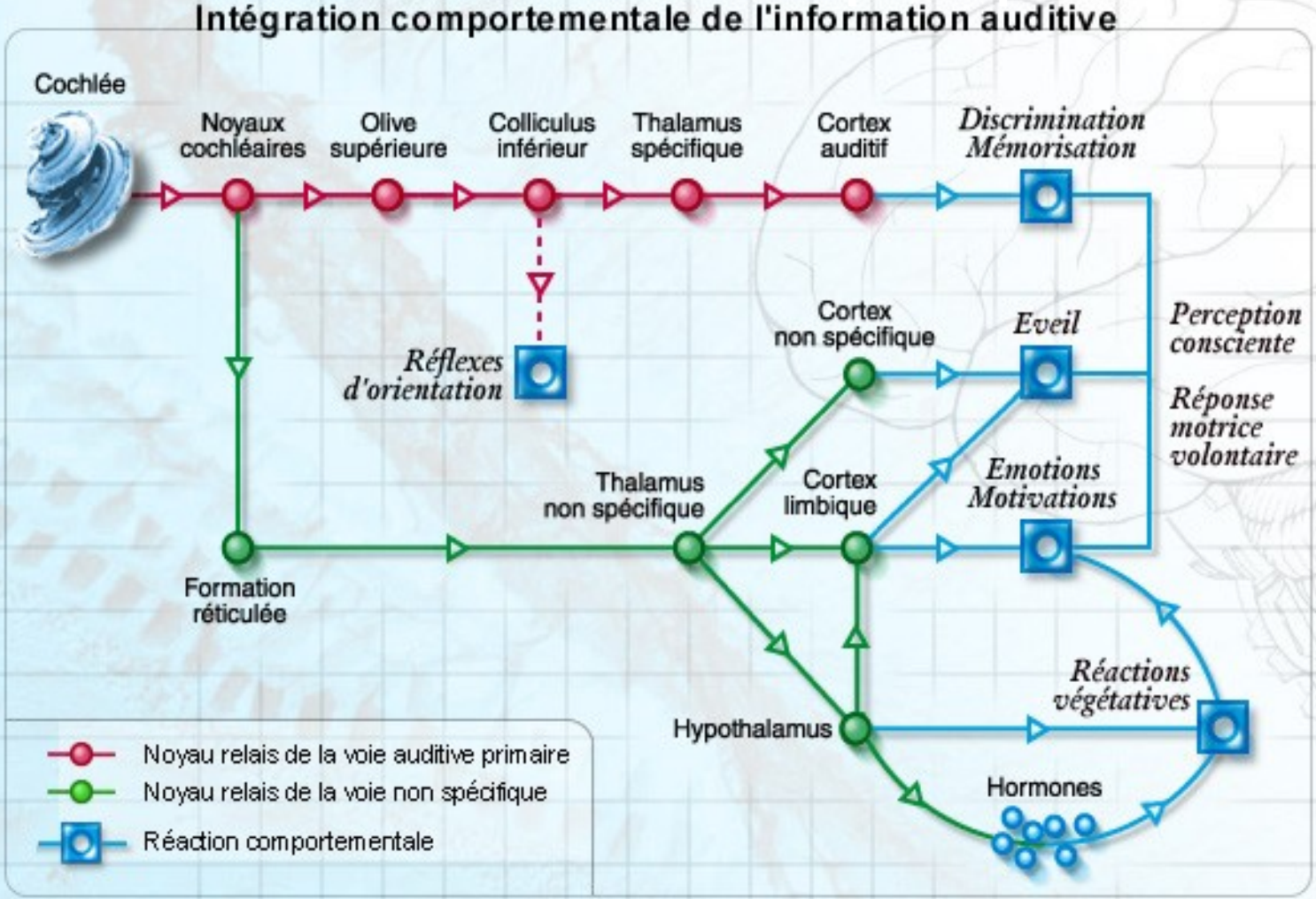


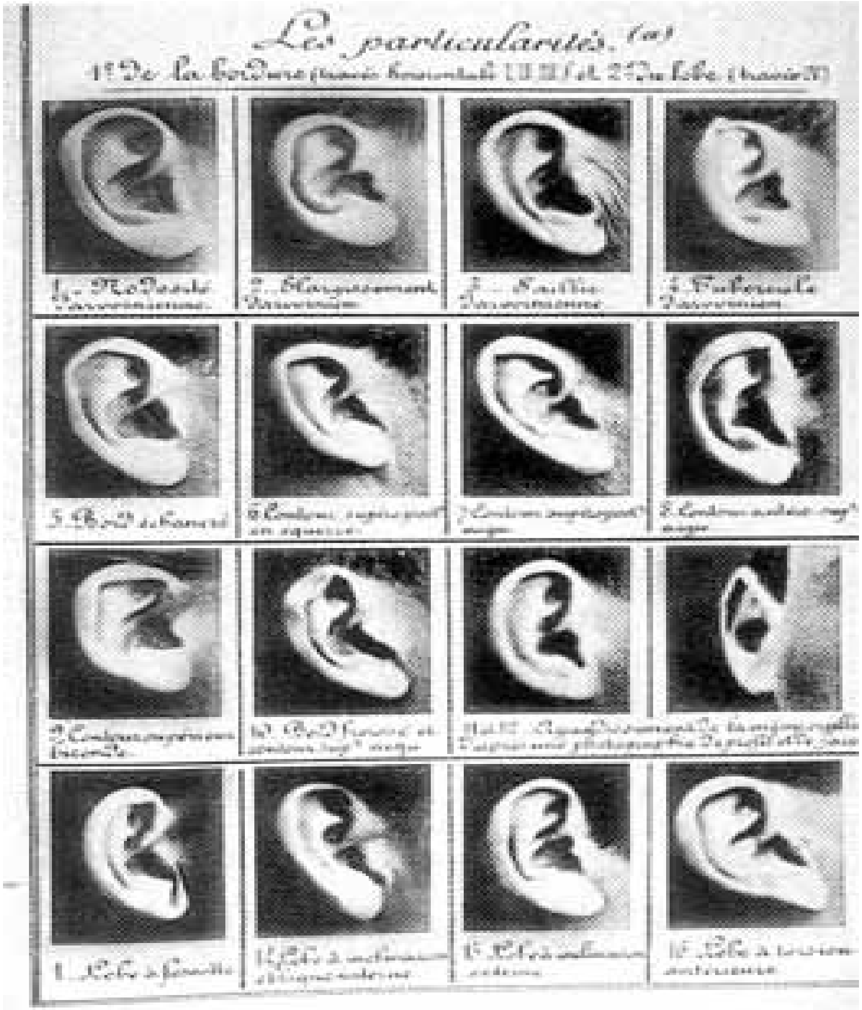
After the reticular formation, the non-primary pathway leads to the thalamus, then to the polysensory cortex.

NB : connections are also made with the hypothalamus and the vegetative centres (not shown on the diagram)

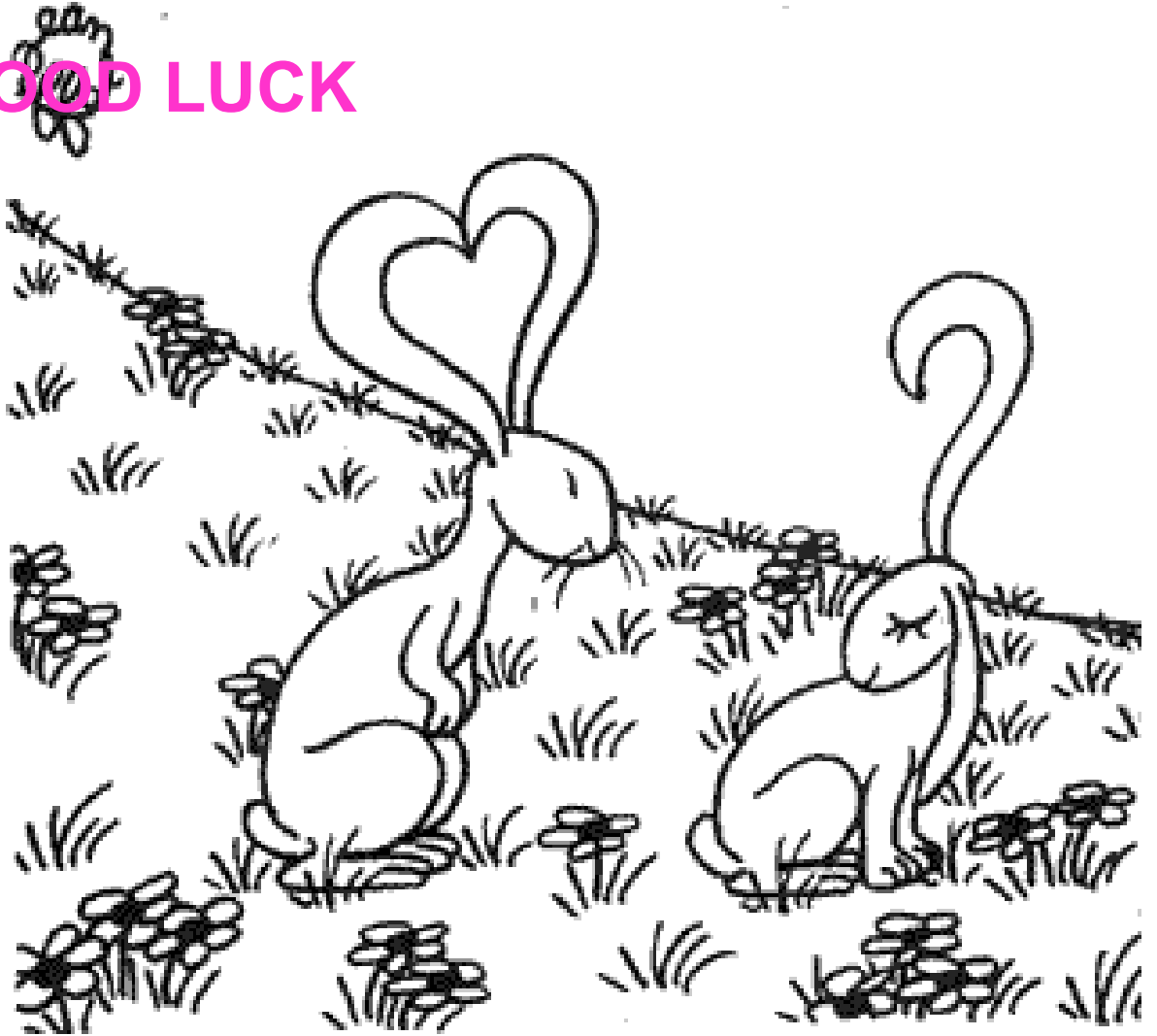
In the reticular pathway of the brainstem and the mesencephalus, several synapses occur. It's here that the auditory information is integrated with all the other sensory modalities to be 'triaged' into which has the highest priority at any given moment. In other words, the reticular pathways participate with the wake and the motivation centres in selectioning the information that should be treated as priority by the brain.

The primary relay, in common with the primary auditory pathway formed in the cochlear nuclei (brainstem). From the bulbar nuclei, the small fibers rejoin the ascending reticular pathway.

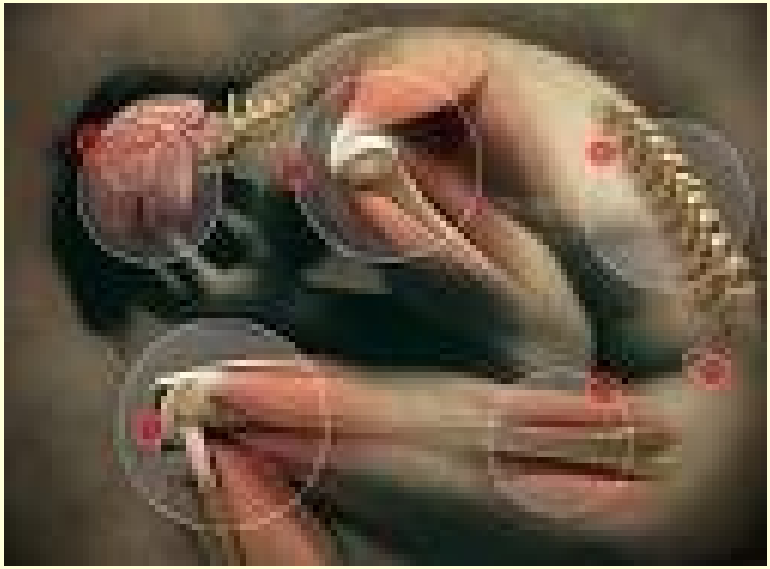

Intégration comportementale de l'information auditive
Cochlée
Noyaux cochléaires
Olive supérieure
Colliculus inférieur
Thalamus spécifique
Cortex auditif
Discrimination Mémorisation
Réflexes d'orientation
Cortex non spécifique
Eveil
Perception consciente
Réponse motrice volontaire
Thalamus non spécifique
Cortex limbique
Emotions Motivations
Formation réticulée
Réactions végétatives
Hypothalamus
Hormones
Noyau relais de la voie auditive primaire
Noyau relais de la voie non spécifique
Réaction comportementale


Les particularités. (a)

GOOD LUCK



PAIN



PAIN - INTRODUCTION

- **Pain is the most important protective sensation.**
- **It is an unpleasant sensation and is the most primitive of all senses.**
- **It is the feeling of distress or suffering or agony caused by stimulation of the receptors for pain.**
- **Pain is associated with emotional component or affect, other accompaniments are arousal response, somatic and autonomic reflexes.**

DEFINITION

DEFINITION OF PAIN – International Association for the Study of Pain (IASP, 1979):

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

(non-human "pain" research)

DEFINITION OF TERMS:

NOXIOUS STIMULUS - tissue damaging or potentially damaging stimulus

NOCICEPTION - response to a noxious stimulus

ANTINOCICEPTION - blockage of nociception

Theories of Pain

- **Specificity Theory**
- Descartes (1664), Muler (1840)
  - Pain occurs due to the stimulation of specific pain receptors (nociceptors) with transmission by nerves directly to the brain
  - Pain is purely an afferent sensory experience
- **Intensity theory**
  - Pain arises from excessive stimulation of any sensory end organ
  - Pain can occurs from summation above a critical at dorsal horn neurones

    <u>but</u>:

    intense stimulation of some end organs never produces pain and lesions of CNS can abolish pain exclusively

Pain Theories

- **Pattern theory**
- Nafe (1934)
  - **sensations are produced by spatial and temporal summation; all end organs are the same**

    fails to agree with known specialisation of end organs and primary afferents
- **Gate control theory**
- Melzack and Wall (1965)
  - **a very important and influential concept**
  - **arose due to failing of above to explain certain observations**
    - **failure of surgical lesions to produce lasting analgesia, hyperalgesia, referred pain, influence of supraspinal centres**
  - **proposed the substantia gelatinosa as a modulating gate where non-noxious stimuli can modify pain**
  - **but: not completely supported by current neuroanatomy**

PHYSIOLOGICAL PAIN

- pain can be differentiated from touch
- protective function
- warns of potential damage
- transient
- well localised
- a defined stimulus response pattern

Clinical pain (pathological pain)

- elicited by Aß as well as C and A∂ fibres
- “pathological” - associated with inflammation, neuropathy
- associated with peripheral and central sensitisation
- pain outlasts duration of the stimulus
- pain sensed in non-injured areas

TYPES OF PAIN:

Fast pain/Slow pain

- Immediately after an injury (i.e., stimulus for pain) a sharp, localised pain is felt, which is called fast pain and is carried by A-delta fibres at higher speed.
- After the fast pain, a diffuse, dull, intense and unpleasant pain sensation occurs, which is called slow pain and is carried by C fibres at slower speed.

TYPES OF PAIN:

Epicritic pain/Protopathic pain

- **Epicritic pain shows low threshold but accurate localisation.**

- **On the other hand, protopathic pain shows high threshold but poor localisation.**

TYPES OF PAIN:

Deep pain/Superficial pain

- Pain arising from deeper structures like periosteum, muscle, tendon, etc. is called deep pain and is poorly localised.
- The superficial pain originates from superficial structures like skin and can be localised.

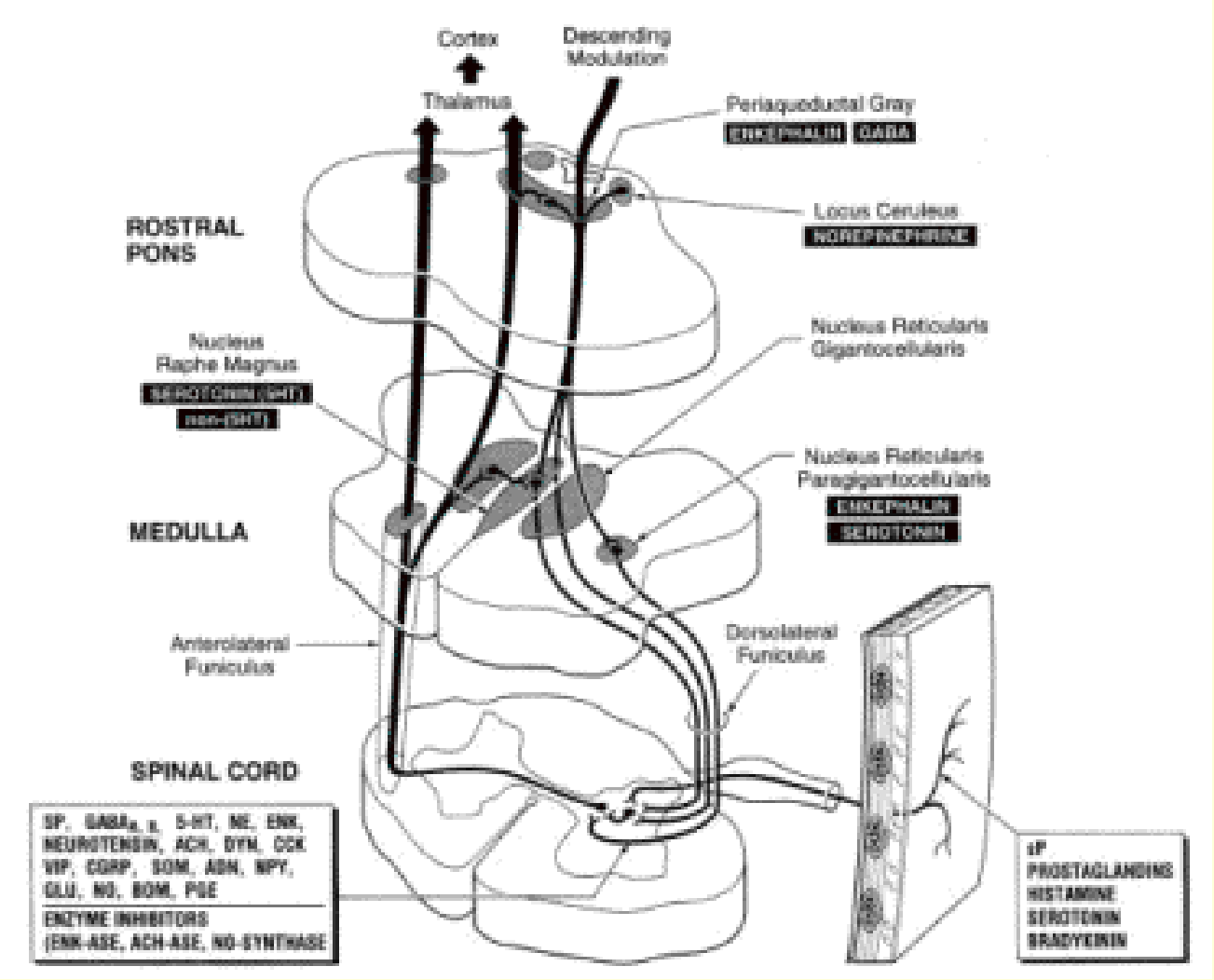
TYPES OF PAIN: Somatic pain/Visceral pain

- Somatic pain arises from somatic structures and may be superficial or deep.
- Visceral pain originates from viscera due to inflammation, spasm, stretching. It is poorly localised, i.e., diffuse in character.
- Visceral pain may radiate or may be referred.
- It is also frequently associated with autonomic involvement like tachycardia, vomiting, etc.

TYPES OF PAIN:
Referred pain and Radiating pain

- **Visceral pain, instead of being felt at the site of the viscera, is frequently felt at some distance, on somatic structures, such pain is called referred pain, e.g., pain of appendicitis is referred to the skin around the umbilicus, cardiac pain is referred to the inner aspect of the left arm.**
- **An inflammed gall bladder (cholecystitis) irritates the under surface of the diaphragm, so the pain is referred to the tip of the right shoulder.**
- **This means the visceral pain is referred to the dermatome which has developed from the same segment.**

DISTRIBUTION OF NEUROTRANSMITTERS



RECEPTORS

- Free nerve endings are the receptors for pain.
- These are mainly of two types and are connected to small myelinated A-delta and unmyelinated C fibers respectively.
- These A and C fibers carry the pain sensation to the CNS.

PRIMARY AFFERENT INPUT

- Cutaneous mechanoreceptors
  - low threshold mechanoreceptors
  - via Aa, Aß, A∂, C fibres
  - terminate in all laminae (except I)

- Nociceptors
  - Widespread - somatic & visceral
    - Mechanical, thermal, chemical
    - Cell bodies in dorsal root ganglia

PRIMARY AFFERENT INPUT

- CUTANEOUS NOCICEPTORS
  - A∂ fiber mechanothermal
    - Brief, prickling pain
  - C fiber polymodal
    - Dull, poorly localised pain
- via A∂
  - Myelinated, 2-5 µm diameter, 6-30 m/s
  - terminate laminae I, V, X
- C fibers
  - Unmyelinated, 2 µm, 0.5-2 m/s,
  - to lamina II

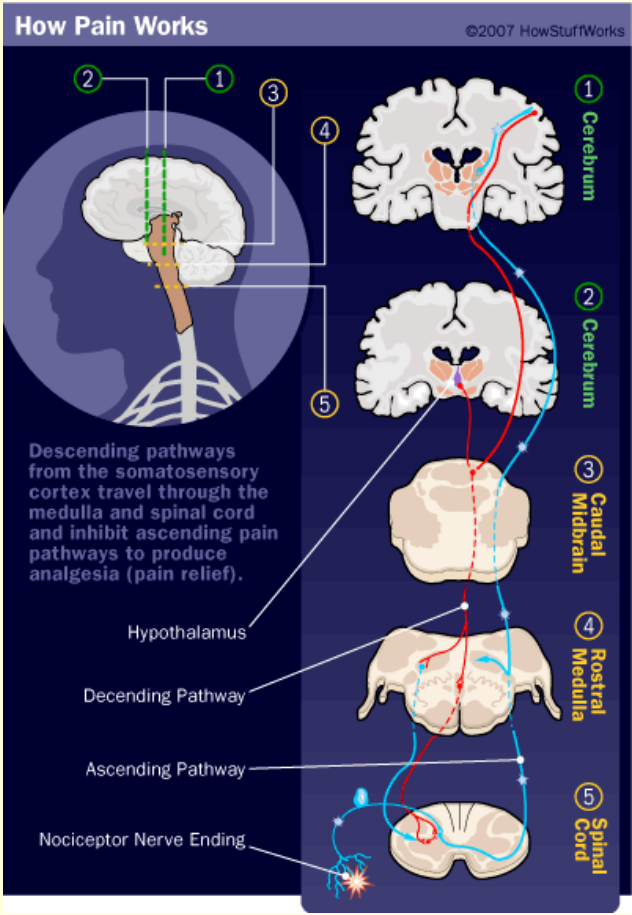
NOCICEPTORS

- VISCERAL NOCICEPTORS
  - From visceral organs
  - Fibers travel with autonomic fibers
  - Large receptive fields
    - Poorly localised pain
  - Referred pain
    - Converge onto second order neurones that receive somatic afferents
- SILENT NOCICEPTORS
  - Normally non-responsive to noxious stimuli
  - Unmyelinated
  - Sensitized by inflammation or chemicals
    - Discharge vigorously, even in response to normal stimuli

NEUROCHEMISTRY

PERIPHERY - injury produces release of endogenous chemicals:

- **Bradykinin**
- **Histamine**
- **Serotonin**
- **Prostaglandins**
- **Substance P**



SPINAL CORD ORGANISATION

- Dorsal horn neurons
  - 10 laminae of Rexed
    - dorsal to ventral ordering
  - I : “marginal zone”, role in nociception, project to thalamus, brainstem, cerebellum
  - II : substantia gelatinosa, small densely packed cells, radially orientated, afferents from *unmyelinated* fibres
  - Functional classification of *second order* neurones
    - WDR – multireceptive wide dynamic range neurones
      - respond to both noxious an a non-noxious stimuli
      - respond to noxious stimuli if sensitized
    - Low threshold (LT)
      - non-noxious stimuli
    - High threshold (HT)
      - nociceptive specific

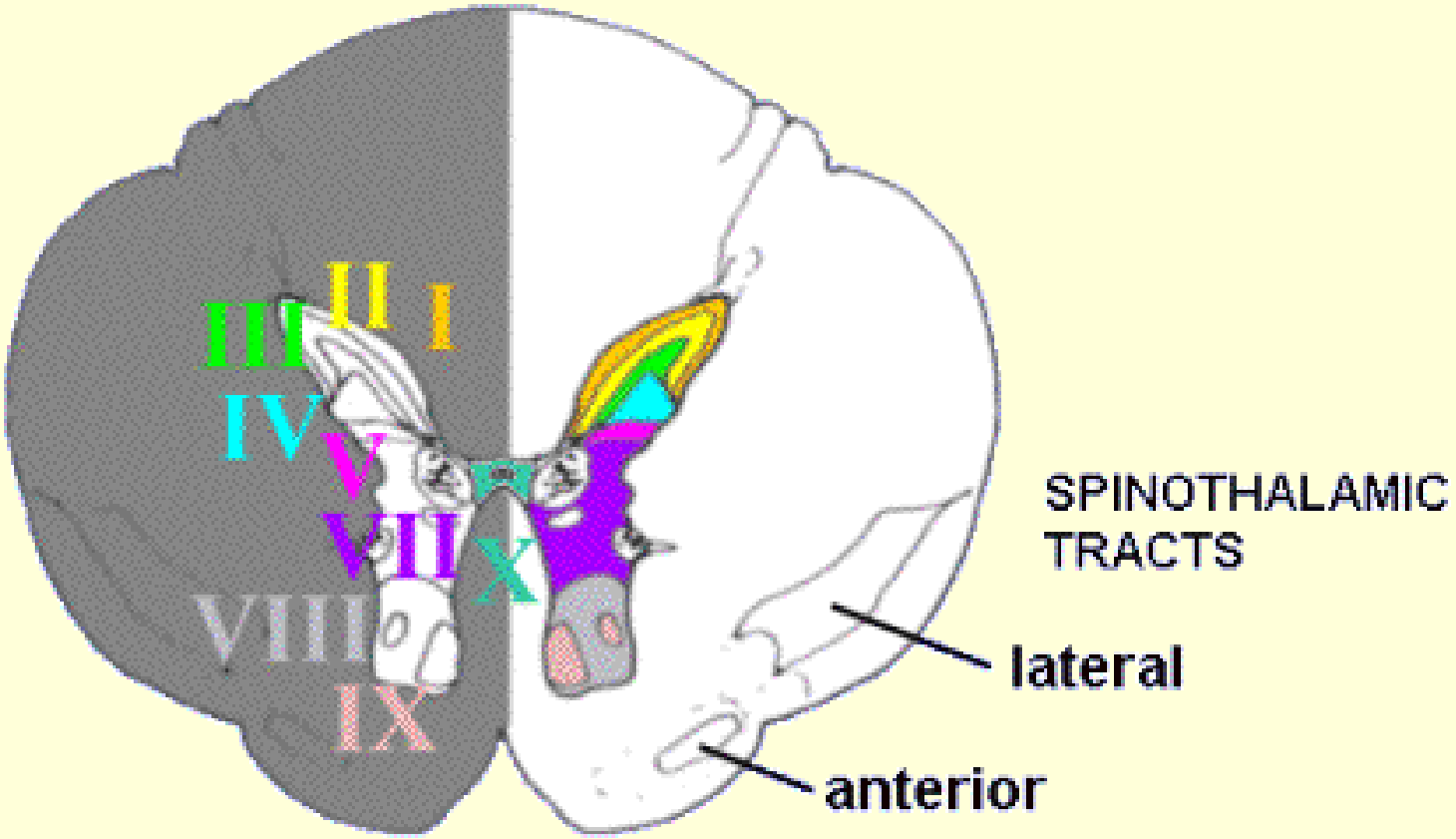
ASCENDING PATHWAYS

- "SPINAL LEMNISCUS" OR "ANTEROLATERAL FASCICULUS"
- SPINOTHALAMIC TRACT
  - originating neurones in laminae I, V, VI, IX
  - Neospinothalamic tract
    - project to VPL, VPM

(Ventral posterolateral nucleus, Ventral posteromedial nucleus)

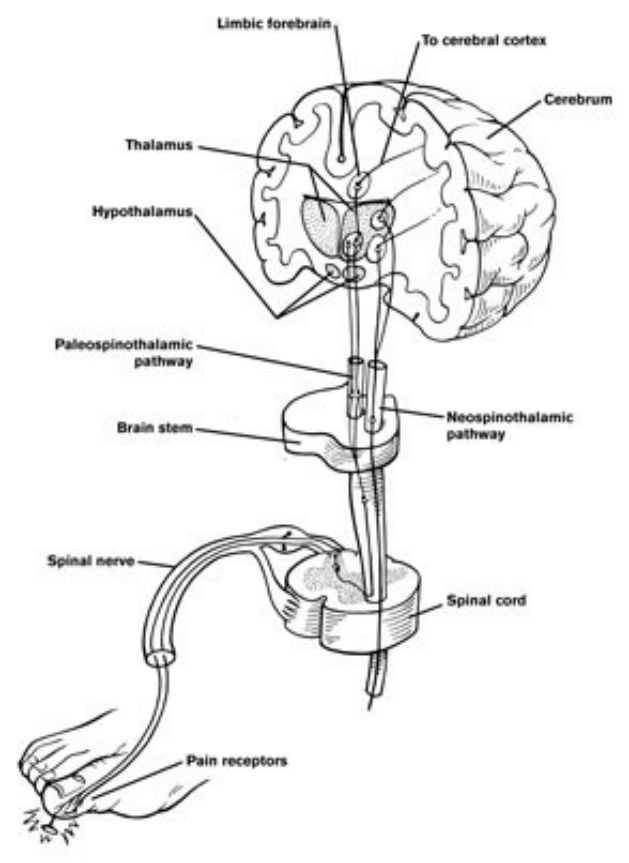
    - synapse and project to somatosensory cortex
  - Paleospinothalamic tract
    - from deeper laminae
    - to thalamus, midbrain, pontine and medullary reticular formation, periaqueductal grey and hypothalmus
  - Somatotopically and contralaterally organised
  - Functions
    - mostly high threshold and multireceptive
    - small discriminative or whole body receptive fields

ASCENDING PATHWAYS



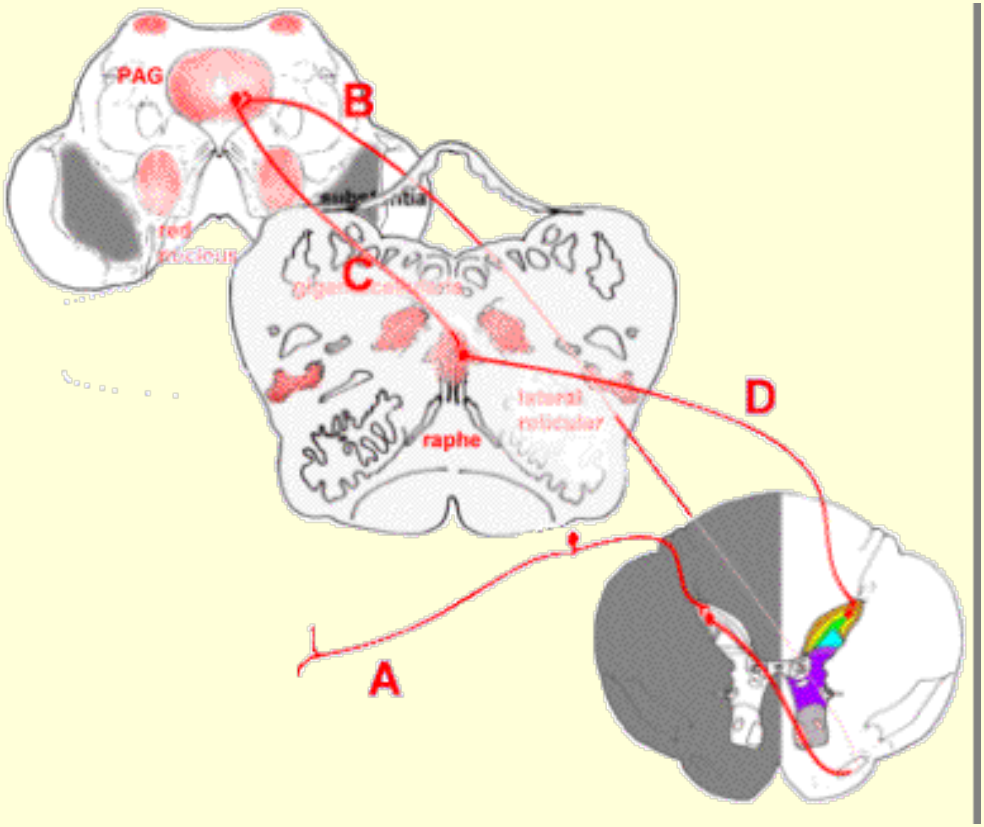
ASCENDING PATHWAYS

- Spinoreticular tract
  - projects to medullary and pontine reticular formation
  - involved in motivational and affective responses to pain
  - ascend medially to spinothalamic tract
  - also responds to non-noxious stimuli
- Spinomesencephalic tract
  - originate in laminae I and V
  - contralateral
  - project to caudal midbrain areas including periaqueductal gray



DESCENDING CONTROL

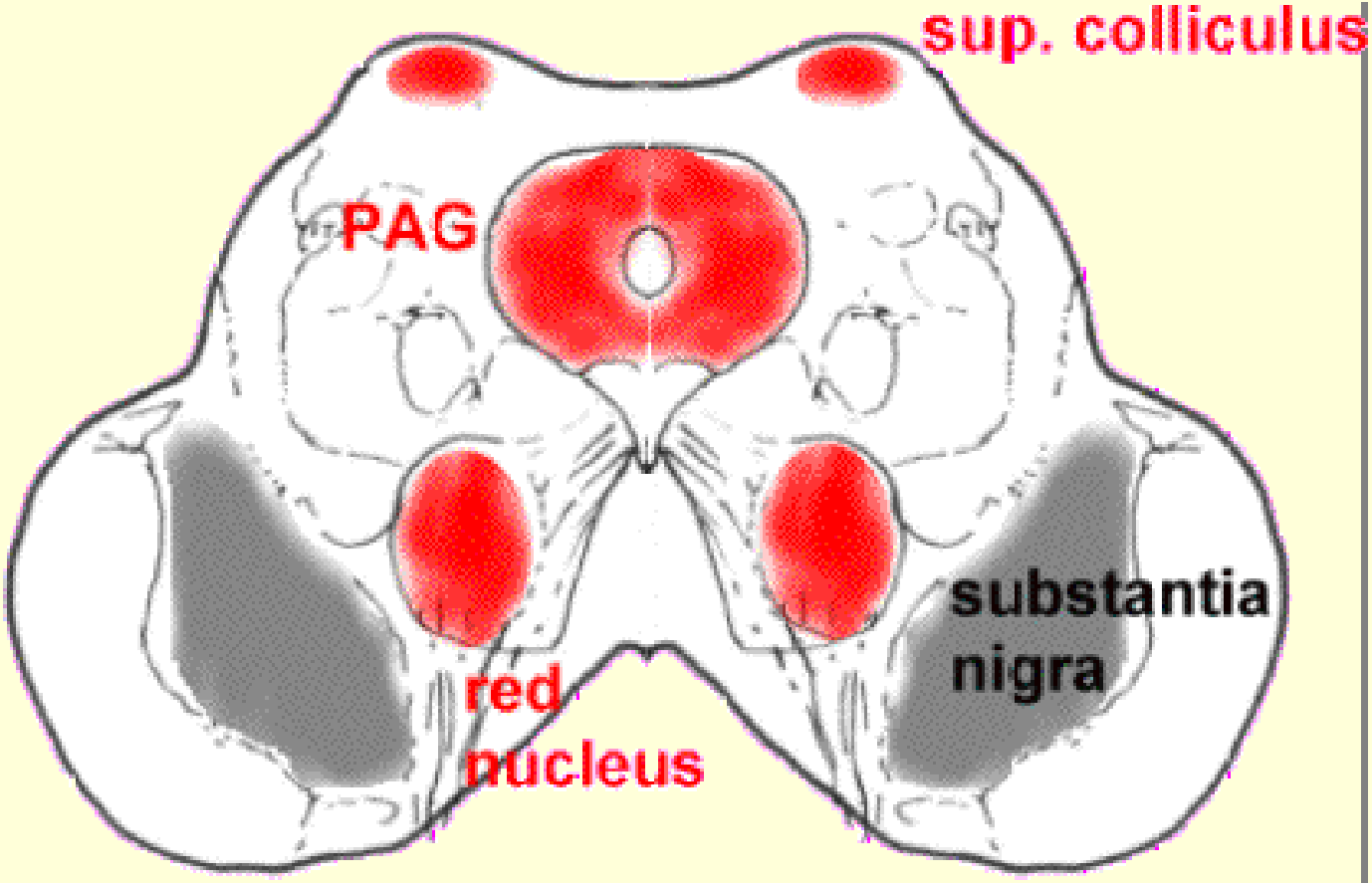
- Studies in animals and man show anti-nociception and analgesia from stimulation or opioid administration to many supraspinal centres
- CORTEX
  - via corticospinal efferents
  - terminations in superficial laminae
  - may be inhibitory *or* excitatory and influence non-noxious stimuli as well
- HYPOTHALAMUS
  - many afferents and efferents - including NTS, PAG, LC (locus coeruleus), parabrachial nuclei, raphe nuclei
  - widespread reciprocal innervation
  - direct projection to lamina I
  - may be bulbospinal relay for descending inhibition


PAG
B
C
D
A
raphe
lateral reticular

MID BRAIN

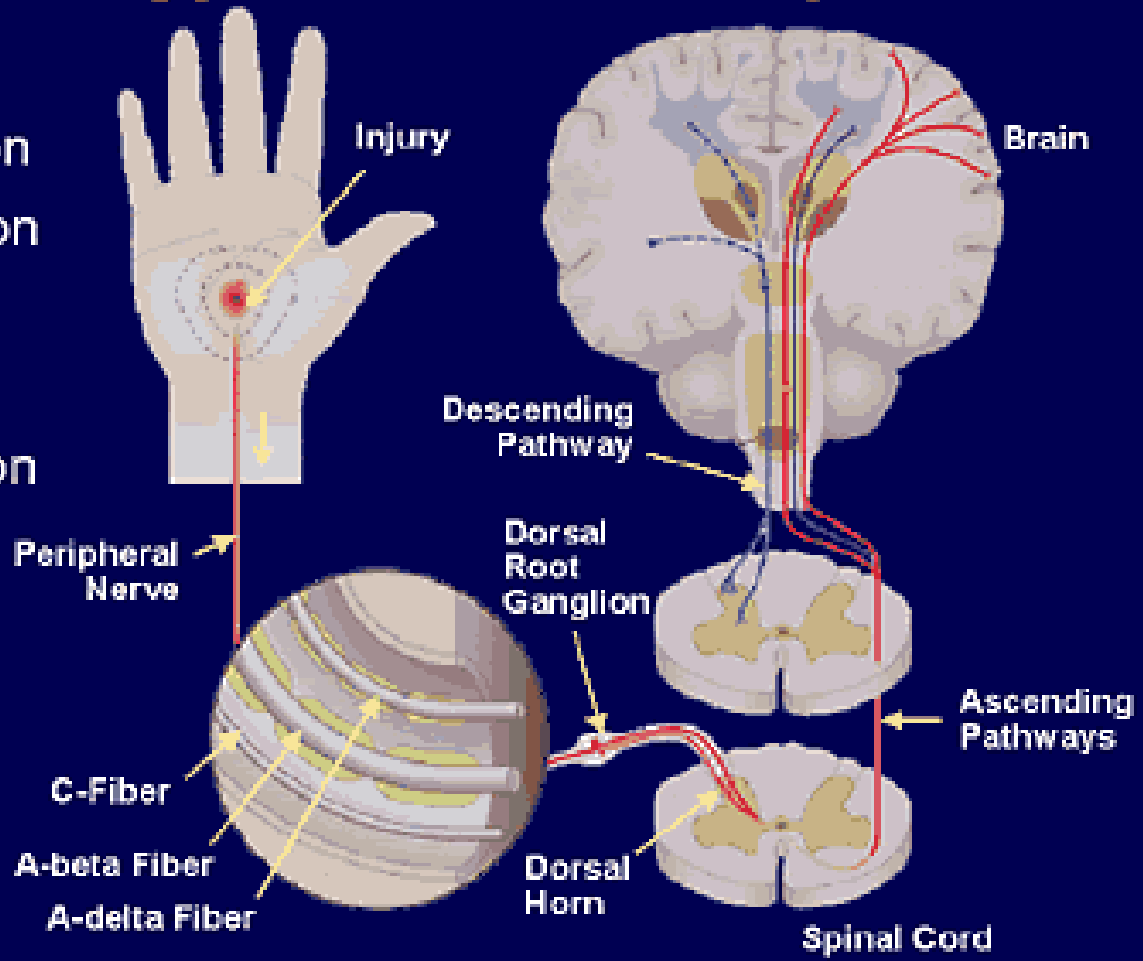
- **PERIAQUECDUCTAL GRAY (PAG)**
  - **surrounds cerebral aqueduct**
  - **extensive afferent and efferent projections**
  - **morphine and electrical stimulation produce potent antinociception**
  - **PAG descending inhibition is** via NRM (nucleus raphe magnus)
  - EAA (excitatory amino acid) are neurotransmitters there (glutamate is a major excitatory amino acid)
- **LOCUS COERULEUS (LC)**
  - **noradrenergic containing neurones**
  - **adjacent to 4th ventricle**
  - **diffusely innnervates CNS at all levels**
  - **descending NAD (nicotin-amide adenine dinucleotide) fibers inhibit dorsal horn nociceptive activity and spinal nociceptive reflexes**

MID BRAIN



Physiology of Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior



SPINAL CORD TRANSMITTERS

- many neurotransmitters in dorsal horns
- substance P
  - has a prime role
  - has been localised in SG (stellate ganglion)
  - other neurotransmitters are co-localised with substance P

EAA (glutamate, aspartate), CGRP (calcitonin gene related peptide)

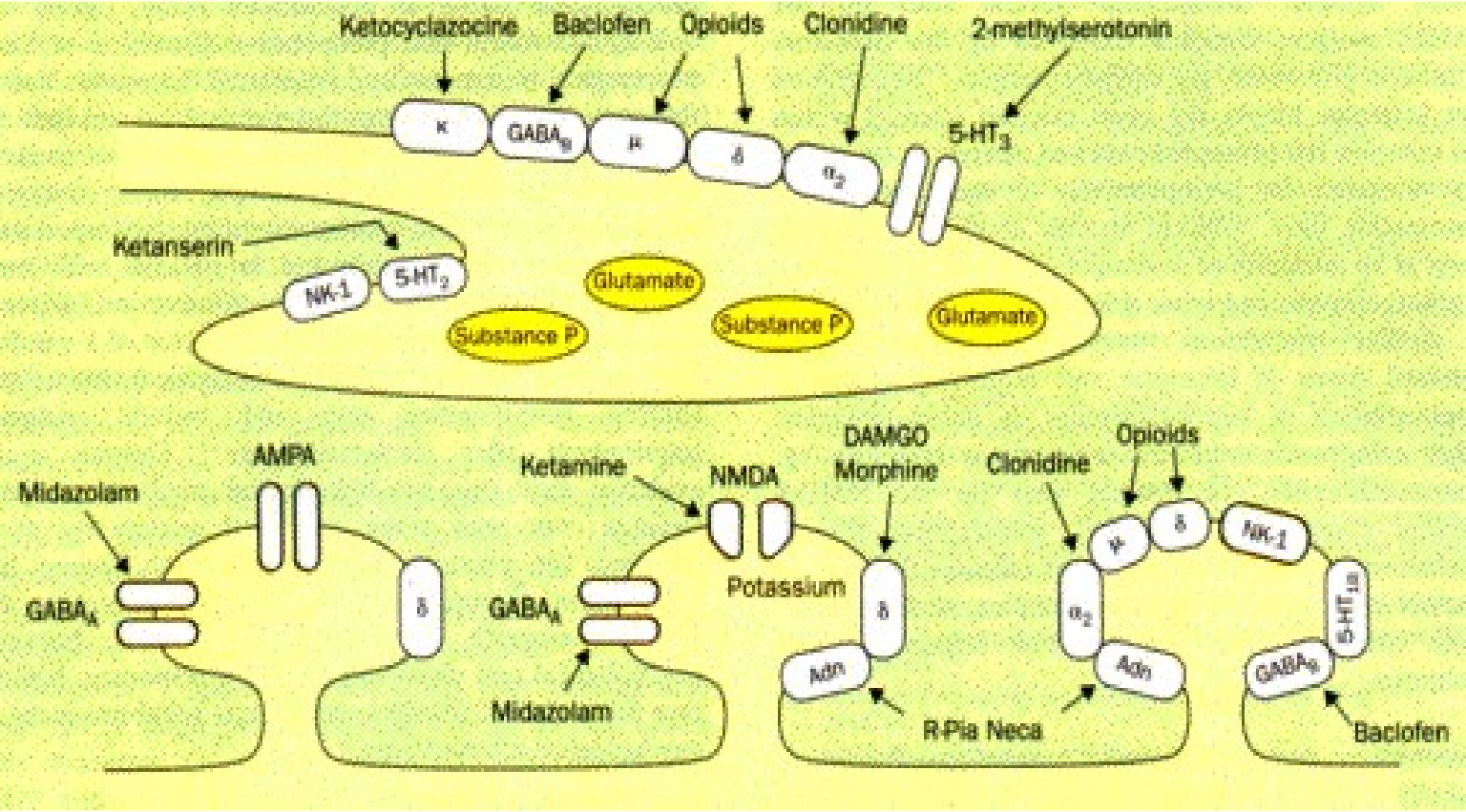
  - Substance P may promote later release of EAA

DORSAL HORN MECHANISMS

NEUROTRANSMITTERS

- excitatory amino acids — e. g. glutamate
- a major role:
  - NMDA receptor (N-methyl D-aspartate)
  - AMPA receptor (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)

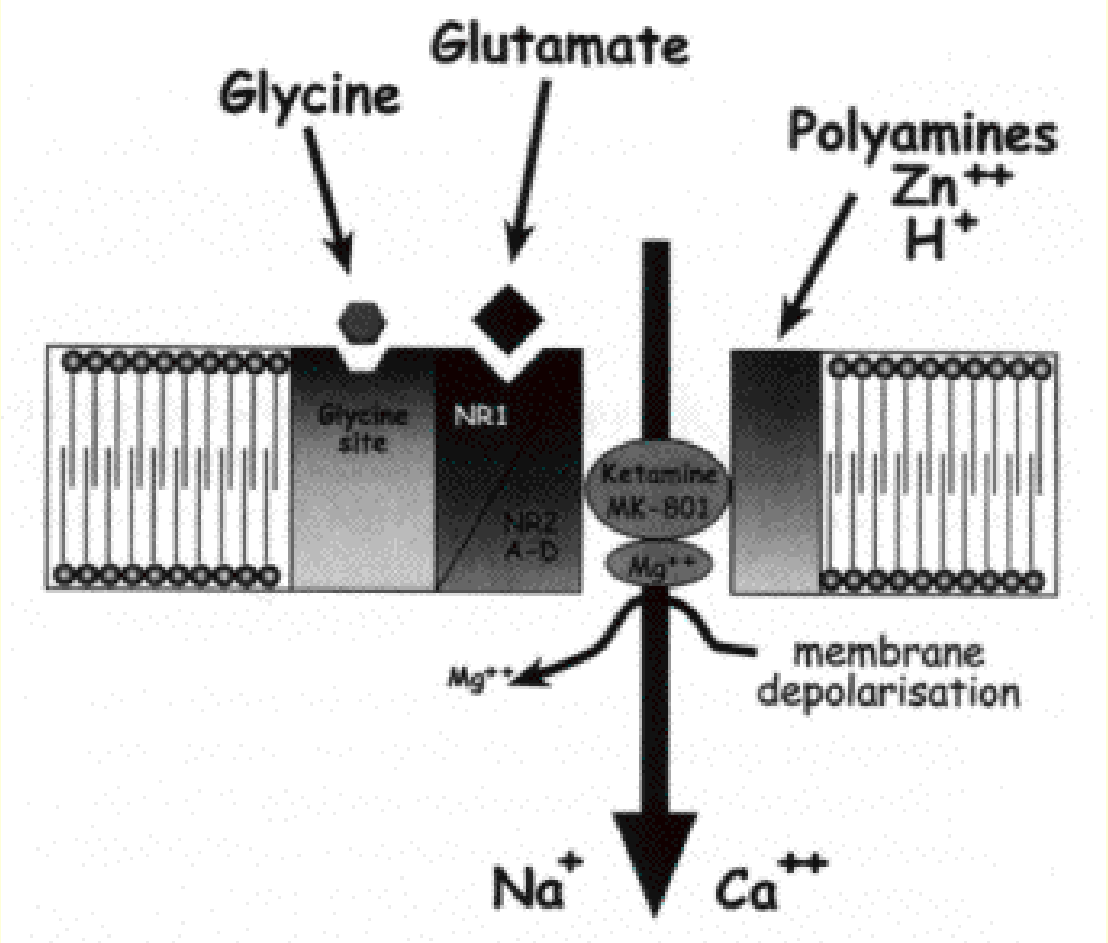
NEUROCHEMISTRY IN DORSAL HORN

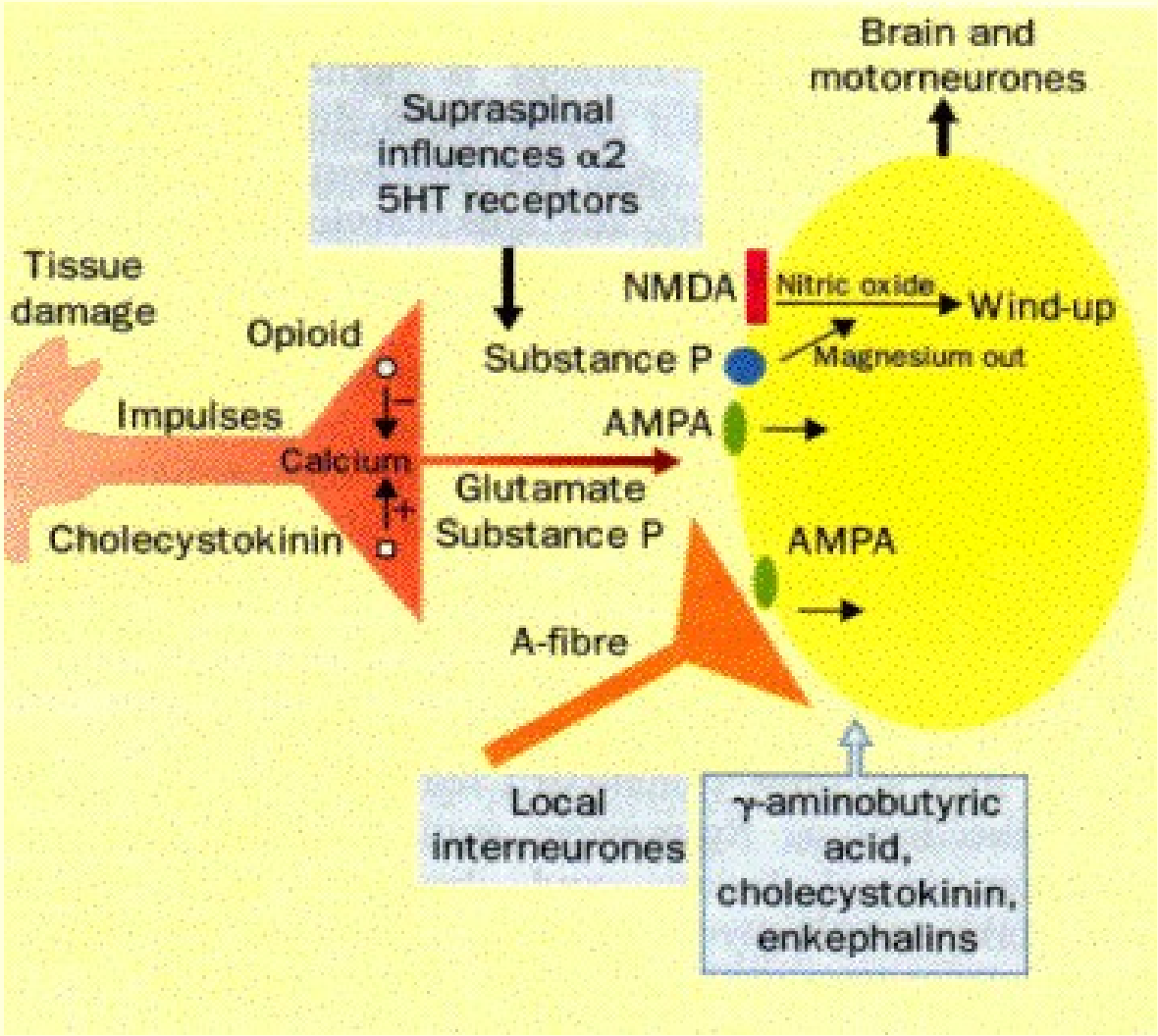


INTRA-CELLULAR EVENTS

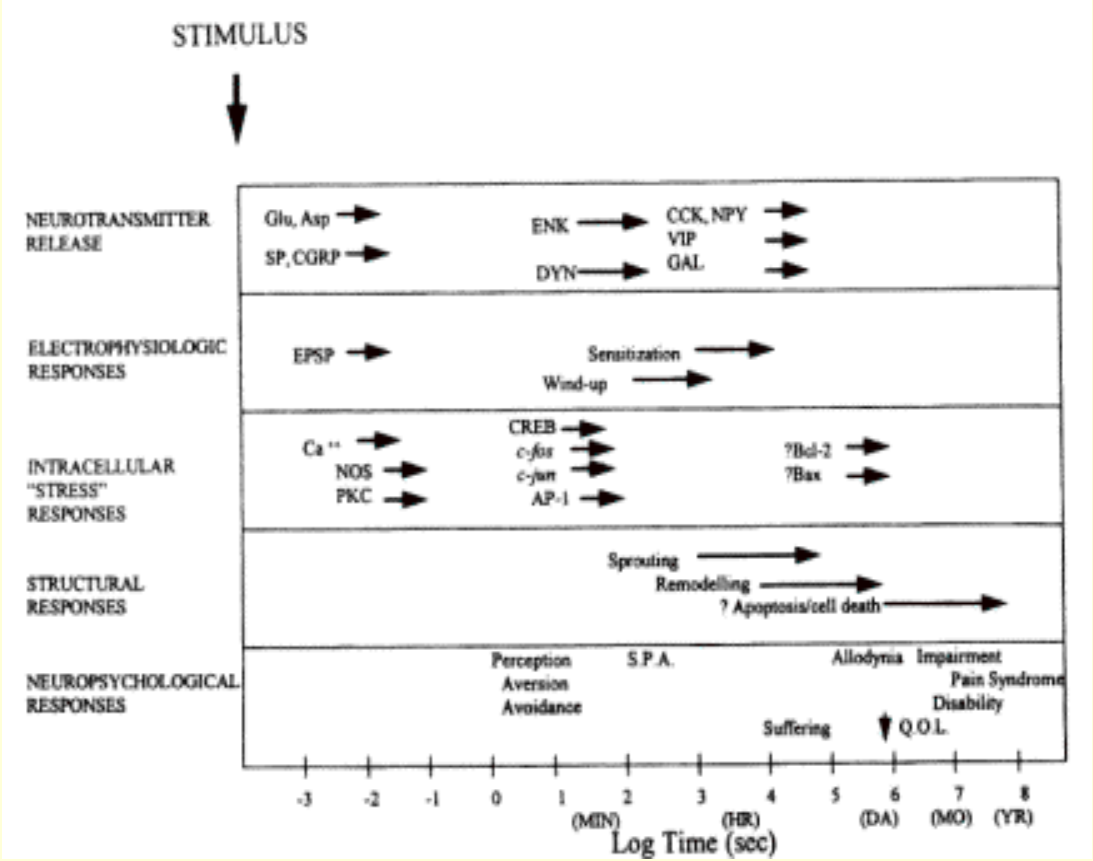
- non-NMDA receptor role in physiological pain
- NMDA role in chronic pain
  - co stimulation of AMPA and NK-1 (Neurokinin I) primes NMDA receptor
  - probable role in
    - “wind up”, central sensitisation, induction of oncogenes and long term potentiation
  - attenuation by NMDA antagonists
    - eg ketamine, MK-801 (Dizocilpine)
- limited by side effects

NMDA-receptor




Brain and motorneurones
Supraspinal influences α2 5HT receptors
Tissue damage
Opioid
NMDA
Nitric oxide
Wind-up
Substance P
Magnesium out
Impulses
AMPA
Calcium
Glutamate
Substance P
Cholecystokinin
AMPA
A-fibre
Local interneurones
γ-aminobutyric acid, cholecystokinin, enkephalins

ACUTE TO CHRONIC PAIN: A TIME-LINE



PAIN EXPERIENCE

Three major psychological dimensions

1. Sensory-discriminative

- rapid conducting spinal systems

2. Motivational-affective

- reticular and limbic systems

3. Cognitive-evaluative

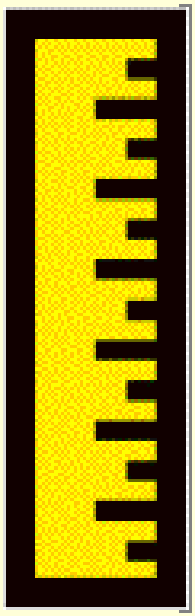
- cortex

RATIONALE FOR PAIN MEASUREMENT

- A scientific way to characterise and quantify pain
- Needed for evaluation of pain treatments
  - reduction in intensity
  - effect on quality/characteristics
    - e.g. burning, stabbing etc.

PAIN MEASUREMENT SYSTEMS

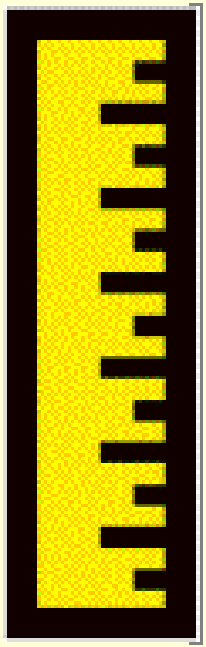
- Observer pain scores
  - heath care staff assessments are inaccurate
    - even if experienced
  - based on behavioural and autonomic signs
    - Non-specific occur with other stressors
    - Not sensitive - may habituate with time



PAIN MEASUREMENT SYSTEMS

PCA (Patient-Controlled Analgesia): no instrument can directly measure pain

- PCA use has been proposed
  - patients will use PCA even if pain free
  - elderly patients may be confused and under use it



PAIN MEASUREMENT

- **Visual Analogue Scales VAS**
  - ***intensity* only**
  - **simple, sensitive, reproducible**
  - **also used for other variables e.g. nausea, satisfaction**
  - **Features:**
    - **100 mm, horizontal line,**
    - **no markings,**
    - **anchors at each end (e.g. 'no pain', 'worst pain ever')**
    - **use same wording from staff at each measurement; no other cues to use.**
    - **More valuable when measured at rest and with movement**
  - **Has ratio properties:**
    - **can be analysed using parametric statistics**
    - **meaningful to use 'percentage' of pain relief**

PAIN MEASUREMENT

Visual Analogue Scales VAS

- **Limitations:**
  - **Limited use in some patients – e.g. cognitively impaired, elderly, children**
  - **Modified VAT (thermometer) were slider is moved for patient until level is reached**
  - **Assumes pain is one-dimensional**
  - **If used to assess pain relief then may be influenced by bias (past memory, expectation of effect)**

VERBAL AND NUMERICAL SYSTEMS

- **Numerical rating score**
  - rate pain intensity from 0 to 10
  - easy to use but affected by assigning specific cues
  - Does not need any equipment
- **Verbal rating scale**
  - using words
    - ‘severe’, ‘moderate’, ‘mild’, ‘none’
    - quick & easy to apply
    - limited precision by restriction in number of points on scale

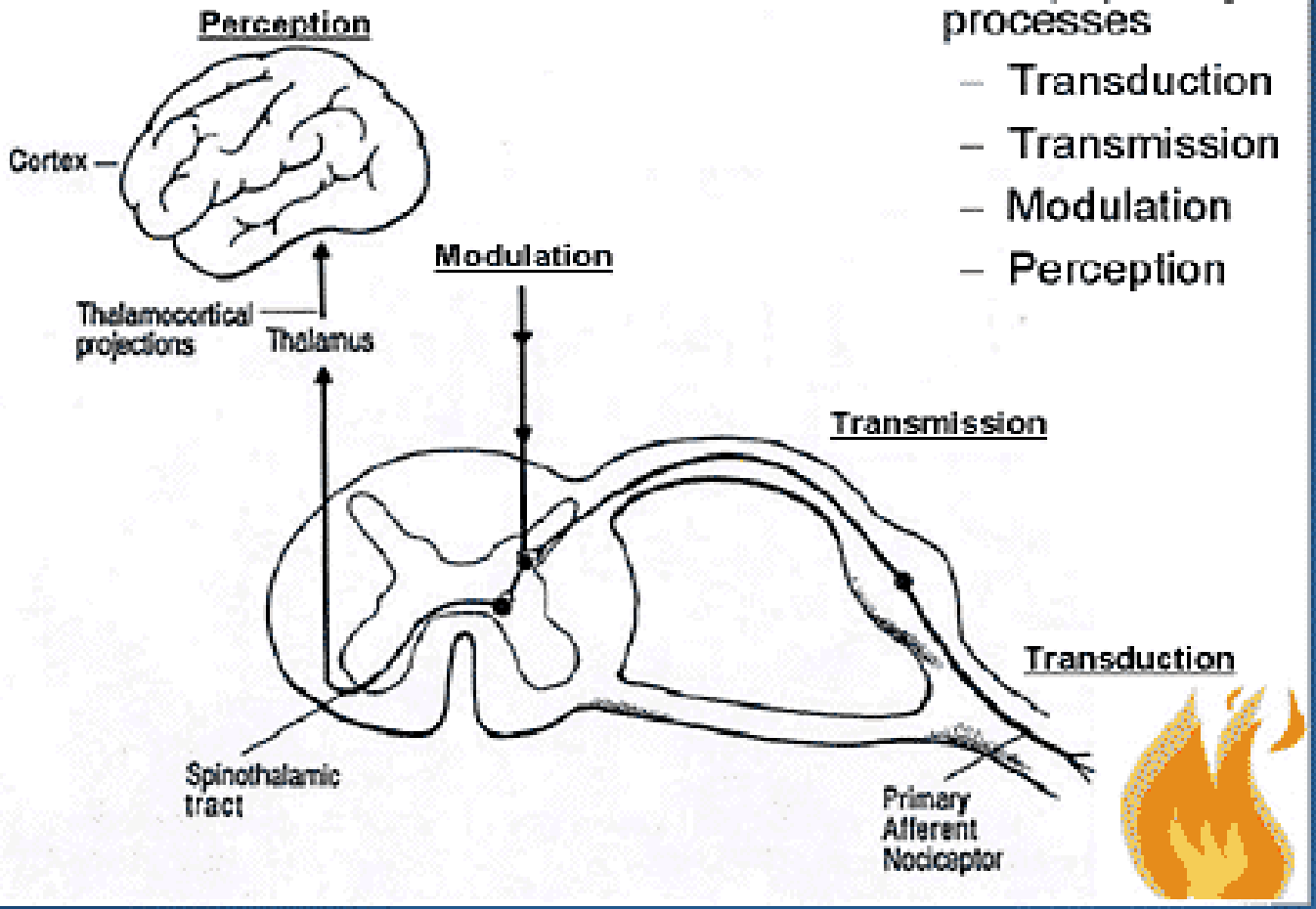
Magill Pain Questionnaire

- Previous systems only rated *intensity*
- Need assessment of other qualities of pain
- Magill Pain Questionnaire
  - Assesses 20 features of pain using 105 descriptors
  - sensory, affective, evaluative components
  - provides data that on qualitative differences in pain and pain relief methods
- Disadvantages
  - too long
  - patients become frustrated
  - in English (but has been translated and validated); patients may not understand words
  - rarely used for acute pain

PAEDIATRIC PAIN MEASUREMENT

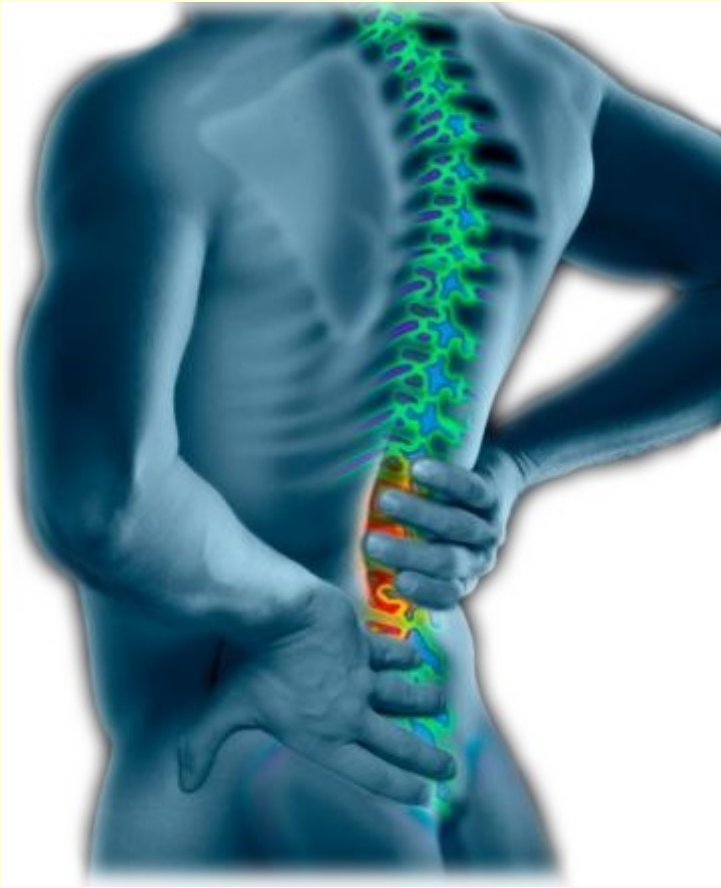
- Adult methods are limited to older children
- Faces rating scale
  - child is asked to chose one of six pictures of faces that represent their pain
  - for verbal children
- Body outlines
  - child is asked to colour in on a picture of a body where the pain is located. Different colours can represent pain intensity
- Pre-verbal children
  - observation of behavioural and physiological scores
    - eg CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)

- Four physiologic processes
  - Transduction
  - Transmission
  - Modulation
  - Perception



CONCLUSIONS

- A rapidly evolving topic
- Classically a three neurone chain
- Separation of function…
  - Discriminative
  - Affective
- Plasticity is evident
- Mechanisms of pain are important to treat pain effectively



GOOD LUCK !