Classical Osteopathic Approach Targeting the Vagus Nerve and the Neuroendocrine-Immune System and monitored by heart rate variability

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1 BUTS

1. To discover osteopathic centers related to the neuroendocrine-immune system
2. Understand how to perform osteopathic treatment specifically targeting the neuroendocrine-immune system
3. Objectivation of the effects of osteopathic treatment on the neuroendocrine-immune system
4. To understand how the osteopathic treatment via effective and adequate techniques acts on this system
5. To bring the basics of neuroendocrine-immunology and appreciate the sympatho-vagal balance in pre and post treatment.

2 OBJECTIFS

1. Understand the principles of inflammation related to neuroendocrine-immunology
2. Understand the "anti-inflammatory reflexes”
3. Understanding the intestines-brain and heart-brain connections in relation with the vagus nerve
4. Understand the functions and roles of brain structures of the autonomic central network as well as the limbic system
5. Understand the principles of HRV as a non-invasive biomarker and how can sympathovagal balance predict disease or health?
6. Set up a classical osteopathic treatment focused on osteopathic centers related to the endocrine system, immune system (including lymphatics) and autonomic nervous system
7. Use HRV data to objectify effects on the neuroendocrine-immune system of osteopathic treatment

D1

1. ANATOMO-PHYSIOLOGY : ANS and VAGUS NERVE
2. LIMBIC SYSTEM and CAN
3. NEUROENDOCRINE-IMMUNOLOGY (NEI)

D2

4. HEART-BRAIN / GUT-BRAIN AXIS
5. HRV – PRINCIPLES and ANALYSIS - PRACTICE
6. OSTEOPATHIC CENTERS – TREATMENT GUIDELINES

D3

7. OSTEOPATHIC and HRV PRACTICE

1. ANATOMOPHYSIOLOGY

1) ANS (Generalities) – 4 systems

- Two anatomical systems with reactions that seem antagonistic, but in fact complementary: sympathetic part and parasympathetic part + two "independent" systems: enteric system (intrinsic) and the autonomous (intrinsic) cardiac system.

- The sympathetic part is **ergotropic**, that is to say that it assumes the expenditure of energy. **Afferences / Efferences = 50%.** The para - sympathetic part is **trophotropic**, that is to say animator of metabolic functions, restorers of energy. **Afferences = 80%, Efferences = 20%.**

- Innervation of milieu interieur, its field of innervation concerns viscera, glands (exocrine and endocrine), vasomotricity and sensitivity. Almost all the functions of the body are concerned. Major role in the mediation of interactions between nervous and immune systems (sympatho-vagal Synergy).

- Sympathetic innervates mainly primary and secondary lymphoid organs (bone marrow, thymus, tonsils, lymph nodes, Peyer's patches, spleen). The ANS works mainly through negative feedbacks (inhibitions - equilibrium) and reflex arcs. But also via positive feedback (stimulation - instability) in case of pathology.

- It uses specific neuronal pathways at the periphery and a specific central organization for its modulatory action, In the motor plane, he innervates all the smooth muscle fibers. Sensitively, it transmits visceral sensitivity, which is expressed by the sensation of hyperperistalsis, pain by tension or repletion of hollow viscera, compression of intraperitoneal effusion or hypertrophy of a solid viscus. Nerve X also transmits somatic sensitivity.

1) ANS (Generalities) – next

a) Brain centers

The hypothalamus is the vegetative brain. It is related to the deep parts of the brain (dorso - medial nucleus of the thalamus, limbic area, pre - frontal areas) and with the sympathetic relays of the pre - frontal cortex (CPF), locus coeruleus (LC), the parasympathetic nuclei of the brainstem, via the midbrain of the telencephalon. It is also in a neuroendocrine relationship with both lobes of the pituitary gland.

b) Brain stem centers

In the reticular substance of the brainstem, there are the tiered nuclei of the para - sympathetic cranial, including the very important cardio - pneumoenteric nucleus which is at the origin of the vagus (or pneumogastric) nerve.

The cell bodies of preganglionic sympathetic neurons are located at the nuclei of RVLM (Rostral, ventro-lateral medulla).

c) Medulla centers (Thoraco-lumbar)

In the central region of the spinal cord are the staggered nuclei of the sympathetic part (T2 - L2), arranged in two parallel columns: the intermedia - medial and intermedio - lateral columns. 22 ganglia.

d) Sacral centers

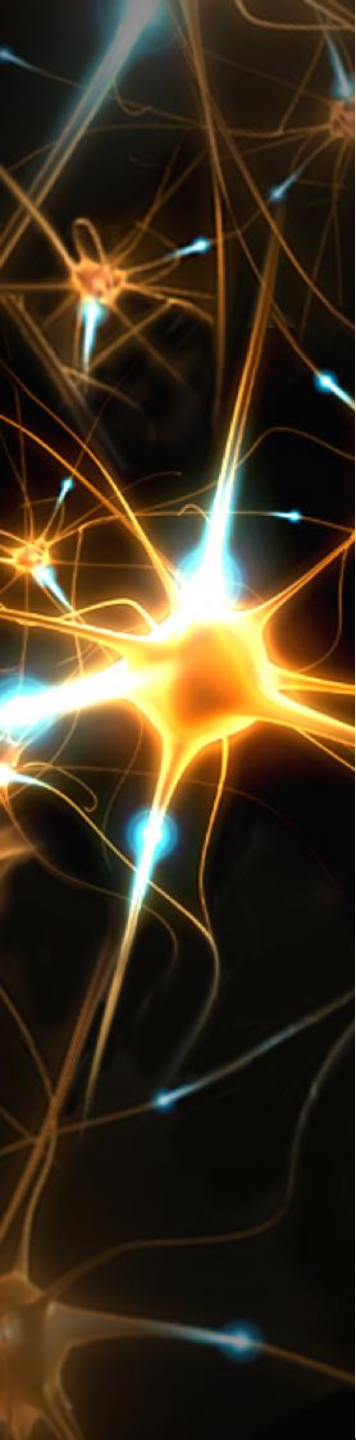
At this level is the pelvic parasympathetic nucleus (S2 - S4).

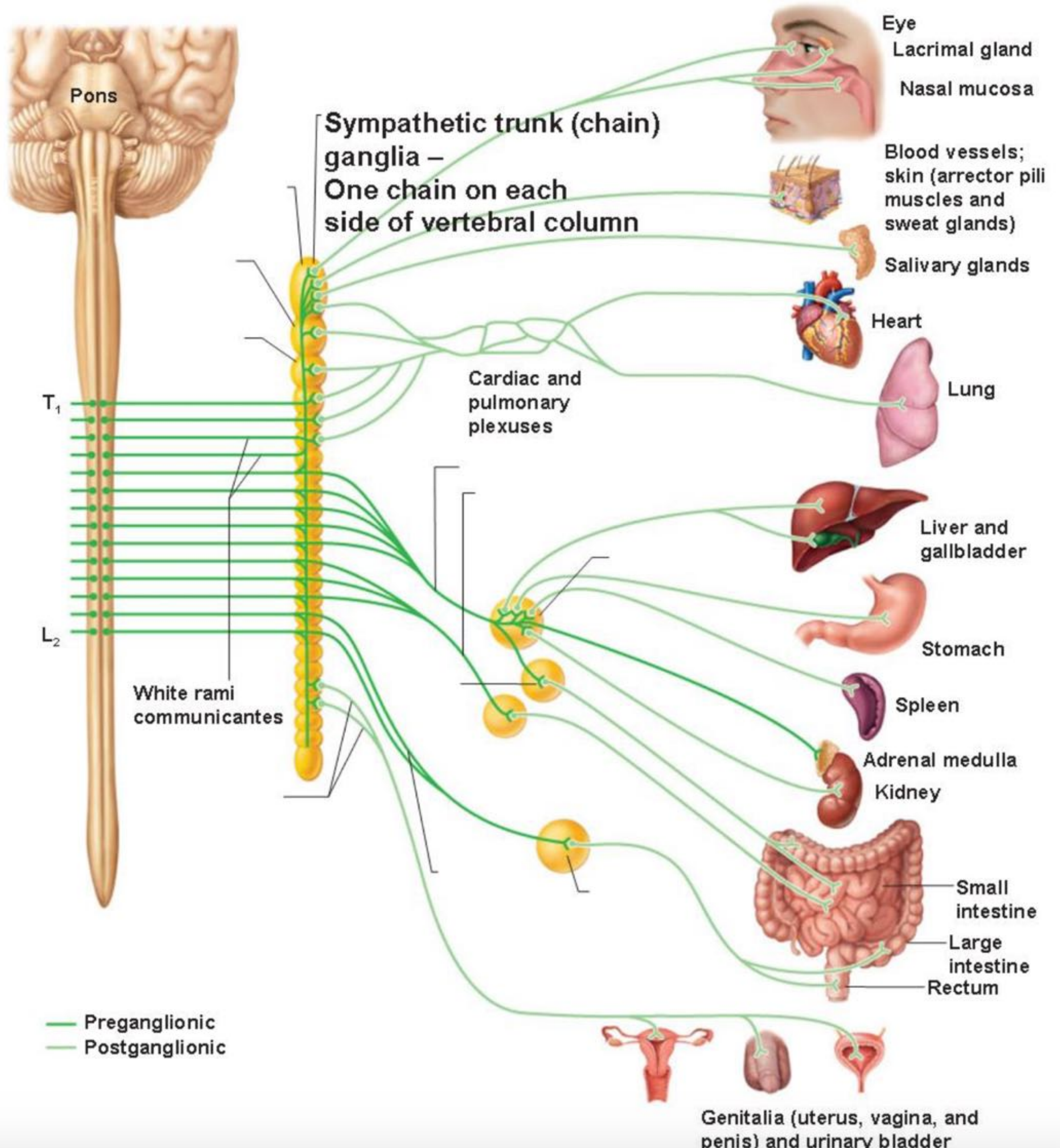
- SNA functions and regulations involve complex integrated and interactive steps (neurotransmission - neurotransmitter synthesis, secretion and degradation, ganglion regulation and receptor mediated effects); most involved in neuroimmune reactions.

- So there exists between the two parts (sympathetic-paraS), a variable balance according to the physical or psychological circumstances of the existence (variation according to the age, for example)

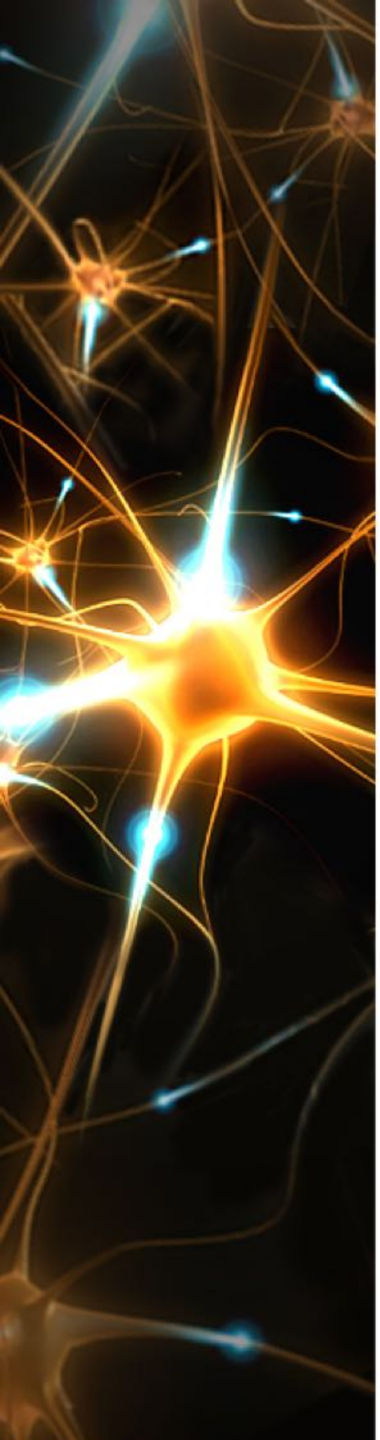
- The severe disturbance of this equilibrium is responsible for neuro-vegetative disorders in the sense of **hyper-sympathicotonia** or **hyper-parasympathicotonia (hyper-vagotonia)**

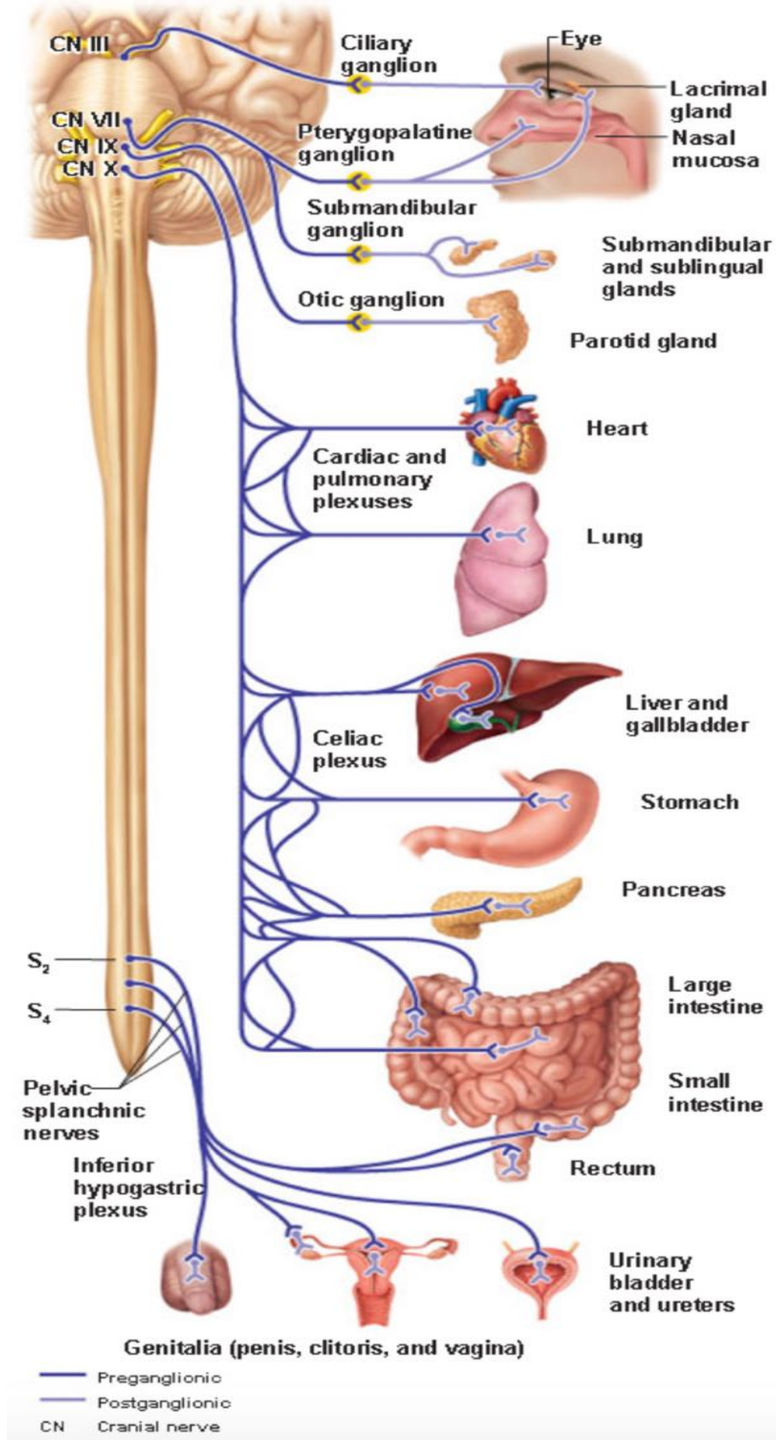
- Dysautonomia represents a rupture of this equilibrium and will be either structural or functional in hypo or hyper.



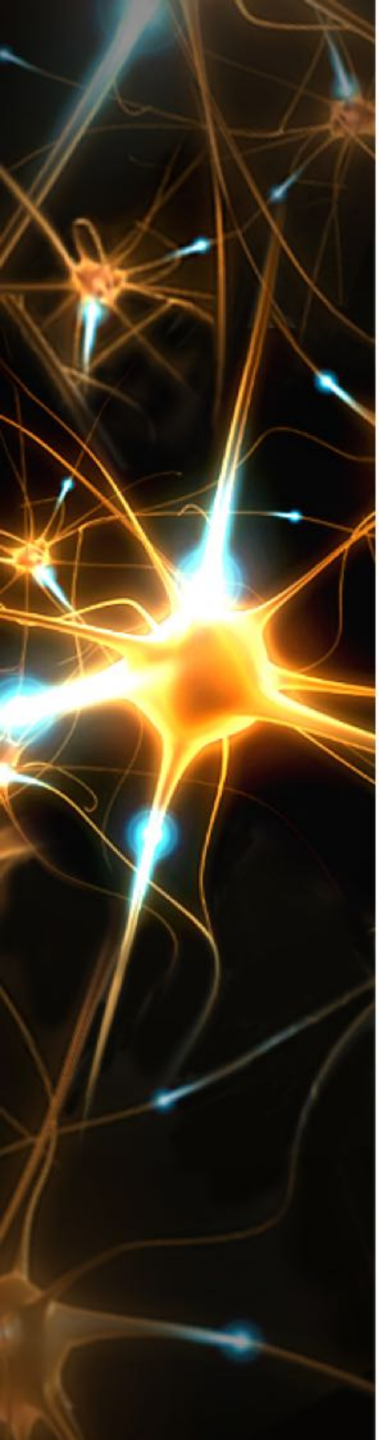


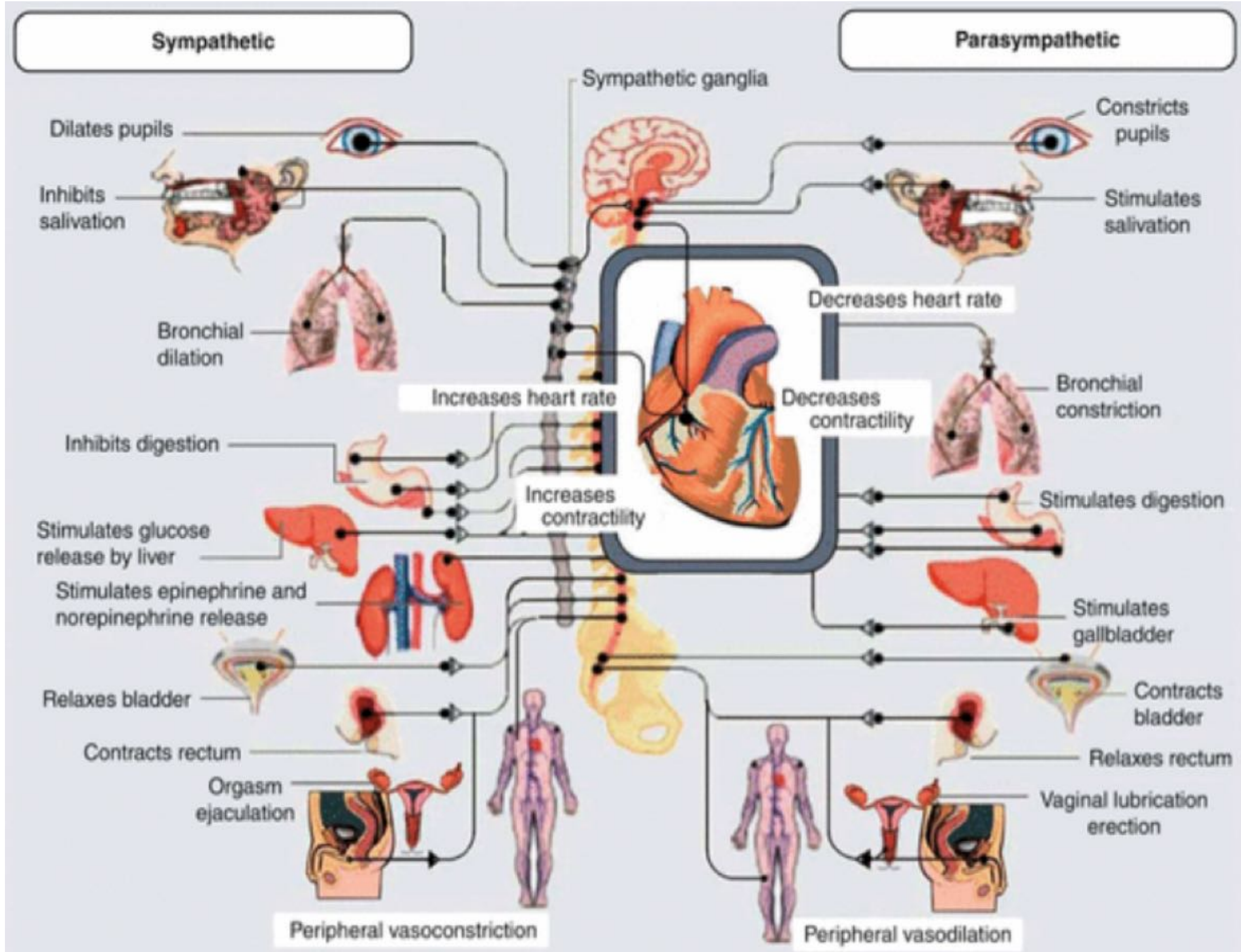
Pons
Sympathetic trunk (chain) ganglia –
One chain on each side of vertebral column
T_1
L_2
White rami communicantes
Cardiac and pulmonary plexuses
Eye
Lacrimal gland
Nasal mucosa
Blood vessels; skin (arrector pili muscles and sweat glands)
Salivary glands
Heart
Lung
Liver and gallbladder
Stomach
Spleen
Adrenal medulla
Kidney
Small intestine
Large intestine
Rectum
Genitalia (uterus, vagina, and penis) and urinary bladder
Preganglionic
Postganglionic



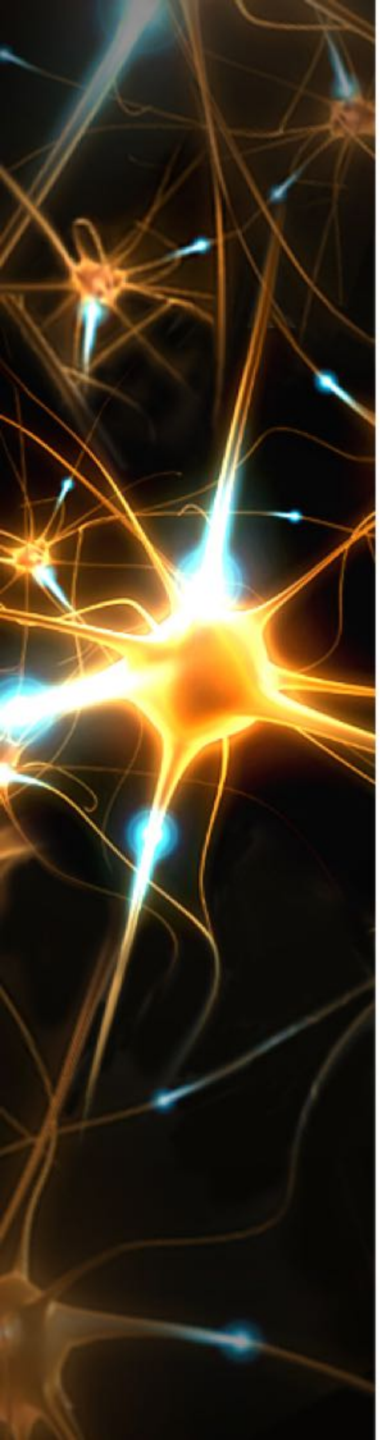


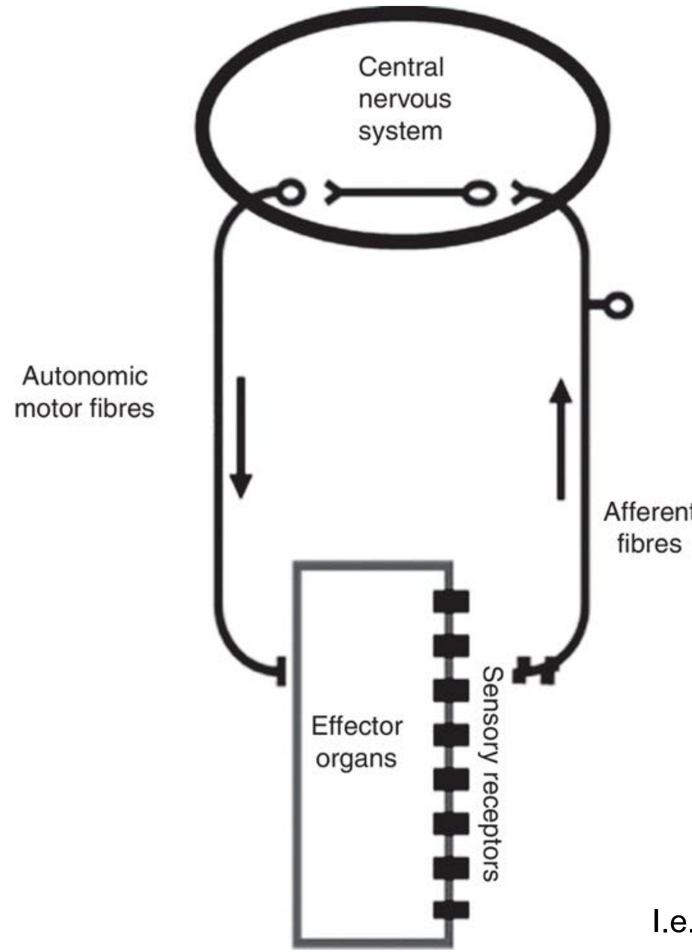
CN III
Ciliary ganglion
Eye
Lacrimal gland
CN VII
CN IX
CN X
Pterygopalatine ganglion
Nasal mucosa
Submandibular ganglion
Submandibular and sublingual glands
Otic ganglion
Parotid gland
Heart
Cardiac and pulmonary plexuses
Lung
Liver and gallbladder
Celiac plexus
Stomach
Pancreas
S2
S4
Large intestine
Small intestine
Pelvic splanchnic nerves
Inferior hypogastric plexus
Rectum
Urinary bladder and ureters
Genitalia (penis, clitoris, and vagina)
Preganglionic
Postganglionic
CN Cranial nerve




Sympathetic
Parasympathetic
Sympathetic ganglia
Dilates pupils
Inhibits salivation
Bronchial dilation
Increases heart rate
Inhibits digestion
Increases contractility
Stimulates glucose release by liver
Stimulates epinephrine and norepinephrine release
Relaxes bladder
Contracts rectum
Orgasm ejaculation
Peripheral vasoconstriction
Constricts pupils
Stimulates salivation
Decreases heart rate
Decreases contractility
Bronchial constriction
Stimulates digestion
Stimulates gallbladder
Contracts bladder
Relaxes rectum
Vaginal lubrication erection
Peripheral vasodilation

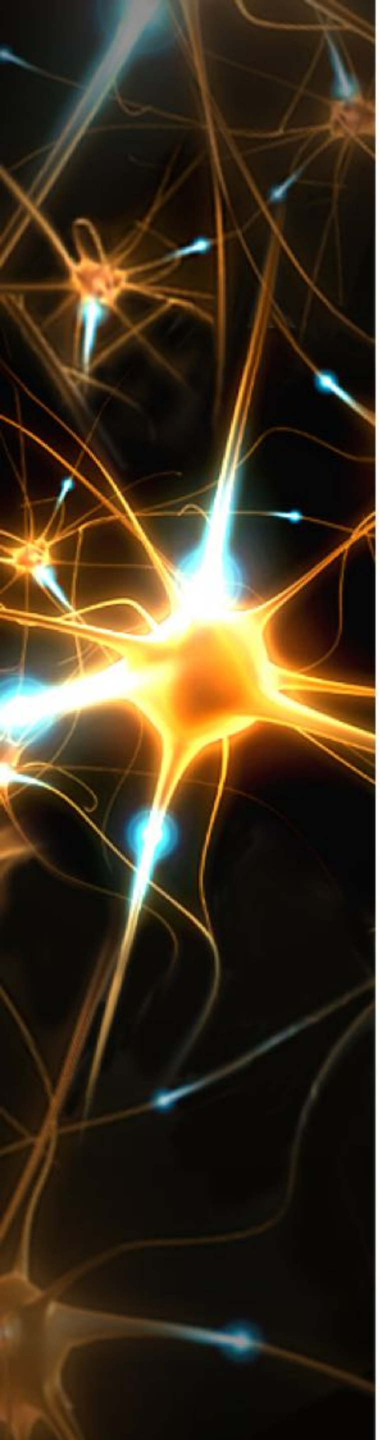
ANS – Reflex arc

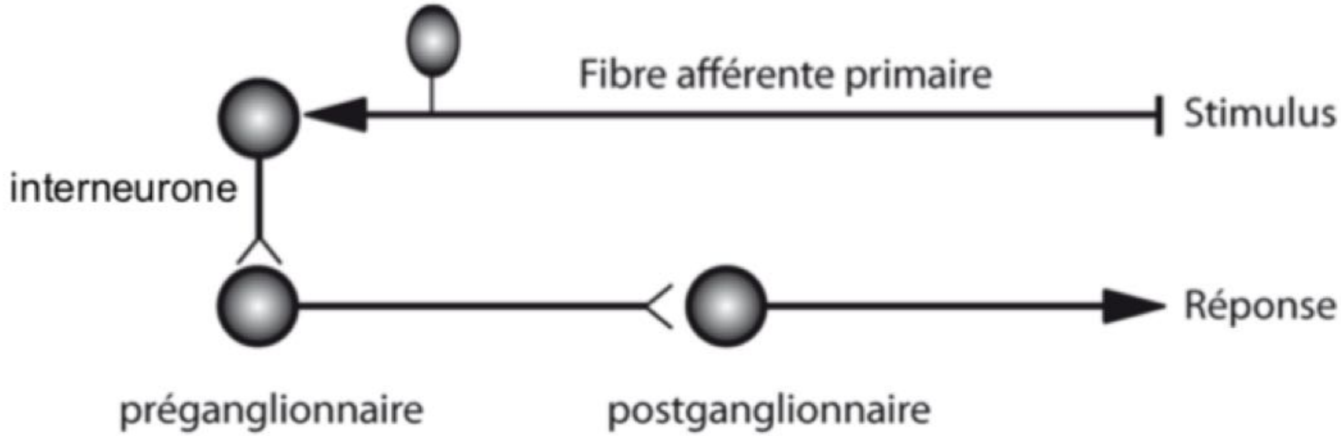




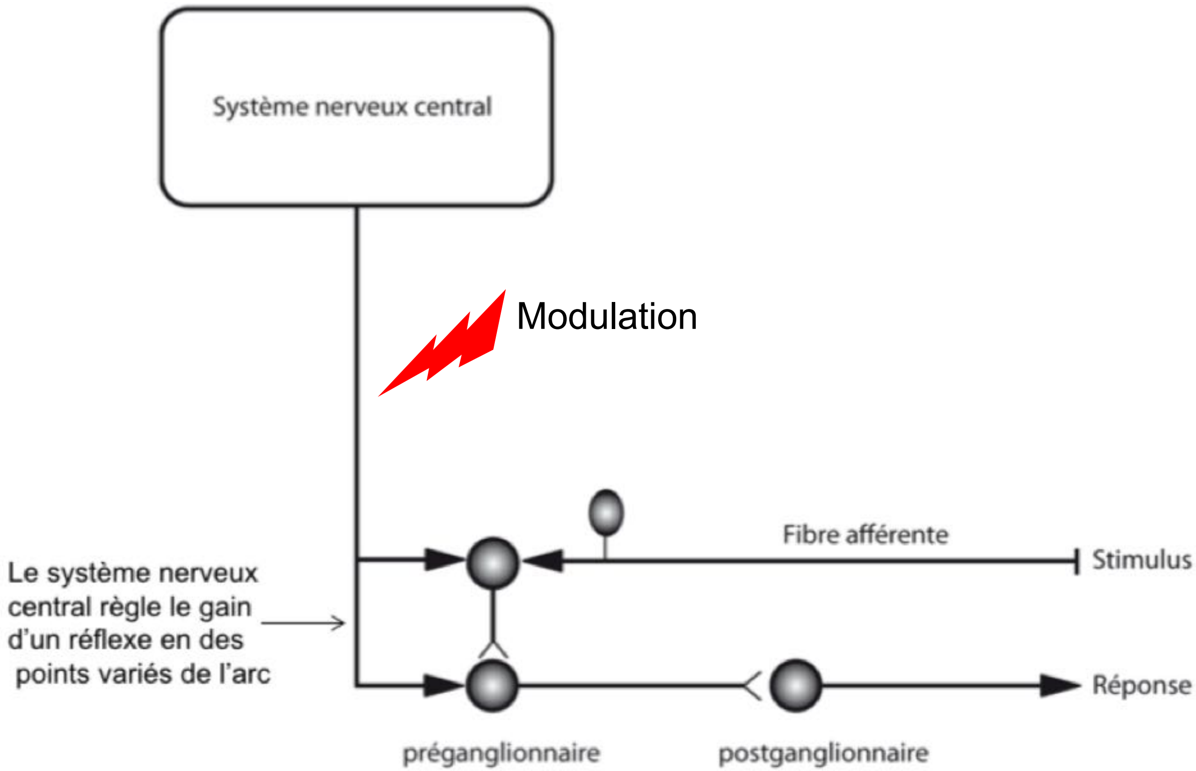
I.e. baroreceptors

The autonomous reflex arc. Autonomic motor fibers include sympathetic, parasympathetic and enteric fibers. After Rochas (2009)

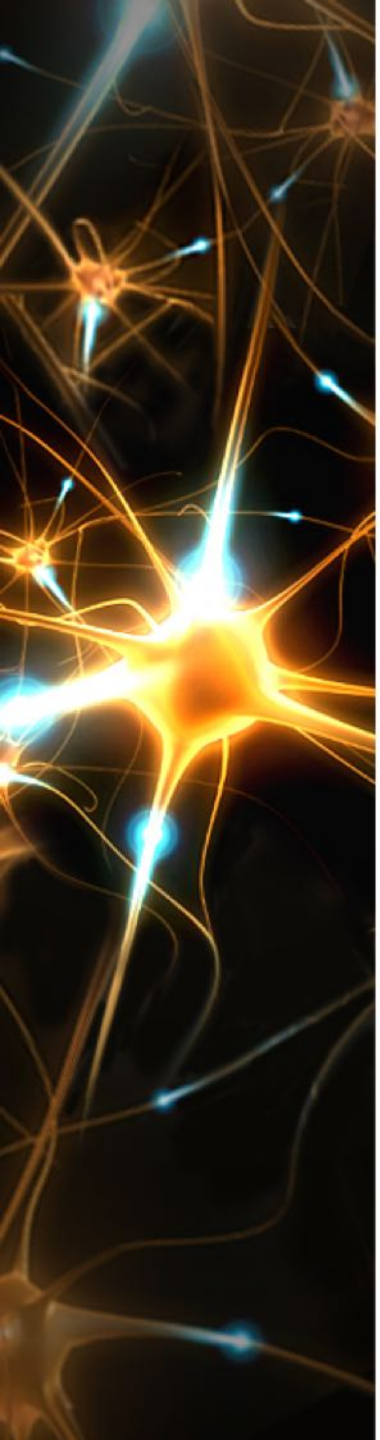


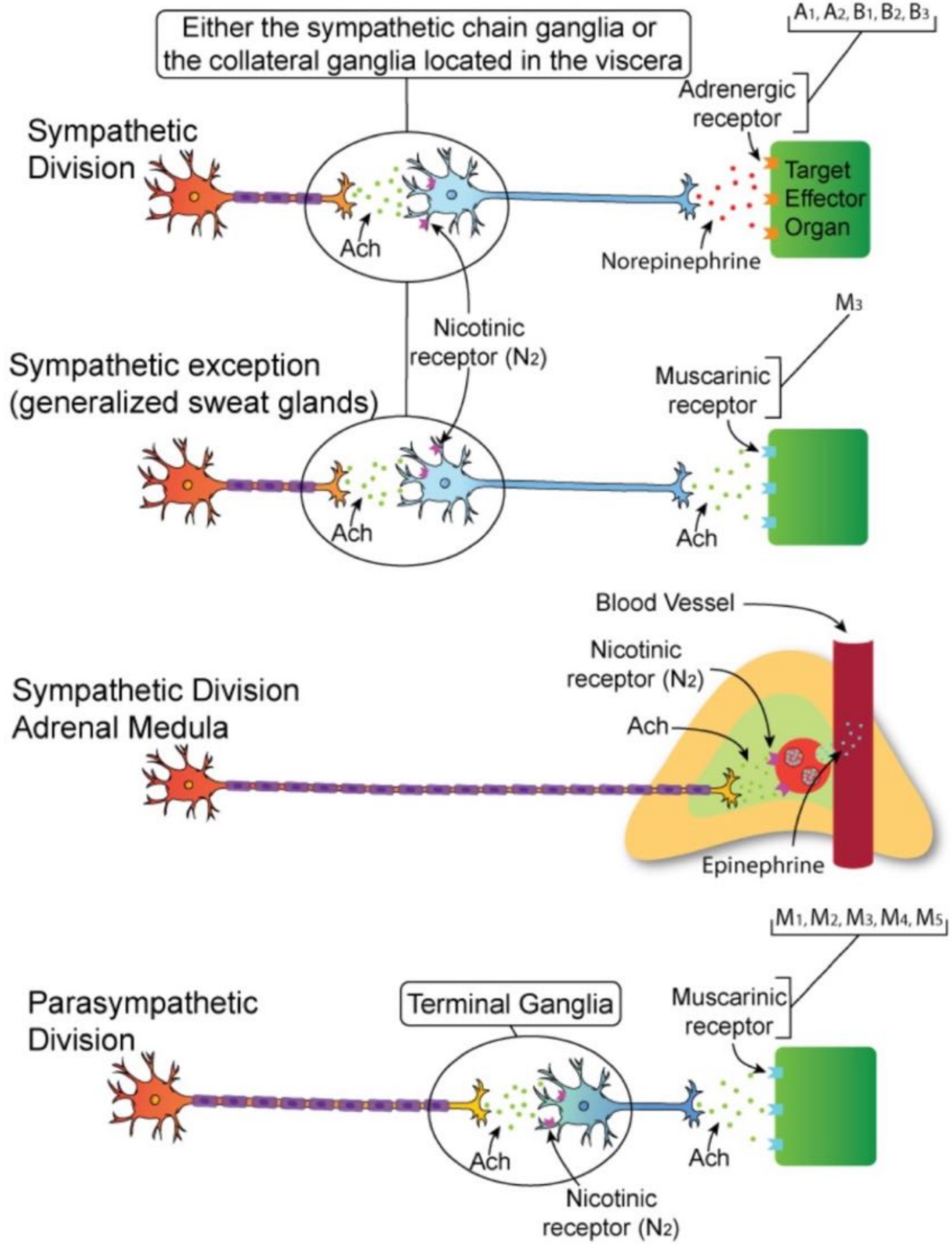


Fibre afférente primaire
Stimulus
interneurone
Réponse
préganglionnaire
postganglionnaire

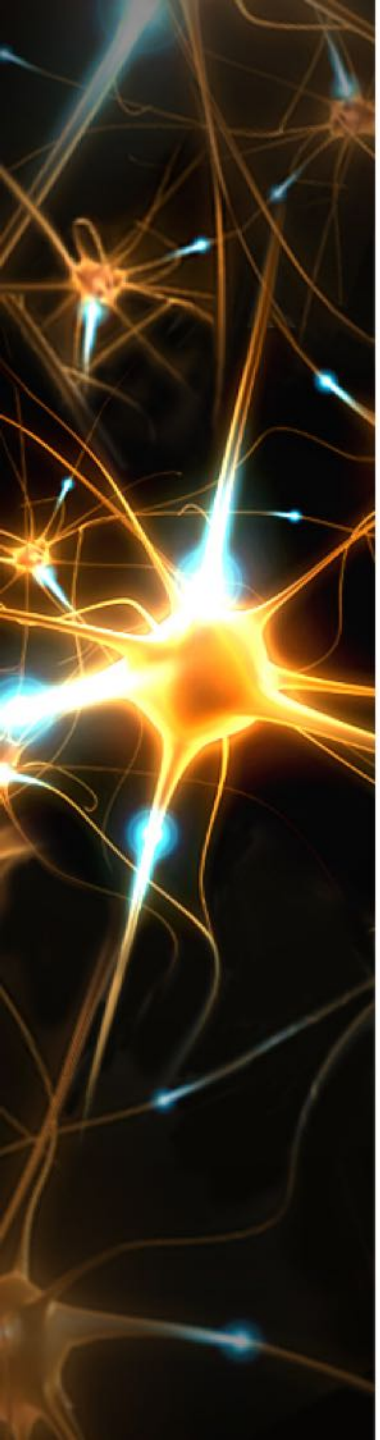


Système nerveux central
Modulation
Fibre afférente
Stimulus
Le système nerveux central règle le gain d'un réflexe en des points variés de l'arc
Réponse
préganglionnaire
postganglionnaire





Either the sympathetic chain ganglia or the collateral ganglia located in the viscera
A_1, A_2, B_1, B_2, B_3
Adrenergic receptor
Sympathetic Division
Target Effector Organ
Ach
Norepinephrine
M_3
Nicotinic receptor (N_2)
Sympathetic exception (generalized sweat glands)
Muscarinic receptor
Ach
Ach
Blood Vessel
Nicotinic receptor (N_2)
Sympathetic Division Adrenal Medula
Ach
Epinephrine
M_1, M_2, M_3, M_4, M_5
Parasympathetic Division
Terminal Ganglia
Muscarinic receptor
Ach
Ach
Nicotinic receptor (N_2)



SNS

Tyrosine

Tyrosine Hydroxylase

(L-) DOPA

Dopa Decarboxylase

Dopamine (DA)

Dopamine *ß-hydroxylase*

Noradrénaline (NA)

Adrénaline (A)

CATECHOLAMINES

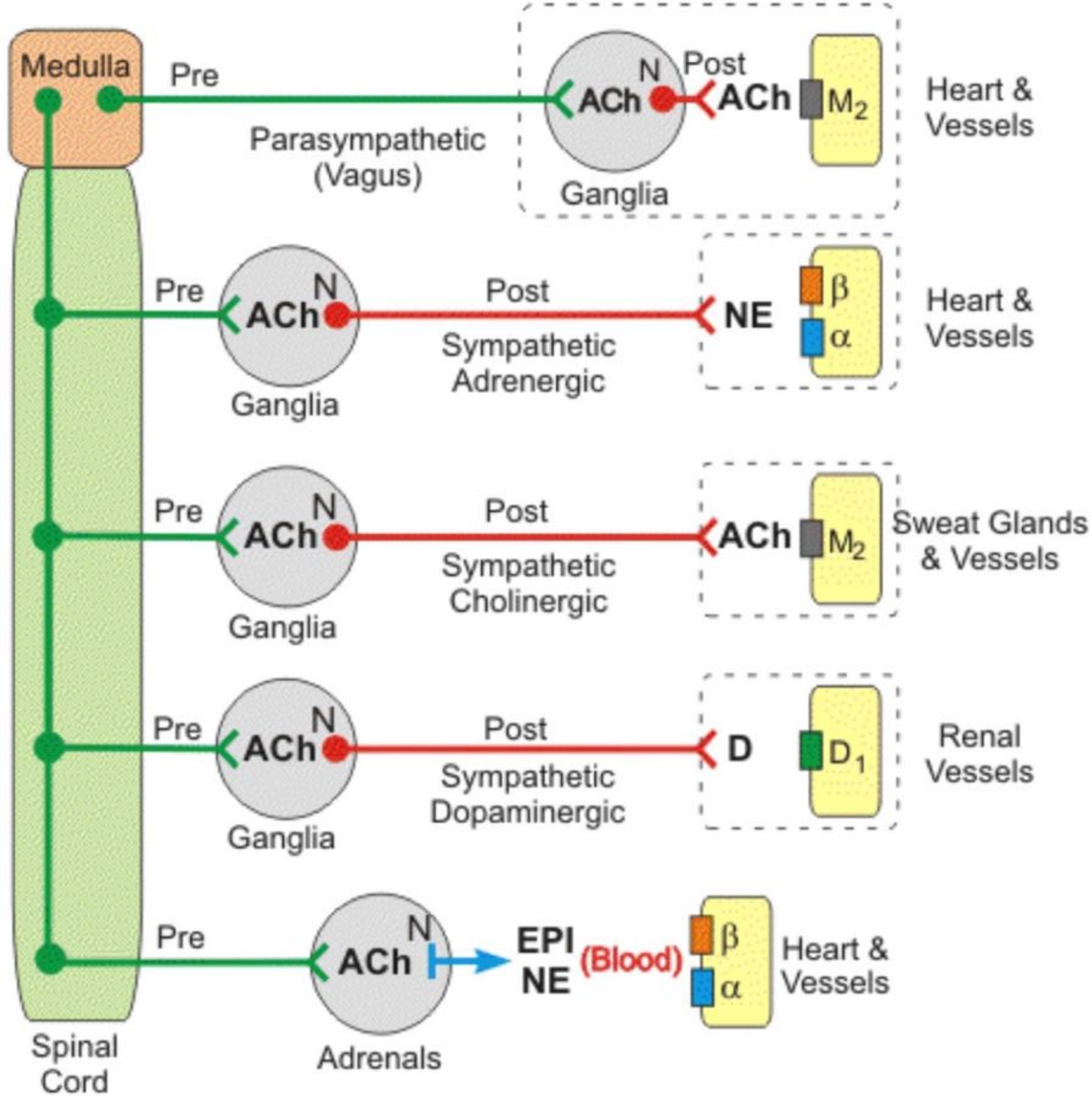
PNS/ENS

Choline

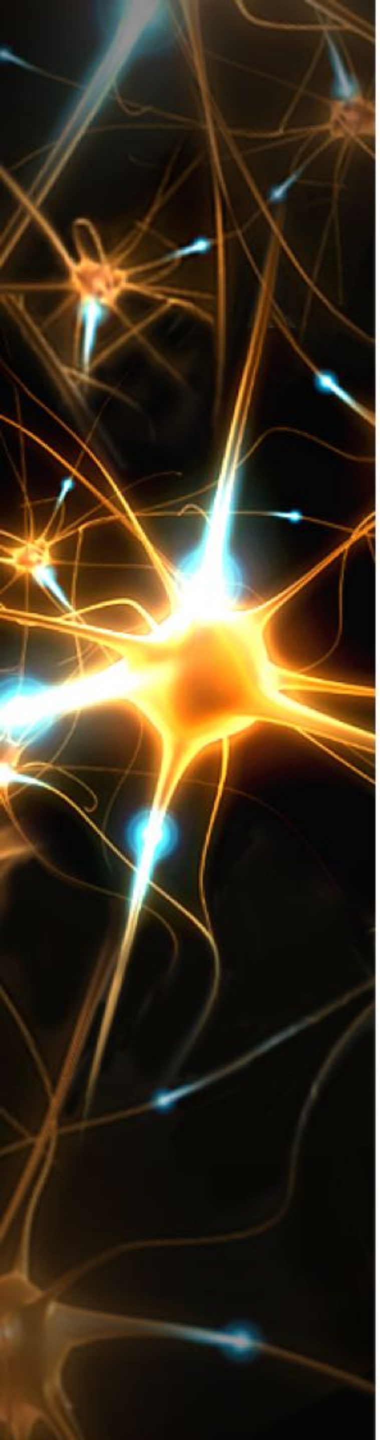
Choline Acetyl transferase

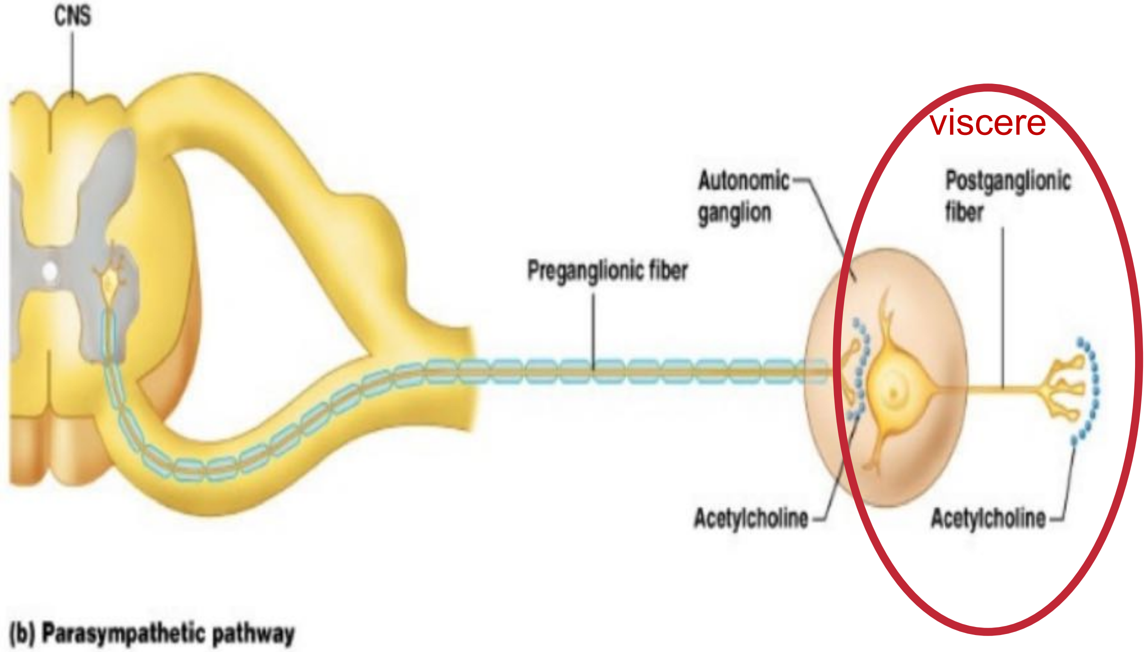
Acéthylcholine (Ach)

ACETHYLCHOLINE

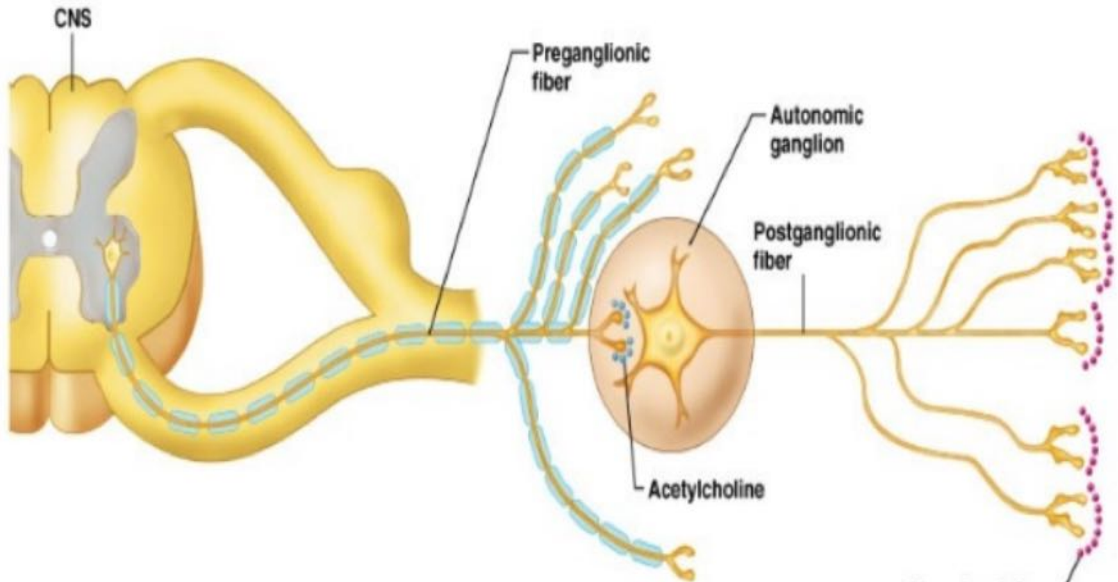


CNS = central nervous system; Pre = preganglionic; Post = postganglionic; ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine; D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor; D_1 = dopaminergic receptor



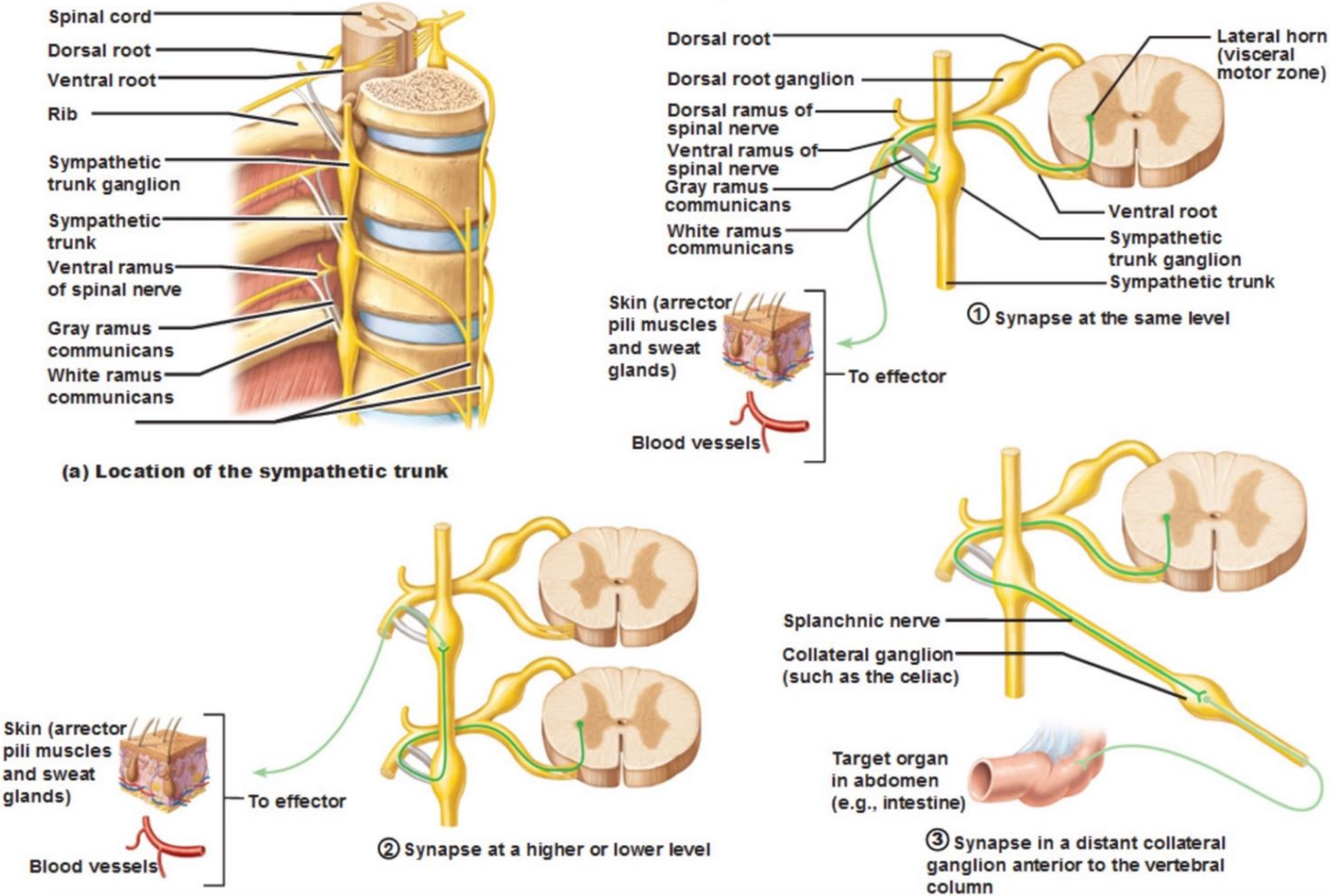


(b) Parasympathetic pathway



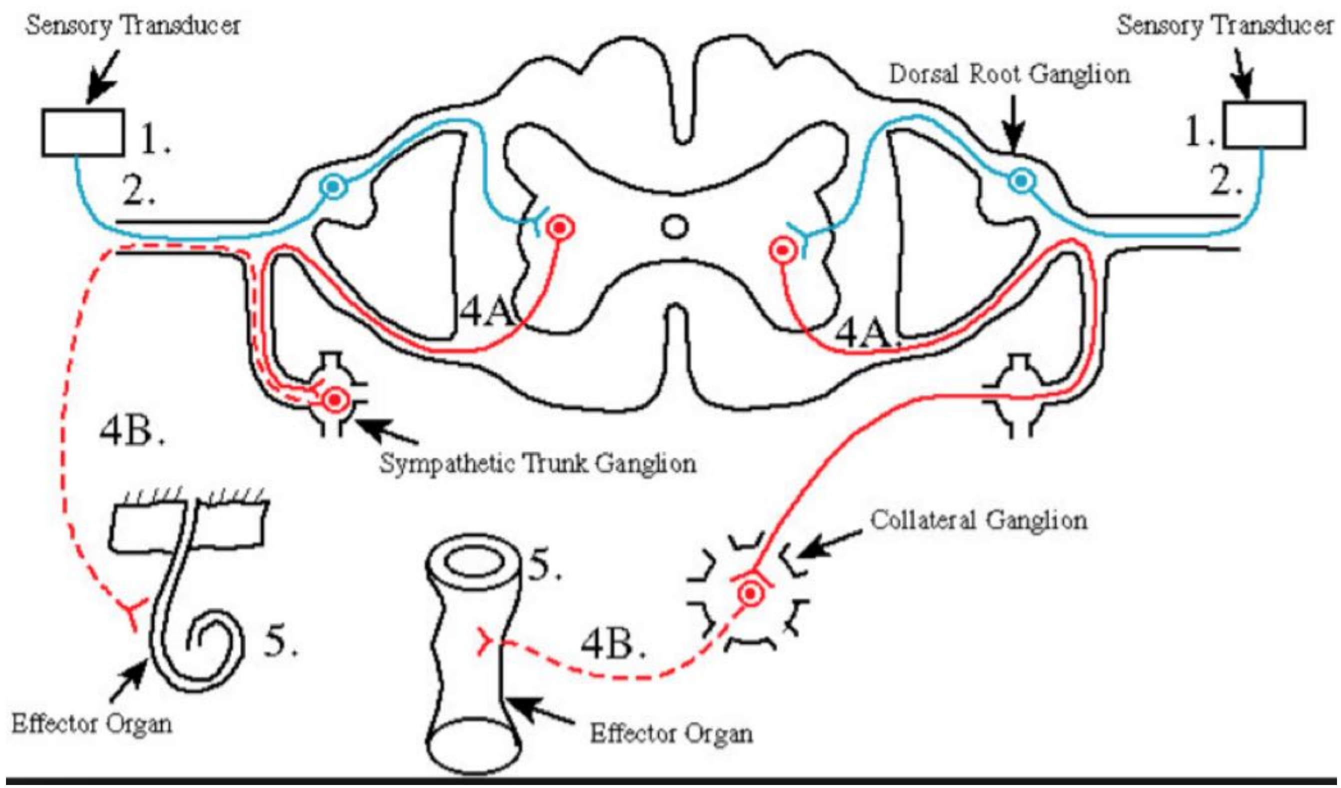
(a) Sympathetic pathway

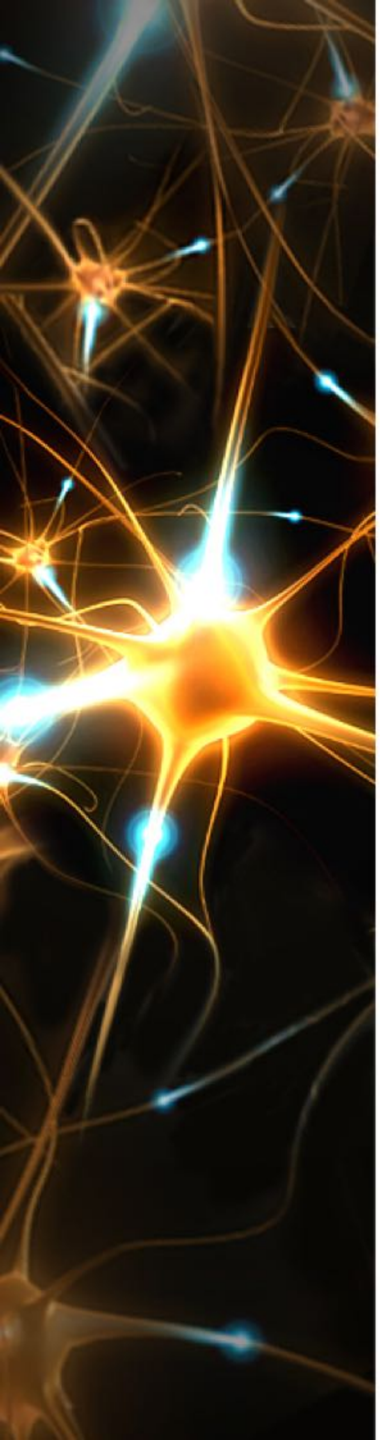
Sympathetic Chain

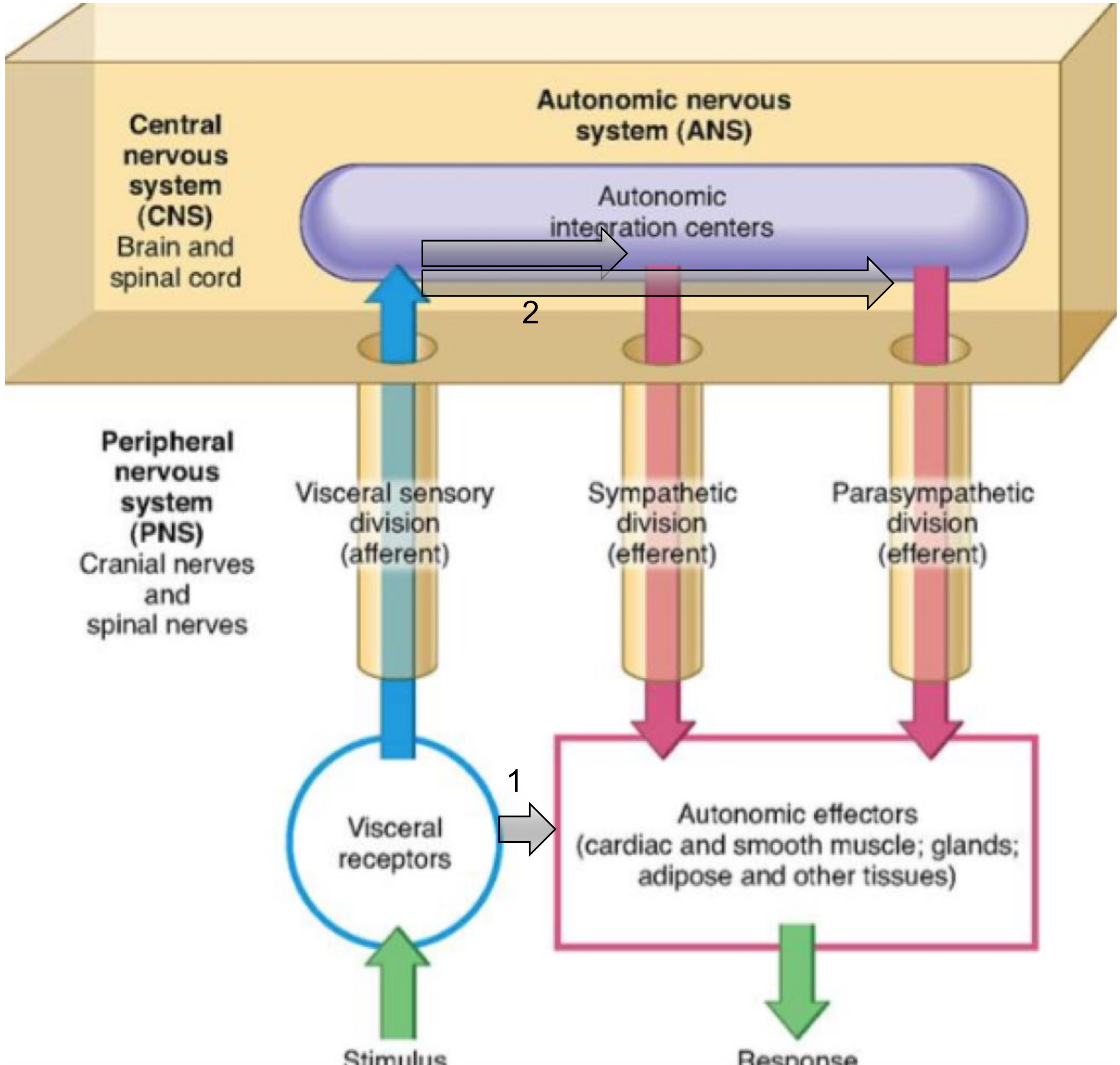


(b) Three pathways of sympathetic innervation

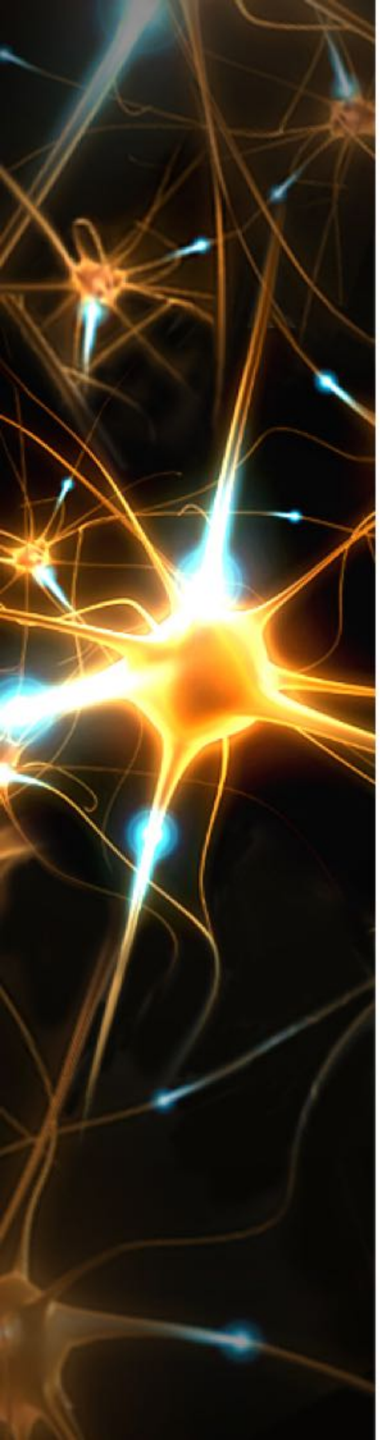
Autonomic Reflex Arc

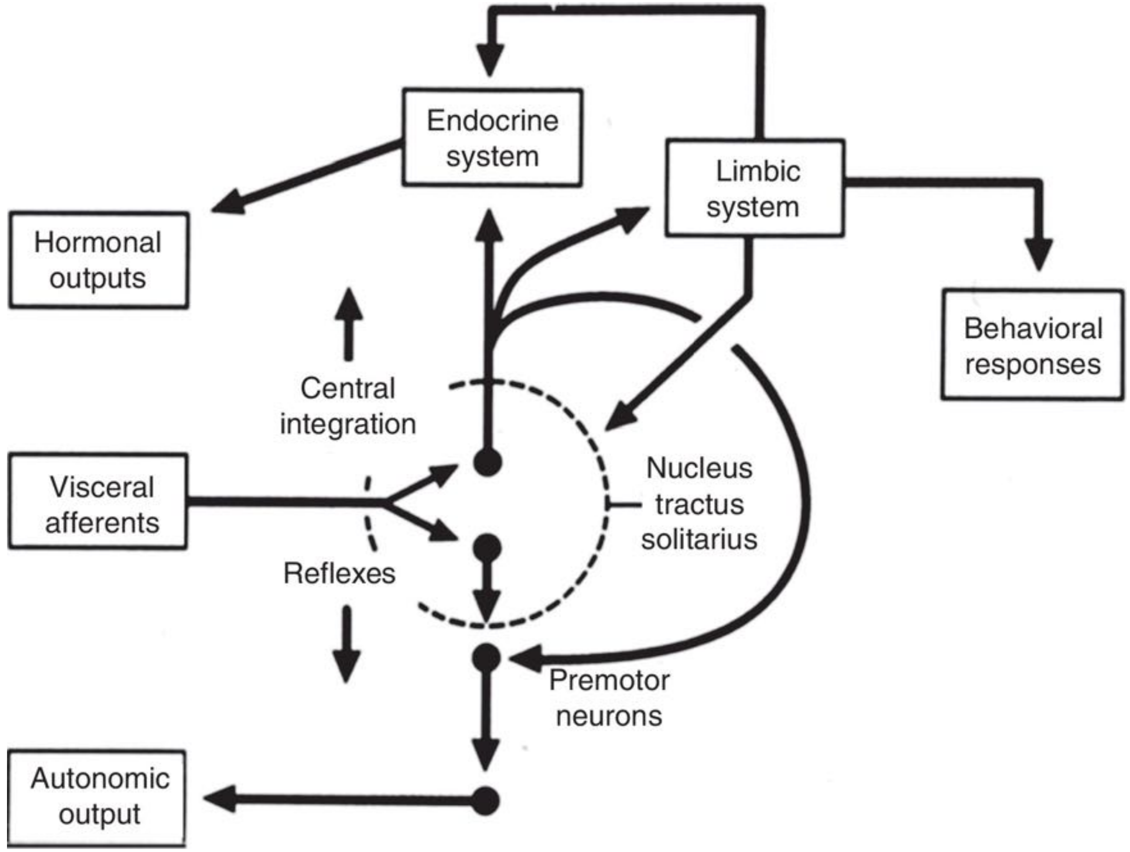




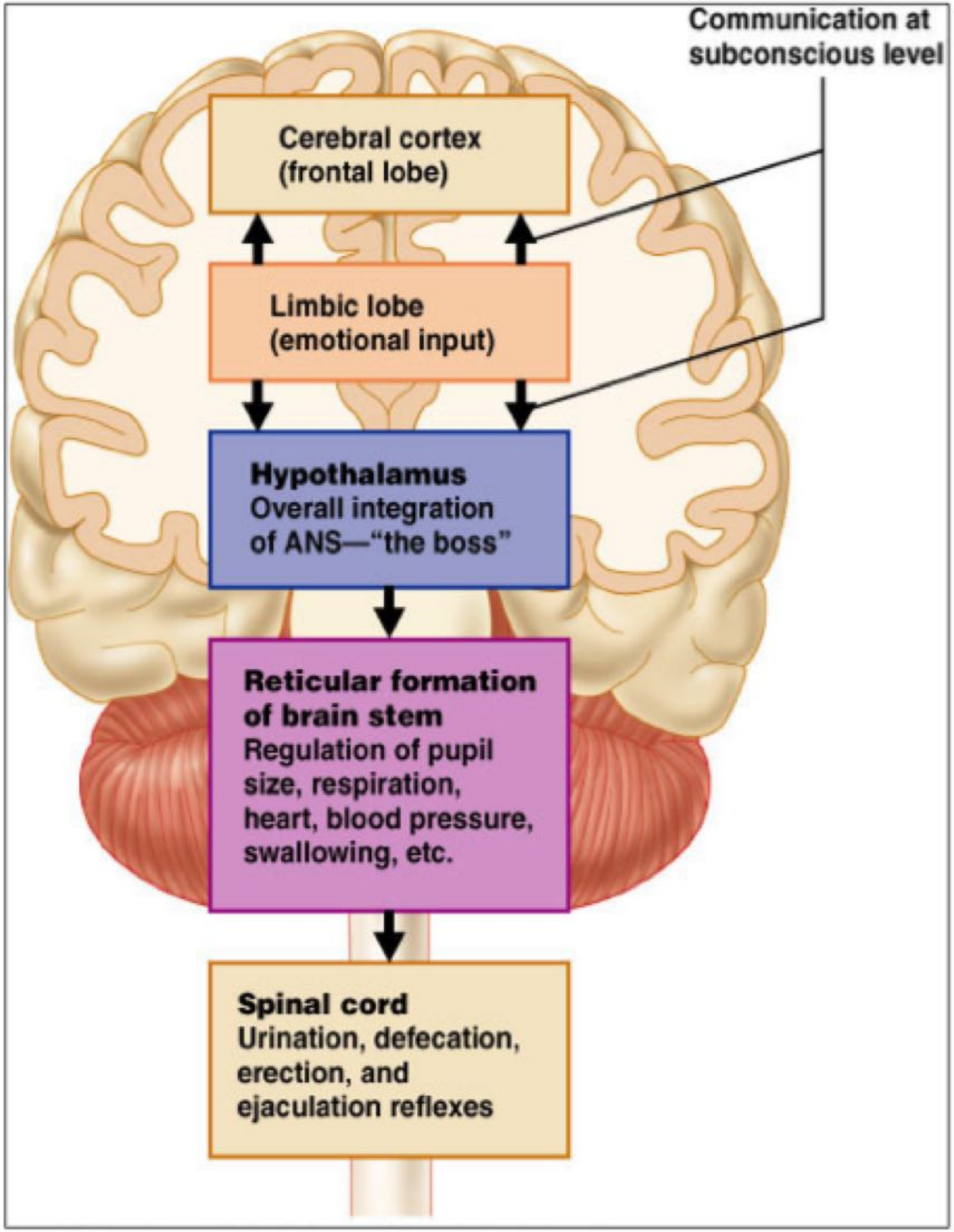


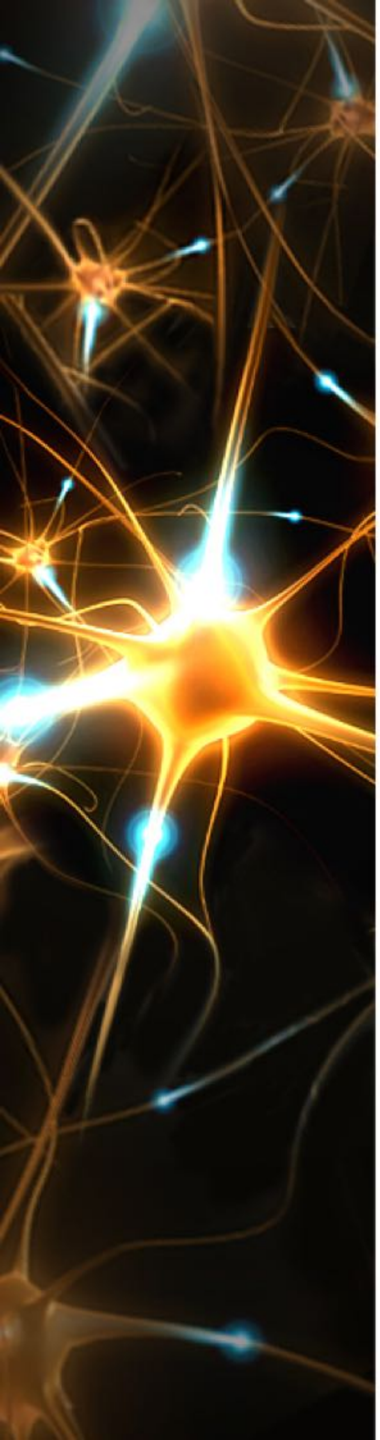
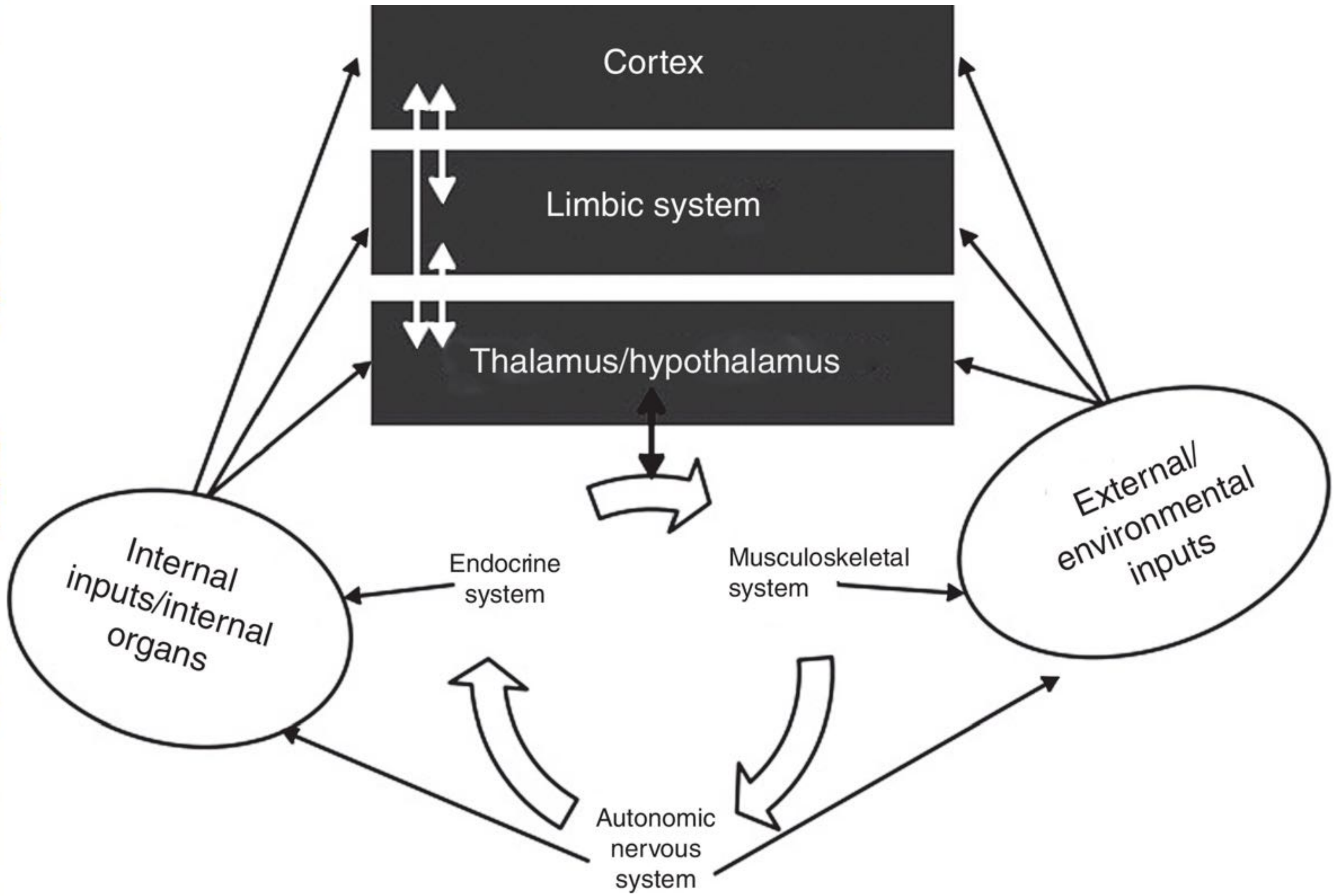
1. Reflexe court. 2. Reflexe long



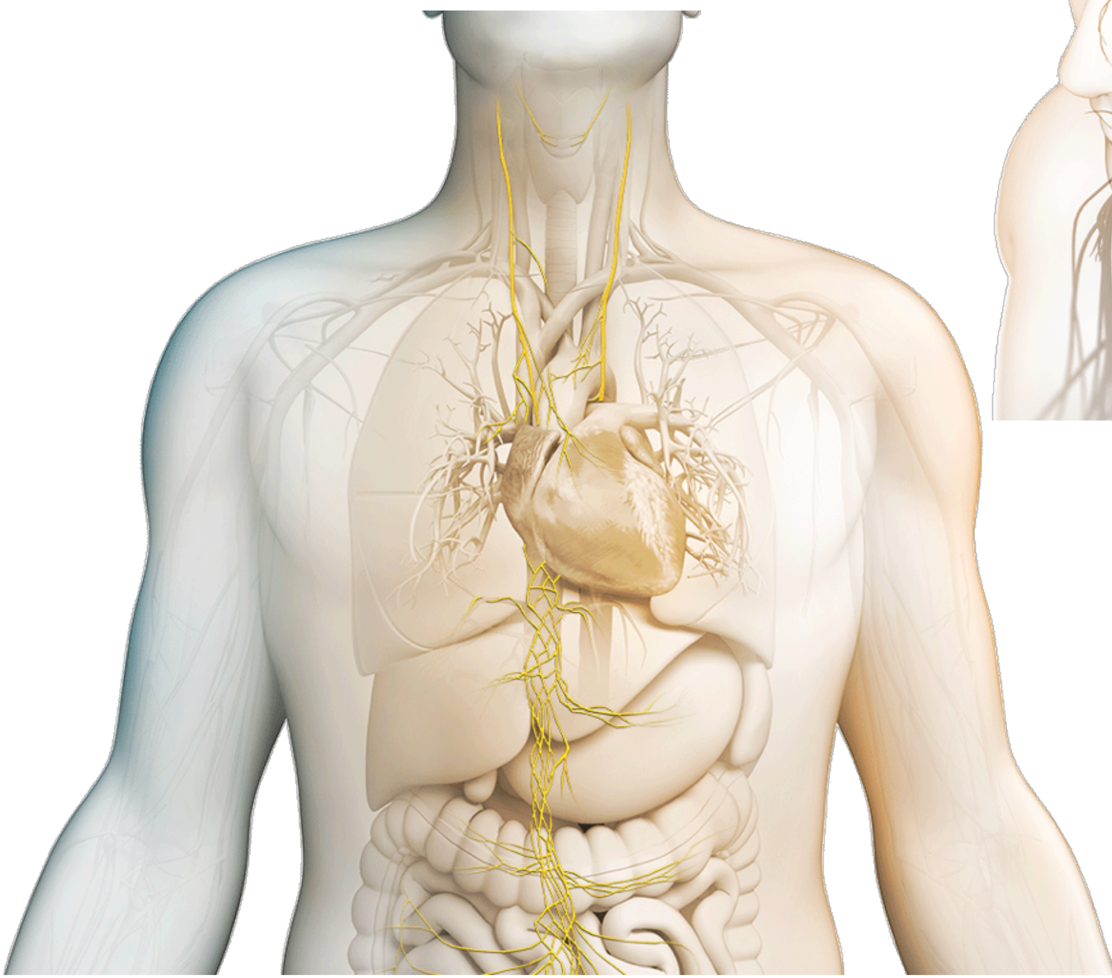
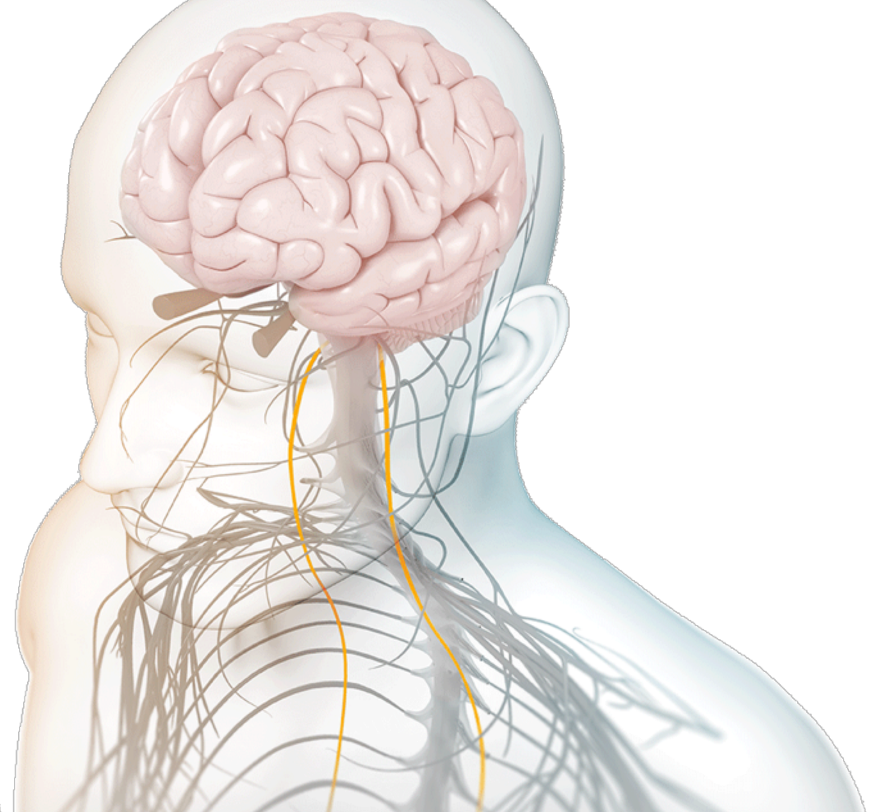


Information from the periphery is analyzed, and produces either a reflex response or an integrated autonomous, hormonal and behavioral response (eg, Thermoregulation). From Loewy and Spyer (1990)


Communication at subconscious level
Cerebral cortex (frontal lobe)
Limbic lobe (emotional input)
Hypothalamus
Overall integration of ANS—"the boss"
Reticular formation of brain stem
Regulation of pupil size, respiration, heart, blood pressure, swallowing, etc.
Spinal cord
Urination, defecation, erection, and ejaculation reflexes

Interactions between the ANS, the brain, the body and the environment. Adapted from W. Janig (2008)

2. Vagus nerve (X) : neuro-anatomo-physiology

- The vagus nerve, the great "protector" wandering is a morphological entity of SNA and the main constituent of the parasympathetic system: different fibers and branches of different origins using different neurotransmitters (Ach, Catecholamines, CKK, Substance P, Vasoactive intestinal peptide, NO, endorphins, GABA, Glutamate, etc.), which can have both parasympathetic and "sympathetic", immune, endocrine, synaptic neuro-regulatory and anti-nociception action.

- It functions as an "internal unconscious brain", our sixth sense, which integrates the "sensations" of the body and provides a hosmeostatic metabolic regulation to different organs and in general.

- 80,000 to 100,000 fibers compose it, mainly non-myelinised, 80% of afferent (sensory) fibers: visceral, somatic and taste sensations, and 20% of efferent (motor) fibers that release acetylcholine (Ach) at the junction synaptic with smooth muscles, intrinsic nerve fibers, secretory cells (neurons, muscular C., glandular C., ...), macrophages.

- It is involved in the detection of peripheral immunological events (inflammation)> generates an appropriate response: autonomic, endocrine, immune, anti-nociceptive and behavioral via complex central reflex networks (eg CAN).

- Double anti-inflammatory action: afferent and efferente, ie: HPA axis - CAP.

- **Pedonculo-pontine nucleus and Meynert nucleus (brain): (cholinergic neurons and GABA). Cholinergic neurons contribute 70% of cortical Ach synthesis and innervate the entire surface of the cortex (cingulate, hippocampus and amygdala cortex).**

- The vagus nerve comes out of the skull by the jugular foramen (with IX)

- Two ganglia at the base of the skull: jugular ganglion (superior) and ganglion nodose (inferior) containing the cellular body of the afferent fibers

- From the jugular ganglion the afferent fibers of the auricular branch of the X (Arnold's or Alderman's nerve) (innervation of the external acoustic meat, conch - cymba and cavum - and tragus) and the afferent fibers innervating the dura Posterior cranial fossa (somatic sensitivity)

- From the inferior ganglion or Nodose, the visceral afferent fibers (pharynx-larynx-thoracic and abdominal) leave (visceral sensitivity)

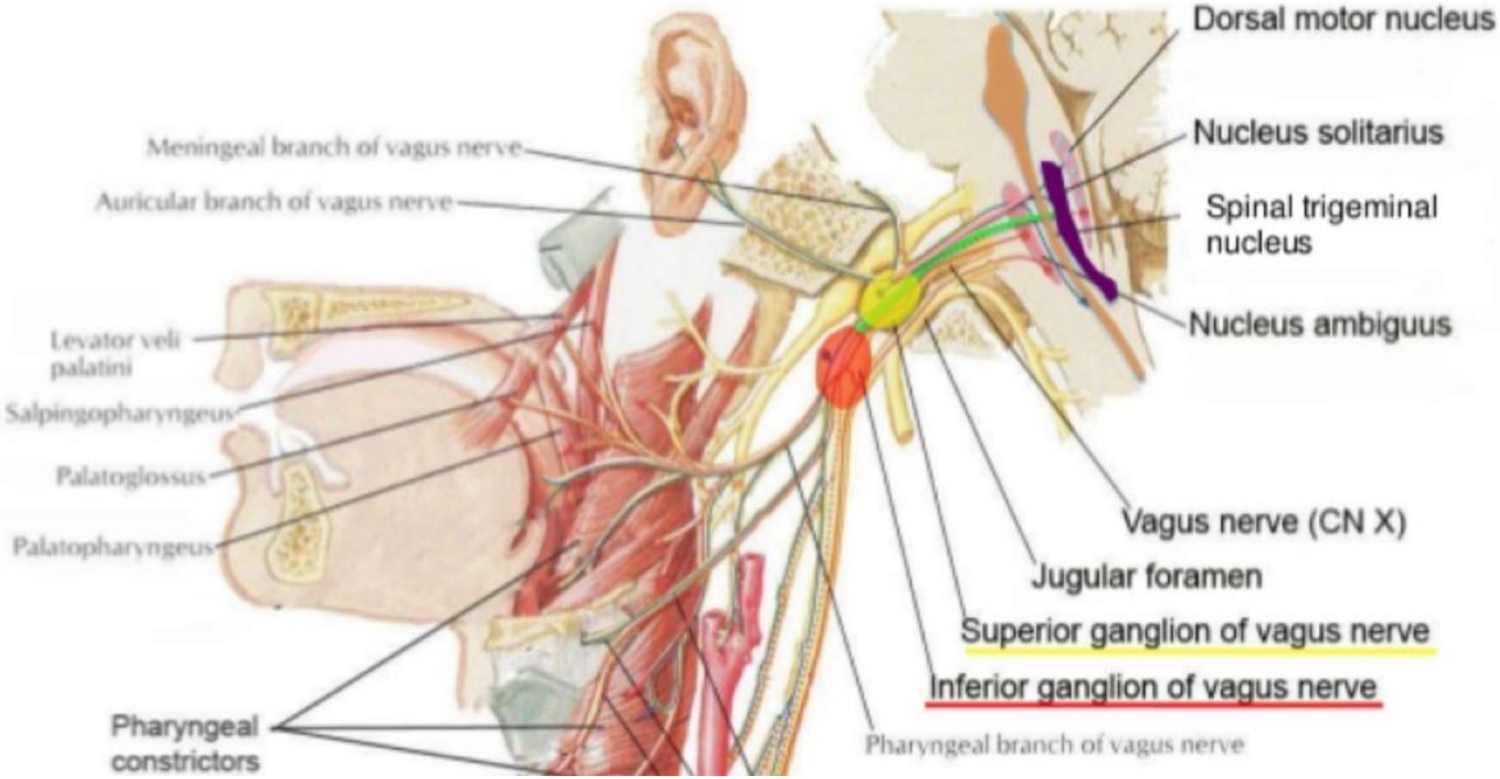
- The lower and upper nodes communicate with the superior cervical ganglion (sympathetic)

- The pre-ganglionnary efferent axons start from the Dorsal nucleus of the vagus and from the nucleus Ambiguus.

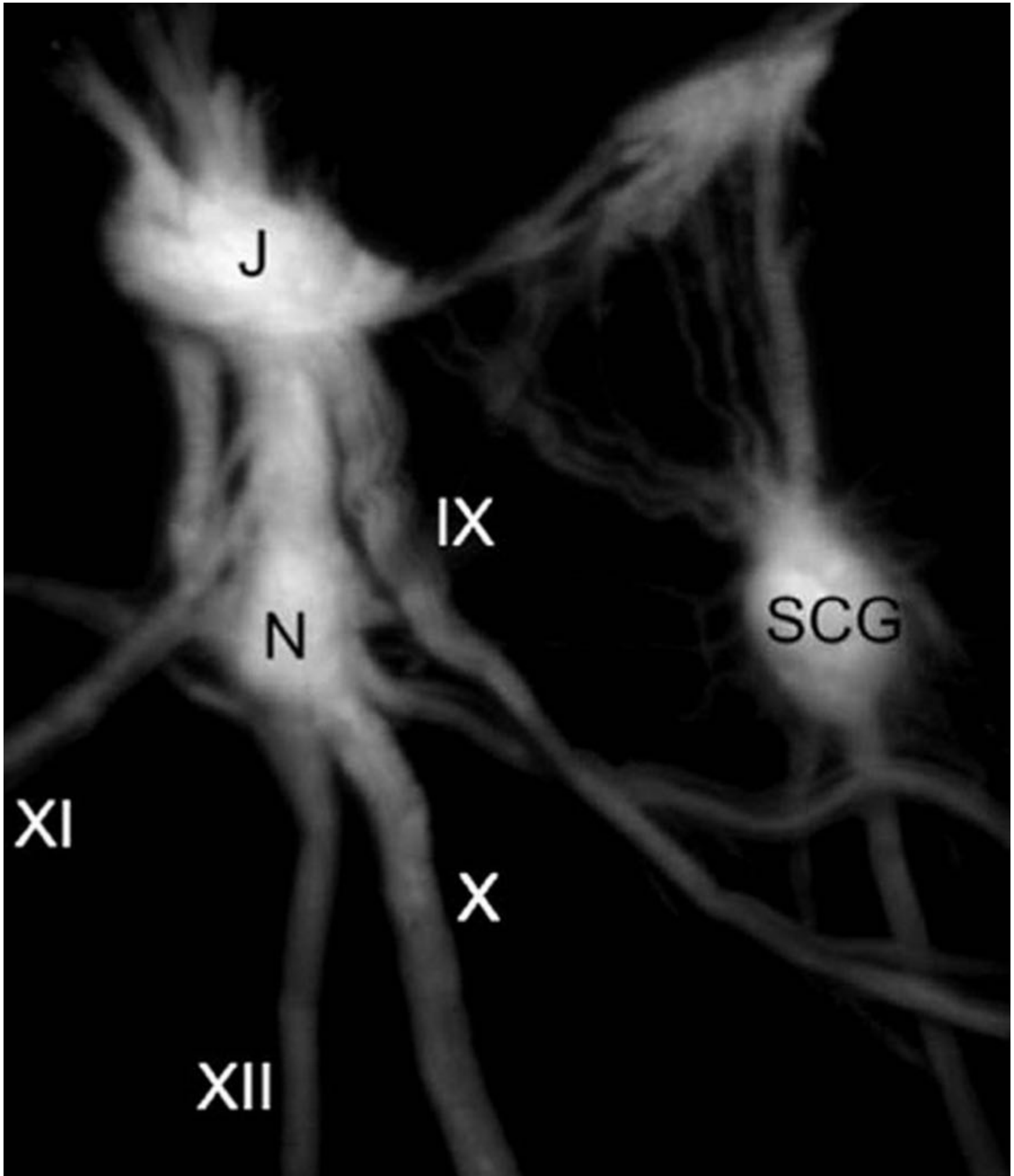
- The neurotransmitters Glutamate (+) and GABA (-) play an important role in the transmission of primary afferent impulses to / from the nucleus of the solitary tract (NTS) and in the vago-vagal reflex

Vagal afferent detection

- **Chemoreceptors** including nutrients and products of microbiota (dysbiosis), glucose, amino acids, cholecystokinin (CCK), fatty acids, IL-1, TNF, GLP-1, somatostatin, 5-HT
- **Mecanoreceptors**: mucosal receptors of "touch", tension - stretching and contraction - and serous
- **Sensors of temperature**: capsaicin- Expression of TRV1 + channel (jugular ganglion / nodose)
- **Osmosensors**
- **Baroreceptors**: Aortic Arch (Nerve of Ludwig-Cyon)
- **Nociception**: activation of C fibers Modulation (+) and (-) via the spino-bulbo-thalamic pathways + capsaicin-sensitive C-fibers at the level of jugular / nodose ganglia
- **Immuno-sensation**: detection of cytokines: IL-1β, TNFα via Toll Like Receptors (TLR) at paraganglionic level
- **Entero-endocrine**: via specific neuronal receptors: serotonin, cholecystokinin, ghrelin, leptin, orexin, ..)

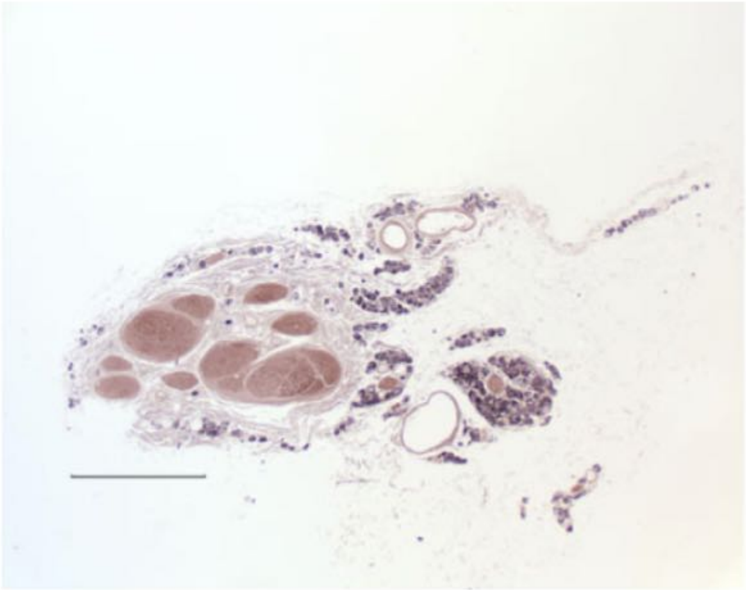


Dorsal motor nucleus
Nucleus solitarius
Spinal trigeminal nucleus
Nucleus ambiguus
Meningeal branch of vagus nerve
Auricular branch of vagus nerve
Levator veli palatini
Salpingopharyngeus
Palatoglossus
Palatopharyngeus
Vagus nerve (CN X)
Jugular foramen
Superior ganglion of vagus nerve
Inferior ganglion of vagus nerve
Pharyngeal constrictors
Pharyngeal branch of vagus nerve

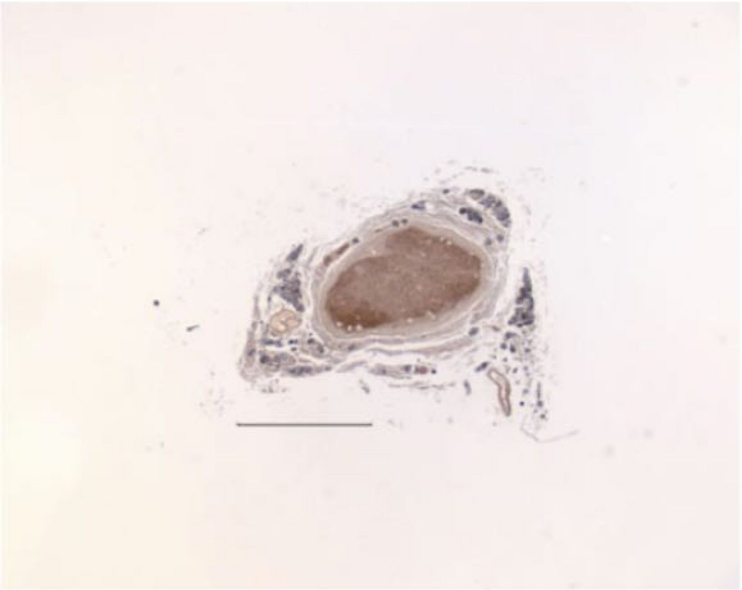


J, Jugular ganglia; N, Nodose ganglia; IX, glossopharyngeal nerve; X, Vagus nerve; XI, Spinal accessory nerve; XII, Hypoglossal nerve; SCG. uperior cervical ganglia (sympathetic)

Coupe du nerf vague au niveau cervical



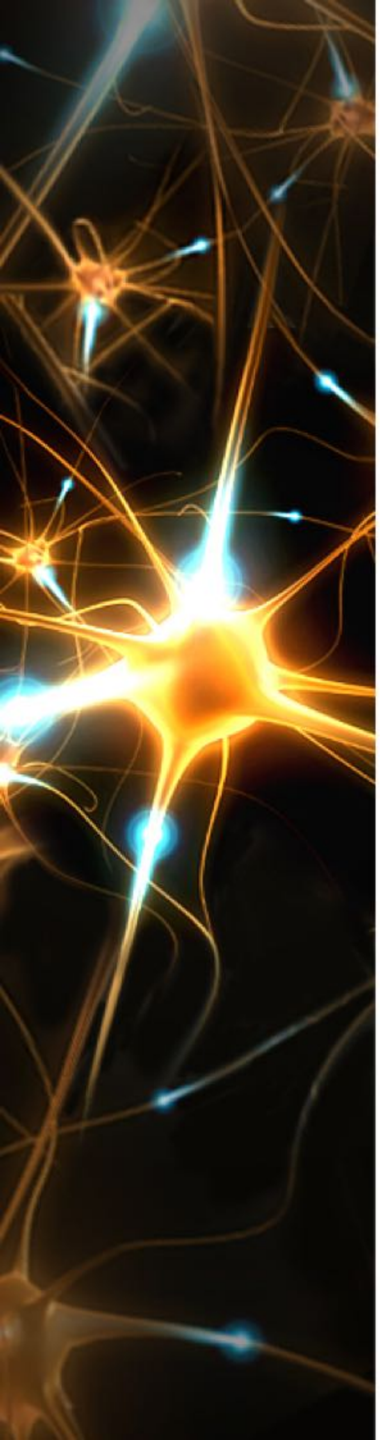
Right human vagus nerve (bar indicates 500µm)



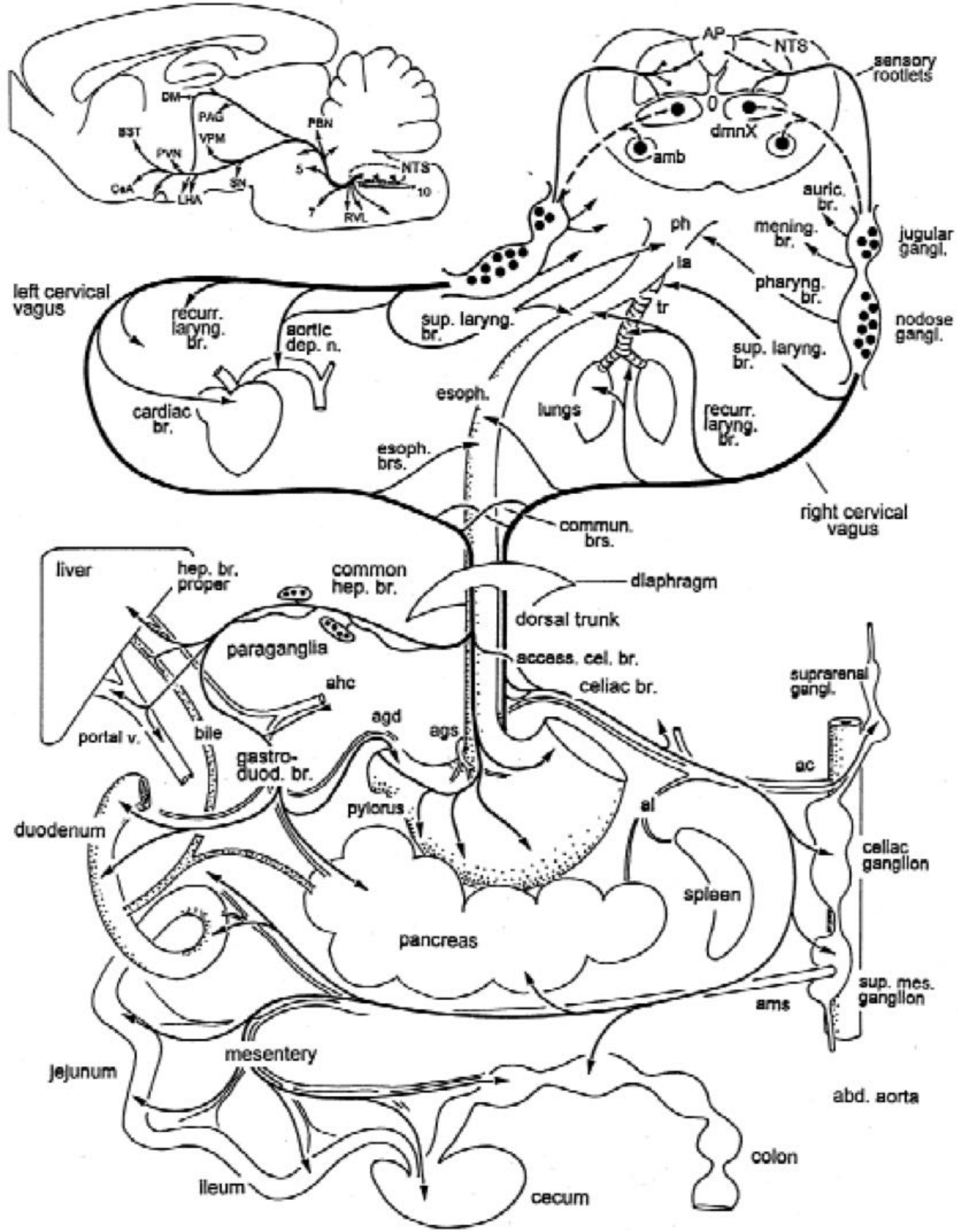
Left human vagus nerve (bar indicates 500µm)

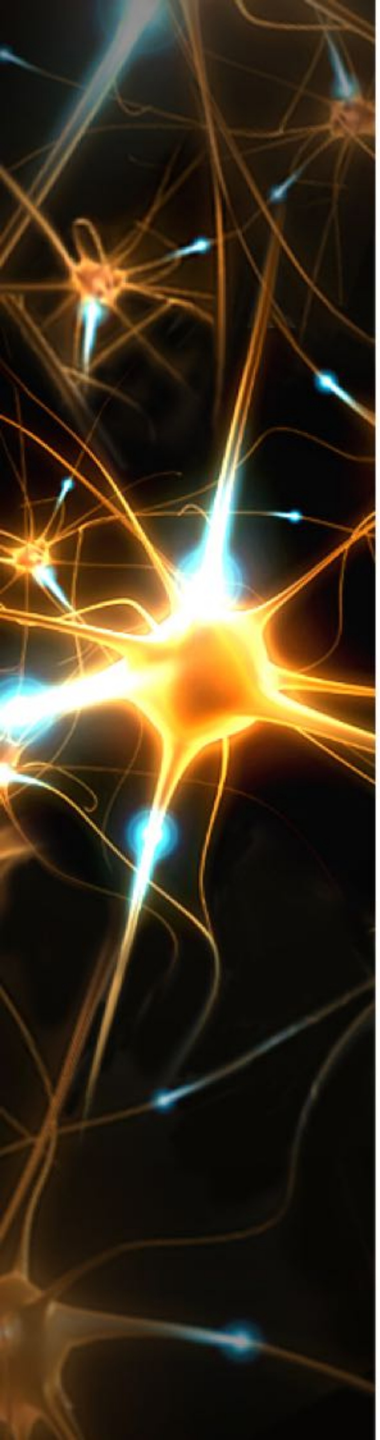
The right vagus nerve has an effective area about 1.5 times larger than the left nerve

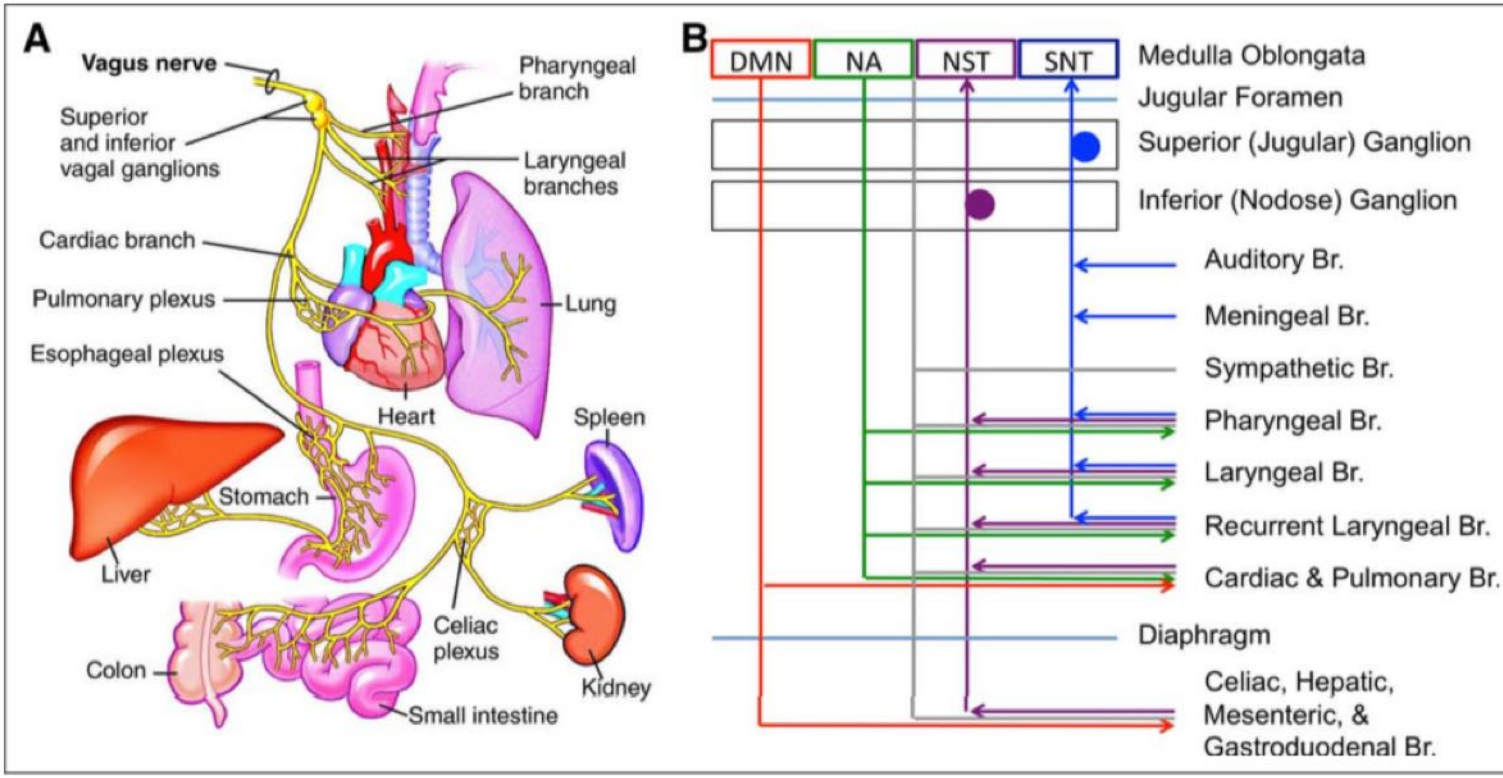
From Verlinden (2016).



H.-R. Berthoud, W.L. Neuhuber / Autonomic Neuroscience: Basic and Clinical 85 (2000) 1–17

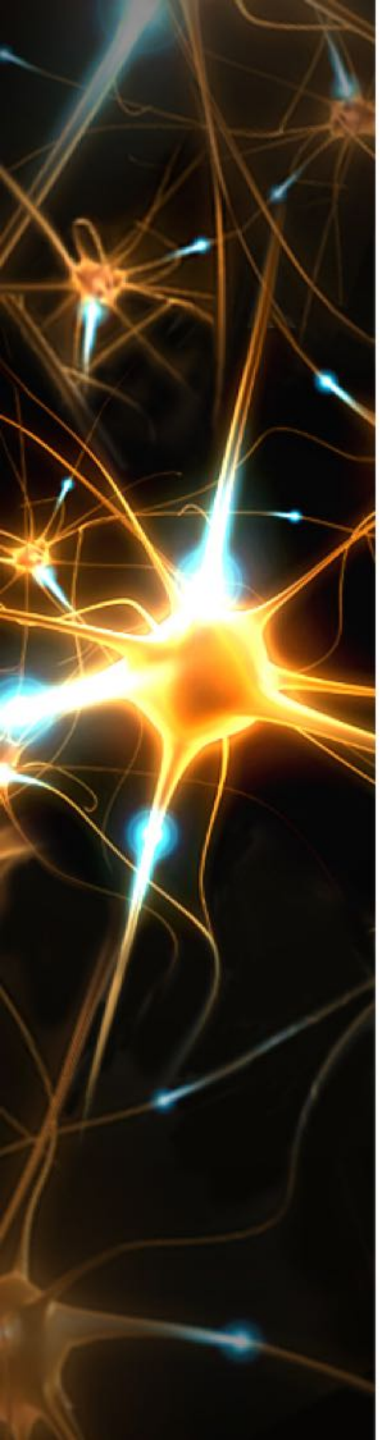




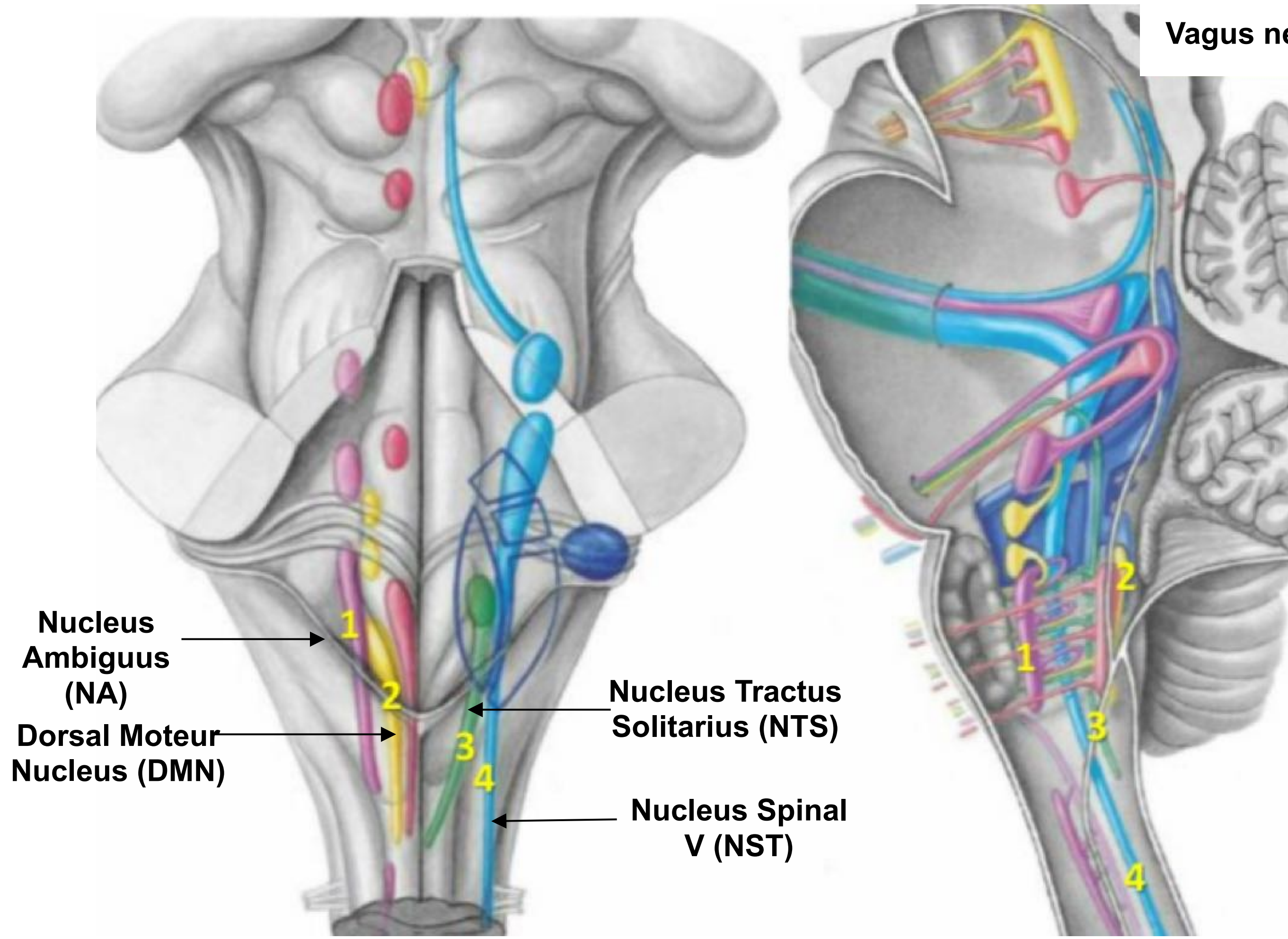


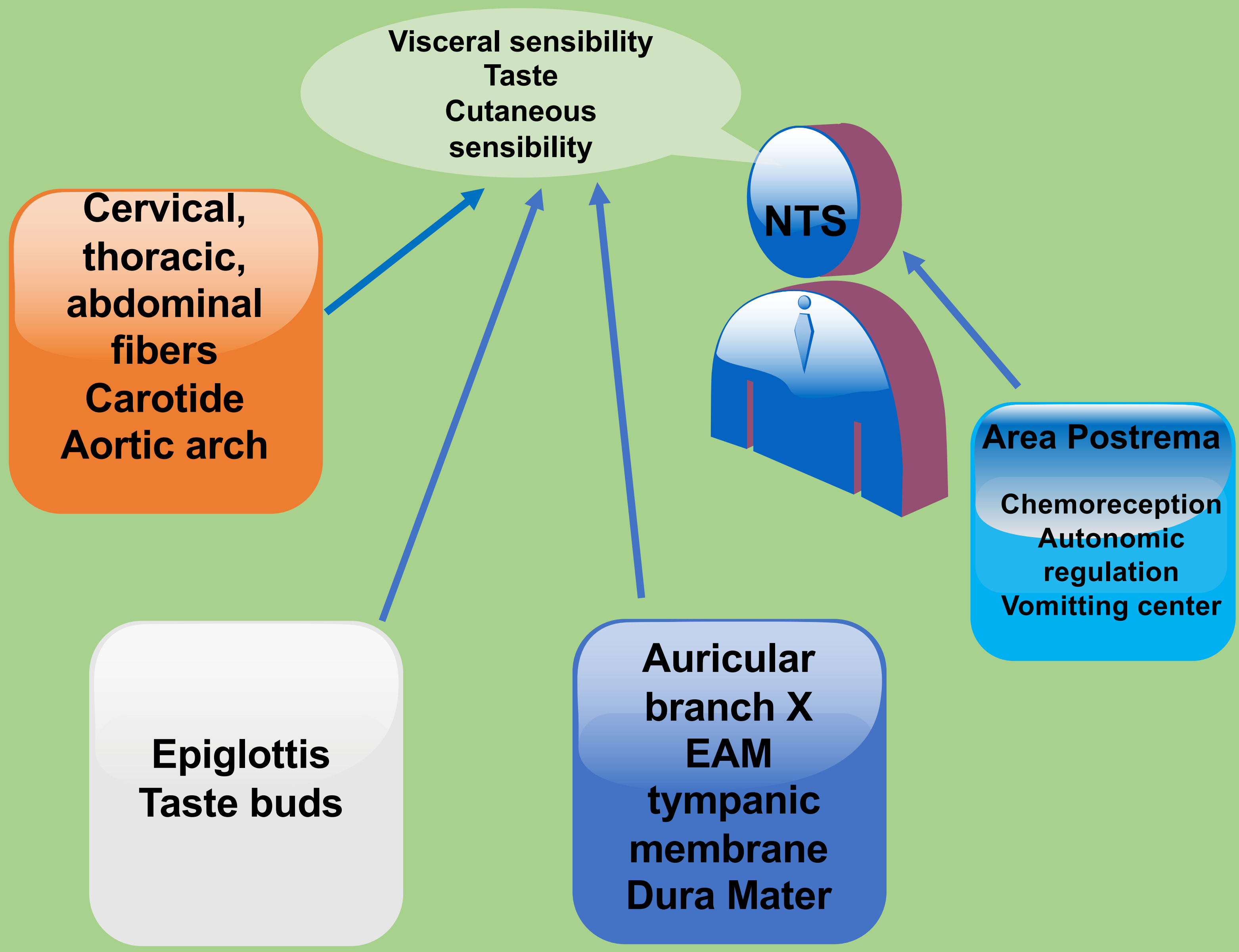
(A) Vagus nerve anatomy.
(B) Vagus nerve nuclei connexion (4 nuclei).

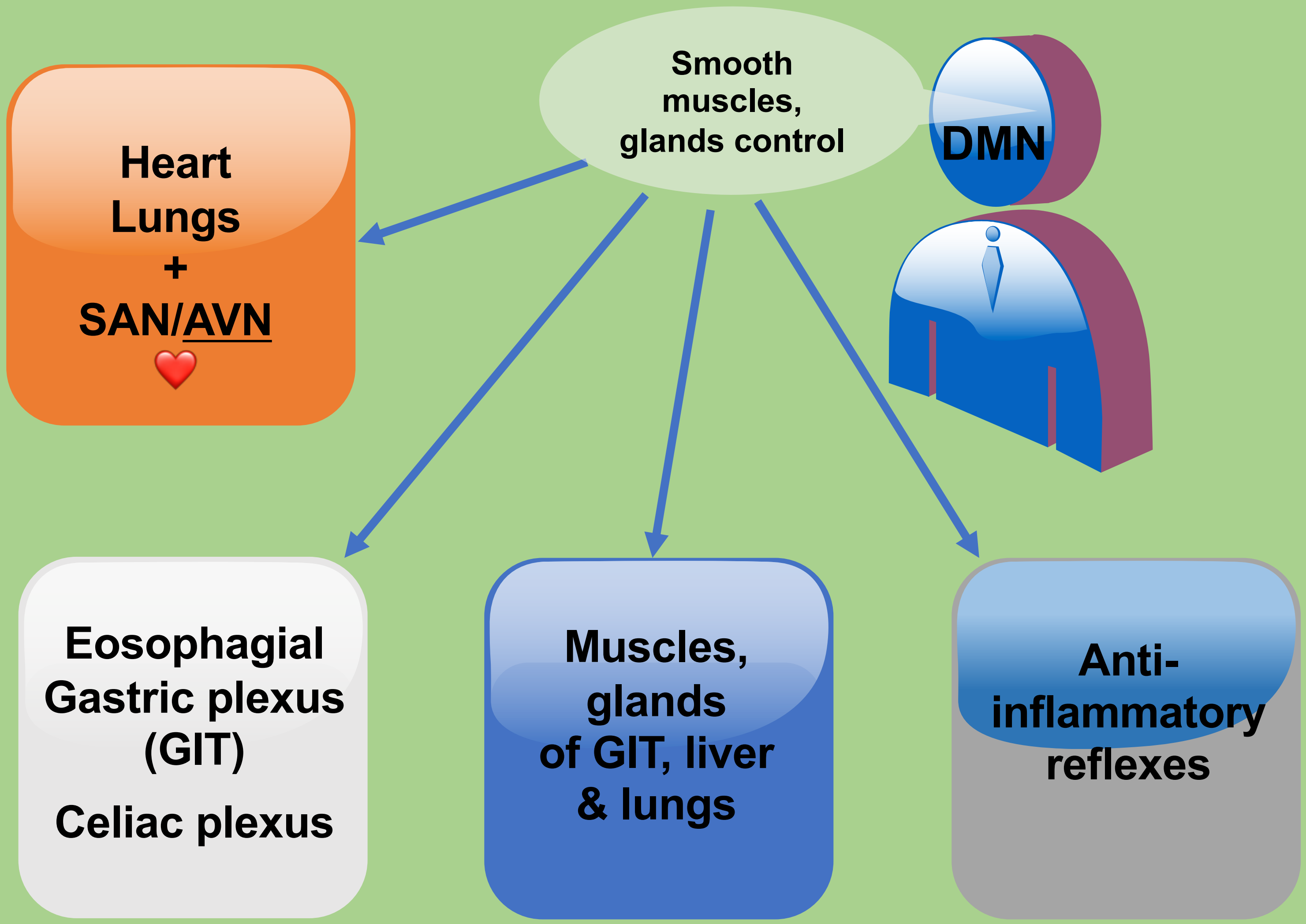
D'apres Yuan et Silberstein (2015).

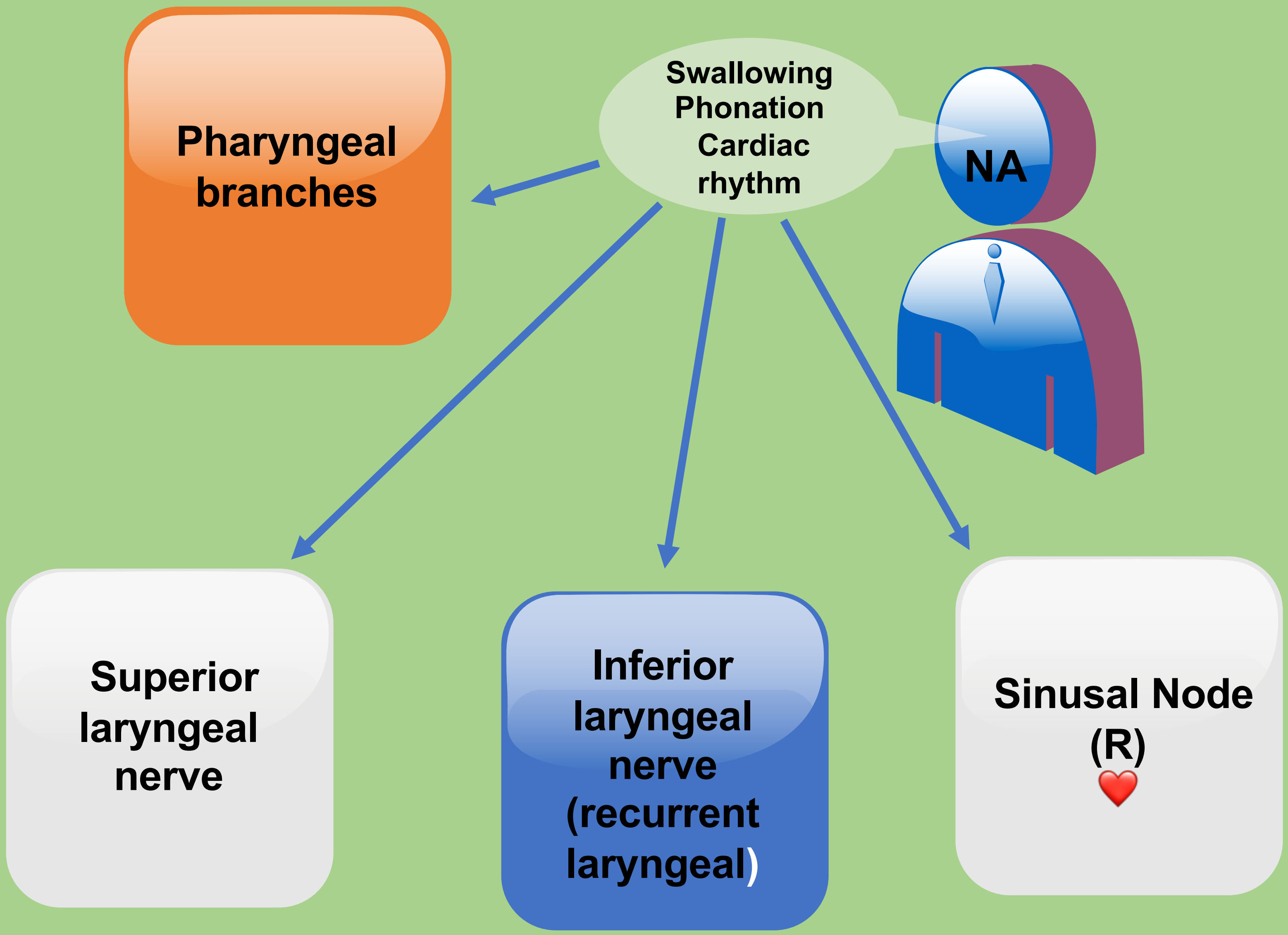


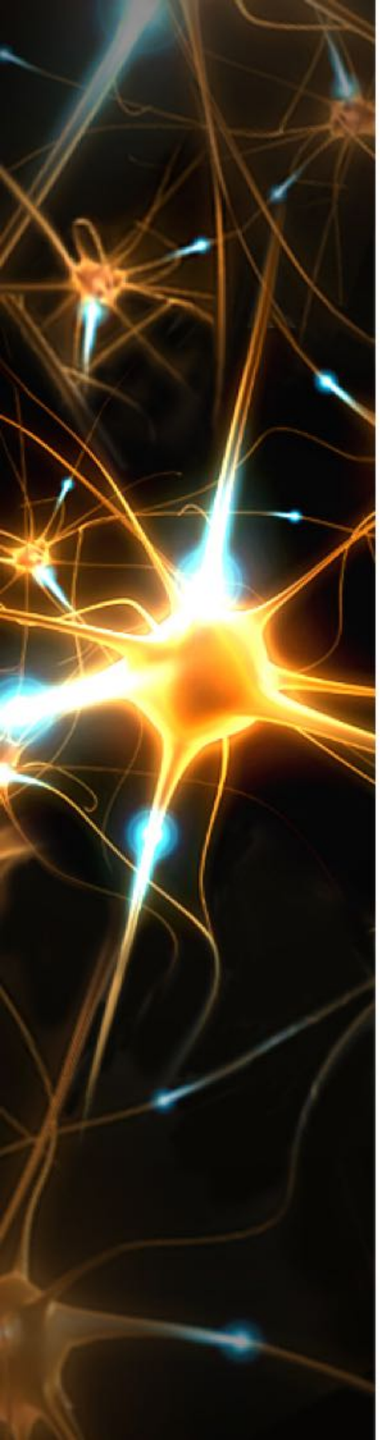
Vagus nerve

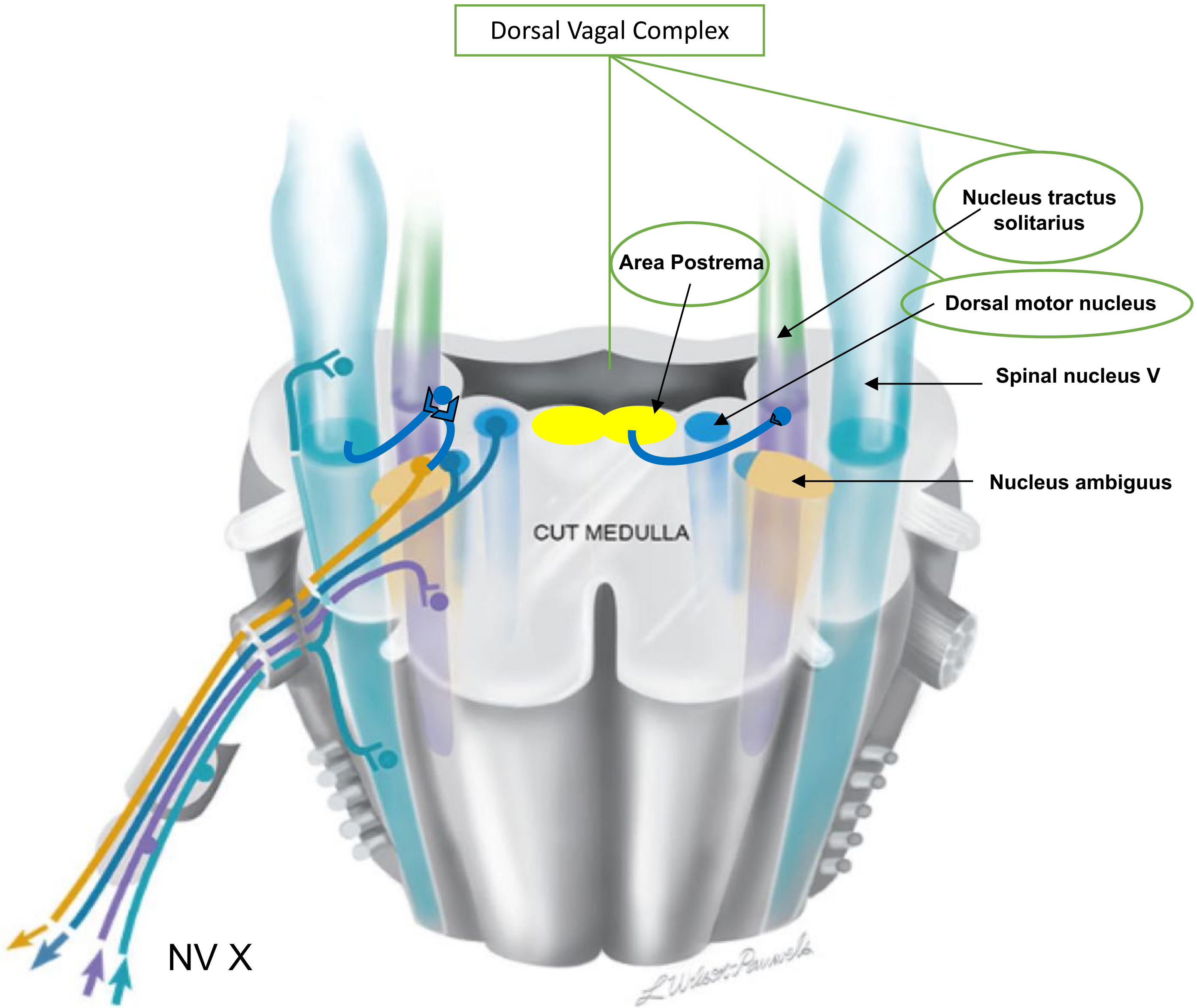

Nucleus Ambiguus (NA)
Dorsal Moteur Nucleus (DMN)
Nucleus Tractus Solitarius (NTS)
Nucleus Spinal V (NST)
1
2
3
4


Visceral sensibility
Taste
Cutaneous sensibility
NTS
Cervical, thoracic, abdominal fibers
Carotide
Aortic arch
Epiglottis
Taste buds
Auricular branch X
EAM
tympanic membrane
Dura Mater
Area Postrema
Chemoreception
Autonomic regulation
Vomitting center


Smooth muscles, glands control
DMN
Heart
Lungs
+
SAN/AVN
Eosophagial Gastric plexus (GIT)
Celiac plexus
Muscles, glands of GIT, liver & lungs
Anti-inflammatory reflexes


Pharyngeal branches
Swallowing
Phonation
Cardiac rhythm
NA
Superior laryngeal nerve
Inferior laryngeal nerve (recurrent laryngeal)
Sinusal Node (R)





Dorsal Vagal Complex
Nucleus tractus solitarius
Area Postrema
Dorsal motor nucleus
Spinal nucleus V
Nucleus ambiguus
CUT MEDULLA
NV X

2. LIMBIC SYSTEM and CAN

Thomas Willis
(1621-1675)

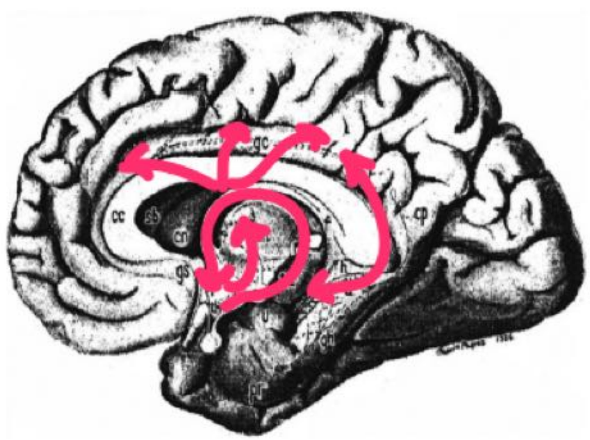
A “limbic” system described by Willis (1664) to indicate the cortical regions around the brainstem

Limbic system

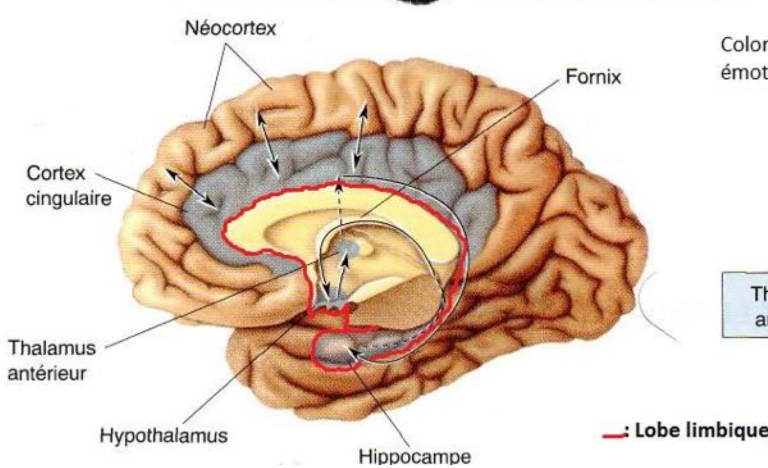
- Limbic system = group of interconnected cortical and subcortical structures linking visceral conditions and emotions to behaviors and cognition

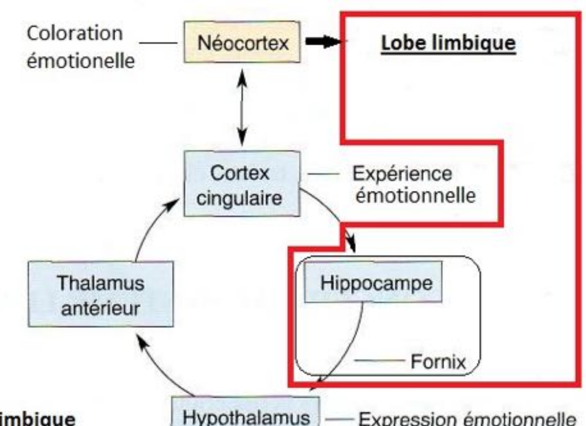
- Link between PERCEPTION - EMOTION – ACTION

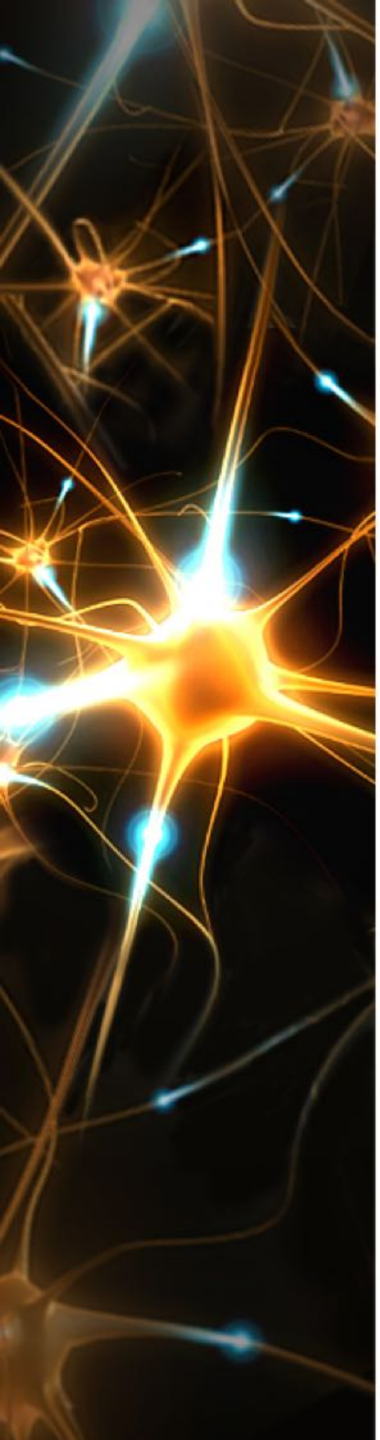
- According to Papez, emotions come either from cognitive action entering the circuit via the hyppocampus or from viceral and somatic perceptions entering the circuit via the hypothalamus

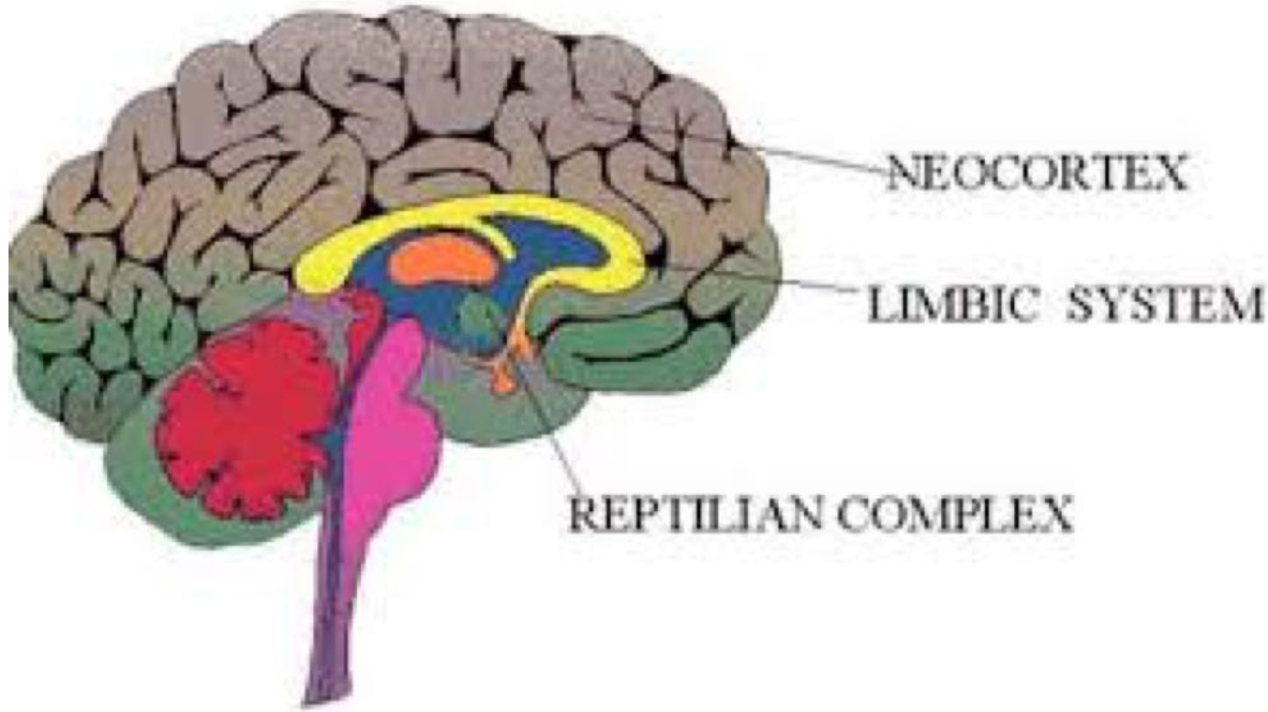


James Papez (1883-1958)








NEOCORTEX
LIMBIC SYSTEM
REPTILIAN COMPLEX

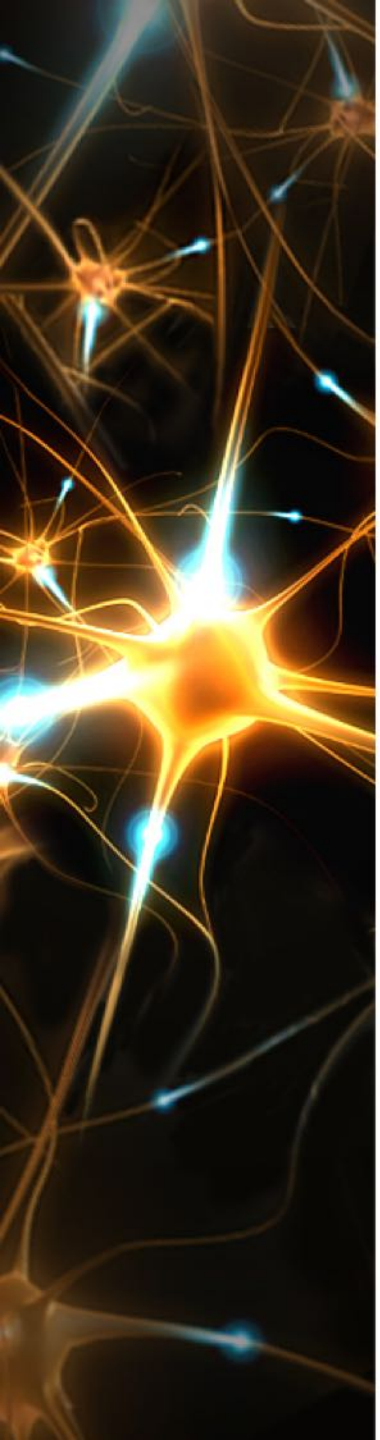
Complex arrangement of transitional structures between a visceral "primitive" subcortical brain and more advanced cortical structures.

- <u>Sub-cortical regions include:</u>

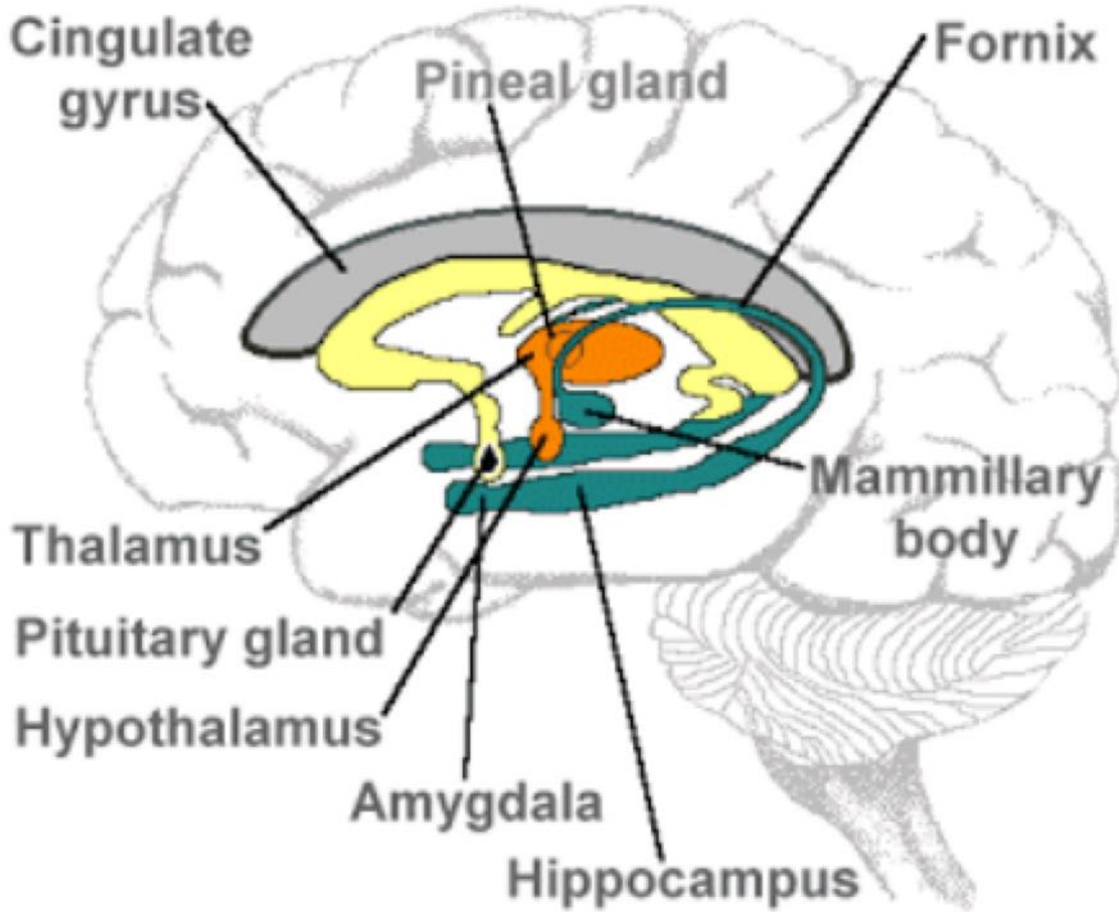
  - Amygdala
  - Mammillary bodies
  - Hypothalamus
  - Thalamus (anterior and median)
  - Anterior striatum (Accubens nucleus + olfactory tubercle) (basal nuclei)

- <u>Cortical regions include:</u>

  - Orbito-frontal cortex
  - Insulaire Cortex
  - Cingular cortex

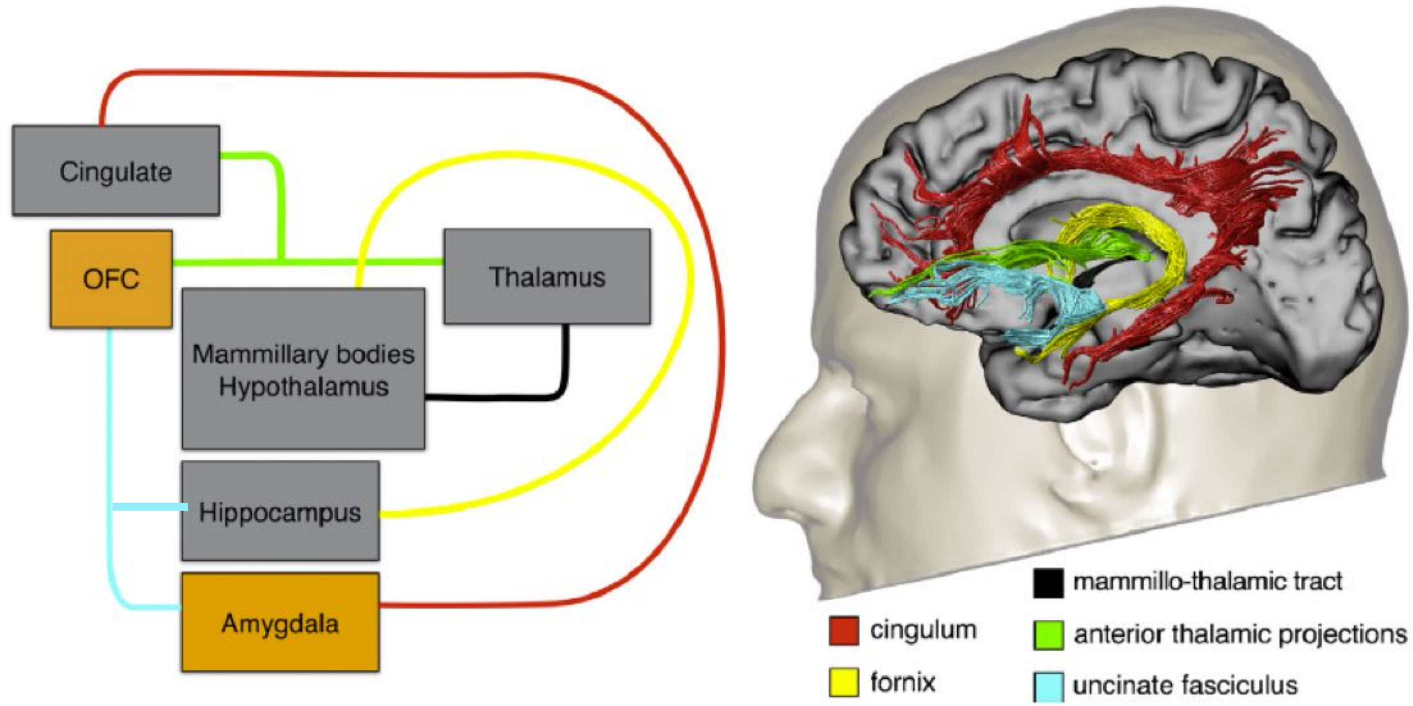


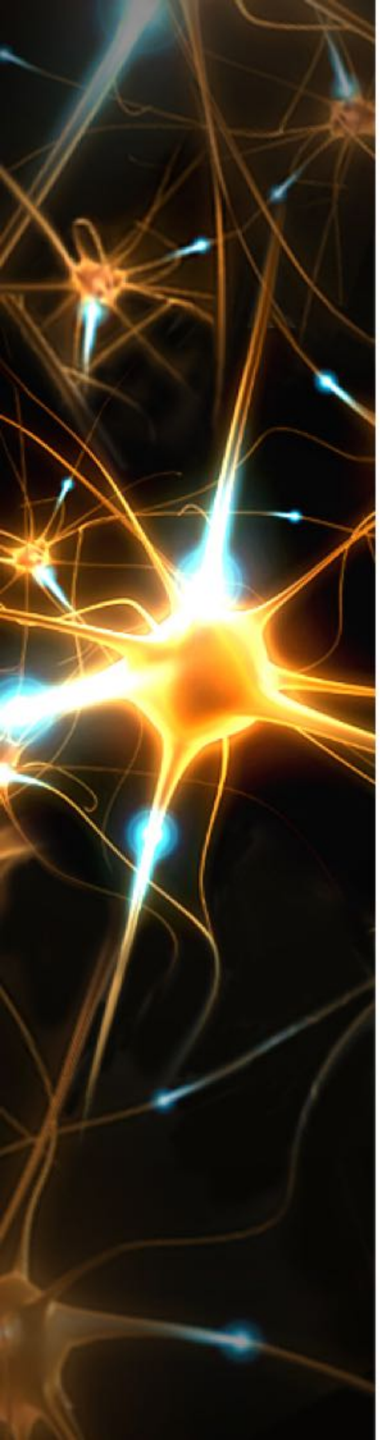
Limbic system

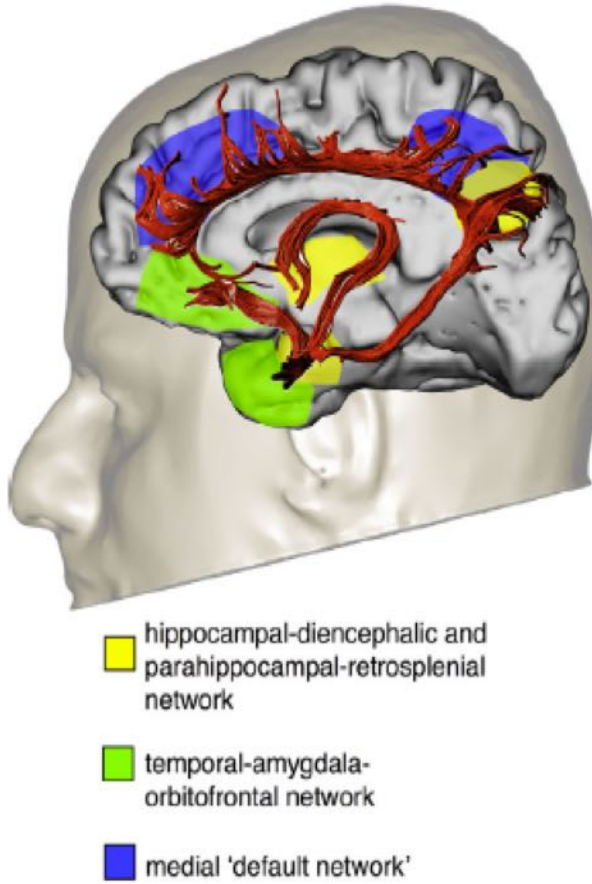


Limbic system (connections)

- Fornix
- **Mammillo-thalamic tract**
- **Anterior thalamic projections**
- **Cingulum**
- **Fasciculus uncinate**







Network	Function	Disorder
Hippocampal-diencephalic and parahippocampal-retrosplenial	•memory •spatial orientation	•Amnesias •Korsakoff's syndrome •Mild Cognitive impairment •Alzheimer's disease (early) •Balint syndrome
Temporo-amydgala-orbitofrontal	•Behavioural inhibition •Memory for temporally complex visual information •Olfactory-gustatory-visceral functions •Multimodal sensory integration •Object-reward association learning •Outcome monitoring	•Alzheimer's Disease (advanced) •Semantic dementia •Klüver-Bucy syndrome •Temporal lobe epilepsy •Geschwind's syndromes •Psychopathy •Bipolar affective disorders
Dorsomedial default network	•Pain perception •Self-knowledge •Attention •Mentalizing •Empathy •Response selection and action monitoring •Autobiographical memory •Person perception	•Depression •Autism •Schizophrenia •Obsessive compulsive disorder •Mild Cognitive Impairmentt •Alzheimer's Disease (early) •Attention Deficit Hyperactivity Disorder •Anxiety

Central autononomic network (CAN) Benarroch 1995

- Autonomic central network = system of internal regulation: the cervau controls the visceromotor, neurodendocrine, pain, temperature, sleep / wake and behavioral responses, essential for survival.
  It is under powerful inhibitory control via GABA (Top - down modulation)
- **Control, balance and maintain homeostasis**
- Control of sympathetic and parasympathetic, cardiac, respiratory, neuroendocrine and sphincterian preganglionic neurons.
- CAN is organized into interconnected structures (different loops) at the level of: spinal cord, medulla oblongata, ponto-mesencephalic and anterior brain (hypothalamus - Limbic system):

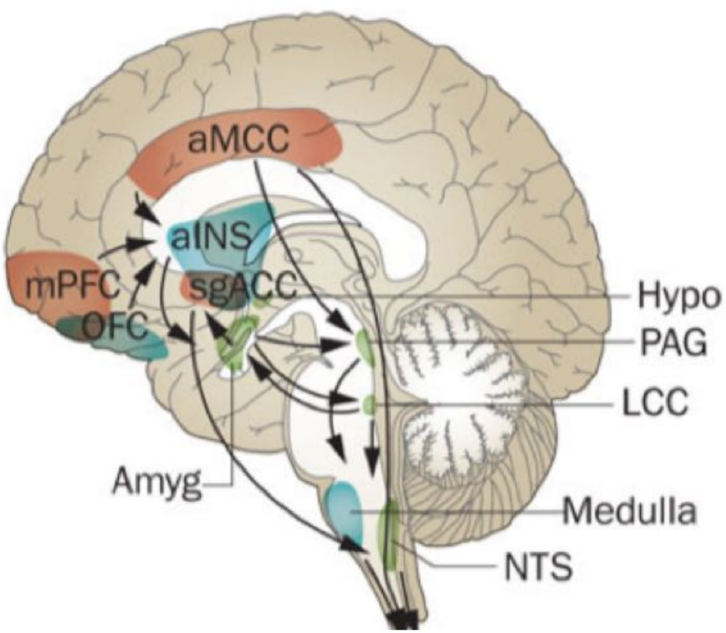
1. Medulla ↔ medulla oblongata : Quick and short term ANS regulation
2. Medulla ↔ medulla oblongata ↔ Hypothalamus : Long term regulation, metabolism and reproduction
3. Medulla ↔ medulla oblongata ↔ Hypothalamus ↔ Limbic system : ancitipative autonomic regulation (behavior, cognition, emotions, stress response)

- 1. The **Spinal bulb region** mediate **parasympathetic and sympathetic reflexes** (NTS, NA, NDMV, Area postrema, Rostro-ventro-lateral medulla)

  2. The **Bulbo-Pontine** region is involved in the control of **respiration, circulation, gastrointestinal function and urination** and transmits **viscero-sensory information** to all other CAN regions (Locus coeruleus, parabrachial nucleus, Barrington nucleus)

  2. The **Ponto-mesencephalic** area controls the **modulation of pain** and the **integration of behavioral responses to stress** (periaqueductal gray)

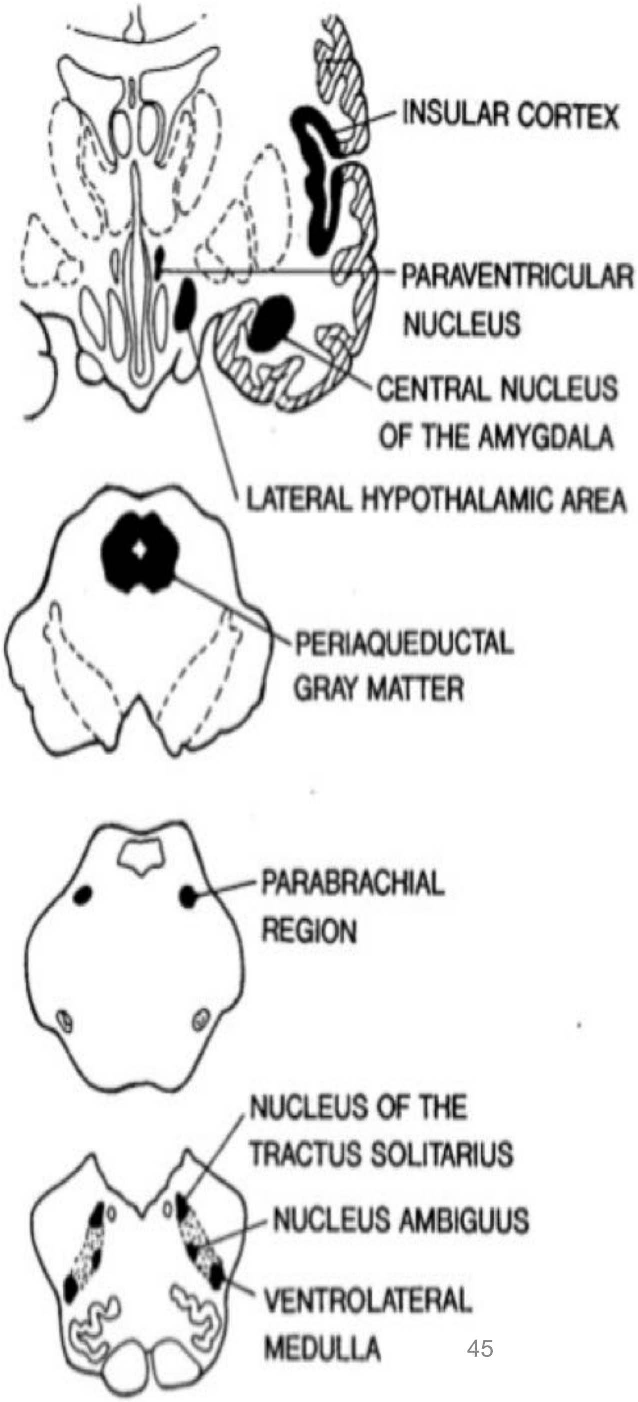
  3. The **Anterior cerebral region** (hypothalamus, insula, anterior cingulate cortex, CPF, amygdala, bed nucleus stria terminalis) is involved in **autonomic, emotional and endocrine responses** for adaptation and homeostasis

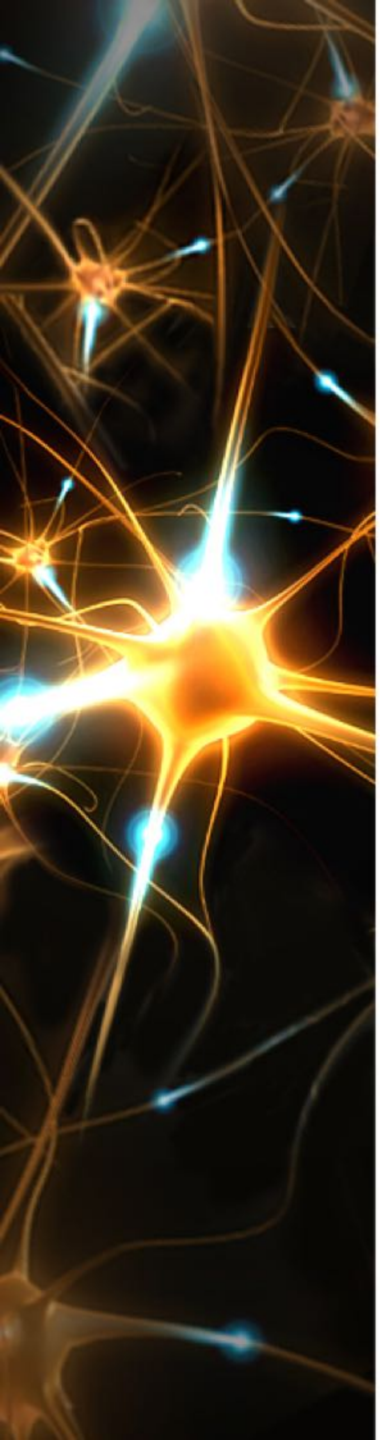


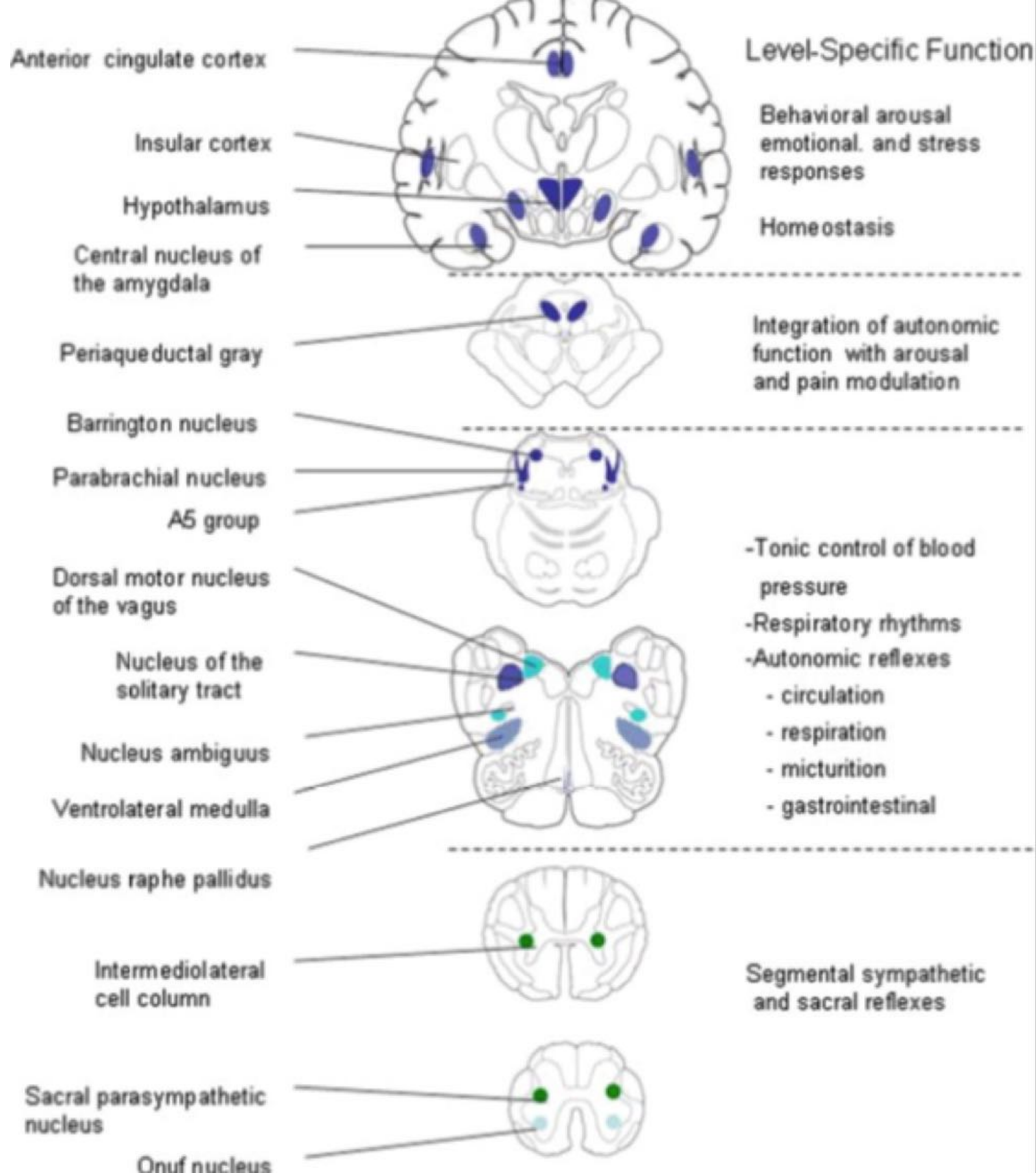
1. Spinal bulb region
2. Brain stem
3. Anterior cerebral regions

CAN is made of:

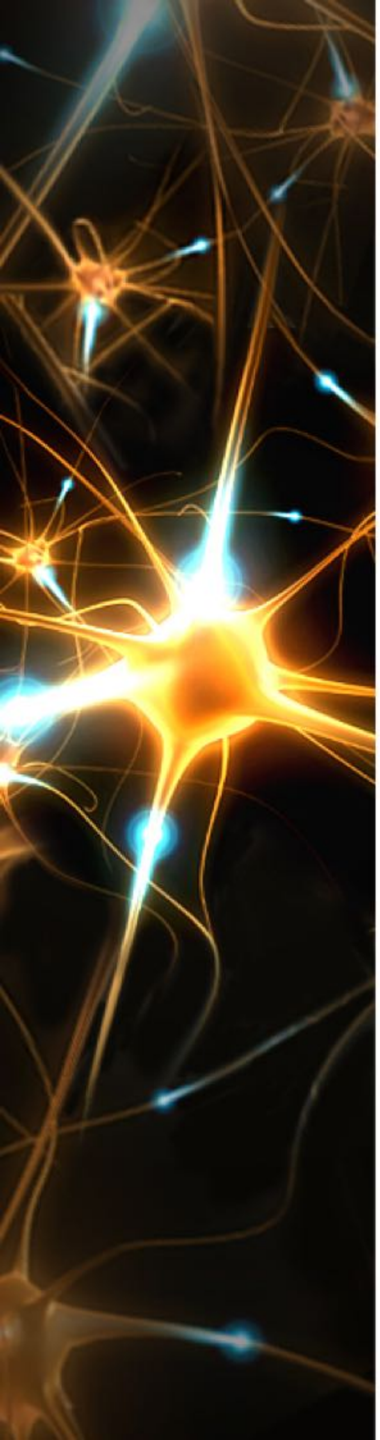
- 3. **Anterior cerebral regions**
  - Insula : SNA visceromotor function, pain and temperature
  - Ant. Cingular cortex. : SNS 7 PNS functions
  - Hypothalamus : autonomic and neuro-endocrines control, stress, sleep-wake cycle, temperature and behaviour
  - Amygdala & Bed nucleus stria terminalis : autonomous expressions of emotional states, regulation of stress responses (N-E-I)
- 2. **Brain stem (subtectal areas):**
  - Peri-acqueductal gray matter: autonomic responses, pain control, stress-related motor action, aggressive behavior, and reproduction
  - Parabrachial nucleus: relays the visceromotor information to the anterior cortex, modulates the circuits related to breathing, circulation and vomiting
  - Locus coeruleus: main cerebral noradrenergic nucleus that relays adrenergic impulses at different levels of the CNS (raphe nuclei, amygdala, thalamus, hypothalamus, hyppocampus) - involves in awakening, attention, memory / anxiety - pain - panic - insomnia - PTSD - depression + other neurovegetative and autonomic controls.
- 1**. Medulla regions**
  - NTS-NA-NDMV-Area postrema-Ventrolateral medulla : initiation of viscerosensory medullary reflexes (cardiovascular, respiratory, digestive, miction) and provides information to all other CAN regions

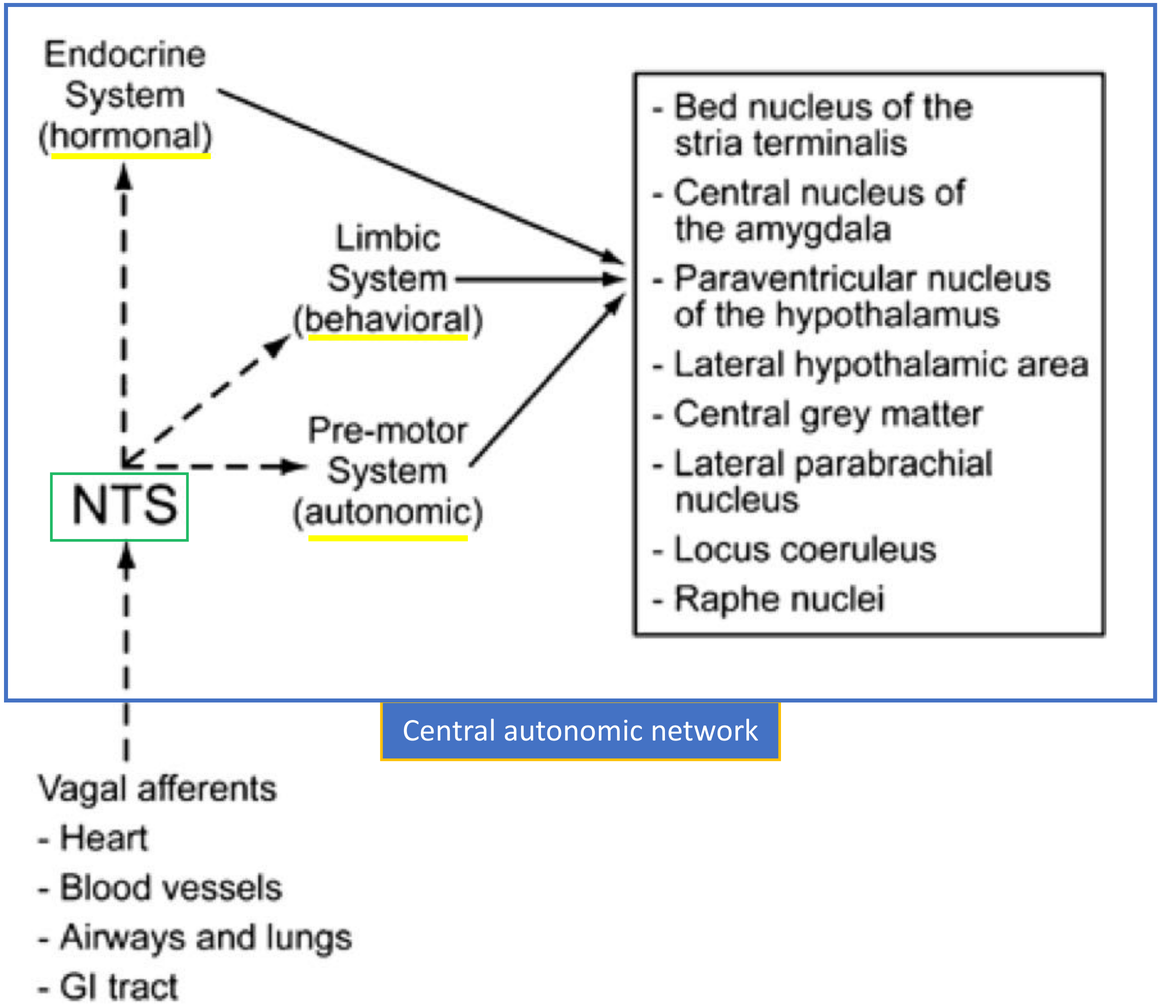




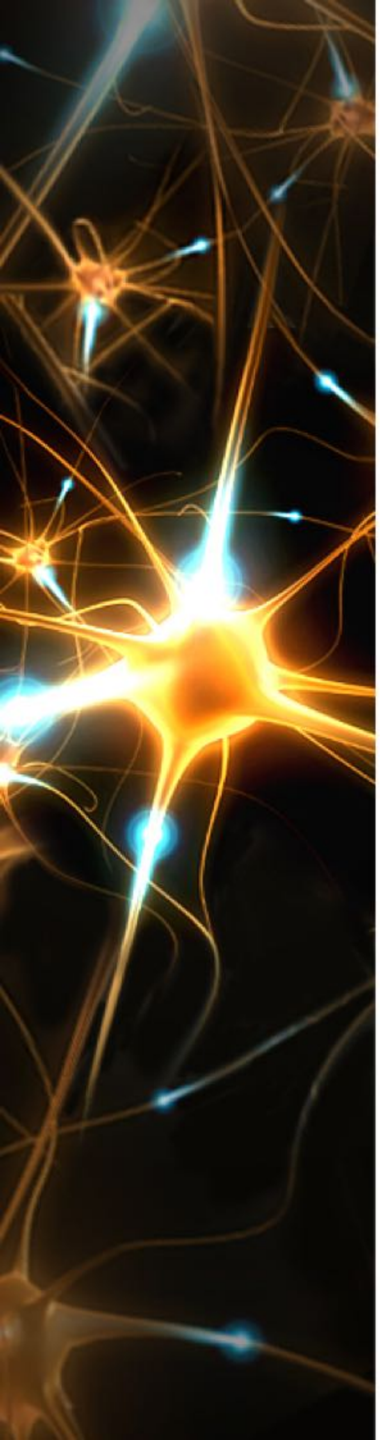


Anterior cingulate cortex
Insular cortex
Hypothalamus
Central nucleus of the amygdala
Periaqueductal gray
Barrington nucleus
Parabrachial nucleus
A5 group
Dorsal motor nucleus of the vagus
Nucleus of the solitary tract
Nucleus ambiguus
Ventrolateral medulla
Nucleus raphe pallidus
Intermediolateral cell column
Sacral parasympathetic nucleus
Onuf nucleus
Level-Specific Function
Behavioral arousal emotional. and stress responses
Homeostasis
Integration of autonomic function with arousal and pain modulation
-Tonic control of blood pressure
-Respiratory rhythms
-Autonomic reflexes
- circulation
- respiration
- micturition
- gastrointestinal
Segmental sympathetic and sacral reflexes

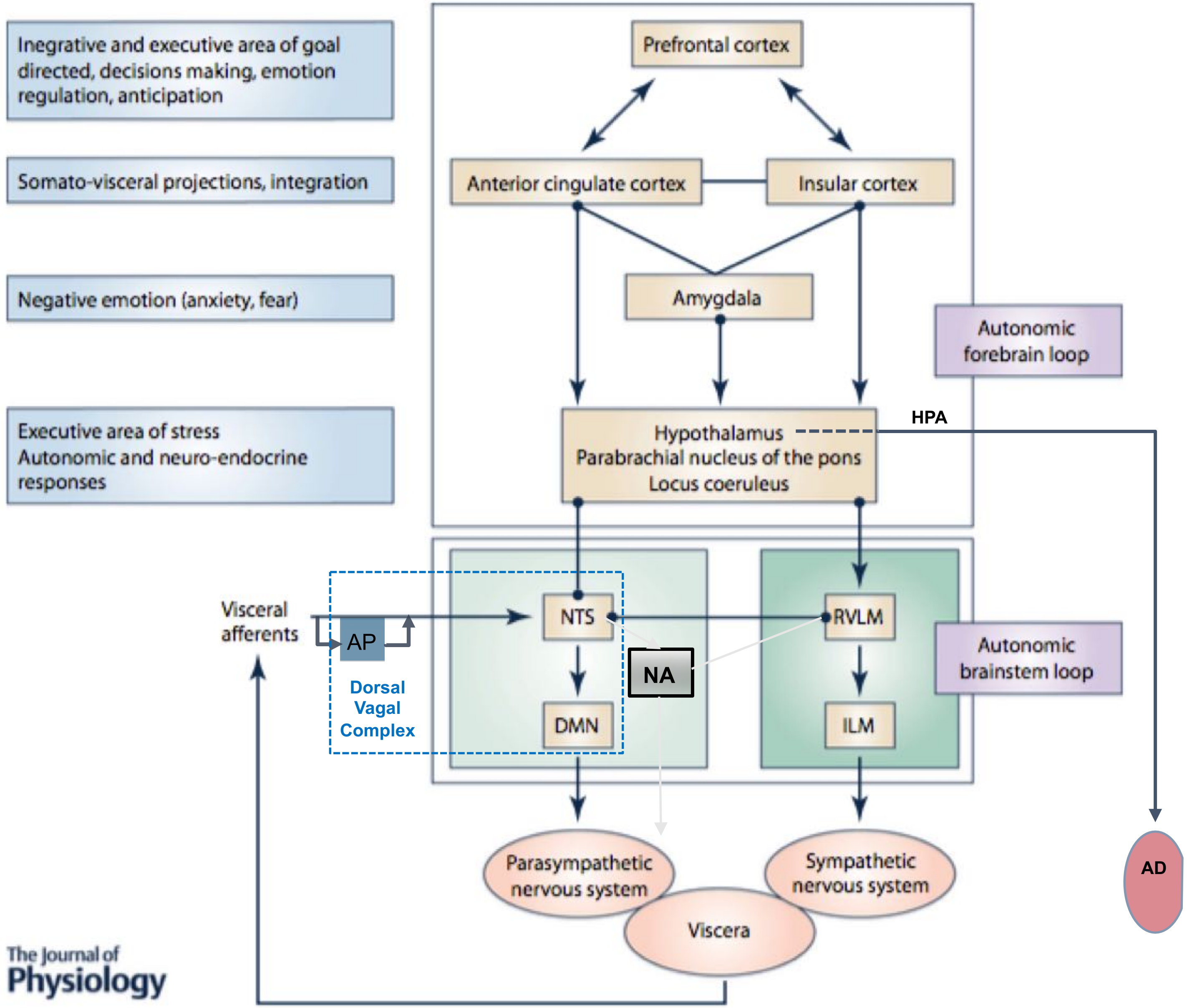




Central autonomic network



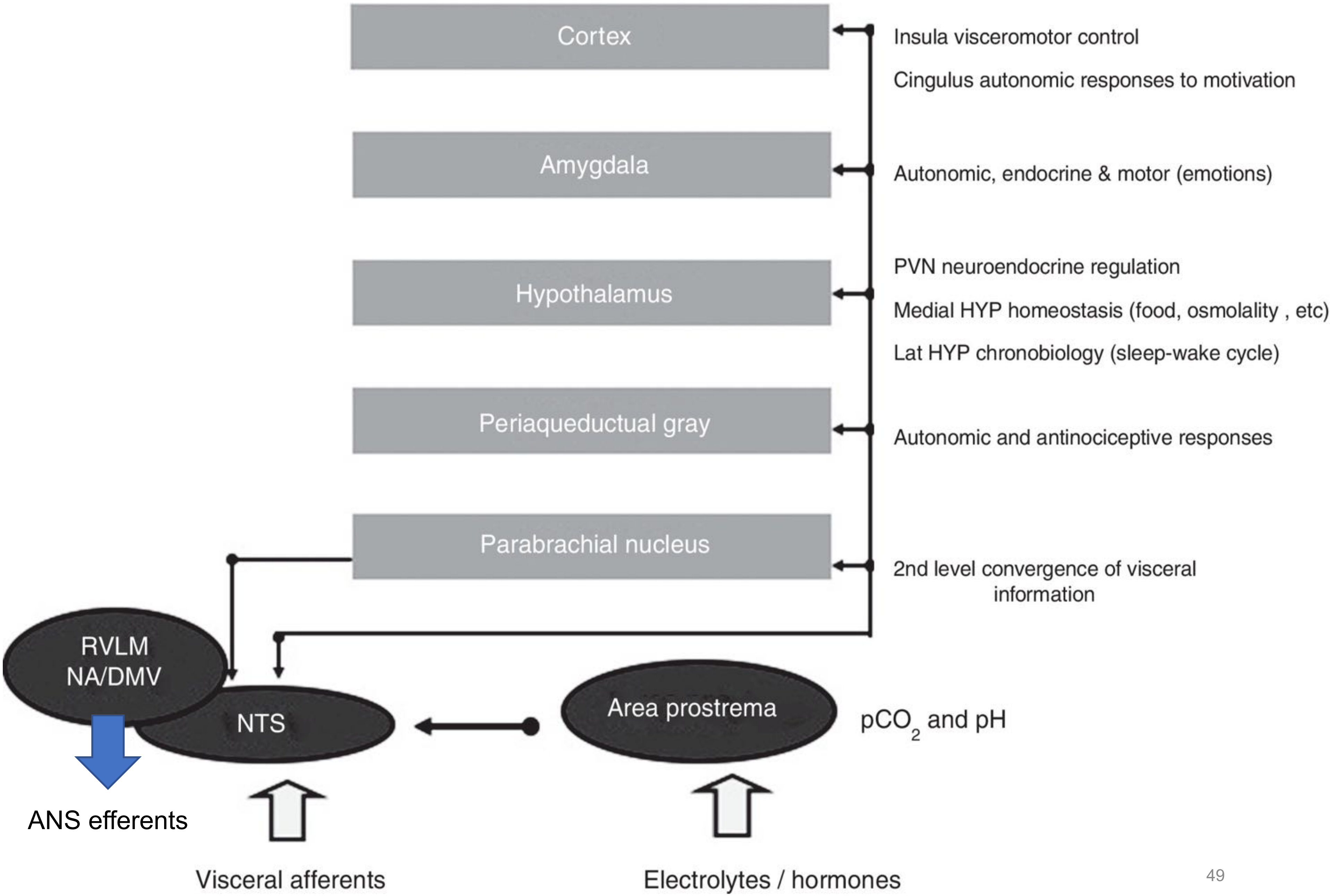
Modulation of visceral activity of the autonomic central network and neuroendocrine response



The Dorsal Vagal Complex is involved in autonomic, endocrine and limbic responses of the ”inner milieu”

NTS, nucleus tractus solitarius; AP, area postrema; DMN, dorsal motor nucleus; ventrolateral medulla; ILM, intermediate lateral medulla; HPA, hypothalamic-pituitary-adrenal axis; AD, adrenal gland. Adapted from Bonaz (2016).

CAN : résumé



Cortex
Amygdala
Hypothalamus
Periaqueductual gray
Parabrachial nucleus
Insula visceromotor control
Cingulus autonomic responses to motivation
Autonomic, endocrine & motor (emotions)
PVN neuroendocrine regulation
Medial HYP homeostasis (food, osmolality , etc)
Lat HYP chronobiology (sleep-wake cycle)
Autonomic and antinociceptive responses
2nd level convergence of visceral information
RVLM
NA/DMV
NTS
Area prostrema
pCO2 and pH
ANS efferents
Visceral afferents
Electrolytes / hormones

3. NEURO-IMMUNOLOGY

- Hyppocrates a Galen (120-200 AD): humoral disease theory based on clinical observation. The cause of the disease lies in the imbalance of the 4 Moods because it regulates the health. (blood, yellow bile, black bile and lymph). **The origin of the disease is due to the imbalance of the body's moods, the fouling and the dysfunctions that result**.

- Claude Bernard (1855). Health is due to the **equilibrium of the internal environment** (extracellular environment) and is maintained by continuous and delicate compensations: **concept of fundamental unification**.

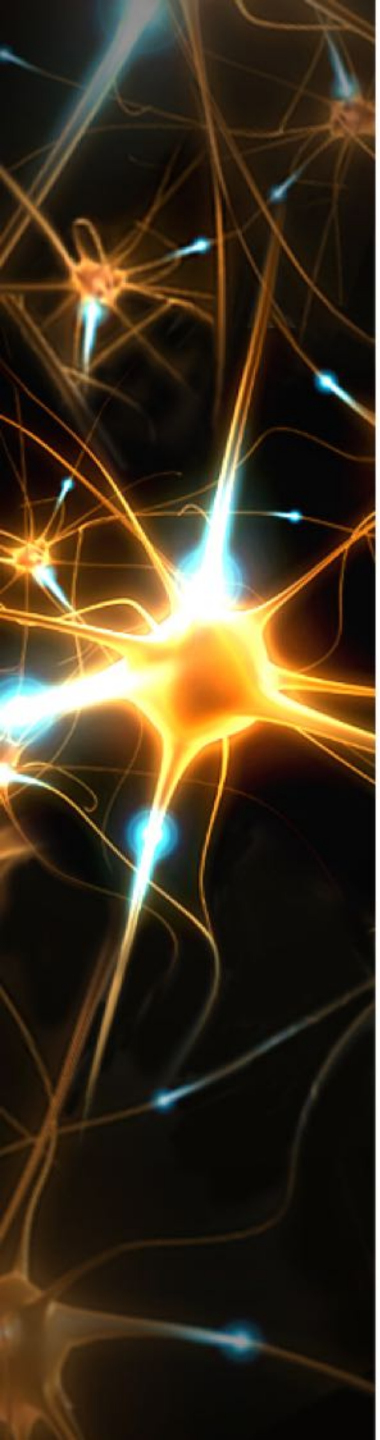
- Louis Pasteur. The microscopic revolution and microbiology proposes **germ theory as the cause of the disease**. The causes are therefore exogenous and not endogenous.

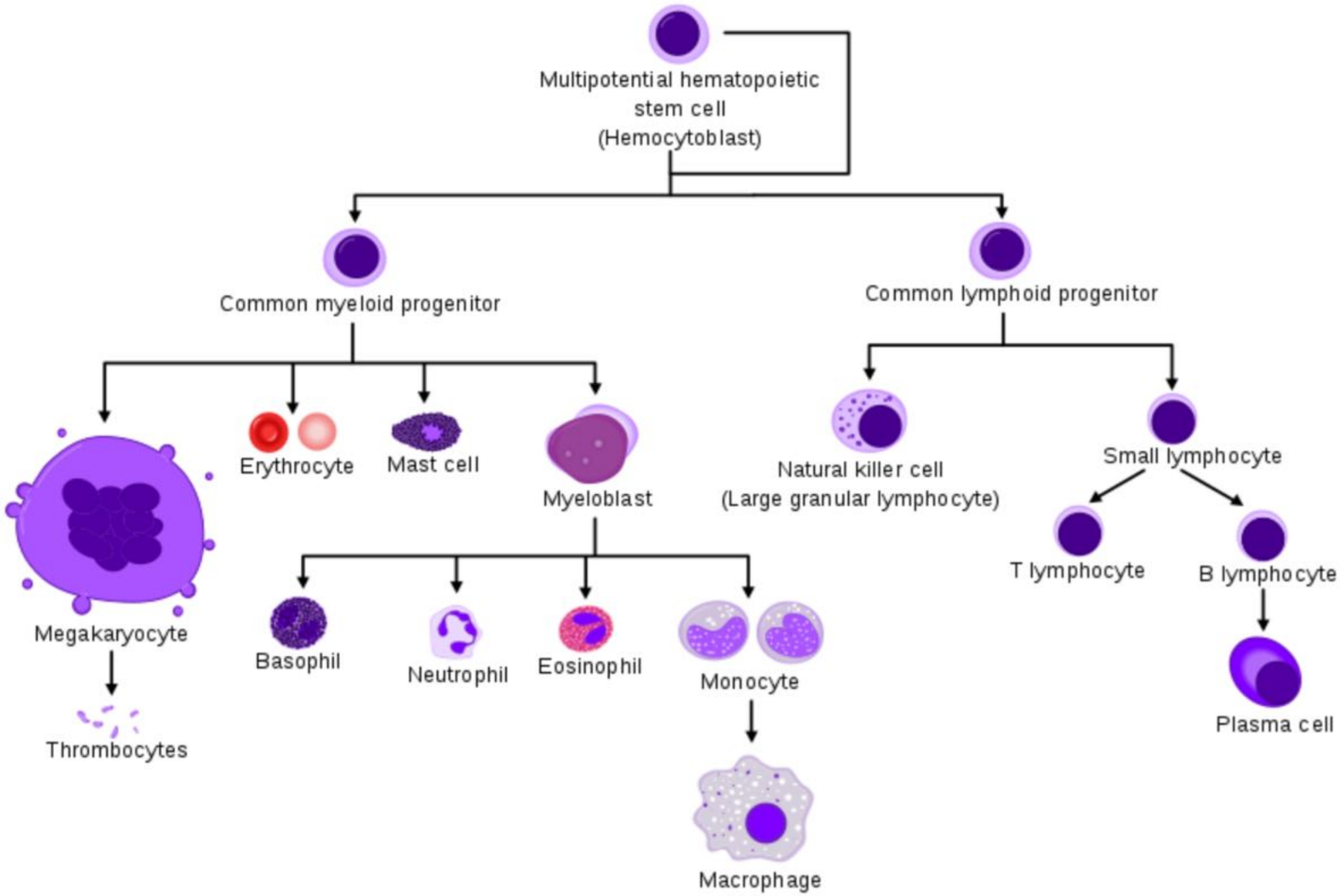
- 1970. The action of the immune system is to neutralize the invaders and stop the potential damage. **Diseases therefore result from pathogenic toxins**.

- 1980. Evidence that **proteins (cytokines) produced by macrophages and other immune cells can cause tissue damage, disease, and syndromes**. They have a plethora of biological activities that can be beneficial or harmful.

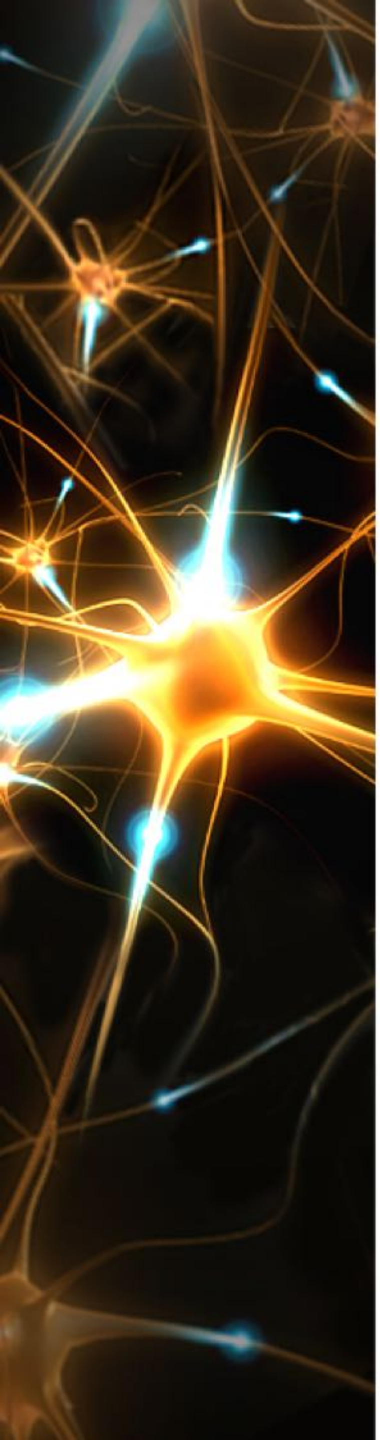
- 1980-1990. **The "cytokine" theory of the disease**. Cytokines produced by the immune system can cause the signs, symptoms and damaging effects of diseases and ... not the pathogens. Ex. Lipopolysacharides (LPS) produced by Gram bacteria (-) -> +++ production of cytokine TNF (via immune cells) -> septic shock lethal. **BIRTH OF NEURO-IMMUNOLOGY**

- Tracey 2002. "The **Cholinergic anti-inflammatory pathway**" (the anti-inflammatory cholinergic pathway)

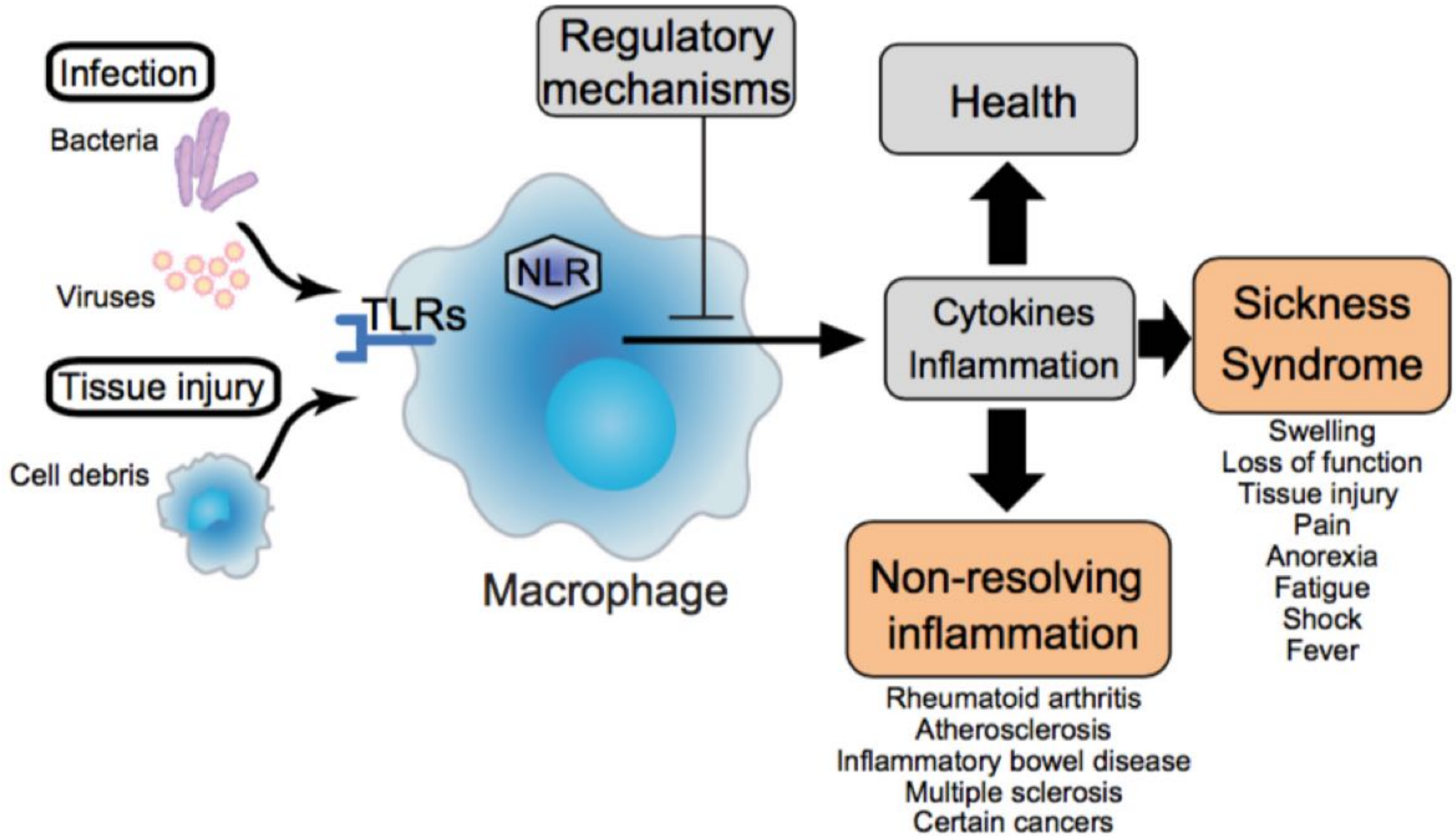




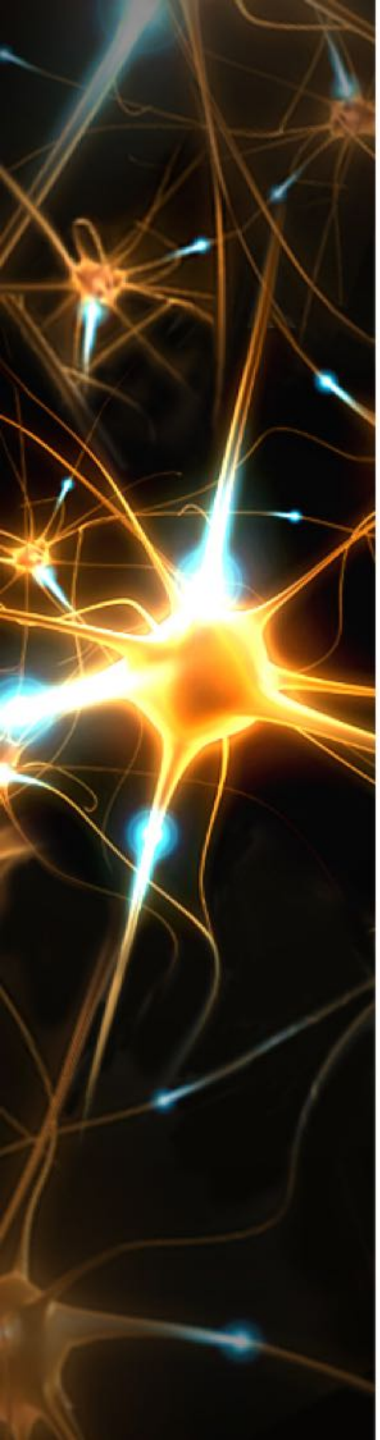
Innate and adaptative immunity

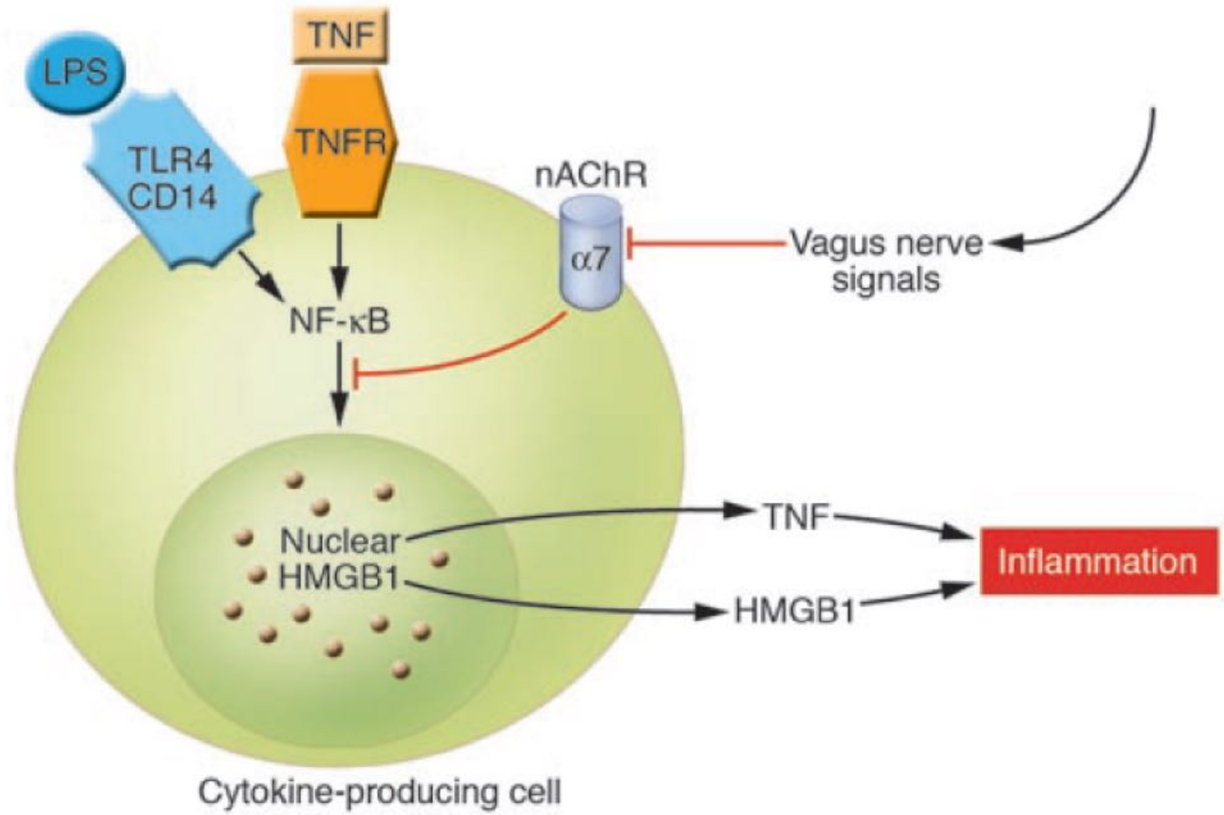


Inflammatory mechanisms in the case of health and diseases



TLRs, Toll-like receptors; NLR, nucleotide-binding oligomerization domain receptors. From Sundman et Olofsson (2014)

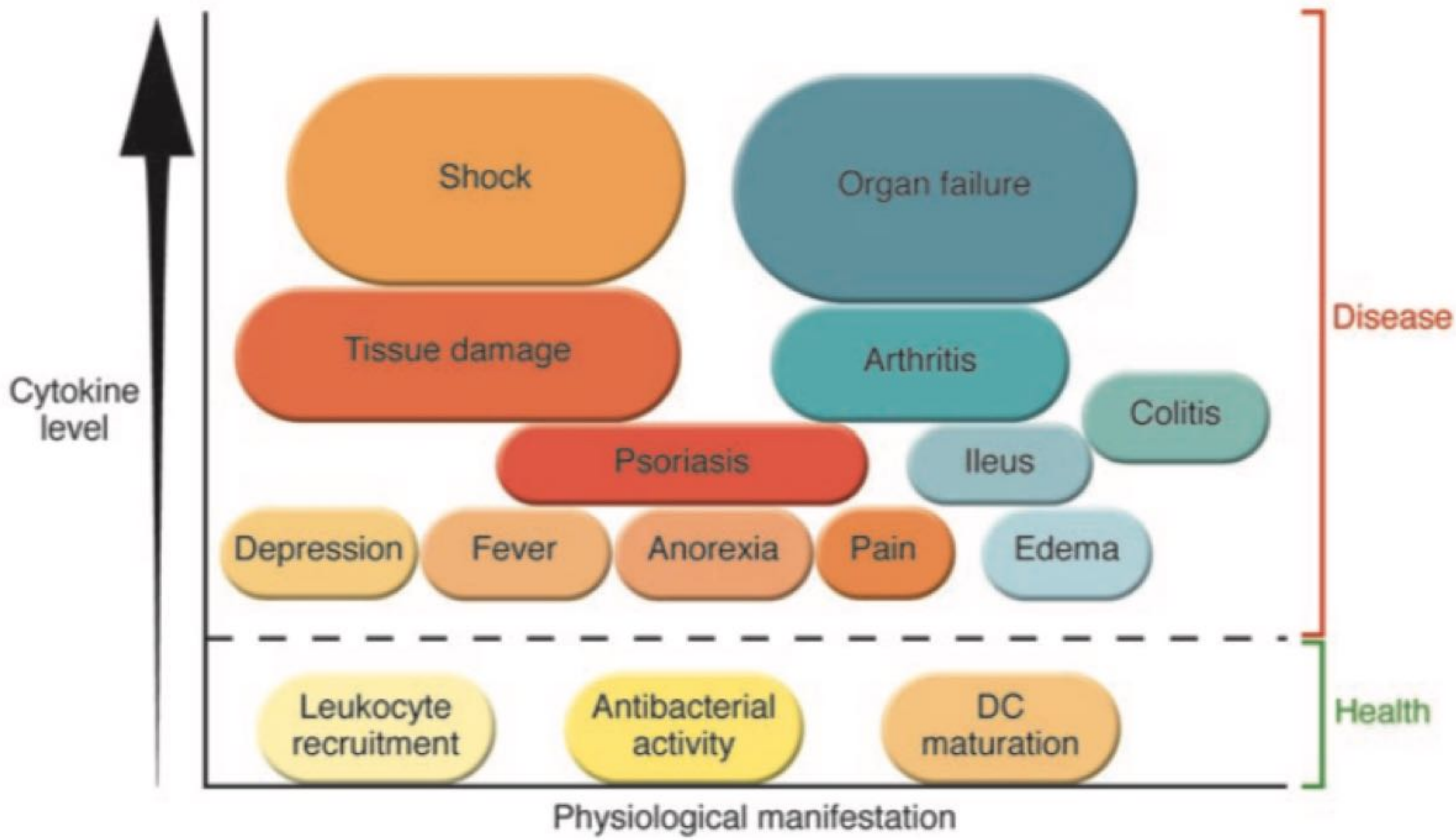




How the LPS-stimulated macrophage produces pro-inflammatory cytokines via NF-kB; Nuclear Factor-KappaB, communication protein pathway (cytokine -> nucleus)

From Tracey (2007)

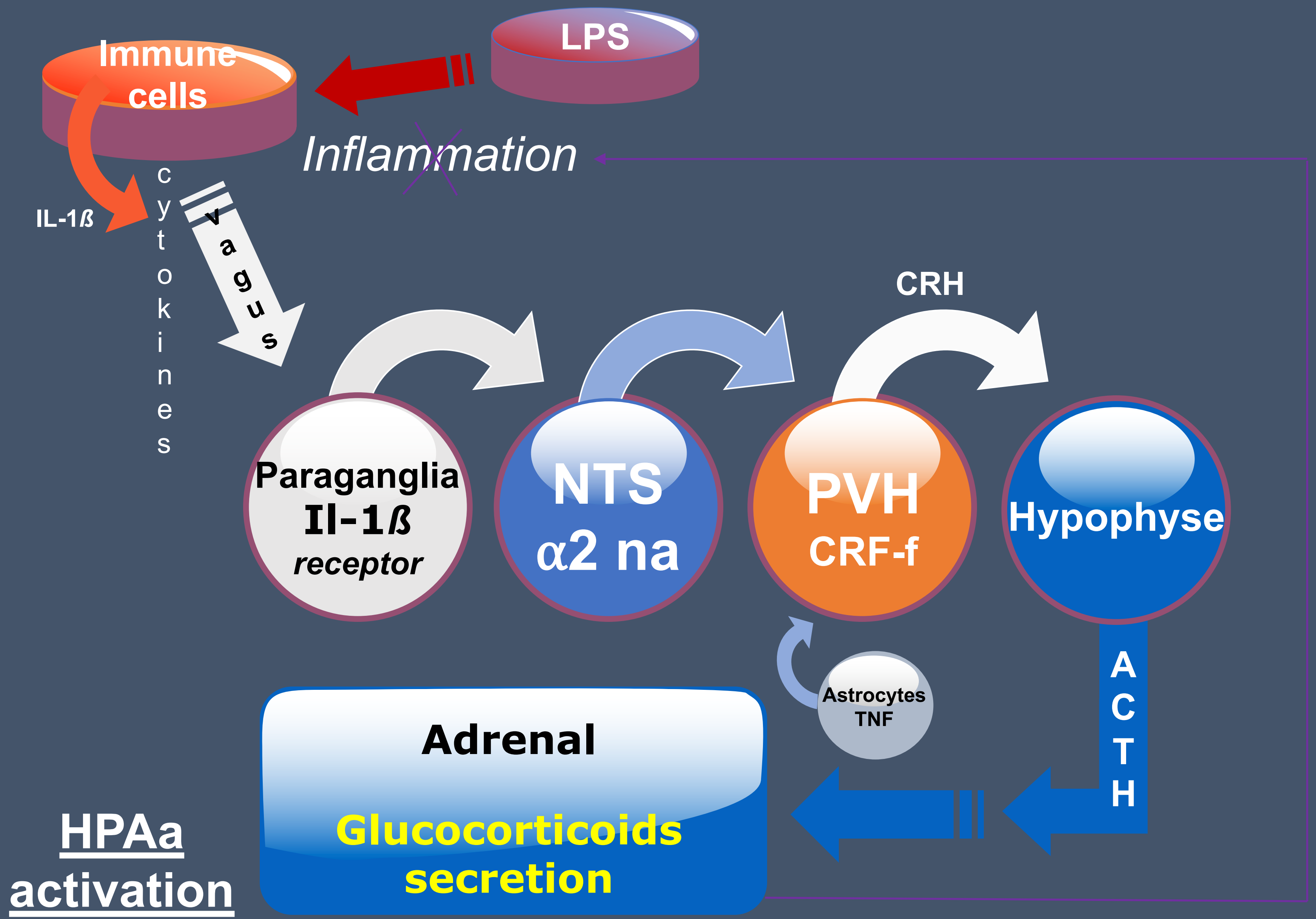
The immune system defends against infections and damage via inflammation. If unresolved, inflammation can also cause inflammatory and autoimmune diseases. (The "**cytokine" theory of inflammation**)



From Tracey (2007)

I. Hypothalamic-pituitary-adrenal (HPA axis)

- The vagus nerve is a major player in the neuro-endocrine axis
- First line of defense: coordination of neural responses - endocrine and behavioral => Homeostasis
- The vagus nerve is sensitive to peripherally pro-inflammatory cytokines: Interleukin (Il) -1, Il-6 and Tumor Necrosis Factor (TNF)α Information on site => NTS (via Il-1ß receptor at the level of paraganglions - ganglion nodose for example)
- Stimulation of release of CRF (paraventricular nuclei of the hypothalamus) ACTCH release by pituitary gland -> adrenal stimulation -> glucocorticoid

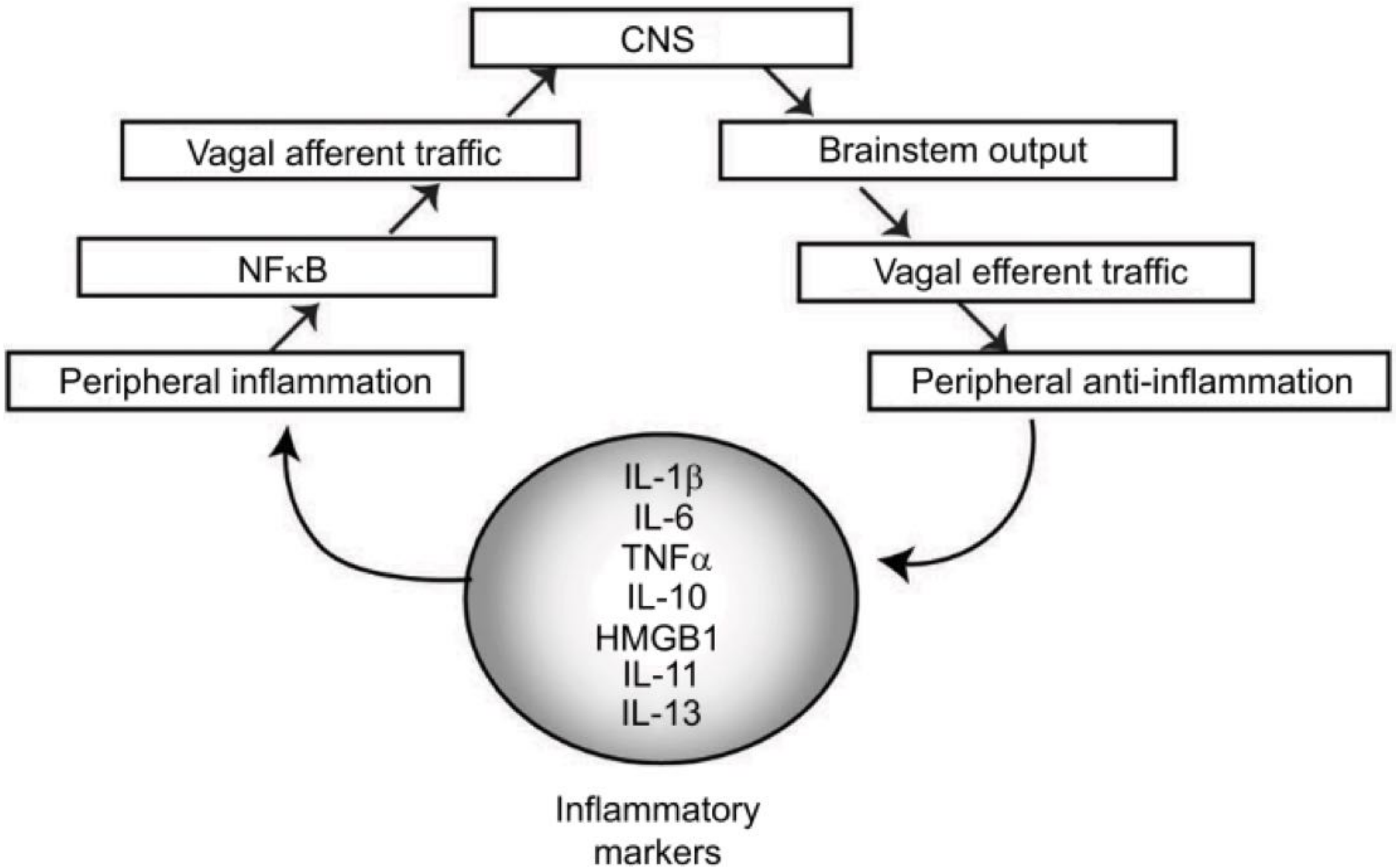


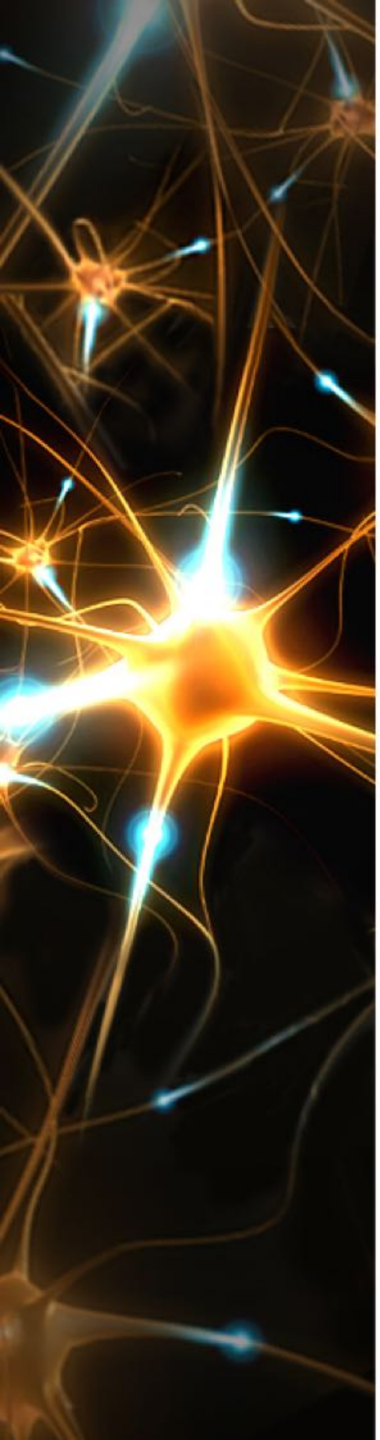
HPAa, hypothalamic-pituitary-adrenal axis; LPS, lipopysaccharide (endotoxin); IL-1ß, Interleukin 1ß; A2na, A2 noradrenergic; PVH, paraventricular hypothalamus nuclei; CRF, corticotrophin-release factor; CRH, corticotrophin-release hormone, ACTH, adreno-corticotrophin hormone

II. Cholinergic anti-inflammatory pathway (CAP)

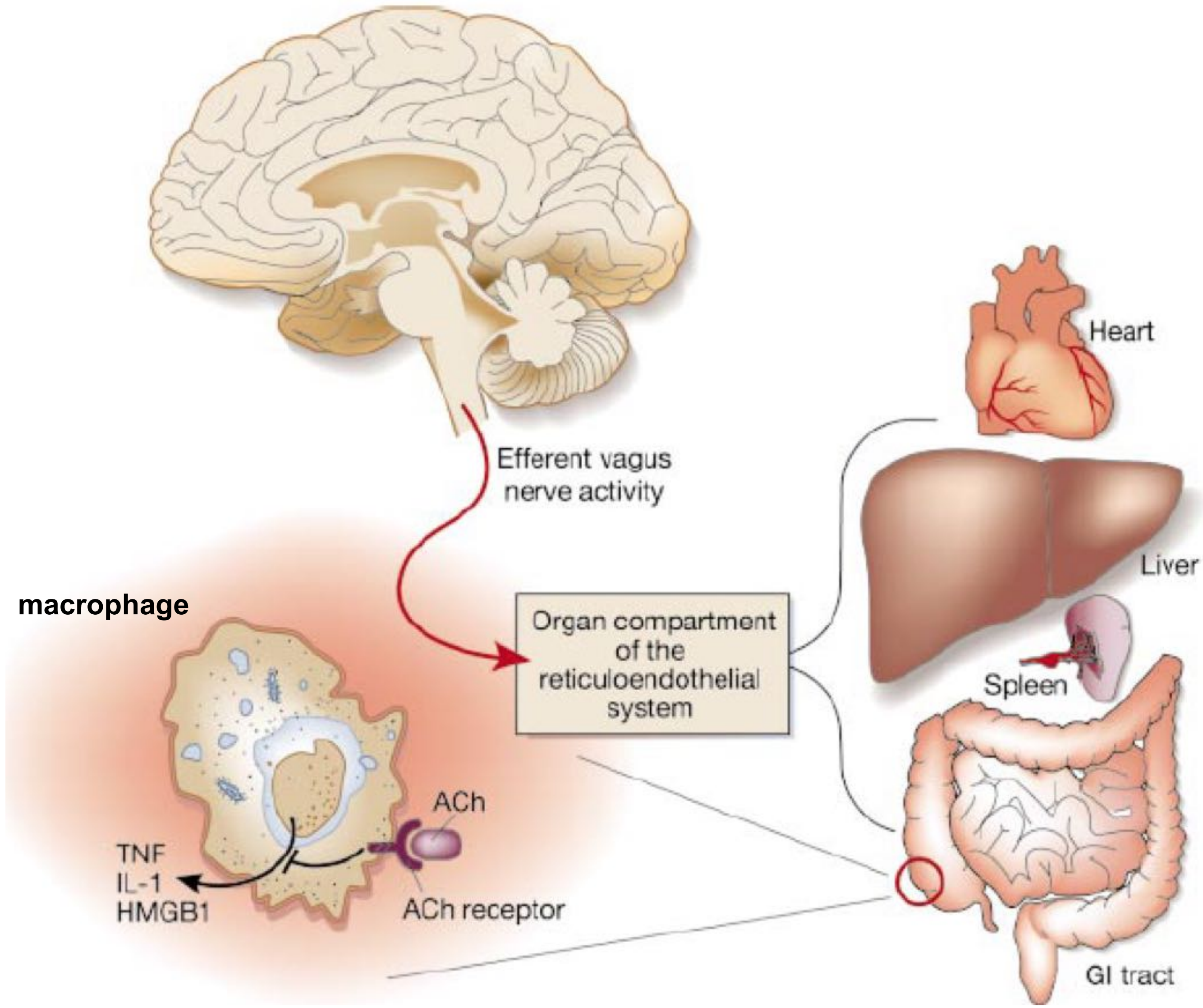
- Inflammatory signals (expression of cytokines) are driven by the vagus nerve (paraganglions -TLR-NLR) and reach the brain via NTS or humoral way (area postrema)
- Anti-inflammatory reflex (vago-vagal reflex) -> efferent response via the NDMV
- Acetylcholine (Ach) release at the level of the coeliac ganglion (stimulation of the splenic nerve (sympathetic) -> release of NA (spleen) -> (ß2AR) active T cells -> release of Ach -> (α7AchR) macrophages - > inhibition of cytokine production (TNFα - IL-6HMGB1)
- Macrophages act on reticuloendothelial system organs (heart, liver, spleen, GIT, lungs, connective tissue)
- Indirect effect on splene (via splanchnic nerve) and intestinal (enteric neurons)
- Macrophages M1 agonist receptors (brain level - Meynert cholinergic nuclei) may increase the anti-inflammatory activity of the cholinergic pathway

Neural inflammatory circuit

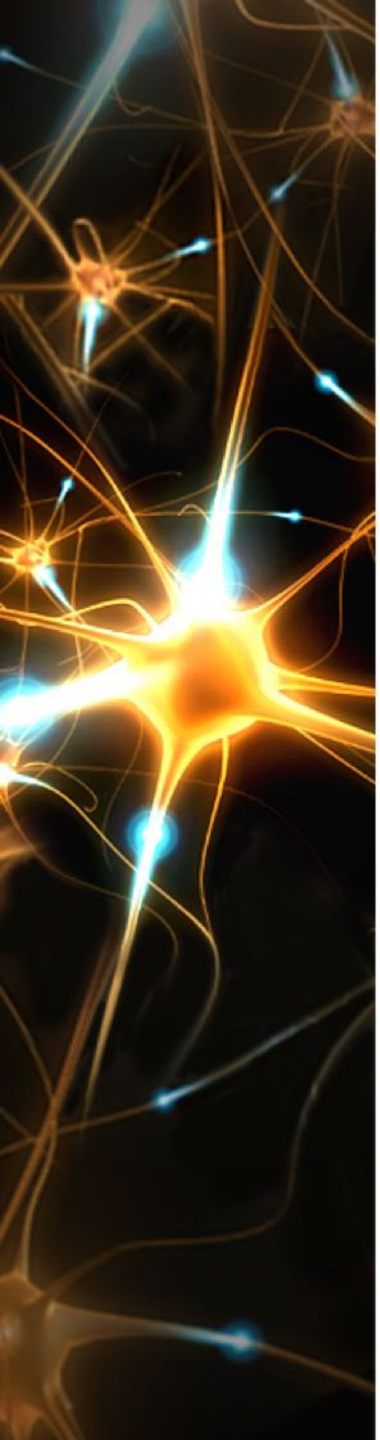




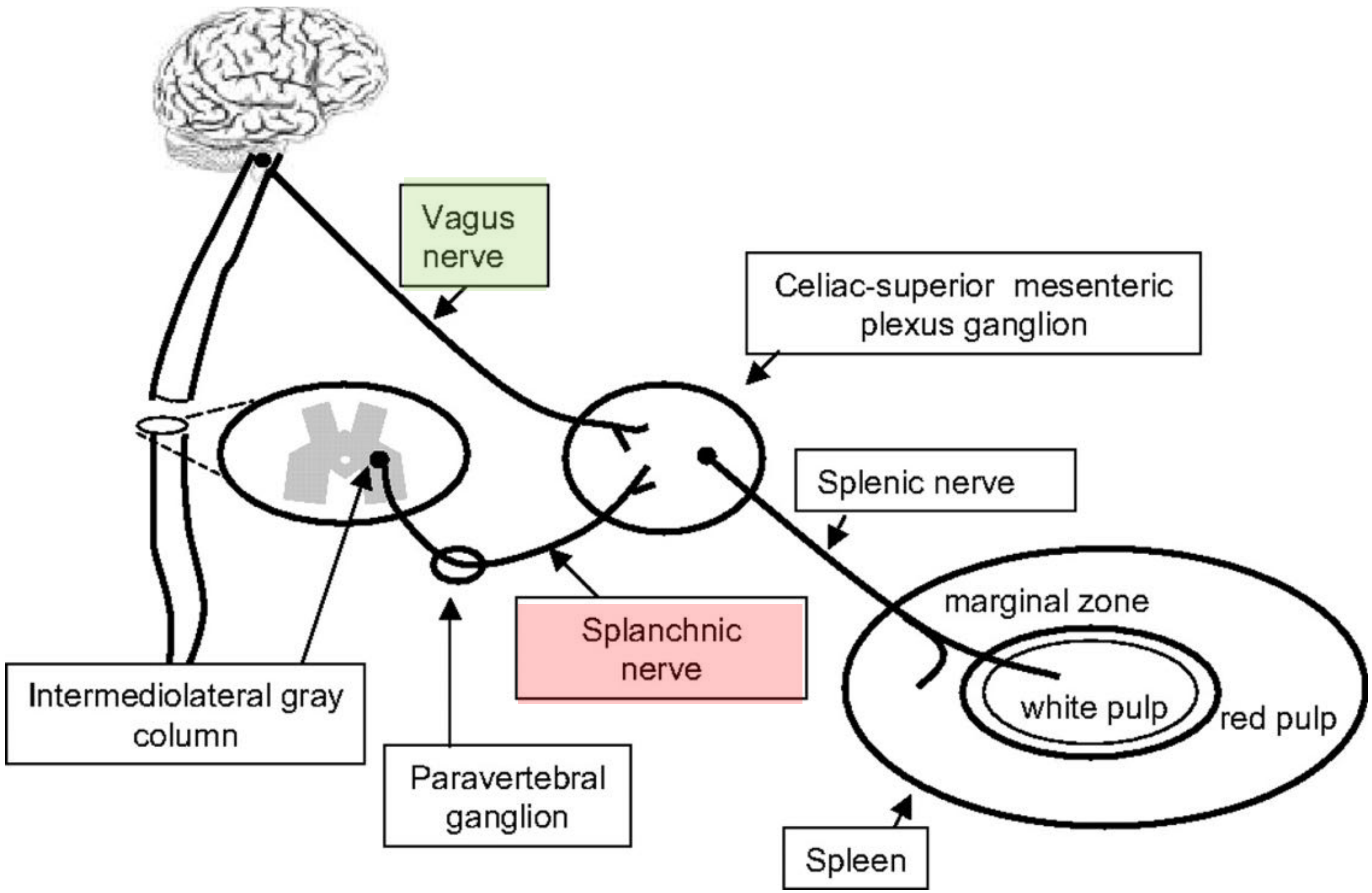
The efferent activity of the vagus nerve produces the release of acetylcholine (Ach) in the organs of the reticuloendothelial system. Reticuloendothelial = (macrophage system)

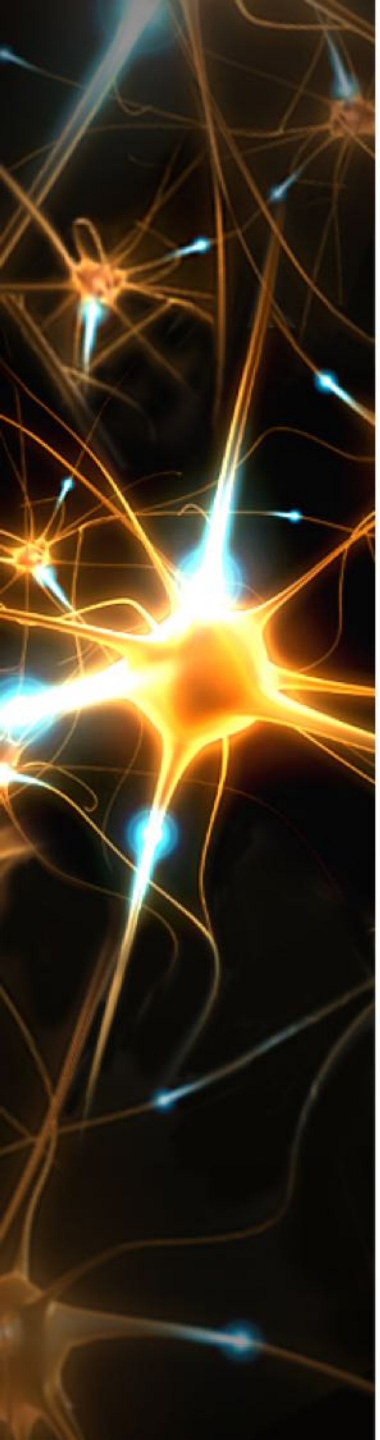


From Tracey (2002)

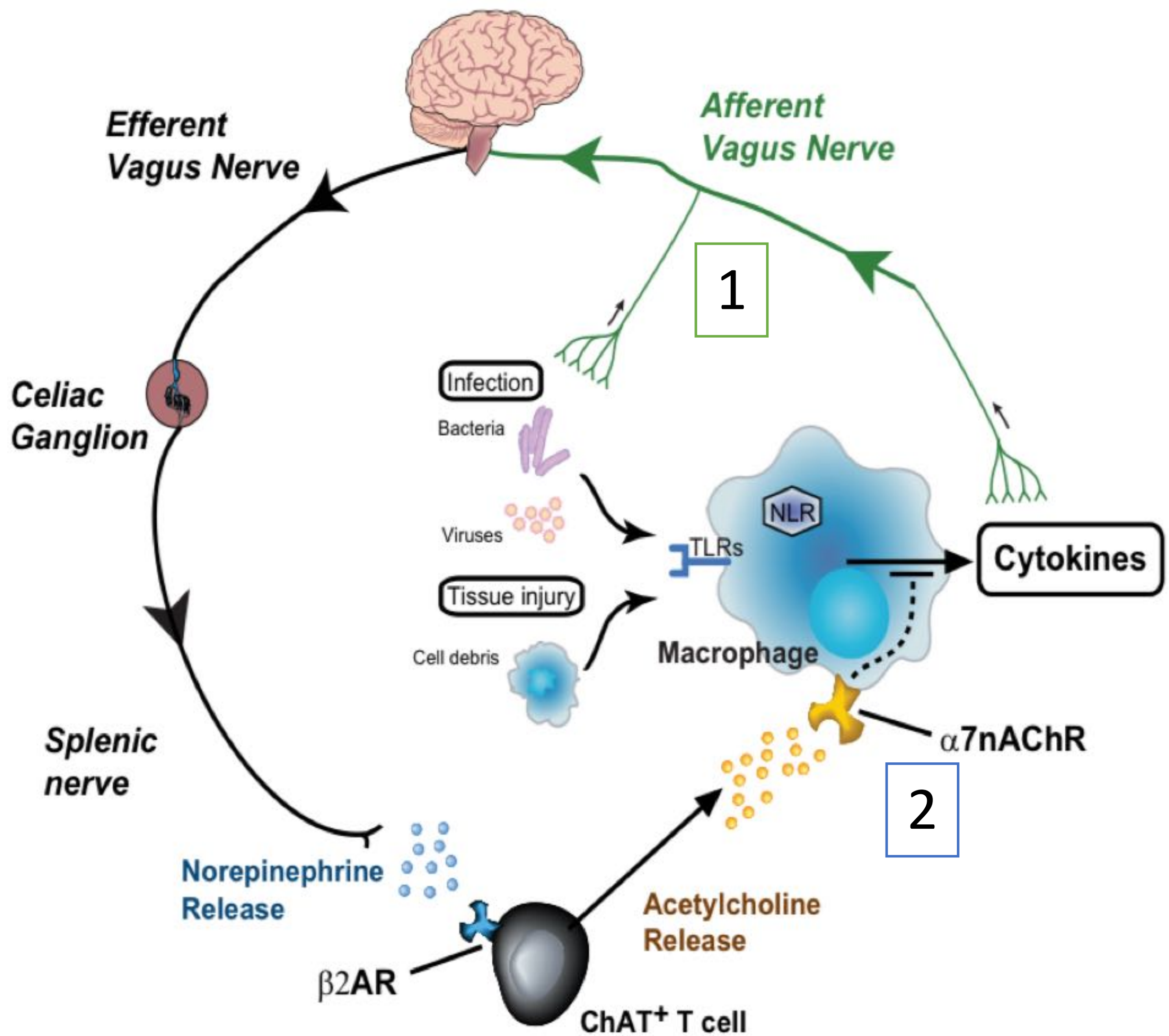


Spleen innervation: splenic nerve

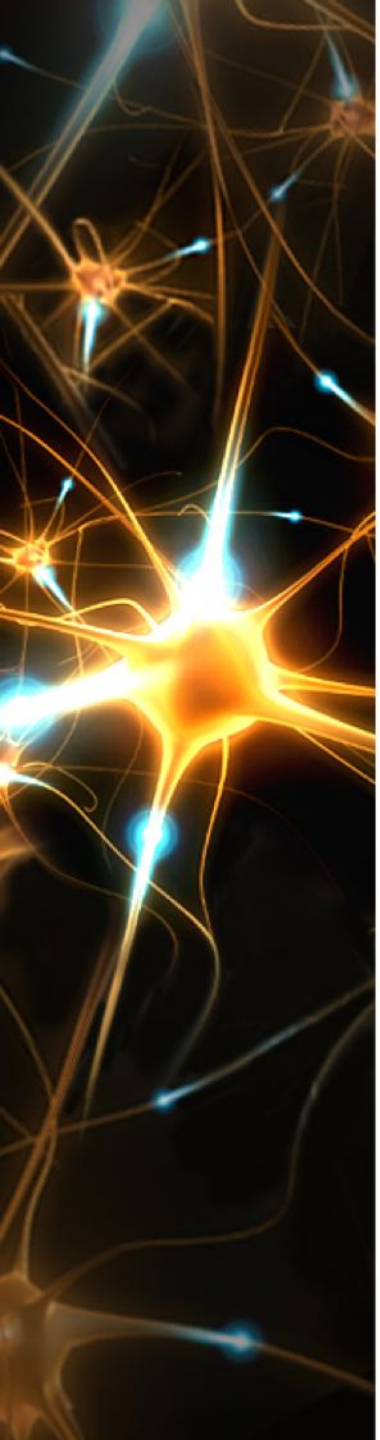




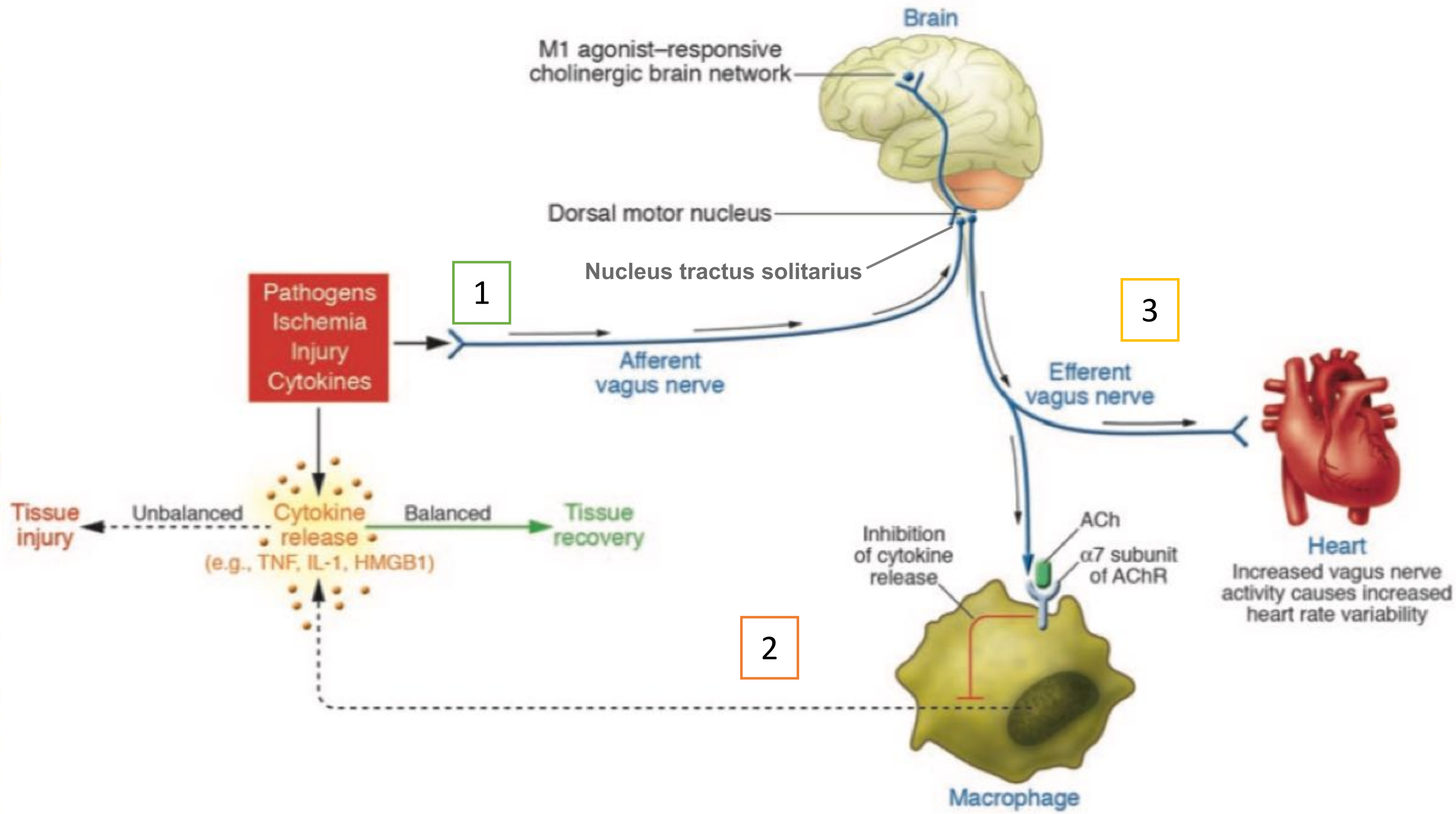
The inflammatory reflex



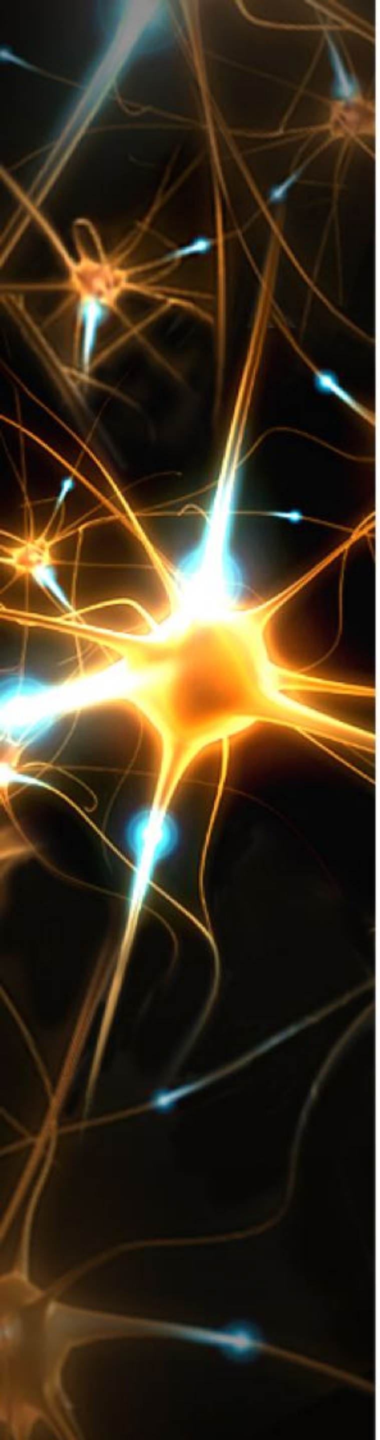
ChAT^{+} T cell, specialized choline acetyl-transferase-expressing T cells; α7nAChR, α-7-nicotinic ACh receptors; NLR, nucleotide-binding oligomerization domain receptors; TLRs, Toll-like receptors. From Sundman et Olofsson (2014).



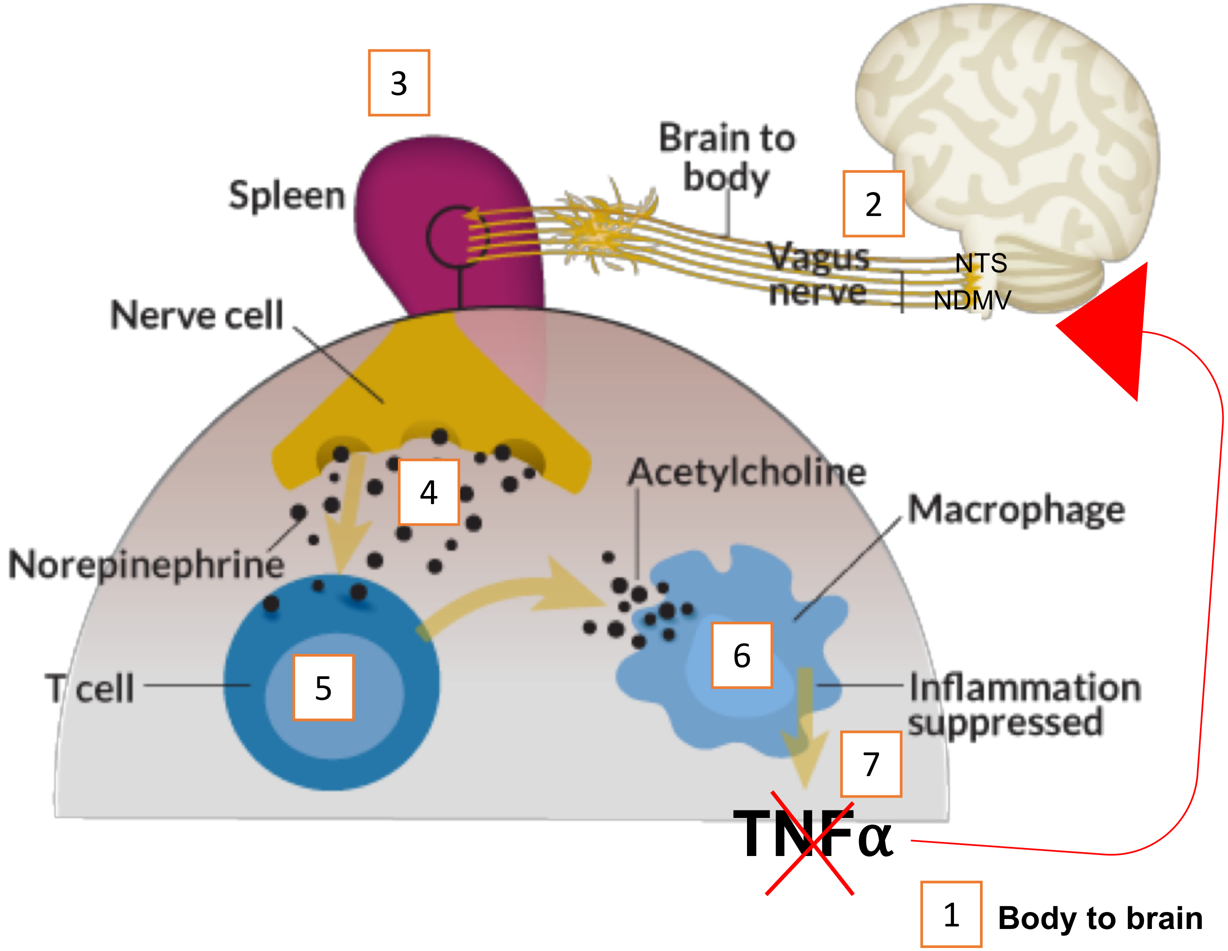
Anti-inflammatory cholinergic pathway balances cytokine production

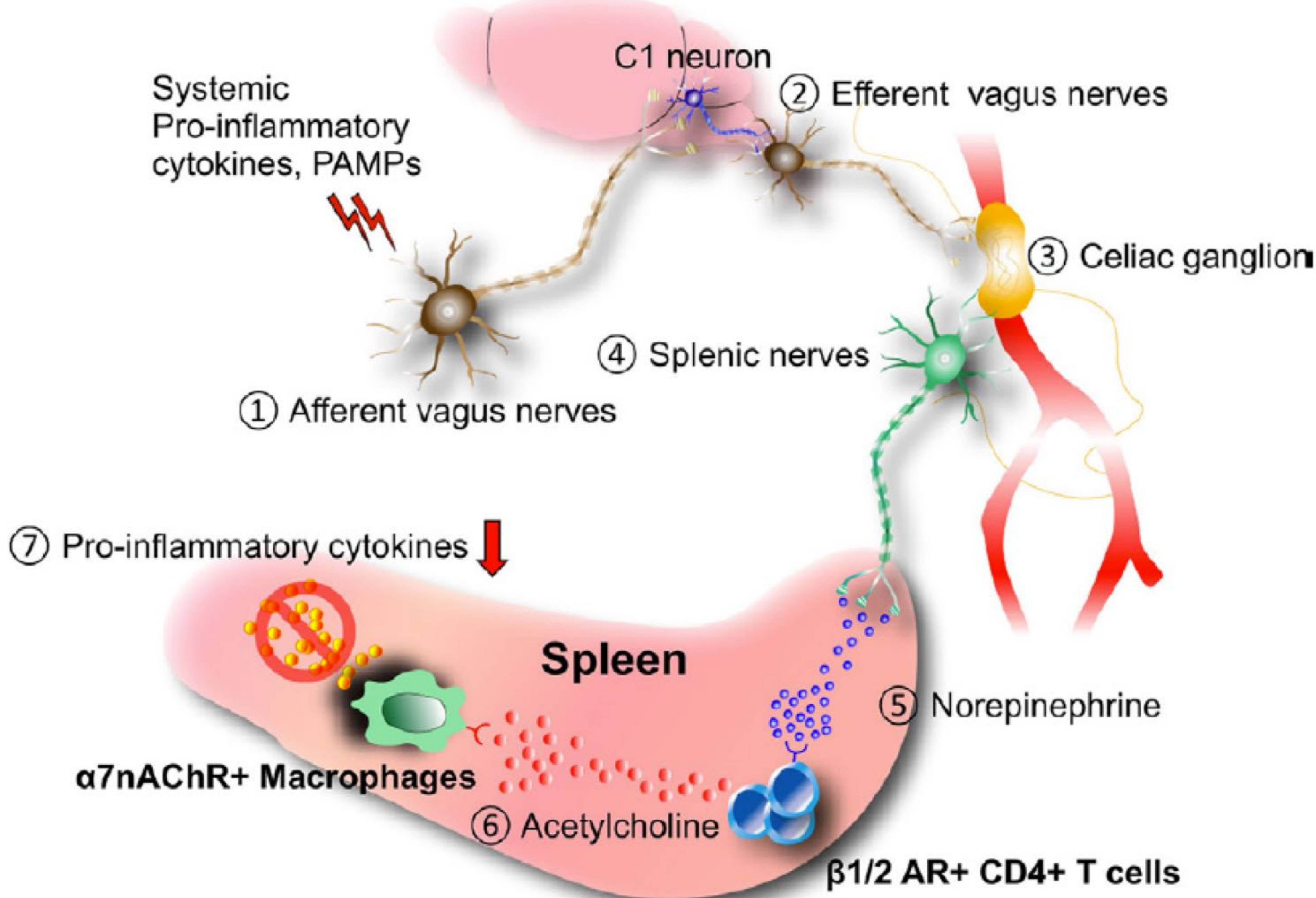


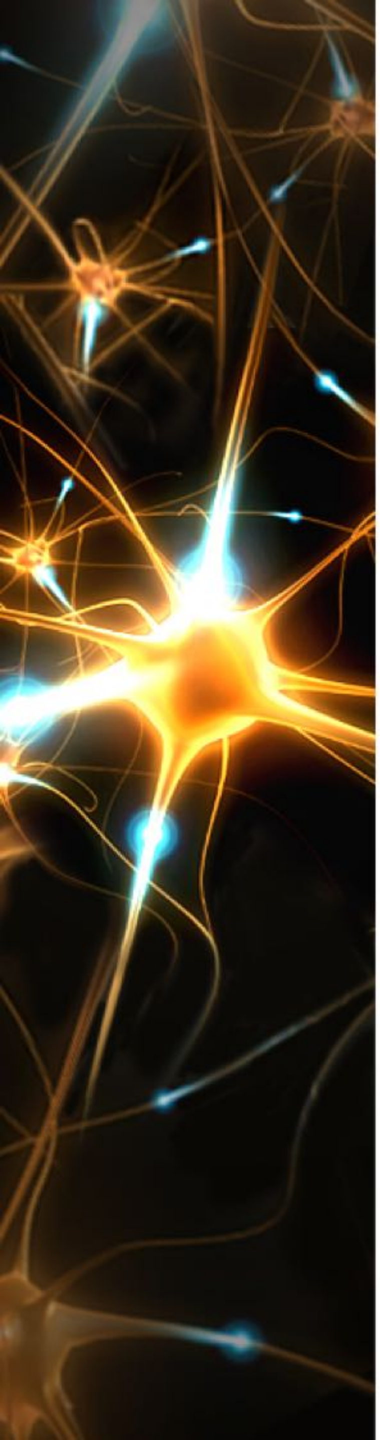
M1 agonist, muscarinique 1 agonist; Ach, acetylcholine; TNF, tumor necrosis factor; IL-1, interleukin-1; HMGB1, high mobility group 1; α7 subunit AChR, α-7 subunit ACh receptors. From Tracey (2007).



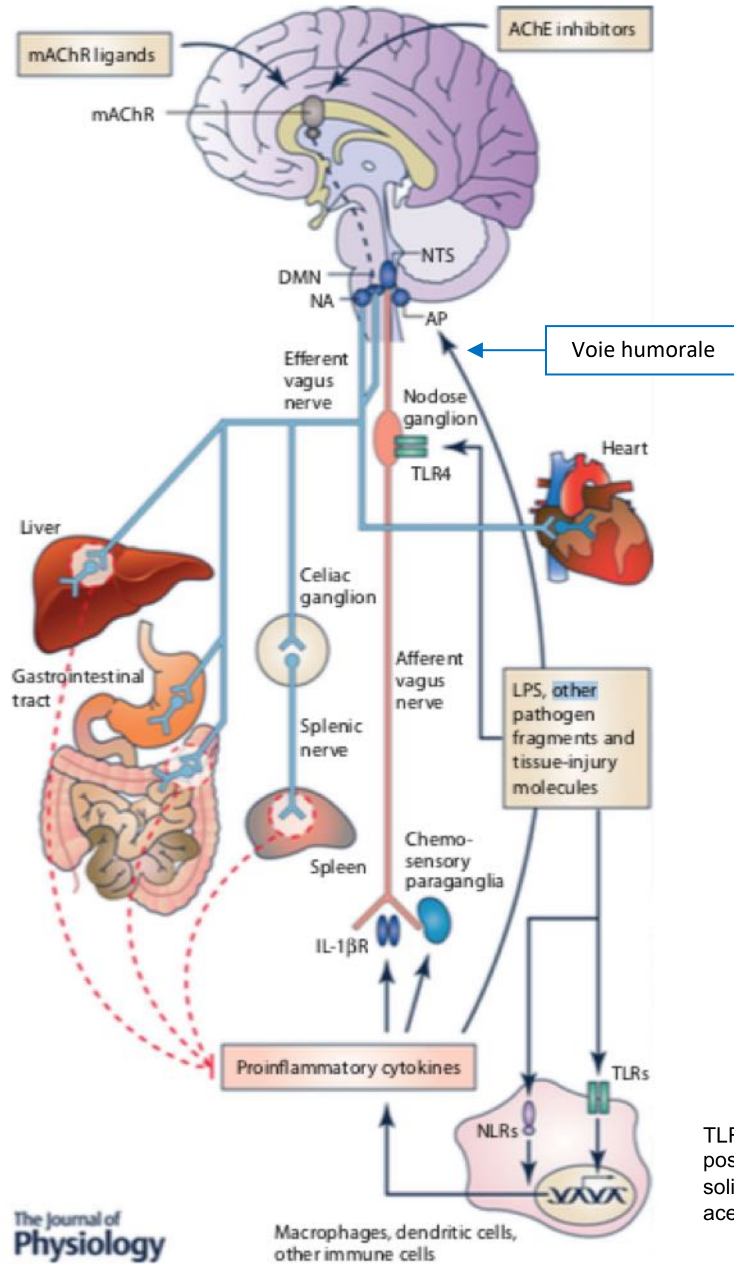
7-step anti-inflammatory cholinergic pathway



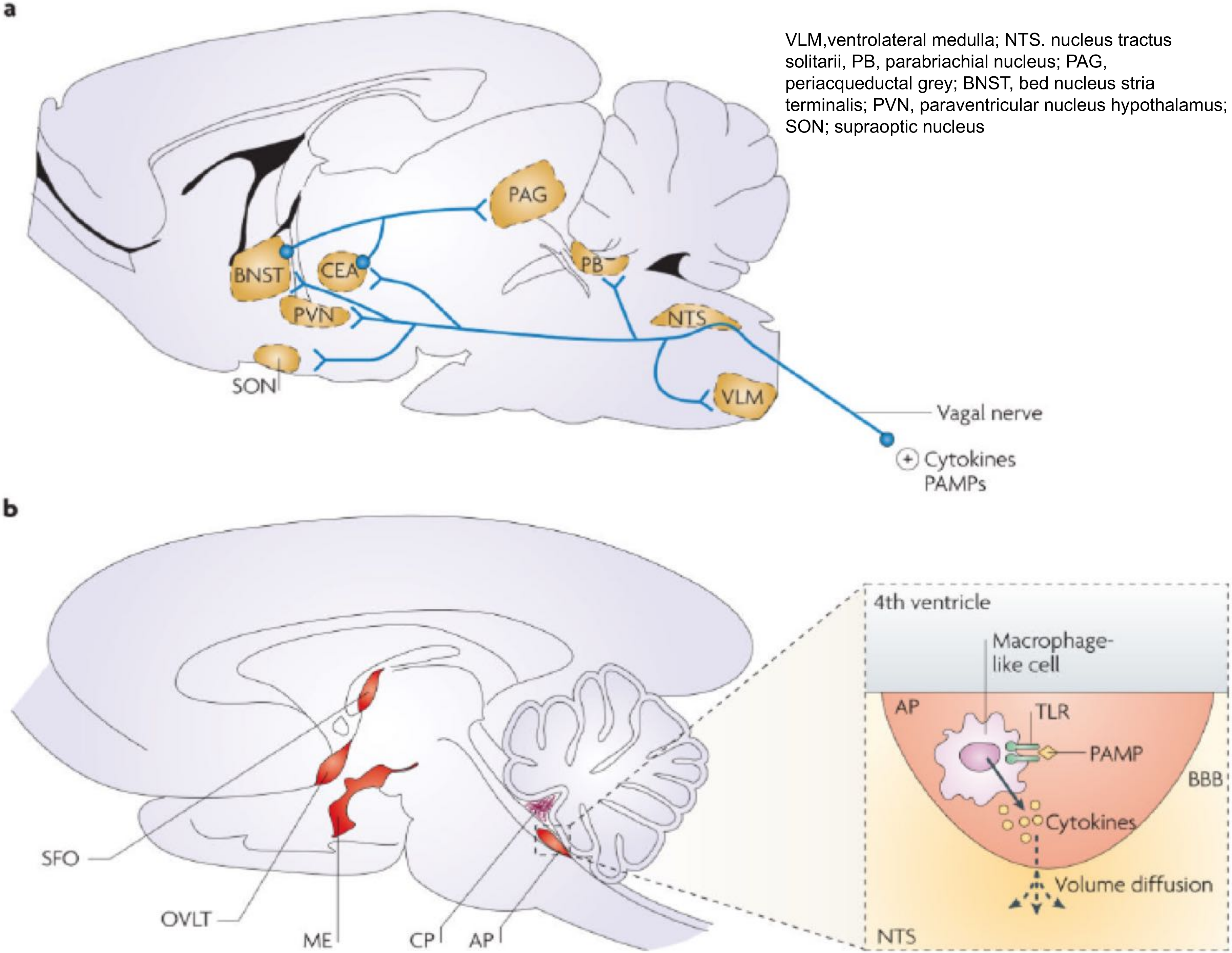

C1 neuron
Systemic
Pro-inflammatory
cytokines, PAMPs
② Efferent vagus nerves
③ Celiac ganglion
④ Splenic nerves
① Afferent vagus nerves
⑦ Pro-inflammatory cytokines
Spleen
⑤ Norepinephrine
α7nAChR+ Macrophages
⑥ Acetylcholine
β1/2 AR+ CD4+ T cells



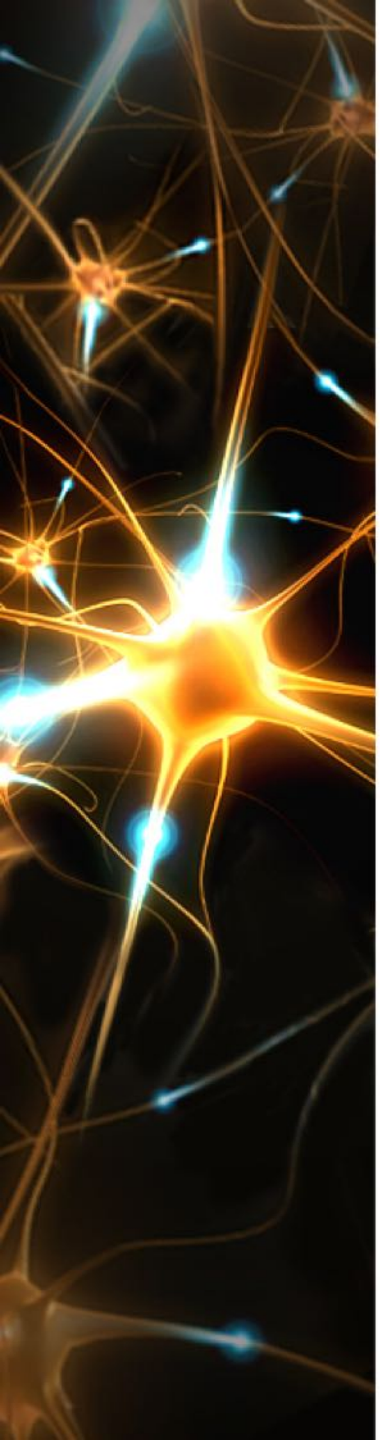
Functional anatomy of inflammatory reflex



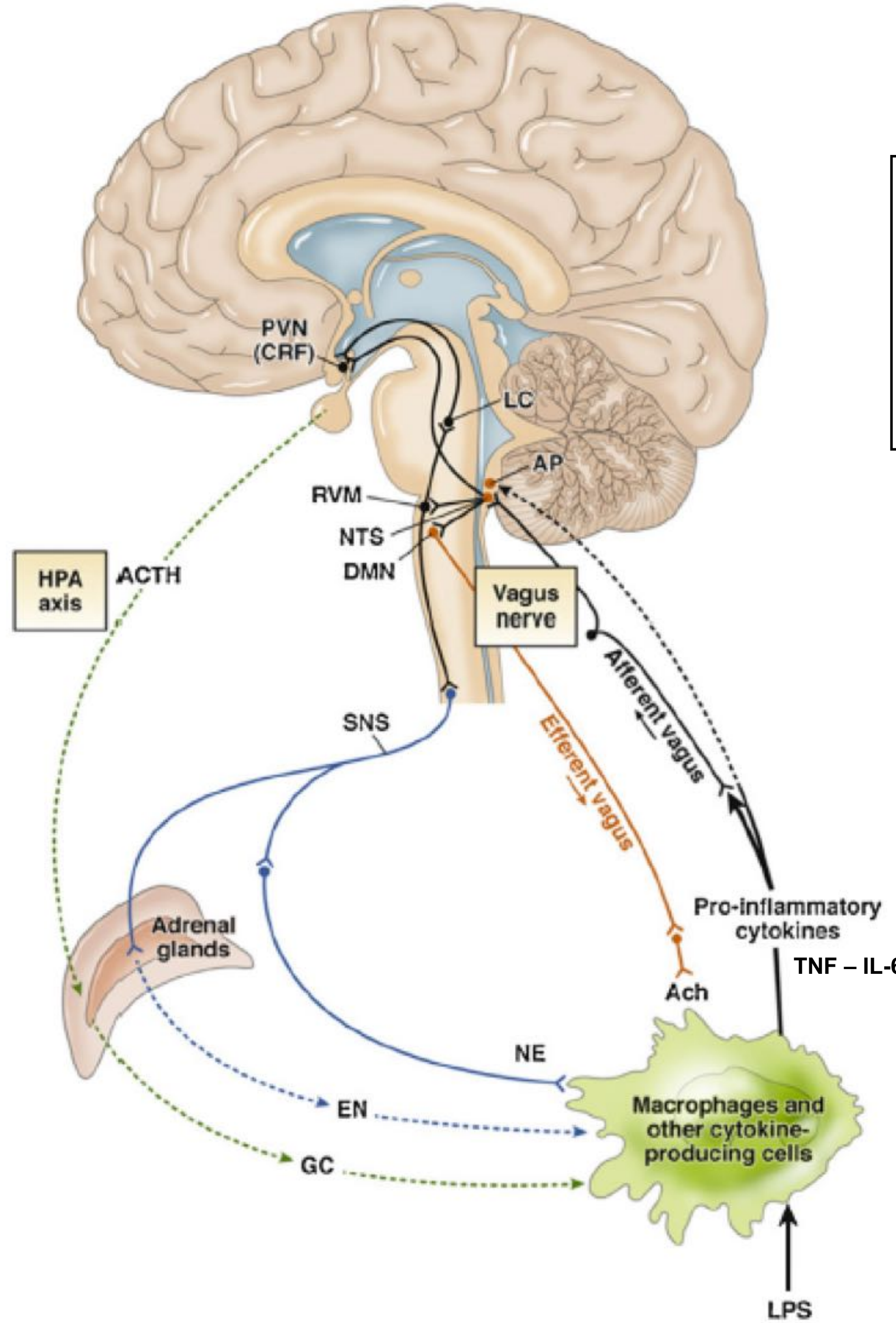
TLR4, toll like receptor4; NA, nucleus amibguus; AP, area postrema; DMN, dorsal motor nucleus; NTS, nucleus tractus solitarius; mAChR, M acetylcholine receptor; AChE; acetylcholinesterase. From Pavlov & Tracey (2015).



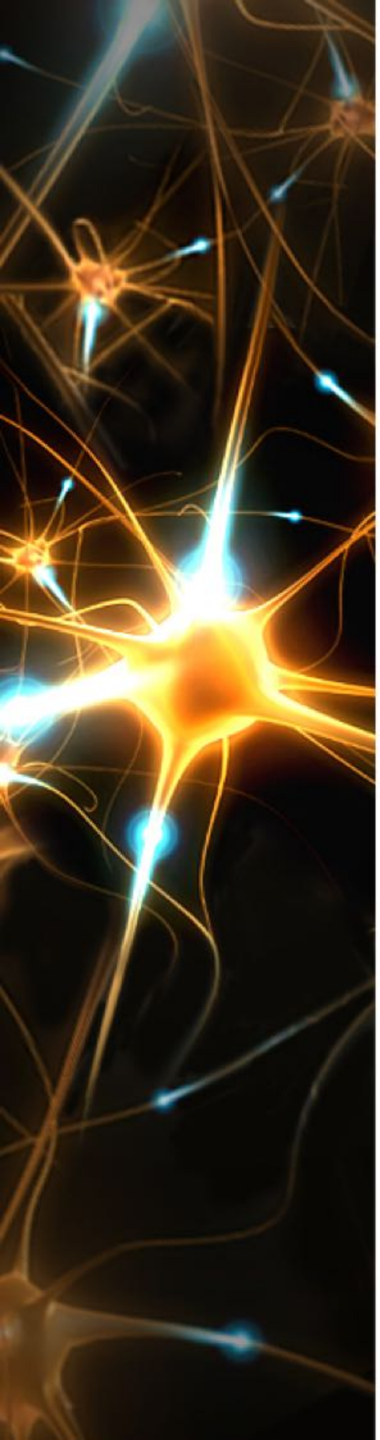
VLM,ventrolateral medulla; NTS. nucleus tractus solitarii, PB, parabriachial nucleus; PAG, periacqueductal grey; BNST, bed nucleus stria terminalis; PVN, paraventricular nucleus hypothalamus; SON; supraoptic nucleus



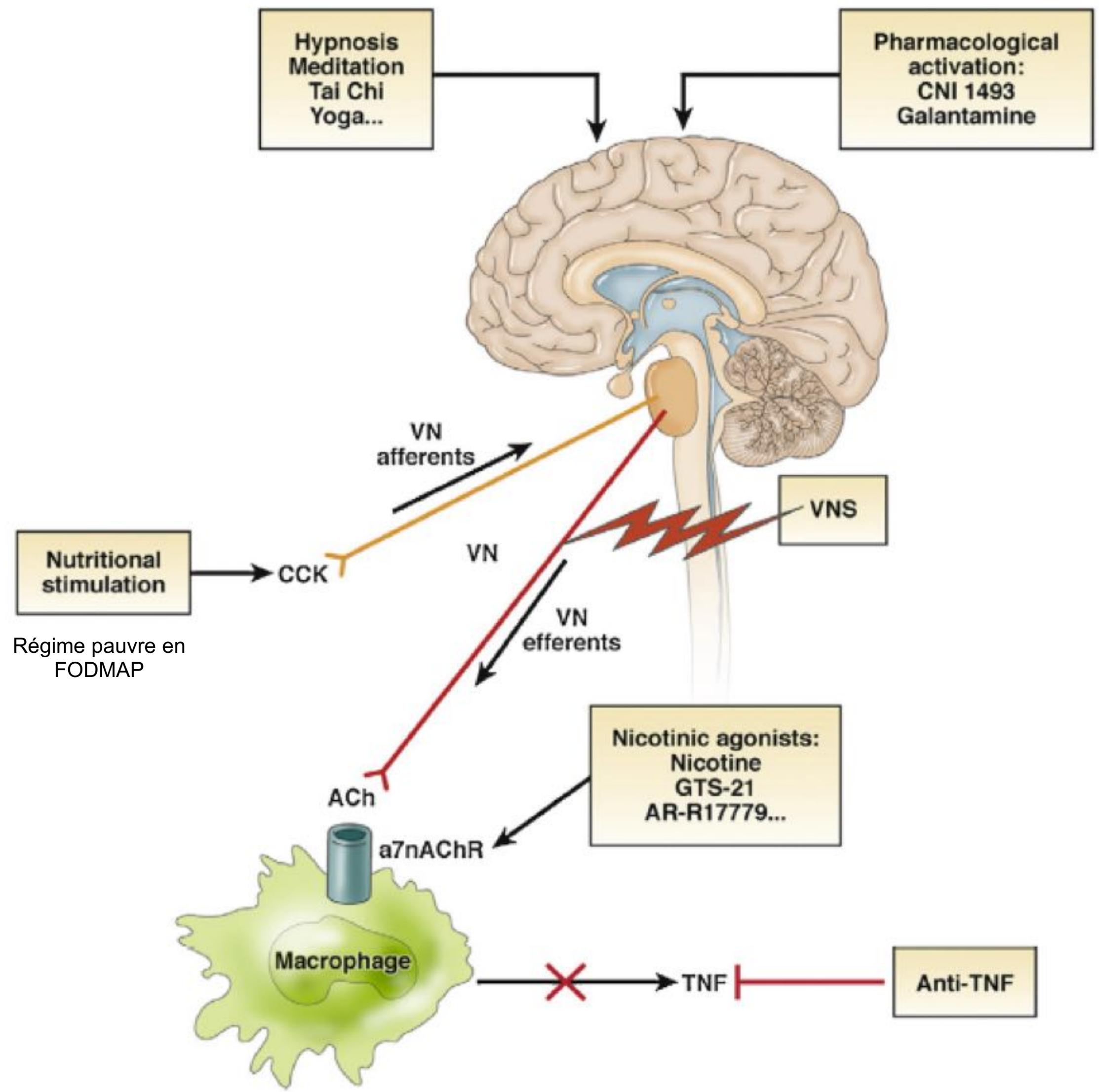
Neuro-endocrine-immune axis and anti-inflammatory cholinergic pathway



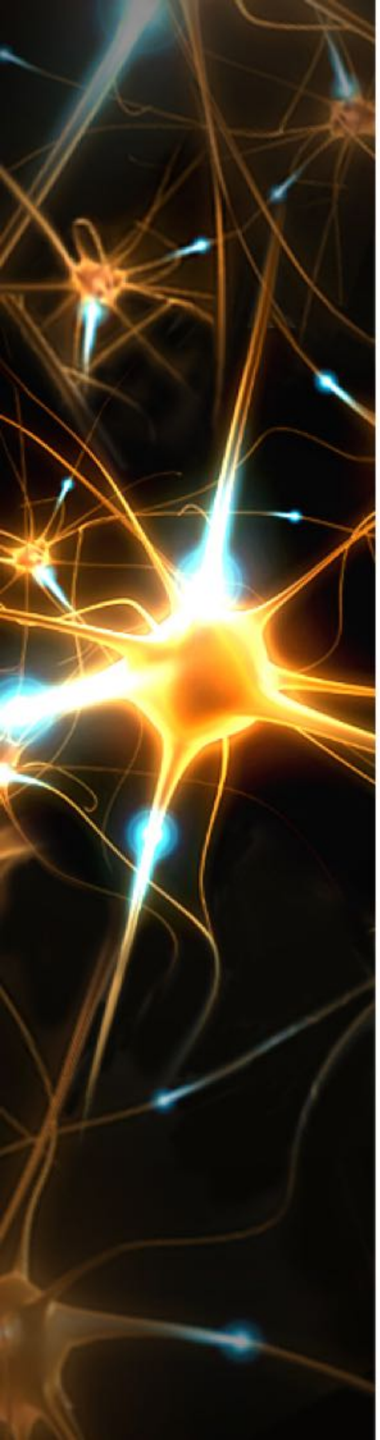
From Bonaz et Pelissier (2013)

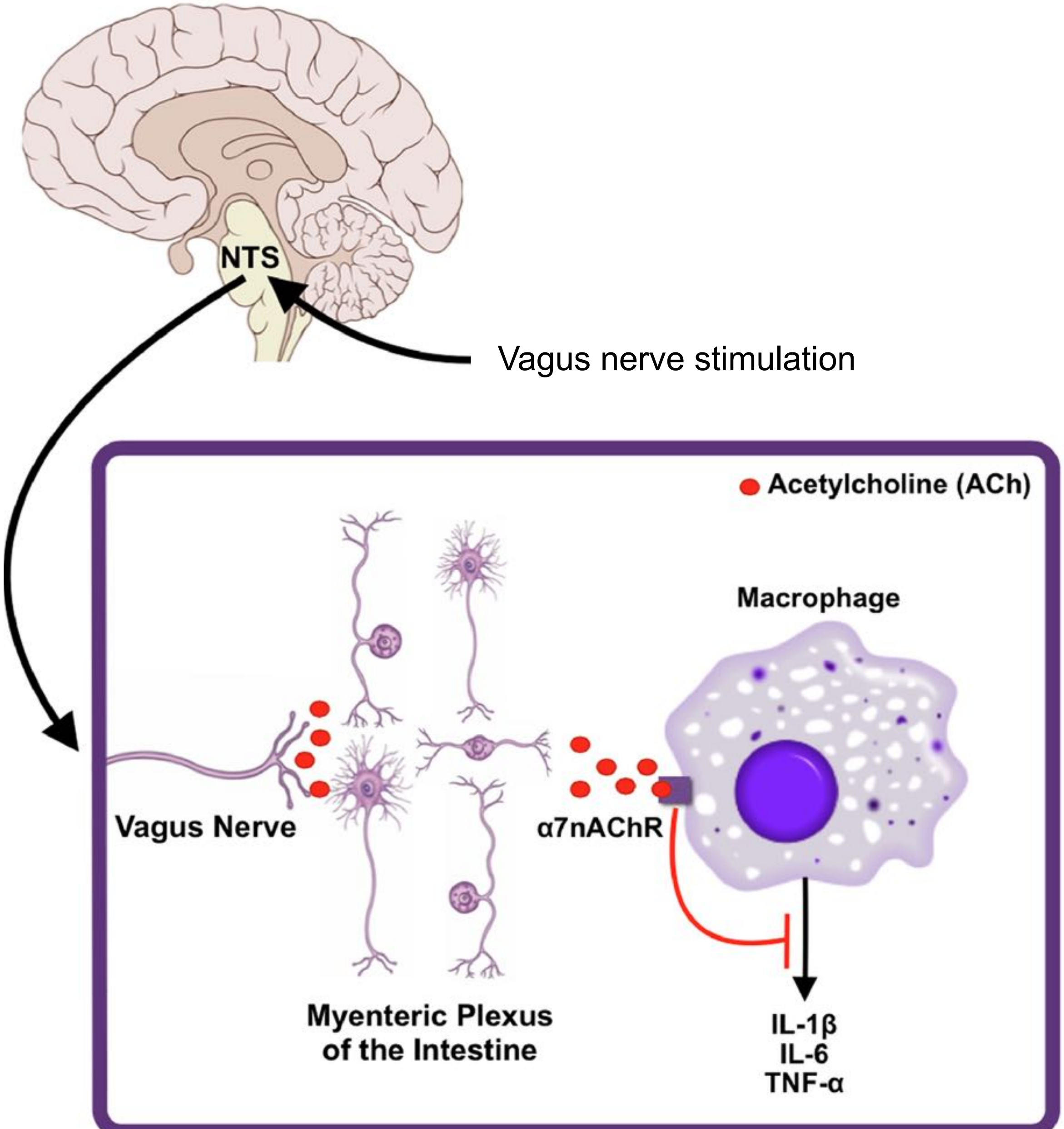


<u>Means of stimulating the anti-inflammatory cholinergic pathway</u>



FODMAP, Fermentable oligo-di and monosaccharides and polyols.
From Bonaz et Pellissier (2013).

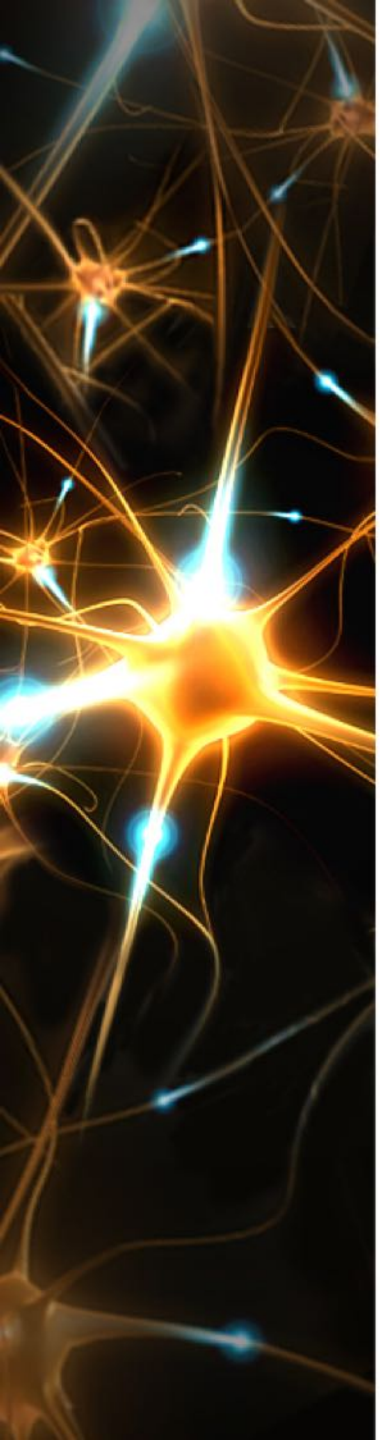




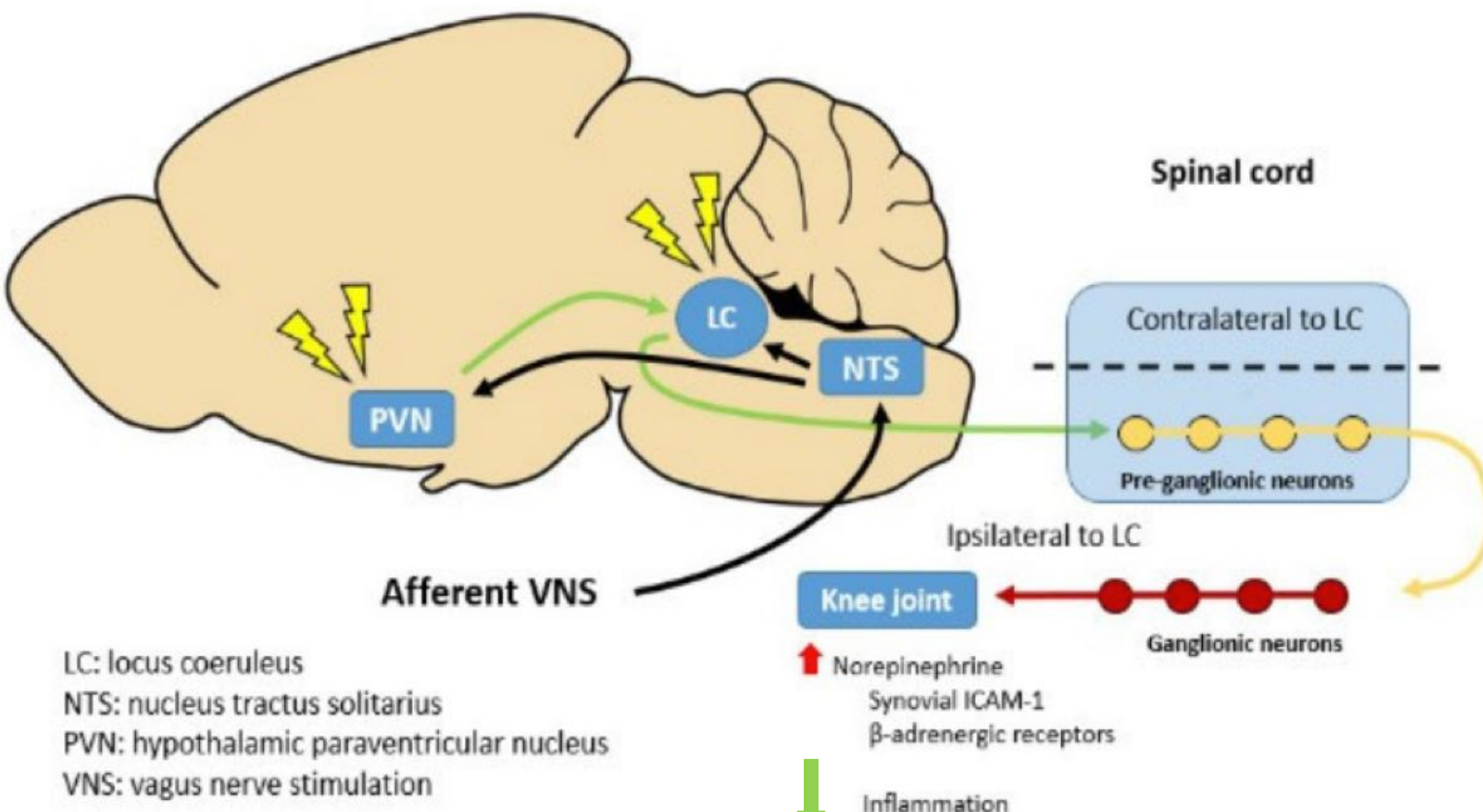
Enteric nervous system

III. Vago-hypothlamo-sympathetic pathway

- Vagal stimulation inhibits joint inflammation in an arthritic animal after sub-diaphragmatic vagotomy, splenectomy or adrenalectomy.
- This mechanism is therefore independent of the sub-diaphragmatic vagus nerve, the spleen and the adrenal glands, and independent of T lymphocytes.
- The efferent vagal approach is not required to control joint inflammation.
- Vagal stimulation -> stimulation of the NTS -> stimulation of the locus coeruleus (LC) + of the paraventricular nuclei of the hypothalamus (PVH) -> activation of a sympathetic local response at the articular level (release of NA), for example at the level of the knee joint.



Vago-Hypothalomo-Sympathetic pathway



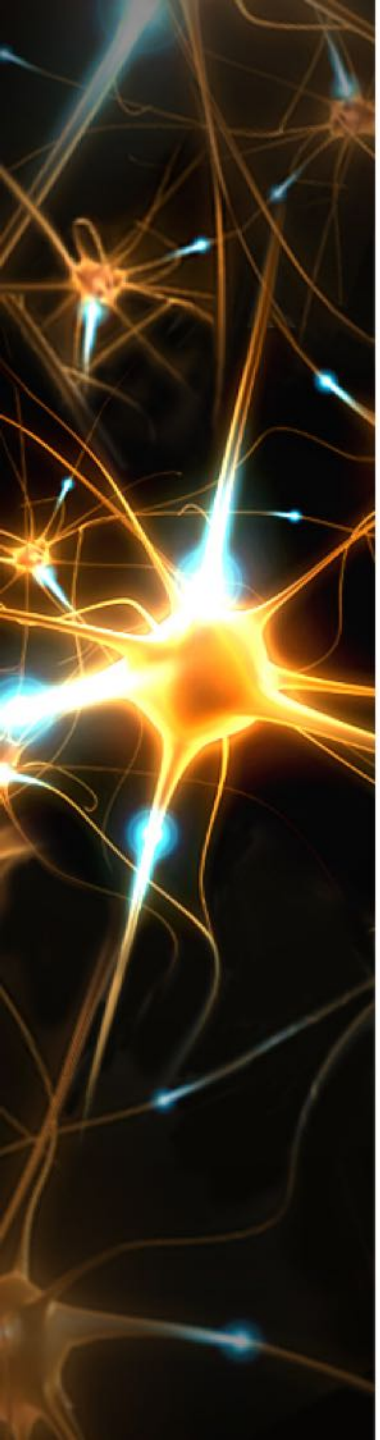
ICAM-1: intercellur adhesion molecule 1

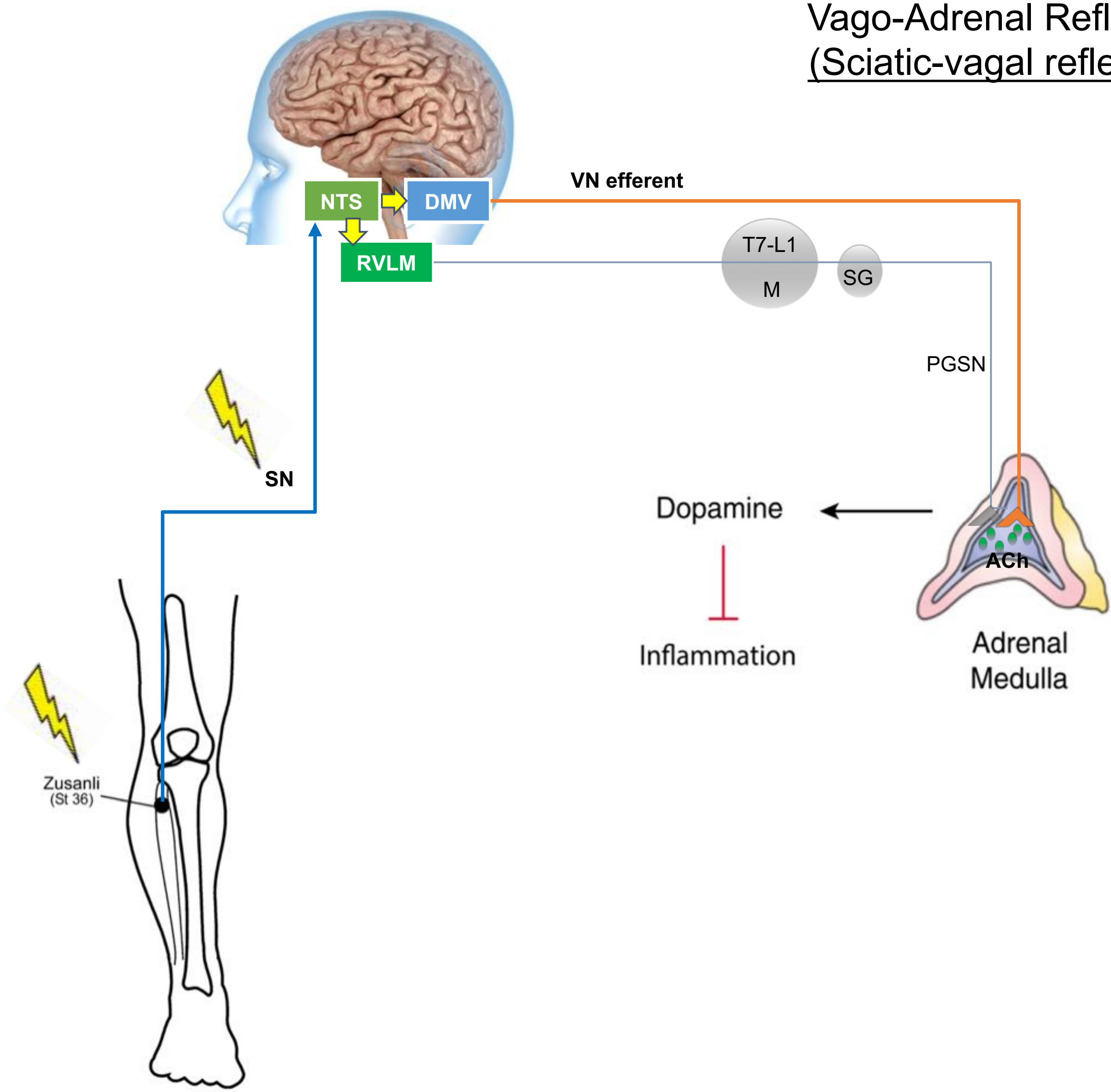
ICAM-1, intercellular adhesion molecule. From Bassi (2017).

IV. Vago-adrenal reflex (sciatic-vagal reflex)

- Immune-regulating reflex using cholinergic and NA-dopaminergic neurons (ParaΣ, Σ)
- Stimulation of the sciatic nerve -> brainstem (NTS) vagus nerve -> NDMV + RVLM -> adrenal medulla
- Adrenal medulla-> increased production of NA and dopamine -> suppression of inflammation (serum reduction of TNF, IL6, Interferon-gamma, ...) in case of infection and autoimmune diseases

Vago-Adrenal Reflex
<u>(Sciatic-vagal reflex)</u>





NTS, nucleus tractus solitarius; DMV, dorsal motor vagus; RVLM, Rostro-ventro-lateral medulla; M, medulla; SG. Sympathetic ganglia; PG, preganglionic splanchnic nerve; SN, sciatic nerve; Ach, Acetylcholine. Modified from Chavan & Tracey (2017).

- **The vagus nerve is sensitive to pro-inflammatory cytokines** released peripherally: Interleukin (IL) -1, Il-6, HMGB1 and TNFα

- In situ information => NTS (via Il-1ß receptor (TLR) in paraganglions) -> **Stimulation of the HPA axis**

- The anti-inflammatory physiological responses inhibit inflammation: cytokine IL-10 release and transforming grow factor-β (TGF-ß) inhibit the production of TNF and other pro-inflammatory cytokines.

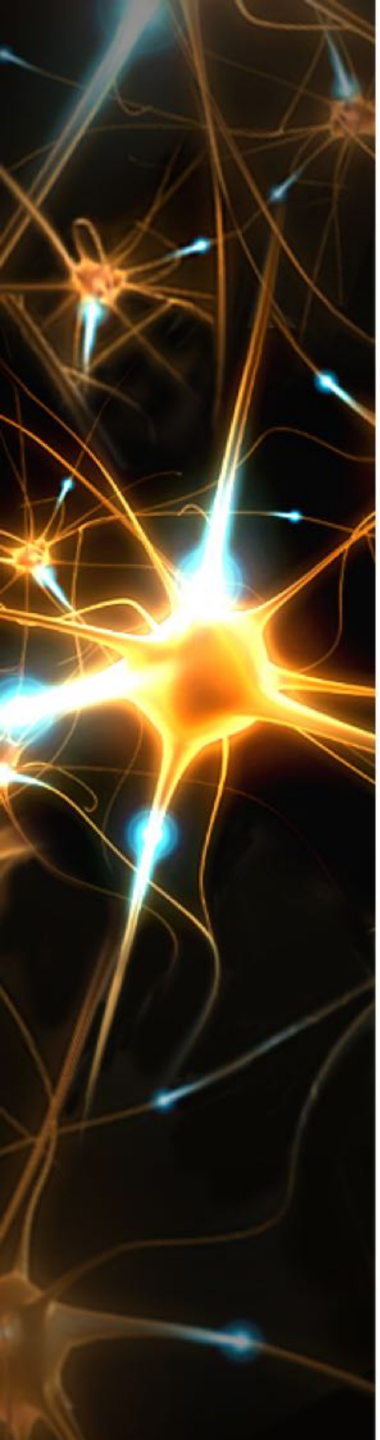
- **Adrenal glucocorticoids and other stress hormones (adrenaline-NA) inhibit cytokine synthesis** and inter-cellular signal transduction. The inflammatory stimulus may activate anti-inflammatory signals at the CNS level.

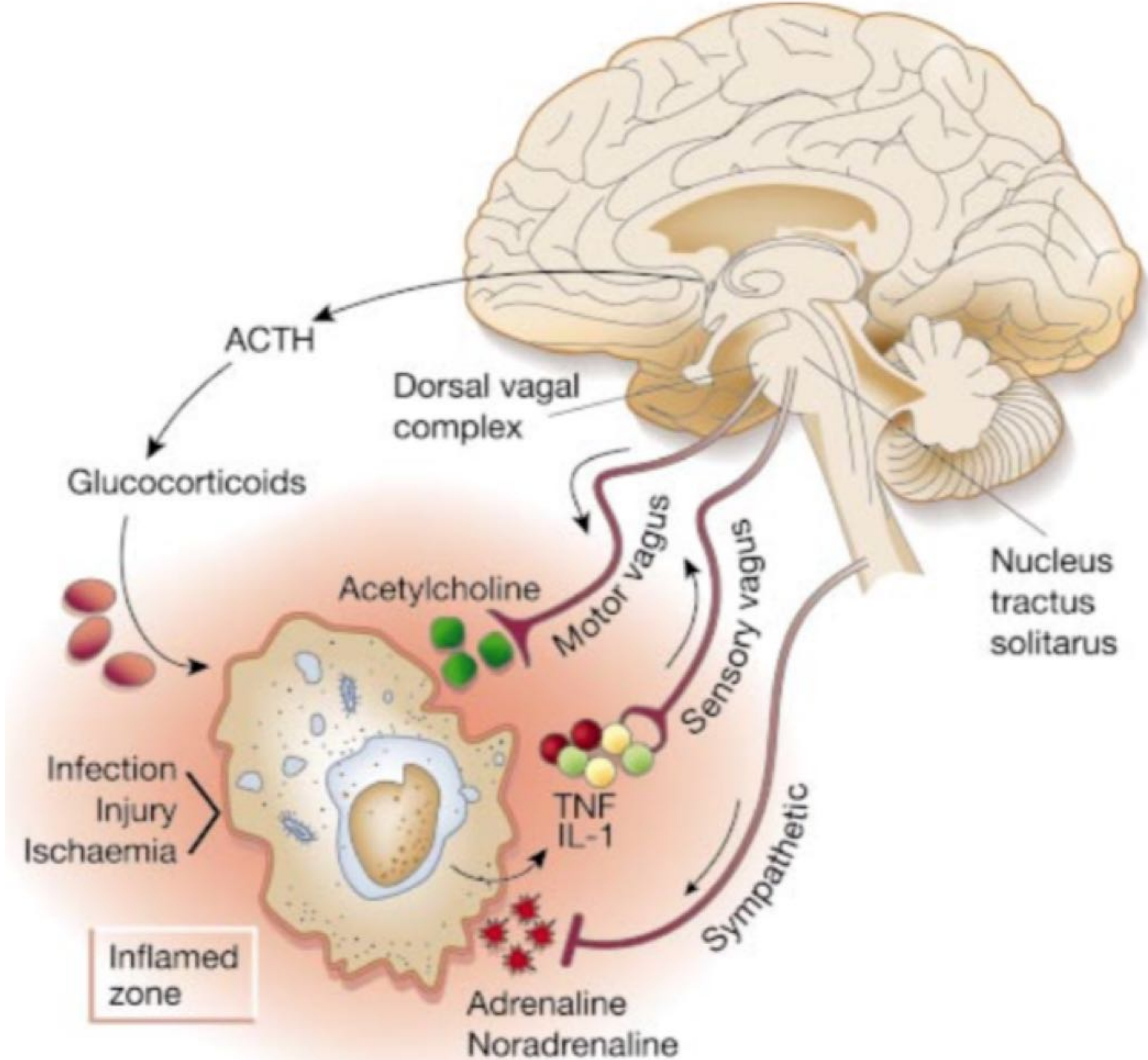
- **CNS neurons can also express and synthesize TNF and IL-1 (these cytokines can therefore participate in neuronal communication). This communication is bi-directional**: these cytokines can activate the HPA axis and the synthesis of glucocorticoids which in turn will suppress other cytokine syntheses

- **Cytokines produced by glial cells and astrocytes modify neuronal excitability** and contribute to the development of refractory pain (fibromyalgia, chronic pain syndromes) -> Glutamate +++; -> GABA ---: neurotoxicity

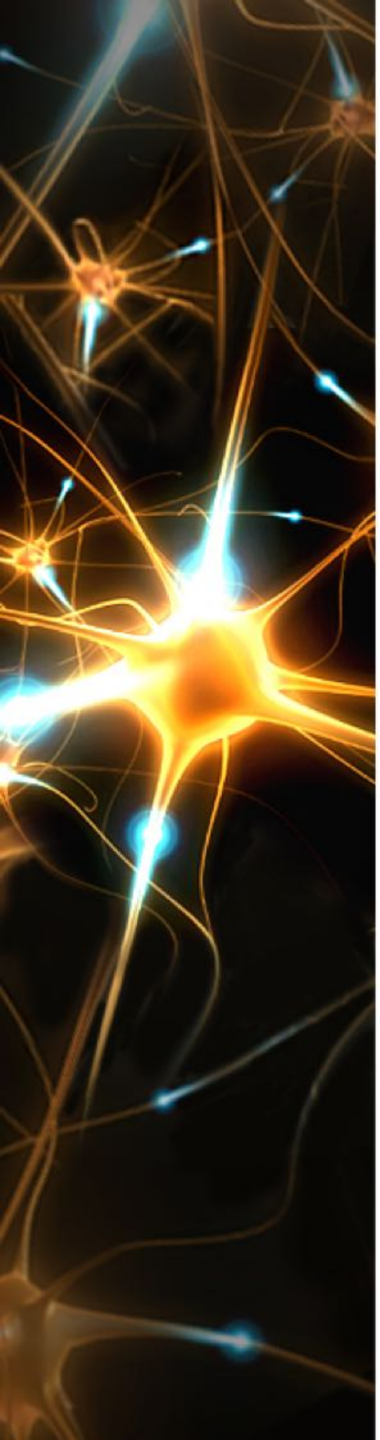
- The vagus nerve innervates major organs, including those containing the reticuloendothelial system (mono-nuclear phagocytic system). **Stimulation of the vagus nerve inhibits the synthesis of TNF produced by this system** (liver, spleen, heart, lungs, connective tissue).

- **Stress via the release of CRF (corticotropin release factor) at the para-ventricular nuclei of the hypothalamus is able to inhibit NDMV (vagal efferent) and stimulate the sympathetic system**. But chronic stress (eg depression) will overstimulate the HPA axis and cause an inadequate immune response -> autoimmune disease.

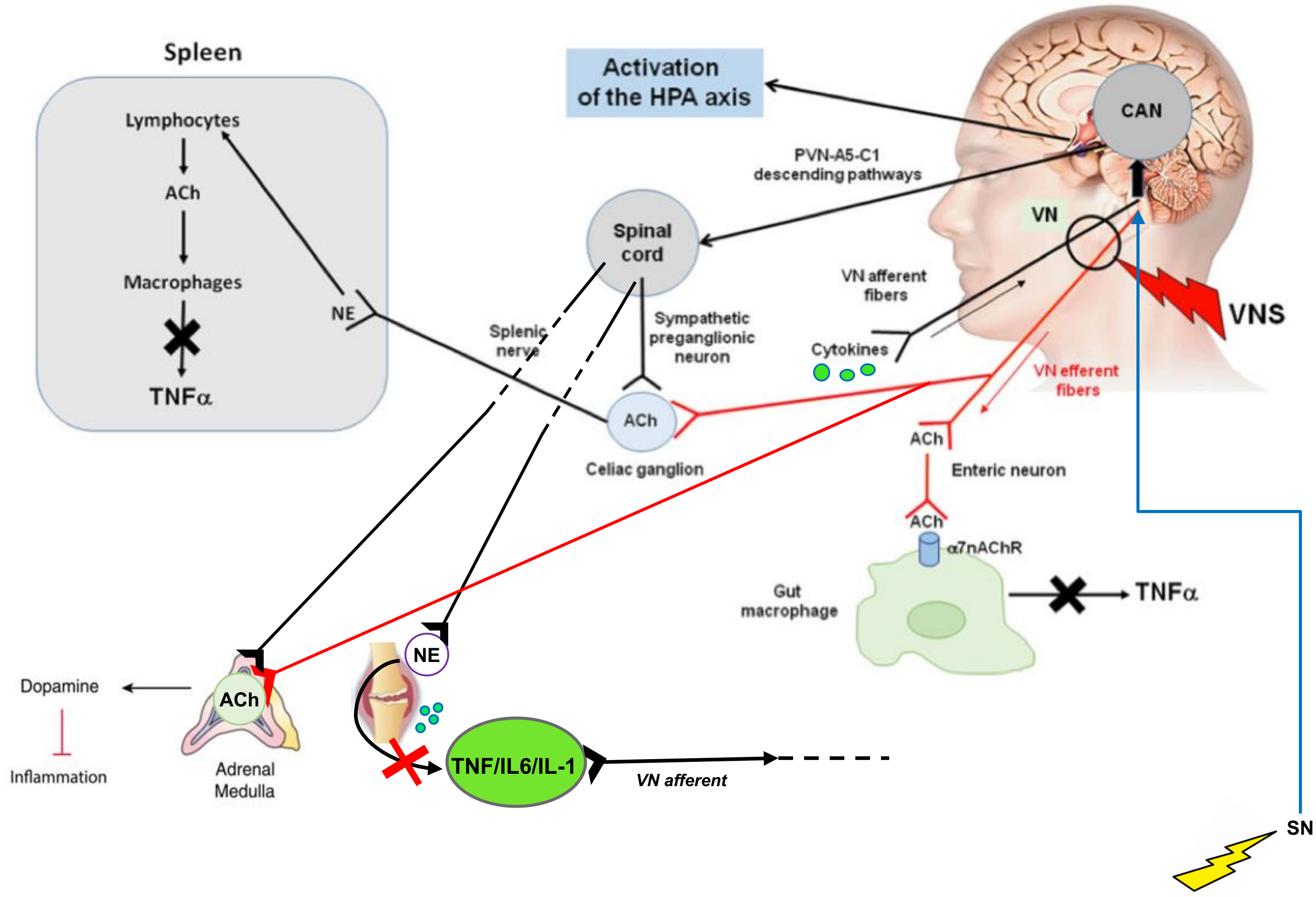




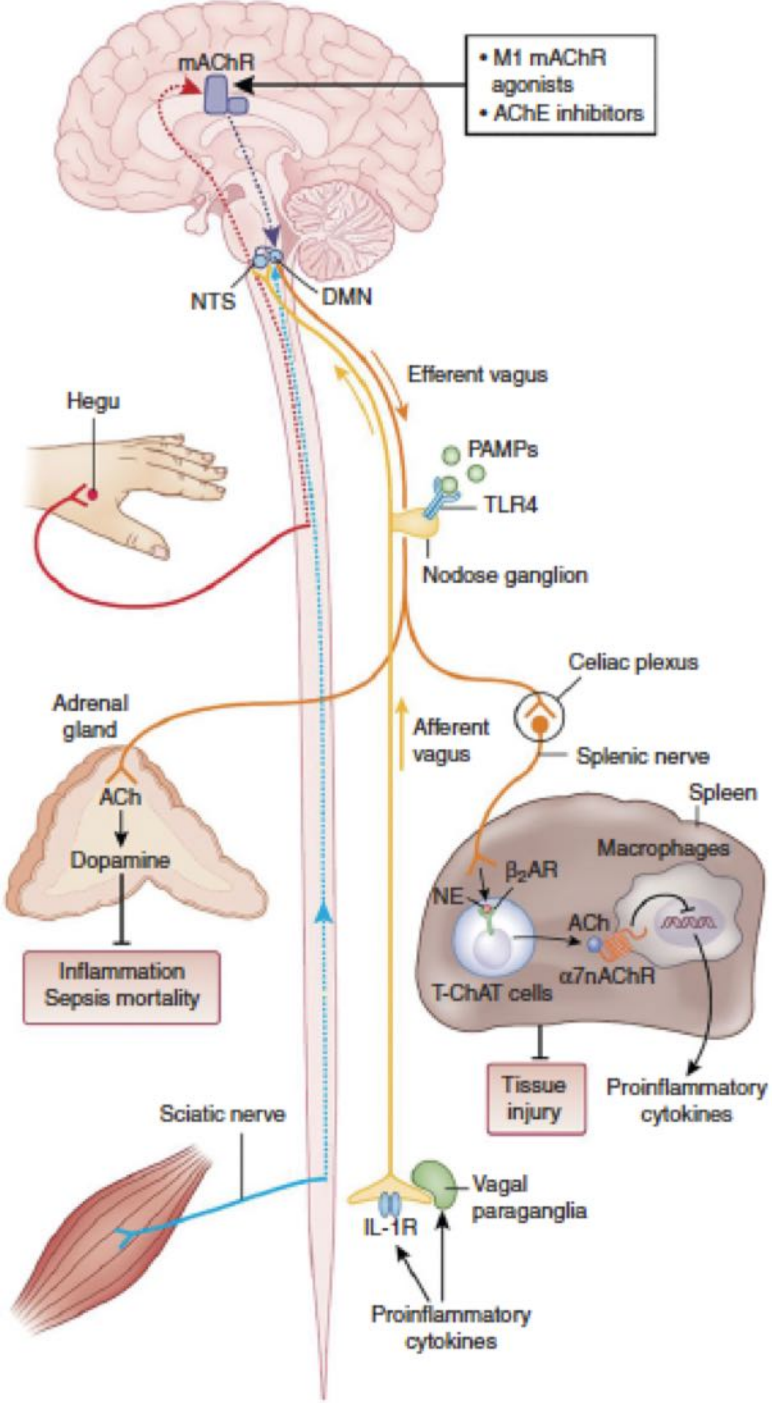
TNF, tumor necrosis factor; IL-1, interleukin-1. From Tracey (2017).



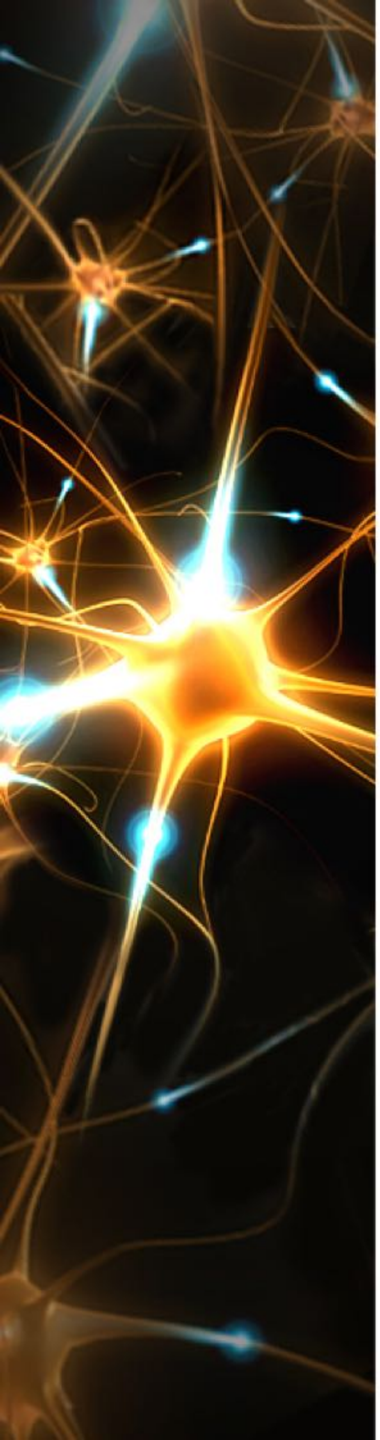
Summary of anti-inflammatory pathways targeted by ANS



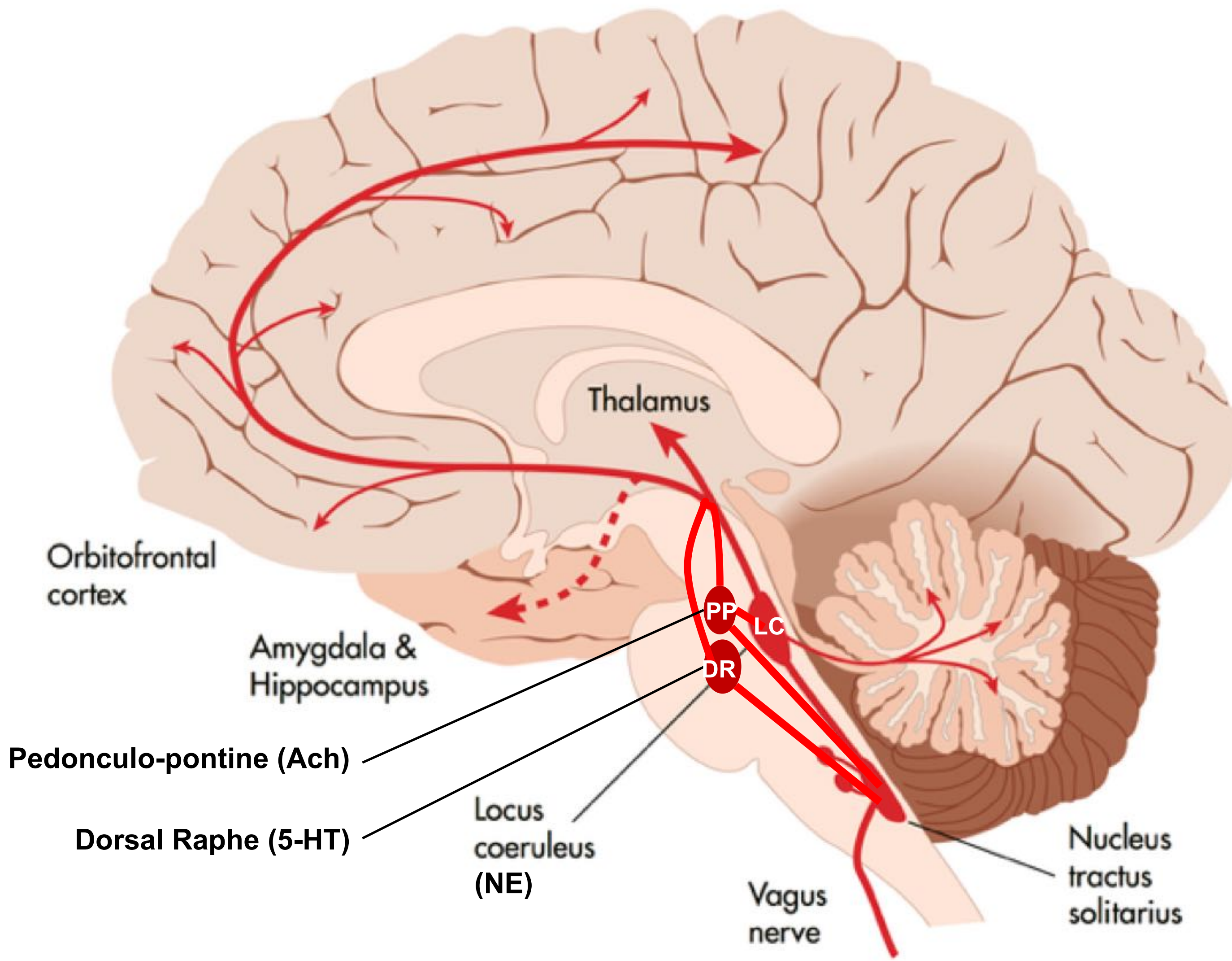
Ach, acetylcholine; TNFa, tumour necrosis factor-alpha; HPA, hypothalamic–pituitary– adrenal; VN, vagus nerve; SN, sciatic nerve; CAN, central autonomic network; a7nAChR, alpha7nicotinic acetylcholine receptor; NE, norepinephrine; EPI, epinephrine. Modified from Bonaz (2017), Chavan (2016) et Bassi (2017).

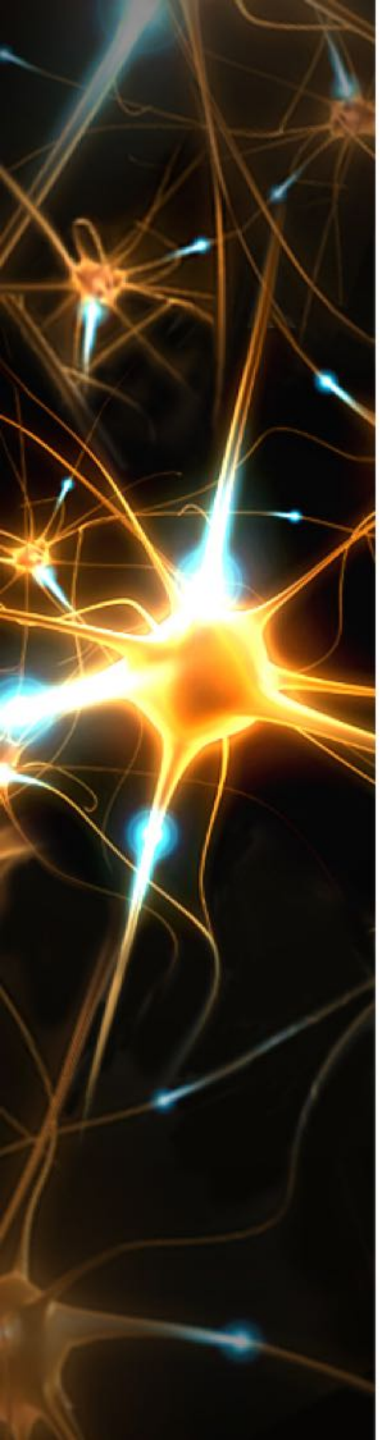


From Pavlov, V.A. 2019 - The inflammatory reflex.

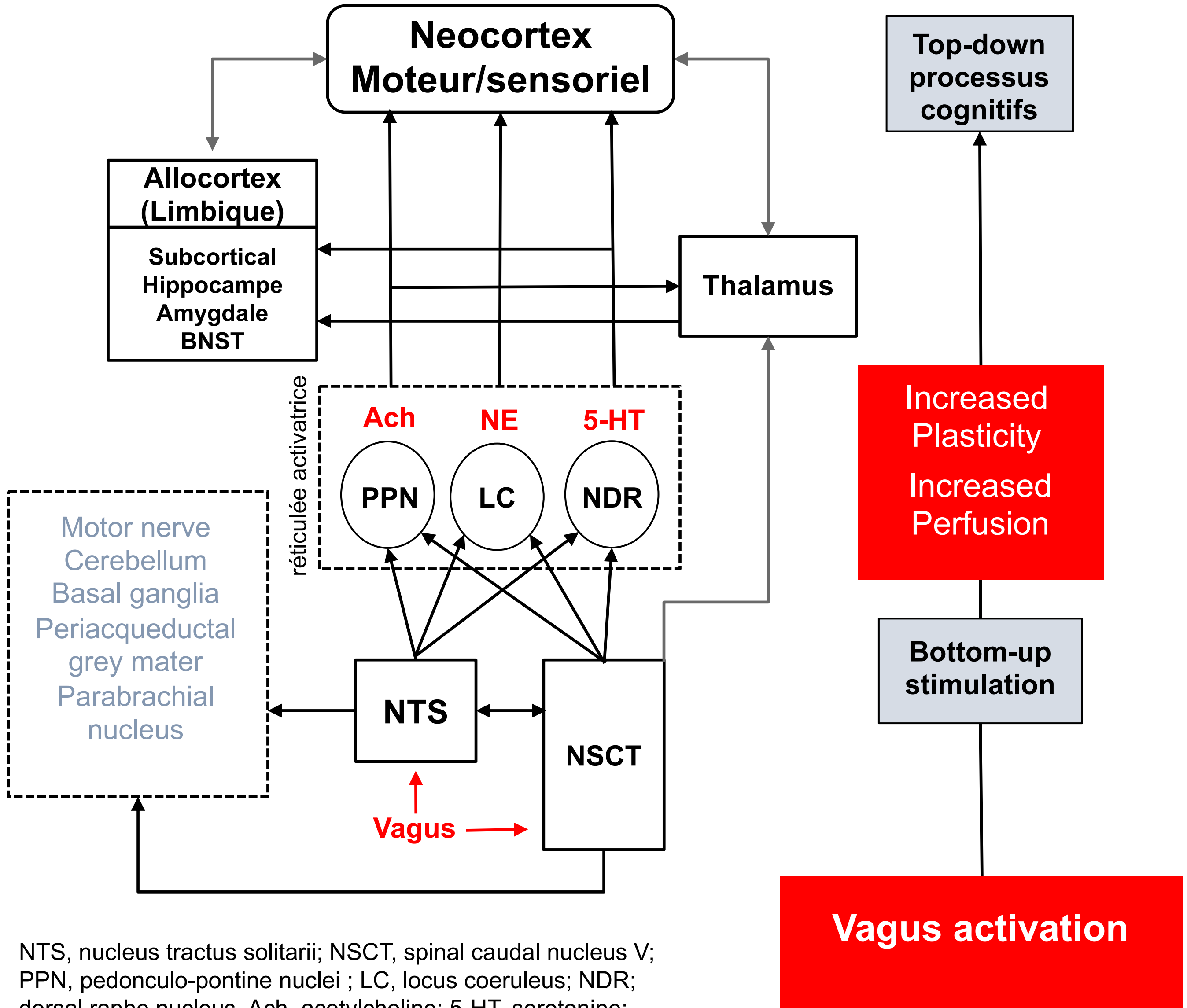


Central vagal projection from NTS

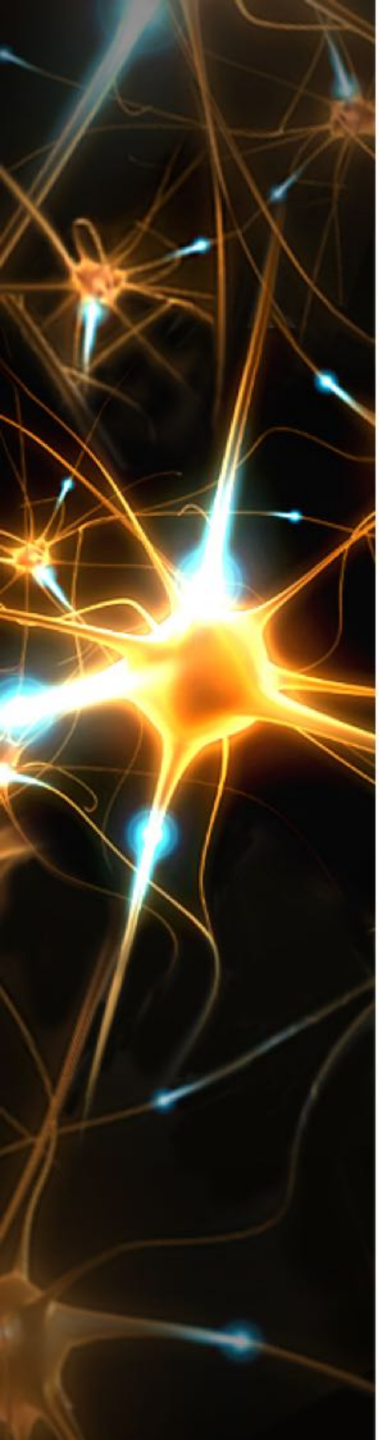


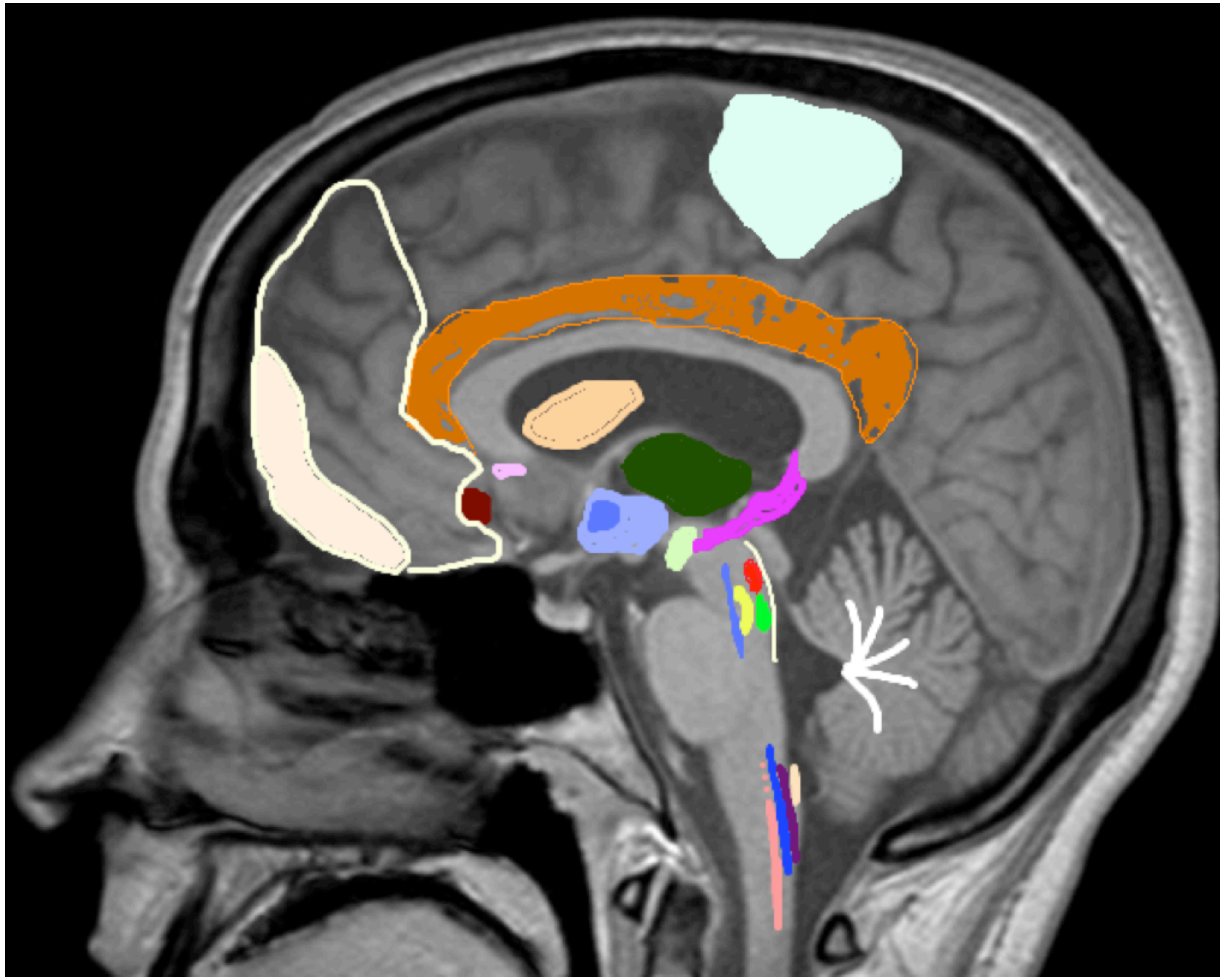


Central effects of vagal activation



NTS, nucleus tractus solitarii; NSCT, spinal caudal nucleus V; PPN, pedonculo-pontine nuclei ; LC, locus coeruleus; NDR; dorsal raphe nucleus, Ach, acetylcholine; 5-HT, serotonine; BNST; bed nucleus stria terminalis





NTS | LC | CB | PVH | NBM
DMV | DR | HIP | TH | CC
AP | PB | AMG | INS | PFC
SNT | PAG | HTH | NA | OFC
MPT | PCL

Vagus nerve projections

Common mechanisms that lead to disease, and in connection with the vagus nerve

- **Cardiovascular disease (CVD), cancer and Alzheimer's disease (AD) are common causes of death**

- The metabolic syndrome (MetS), a set of risk factors including obesity, hyperlipidemia, hyperglycemia and high blood pressure, can be considered as a disease as such (inducing a constant systemic inflammatory rate), but it is also a risk factor for the other three major diseases

- Question! Is there a common denominator related to the multiple underlying physiophatological mechanisms?

- Can we benefit from a simple, non-invasive and inexpensive method of analysis to identify people at risk and possibly prevent these diseases by a classical osteopathic approach?

I. <u>Why could the vagus nerve be the common denominator?</u>

1. **The weak activity of the vagus nerve (low tone) is a risk factor for diseases**, for example: CVD, cancer and AD.

2. Inadequate vagal activity acts as a risk factor for these diseases by exacerbating their underlying underlying mechanisms: inflammation, oxidative stress, and excessive sympathetic nervous system (SNS) activity.

3. **Vagal activity moderates and interacts with these underlying mechanisms** and with risk factors related to other diseases (eg diabetes) **by predicting the risk of these diseases**

These three basic mechanisms, oxidative stress and DNA damage, excessive inflammation, and excessive SNS activity play a crucial role in these diseases as well as in the metabolic syndrome (MetS)

a) Oxydative stress

- **Oxidative stress occurs when there is an imbalance between oxidants and antioxidants**, in favor of the first, a process leading to DNA damage, ex. coronary heart disease (LDL oxidation (low-density lipoprotein) -promising inflammation of atherosclerotic plaques of coronary arteries)

- **Oxidative stress is pivotal in the transformation of healthy cells into cancer cells as it contributes to DNA mutations**, especially if TK (tumor killer) and pro-oncogene genes are affected.

- **Oxidative stress** is also increased in cerebrovascular accidents and **can lead to DNA damage** in the brain tissue

- **Oxidative stress induces neuronal apoptosis** in Alzheimer's disease

b) Inflammation

- In CVD, particularly atherosclerosis, **inflammation leads to the recruitment and migration of immune cells (eg macrophages) to arterial lesions**. Inflammation induces the destabilization and the rupture of the plates, and the elevation of the arterial pressure.

- **Inflammation induces thrombosis In neo-cancer, inflammation prevents apoptosis** by inhibiting tumor suppressors (TK), and stimulates angiogenesis (eg via vascular endothelial growth factor) and then metastases

- **In Alzheimer's disease, inflammation may mediate the negative effects of β-amyloid peptide peptides on brain neurons**, leading to neurodegenerescence

Inflammation, when excessive in magnitude and time, is a major factor contributing to the onset of multiple chronic and autoimmune diseases

c) Excessive sympathetic activity

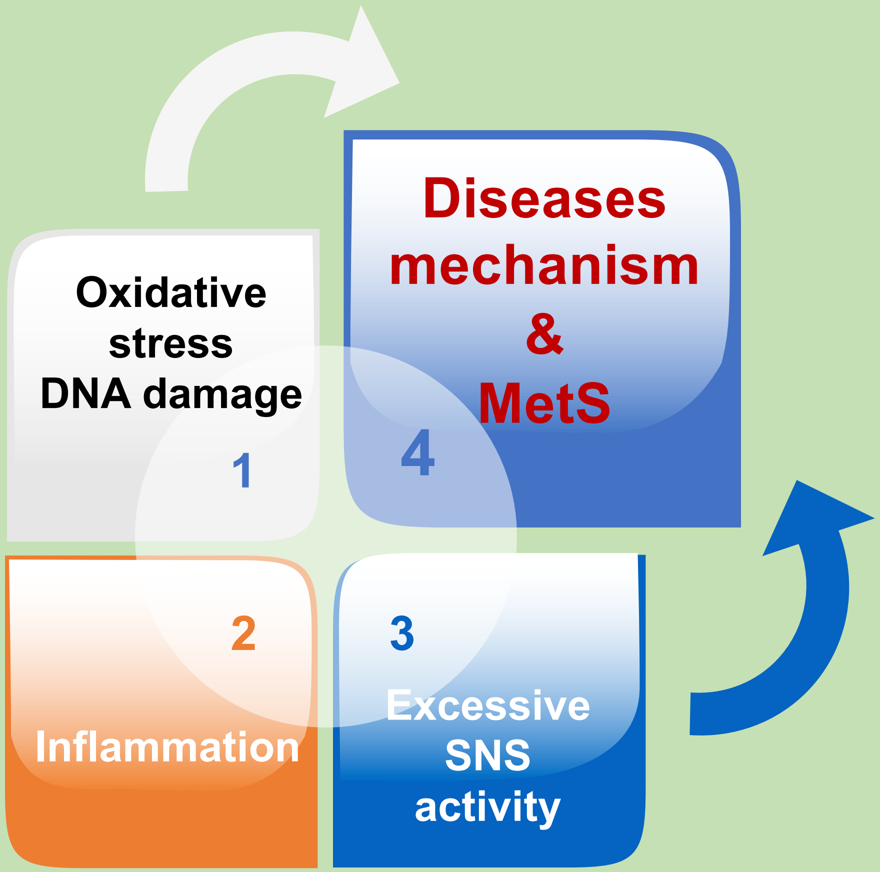
- In CVD, **SNS activity contributes to vascular wall damage due to increased vasoconstriction**, increased BP, and ultimately to atherosclerotic and ischemic processes.

- In cancer, **the excessive release of sympathetic neurotransmitters (NA) induces angiogenesis and influences the metastatic process**, and their blockage can slow down this process.

- In Alzheimer's disease, **cerebral blood flow is decreased, probably due to excessive SNS activity** (which is countered by Ach agonist medications).

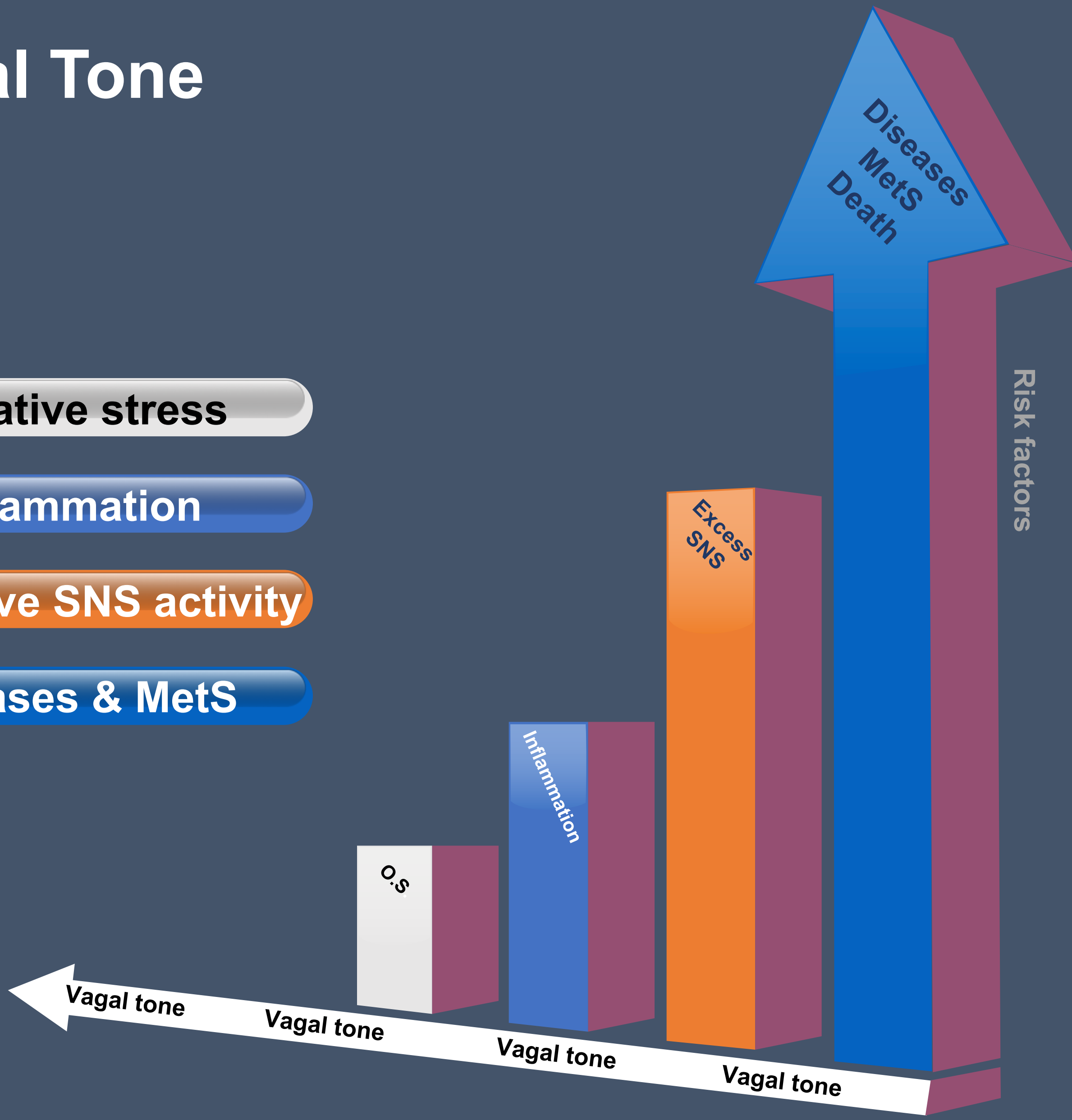
Oxidative stress and DNA damage, inflammation and excessive SNS activity contribute to the development of inter-related diseases, such as: hypertension, dyslipidemia and diabetes, which are themselves risk factors for CVD, cancer and Alzheimer's disease

These diseases may peak in the MetS, other risk factors for these diseases


Oxidative stress
DNA damage
1
Diseases mechanism
&
MetS
4
2
Inflammation
3
Excessive SNS activity

Vagal Tone

1. Oxidative stress
2. Inflammation
3. Excessive SNS activity
4. Diseases & MetS



B. Conclusion

- THE VAGUS NERVE MODULES THE PHYSIOPATHOLOGICAL MECHANISMS CONTRIBUTING TO THE DEVELOPMENT OF DISEASES
  - ✓ Vagus Nerve Stimulation (VNS) Reduces Oxidative Stress and Particularly Defragmentation of DNA in CVDs
  - ✓ Acetylcholine agonist inhibits cell proliferation and increases levels of TK proteins in experimental studies
  - ✓ Vagotomy or capsaicin-induced denervation stimulates cancerous metastases
  - ✓ Anti-inflammatory drugs that activate the vagus nerve (altering substance level P) reduce tumor growth in a model of breast cancer in mice
  - ✓ High vagal activity significantly moderates the prostate-specific antigen (PSA) effects in affected patients

II. VAGAL ACTIVITY INTERACTS WITH PHYSIOPATHOLOGICAL MECHANISMS AND RISK FACTORS PREDICTING DISEASE

- ✓Low vagal activity can also interact with genetic and environmental factors, which may explain why, in people with the same vagal activity, some will develop AD, while others will develop cancer or CVD.

- ✓Low vagal activity potentiates the effects of CRP in the prognosis of myocardial infarction.

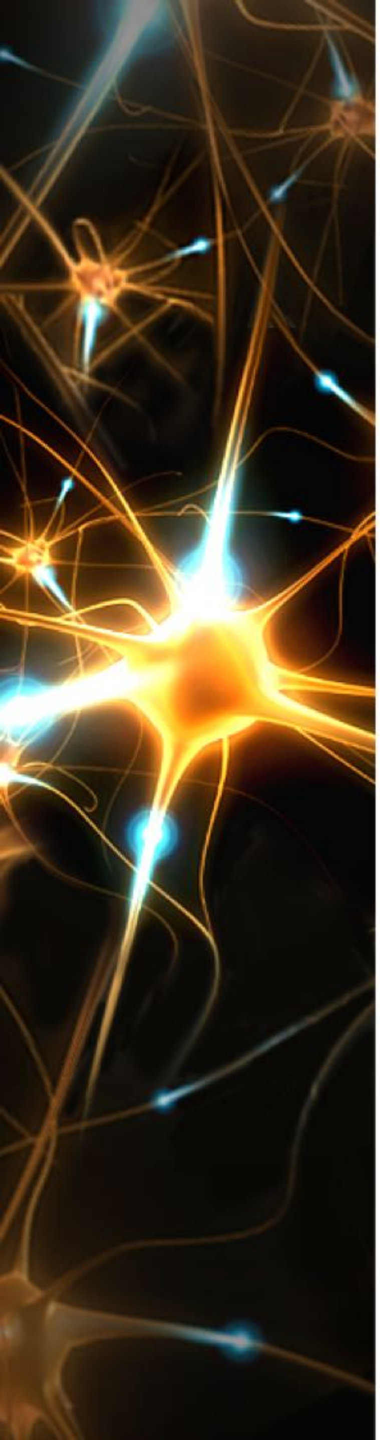
- ✓It is however possible to have a risk factor, ex. hypertension, and to have normal vagal activity, probably because the risk factor may have other origins, such as, genetic, environmental or other acute illness

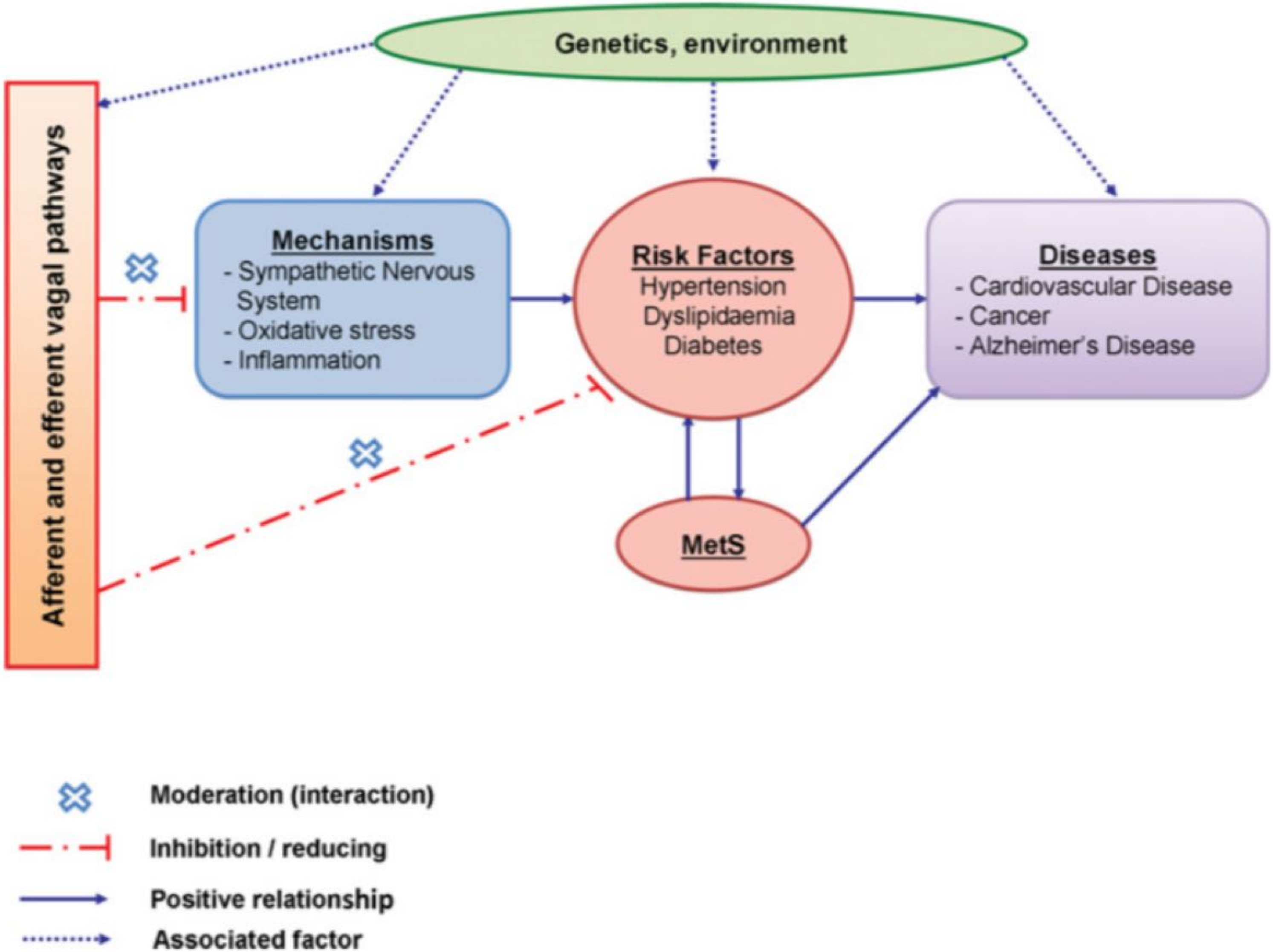
- ✓Low vagal tone is associated with depressive and anxiety disorders. Depression is a risk factor for prostate cancer and metastasis via sympathetic signaling

- ✓Hyper activation of SNS can modulate gene expression programs by stimulating macrophage infiltration, inflammation, angiogenesis, tumor invasion and by inhibiting immune cell responses and inhibiting apoptosis -> promoting metastasis of solid tumors

III. ADEQUATE VAGUE ACTIVITY PREDICTS RISK REDUCES DISEASES AND ENHANCES PROGNOSIS

- Low vagal activity may be a risk factor for disease and poor prognosis
- The efferent vagal activity can be easily assessed by analysis of the variability of heart rate (HRV)
- HRV is inversely correlated with the risks of, and poor prognosis of CVD
- HRV is positively correlated with longevity in case of cancer
- HRV is positively correlated with better cognitive performance in AD patients
- Vagal activity is inversely related to the presence of Mets components, the risk of developing Mets and other risk factors (diabetes, hypertension, etc.)
- Specific osteopathic treatment to help restoring sympatho-vagal balance in dysautonomia or when the sympathetic activity is abnormal and parasympathetic too weak





Mets, metabolic syndrome. From De Couck (2012).

4. Heart-brain axis

- The heart has its own brain (intrinsic cardiac nervous system): +/- 40,000 neurons - the intelligence of the heart (nodal tissue: sinus node, atrio-ventricular node, AV or His bundle, Purkinje network)

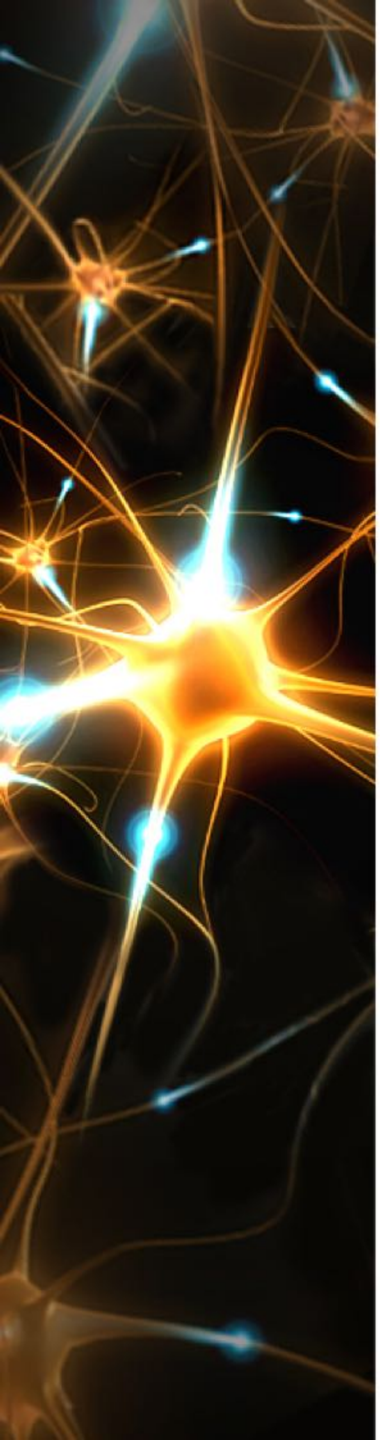
- The nodal tissue ensures heart autonomy

- The heart-brain connection has been known for several centuries. For example, syncope and sudden death after strong emotions and stressors

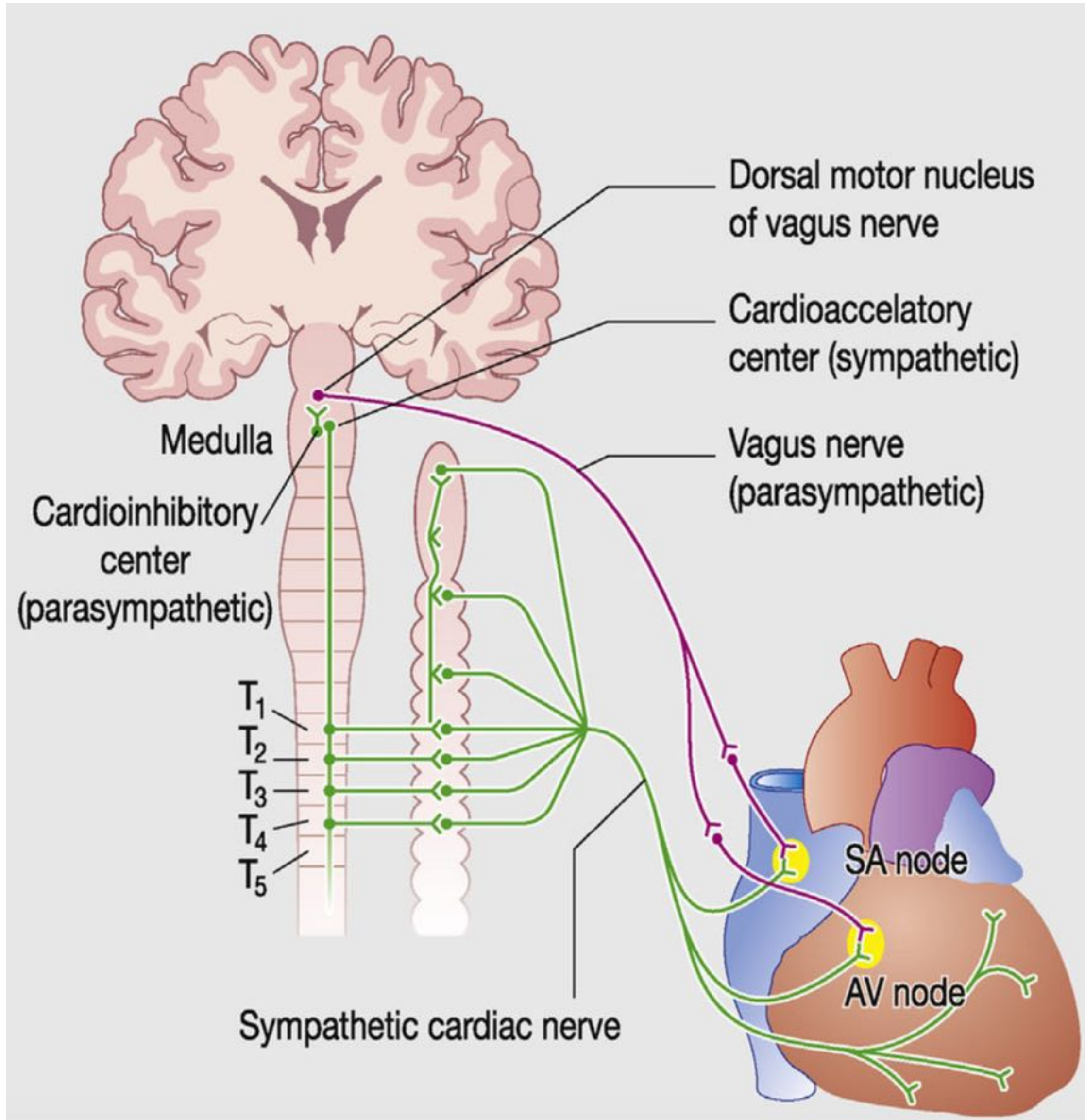
- Homeostatic processes are mediated by the SNA and endocrine system and coordinated by the CNS (Cannon 1930). Cannon notes that deaths due to strong emotions are probably related to the hyper activity of the sympathetic system.

- The heart-brain axis can be considered by: the effects of cardiovascular diseases on the nervous system (myocardial infarction affecting the limbic system and the cerebral trunk -> depression / sleep disorder); the effects of neurological disorders on the cardiovascular system (cardiomyopathic stress after subarachnoid haemorrhage).

- Cortical and subcortical networks implicated in the activity and control of cardiovascular function: the orbito-frontal cortex, the cingulate cortex, the insula, the amygdala, the hyppocampus, the hypothalamus, the bed nucleus of the stria terminalis, the periaqueductal gray, the parabrachial region, the NTS and the ventrolateral spinal cord region.



Heart innervation



- The amygdala plays a central role: receives inhibitory projections from the pre-frontal and orbito-frontal areas and is connected to the hypothalamus and lower (subtectal) nuclei involved in the control of cardiac function.

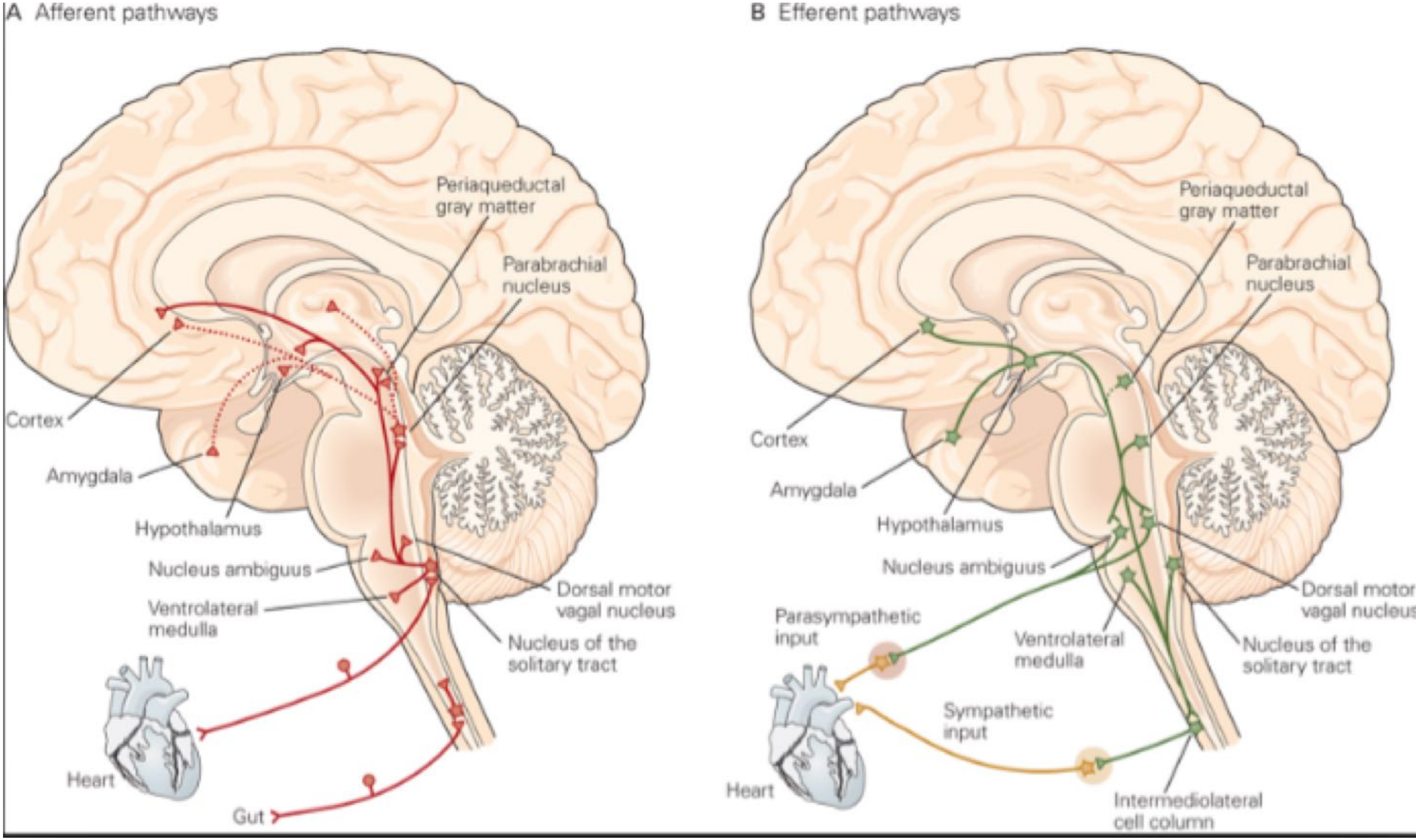
- The amygdala modulates the effects of (negative) emotions on the heart.

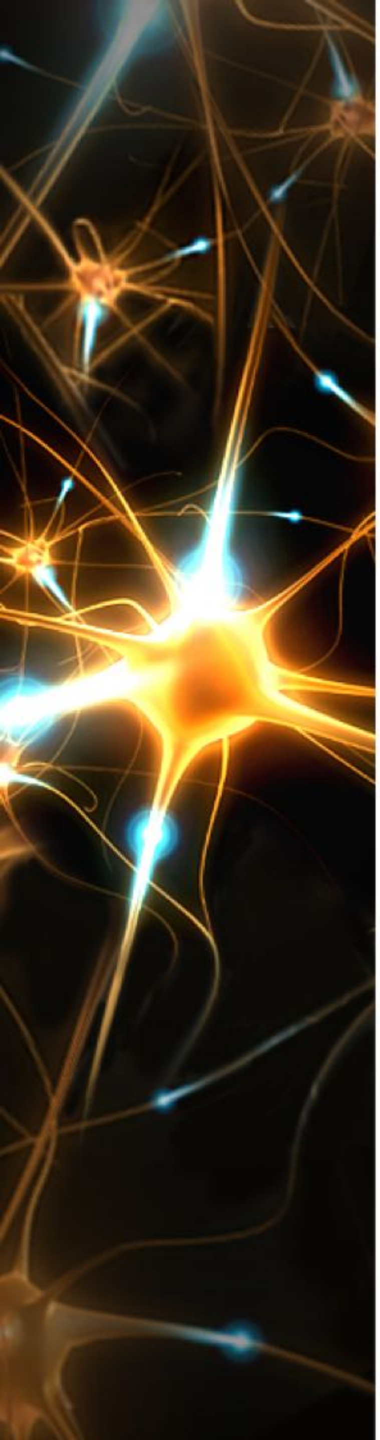
- The hypothalamus plays an essential role in the transmission of autonomous information from the higher cortical centers to the medullary subtectal regions (solitary tract nucleus, periaqueductal gray, parabrachial nuclei, rostral ventrolateral medual (RVLM), and the back motor nucleus of the X (DMN)

- The nucleus of the solitary tract receives haemodynamic information from vagal afferents and sends inhibitory or stimulatory responses to the ventrolateral medullary rostral nucleus (RVLM) to the NA and the motor dorsal nucleus of the X (DMN) -> modulation of sympathetic / parasympathetic activity (reflexes with / without superior control).

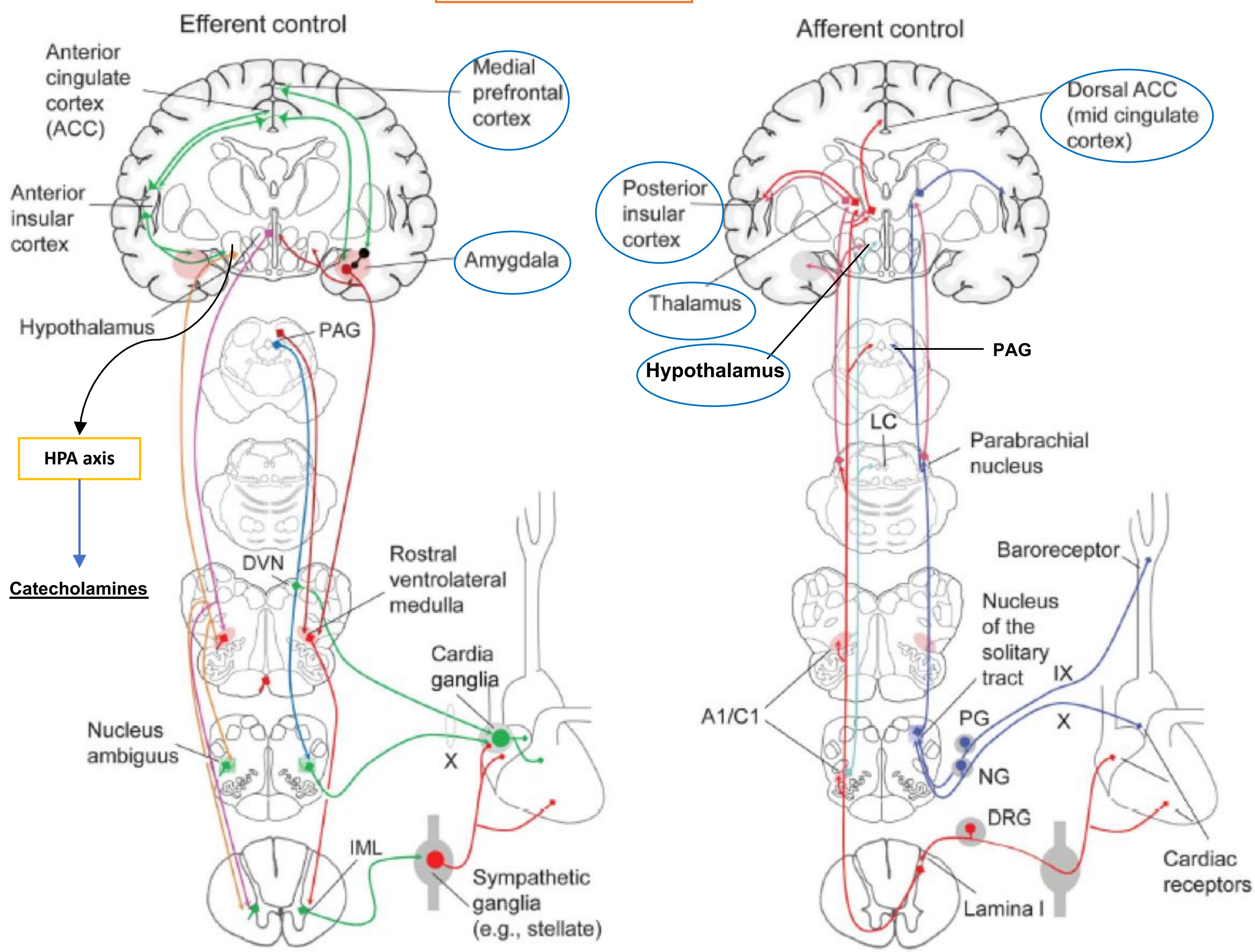
- The balance between sympathetic / parasympathetic activity also depends on coronary and myocardial neuromodulators (Renin-angiotensin II system), common co-transmitters (Vasoactive Intestinal peptide, NO), baroreceptors, substance P release (medulla posterior horn). calcitonin gene-related peptide (CGRP) (protective action)

- Afferent fibers via the X and IX nerves project into the central autonomic network (solitary tract nucleus, parabrachial nucleus, locus coeruleus, periaqueductal gray, thalamus, amygdala, hypothalamus, cortex).

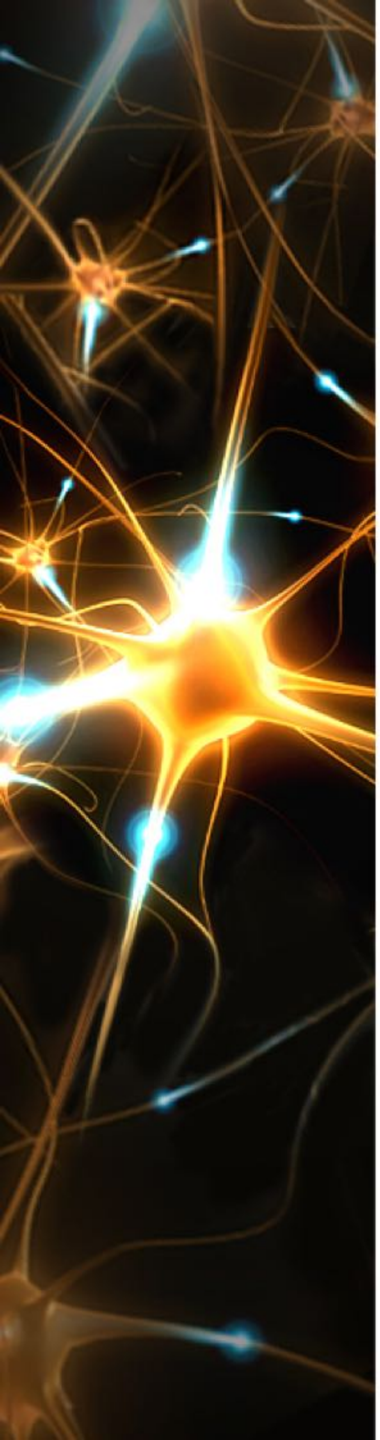

A Afferent pathways
Periaqueductal gray matter
Parabrachial nucleus
Cortex
Amygdala
Hypothalamus
Nucleus ambiguus
Ventrolateral medulla
Dorsal motor vagal nucleus
Nucleus of the solitary tract
Heart
Gut
B Efferent pathways
Periaqueductal gray matter
Parabrachial nucleus
Cortex
Amygdala
Hypothalamus
Nucleus ambiguus
Dorsal motor vagal nucleus
Parasympathetic input
Ventrolateral medulla
Nucleus of the solitary tract
Sympathetic input
Heart
Intermediolateral cell column



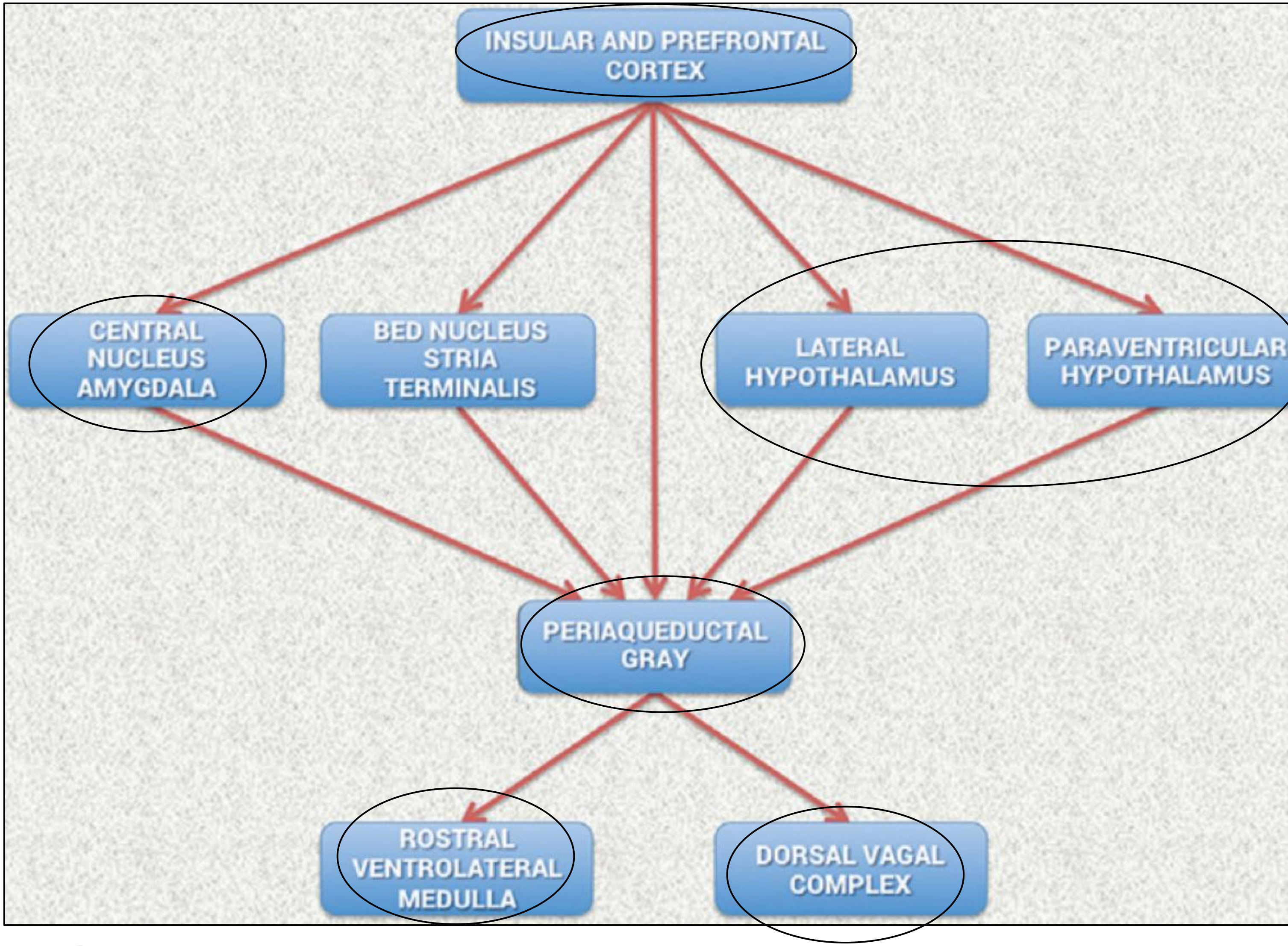
Axe cœur-cerveau



X, vagus nerve; IML, intermedio-lateral; DVN, dorsal vagal nucleus; PAG, periaqueductal grey; A1/C1, cathecholaminergic A1/C1 neurons; DRG, dorsal root ganglia; IX, glossopharyngeal nerve; NG, nodose ganglia; PG, petrose ganglia; LC, locus coeruleus. Modified from Palma et Benarroch (2014)



Cortical, subcortical and truncular structures involved in cardiac regulation (schematically from top to bottom)

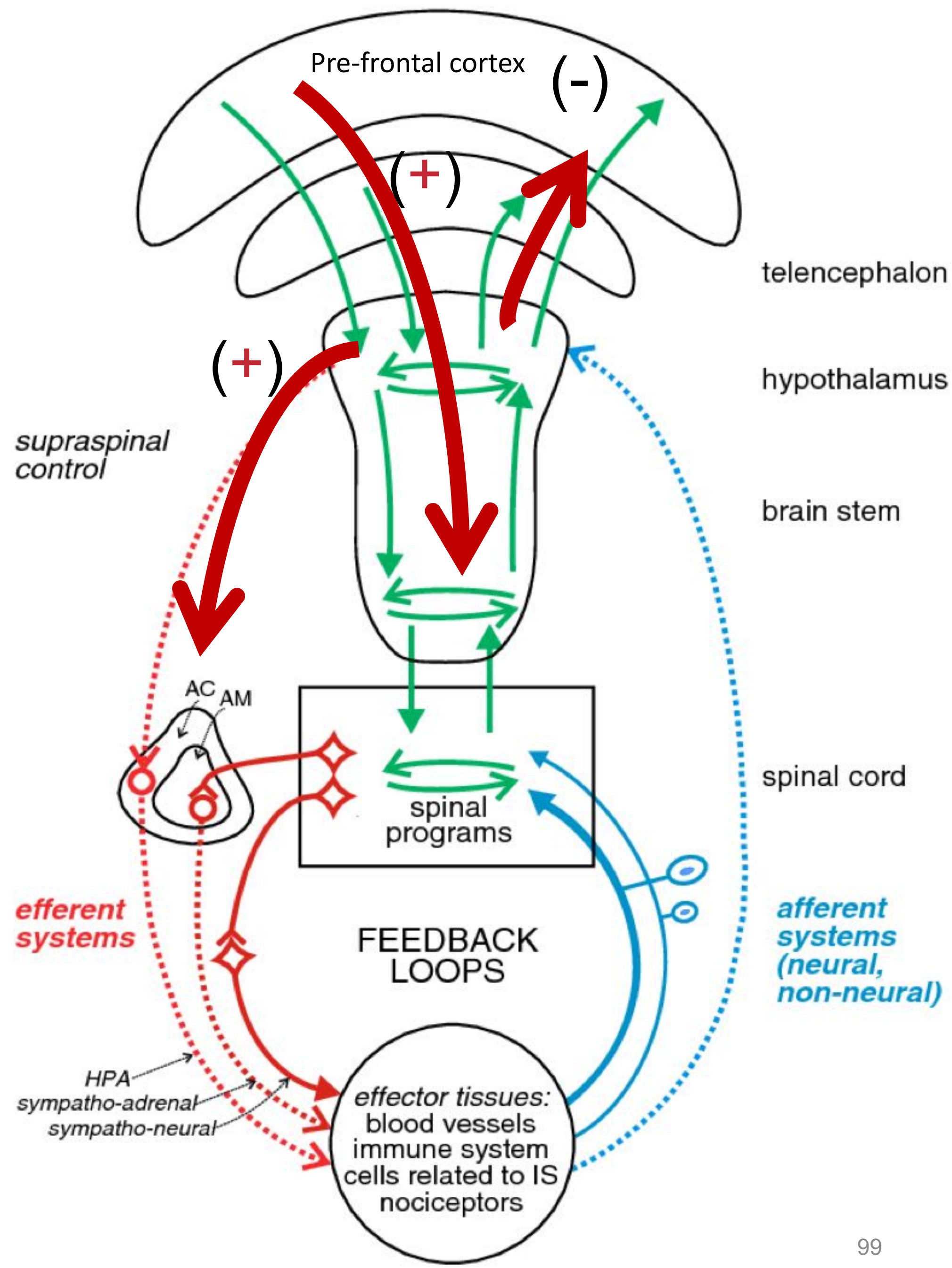


: regions involved in rhythm disorders

From Oppenheimer et Hopkins (1994)

Inhibition of pre-frontal cortex will stimulate SNS activity+++

Sympathetic outflow



Scheme for the feedback loops between the spinal cord and brain stem on one side and the effector tissues involved inprotective body reactions on the other side. Effector tissues (blood vessels, immune tissue, cells related to the immune system [IS], nociceptors) are modulated by the sympatho-neural, the sympatho-adrenal and the hypothalamopituitary-adrenal (HPA) systems. Adapted from Janig,W. 2011.

5. GUT-Brain axis

- Enteric nervous system (ENS): Submucous and myenteric nervous plexus: 100-500 million neurons = spinal cord neurons but 2 to 10x more glial cells (plasticity: neuron survival, neuronal function regulation, regeneration)

- 3 entrance gates to the SNC: bi-directional connection 1-2) with the sympathetic and parasympathetic nervous system (+ vagus nerve) and, 3) circumventricular organs (CVOs)

- Digestive tract (GIT) = mucosa, submucosa, muscularis and serosa, The GIT wall contains the intrinsic nervous system (all along Tract)

- ENS: driving autonomy and secrecy of GIT

- ENS abnormalities in Parkinson's disease: Digestive disorders < Neurological disease via the vagus nerve (idem Autism, Alzheimer)

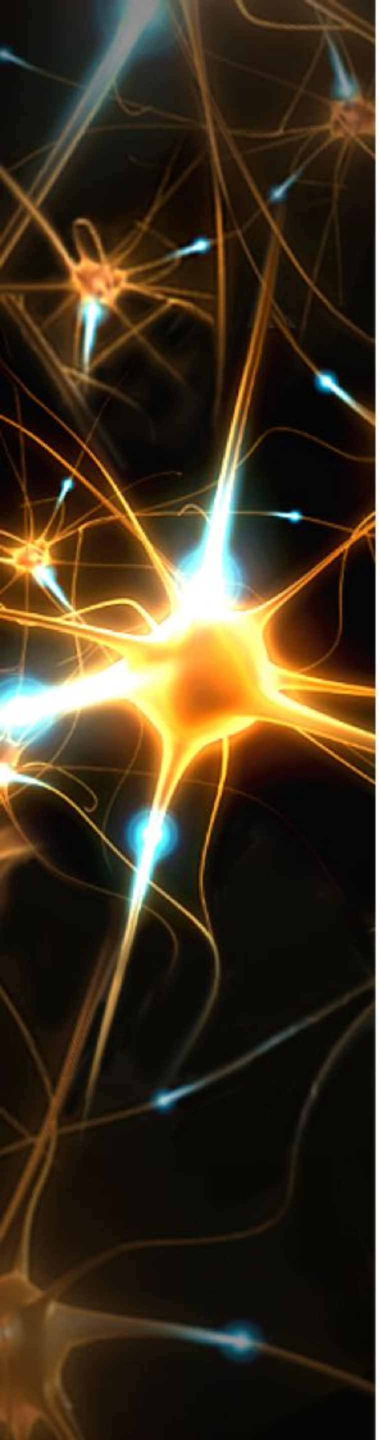
- Disruption of this axis in GIT pathologies (IBS, IBD, gastroparesis, gastritis, gastroesophageal reflux disease, infections, bio-psychosocial diseases)

- Connection with sympathetic (splanchnic nerves) + parasympathetic (vagus + S2-S4)

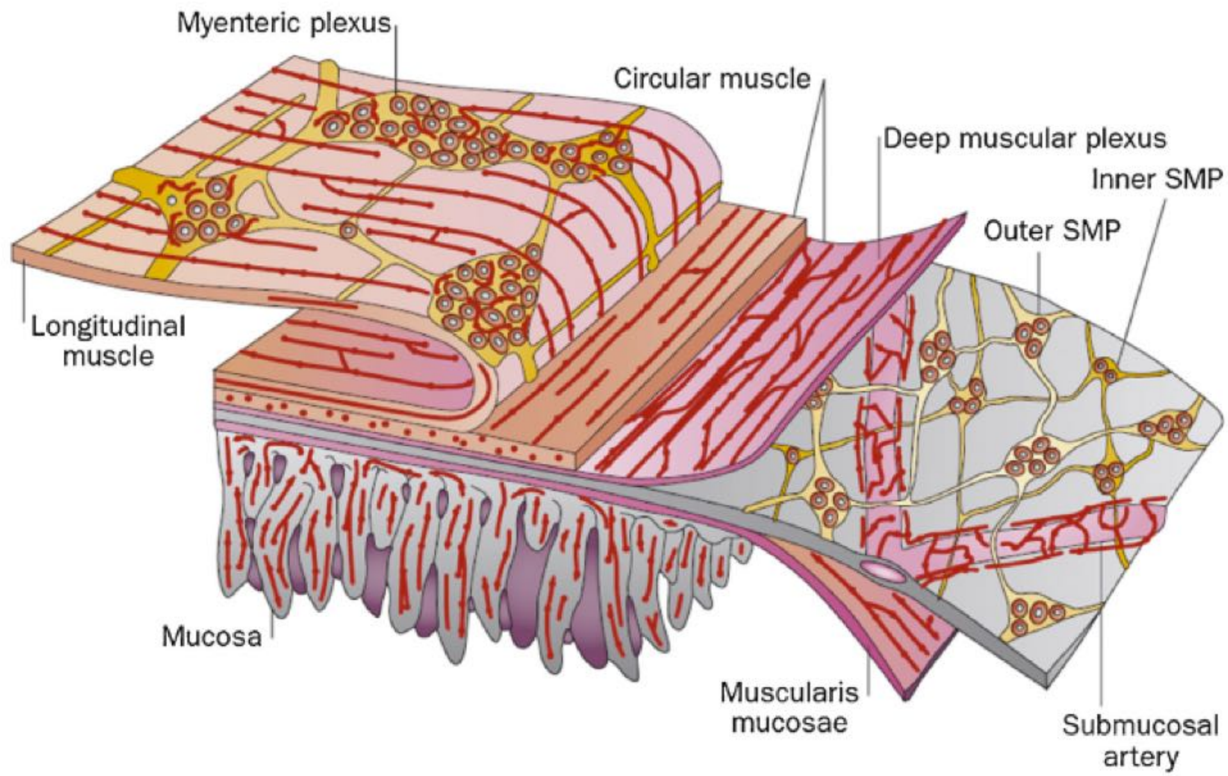
- Sympathetic afferent: ways of visceral pain. Parasympathetic afferent: non-painful digestive sensations (satiety, non-painful distension)

- 1st vagal efferent neuron: NDMV -> post-ganglionic cholinergic neuron in the digestive tract

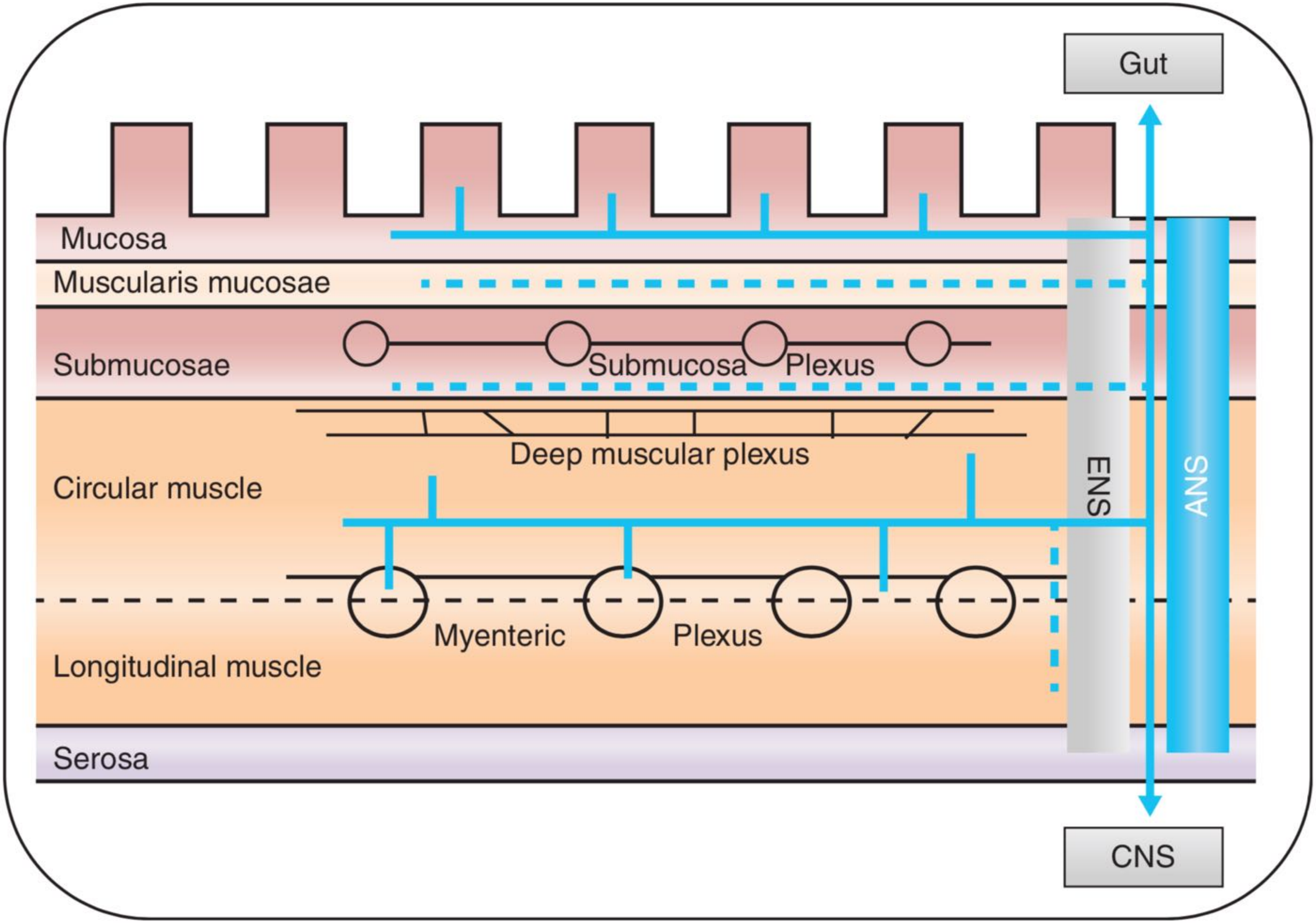
- 1st sympathetic efferent neuron: zone IML medulla (T6-T12) -> neuron postganglionic adrenergic (celiac ganglion, mesenteric ganglia, sup or inf.)

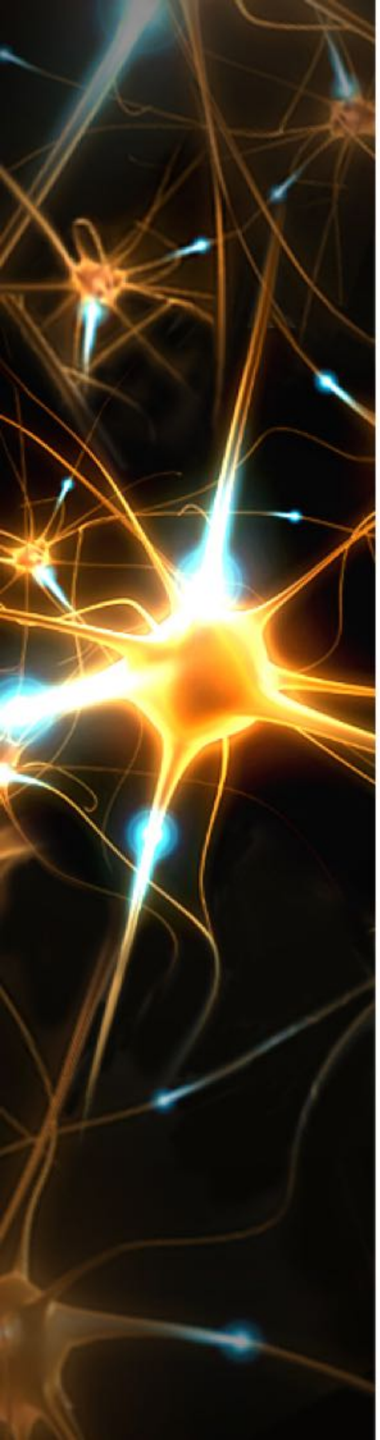


Digestive tract layers

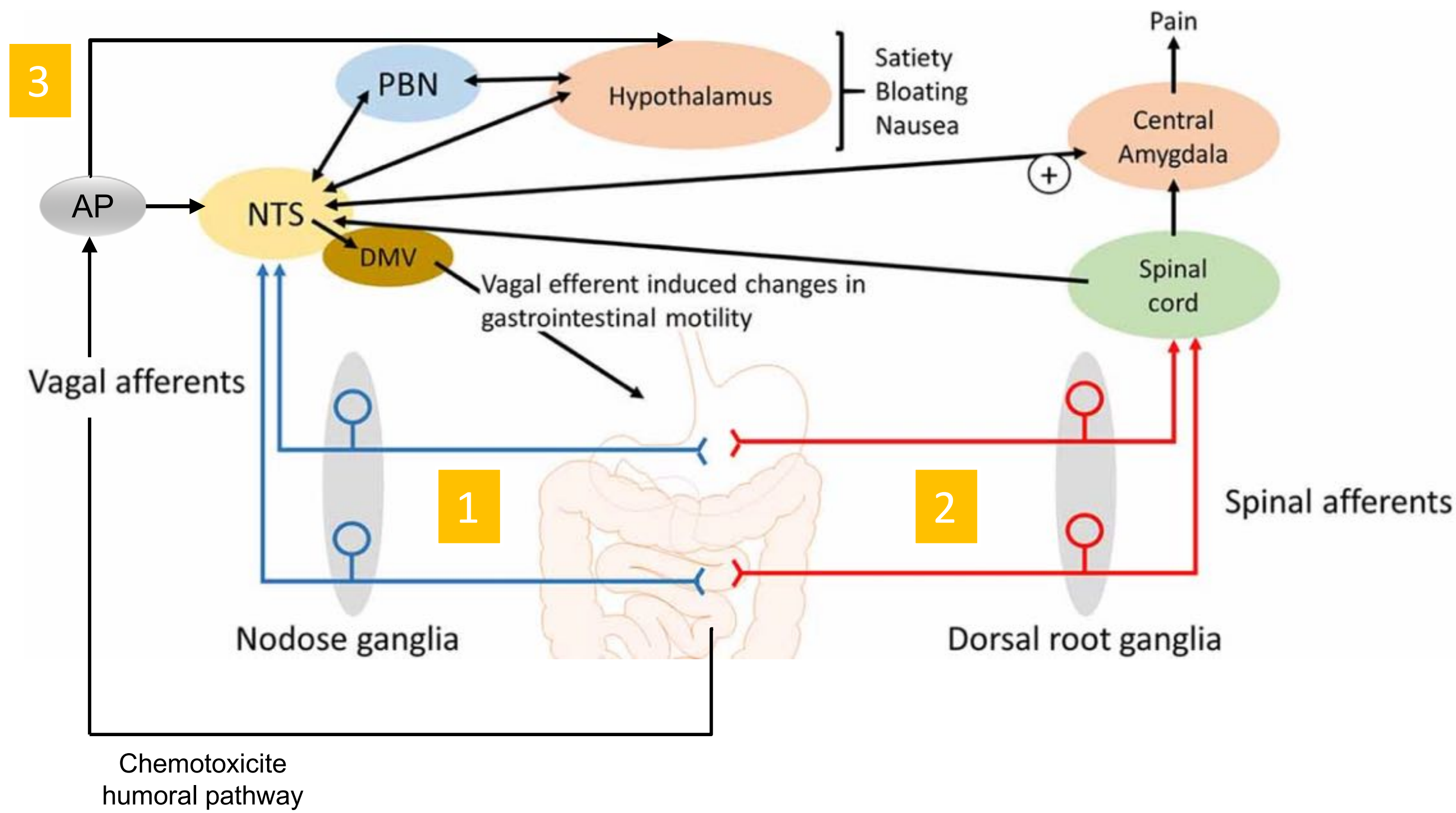


SMP; sub mucosal plexus. From Bonaz et Pellissier (2013)


Gut
Mucosa
Muscularis mucosae
Submucosae
Submucosa
Plexus
Deep muscular plexus
Circular muscle
Myenteric
Plexus
Longitudinal muscle
Serosa
ENS
ANS
CNS

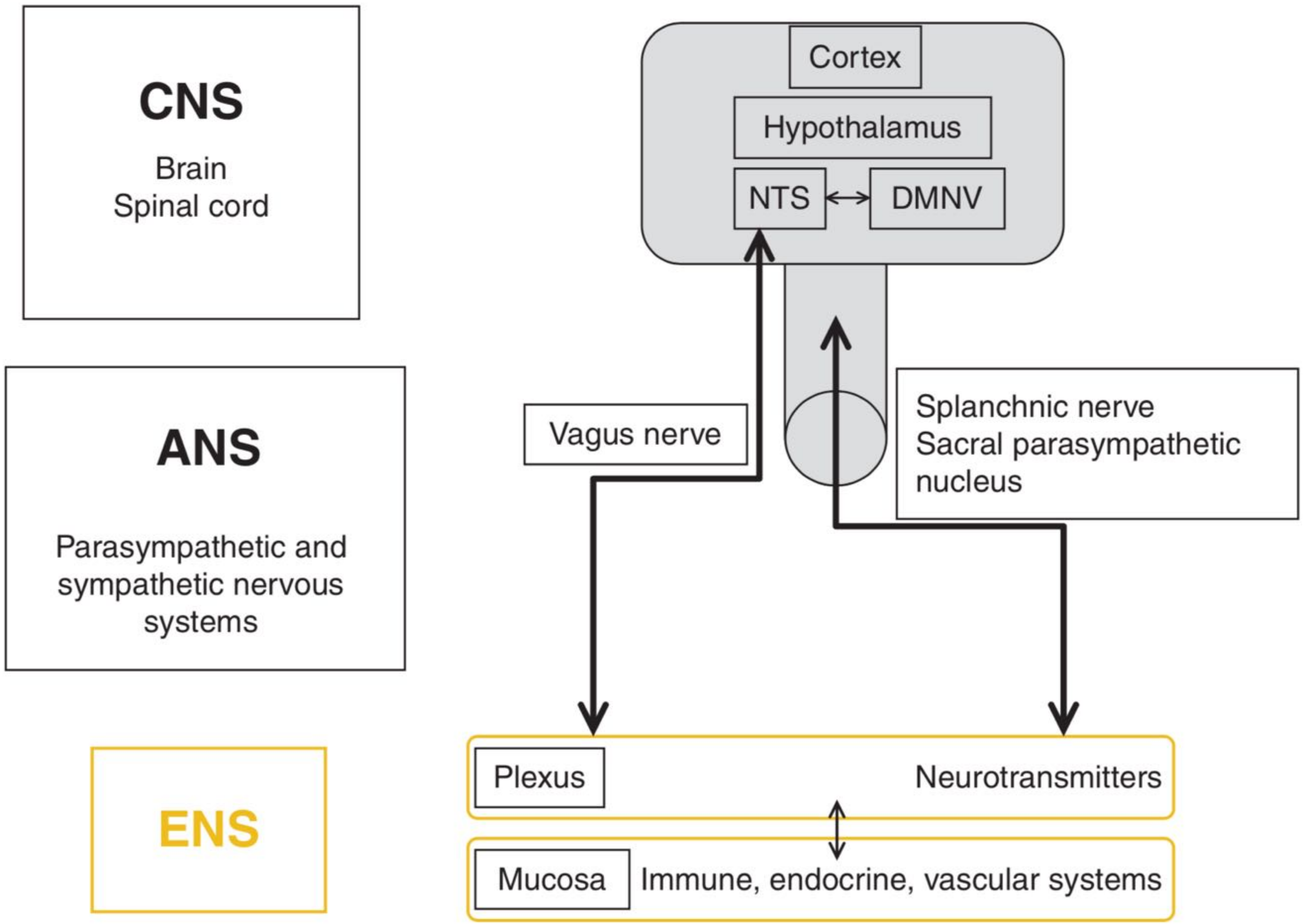


Gut-brain communication (main centers)



1. Vagus nerve; 2. sympathetic; 3. circumventricular organs

Brain–gut axis



- The vagus nerve innervates the digestive tract to the left colic angle. The rest is innervated by the parasympathetic (sacral nerves of S2-S4)

- The vagal afferences end in the NTS

- Sympathetic afferent terminate at the spinal level (cell body in posterior spinal ganglion)

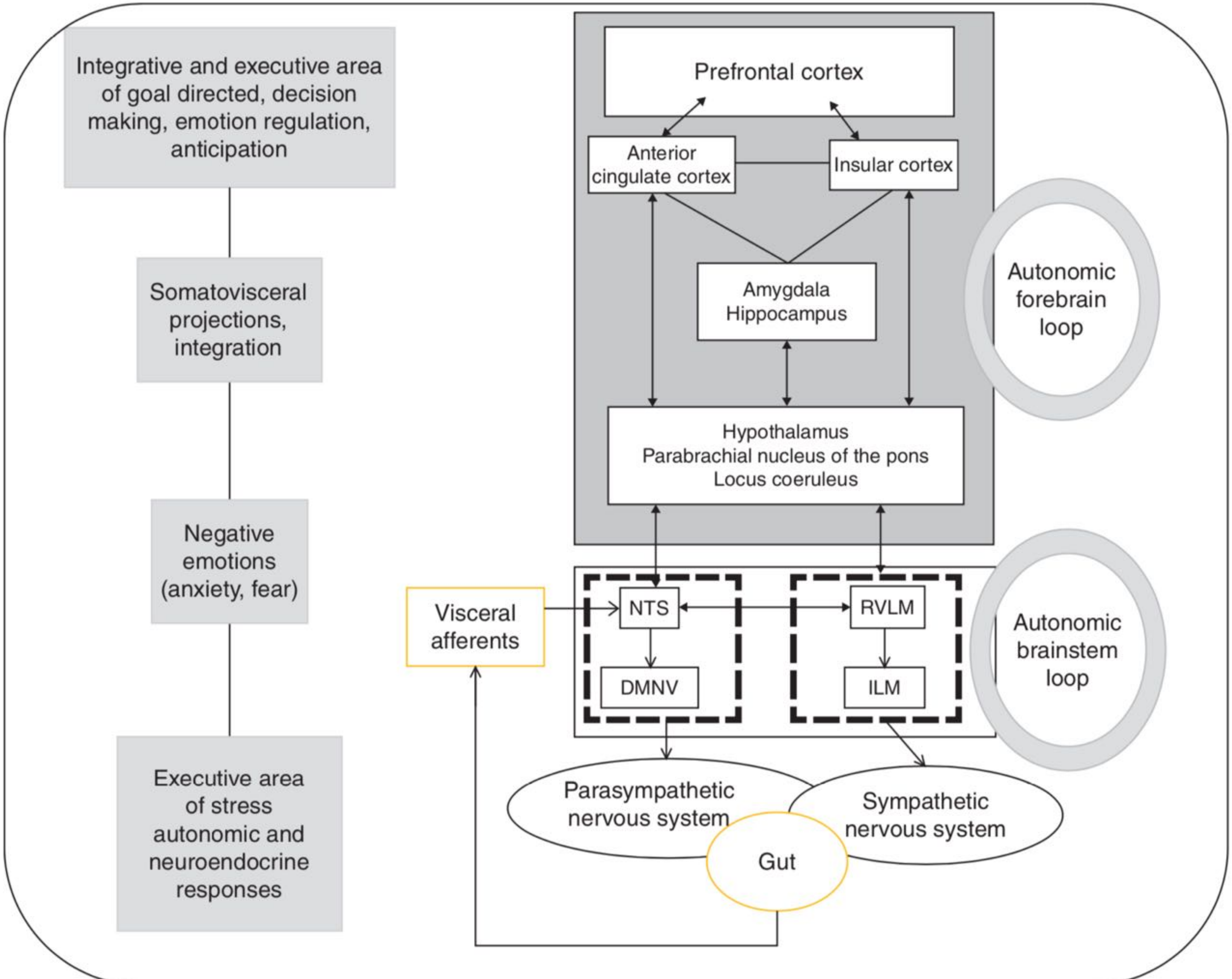
- Neurons of NDMV -> NTS which articulate with vagal afference => reflex vago-vagal (inhibitor - GABA / exitatory - Glutamate)

- Sympathetic-sympathetic reflex loop: loop between efferent neuron (TIML) and afferent neuron Pathways of sympathetic visceral pain via lemniscal and extra-lemniscal (spino-thalamic and spino-reticular) tract

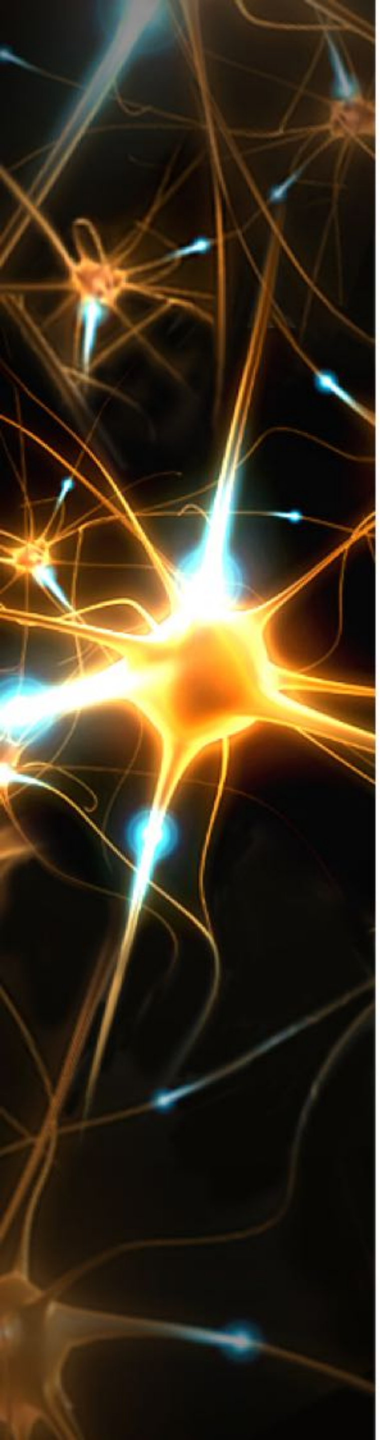
- Projections of pain on the thalamus -> anterior, prefrontal and insular cingulate cortex. Vagal afferent pathways -> NTS -> parabrachial nucleus - locus coeruleus - amygdala - paraventricular nucleus hypothalamus -> activation HPA Axis. H (CRH) - P (ACTH) - A (corticosteroid): neuroendocrie-immune axis

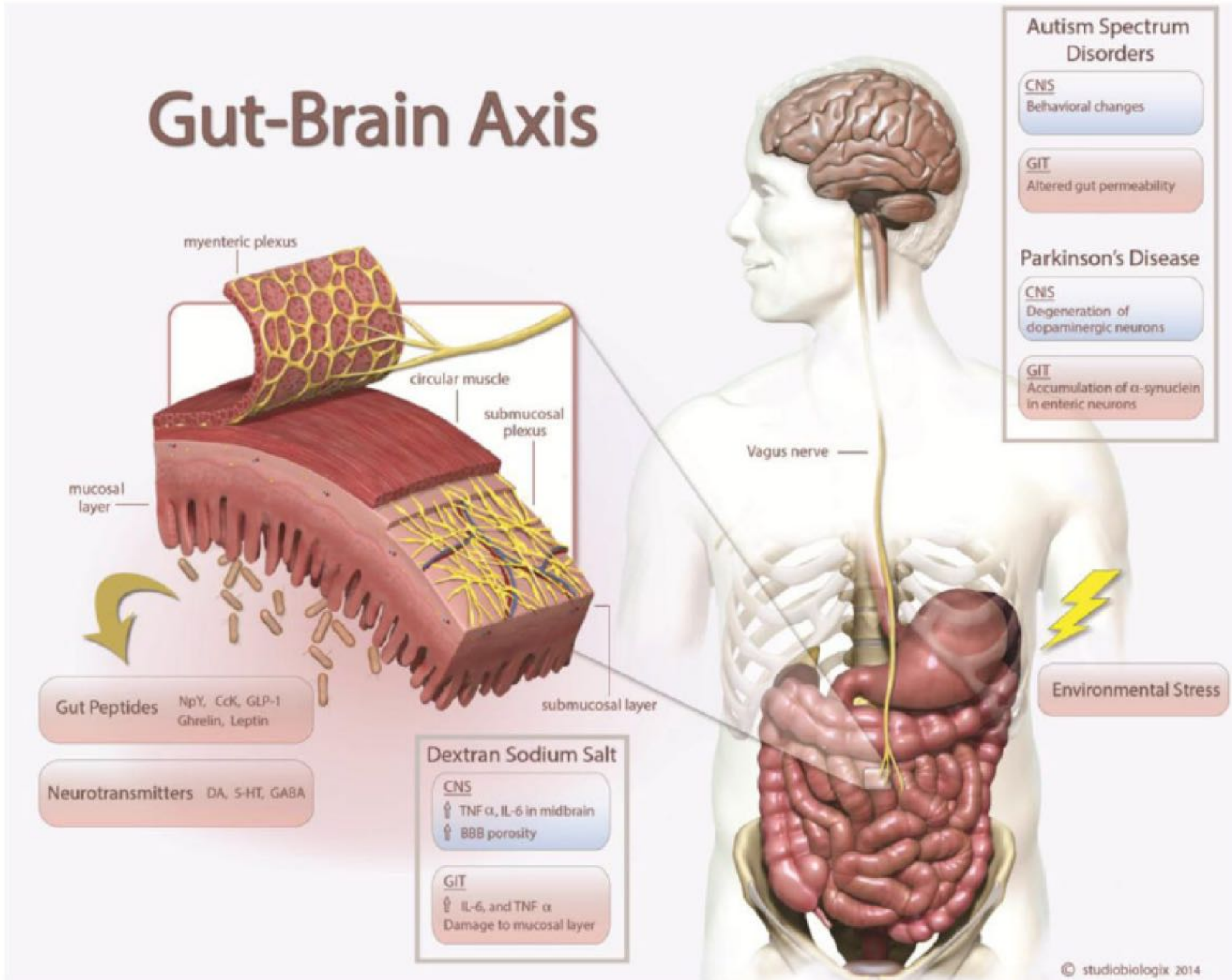
- Afferent parasympathetic and sympathetic pathways -> SNA: NTS, Ventro-lateral medulla, NDMV, parabrachial nucleus, locus coeruleus, A5-C1 nuclei, periacqueductal gray matter (PAGM), hypothalamus, amygdala, cingulate cortex, pre-frontal cortex, Insula

- In response to central ANS -> motor, behavioral, cognitive, emotional and endocrine changes (HPA axis)
- The third way of communication: the circumventricular organs (CVOs) (6) (around the third and fourth ventricles)
  - No hematoencephalic barrier
  - Subfornical organ (SFO) (around the hole of Monroe - 3rd ventricle), pineal gland (PG), subcommisural organ (SCO) (posterior commissure), vascular organ of the lamina terminalis (OVLT), neuro-hypophysis (post-pituitary), area postrema
  - These organs are "sensitive" to circulating vascular content (ions, glucose, hormones, endotoxins, pro-inflammatory cytokines, PGE) -> CNS neuron activations via PGE of neighboring astrocytes -> NPVH projections (paraventricular nucleus hypothalamus)
  - The message of these actived neurons (indirectly), will allow (via their projections) the integration of the peripheral message within the SNC -> adapted reaction to ensure homeostasis
  - Hypothalamus (paraventricular nucleus) is the main seat of these projections and the integration of the peripheral message.
  - In this case, the peripheral afferent information thus reaches the SNC via the CVOs and not via the vague nerve.
  - CVOs therefore allow the entry into the CNS of pro-inflammatory cytokines (IL-1β, IL-6, TNFα, etc.) as part of inflammation -> stimulation of HPA axis -> glucocorticoids -> homeostasis



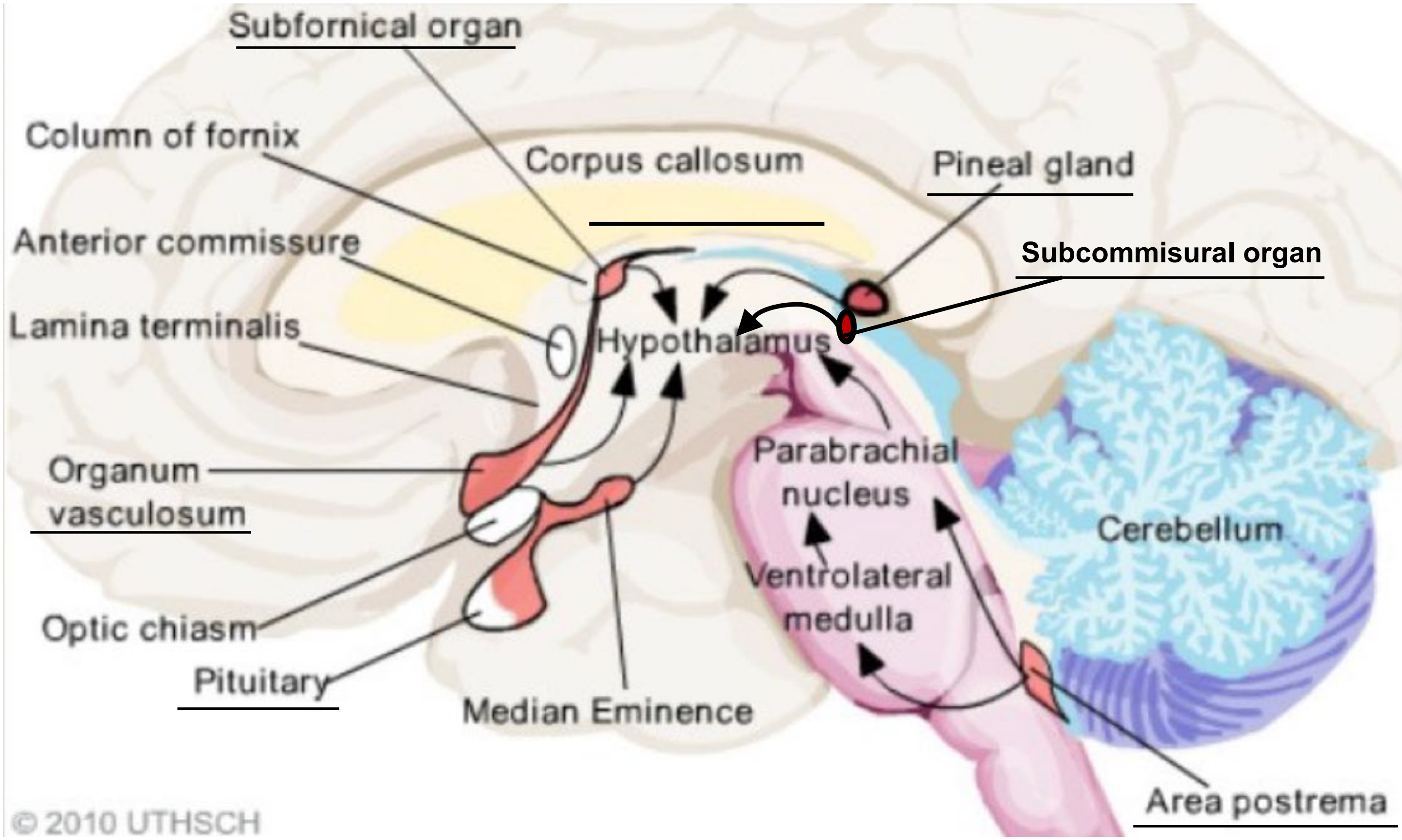
Integrative and executive area of goal directed, decision making, emotion regulation, anticipation
Somatovisceral projections, integration
Negative emotions (anxiety, fear)
Executive area of stress autonomic and neuroendocrine responses
Prefrontal cortex
Anterior cingulate cortex
Insular cortex
Amygdala
Hippocampus
Hypothalamus
Parabrachial nucleus of the pons
Locus coeruleus
Autonomic forebrain loop
Visceral afferents
NTS
DMNV
RVLM
ILM
Autonomic brainstem loop
Parasympathetic nervous system
Sympathetic nervous system
Gut





NpY, Neuropeptide gamma; CcK, Cholecystokinine; GLP-1. Glucagon-like peptide-1; DA, dopamine; 5-HT, Serotonine; GABA, Gamma aminobutyric acid; TNF-α, Tumor necrosis factor- α; IL-6, Interleukine-6. From Ghaisas et al. (2013)

Projections of information from circumventricular organs for integration and reaction on HPA axis



6. Heart Rate Variability (HRV)

- Heart Rate Variability (HRV) is a process of physiological adaptation

- HRV, based on a short-term (+/- 5 min) ECG record, is a recognized biomarker of sympatho-vagal balance or an index of parasympathetic activity.

- 3-lead ECG, samples at 250 HZ, 500Hz, 1000HZ

- ANS monitoring:

  - SNA disorders or imbalances can cause organ damage and other complications

  - Diseases, Infections and Injuries Can Cause ANS Nerve Damage

- Heart Rate Variability (HRV) refers to the continual fluctuations in the time between successive cardiac contractions over time (QRS complex R-R intervals)

- The heart is not a metronome

- HRV reflects the regulation of SNA balance, blood pressure, gaze exchange, intestinal, cardiac and vascular tone

- HRV may be low, normal or high

- SNS Activity Increases HR and Decreases HRV

- SNP activity decreases HR and increases HRV

- A high HRV is usually synonymous with good health. BUT disorders of cardiac conduction can cause high HRV (atrial fibrillation), in this case it is related to a high risk of mortality (especially in the elderly)

- A low HRV is symptomatic of health problems and can affect immune functions, self-regulation and psychosocial abilities

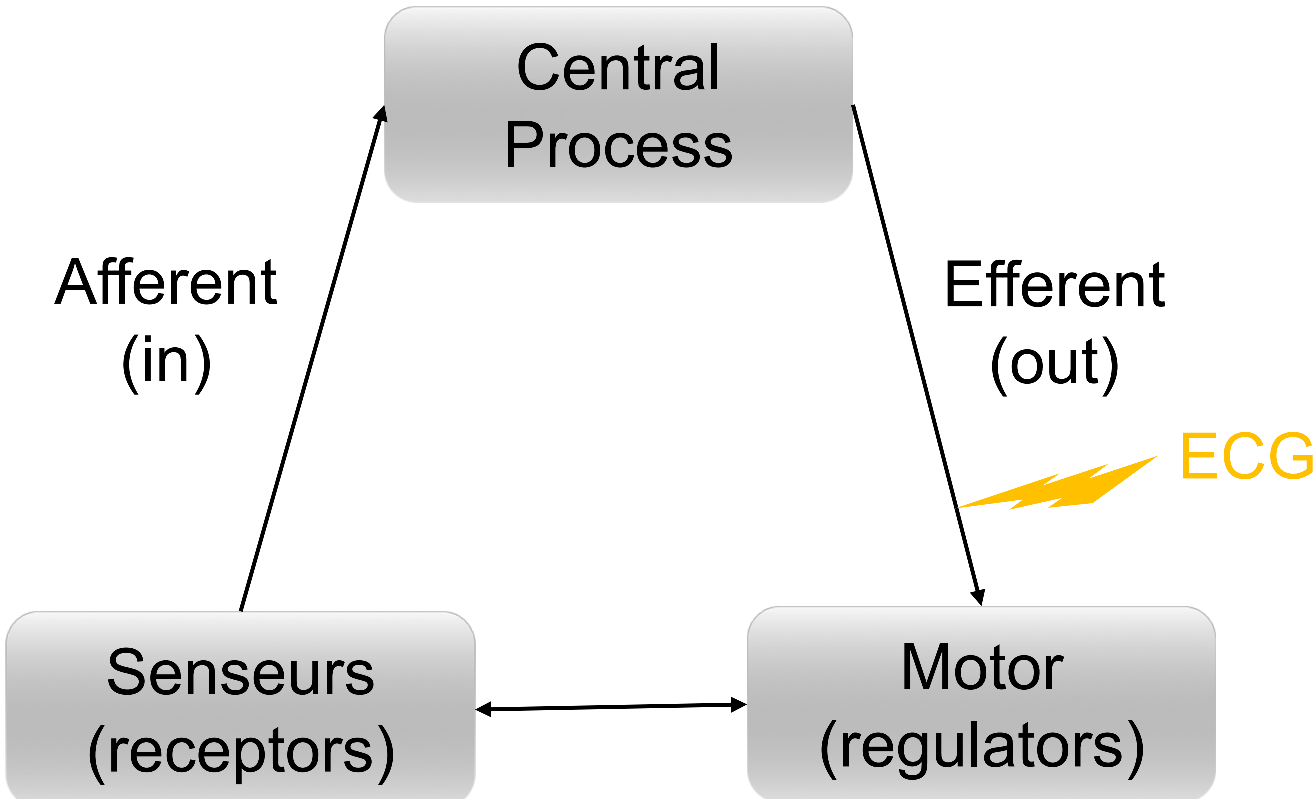
- The pathologies that most affect the HRV are cardiovascular diseases and depressive syndromes.

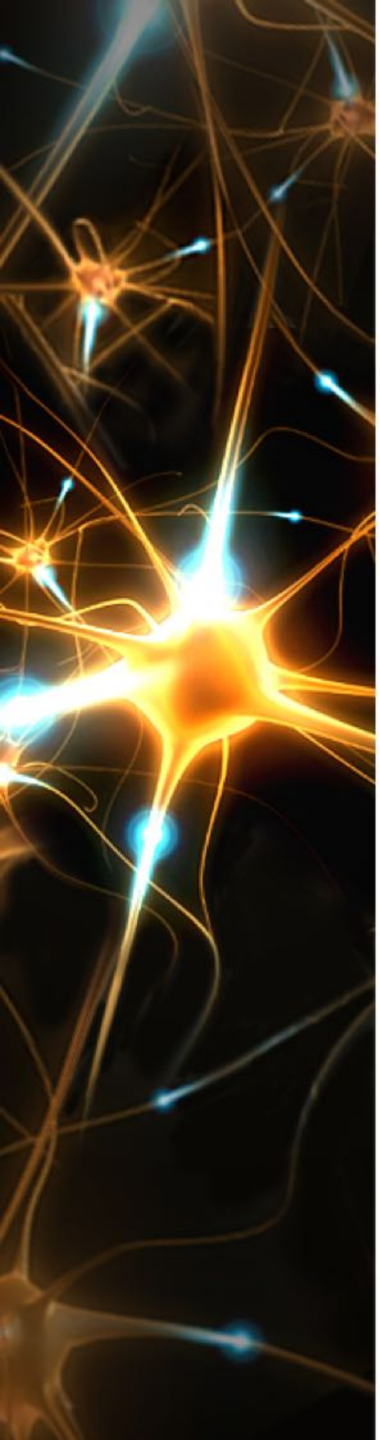
- An optimal level of HRV is associated with good health and a high capacity for self - regulation, adaptation and resistance.

- At rest, high levels of vagal tone are related to the performance of executive actions such as attention and emotion processes mediated by the prefrontal cortex (related information from the intrinsic cardiac nerve system may modulate fronto-cortical activity and impact high-level functions - CAN modulation.

Note: abnormally high HF and low LF values can be found, with a low LF / HF ratio in depressive and anxious patients

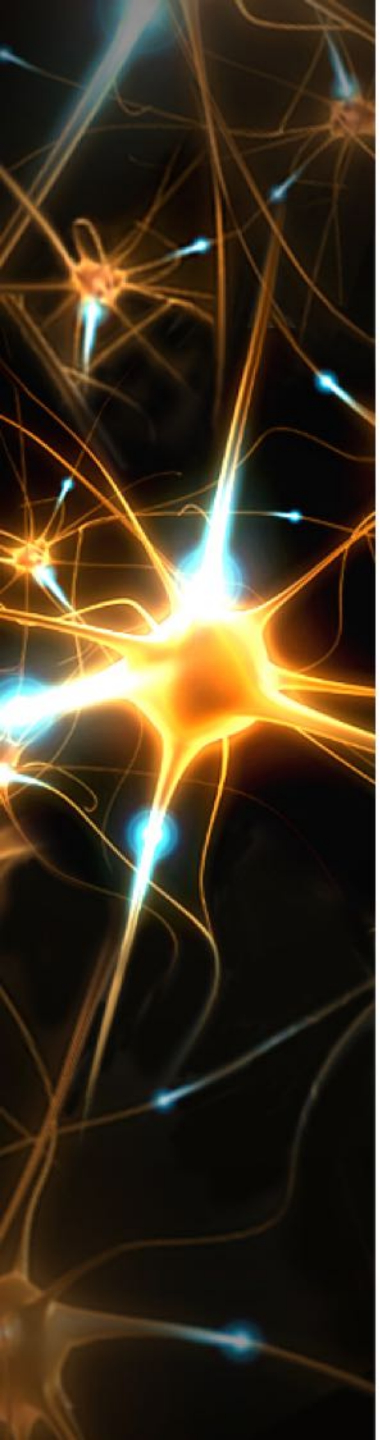
Feedback loop ANS : BP, HR, Temperature, etc

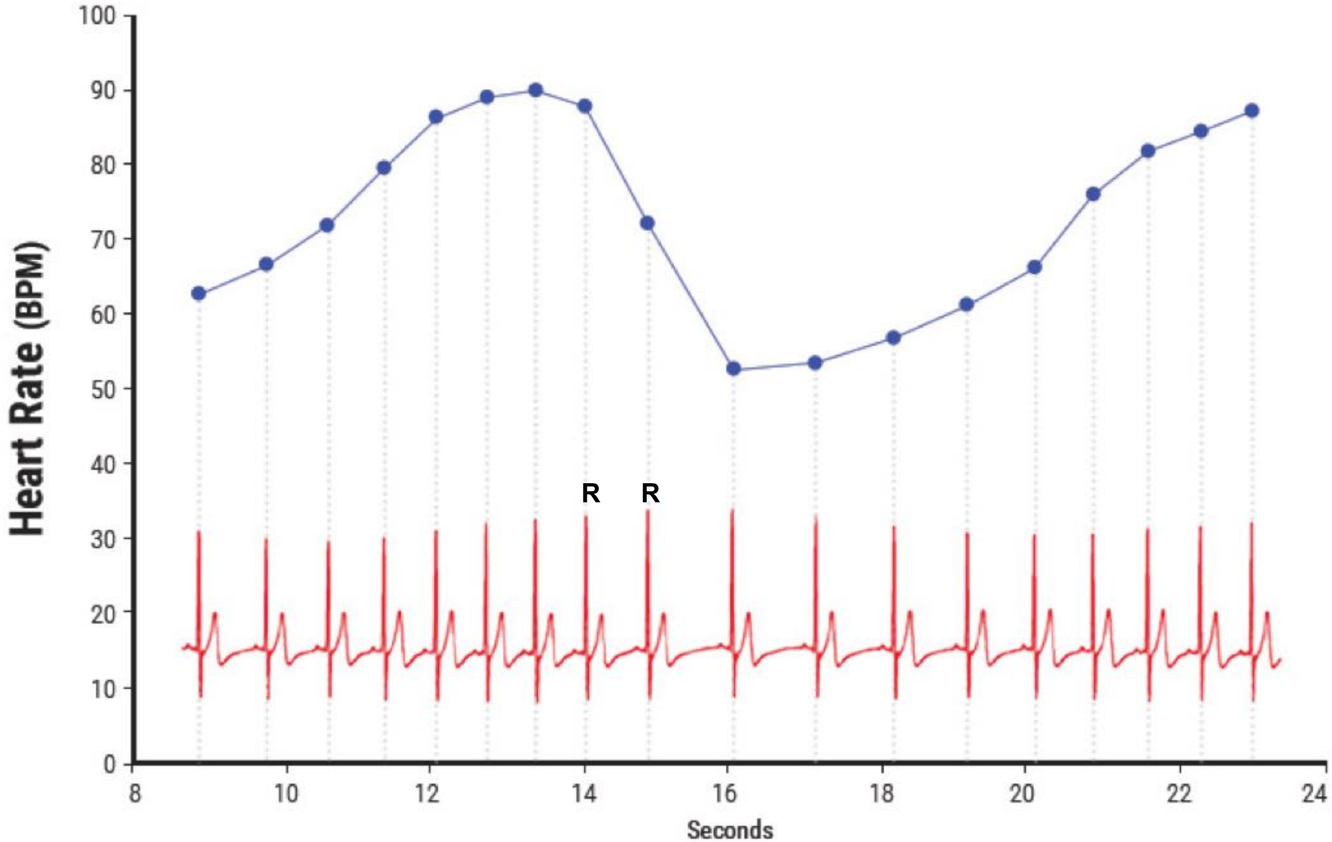




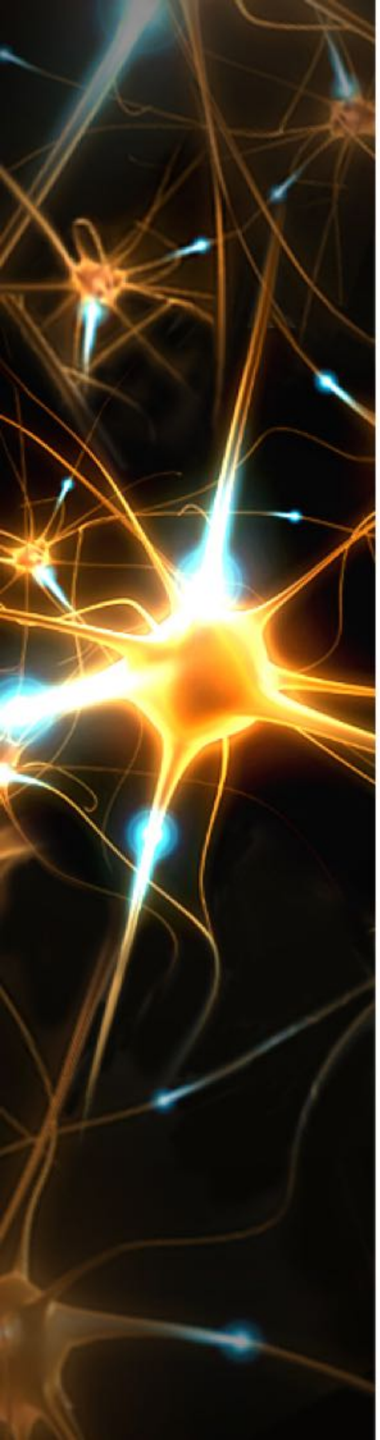
Detect and measure abnormal ANS behavior

BP, blood pressure; HR, cardiac rhythm

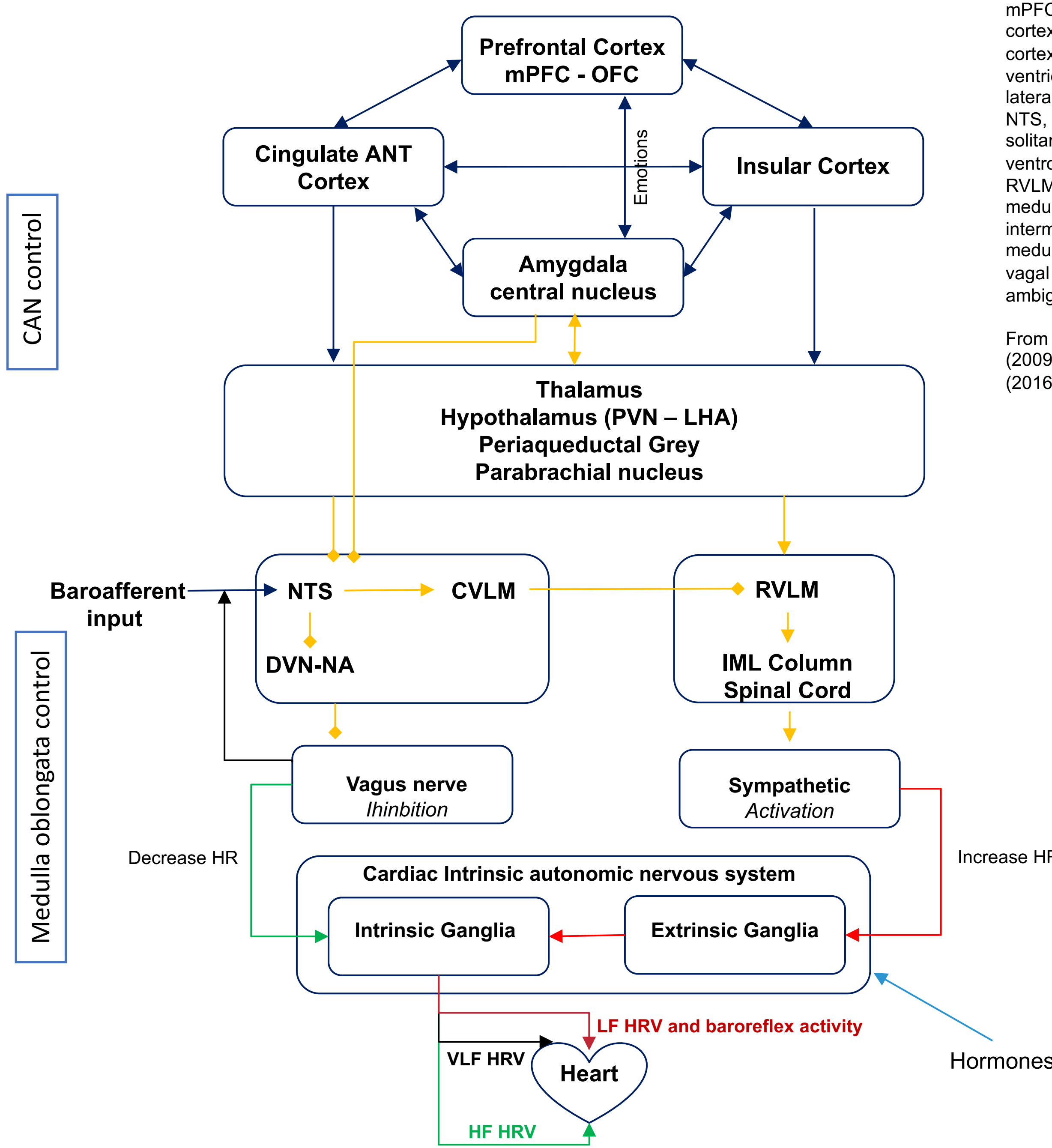




In red: ECG, in blue: heart rate

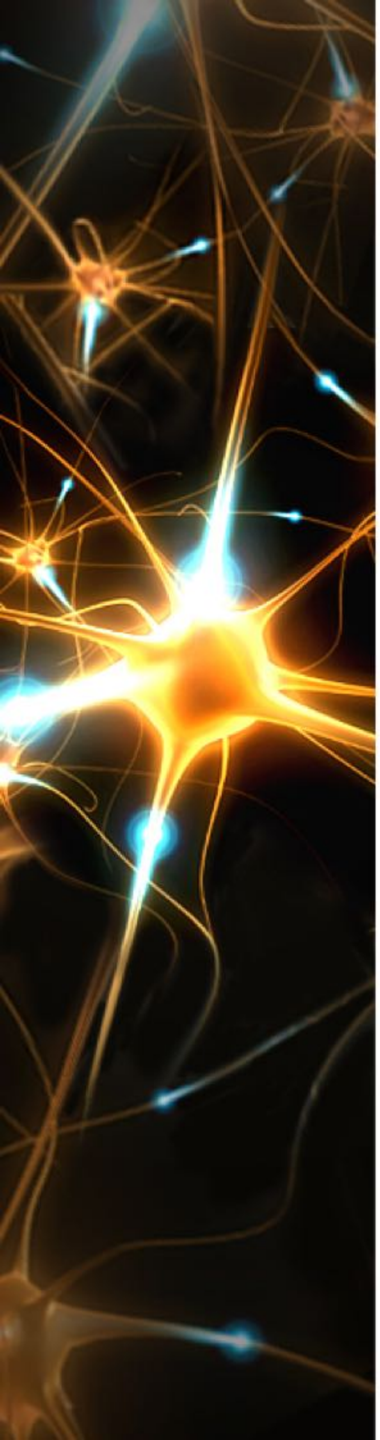


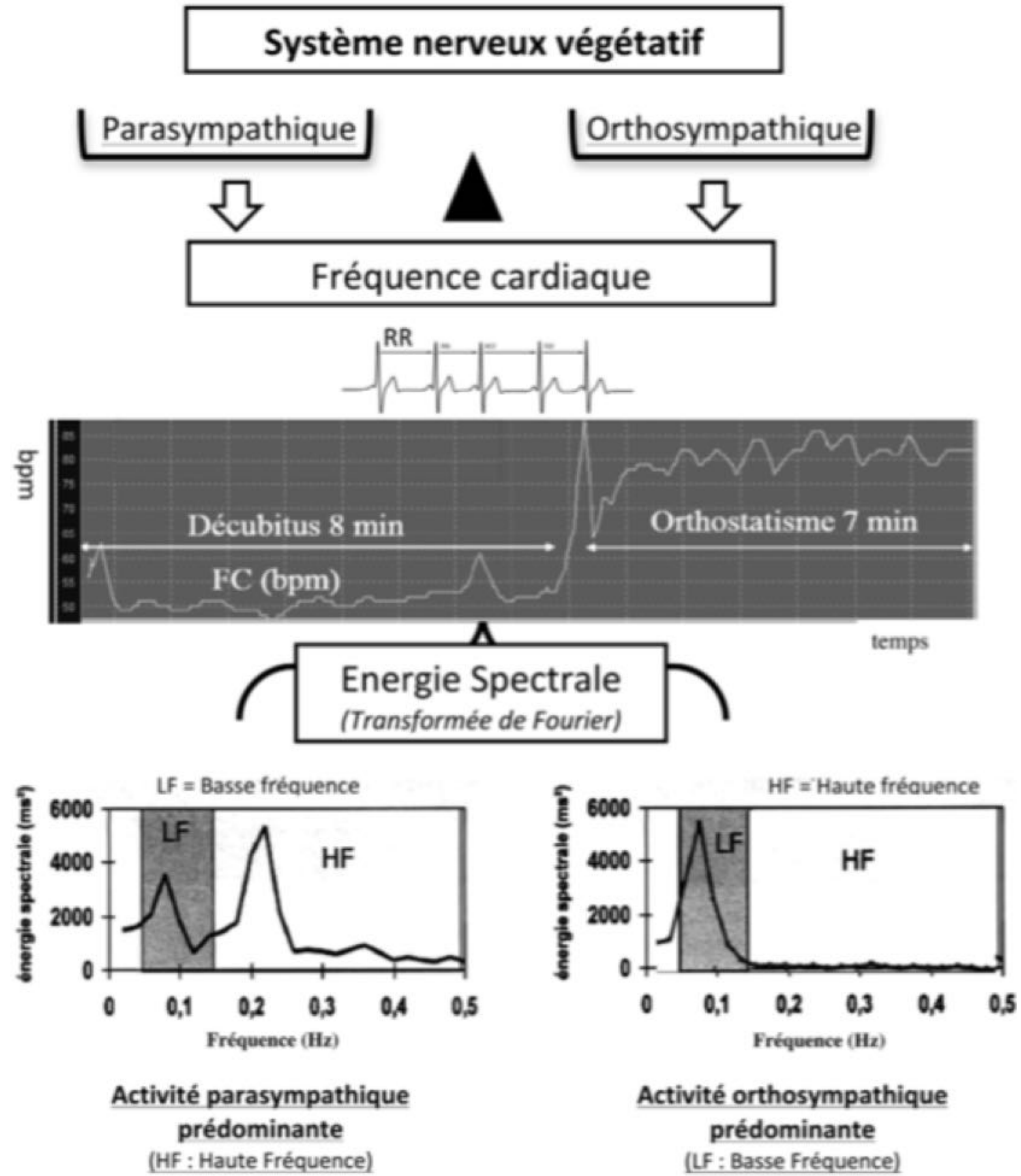
Control paths of HR and HRV

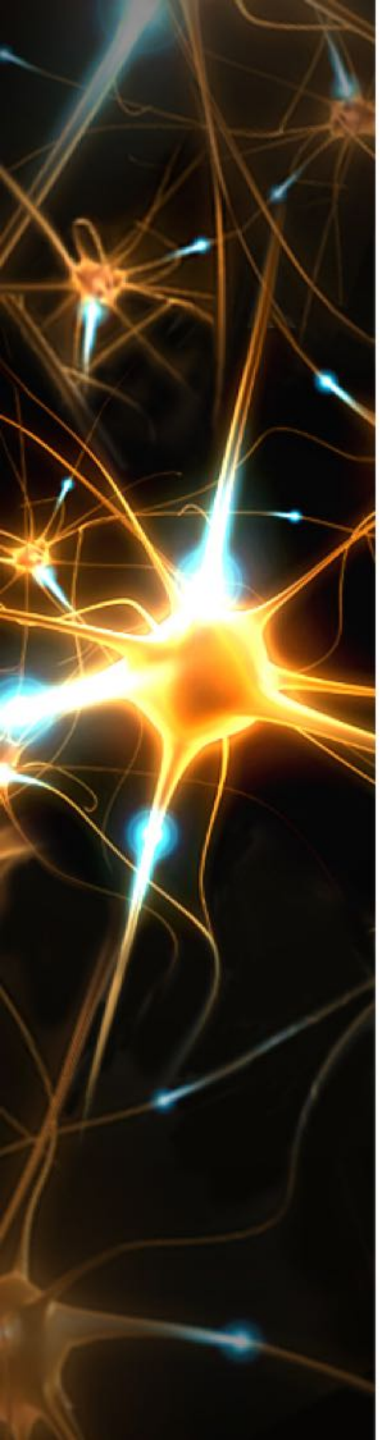


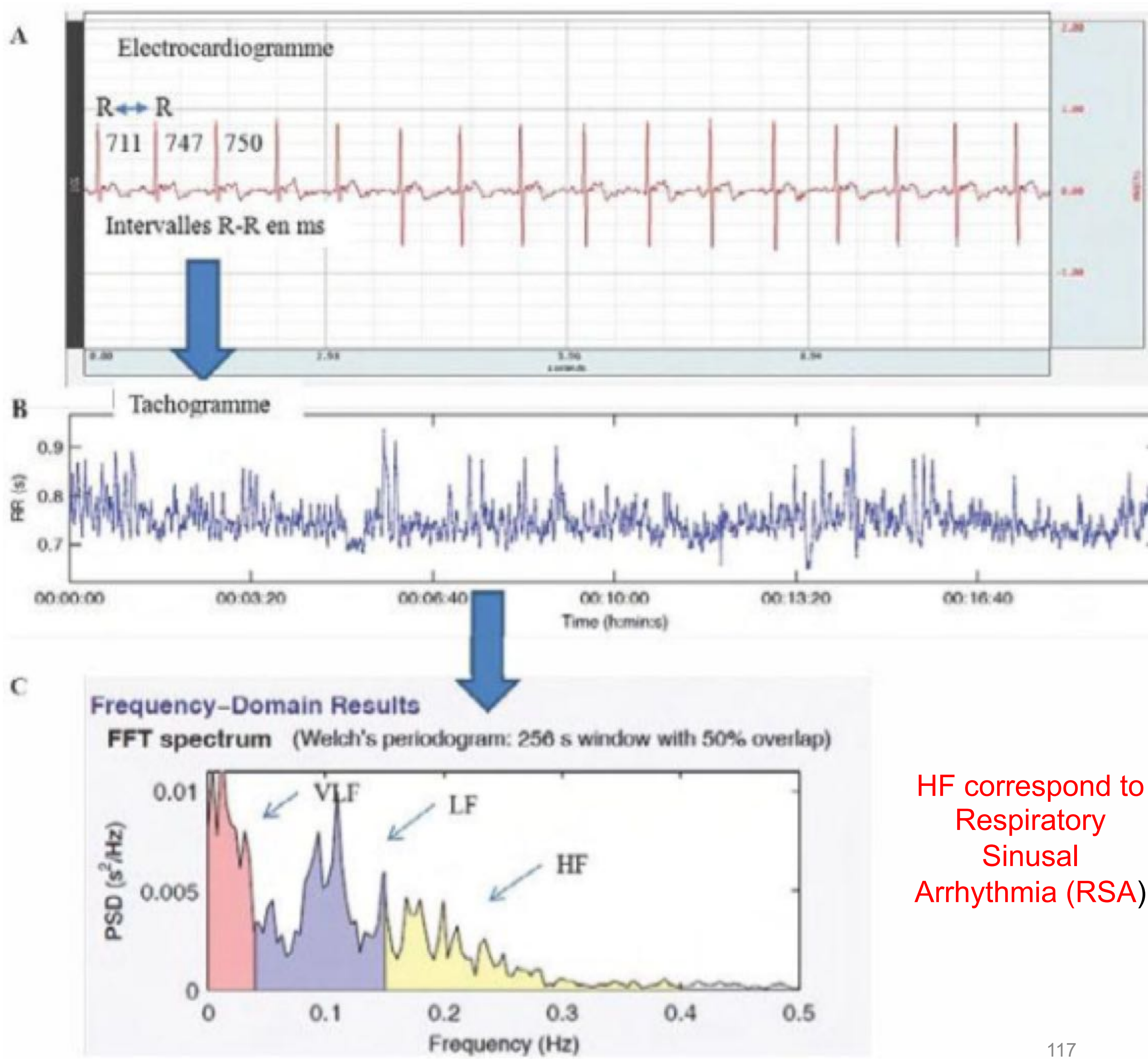
mPFC, medial prefrontal cortex; OFC, orbito frontal cortex; PVN, para ventricular nucleus; LHA, lateral hypothalamic area; NTS, nucleus tractus solitarius; CVLM, caudal ventrolateral medullary; RVLM, rostral ventrolateral medullary; IML, intermediolateral medullary; DVN/NA, dorsal vagal nucleus/nucleus ambiguus; HR, heart rate.

From Thayer and Lane (2009) et Fatisson et al (2016)

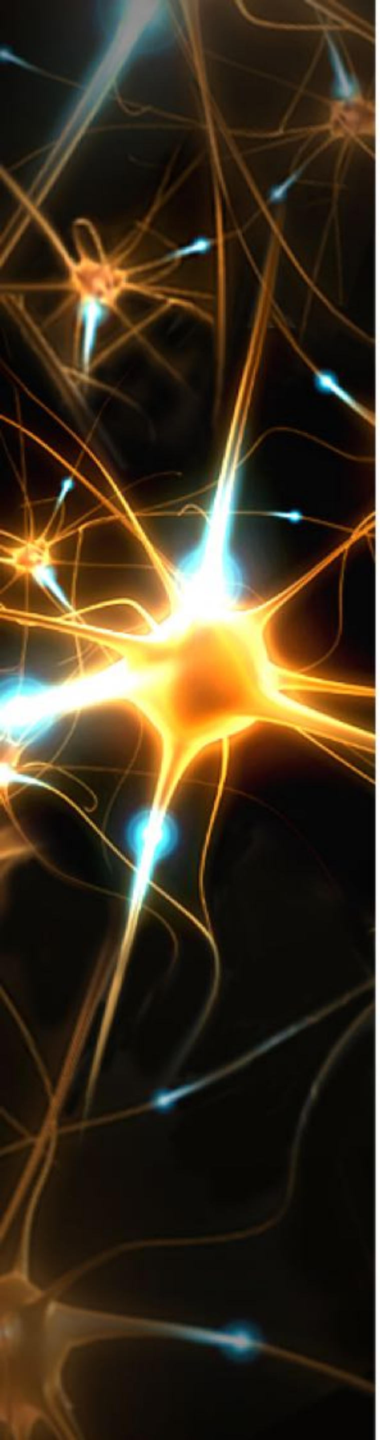



Système nerveux végétatif
Parasympathique
Orthosympathique
Fréquence cardiaque
RR
bpm
Décubitus 8 min
Orthostatisme 7 min
FC (bpm)
temps
Energie Spectrale
(Transformée de Fourier)
LF = Basse fréquence
HF = Haute fréquence
énergie spectrale (ms²)
6000
4000
2000
0
LF
HF
0
0,1
0,2
0,3
0,4
0,5
Fréquence (Hz)
Activité parasympathique prédominante
(HF : Haute Fréquence)
Activité orthosympathique prédominante
(LF : Basse Fréquence)





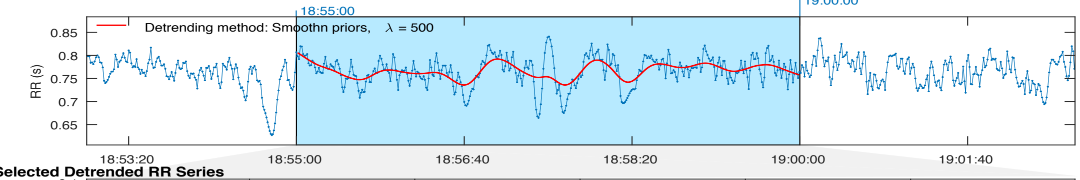
HF correspond to Respiratory Sinusal Arrhythmia (RSA)



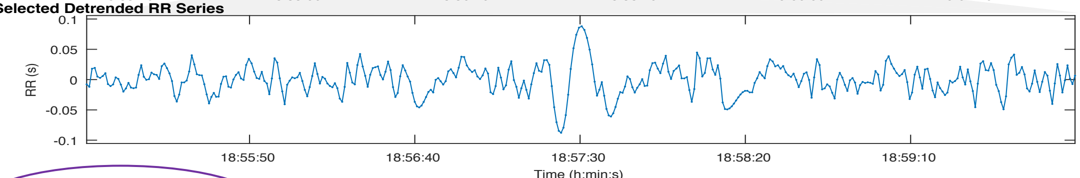
HRV Analysis Results

RR Time Series (Artifact correction "Threshold (very strong)": 12.8% of beats corrected)

Results for a single sample



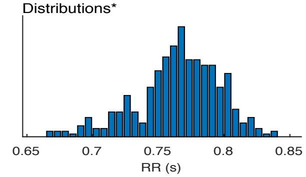
Selected Detrended RR Series

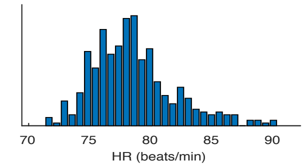


Time-Domain Results

Variable	Units	Value
Mean RR*	(ms)	765.3
STD RR (SDNN)	(ms)	24.2
Mean HR*	(beats/min)	78.40
Min/Max HR	(beats/min)	72.08/88.72
RMSSD	(ms)	16.2
NNxx	(beats)	2
pNNxx	(%)	0.5
RR triangular index		6.426
TINN	(ms)	131.0

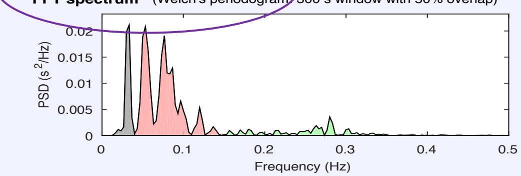
Distributions*





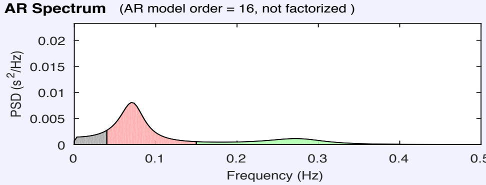
Frequency-Domain Results

FFT spectrum (Welch's periodogram: 300 s window with 50% overlap)



Frequency Band	Peak (Hz)	Power (ms^2)	Power (log)	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0333	163	5.092	17.4	
LF (0.04-0.15 Hz)	0.0533	655	6.484	70.1	84.9
HF (0.15-0.4 Hz)	0.2800	116	4.756	12.5	15.1
Total		934	6.839		
LF/HF		5.628			

AR Spectrum (AR model order = 16, not factorized)

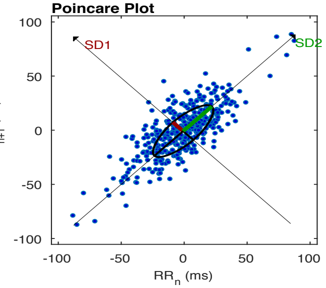


Frequency Band	Peak (Hz)	Power (ms^2)	Power (log)	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0400	71	4.259	12.4	
LF (0.04-0.15 Hz)	0.0700	366	5.903	64.3	73.4
HF (0.15-0.4 Hz)	0.2733	133	4.888	23.3	26.6
Total		570	6.345		
LF/HF		2.759			

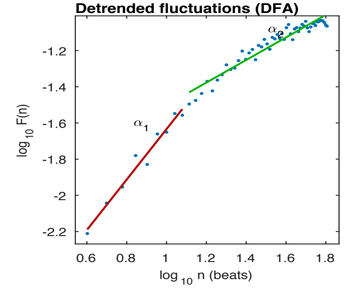
Nonlinear Results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	11.5
SD2	(ms)	32.2
SD2/SD1		2.805
Approximate Entropy (ApEn)		1.195
Sample Entropy (SampEn)		1.655
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha 1$		1.395
Long-term fluctuations, $\alpha 2$		0.624

Poincare Plot



Detrended fluctuations (DFA)



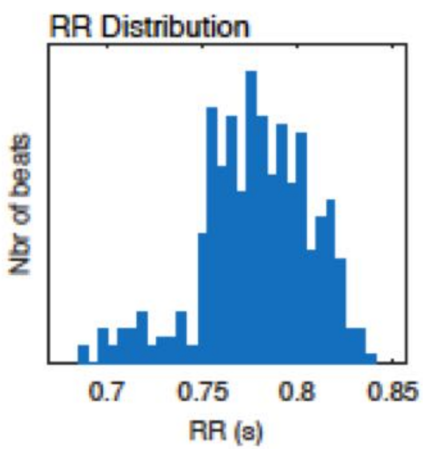
*Results are calculated from the non-detrended selected RR series.

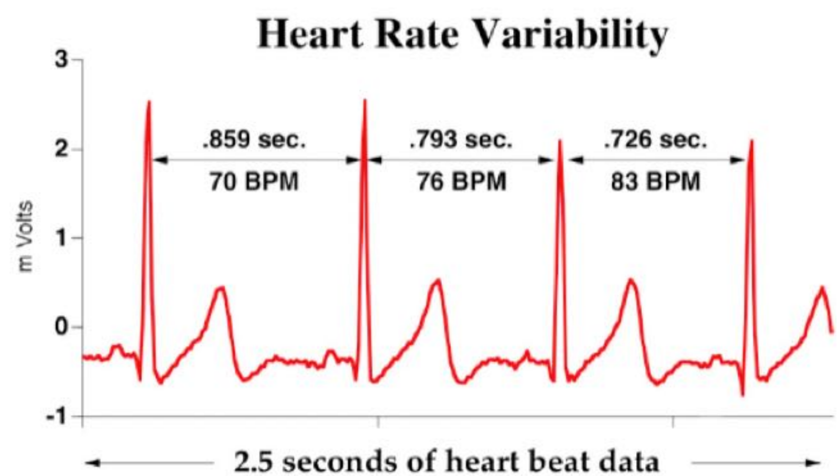
HRV analysis with Kubios software HRV

- **Time domain**: Quantification of the HRV rate by measuring the inter-beat intervals (R-R) of the ECG (2min to 24h). Values are mainly expressed in original units (ms)
- The time-based analysis investigates the cyclic fluctuation of the R-R intervals and the standard deviation of the successive normalized R-R intervals (SDNN)
- It is a method that allows easy calculation of variability but provides less detailed information than spectral analysis

Time-Domain Results

Variable	Units	Value
Mean RR*	(ms)	778
Mean HR*	(bpm)	77
Min HR	(bpm)	73
Max HR	(bpm)	86
SDNN	(ms)	16.8
RMSSD	(ms)	15.6
NN50	(beats)	0
pNN50	(%)	0.00
RR triangular index		5.22
TINN	(ms)	97.0
Stress Index (SI)		21.2





- **Frequency domain:** measures the cyclic fluctuation of the R-R intervals by performing Fourier transform spectral analysis or Autoregressive analysis.

- **Frequency-based analysis estimates the absolute or relative power distribution in four frequency bands (ULF), (VLF), (LF) and (HF).** It distinguishes the low frequency band (**LF = 0.04 to 0.15Hz**) which is mainly a **reflection of the sympathetic and baroreflex activity**, and the high frequency band (**HF = 0.15 to 0.50Hz**) which is an **indicator of parasympathetic activity**.

  The normalized (n.u.) ratio of these spectral indices (LF / (LF + HF)) is used to evaluate the sympatho-vagal balance.

- The measurement of the domain of the frequency can be expressed in relative or absolute power.

  Absolute Power = ms2
  Relative Power (expressed in normal units (nu)) LF (nu) = LF / (LF + HF)
  HF (nu) = HF / (LF + HF) HF (nu): **modulation index of parasympathetic activity of ANS**
  LH (nu): modulation index of sympathetic activity of ANS
  LF (nu) / HF (nu): index of sympatho-vagal balance

Frequency domain: adult band

- HF (0.15 – 0.40 Hz, ms2) : 90% fluctuation of parasympathetic tone due to respiratory sinus arrhythmia
- LF (0.04 – 0.15 Hz, ms2) : resting and semi-sitting (45 deg) = 50% parasympathetic tone and 25% sympathetic (baroreflex modulation)
- VLF (0.0033 – 0.04 Hz, ms2) : action of the intrinsic cardiac nervous system

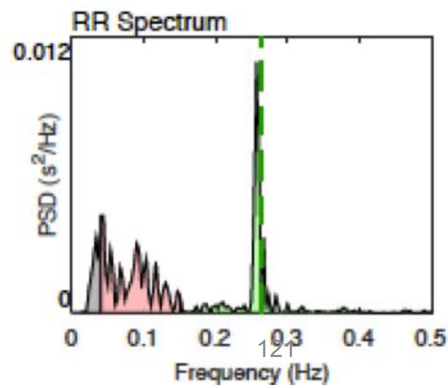
Frequency domain: child band

- VLF: 0.0033 - 0.040 Hz,ms2
- LF : 0.040 – 0.240 Hz,ms2
- HF : 0.240 – 1.040 Hz,ms2

Frequency-Domain Results (FFT spectrum)

Variable	Units	VLF	LF	HF
Frequency band	(Hz)	0.00-0.04	0.04-0.15	0.15-0.40
Peak frequency	(Hz)	0.040	0.043	0.257
Power	(ms^2)	42	154	123
Power	(log)	3.732	5.036	4.815
Power	(%)	13.09	48.22	38.67
Power	(n.u.)		55.48	44.50

Total power	(ms^2)	319		
Total Power	(log)	5.765		
LF/HF ratio		1.247		
EDR	(Hz)	0.26		



- ULF (<0.0033 Hz): circadian oscillations, body temperature, metabolism and renin-angiotensin system (24 hours of recording: we are not concerned!)
- **VLF** (0.0033 Hz - 0.04Hz): **long-term regulation mechanisms, thermoregulation and general hormonal regulation (renin-angiotensin)**
- **LF** (0.04 Hz - 0.15Hz): **reflects a mix of SNS, PNS and baroreflex activity**
- **HF** (0.15 Hz - 0.40Hz): **Vagal tone**: **Respiratory band** (heart rate / rate variation resp: respiratory sinus arrhythmia) = (**9 cycles / min | 0.15Hz, at 24 cycles / min | 0.40Hz**)

  Note: **when breathing is between these cycles / min the HRV actually reflects vagal tone. Check the EDR (ECG-Derived-Respiration) in Kubios!**

  -> if the respiratory rate. is in the HF -> peak in high frequencies <u>(HF reflects vagal tone)</u>
  -> if the respiratory rate is in the LF -> peak in LF (<u>HF no longer accurately represents vagal tone</u>)

- The respiratory rate thus influences the HRV: Low respiratory rate (<9cycles / min = <0.15Hz) -> RMSSD

- **Respiratory rate <9 or> 24 does not reflect a HRV related to vagal tone**
  HRV should be made therefore with respiratory rate> = 9 - 24 <=

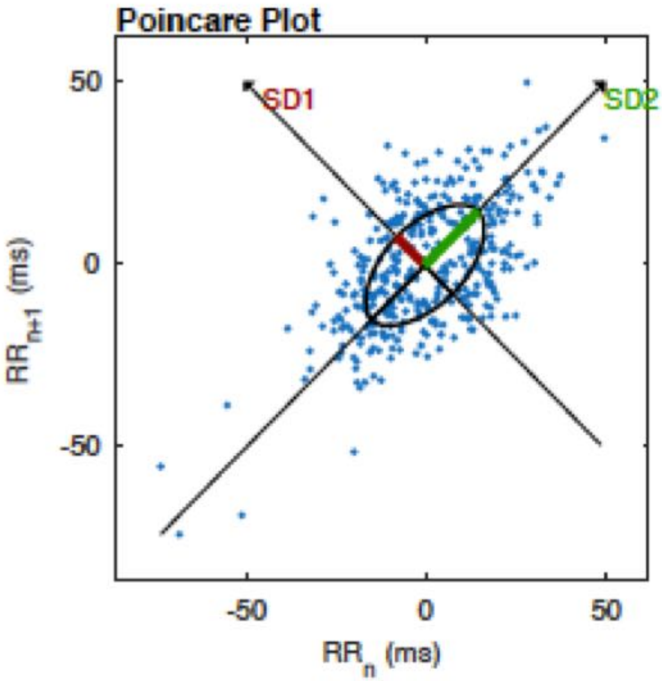
- Do not forget to change the value of LF and HF for children!

- **<u>Nonlinear measurements:</u>** Quantification of the complexity and non-predictability of a series of intervals (R-R)

  Nonlinear indices correlate with specific measures of time and frequency domains.

Nonlinear Results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	11.0
SD2	(ms)	21.0
SD2/SD1		1.906
Approximate Entropy (ApEn)		1.254
Sample Entropy (SampEn)		1.835
Detrended Fluctutation Analysis (DFA)		
Short-term fluctuations, $\alpha 1$		0.892
Long-term fluctuations, $\alpha 2$		0.570
Correlation Dimension (D2)		0.057
Recurrence Plot Analysis (RPA)	(beats)	
Mean line length (Lmean)	(beats)	8.99
Max line length (Lmax)	(%)	75
Recurrence rate (REC)	(%)	22.58
Determinism (DET)		96.51
Shannon Entropy (ShanEn)		2.954
Multi-Scale Entropy (MSE)		0.579 - 2.087



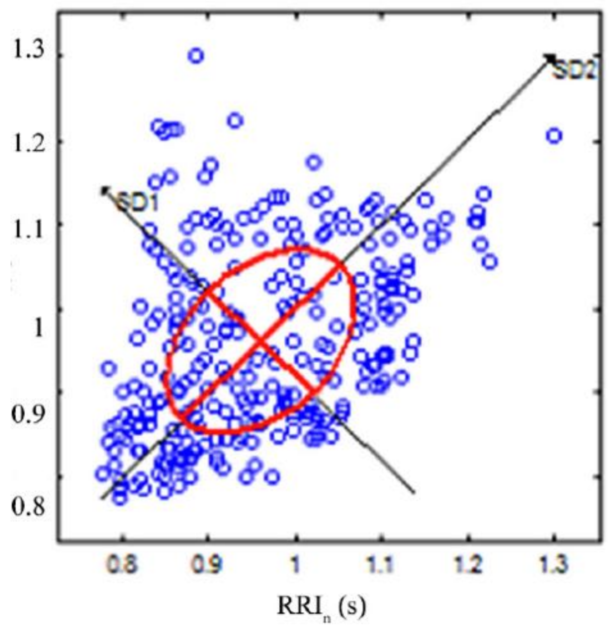
- **<u>Poincare Plot:</u>** graph pointing each R-R interval with respect to the preceding one (graph of R-R successive values) on two axes (SD1 - SD2

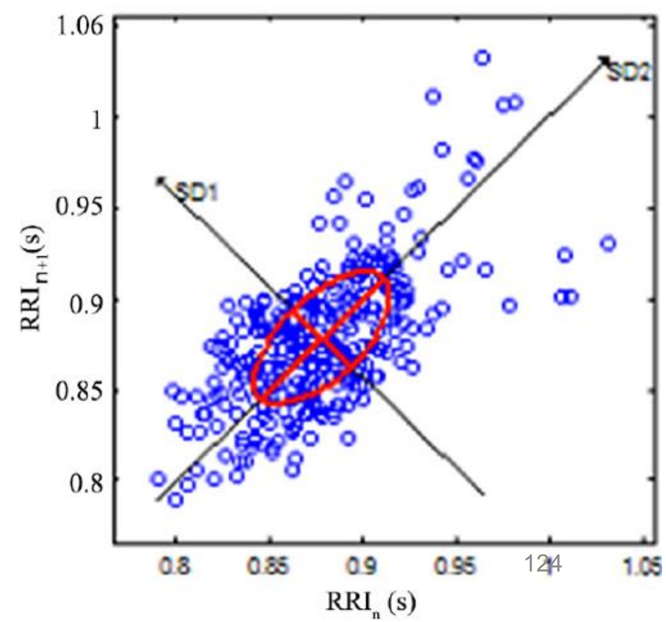
SD1: reflects short-term variability = **RMSSD, linked to HF**
SD2: reflects short-term + long-term variability (Baroreflex + LF)

S: is correlated with baroreflex sensitivity, LF, HF and RMSSD.

S (area of the elipse) corresponds to the total VFC.

SD1 / SD2 is correlated with LF / HF, **measures the sympatho-vagal balance**.



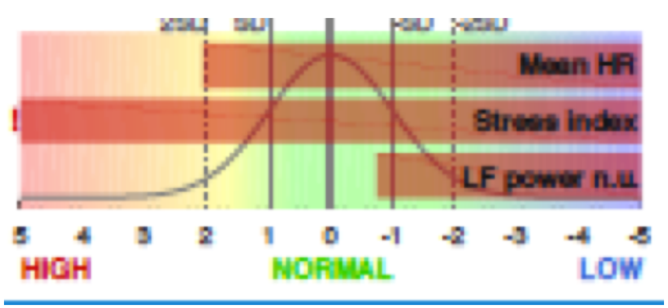


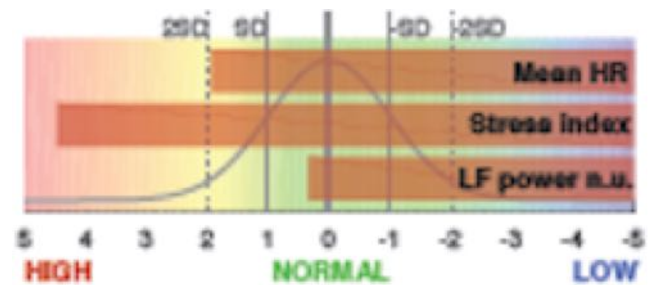
- **Baevsky stress index (Kubios ver 3.1)**

The index shows the degree of centralization in heart rate management.

Normally, under normal resting conditions, the heart rate is mainly regulated by the system. Intrinsic cardiac (own pacemaker), by local inputs of the SNA ganglia and the usual hormones -> the FC fluctuates in wave, the interval of time between two beats is great and the index is weak.

In conditions requiring a high alert level, a rapid response, in the event of stress and certain pathological conditions (e.g. cardiovascular diseases, anxiety, depression), the superior structures (CAN) intervene in the regulation of the HR - > the HR becomes more regular, the time intervals between the beats are +/- the same (HRV. ↘) -> the index increases.





Index de stress de Baevsky est inversement proportionnel à RMSSD

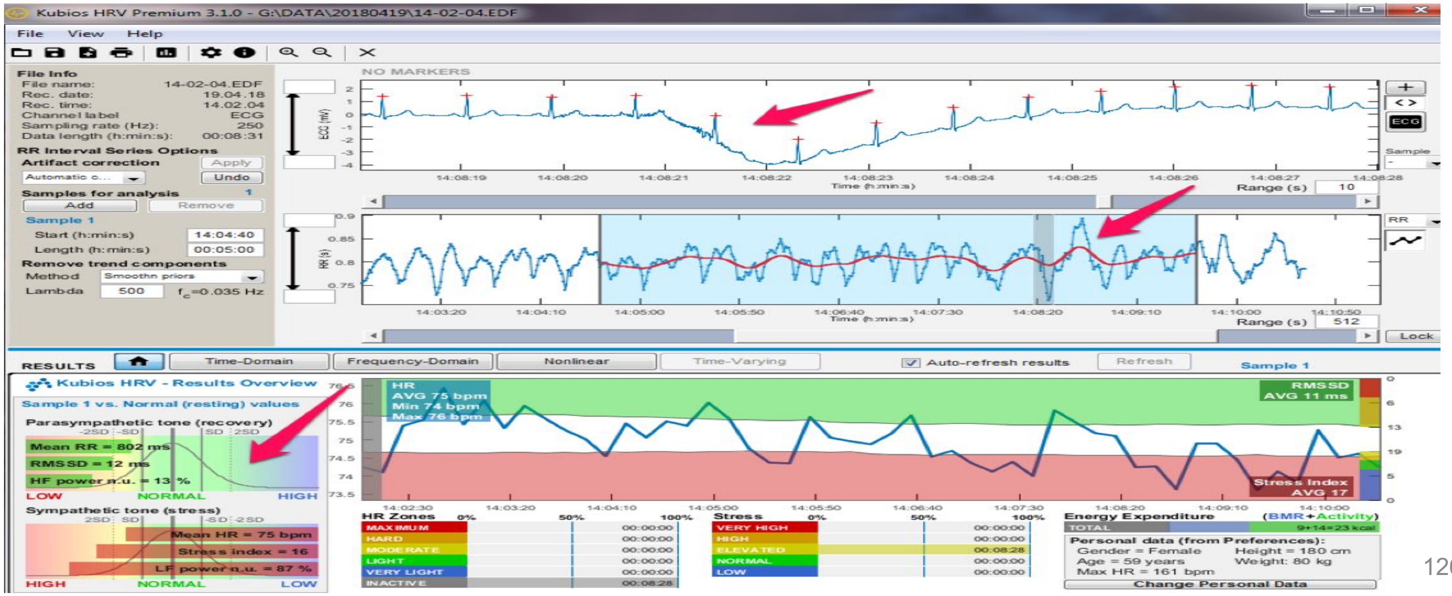


TABLE 1 | Summary of the main heart rate variability parameters and their physiological origin.

	Variable	Description	Physiological origin
Time-domain	SDNN	Standard deviation of all R–R intervals	Cyclic components responsible for heart rate variability
	RMSSD	Root mean square of successive differences	Vagal tone
	pNN50	Percentage of successive normal sinus RR intervals more than 50 ms	Vagal tone
	Peak-valley	Time-domain filter dynamically centered at the exact ongoing respiratory frequency	Vagal tone
Frequency-domain	ULF	Ultra-low frequencies	Circadian oscillations, core body temperature, metabolism and the renin-angiotensin system
	VLF	Very-low frequencies	Long-term regulation mechanisms, thermoregulation and hormonal mechanisms
	LF	Low frequencies	Mix of sympathetic and vagal activity, baroreflex activity
	HF	High frequencies	Vagal tone
	LF/HF	Low frequencies/high-frequencies ratio	Mix of sympathetic and vagal activity
Non-linear indices	SD1	Standard deviation – Poincaré plot Crosswise	Unclear, depicts quick and high frequent changes in heart rate variability
	SD2	Standard deviation – Poincaré plot Lengthwise	Unclear, depicts long-term changes in heart rate variability

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- **RMSSD is correlated with HF** (RMSSD provides the best assessment of vagal tone)
- **pNN50 is correlated with RMSSD and HF**

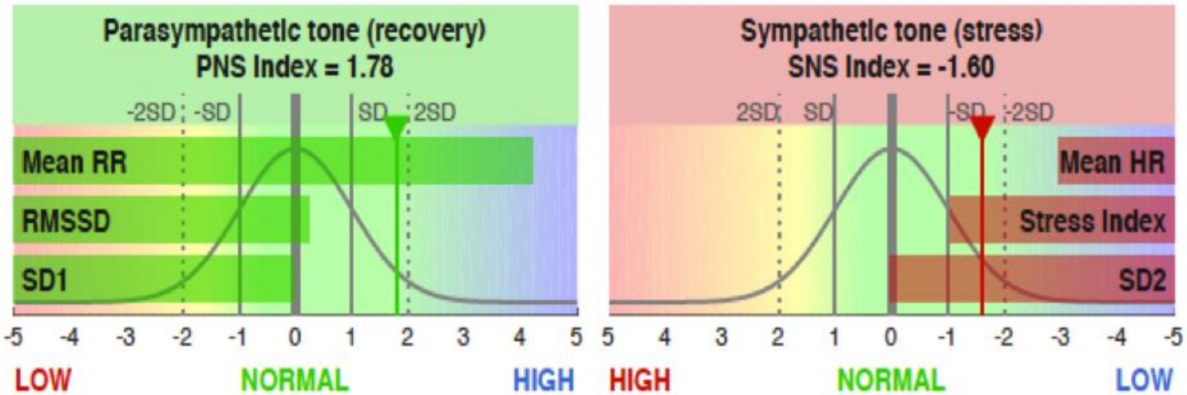
Men show a relative SNS dominance
Women show a relative PNS dominance
SNS tone increases with age, PNS decreases.

Standard HRV analysis

- Min. 5 to 10 minutes rest before ECG
- Record 5min (gold standard) (> 1min)

- Standard recording conditions
  - Patient seated, knees 90 deg., feet flat or layer down, semi-supine (30 deg).
  - Controlled / spontaneous breathing (normally 9 to 12 / min), palms up, eyes firm, atmosphere of the room relax.
  - Alcohol +++, taking drugs, hormones (tricyclic antidepressants) influence HRV
  - Good night's sleep (> 6h) before examination
  - No intense efforts 24h before exam
  - Fasting or light breakfast before examination
  - No stimulating drinks (coffee, tea, coca, etc) min 2 hours before exam.
  - No alcohol 24h before exam
  - Position the electrodes correctly (see manual)
  - Shave well (men) the area of the electrodes: optimal contact

Kubios HRV - Results compared to normal (resting) values



Parasympathetic Nervous System (PNS)

Mean RR	RMSSD	SD1
1306 ms	**45.8** ms	**31.5** %

PNS Index = 1.78

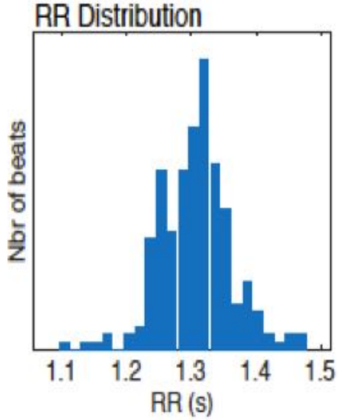
Sympathetic Nervous System (SNS)

Mean HR	Stress index	SD2
46 bpm	**7.0**	**68.5** %

SNS Index = -1.60

Time-Domain Results

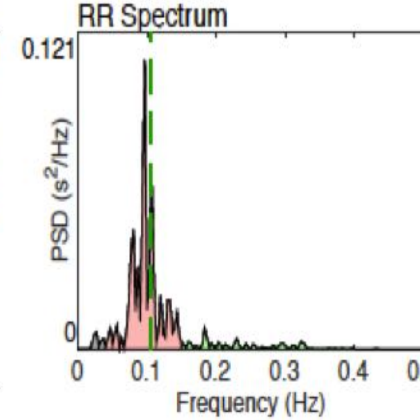
Variable	Units	Value
Mean RR*	(ms)	1306
Mean HR*	(bpm)	46
Min HR	(bpm)	43
Max HR	(bpm)	51
SDNN	(ms)	48.8
RMSSD	(ms)	45.8
NN50	(beats)	52
pNN50	(%)	22.81
RR triangular index		9.96
TINN	(ms)	237.0
Stress Index (SI)		7.0

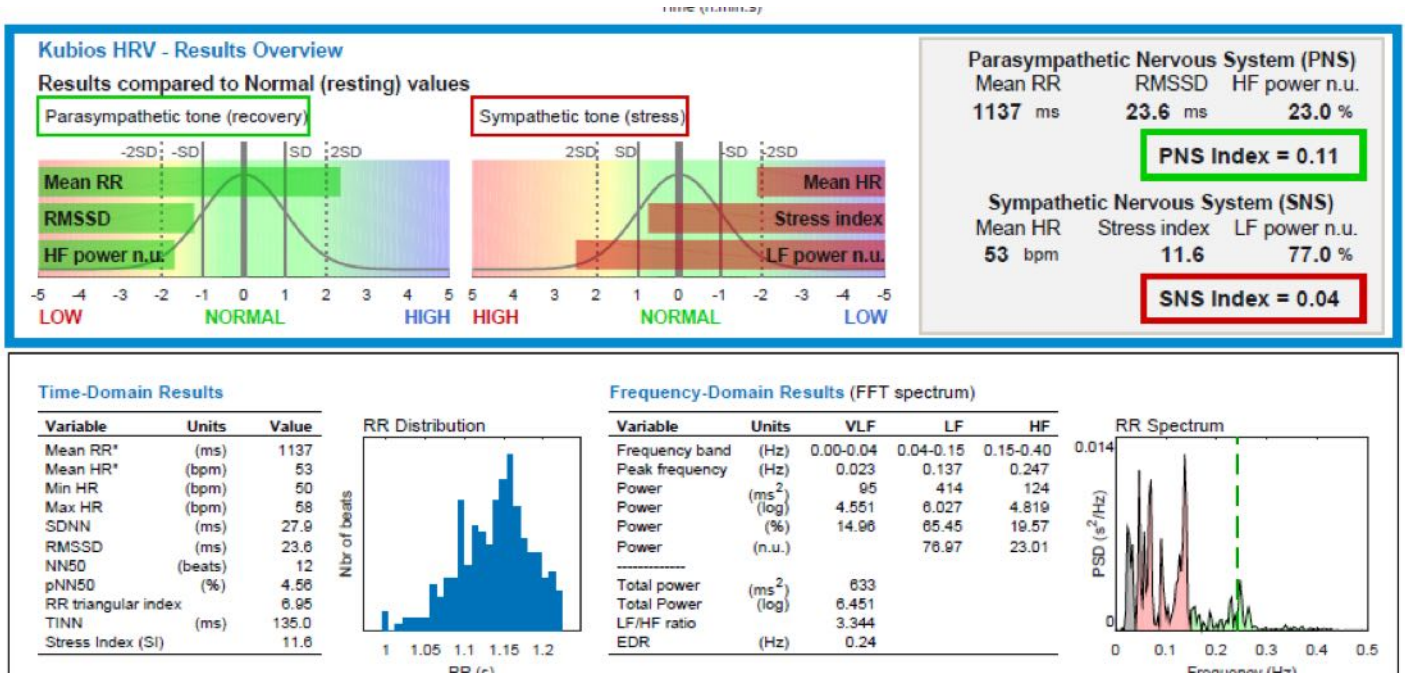


Frequency-Domain Results (FFT spectrum)

Variable	Units	VLF	LF	HF
Frequency band	(Hz)	0.00-0.04	0.04-0.15	0.15-0.40
Peak frequency	(Hz)	0.027	0.097	0.183
Power	(ms^2)	73	1998	265
Power	(log)	4.284	7.600	5.578
Power	(%)	3.11	85.56	11.33
Power	(n.u.)		88.30	11.70

Total power	(ms^2)	2335		
Total Power	(log)	7.756		
LF/HF ratio		7.549		
EDR	(Hz)	0.11		

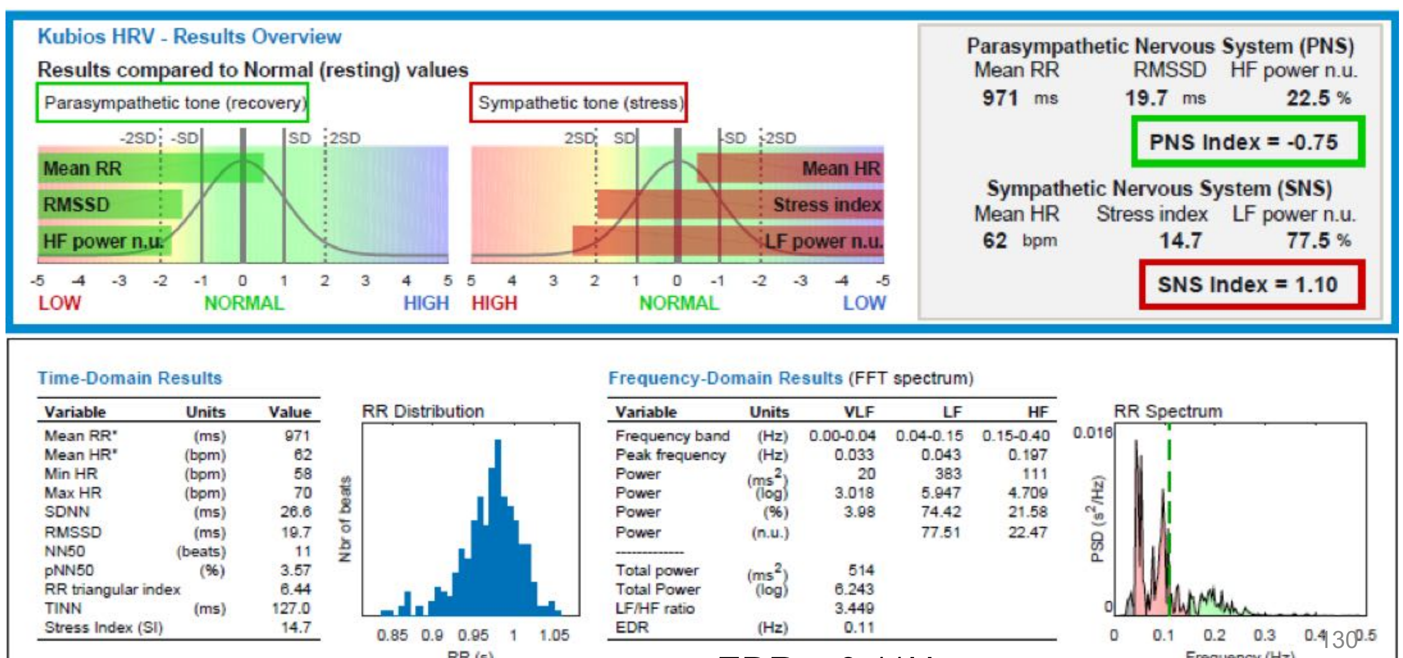




Variable	Units	Value
Mean RR*	(ms)	1137
Mean HR*	(bpm)	53
Min HR	(bpm)	50
Max HR	(bpm)	58
SDNN	(ms)	27.9
RMSSD	(ms)	23.6
NN50	(beats)	12
pNN50	(%)	4.56
RR triangular index		6.95
TINN	(ms)	135.0
Stress Index (SI)		11.6

Variable	Units	VLF	LF	HF
Frequency band	(Hz)	0.00-0.04	0.04-0.15	0.15-0.40
Peak frequency	(Hz)	0.023	0.137	0.247
Power	(ms^2)	95	414	124
Power	(log)	4.551	6.027	4.819
Power	(%)	14.96	65.45	19.57
Power	(n.u.)		76.97	23.01
Total power	(ms^2)	633		
Total Power	(log)	6.451		
LF/HF ratio		3.344		
EDR	(Hz)	0.24		

EDR = 0.24Hz



Variable	Units	Value
Mean RR*	(ms)	971
Mean HR*	(bpm)	62
Min HR	(bpm)	58
Max HR	(bpm)	70
SDNN	(ms)	26.6
RMSSD	(ms)	19.7
NN50	(beats)	11
pNN50	(%)	3.57
RR triangular index		6.44
TINN	(ms)	127.0
Stress Index (SI)		14.7

Variable	Units	VLF	LF	HF
Frequency band	(Hz)	0.00-0.04	0.04-0.15	0.15-0.40
Peak frequency	(Hz)	0.033	0.043	0.197
Power	(ms^2)	20	383	111
Power	(log)	3.018	5.947	4.709
Power	(%)	3.98	74.42	21.58
Power	(n.u.)		77.51	22.47
Total power	(ms^2)	514		
Total Power	(log)	6.243		
LF/HF ratio		3.449		
EDR	(Hz)	0.11		

EDR = 0.11Hz

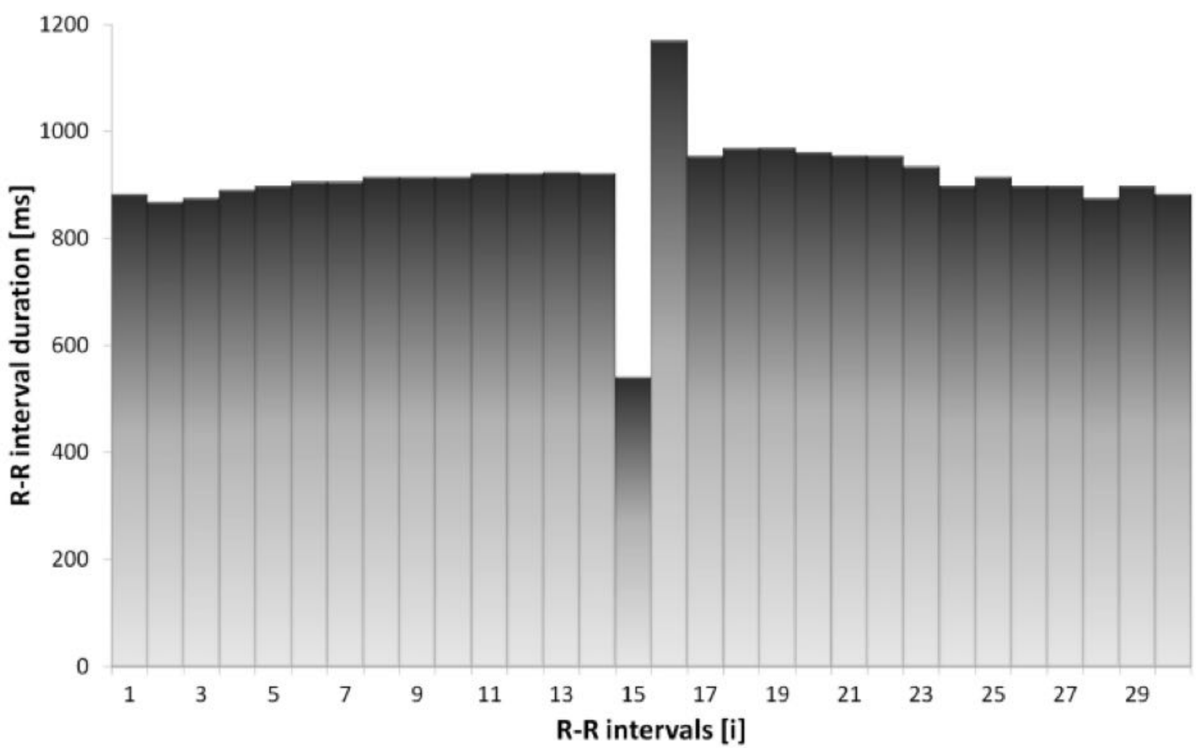
Note: abnormally high HF and low LF values can be found, with a low LF / HF ratio in depressive and anxious patients

Autonomic Function Imbalances Are Associated With:

- Depression
- Hypoglycemia
- Panic Disorder
- Sleep Disorder
- Asthma
- Fatigue
- Dizziness
- Nausea
- Irritable Bowel
- Fibromyalgia
- Hypertension
- Chemical Sensitivity
- Premenstrual Syndrome
- Anxiety
- Migraine
- Arrhythmia

Artifacts – Arrhythmia

- Artifacts due to movement, electrode connections, coughing, etc.
- Rhythmic disorder: Ventricular and atrial extrasystoles, fibrillation, bundle block



Intervalle court suivi d'un long

- Artifacts due to movement, electrode connections, coughing, etc.

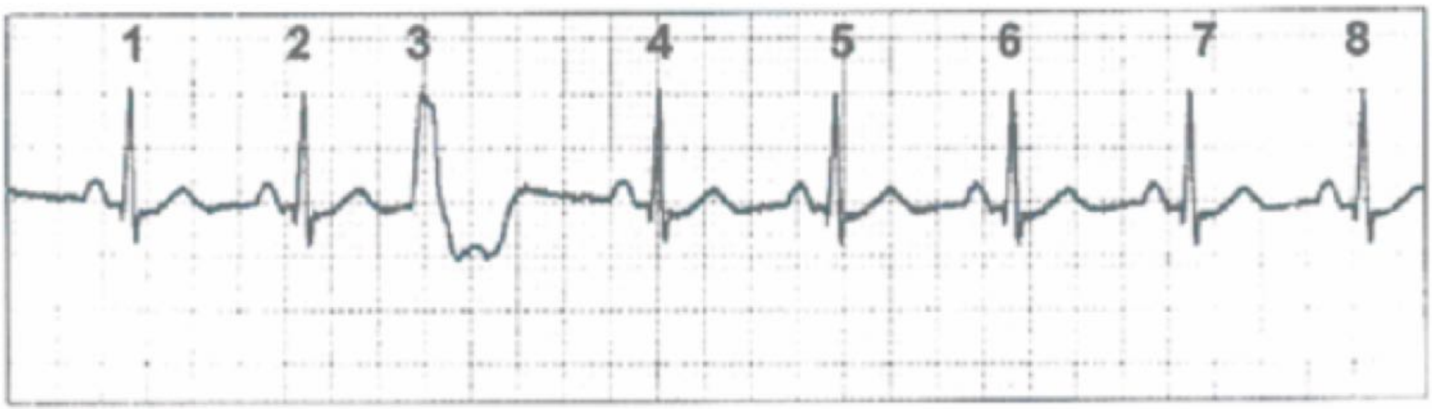

Kubios HRV Premium 3.1.0 - G:\DATA\20180419\14-02-04.EDF
File View Help
File Info
File name: 14-02-04.EDF
Rec. date: 19.04.18
Rec. time: 14.02.04
Channel label ECG
Sampling rate (Hz): 250
Data length (h:min:s): 00:08:31
RR Interval Series Options
Artifact correction
Apply
Undo
Samples for analysis 1
Add
Remove
Sample 1
Start (h:min:s) 14:04:40
Length (h:min:s) 00:05:00
Remove trend components
Method Smoothn priors
Lambda 500 f_c=0.035 Hz
NO MARKERS
Time (h:min:s)
Range (s) 10
Range (s) 512
Lock
RESULTS
Time-Domain
Frequency-Domain
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Sample 1
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
Mean RR = 802 ms
RMSSD = 12 ms
HF power n.u. = 13 %
LOW NORMAL HIGH
Sympathetic tone (stress)
Mean HR = 75 bpm
Stress index = 16
LF power n.u. = 87 %
HIGH NORMAL LOW
HR
AVG 75 bpm
Min 74 bpm
Max 76 bpm
RMSSD
AVG 11 ms
Stress Index
AVG 17
HR Zones
Stress
Energy Expenditure (BMR+Activity)
TOTAL 9+14=23 kcal
Personal data (from Preferences):
Gender = Female
Height = 180 cm
Age = 59 years
Weight: 80 kg
Max HR = 161 bpm
Change Personal Data

Ectopic beat : pre-auricular contraction (PAC)

Pre-auricular contraction can appear in the following cases:

- Benign incidental discovery
- Anxiety
- Med and stimulants, ex. alcohol, tobacco +++
- Cardiac decompensation
- Atrial hypertrophy
- Electrolyte disorders

Ectopic beat : pre-ventricular contraction (PVC)



Pre-ventricular contraction can appear in the following cases:

- Benign incidental discovery
- Anxiety, depression
- Med and stimulants, ex. alcohol, tobacco +++
- Cardiac decompensation
- Ventricular hypertrophy
- Electrolyte disorders

PVC

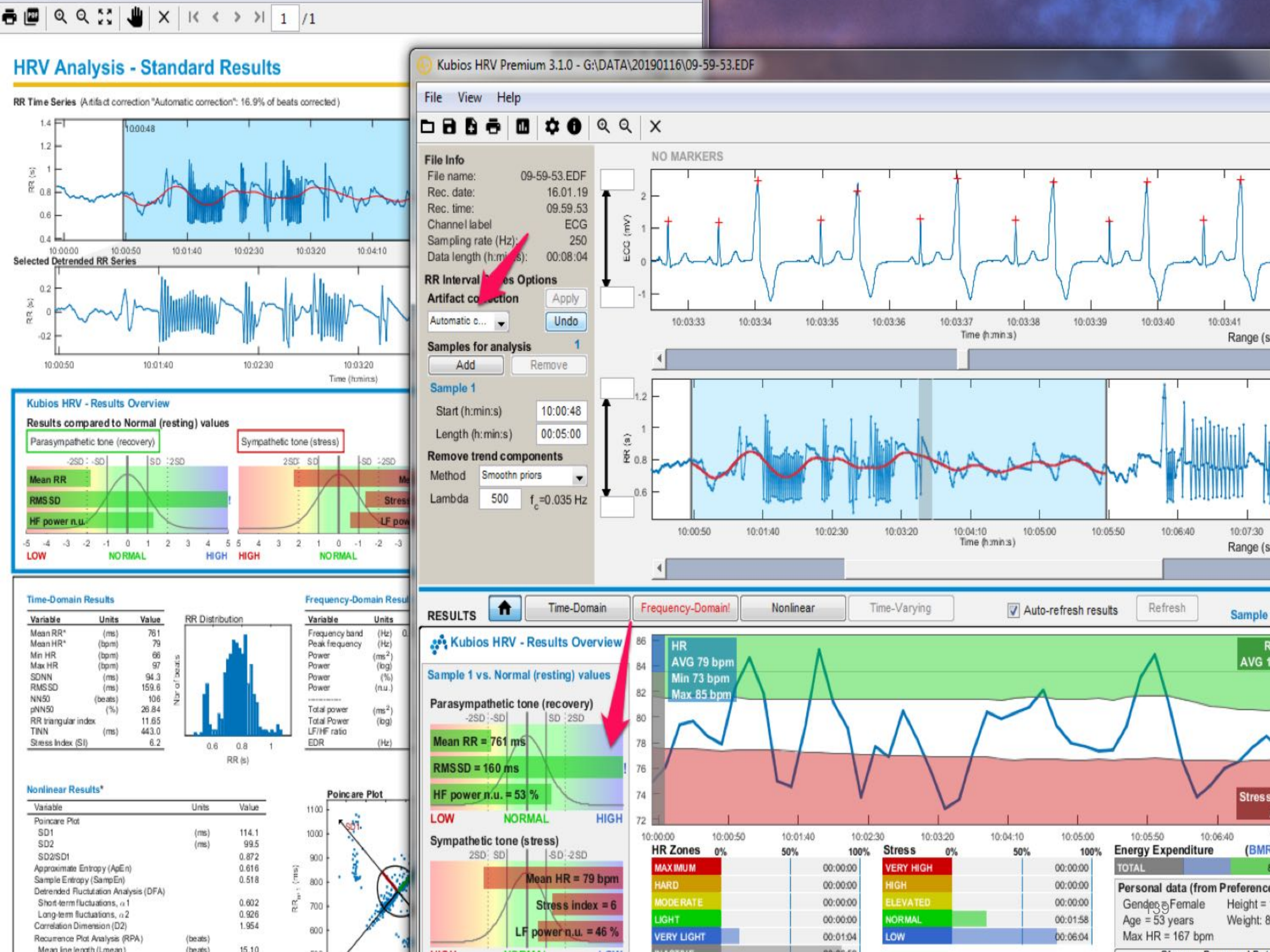
Ventricular uniform

Ventricular multiform

PVC

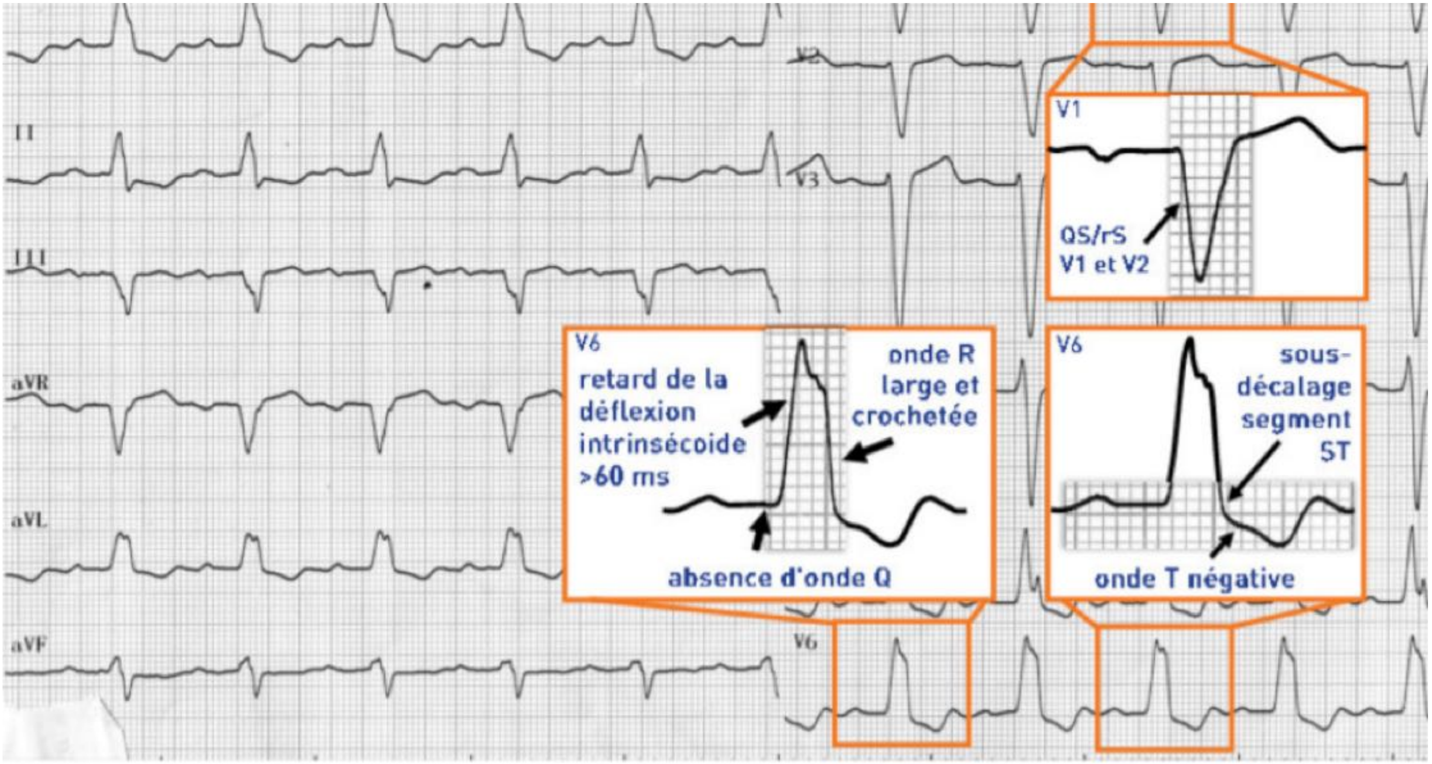

eMotion EDF Viewer
File Tools Help
Open EDF Gain: 1/4 Default 2x 4x Speed: 2/5 Default 2x
ECG - 10-11-14 x ECG - 10-46-51 x
500 µV
0.2 s
ECG


Kubios HRV Premium 3.1.0 - G:\DATA\20180419\14-02-04.EDF
File View Help
File Info
File name: 14-02-04.EDF
Rec. date: 19.04.18
Rec. time: 14.02.04
Channel label ECG
Sampling rate (Hz): 250
Data length (h:min:s): 00:08:31
RR Interval Series Options
Artifact correction
none
Apply
Undo
Samples for analysis 1
Add Remove
Sample 1
Start (h:min:s) 14:03:40
Length (h:min:s) 00:05:00
Remove trend components
Method Smoothn priors
Lambda 500 fc=0.035 Hz
NO MARKERS
Time (h:min:s)
Range (s) 10
Range (s) 512
Lock
RESULTS
Time-Domain
Frequency-Domain
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Sample 1
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
Mean RR = 802 ms
RMSSD = 60 ms
HF power n.u. = 31 %
LOW NORMAL HIGH
Sympathetic tone (stress)
Mean HR = 75 bpm
Stress index = 7
LF power n.u. = 69 %
HIGH NORMAL LOW
HR
AVG 75 bpm
Min 70 bpm
Max 76 bpm
RMSSD
AVG 63 ms
Stress Index
AVG 10
HR Zones
MAXIMUM
HARD
MODERATE
LIGHT
VERY LIGHT
INACTIVE 00:08:28
Stress
VERY HIGH
HIGH
ELEVATED 00:03:39
NORMAL
LOW 00:04:49
Energy Expenditure (BMR+Activity)
TOTAL 9+14=22 kcal
Personal data (from Preferences):
Gender = Female
Height = 180 cm
Age = 59 years
Weight: 80 kg
Max HR = 161 bpm
Change Personal Data



HRV Analysis - Standard Results
RR Time Series (Artifact correction "Automatic correction": 16.9% of beats corrected)
Selected Detrended RR Series
Time (h:min:s)
Kubios HRV - Results Overview
Results compared to Normal (resting) values
Parasympathetic tone (recovery)
Sympathetic tone (stress)
Mean RR
RMSSD
HF power n.u.
LOW
NORMAL
HIGH
Time-Domain Results
RR Distribution
Frequency-Domain Results
Nonlinear Results*
Poincare Plot
Kubios HRV Premium 3.1.0 - G:\DATA\20190116\09-59-53.EDF
File
View
Help
File Info
File name: 09-59-53.EDF
Rec. date: 16.01.19
Rec. time: 09.59.53
Channel label ECG
Sampling rate (Hz): 250
Data length (h:min:s): 00:08:04
RR Interval Series Options
Artifact correction
Apply
Automatic c...
Undo
Samples for analysis 1
Add
Remove
Sample 1
Start (h:min:s) 10:00:48
Length (h:min:s) 00:05:00
Remove trend components
Method Smoothn priors
Lambda 500 f_c=0.035 Hz
NO MARKERS
RESULTS
Time-Domain
Frequency-Domain!
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
Mean RR = 761 ms
RMSSD = 160 ms
HF power n.u. = 53 %
Sympathetic tone (stress)
Mean HR = 79 bpm
Stress index = 6
LF power n.u. = 46 %
HR
AVG 79 bpm
Min 73 bpm
Max 85 bpm
HR Zones
MAXIMUM
HARD
MODERATE
LIGHT
VERY LIGHT
Stress
VERY HIGH
HIGH
ELEVATED
NORMAL
LOW
Energy Expenditure
TOTAL
Personal data (from Preferences)
Gender = Female
Age = 53 years
Max HR = 167 bpm

Bundle block left



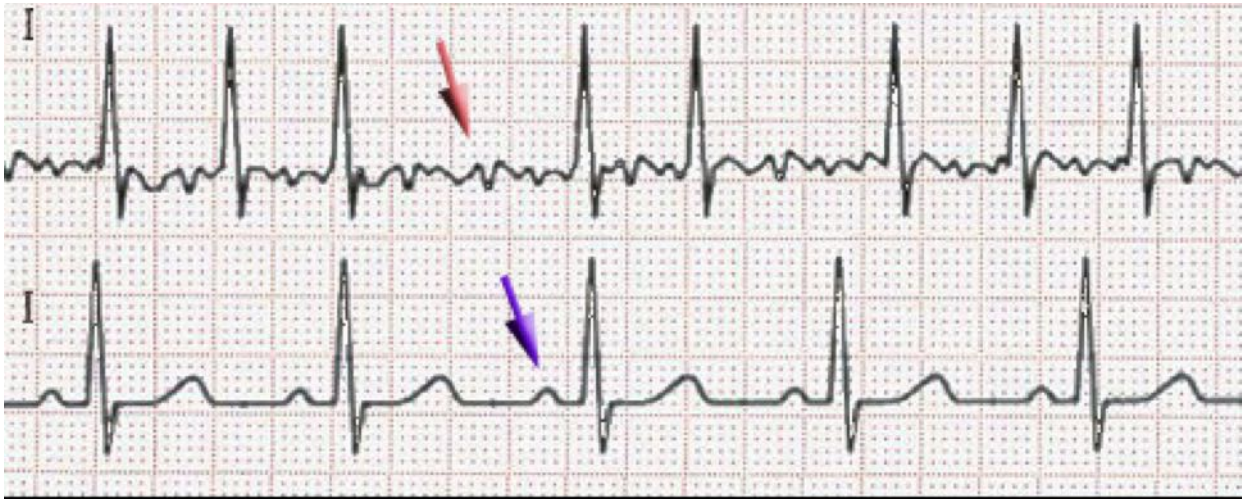
Bundle block left


Kubios HRV Premium 3.1.0 - G:\DATA\20180815\11-35-08.EDF
File
View
Help
File Info
File name: 11-35-08.EDF
Rec. date: 15.08.18
Rec. time: 11.35.08
Channel label ECG
Sampling rate (Hz): 250
Data length 00:06:50
RR Interval Series Options
Artifact correction
Apply
Undo
Samples for analysis 1
Add
Remove
Sample 1
Start (h:min:s) 11:35:08
Length (h:min:s) 00:05:00
Remove trend components
Method Smoothn priors
Lambda 500
NO MARKERS
Time (h:min:s)
Range (s) 10
Range (s) 411
Lock
RESULTS
Time-Domain
Frequency-Domain
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Sample 1
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
Mean RR = 939 ms
RMSSD = 84 ms
HF power n.u. = 74 %
LOW
NORMAL
HIGH
Sympathetic tone (stress)
Mean HR = 64 bpm
Stress index = 6
LF power n.u. = 25 %
HIGH
NORMAL
LOW
HR
AVG 64 bpm
Min 62 bpm
Max 66 bpm
RMSSD
AVG 105 ms
Stress Index
AVG 7
HR Zones
MAXIMUM
HARD
MODERATE
LIGHT
VERY LIGHT
INACTIVE 00:06:47
Stress
VERY HIGH
HIGH
ELEVATED
NORMAL 00:01:29
LOW 00:05:18
Energy Expenditure
(BMR + Activity)
TOTAL
Personal data (from Preferences):
Gender = Female
Height = 180 cm
Age = 59 years
Weight: 80 kg
Max HR = 161 bpm
Change Personal Data

Kubios HRV Premium 3.1.0 - G:\DATA\20180202\10-48-54.EDF
File View Help
File Info
File name: 10-48-54.EDF
Rec. date: 02.02.18
Rec. time: 10.48.54
Channel label ECG
Sampling rate (Hz): 250
RR Interval Series Options
Samples for analysis 1
Add
Remove
Sample 1
Start (h:min:s) 10:49:19
Length (h:min:s) 00:05:00
Remove trend components
Method Smoothn priors
Lambda 500
NO MARKERS
Range (s) 10
Range (s) 370
Lock
RESULTS
Time-Domain
Frequency-Domain
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Sample 1
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
Mean RR = 969 ms
RMSSD = 58 ms
HF power n.u. = 88 %
LOW NORMAL HIGH
Sympathetic tone (stress)
Mean HR = 62 bpm
Stress index = 8
LF power n.u. = 11 %
HIGH NORMAL LOW
HR
AVG 62 bpm
Min 60 bpm
Max 65 bpm
RMSSD
AVG 48 ms
Stress Index
AVG 14
HR Zones
Stress
Energy Expenditure
Personal data (from Preferences):
Gender = Male
Age = 59 years
Max HR = 161 bpm
Height = 180 cm
Weight: 80 kg
Change Personal Data

Auricular fibrillation

- The most common arrhythmia
- One of the main causes of ischemic stroke
- Old person ATCD of CV troubles
- OH +++
- Narcotics
- Parkinson
- Sportsman (endurance: cycling and / or running +++)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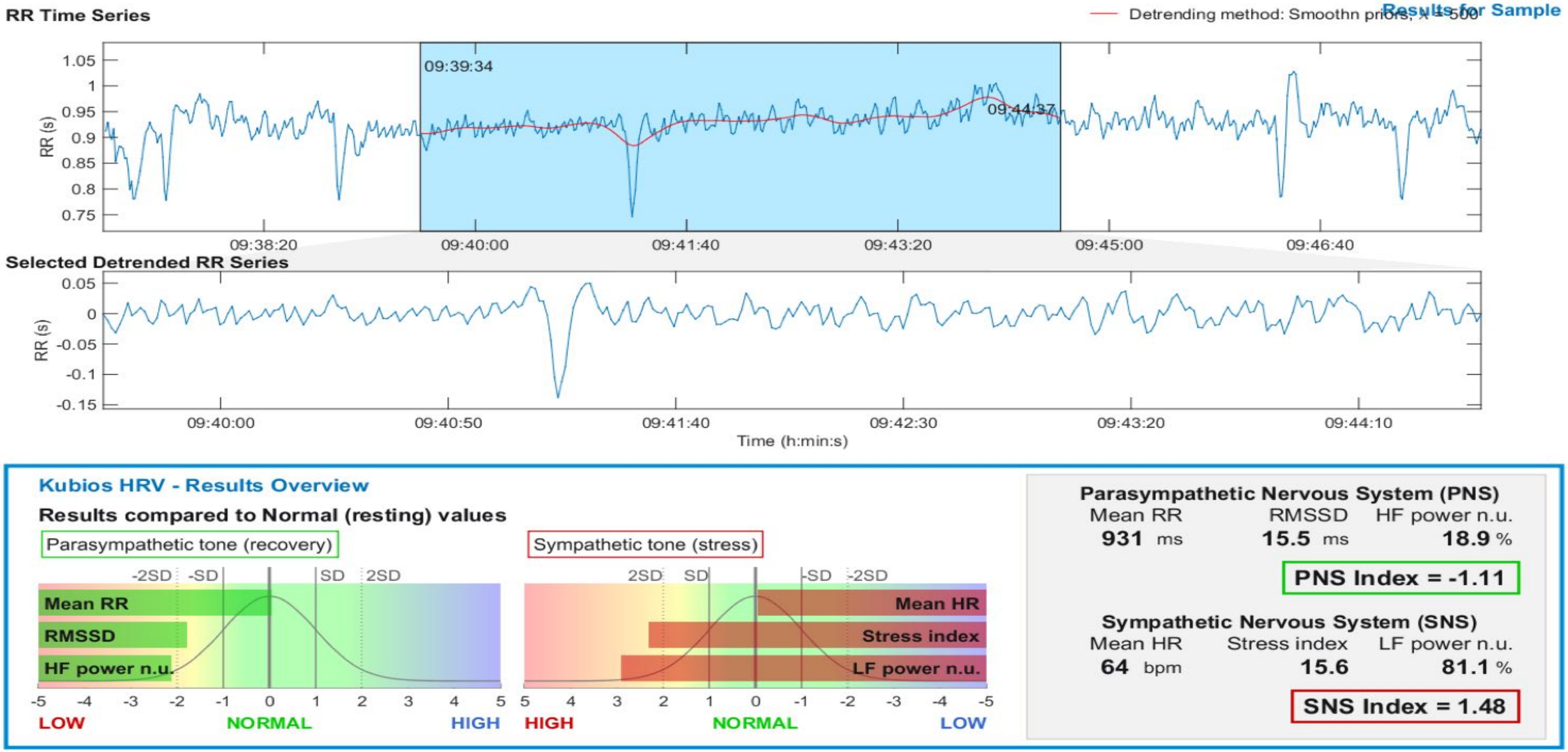
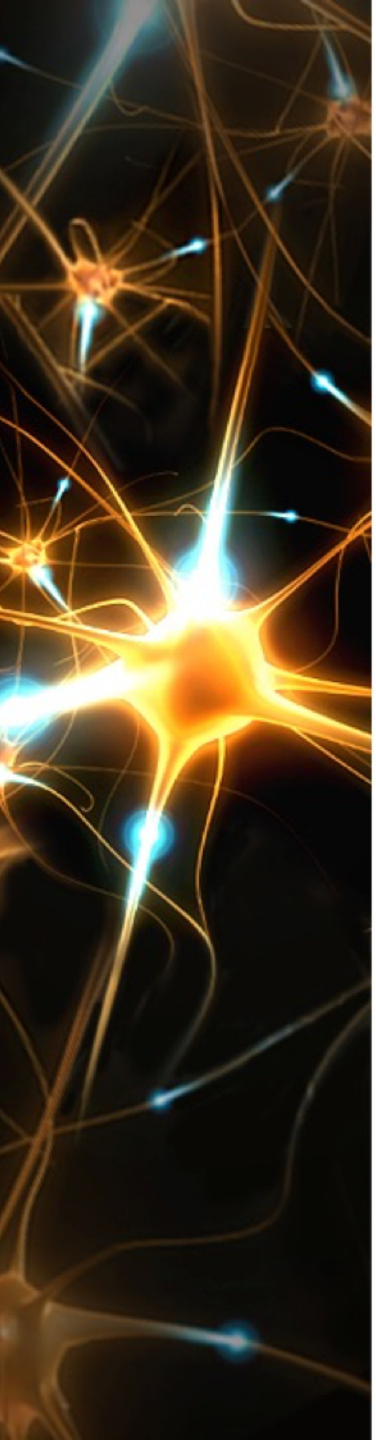
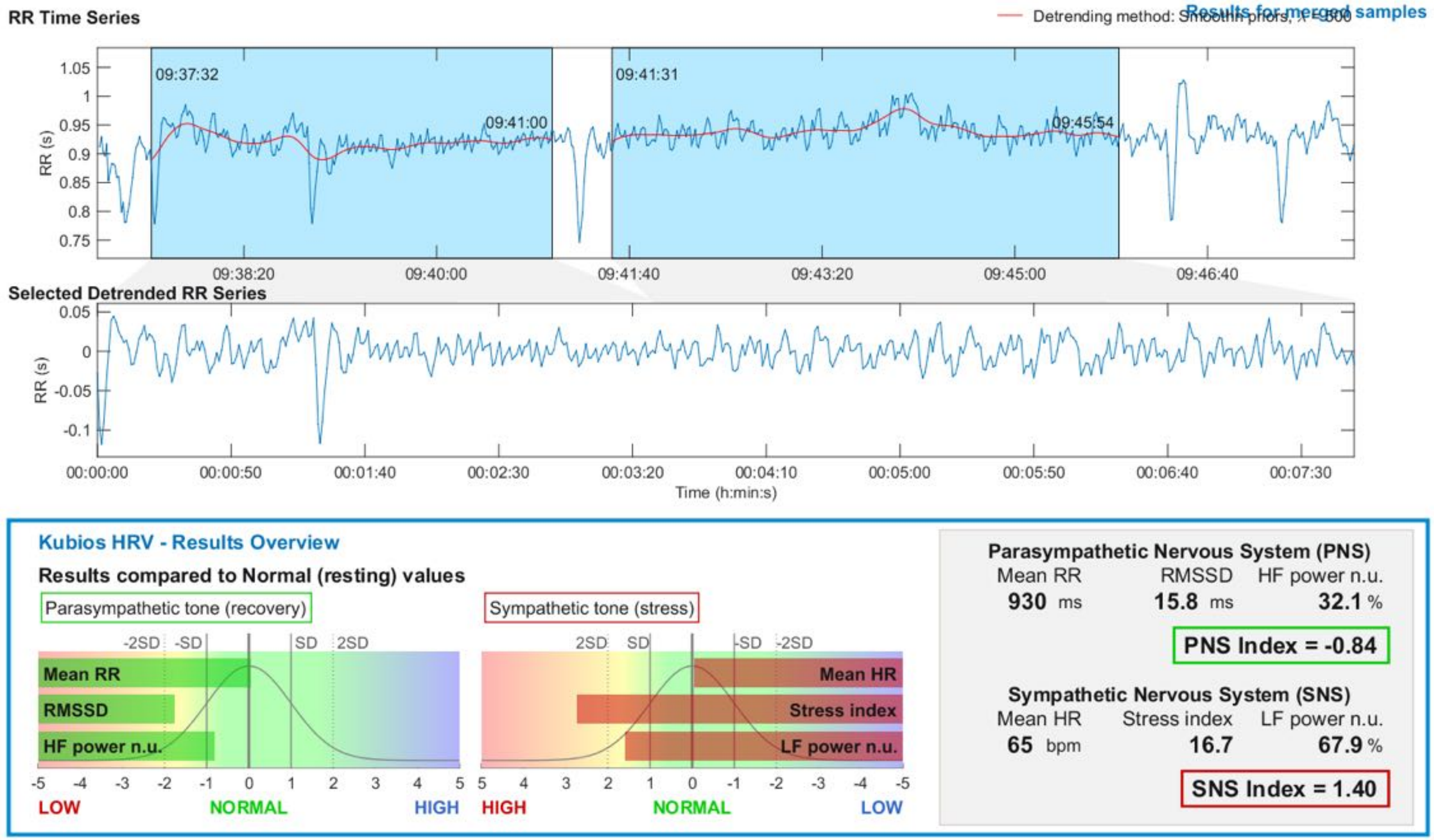
Kubios HRV Premium 3.2.0 - G:\DATA\20190205\11-31-39.EDF
File View Tools Help
File Info
File name: 11-31-39.EDF
Rec. date: 05.02.19
Rec. time: 11.31.39
Channel label ECG
Sampling rate (Hz): 250
Data length (h:min:s): 00:10:19
Artifact correction
none 0.3
Samples for analysis 1
Add Remove
Sample 1
Start (h:min:s) 11:35:11
Length (h:min:s) 00:05:00
Sample Label
Sample Color Color
Sample artifacts Uncorrected
NO MARKERS
ECG (mV)
Time (h:min:s)
Range (s) 10
RR (s)
Show/hide original RR
Range (s) 620
RESULTS
Time-Domain
Frequency-Domain
Nonlinear
Time-Varying
Auto-refresh results
Refresh
Sample 1
Kubios HRV - Results Overview
Sample 1 vs. Normal (resting) values
Parasympathetic tone (recovery)
PNS Index = 1.26
Mean RR = 1179 ms
RMSSD = 48 ms
SD1 = 29 %
LOW NORMAL HIGH
Sympathetic tone (stress)
SNS Index = -1.23
Mean HR = 51 bpm
Stress index = 7
SD2 = 71 %
HIGH NORMAL LOW
HR
AVG 51 bpm
Min 48 bpm
Max 53 bpm
RMSSD
AVG 48 ms
Stress Index
AVG 9
HR Zones
MAXIMUM 00:00:00
HARD 00:00:00
MODERATE 00:00:00
LIGHT 00:00:00
VERY LIGHT 00:00:00
INACTIVE 00:10:17
Stress
VERY HIGH 00:00:00
HIGH 00:00:00
ELEVATED 00:00:00
NORMAL 00:06:58
LOW 00:03:19
Energy Expenditure 0 / 9 kcal
BMR
Personal data (from Preferences):
Gender = Female
Age = 54 years
Max HR = 166 bpm
Height = 173 cm
Weight: 60 kg
Change Personal Data

One or more sample





… same patient…same record



Result comes from the merge of the two samples

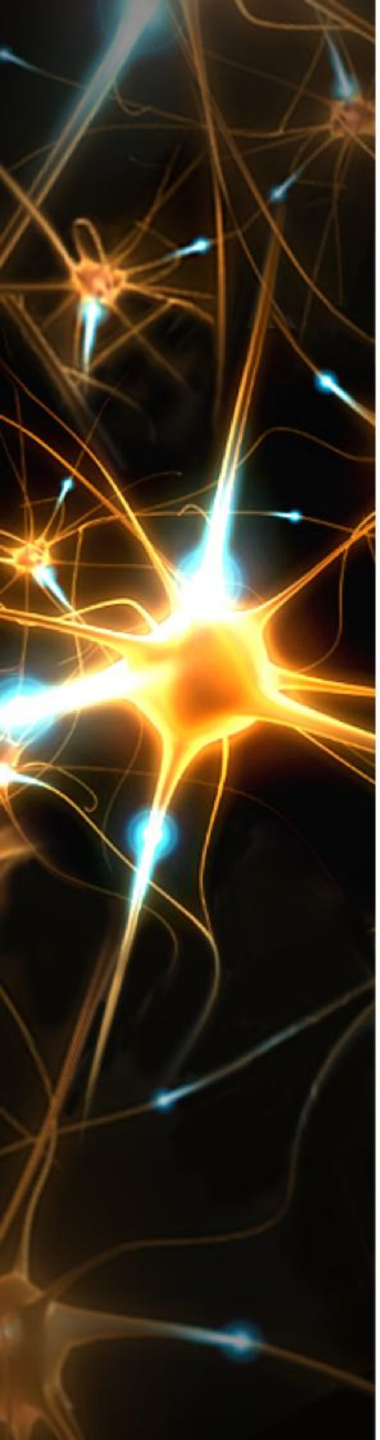


Table 1: Time domain measures

Parameter	Unit	Description
SDNN	ms	Standard deviation of NN intervals
SDRR	ms	Standard deviation of RR intervals
SDANN	ms	Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording
SDNN index (SDNNI)	ms	Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms
HR Max – HR Min	bpm	Average difference between the highest and lowest heart rates during each respiratory cycle
RMSSD	ms	Root mean square of successive RR interval differences
HRV triangular index		Integral of the density of the RR interval histogram divided by its height
TINN	ms	Baseline width of the RR interval histogram

Interbeat interval, time interval between successive heartbeats; NN intervals, interbeat intervals from which artifacts have been removed; RR intervals, interbeat intervals between all successive heartbeats.

(red ellipse) : reflects parasympathetic activity in short term recordings (HF)

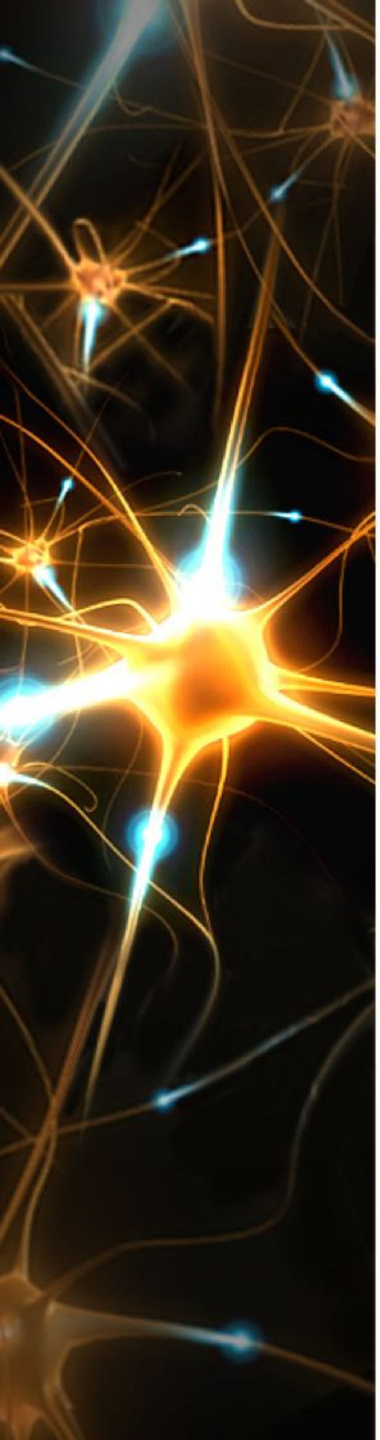


Table 2: normal reference values (healthy subjects) - short-term variability (5min)

Age Range	Gender	Mean NN (ms)	rMSSD (ms)	ln(rMSSD) (ms)	SDNN (ms)	PNN50 (%)	LF (Hz)	HF (Hz)	LF/HF	SD1/SD2
25 - 34	**Male** (330)	939 ± 129	39.7 ± 19.9	3.68	50.0 ± 20.9	20 ± 17	242 ± 325	133 ± 174	2.79 ± 3.20	0.44 ± 0.12
	Female (208)	900 ± 116	42.9 ± 22.8	3.76	48.7 ± 19.0	23 ± 20	184 ± 199	161 ± 167	1.75 ± 1.78	0.49 ± 0.16
35 - 44	**Male** (292)	925 ± 138	32.0 ± 16.5	3.47	44.6 ± 16.8	13 ± 15	191 ± 206	89 ± 118	3.62 ± 3.73	0.39 ± 0.13
	Female (259)	903 ± 122	35.4 ± 18.5	3.57	45.4 ± 20.5	16 ± 17	161 ± 177	121 ± 145	2.21 ± 2.16	0.43 ± 0.15
45 - 54	**Male** (235)	923 ± 134	23.0 ± 10.9	3.14	36.8 ± 14.6	6 ± 8	113 ± 141	41 ± 49	4.10 ± 3.48	0.34 ± 0.13
	Female (158)	903 ± 109	26.3 ± 13.6	3.27	36.9 ± 13.8	8 ± 12	107 ± 136	62 ± 83	2.43 ± 1.99	0.39 ± 0.13
55 - 64	**Male** (183)	904 ± 123	19.9 ± 11.1	2.99	32.8 ± 14.7	4 ± 7	80 ± 103	29 ± 38	4.17 ± 3.60	0.32 ± 0.11
	Female (95)	868 ± 118	21.4 ± 11.9	3.06	30.6 ± 12.4	5 ± 8	57 ± 59	35 ± 53	2.87 ± 3.32	0.38 ± 0.16
65 - 74	**Male** (84)	906 ± 123	19.1 ± 10.7	2.95	29.6 ± 13.2	4 ± 7	70 ± 112	22 ± 29	4.77 ± 5.34	0.36 ± 0.19
	Female (62)	873 ± 110	19.1 ± 11.8	2.95	27.8 ±11.8	4 ± 6	45 ± 56	29 ± 38	2.97 ± 3.18	0.36 ± 0.15

Source: Voss A et al., 2015
N = 1906 healthy subjects age 25-74 years (excluded 2201 subjects from study due to cardiac arrhythmia, diseases, medication, and pregnancy)
Short term 5 minute duration measurements using ECG

7. Osteopathic Centers

An osteopathic center is that point on the surface of the body which has been shown to be in close central relation to a physiological center, or in relation to a nervous bundle. Tasker, D.L. (1903)

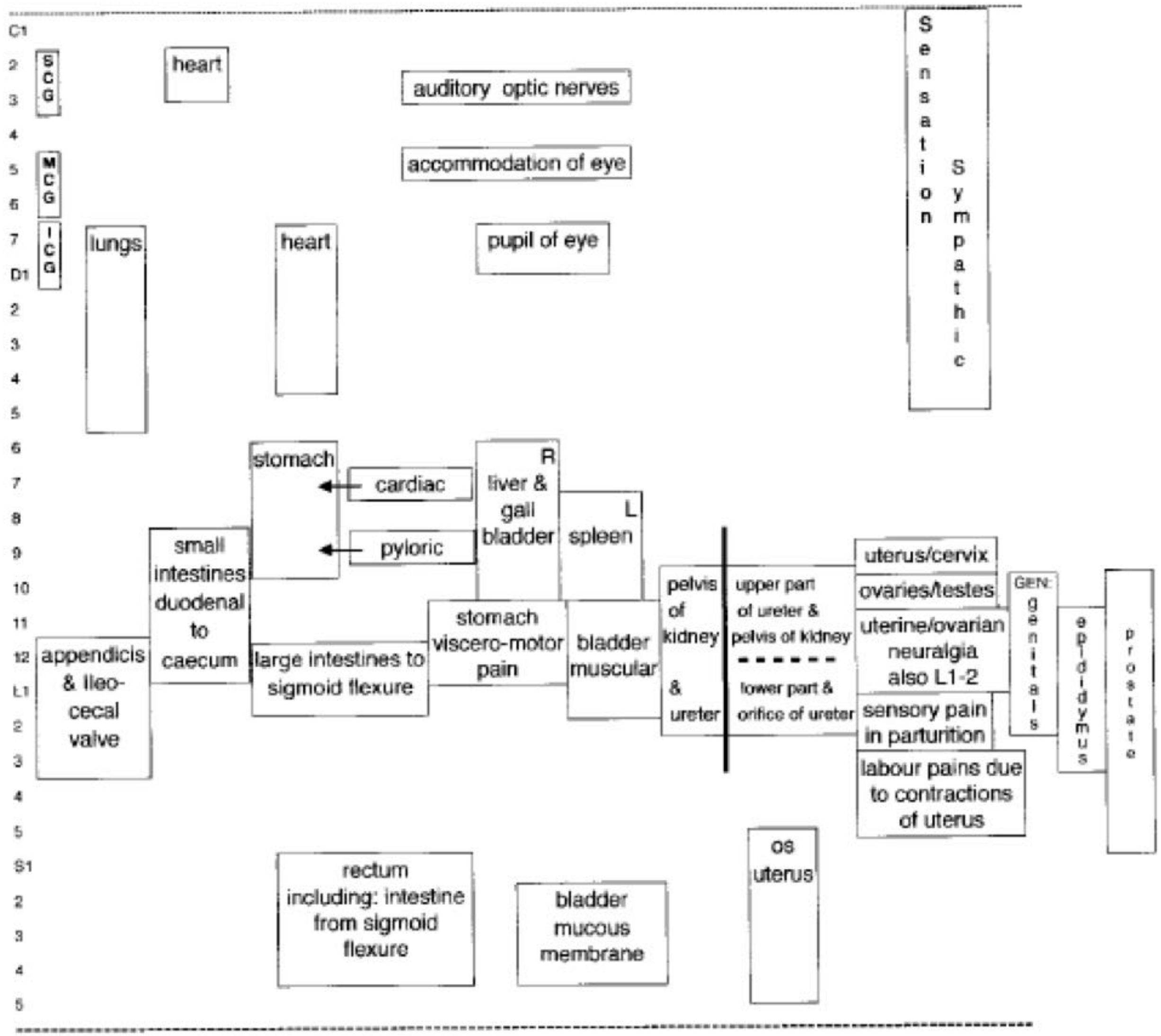
The concept of the osteopathic center provides indications for the treatment, in general, but does not represent a button for the treatment of the organ or structure with which it is related. (~~push-button therapy~~)

<u>Sensitive</u>: They represent the different organs in relation to the column. "Almost all diseases start on the sensitive side". Sensitive dimension of primary lesion => inhibitory treatment. JM. Littlejohn (1911) Ex. Pain, muscle contractures.

<u>Motors</u> (included secretomotors): related to the function of the organ or viscera.

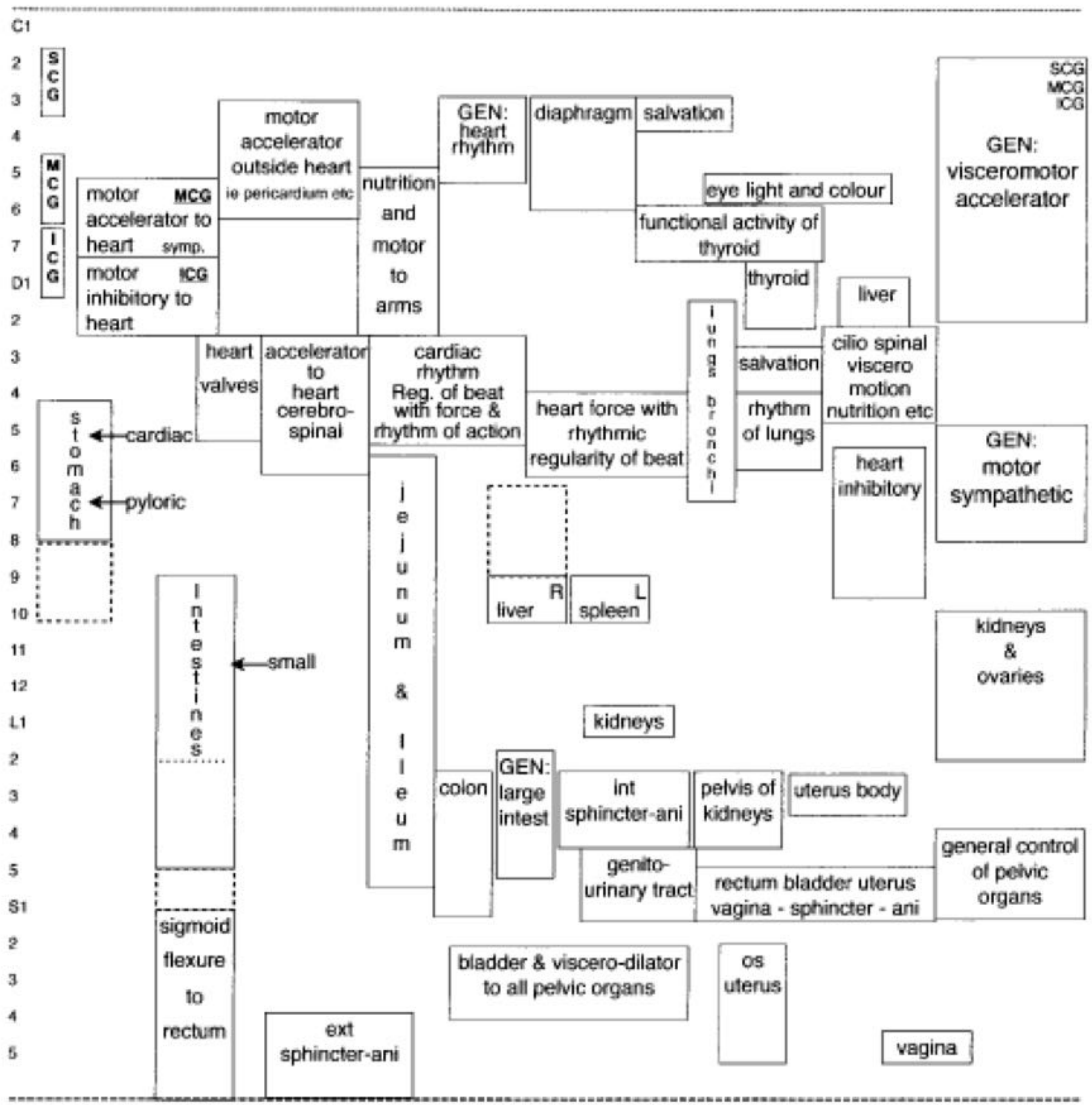
<u>Vasomotors:</u> control and coordination of blood and lymphatic circulation in different parts of the body.

Sensory Centres



R Vagus, Body of Stomach
Endocrine
Pituitary, Base of Skull, Bridge of Nose, C3, C7/D1, S2
Thyroid, D2, C6/7 (Sensory), D4 in Relation to Adrenals
Adrenals, D11, D7/8, Sciatic Nerve, D4
D2, Centre for Lymphatics and Indirectly Thyroid
D4, General Endocrine Centre with C3 and D11

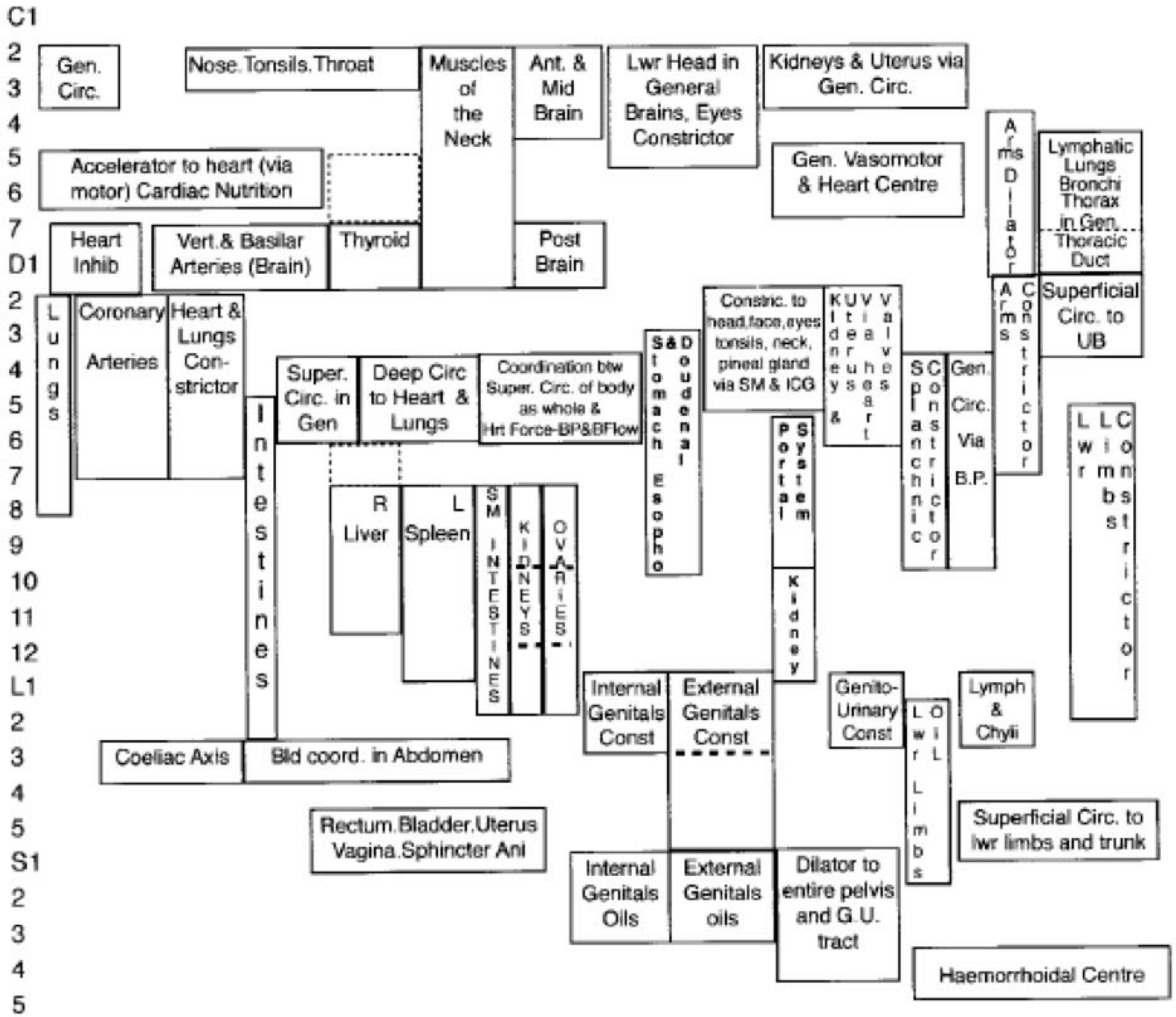
Motor Centres



Vagus: Heart (R)
Bronchi and lungs
Body of stomach (R)
Intestine to sigmoid flexure
Spleen (L)

Vagus C1-6 spinal accessary inhibitory to heart

Vaso-Motor Centres

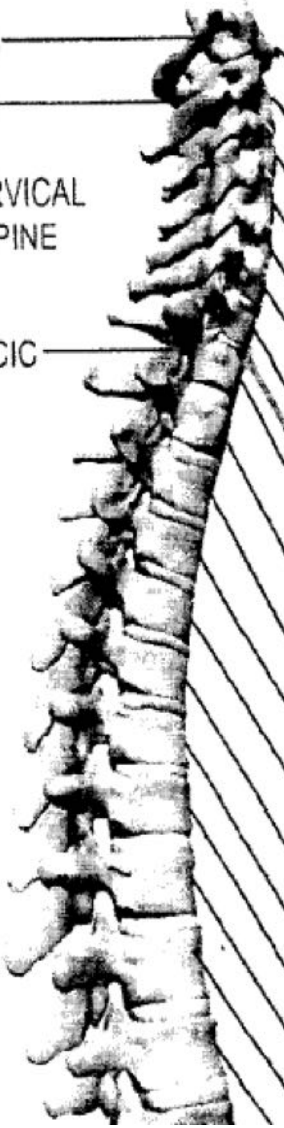


Body Trunk (1) D2-L2 Vaso-constrictor at segments corresponding with body
(2) Cutaneous Vasoconstrictor direct from sympathetic ganglion.
(3) Vaso-Dilator via motor nerves to muscles.

Spleen: Vagus Vaso-Motor Constrictor
Heart: Vagus (L)
Mesenteric: D5-10 Constrictor:Dilators via spinal nerves not ganglia
Tongue: Dilator: Cranial Nerve 5 via Cranial Nerve 9
Nose.Tonsils.Throat. via Cranial Nerve 9-10

Splanchnics

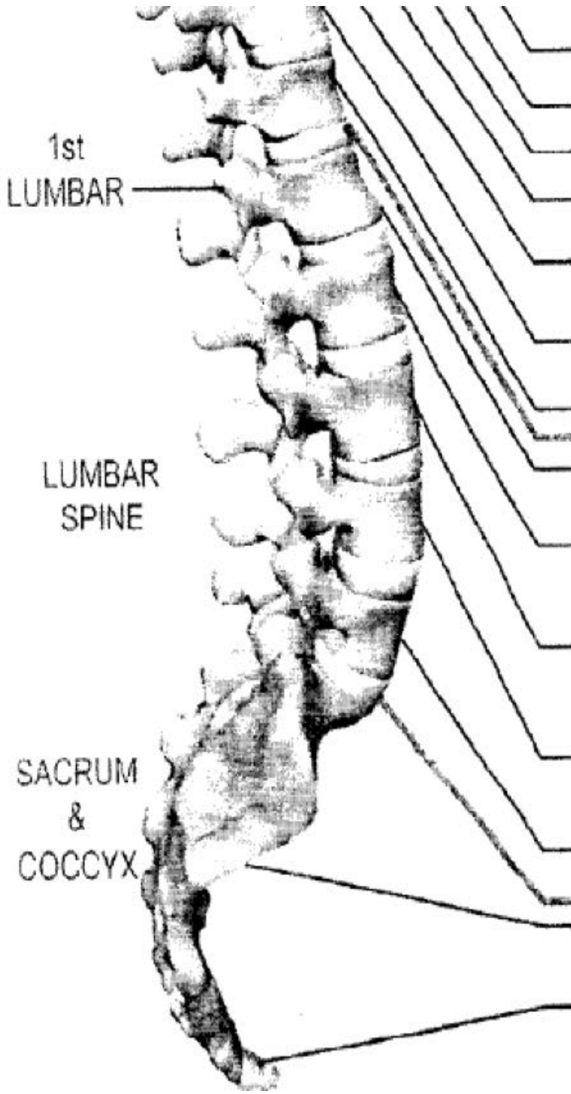
GT - (D1-4), D5-10
LSR - D10-11
LST - D12



Vertebrae	Areas & Parts of Body	Possible symptoms
C1	Blood supply to the head, pituitary gland, scalp, bones of the face, brain, inner and middle ear, sympathetic nervous system.	❑ Headaches ❑ nervousness ❑ insomnia ❑ head colds ❑ high blood pressure ❑ migraine headaches ❑ nervous breakdowns ❑ amnesia ❑ chronic tiredness ❑ dizziness
C2	Eyes, optic nerves, auditory nerves, sinuses, mastoid bones, tongue, forehead.	❑ Sinus trouble ❑ allergies ❑ pain around the eyes ❑ earache ❑ fainting spells ❑ certain cases of blindness ❑ crossed eyes ❑ deafness
C3	Cheeks, outer ear, face bones, teeth, trifacial nerve.	❑ Neuralgia ❑ neuritis ❑ acne or pimples ❑ eczema
C4	Nose, lips, mouth, eustachian tube.	❑ Hay fever ❑ runny nose ❑ hearing loss ❑ adenoids
C5	Vocal cords, neck glands, pharynx.	❑ Laryngitis ❑ hoarseness ❑ throat conditions such as sore throat or quinsy
C6	Neck muscles, shoulders, tonsils.	❑ Stiff neck ❑ pain in upper arm ❑ tonsillitis ❑ chronic cough ❑ croup
C7	Thyroid gland, bursae in the shoulders, elbows.	❑ Bursitis ❑ colds ❑ thyroid conditions
T1	Arms from the elbows down, including hands, wrists, and fingers, esophagus and trachea.	❑ Asthma ❑ cough ❑ difficult breathing ❑ shortness of breath ❑ pain in lower arms and hands
T2	Heart, including its valves and covering, coronary arteries.	❑ Functional heart conditions and certain chest conditions
T3	Lungs, bronchial tubes, pleura, chest, breast.	❑ Bronchitis ❑ pleurisy ❑ pneumonia ❑ congestion ❑ influenza
T4	Gallbladder, common duct.	❑ Gallbladder conditions ❑ jaundice ❑ shingles
T5	Liver, solar plexus, circulation (general).	❑ Liver conditions ❑ fevers ❑ blood pressure problems ❑ poor circulation ❑ arthritis
T6	Stomach.	❑ Stomach troubles including: ❑ nervous stomach ❑ indigestion ❑ heartburn ❑ dyspepsia ❑

NECK REGION

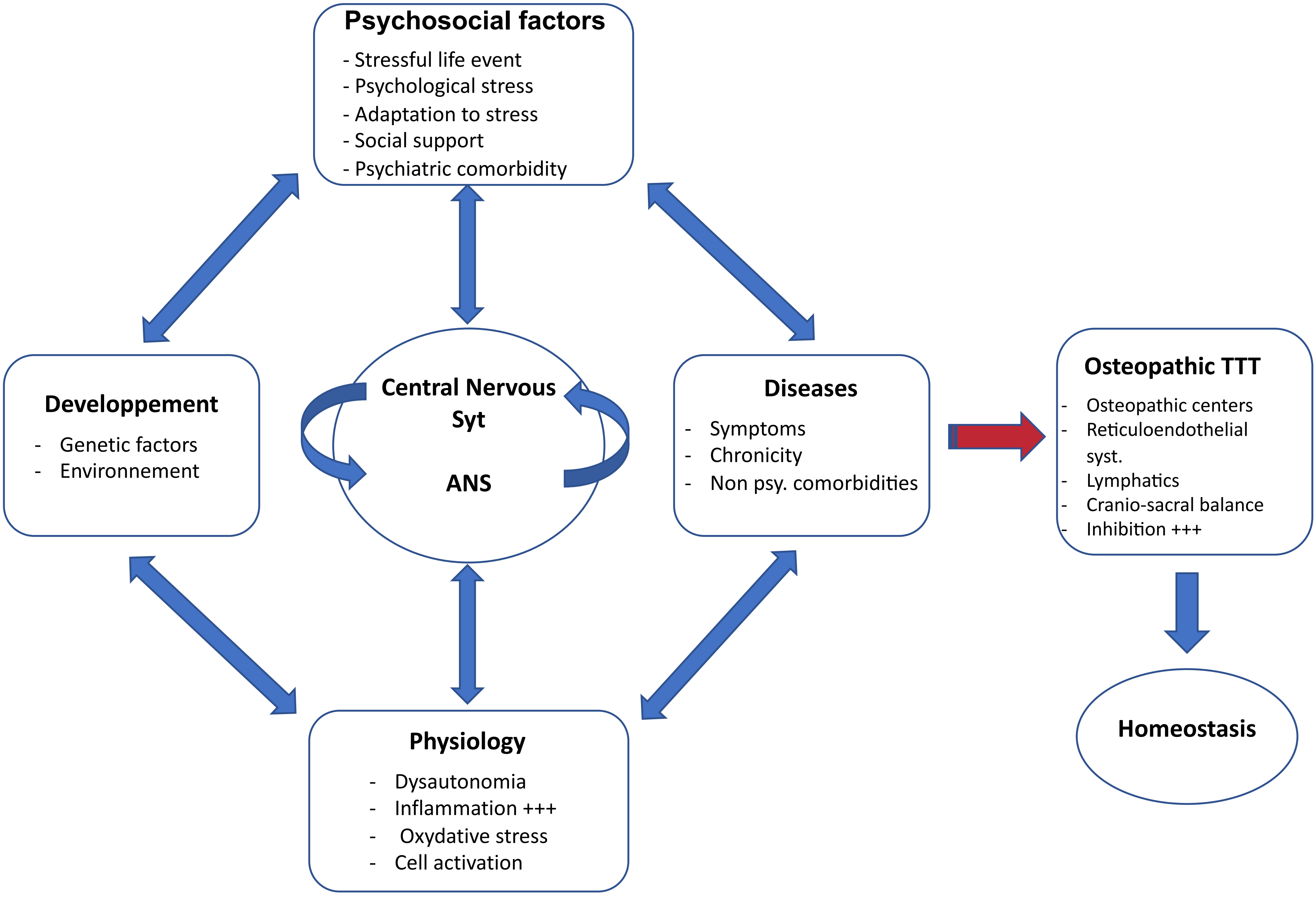
BACK



T6	Stomach.	MID-BACK	❏ Stomach troubles including: ❏ nervous stomach ❏ indigestion ❏ heartburn ❏ dyspepsia ❏
T7	Pancreas, duodenum	MID-BACK	❏ Ulcers ❏ gastritis
T8	Spleen.		❏ Lowered resistance
T9	Adrenal and suprarenal glands.		❏ Allergies ❏ hives
T10	Kidneys.		❏ Kidney troubles ❏ hardening of the arteries ❏ chronic tiredness ❏ nephritis ❏ pyelitis
T11	Kidneys, ureters		❏ Skin conditions such as acne ❏ pimples ❏ eczema ❏ boils
T12	Small intestines, lymph circulation.		❏ Rheumatism ❏ gas pains ❏ certain types of sterility
L1	Large intestines, inguinal rings.	LOW-BACK	❏ Constipation ❏ colitis ❏ dysentery ❏ diarrhea ❏ some ruptures or hernias ❏
L2	Appendix, abdomen, upper leg.	LOW-BACK	❏ Cramps ❏ difficult breathing ❏ minor varicose veins
L3	Sex organs, uterus, bladder, knees.	LOW-BACK	❏ Bladder troubles ❏ menstrual troubles such as painful or irregular periods ❏ miscarriages ❏ bed wetting ❏ impotency ❏ change of life symptoms ❏ many knee pains
L4	Prostate gland, muscles of the lower back, sciatic nerve.	LOW-BACK	❏ Sciatica ❏ lumbago ❏ difficult, painful or too frequent urination ❏ backaches
L5	Lower legs, ankles, feet.	LOW-BACK	❏ Poor circulation in the legs ❏ swollen ankles ❏ weak ankles and arches ❏ cold feet ❏ weakness in the legs ❏ leg cramps
SACRUM	Hip bones, buttocks.	PELVIS	❏ Sacroiliac conditions ❏ spinal curvatures
COCCYX	Rectum, anus.	PELVIS	❏ Hemorrhoids (piles) ❏ pruritus (itching) ❏ pain at end of spine on sitting

ANS - Résumé des centres vertébraux

Structures & Organs	Sympathetic Innervation	Parasympathetic Innervation
Head and neck	T1-T4	Cranial nerves III, VII, IX, X
Heart	T1-T5	Vagus nerve (X)
Respiratory system	T1-T7	Vagus nerve (X)
Esophagus	T2-T8	Vagus nerve (X)
Upper GI tract	T5-T9	Vagus nerve (X)
Stomach	T5-T9	Vagus nerve (X)
Liver	T5-T9	Vagus nerve (X)
Gallbladder	T5-T9	Vagus nerve (X)
Spleen	T5-T9	Vagus nerve (X)
Portions of the pancreas		
and Duodenum	T5-T9	Vagus nerve (X)
Middle GI tract		
Jejunum	T9-T12	Vagus nerve (X)
Ileum	T9-T12	Vagus nerve (X)
Ascending colon	T9-T12	Vagus nerve (X)
Proximal 2/3 of transverse Colon		
Lower GI tract	T12-L2	S2-S4
Distal 1/3 of transverse colon		
Descending colon	T12-L2	S2-S4
Sigmoid colon	T12-L2	S2-S4
Rectum	T12-L2	S2-S4
Kidneys	T11-L1	Vagus nerve (X)
Upper portion ureter	T10-L1	Vagus nerve (X)
Lower portion ureter	L1-L2	S2–S4
Urinary bladder & urethra	T11-L2	S2–S4
Gonads	T10-T11	S2–S4
Uterus and cervix	T10-L2	S2–S4
Erectile tissue-penis/clitoris	T11-L2	S2–S4
Extremities		
Arms	T5-T7	None
Legs	T10-T12	None



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“The germ is nothing, the terrain is everything”

Louis Pasteur