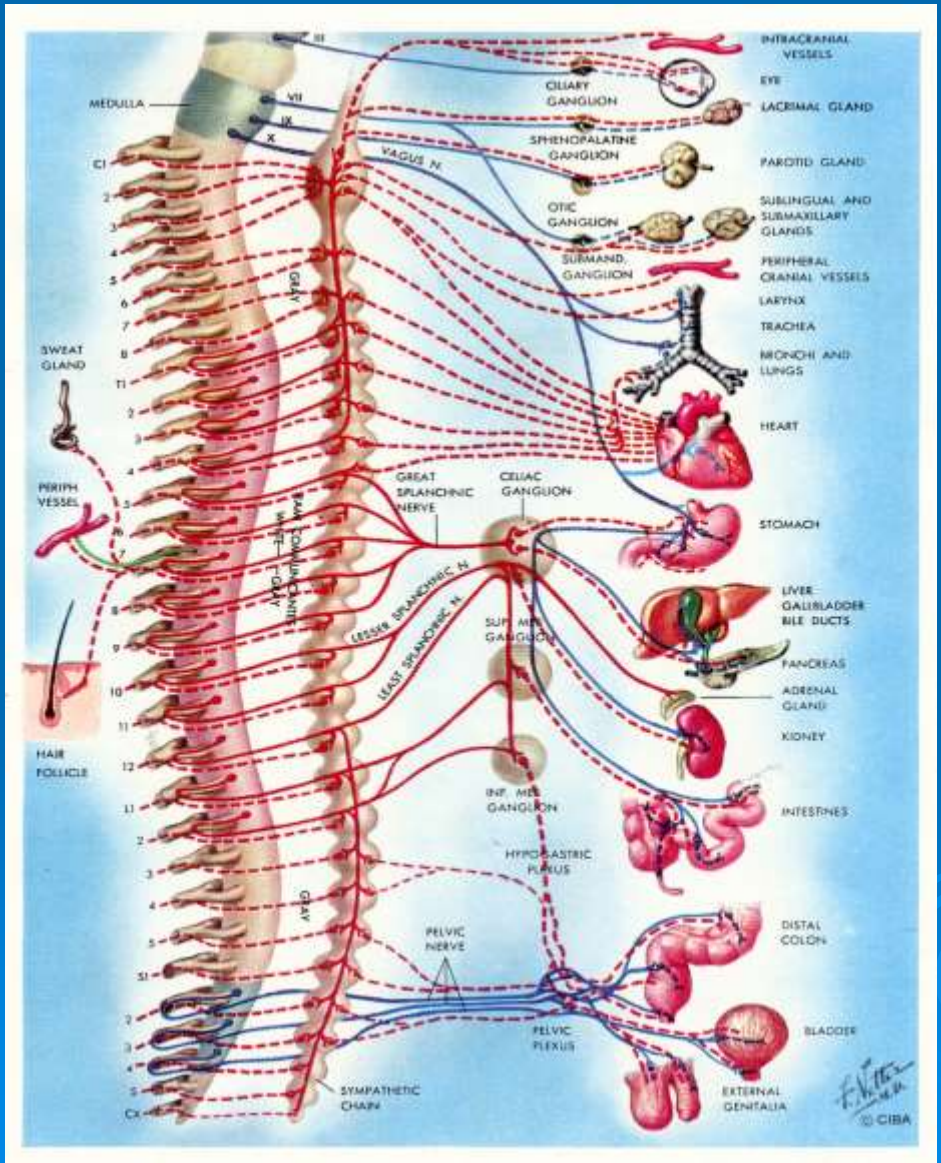
Autonomic Nervous System and Sleep Disorders

Prof. Carlo Ferrarese

Sympathetic & parasympathetic peripheral autonomic nervous system



Sympathetic peripheral autonomic nervous system

1. Cells bodies in the thoracolumbar section of the spinal cord (intermedio-lateral cell column)
2. Ganglia dispersed in: paravertebral, prevertebral, previsceral
3. Preganglionic fibers are short and postganglionic quite long with axons small and unmyelinated
4. Target organs: smooth and cardiac muscles, glandular structure, parenchimal organs and cutaneous structure
5. Preganglionic neurons are cholinergic and postganglionic are noradrenergic

Sympathetic peripheral autonomic nervous system

- The structural organization of the sympathetic nervous system permits the integrations and dissemination of responses depending on the need

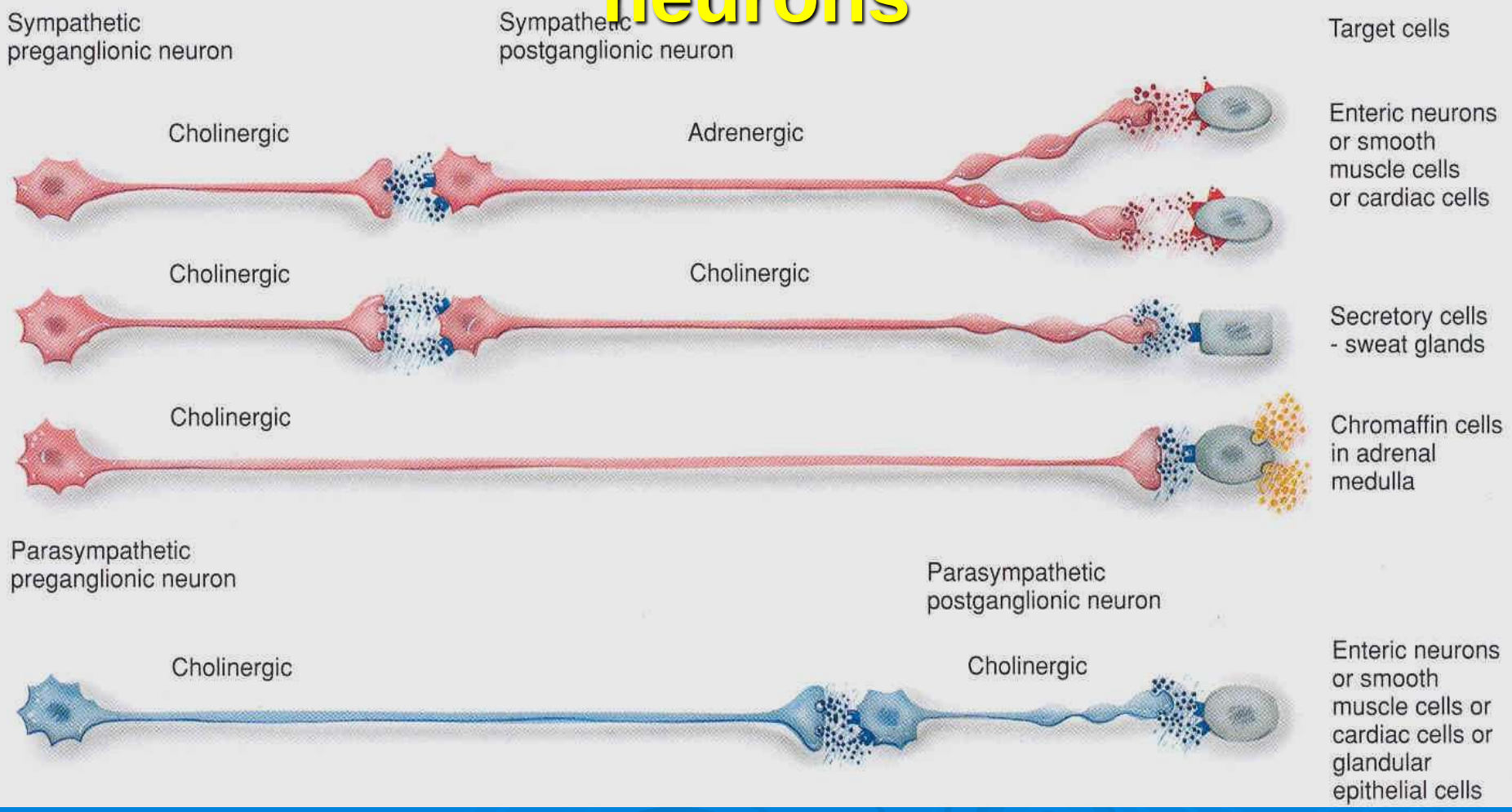
Parasympathetic peripheral nervous system

1. Cells bodies in the nuclei of cranial nerve III, VII, IX, X and at sacral cord level 2,3,4
2. Ganglia located close to or within target organs
3. Preganglionic fibers are long and postganglionic quite short with axons small and unmyelinated
4. Target organs: iris and ciliary muscle, lacrimal and salivatory glands, all organ sistems within the chest and abdomen, pelvic viscera
5. Preganglionic and postganglionic neurons are cholinergic

Parasympathetic peripheral autonomic nervous system

- The parasympathetic nervous system is poised for more focal response but some effects may be quite broad, particularly with the wide-ranging innervation of the vagus nerve

Adrenergic & cholinergic receptors expressed by pre- & postganglionic neurons



(Wilson-Pauwels et al.,1997)

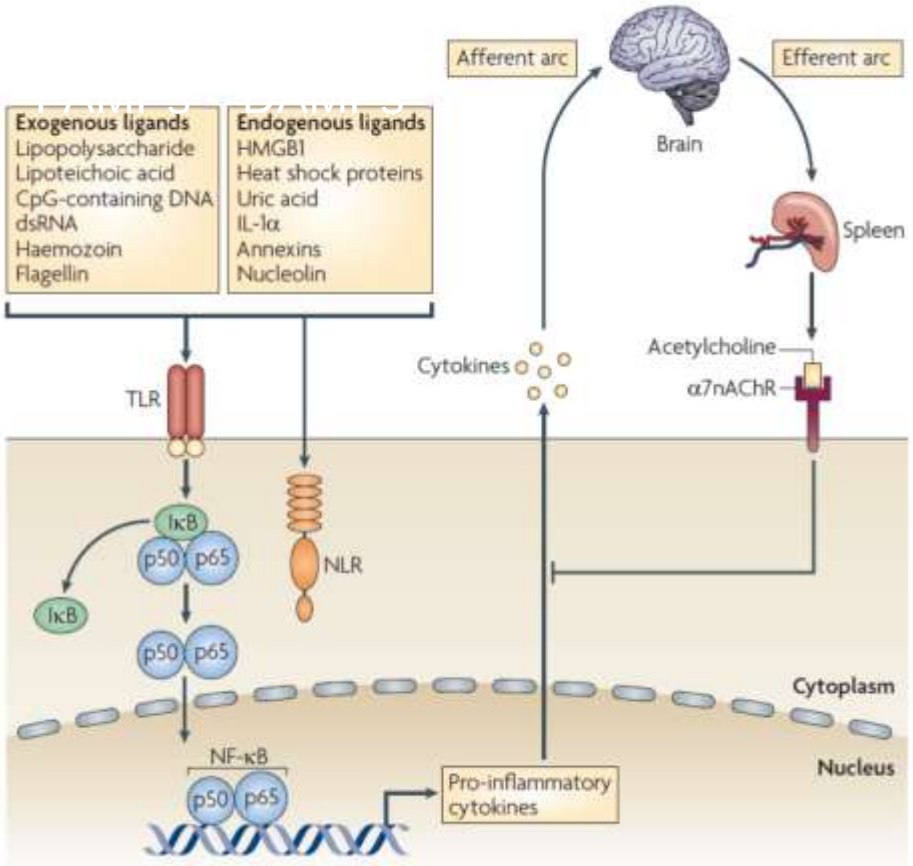
Reflex control of immunity

Kevin J. Tracey

Nature Reviews Immunology **9**, 418–428 (2009)

Afferent arc:
peripheral cytokines and vagus nerve

Efferent arc:
vagus nerve



Modified from

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Peripheral ANS is well structured to provide:

- The physiological responses critical for homeostasis and acute adaptation to stressful, perhaps life-threatening, circumstances
- Multiple organ systems respond to neurotrasmitter release from autonomic endings and circulating cathecolamine release from the adrenal medulla

Table 2. Autonomic Nervous System Functions

Organ	SNS	PNS
Eye		
Pupil	Dilatation	Constriction
Ciliary muscle	Relax (far vision)	Constrict (near vision)
Lacrimal gland	Slight secretion	Secretion
Parotid gland	Slight secretion	Secretion
Submandibular gland	Slight secretion	Secretion
Heart	Increased rate	Slowed rate
	Positive inotropism	Negative inotropism
Lungs	Bronchodilation	Bronchodilation
Gastrointestinal tract	Decreased motility	Increased motility
Kidney	Decreased output	None
Bladder	Relax detrusor, contract sphincter	Contract detrusor, relax sphincter
Penis	Ejaculation	Erection
Sweat glands	Secretion	Palmar sweating
Piloerector muscles	Contraction	None
Blood vessels		
Arterioles	Constriction	None
Muscle		
Arterioles	Constriction or dilatation	None
Metabolism	Glycogenolysis	None

Sympathetic activation

1. Dilatation of pupil
2. Slight increase of glandular secretions,
3. Bronchodilatation
4. Increased HR and force contraction
5. Decreased gastrointestinal motility
6. Decreased function of reproductive organs
7. Mobilization of energy substrates to meet demands

Parasympathetic activation

1. Pupillary constriction
2. Substantial secretion from lacrimal and salivatory glands
3. Slowed HR and negative inotropism
4. Bronchocostriction
5. Enhanced gastrointestinal motility
6. Contraction of detrusor muscle of the bladder
7. PNS does not appear to influence metabolic or endocrine processes in a major way (except pancres)

Parasympathetic and sympathetic peripheral autonomic nervous system

- Traditional teaching indicates that the effects of activation of SNS and PNS are generally antagonistic; this is still largely the case but the integrated role of the SNS and PNS is expanding

Parasympathetic

Sympathetic

The relationships between SNS and PSN is far from simple!!!

- Not all organs receive equal number of both sets of fibers
- In some situations, SNS and PNS responses are in the same directions

ANS: definitions, functions and role as an outcome of its evolutionary story

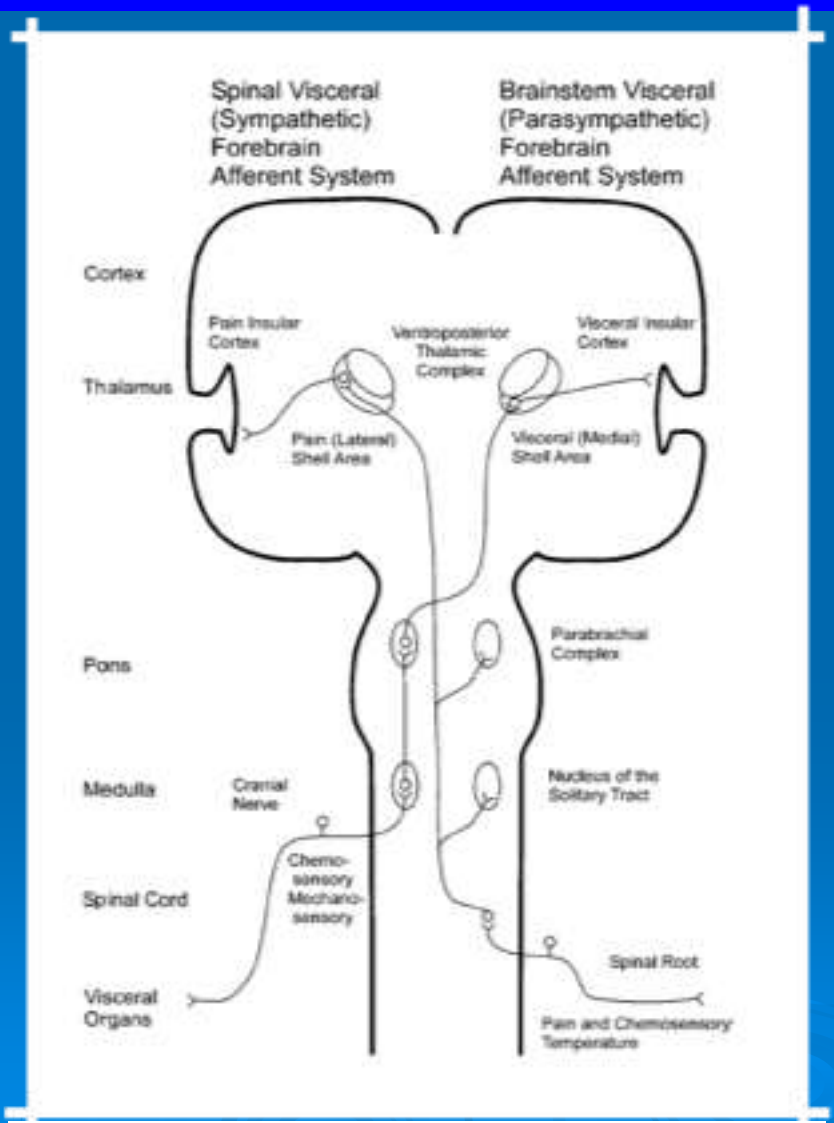
1. The sympathetic and parasympathetic activities are forces better described as reciprocal rather than antagonist because each modality of action is a necessary condition for the appearance of the other

2. The functional organization of the system is the result of a continuous interplay between structure, function and fluctuations ("fluctuations": changes around an average value of some physical quantity in time).

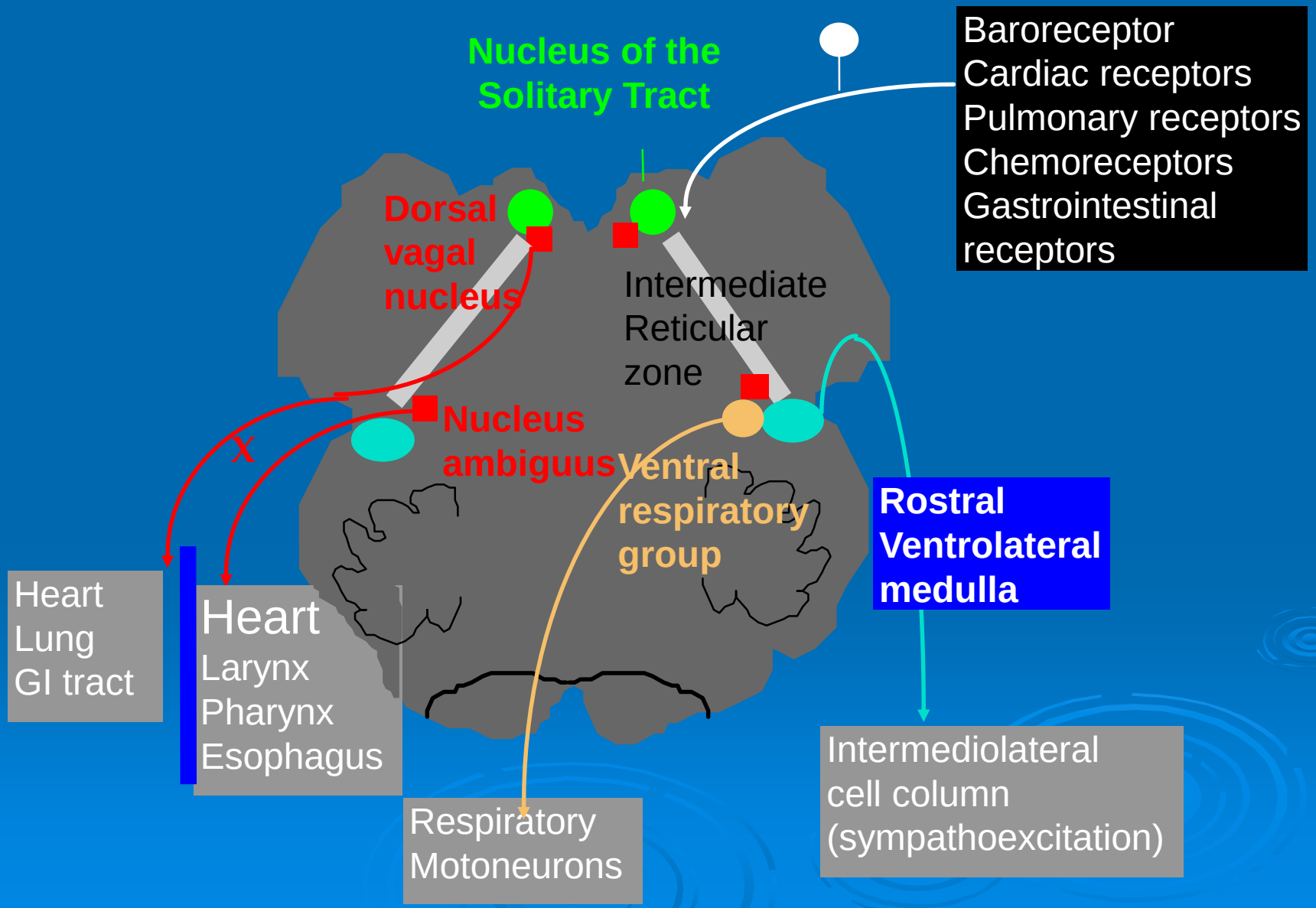
Theories about the functional role of the two main divisions of the autonomic nervous system

	Sympathetic	Parasympathetic
WB Cannon	Homestasis Emergency	Homeostasis
WR Hess	Ergotropic	Trophotropic
J Pick	catabolic	anabolic
Thermodinamic hypothesis	Work related to external environ.	Work related to internal environ. Self-protection, recovery

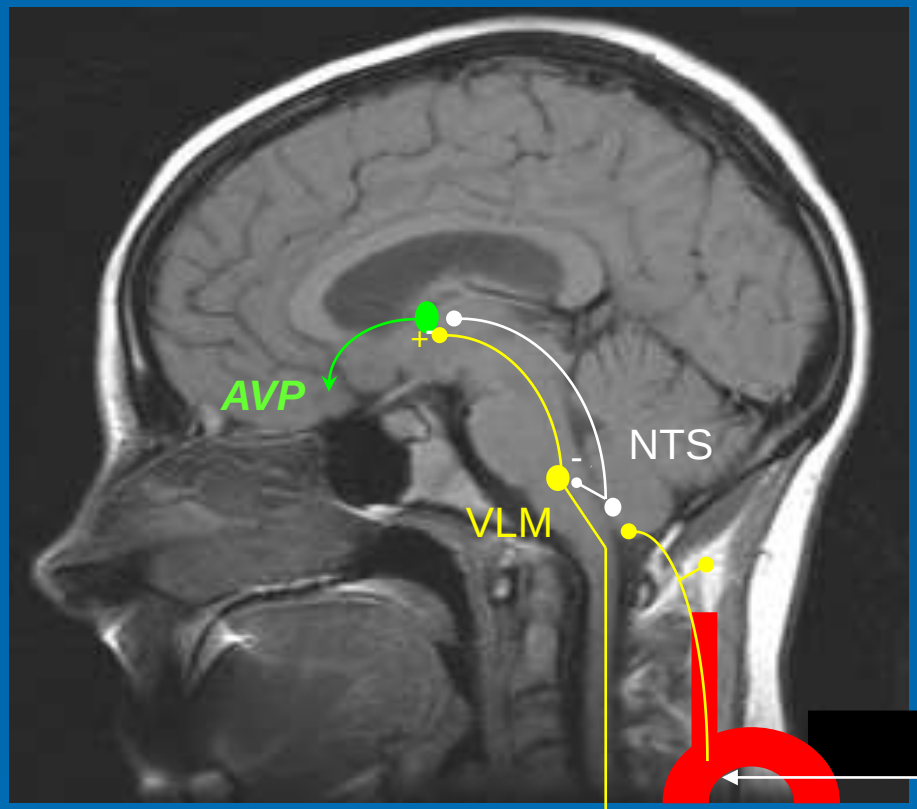
Spinal (sympathetic) and brainstem (parasympathetic) visceral sensory pathways to the thalamus and cerebral cortex.



Basic Circuitry of Medullary Reflexes



Baroreflex mechanisms of orthostatic tolerance



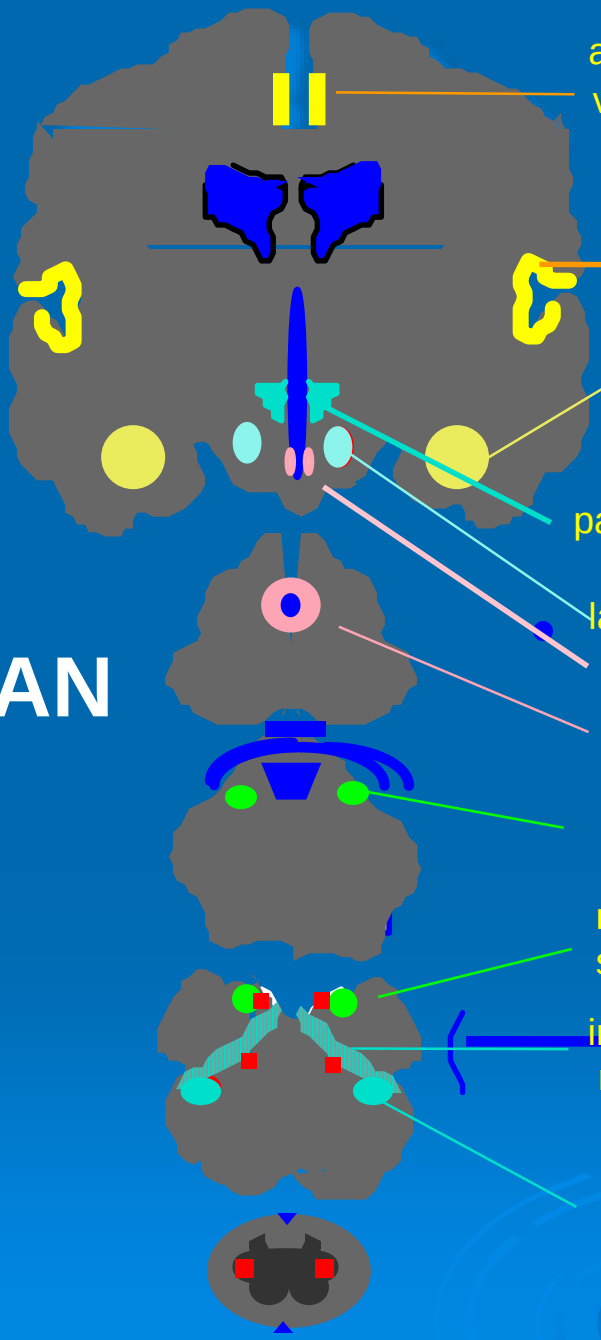
Arterial Blood Pressure

IML

SG

NE

CAN



anterior cingulate and ventromedial prefrontal → Motivation and emotional control

insular cortex → Primary viscerosensory

central nucleus of the amygdala → emotional responses

paraventricular nucleus → response to stress

lateral hypothalamic area → behavioral arousal thermoregulation

preoptic area → osmoregulation, sleep, sexual

periaqueductal gray → Pain control and stress

parabrachial region → Viscerosensory , cardio-respiratory, micturition

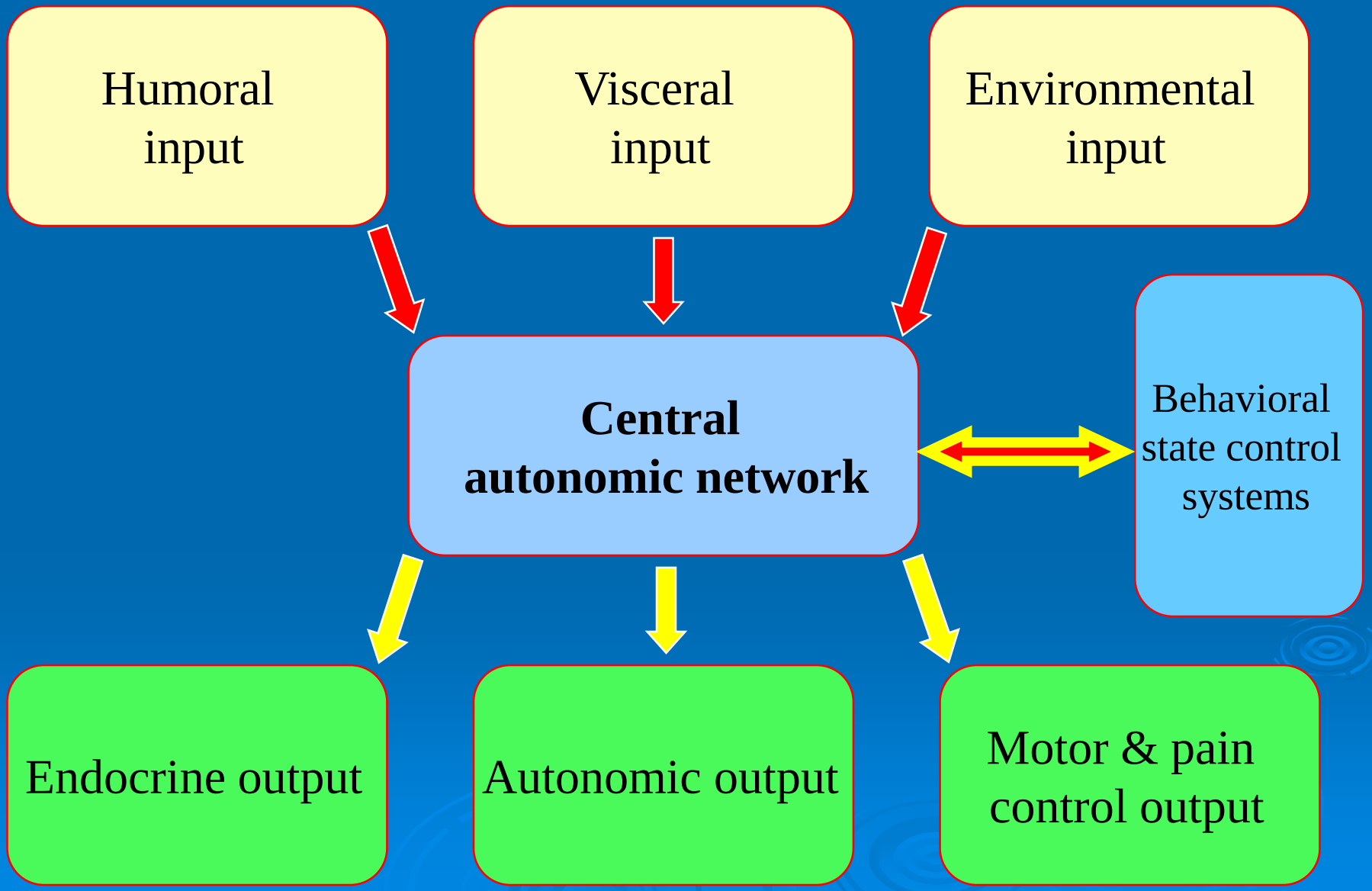
nucleus of the solitary tract → First relay of viscerosensory afferents

intermediate reticular zone

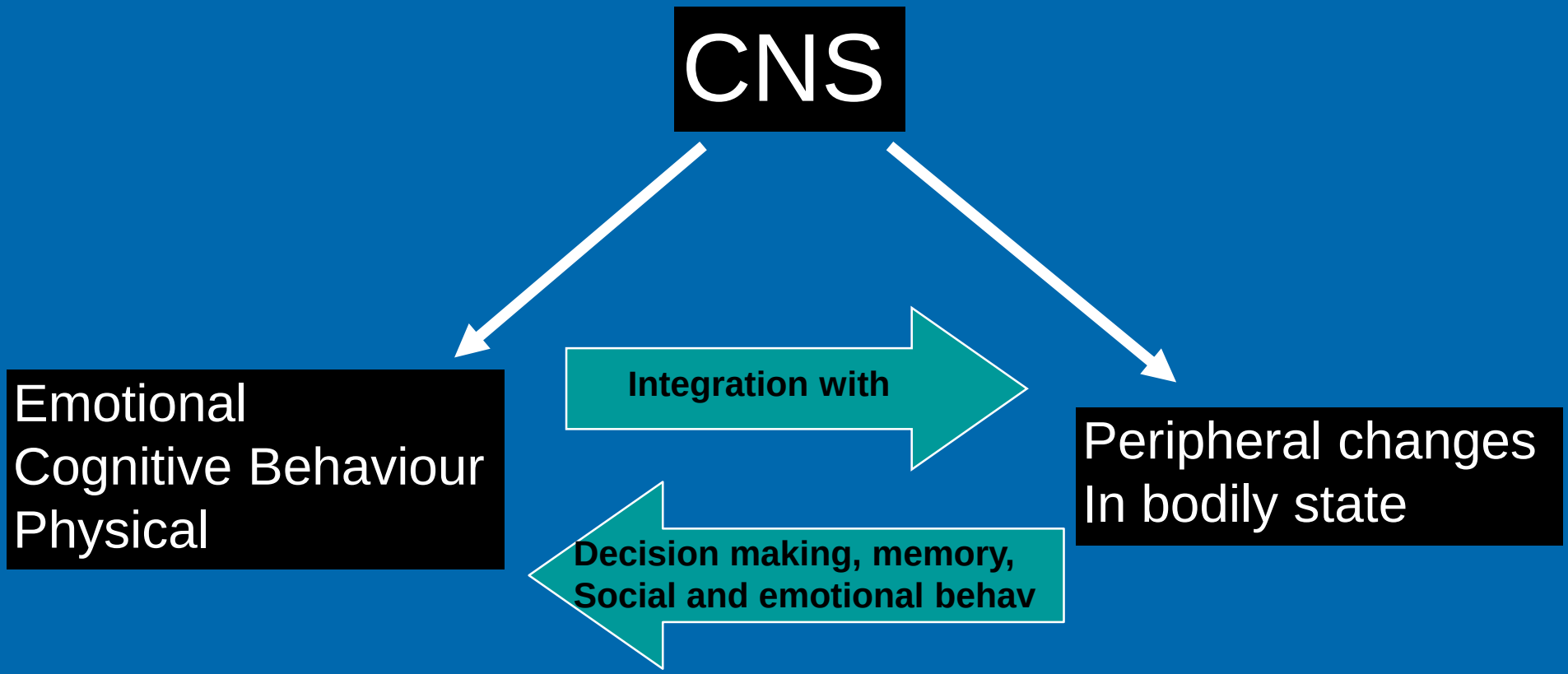
ventrolateral medulla → “premotor” sympathoexcitatory and respiratory neurons

(Benarroch 1997)

Operation of the autonomic nervous system



(Benarroch 1997)



EMOTIONS ARE A HOMEOSTATIC MECHANISM THAT UNDERLIE SURVIVAL OF THE ORGANISM

Pain is an enigma

- It differs from the classical senses because it is both
  - A discriminative sensation
  - A graded motivation or behavioural drive
- The neural basis of pain has been debated from two opposing views
  - Specificity
  - Convergence

PAIN. Conventional view

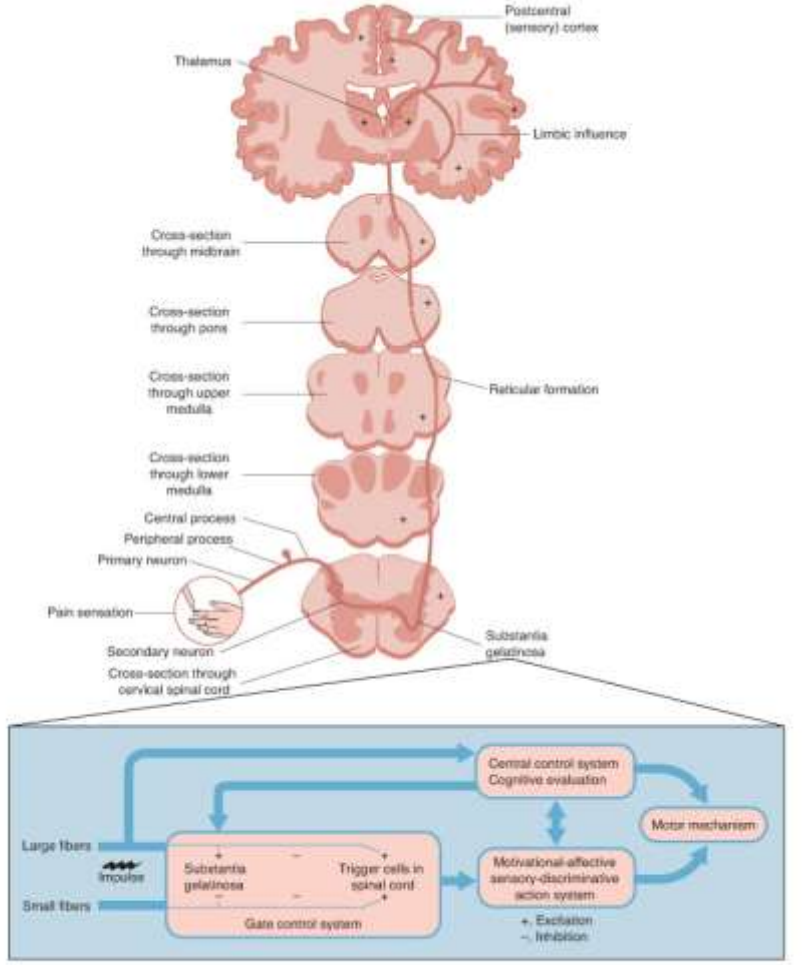
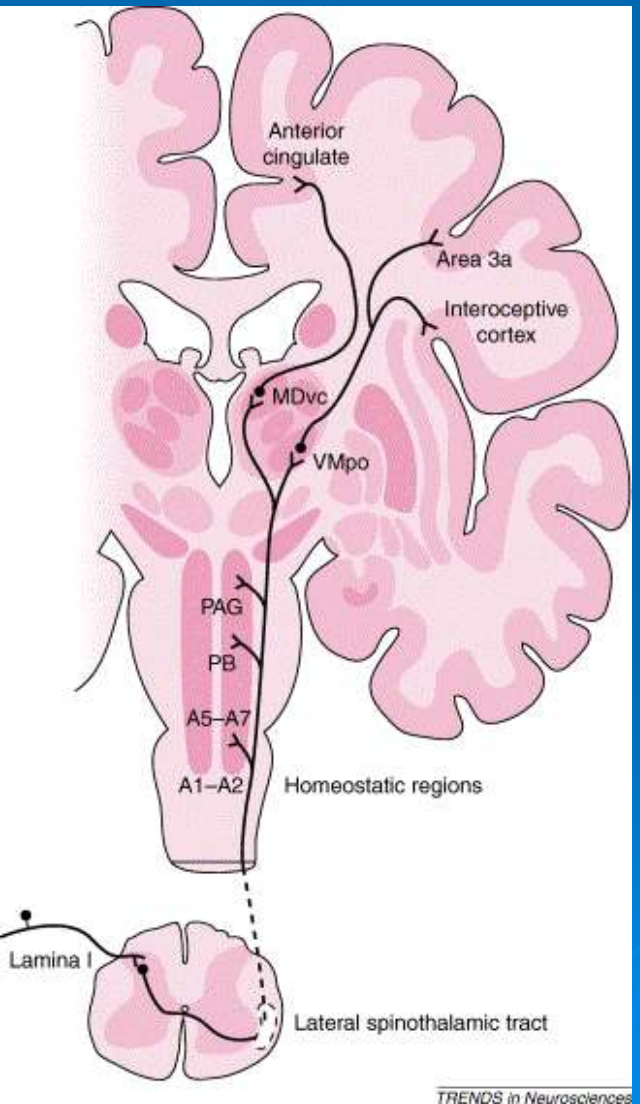


Figure 32-2 Ascending sensory pathways: anterior spinothalamic tract with a schematic diagram of the gate control theory of pain mechanism.

1. Pain as a submodality of cutaneous sensation and exteroception
2. Convergent somatosensory activity
3. Contradicted by

- Neither damage or stimulation of somatosensory cortices affect pain
- Stimulation of the somatosensory thalamus can alleviate the pain

New view of pain as a visceral sensation (homeostatic emotion)



- Functional, anatomical and immaging findings indicate that pain is generated by specific sensory channels that ascend in a **central homeostatic afferent pathway**
- Phylogenetically new thalamocortical projections in primates provide a **sensory image of the physiological condition of the body** and, in addition, **direct activation of limbic motor cortex**.

New of view of pain as a homestatic emotions

- Pain **is NOT** part of the exteroceptive somatosensory system

- **Pain is** represented in a **novel pathway** in humans that is part of a hierarchical system subserving
  - Homeostasis
  - the sense of the physiological condition of the body **(interoception)**
  - the subjective awareness of feelings and emotion

ANS functions: take home messages

1. **Supportive function of the ANS for supporting somatic tissue performances**
2. **Integrative function: it unites, integrates the functions of all body and organize visceral reactions associated with somatic actions**
3. **Modulatoy function and not purely “on” or “off” effect**
4. **Extension of the emergency function concept from the “fight or flight” to “alerting” e “defense reaction”. The ANS acts in anticipating stress as well as in meeting stressful cicumstances. It is the neurobiological basis of the stress response and its consequences.**

ANS functions: take home messages

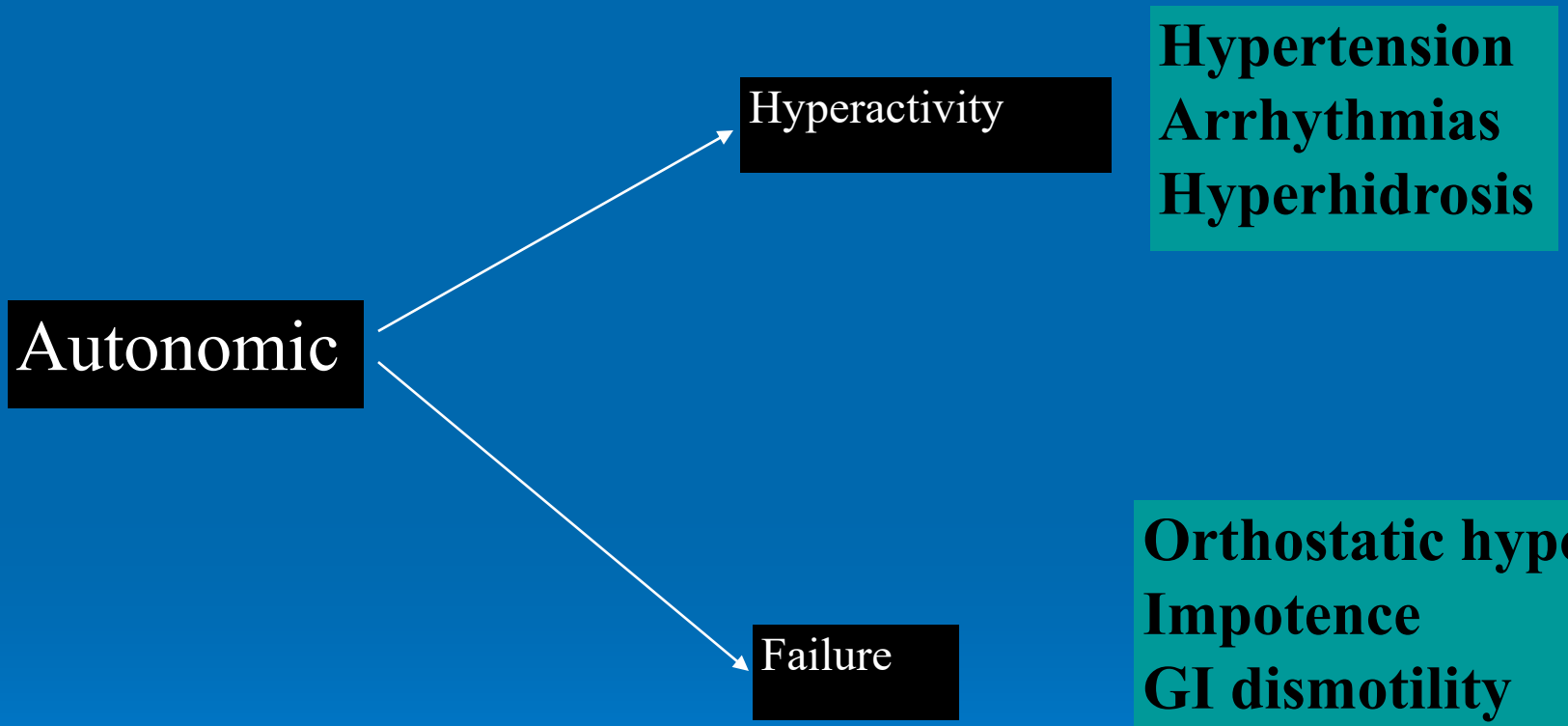
5. **Determinative function: the ANS molds and determines the quality and the nature of behavioural reactions**
6. **The ANS possesses adaptative potentiality**
7. **The ANS plays a major role in conditioning and learning**

Clinical features of dysautonomia

ANS disorders: general aspects

- May present at any age
- The majority are sporadic
- Drugs may unmask autonomic deficits
- May vary geographically (Chaga's disease affect million in South America)
- May affect only one organ or system or may be a sign of a generalised autonomic failure

Disorders of ANS may manifest with



Manifestations of ANS dysfunction may be

Asymptomatic — **Detected on clinical examination or autonomic testing**

Symptomatic — **Produce severe impairment of daily activities (orthostatic hypotension)**

Life threatening — **Ventricular arrhythmias, stridor**

First symptoms of autonomic failure

- Insidious in their onset, with mild symptoms which are concealed for years because of autonomic compensatory mechanisms
- Persistent postural hypotension is the cardinal feature of AF

Classification of autonomic disorders

- Classification of autonomic disorders has been broadly divided into primary (unknown etiology) and secondary (autonomic dysfunction arising out of specific disease processes) causes.

- Is useful to recognize neurogenic and non neurogenic causes of autonomic failure

Neurogenic causes of Autonomic Failure

1. Primary autonomic failure
   - Chronic
   - Acute/subacute

2. Secondary autonomic failure

Primary autonomic failure

- chronic
  - Pure Autonomic Failure (PAF)
  - Multiple System Atrophy
    - with parkinsonian features
    - with cerebellar and pyramidal features
    - with multiple system atrophy (combination)
  - Autonomic Failure with Parkinson Disease

Primary autonomic failure

- acute or subacute dysautonomias
  - Pure pandysautonomia
  - Pandysautonomia with neurological features
  - Pure cholinergic dysautonomia

Acute pandysautonomia

- severe sympathetic and parasympathetic dysfunction:

- **Clinical manifestations:**
- **orthostatic hypotension**
- anhidrosis
- dryness of skin, eyes & mouth
- gastrointestinal dysfunction
- (incl. nausea, vomiting, meteorism, diarrhea, constipation)
- bladder dysfunction
- sexual dysfunction
- mild sensory neuropathy
- albuminocytologic dissociation in cerebrospinal fluid

First symptoms of autonomic failure

- Insidious in their onset, with mild symptoms which are concealed for years because of autonomic compensatory mechanisms
- Persistent postural hypotension is the cardinal feature of AF

Cardiovascular dysautonomia

- Orthostatic hypotension
- Orthostatic intolerance
- Supine hypertension
- Loss of respiratory arrhythmia
- Cardiac arrhythmia

Orthostatic Hypotension

orthostatic hypotension defined as:

drop in BP within 3 min. after active standing up or 60 head-up tilt

$BP_{sys} \geq 20$ mmHg **or** $BP_{dia} \geq 10$ mmHg

(Am. Autonomic Society & Am. Academy of Neurology,1996)

Symptoms

- Weakness
- dizziness
- blurred vision
- difficulties to concentrate
- coat-hanger-like neck pain
- nausea
- palpitations
- syncope

" SYMPTOMS RESULTING FROM POSTURAL HYPOTENSION"

HYPOPERFUSED ORGAN	SYMPTOMS
BRAIN	• Dizziness • Visual disturbances (blurred vision, scotoma, greying-out, blakting-out, colour defects) • Loss of consciousuess (faiting, syncope) • Impaired cognition
MUSCLE	• Paracervical and sub-occipital ache
HEART	• Angina pectoris
KIDNEY	• Oliguria
NON SPECIFIC	• Weakness, lethargy, fatigue, falls

Importance of diagnosing Orthostatic Hypotension

- OH may underlie symptoms of cerebral hypoperfusion
- OH is a risk factor for falls (Ooi WL, 2000)
- OH is an independent predictor of all cause of mortality (Masaki 1998, Rose 2006)
- OH is predictor in elderly people
  - of ischemic stroke (Eigenbrodt 2000)
  - of white matter findings on cerebral MR (Longstreth 1996)
- The risk of vascular death associated with OH is especially high among diabetic pts (Luukinen 2005)

Non-neurogenic causes of hypotension or orthostatic hypotension

- cardiac impairment
  - Myocardial, impaired ventricular filling,
  - impaired output, cardiac arrhythmia
- vasodilatation
- low intravascular volume
  - blood / plasma loss fluid / electrolytes
- miscellaneous

Orthostatic intolerance

- symptoms during standing, relieved upon recumbency
- **not** accompanied by orthostatic hypotension
  - *(Schondorf 2004)*
- **Clinical manifestations:**
- exercise intolerance
- reduced concentration
- nausea
- lightheadedness
- dizziness
- visual blurring
- anxiety
- palpitations
- rarely syncope

Symptoms of OH or intolerance may be worsened or unmasked by

- Prolonged bed rest
- Food ingestion
- Alcohol
- Fever
- Hot weather or environment
- Hot bath
- Exercise
- Hyperventilation

Skin

- Hypoidrosis (generalized, localized)
  - Dry skin
  - Dry socks and feet
  - Absent pilomotor reactions
  - Reduced skin wrinkling
  - Excessive sweating in intact regions
- Hyperidrosis (generalized, localized)

Eye

- Impaired pupillary motor function (miosis, hippus, mydriasis)
- Dryness of eyes (redness, itching)
- Ptosis

Genitourinary Dysautonomia

- Impotence (male, impaired morning erection, retrograde ejaculation)
- Nocturia
- Urinary retention
- Urinary incontinence
- Recurrent urinary tract infection

Gastrointestinal dysautonomia

- Reduced salivation
- Constipation
- Postprandial fullness
- Anorexia
- Diarrhea
- Fecal Urgency and incontinence
- Weight loss

Respiratory dysfunction

- In the case of hypoxia & hypercapnia ***lack of*** adequate reflex hyperventilation (chemoreceptor dysfunction)

- during sleep: sleep apnea, disturbed respiratory pattern, stridor (MSA) and disturbed heart rate - respiratory frequency relation.

Thermoregulation

- Hypertermia *(“fever resistent to Tx”)*
- Hypotermia
- Reduced metabolic rate

Therapy of ortostatic hypotension

- Behavioural counseling (slow onset of orthostatic posture: remain seated for few minutes)
- Elastic socks
- Drugs

Fludrocortisone (Florinef®)

Mechanisms of Action

- Sale sparing
- Plasma volume expansion
- Increased response to adrenergic receptors
- *Dose:* 0,1-0,4 mg/die

Collateral effects

- Clinostatic hypertension
- Depletion K-Mg
- Wheight increase
- Cardiac failure
- Metabolic alcalosis

Midodrine (Gutron®)

- Alpha1 selective agonist → peripheral effect
- Only drug for Tx OH with class I studies
- Indicated for monoTX or in association with Florinef
- Dose 2.5-10 mg x 3<; effect lasts 2-4 hrs
- Improvement of symtoms → 2 weeks
- Collateral effects: Clinostatic hypertension (25%) (last dose late afternoon) , orripilation (13%), urinary retention (6%)
- Controindicated: severe cardiopaty, IR, prostatic hyperplasisa, feocromocitoma, hypertiroidism
- Alpha-agonism of midodrine may be helpful to ameliorate urinary incontinence.

Octreotide (sandostatin): Somatostatine analog

- Indicated for after-lunch hypotension
- 25-50 ug sc ½ hr before meal
- Does not increase nocturnal AP
- Collateral effects: nausea, addominal pain
- Synergic effect with Midodrine

Sleep Disorders

- Insomnias
- Hypersomnias
- Breath-related sleep disorders (OSA)
- Circadian sleep disorders (workers and jet lags)
- Sleep-related movement disorders (RLS-RBD)
- Parasomnias (somnambulism)

Narcolepsy

What is narcolepsy?

Narcolepsy is a neurologically based, chronic, hypersomnic sleep disorder that is associated with REM sleep disturbances and includes:

- Poor sleep-wake cycles
- Poor overnight sleep and periods of extreme daytime sleepiness
- Sudden irresistible bouts of sleep that can strike at any time lasting a few seconds to several minutes

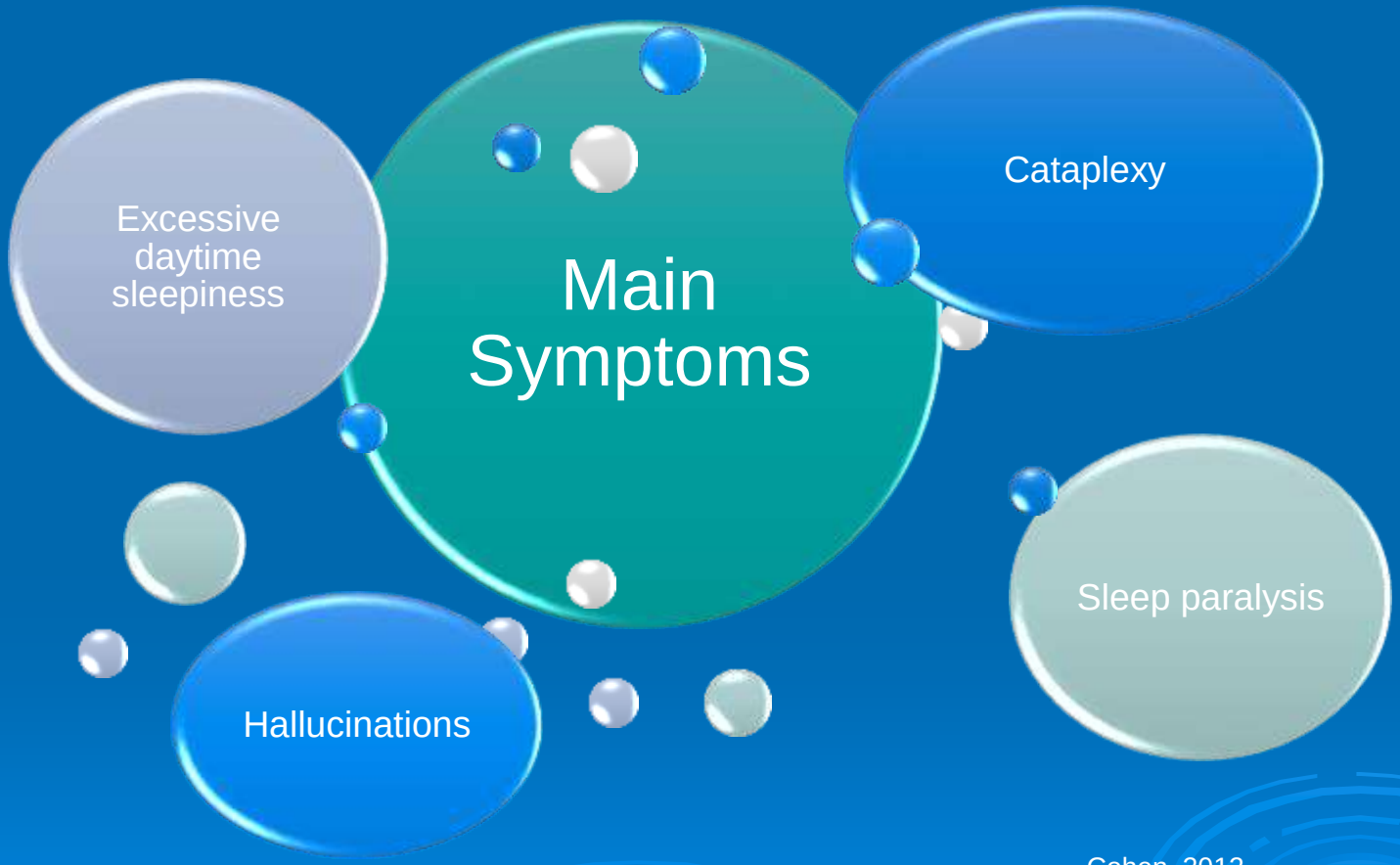
The patient voice—Narcoleptic symptoms

- “It’s hard to plan my day, because sometimes I get sleep attacks. It won’t go away unless I close my eyes for 5-10 minutes and kind of sleep.”

- “People in my field don’t understand that you need to take a nap. I always have to be on call.”

Who gets narcolepsy?

- Males and females equally throughout the world
- Narcolepsy typically appears in childhood, adolescence or young adulthood (between ages of 7-25)
- Symptoms can sometimes present later in life and are lifelong
- 1:3000


Main Symptoms
Excessive daytime sleepiness
Cataplexy
Sleep paralysis
Hallucinations

Cohen, 2012

1) Excessive daytime sleepiness (EDS)

- "a persistent sense of mental cloudiness, a lack of energy, a depressed mood, or extreme exhaustion" (NIH fact sheet, 2016)

- **Most common symptom of narcolepsy**

2) **Cataplexy**

- Sudden loss of muscle tone and a loss of voluntary muscle control while awake
- Resembles interruption of muscle activity while in REM sleep that inhibits movement- same group of neurons becomes inactive during cataplectic attacks
- Usually occurs several weeks/months after onset of EDS
- 50% of people develop cataplexy within 1 yr; 85% in 3 years

Cataplexy

- Can be minor or result in complete physical collapse where individuals are unable to move, speak or keep their eyes open
- During any type of episode, people remain fully conscious (distinguishing it from seizure disorders)
- Can occur spontaneously, but usually has a trigger, ie: sudden, strong emotion, ie: fear, anger, stress, excitement, or humor

- *Laughter* is allegedly the most common trigger!

3) **Sleep paralysis**

- Temporary inability to move or speak before falling asleep or waking
- Similar to REM inhibitions to voluntary muscle activity
- Lasts a few seconds to minutes; person remains fully conscious
- Feels as if person is undergoing cataplectic attack affecting the entire body

4) **Hallucinations**

- Can accompany sleep paralysis and occur when falling asleep, waking, or during sleep
- ***Hypnagogic***- occur during sleep onset
- ***Hypnopompic***- occur during waking
- Images are unusually vivid, seem real, can be frightening; sometimes involve other senses besides sight

Symptoms of narcolepsy

- Most people with narcolepsy do not have difficulty falling asleep but do have trouble staying asleep
- REM sleep disturbances may include insomnia, vivid dreaming, sleep talking, acting out while dreaming, leg movements
- 10-25% of people with narcolepsy display all four symptoms during the course of illness

Symptoms of narcolepsy

- Tend to begin subtly and may change over time
- Contrary to myth, people with narcolepsy do NOT spend more time asleep than others in 24 hours
- May fall asleep in inappropriate times and places, which may be dangerous, ie: driving, hazardous activities

Symptoms of narcolepsy

- If left untreated, narcolepsy can affect psychological, social and cognitive function and undermine work and social activities, ie:
- An increase in work-related and transit accidents,
- Sexual dysfunction
- Neuropsychological alterations (ie: increased reaction time, decreased executive function)
- Overall reduction in quality of life (school, jobs, marriages, social life)

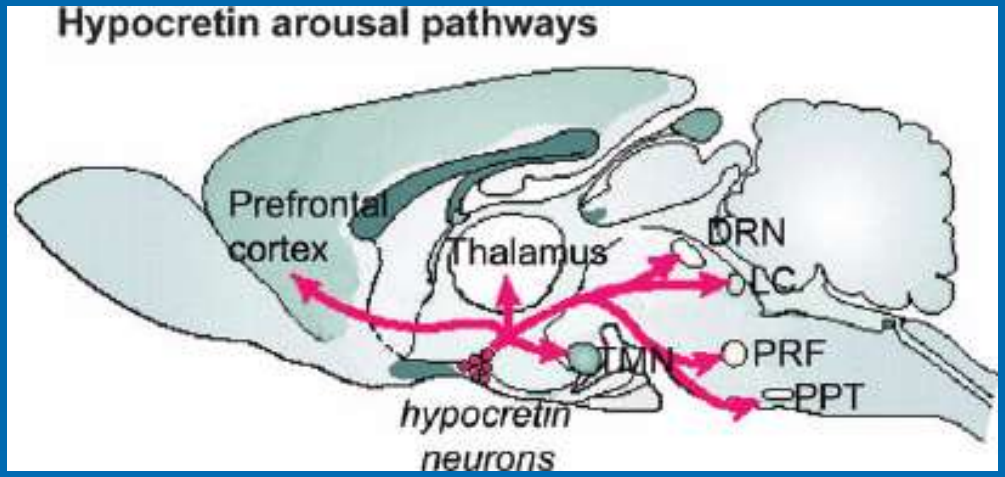
Differential Diagnoses

- Other sleep disorders (ie: sleep apnea)
- Viral or bacterial infections
- Mood disorders (ie: depression)
- Chronic illnesses
- Medications, caffeine, alcohol, nicotine, drugs
- Sleep deprivation and interruption of work-sleep cycle

Etiology of narcolepsy

- Hypocretin, aka Orexin
- Genetic factors
- Autoimmune Hypothesis
- Environmental factors

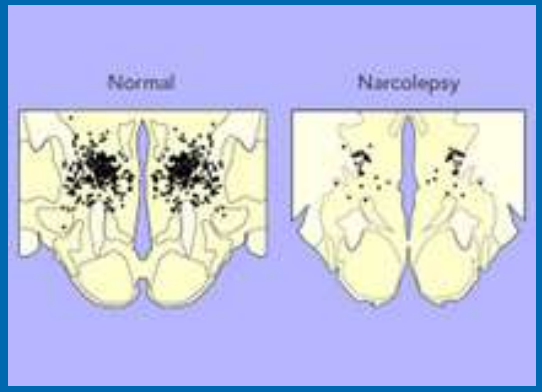
Hypocretin, aka Orexin

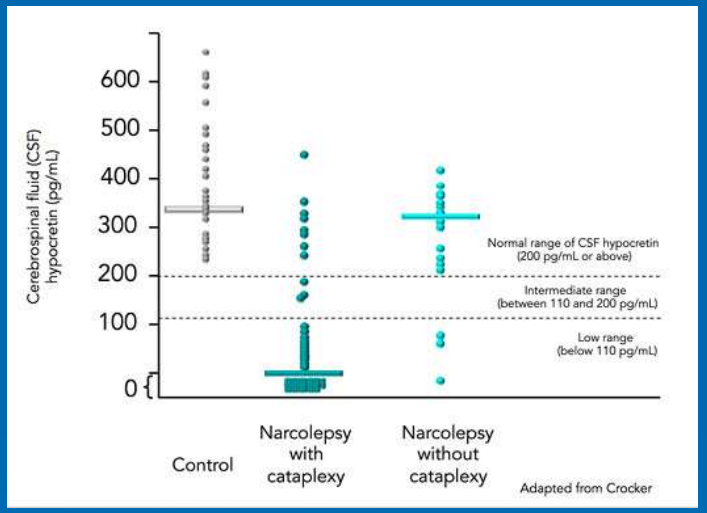


Hypocretin, aka Orexin

- Most people with narcolepsy have low levels of the neurotransmitter **HYPOCRETIN** which promotes and sustains wakefulness
- People who have narcolepsy have greatly reduced numbers of hypocretin-producing neurons

Hypocretin, aka Orexin





http://healthysleep.med.harvard.edu/narcolepsy/what-is-narcolepsy/science-of-narcolepsy

Genetic factors

- Most cases of narcolepsy are sporadic, aka no known family history
- Only 25% of monozygotic twins have narcolepsy
- BUT some families do show a tendency: up to 10% of people with narcolepsy have a close relative with same symptoms

Genetic factors

- Majority of people who have narcolepsy have a specific human leucocyte antigen (HLA) gene variant called DQB1*0602
- Also have specific alleles at a gene called the T-cell receptor alpha (TCRA)
- Variations in these genes may predispose an individual to develop narcolepsy through a route that involves changes in autoimmune system function when other causative factors are also present

Genetic factors

- Other genes may contribute to the development of narcolepsy
- Groups of neurons especially in brain stem and central brain interact to control sleep
- Studies on dogs with narcolepsy have found a gene mutation that disrupts the signal from hypocretins produced by neurons in the hypothalamus and produces narcolepsy symptoms

AUTOIMMUNE HYPOTHESIS

- People with narcolepsy have greatly reduced numbers of hypocretin-producing neurons and certain genetic subtypes
- They may have an increased susceptibility to immune attack on hypocretin neurons in the hypothalamus leading to their degeneration and destruction
- Reasons for this are still unknown and being studied…

AUTOIMMUNIE HYPOTHESIS and Environmental Factors

- ALSO…
- Growing evidence suggests exposure to H1N1 virus (swine flu) or a special form of the vaccine (*Pademrix,* administered in Europe) may act as rare triggers for the disease
- Not understood if infectious agents are direct triggers or increase likelihood of autoimmune response and disease indirectly

Other Environmental factors

- Some narcolepsy can be caused by traumatic injury to the parts of the brain involved in REM sleep
- Tumor growth, vascular malformations, other disease processes
- Infections, exposure to toxins, dietary factors, stress, hormonal changes (puberty, menopause), alterations in sleep schedule

How is narcolepsy diagnosed?

- Clinical exam
- Thorough mental health history
- Sleep journal (cataplexy most specific symptom- rarely present outside narcolepsy)

How is narcolepsy diagnosed?

- **Polysomnogram** (PSG)
- **Multiple Sleep Latency Test** (MSLT)-
- Performed during the day
- Measures time it takes to fall asleep and if REM is intruding during waking hours
- Pinpoints occurrence of abnormally timed REM episodes through EEGs
- Person takes multiple naps
- IF person enters REM within a few minutes of sleep onset in at least two of the naps, narcolepsy is indicated

How is narcolepsy diagnosed?

Now with autoimmune hypothesis:

- **Human leukocyte antigen (HLA) typing** may also help diagnose narcolepsy
- HLA typing is a marker of viral infection, and most HLA-associated disorders are autoimmune
- Certain alleles (genetic information) located on chromosome 6 are strongly associated with narcolepsy/cataplexy
- **GOLD-STANDARD TEST**: Cerebrospinal fluid (CSF) is tested, and if level of hypocretin is low, hypocretin deficiency can be established as the cause of narcolepsy

Therapy

- Modafinil (provigyl) is the drug of first choice.
  - 200–400 mg as single day dose
    - Long half life permits single day dose
    - Some patients respond better to split doses
  - Less collateral effects respect to amphetamines
  - Safe in patients with hypertension and heart problems

- Amphetame-like drugs may be used for unresponsive patients:
  - Metilfenidate (10 mg bid up to 20 mg qid)
  - Dextroamphetamine (10 mg bid)
  - Collateral effects include: irritability, insomnia, hypertension, tachicardia

Therapy

A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy

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Objective: Solriamfetol (JZP-110) is a selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects. This phase 3 study (NCT02348593) evaluated the safety and efficacy of solriamfetol in narcolepsy.

Methods: Patients with narcolepsy with mean sleep latency <25 minutes on the Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS) score ≥ 10, and usual nightly sleep ≥6 hours were randomized to solriamfetol 75, 150, or 300 mg, or placebo for 12 weeks. Coprimary endpoints were change from baseline to week 12 in MWT and ESS. Improvement on the Patient Global Impression of Change (PGI-C) was the key secondary endpoint.

Results: Safety and modified intention-to-treat populations included 236 and 231 patients, respectively. Solriamfetol 300 and 150 mg were positive on both coprimary endpoints. Least squares mean (standard error [SE]) changes from baseline were 12.3 (SE = 1.4) and 9.8 (SE = 1.3) minutes for solriamfetol 300 and 150 mg on the MWT, respectively, versus 2.1 (SE = 1.3) minutes for placebo, and −6.4 (SE = 0.7) for 300 mg and −5.4 (SE = 0.7) for 150 mg on the ESS versus −1.6 (SE = 0.7) for placebo (all $p < 0.0001$). At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) and 300 mg (84.7%) reported PGI-C improvement relative to placebo (39.7%; both $p < 0.0001$). Adverse events ≥5% across all solriamfetol doses included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%), and anxiety (5.1%).

Interpretation: Solriamfetol has the potential to be an important therapeutic option for the treatment of impaired wakefulness and excessive sleepiness in patients with narcolepsy.

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Restless legs syndrome

Definition

- Restless legs syndrome (RLS) is a movement disorder affecting legs before sleep
- Patients refer an unpleasant sensation agitation or restlessness of legs with the need mooving them
- Symptoms arise usually in the evening when the patient relaxes before sleep (watching TV, etc).

Main characteristics of RLS

- Need to move, linked to unpleasant sensations of legs ,
- Symptoms worsen when patient tries to relax
- Symptoms worsen in the evening

Associated symptoms and characteristics

- Periodic limb movements during sleep
- Sleep alterations, in particular at the onset of sleep

- Familiarity of RLS
- Onset at any age, with a chronic and progressive course, sometimes with remissions

therapy

- Dopaminergic drugs
  - Pramipexole: 0,25–1,0 mg
  - Ropinirole: 0,5–4,0 mg
  - Other dopamine-agonists and L-dopa are also effective
  - Tolerance may manifest with time, with the need to change drug.
- Narcotic drugs (MScontin 10 mg), benzodiazepines (clonazepam 1-3 mg) and some antiepiletic drugs may also be effective