Inserm

Optimisation Thérapeutique en Neuropsychopharmacologie

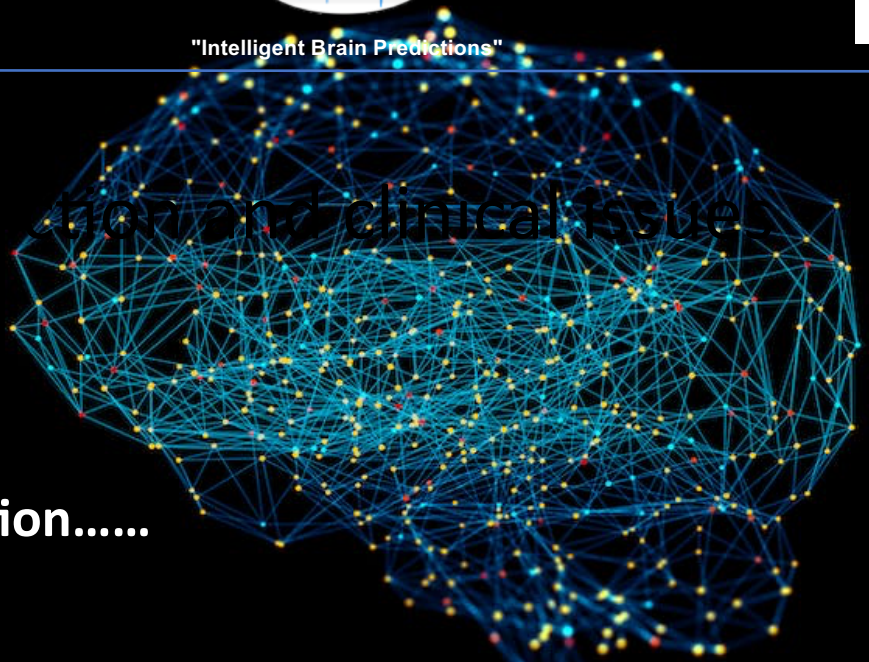
SignalMed+

"Intelligent Brain Predictions"

Université Paris Cité

AP-HP. Nord Université Paris Cité

DMU DREAM



From brain function……
To clinical issues

Advanced Course in Computational Neuroscience

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October 4th 2023

Hôpital Lariboisière
Fernand-Widal
AP-HP

DISCLOSURES

- Start-up « SIGNALMED+ »



"Intelligent Brain Predictions"

CONTENTS

I - Introduction

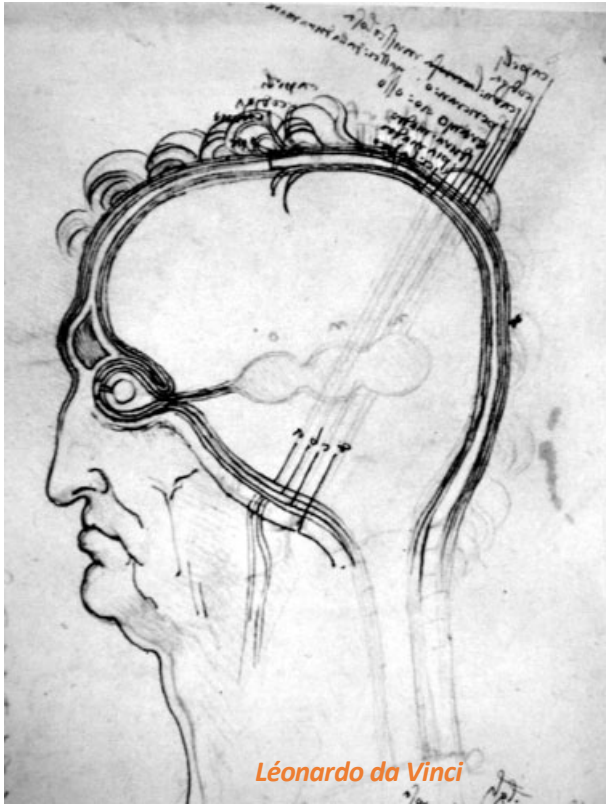
II – Organization and function of the nervous system (CNS, PNS)

III – Higher-order functions (wakefulness and awareness)

IV – How to measure brain functions? (EEG and EP)

V- Clinical issue: how to evaluate coma prognosis?

VI – Development of a predictive algorithm

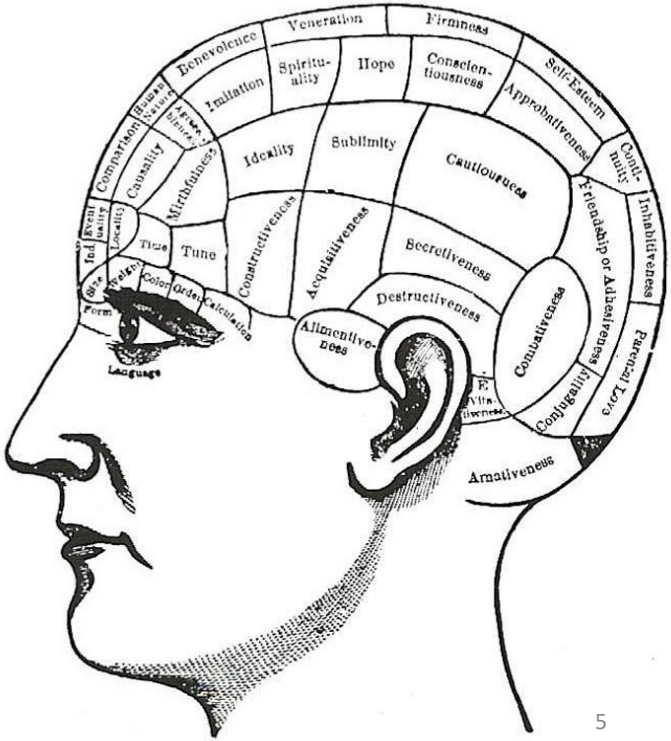

Léonardo da Vinci

- **Until the XVIIIth century: Theory of the Pneuma and the ventricles**
- **Claude GALIEN (131-201 AD)**
  - *« pneuma » (vital spirit) is produced by heart*
  - *Carried to the skull by carotid arteries*
  - *Blood penetrates at the skull basis, by the **Rete Mirabile** (réseau merveilleux or marvellous network)*
  - *« pneuma » est turned into the «animal spirit»*
  - *Stored in lateral ventricles*
  - *Then distributed to motor nerves and circulates inside*

XIXth century: Phrenology and maps of psychic qualities are delimited by humps

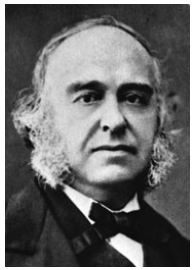


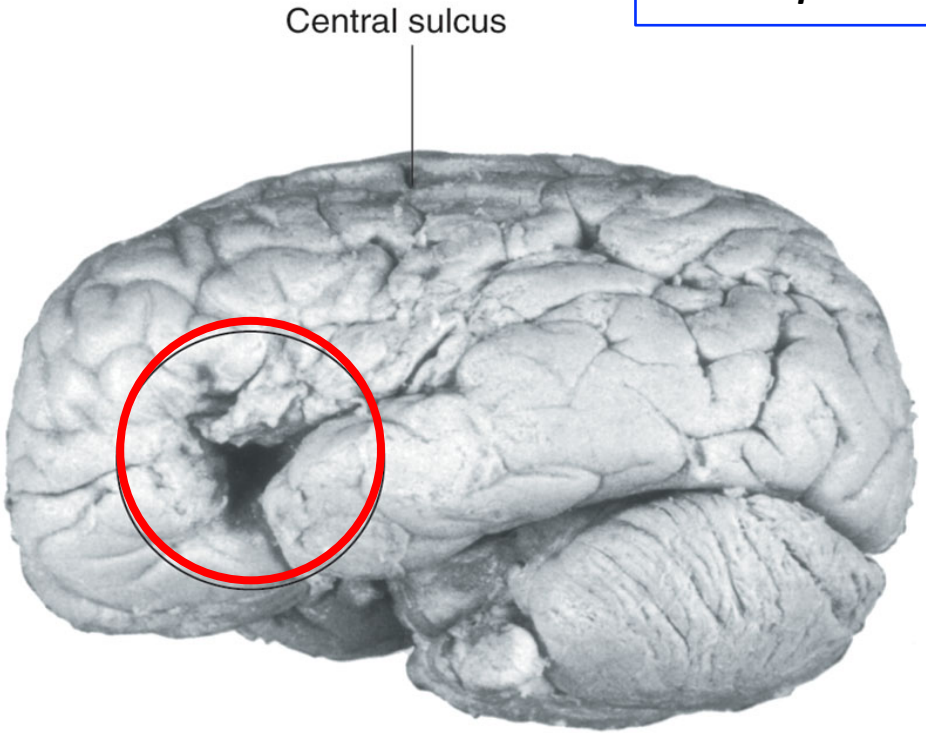
Franz Joseph Gall (1758-1828)



End of the XIXth century →the anatomo-clinical theory

Motor aphasia



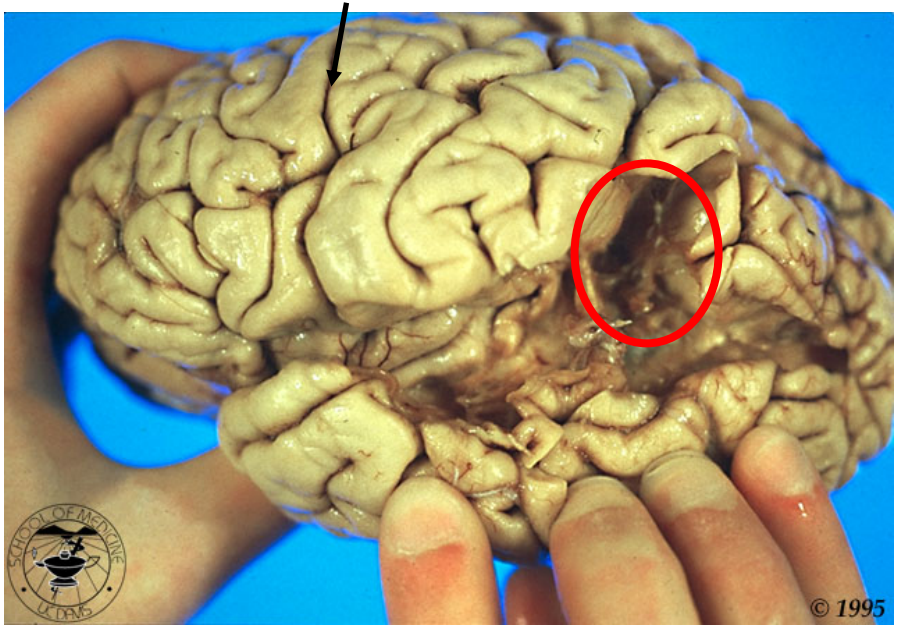


Leborgne's brain (« one-eyed »), so-called « Tan-Tan » (1861), autopsied by ***Paul Broca: one speaks with left frontal lobe***

End of the XIXth century →the anatomo-clinical theory

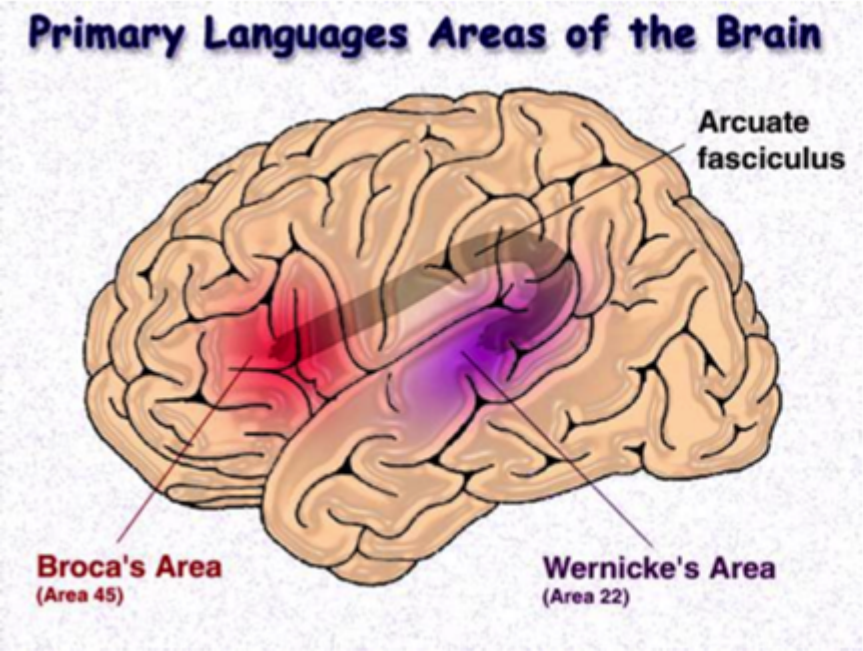
Sensory aphasia





Carl Wernicke: one speaks with left temporal lobe (1874)

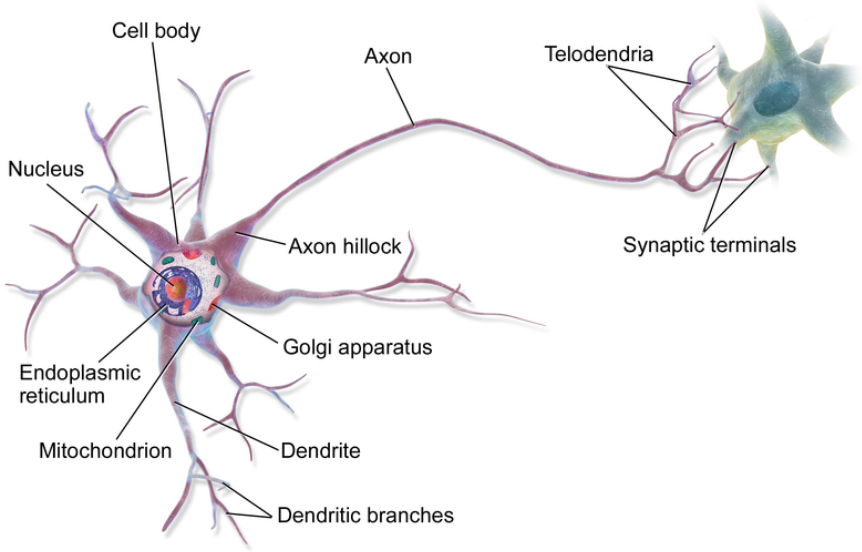
Network organization: Language is located in left hemisphere which is then said to be the dominant hemisphere



Wernicke's area receives and processes information, which travels along the Arcuate fasciculus to Broca's area, where speech is produced.

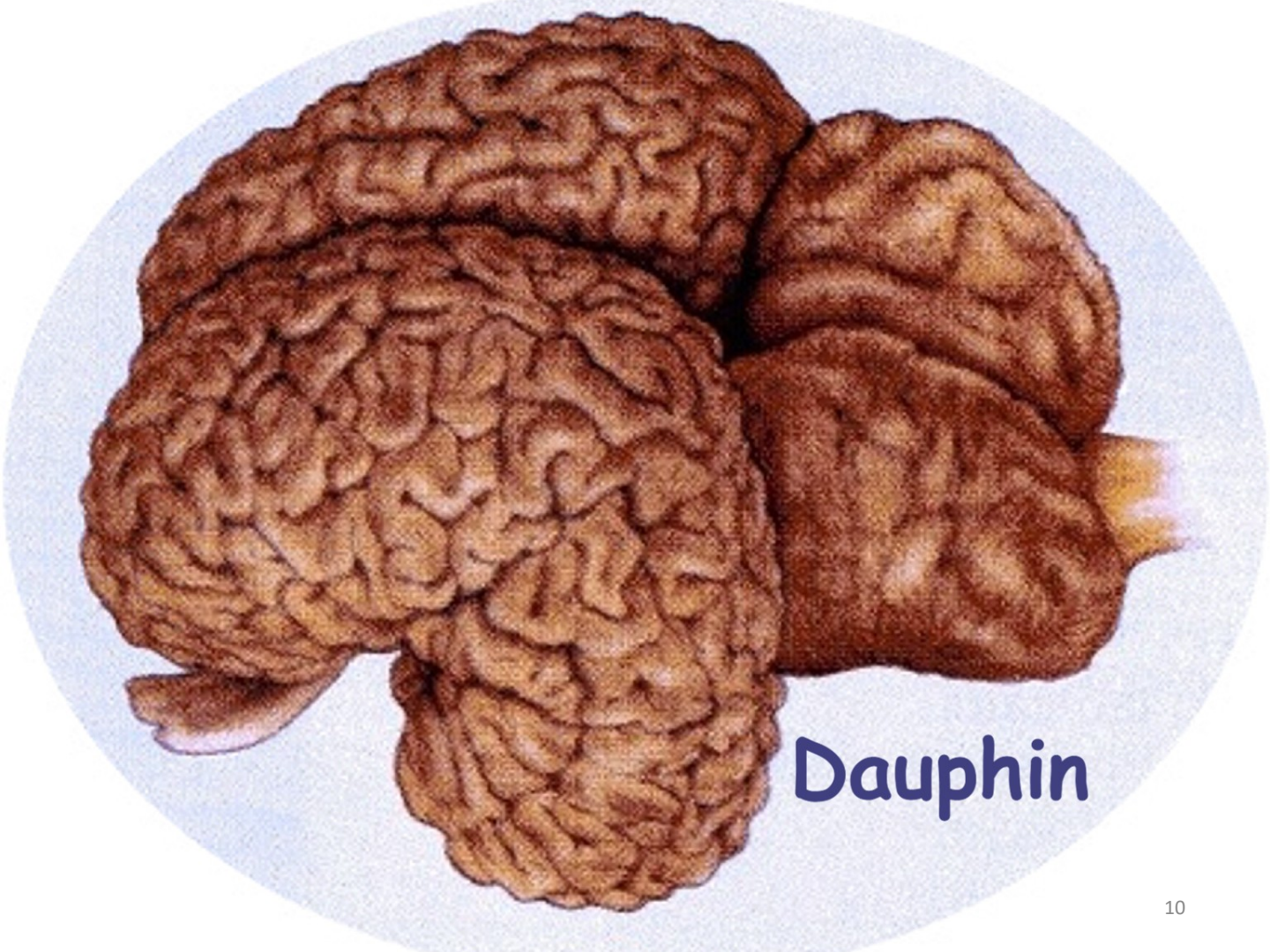
Brain

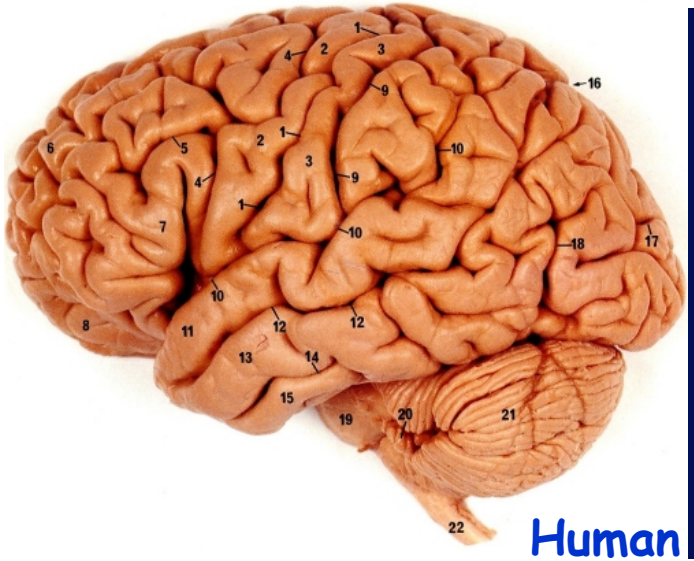
- 100 billion neurons
- « Fibers » = axons
- 1 neuron has 10 000 contacts with other neurons (synapses)
- Brain = 1,3 - 1,5 kg (2% of the body weight)
- 20% of oxygen consumption
- Energy enough for a 10-20 watts bulb



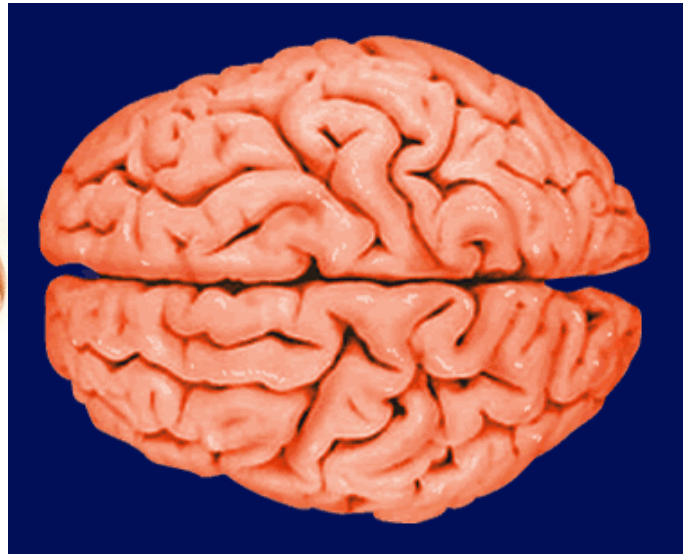


Blausen 0657 MultipolarNeuron.png


Dauphin



Lateral view

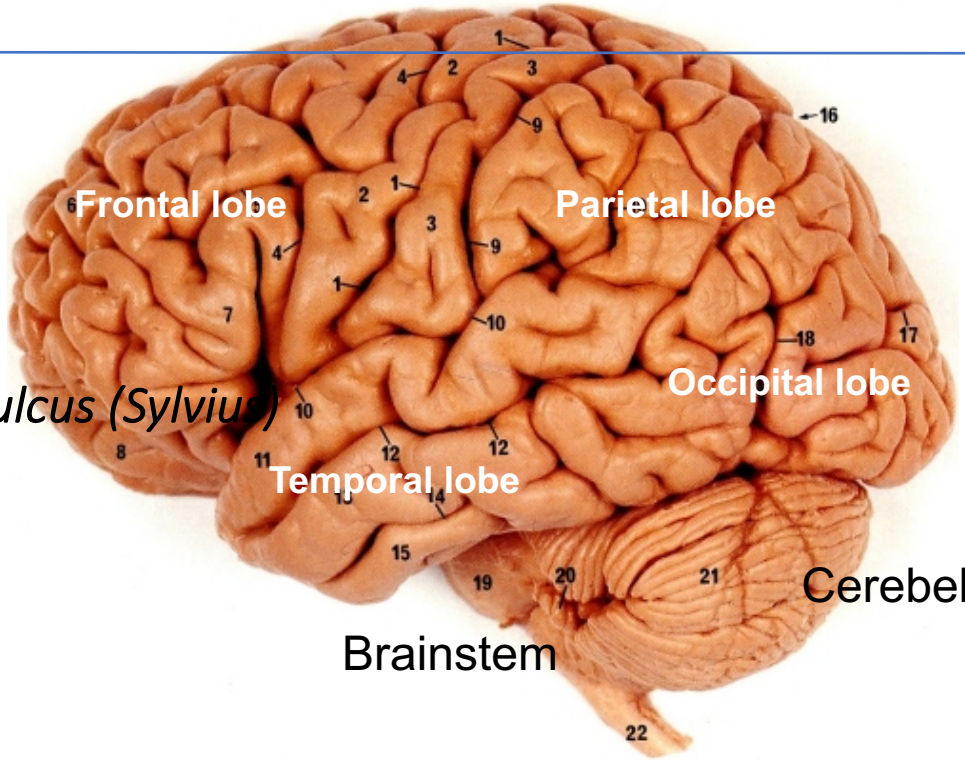


View from above



Total area = 0.45m^2 (adult)

Central sulcus (Rolando)

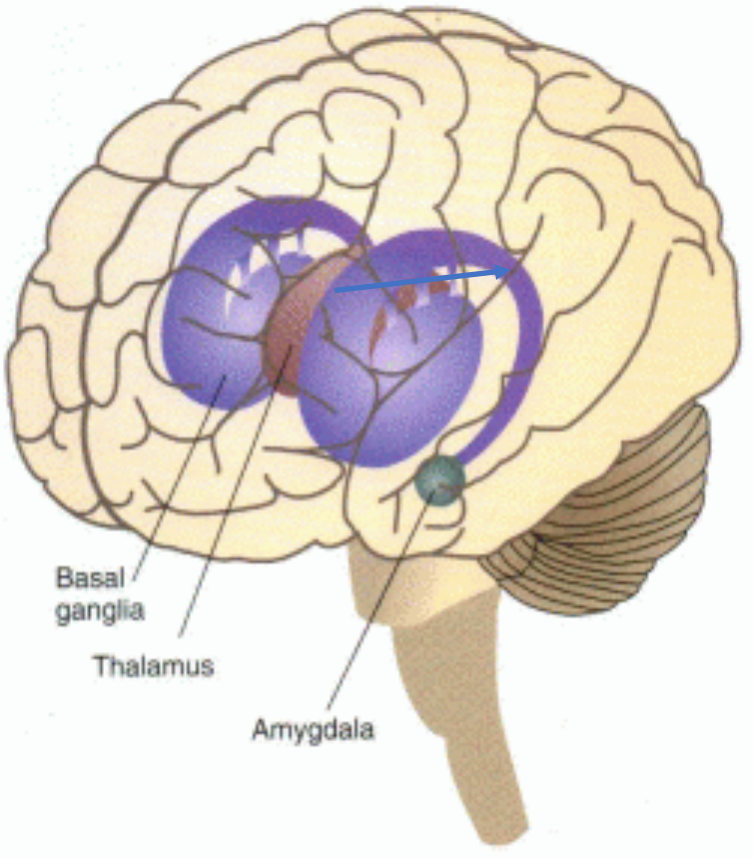


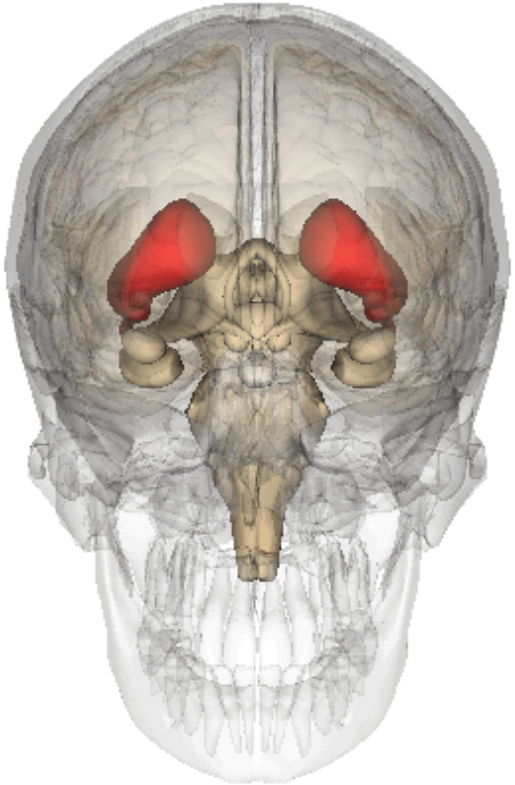
Lateral sulcus (Sylvius)

Cerebral hemispheres

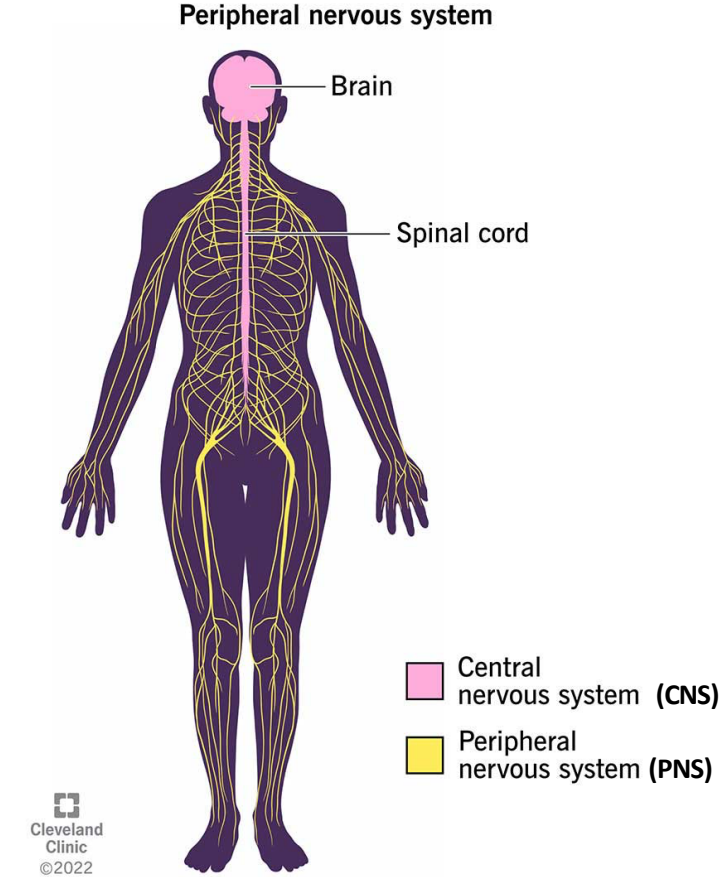
- Organization-

Basal ganglia

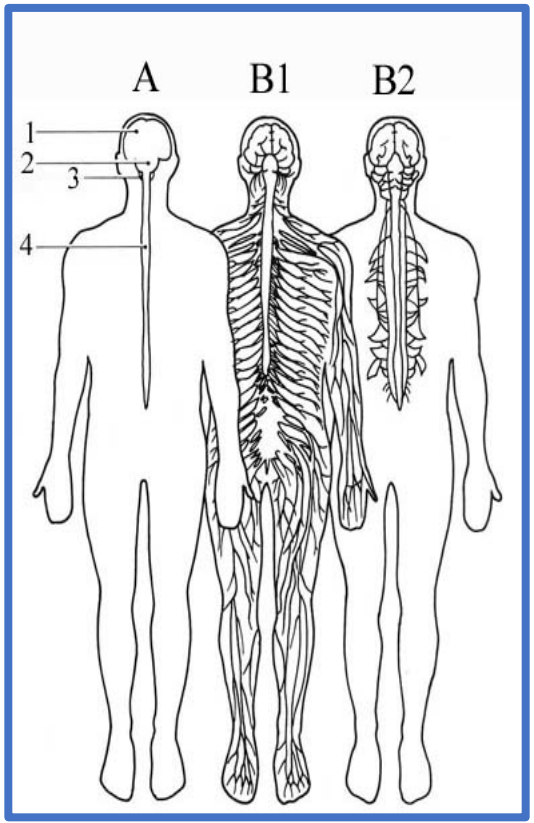




Peripheral and central nervous system organization



- The PNS brings *afferent* or *sensory* information from periphery to the CNS
- The CNS analyses, « integrates » the information
- The PNS brings back *efferent* or *motor* information from the CNS to periphery



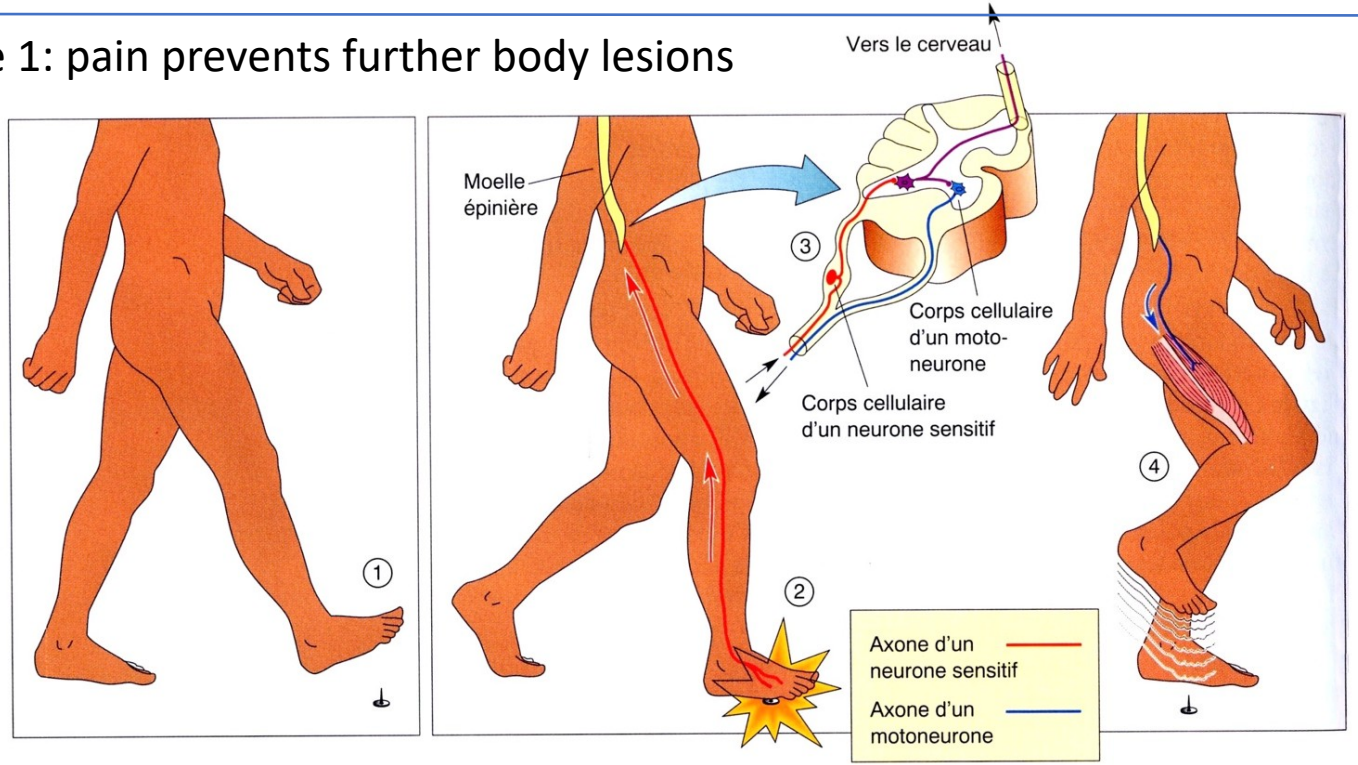
The information that is conveyed from and to the periphery concerns

- All 4 limbs, skin, muscles, joints, sweat glands… (B1)
- Internal organs (B2)

Functions

- To bring to conscience somatosensory information such as pain, vibration, gentle tact that will in return induce/or not a voluntary movement
- To regulate unvoluntary body functions such as heart beat or intestinal motility & secretions
- To maintain homeostasis and adapted behaviour

Example 1: pain prevents further body lesions

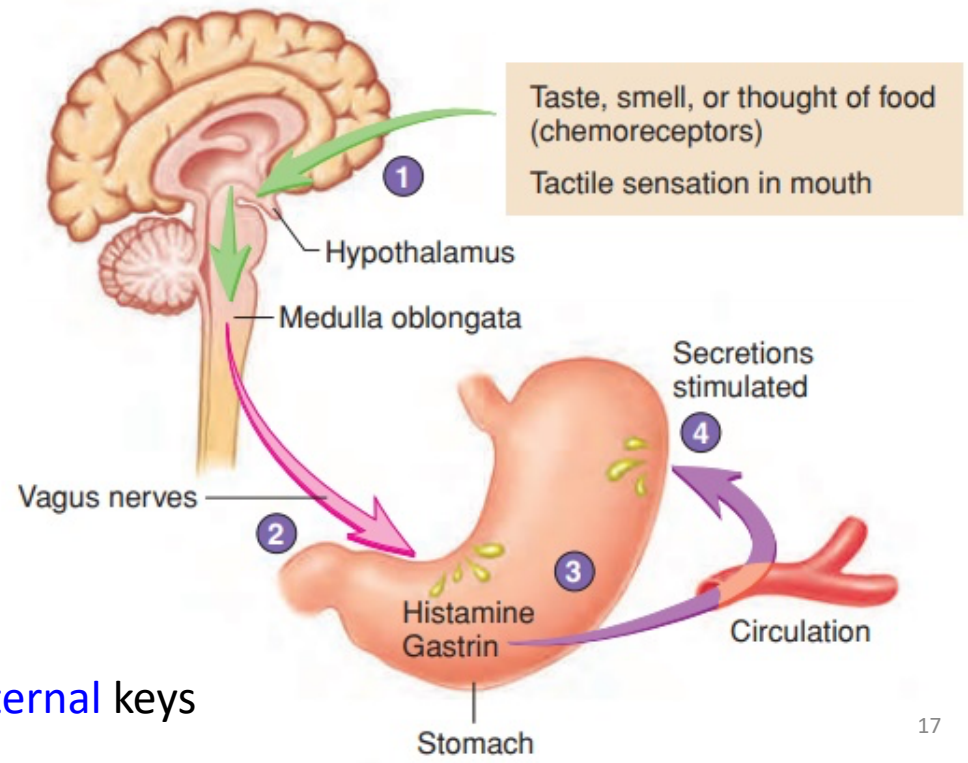


Behaviour is defined by external keys

Example 2: smell of food prepares digestion

Cephalic Phase

1. The taste, smell, or thought of food or tactile sensations of food in the mouth stimulate the medulla oblongata (*green arrows*).
2. Vagus nerves carry parasympathetic action potentials to the stomach (*pink arrow*), where enteric plexus neurons are activated.
3. Postganglionic neurons stimulate secretion by parietal and chief cells and stimulate gastrin and histamine secretion by endocrine cells.
4. Gastrin is carried through the circulation back to the stomach (*purple arrow*), where, along with histamine, it stimulates secretion.



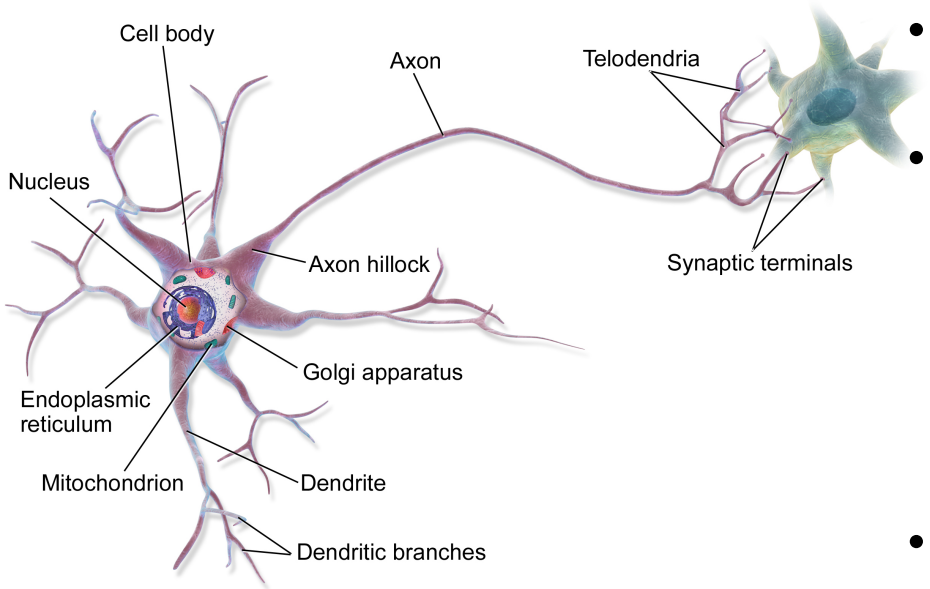
Behaviour is defined by external keys

Example 3: project planning



Behaviour is defined by internal keys

The functional unit of brain is neuron



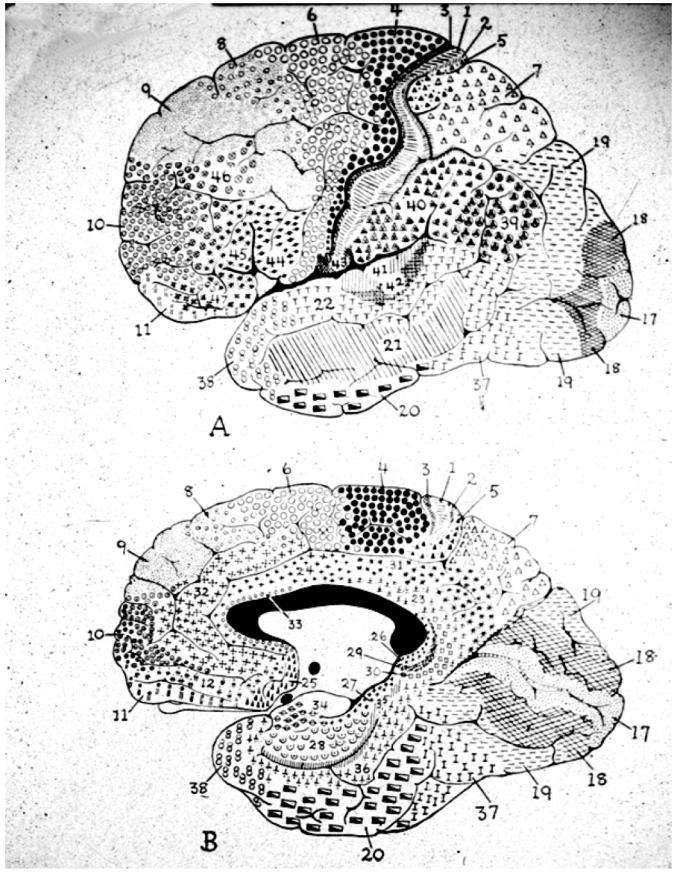
- Cell bodies are in the cortex and in the basal ganglia
- Neurons send/receive axons from a region to another inside the brain, and outside the brain to the PNS (sensory, motor neurons and interneurons), myelinated (white matter)
- They translate information that is conveyed as an action potential

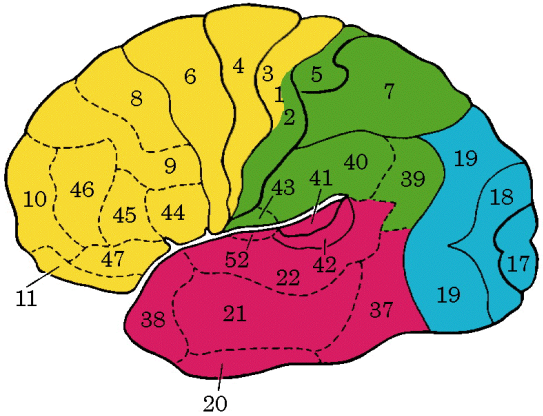
Grey substance **White matter**

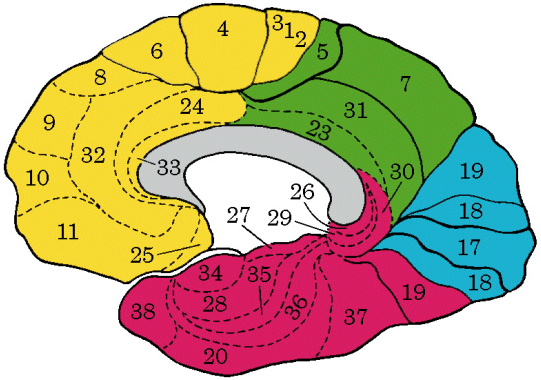
Blausen 0657 MultipolarNeuron.png

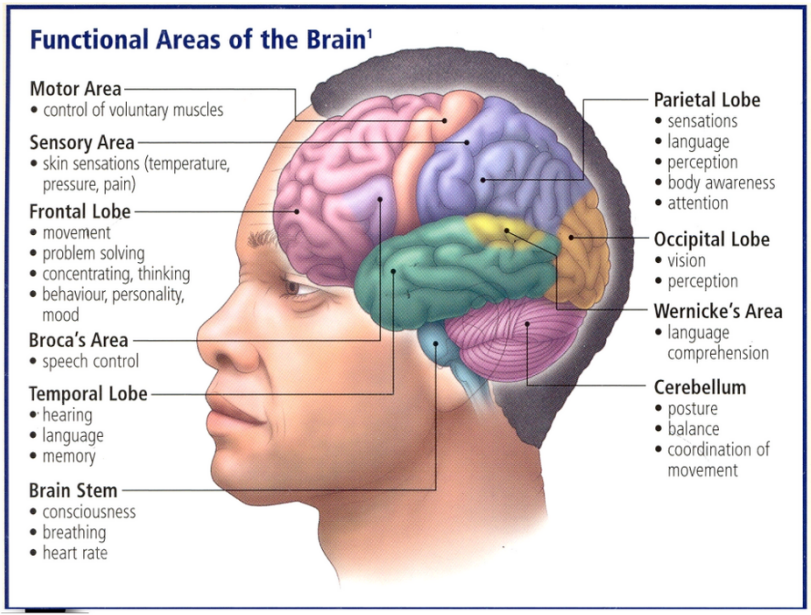
Brodmann's area

(cytoarchitectonic map of the cortex)



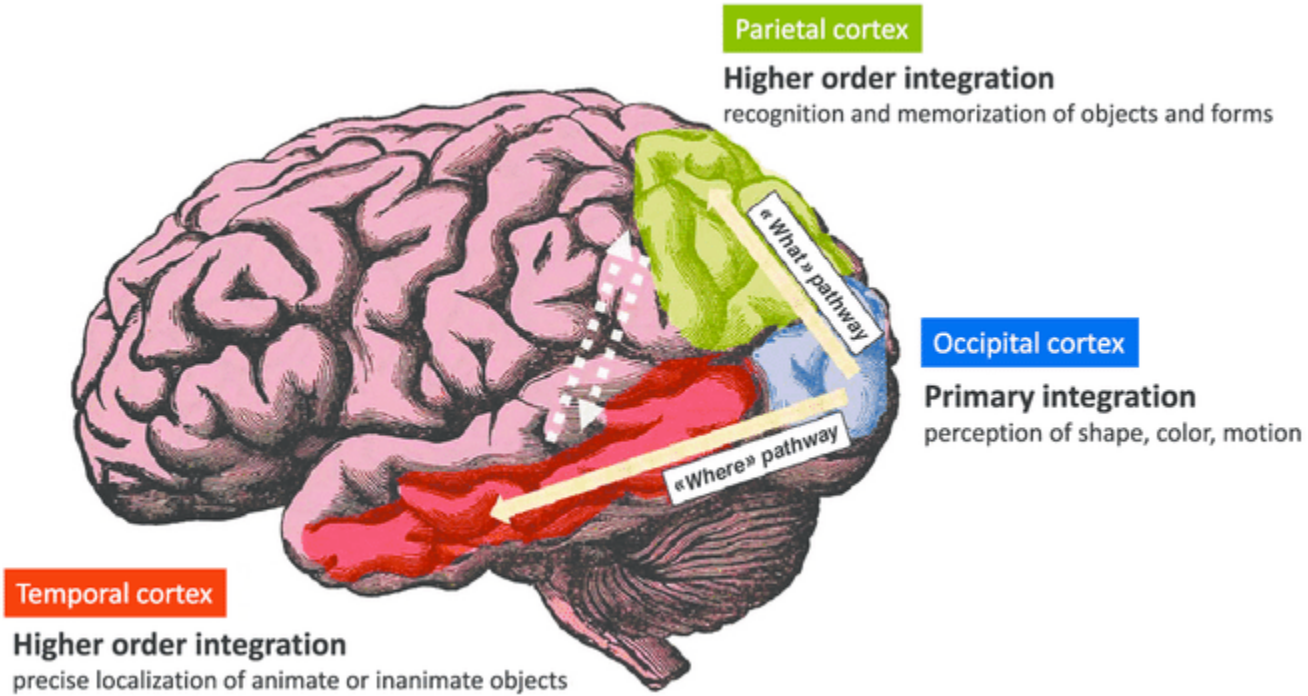






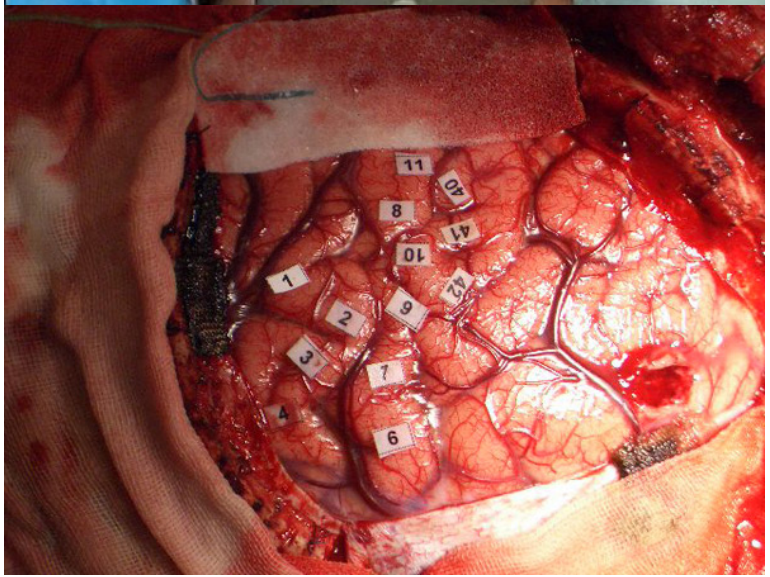
Primary cortices versus associative cortices

Quizlet



Nataf S, F1000Research 2016





Awake brain surgery

- The patient names the figures that appear on the screen
- Electrical current stops the function of underlying neurons: if the patient stops talking → stimulated neurones concern the speech area

- Higher order functions-



Cognitive Functions

- Wakefulness
- Awareness
- Attention

- Memory

Instrumental Functions (language, calculation, gnosies, praxies gestural praxies, visuo-spatial and visuo-contructive capacities)

Executive Functions (conceptualization, reasonning and problem solving, planification, routines inhibition, decision making)

→ Interconnected networks

Some definitions….

- Dominant hemisphere

✓ where language is localized

✓ - Left hemisphere in the right-handed (96%)

- Left hemisphere

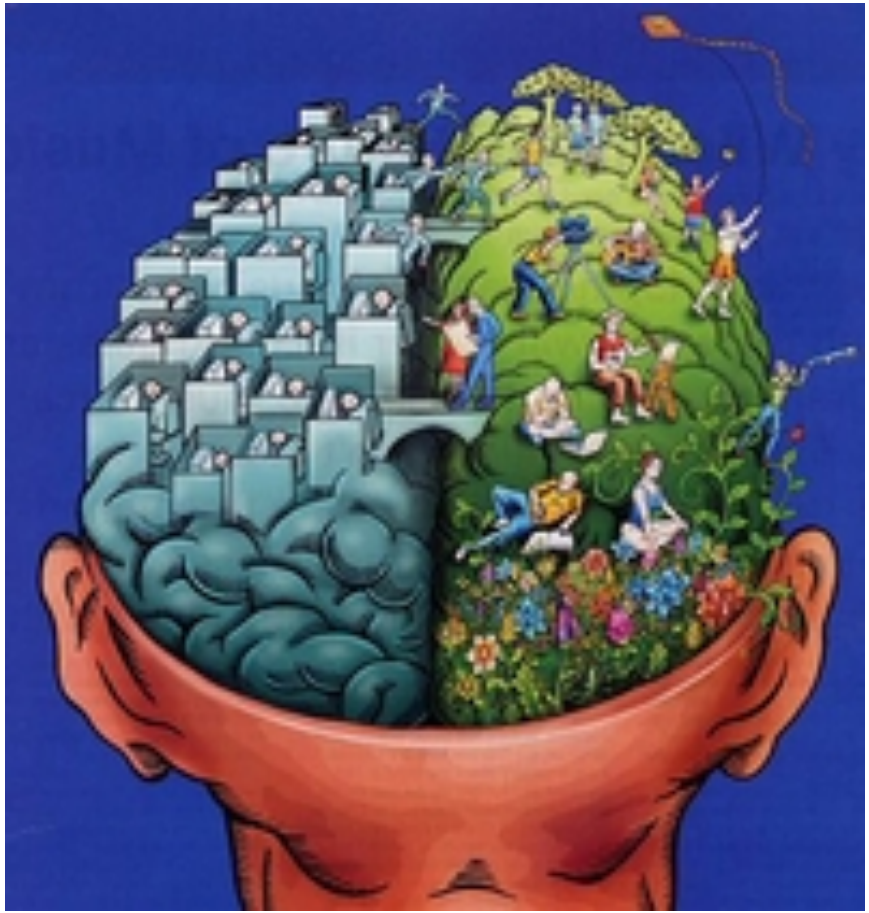
✓ categorical hemisphere

✓ specialized for the verbal and sequential processing of higher functions

- Right hemisphere

✓ representational hemisphere

✓ specialized in nonverbal, nonmathematical and non-sequential processing of higher functions, (size or distances evaluation, spatial construction…)

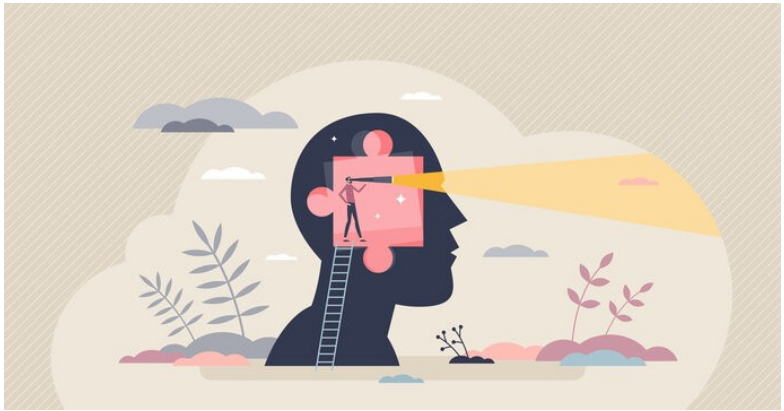


Plasticity+++

Wakefulness and awareness



From Jaimi Jansen, May 17, 2018

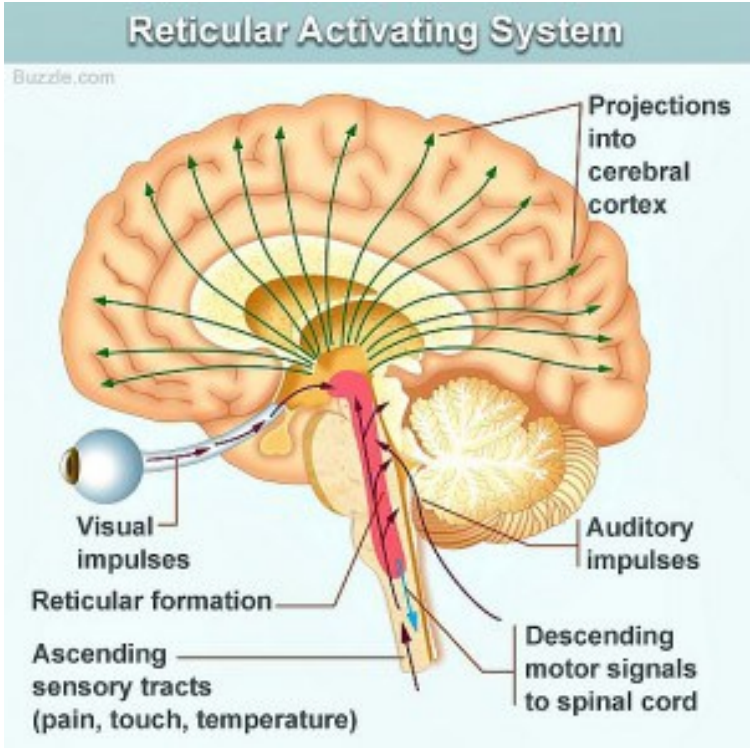


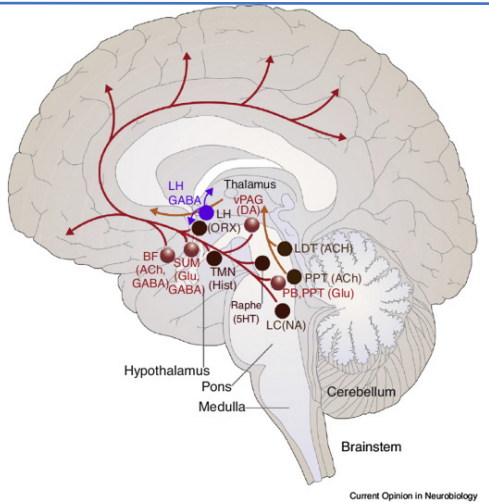
From Dhaval Gajera, March 8, 2023

Wakefulness

- «The vigilant organism is one that is not only ready for action, but ready to carry out this action to the best of its ability, whatever the circumstances.» (***Head***)

- Allows an optimal interaction with the environment





Impact of numerous medications
→ drowsiness

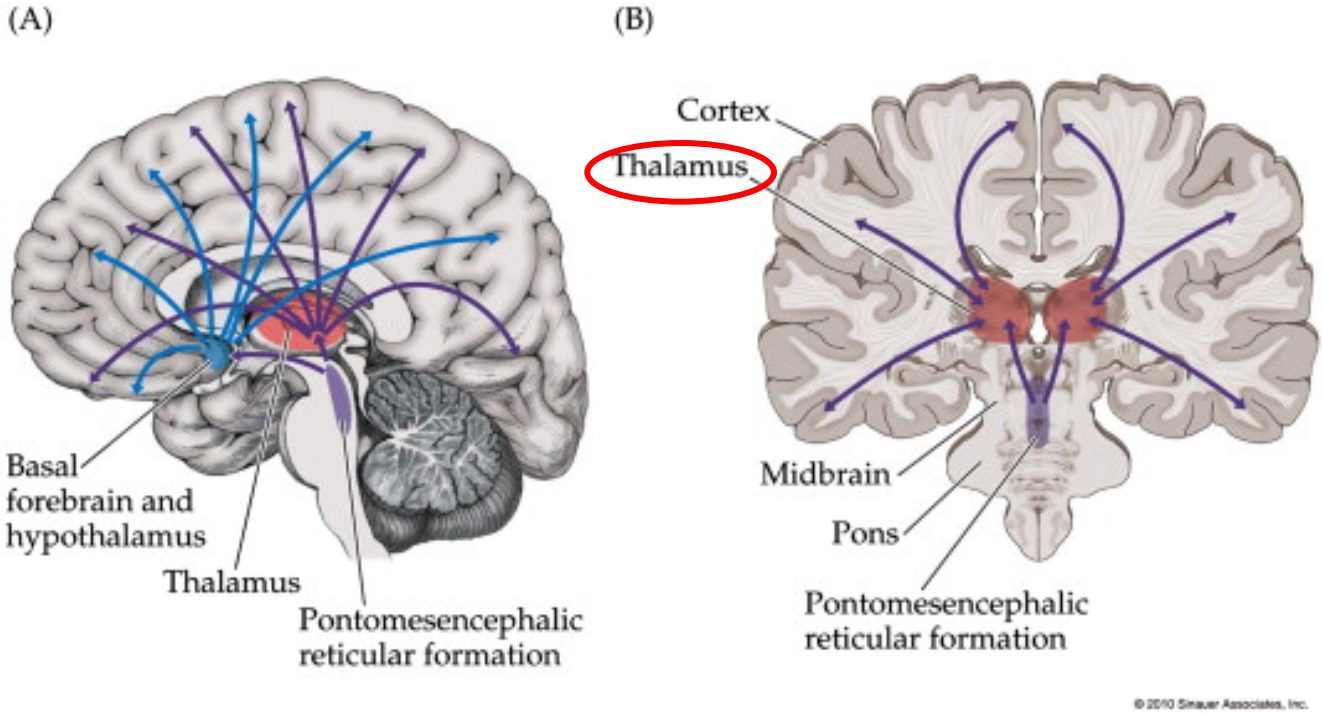
Awakening: Ascending reticular activating system (ARAS) (diffuse projections to both hemispheres)

Conscience/Awareness

- «Reportability»

- An information (visual, emotionnal, …) is conscious when
  - when we can relate it to ourselves
  - and to others, whatever the mean (speech, gesture, behaviour)

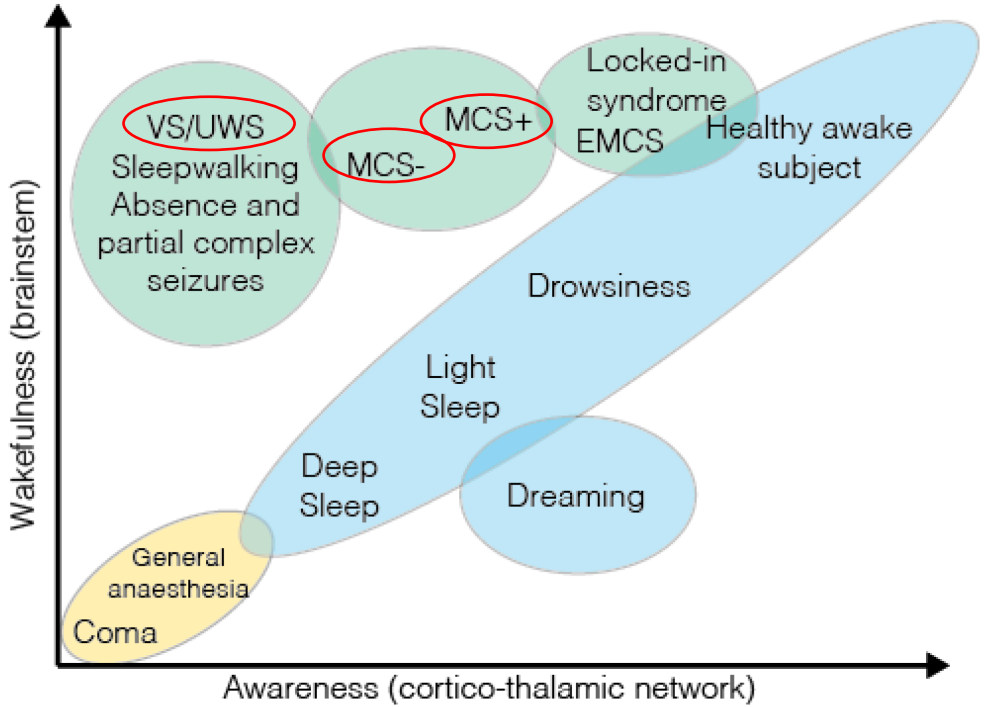
- Mandatory integrity of
  - ARAS
  - AND of an interconnected network of neurons in the frontal and parietal areas

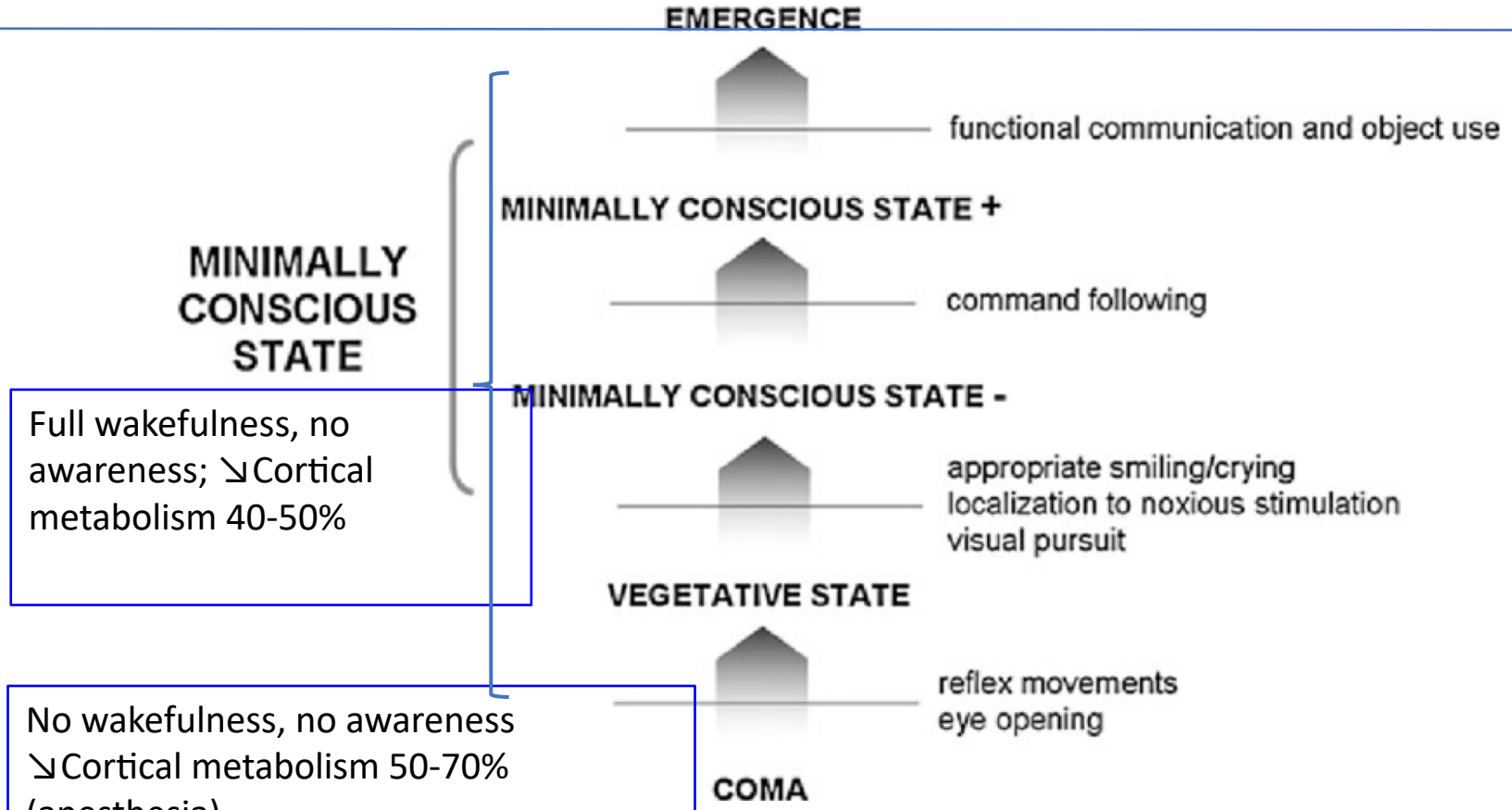


Conscience: frontoparietal network + ARAS

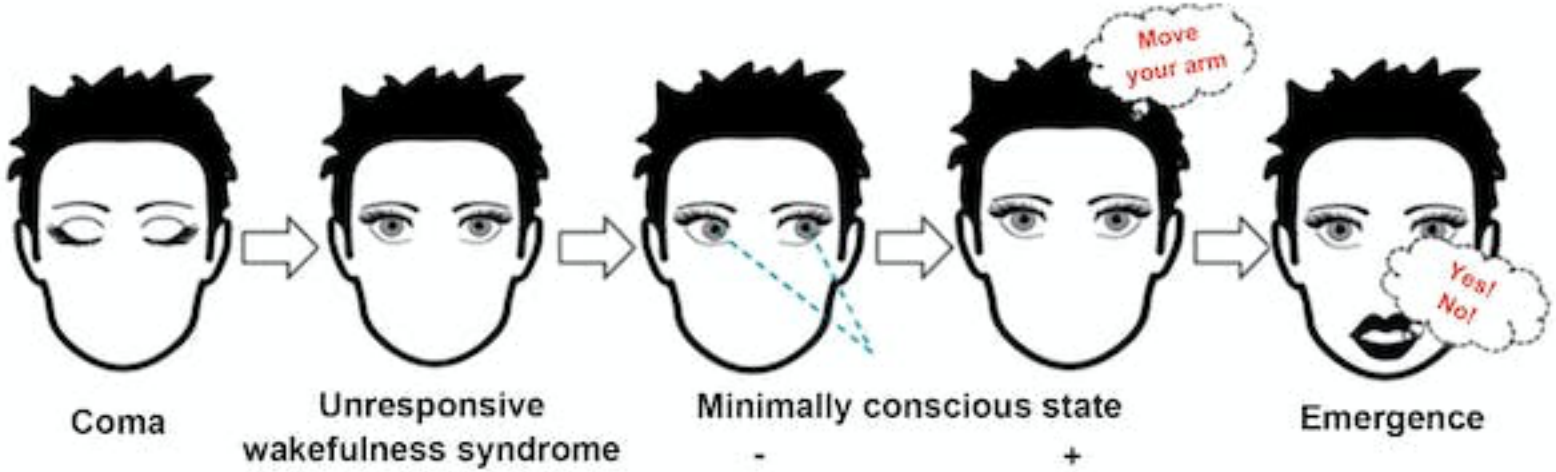
Different states of consciousness

- Sleep
- Anesthesia
- Coma
- Minimally conscious states
- Vegetative state (unresponsive wakefulness syndrome)





Bruno MA, J Neurol 2011



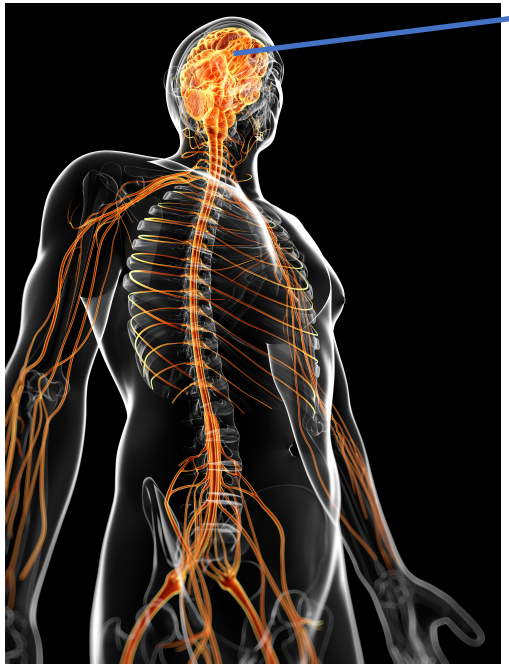
Diagnosis of the state of consciousness following brain damage: coma, unresponsive wakefulness syndrome (vegetative state), minimally conscious state minus, minimally conscious state plus and emergence.

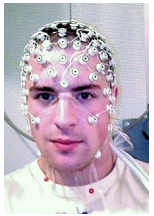
Wislowska et al. (2017)

How to measure nervous system function?

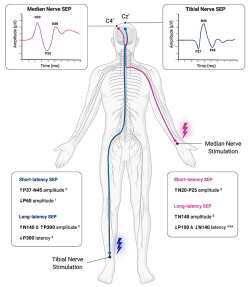


Electroneuromyography (mV)/PNS





Electroencephalography (µV)/CNS



(Sensory) evoked potentials (µV)/PNS+CNS

Electroencephalography (EEG)





- Continuous recording of electrical oscillations as « wavy lines » on the computer, in real time
- Thanks to electrodes attached to the scalp and connected to amplifier and recording consoles
- Fast rythms ~ awake
- Slow rythms ~ sleep, coma

EEG- definitions - electrodes

Number :
Odd : left
Even : right

Equidistant positionning of the electrodes

Letter :

A : Auriculaire

Fp : Fronto-polar

F : Frontal

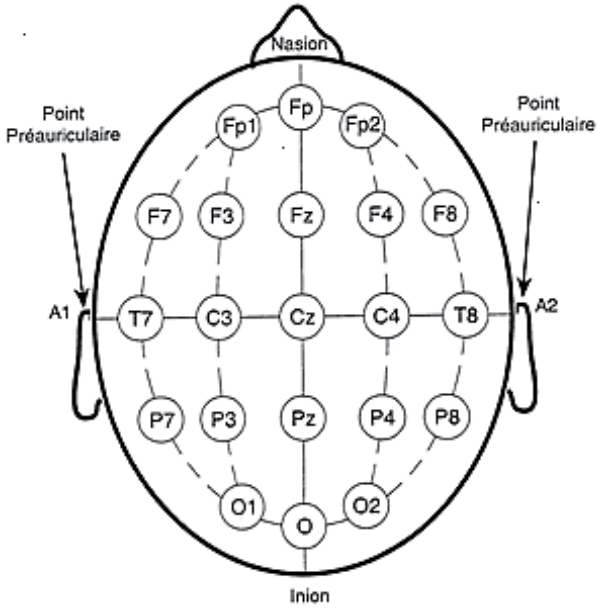
T : Temporal

C : Central

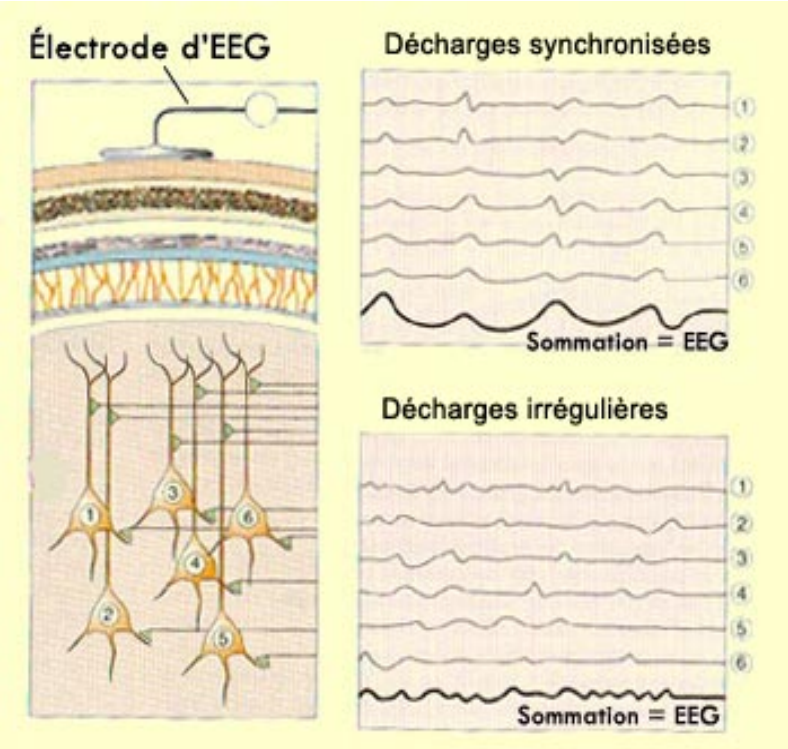
P : Pariétal

O : Occipital

Z : median line



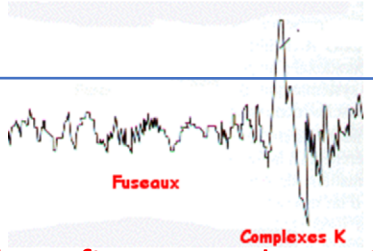
EEG



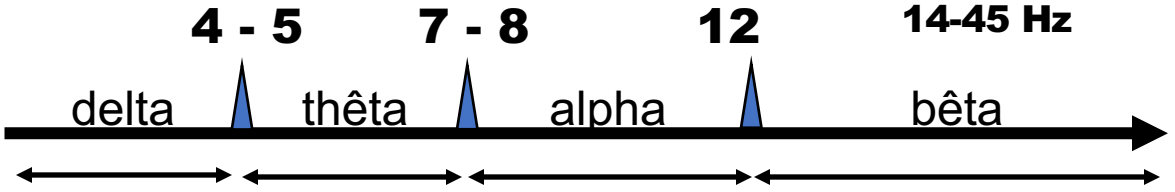
- EEG measures brain electrical activity
- Recording of the simultaneous activity of several thousand synchronous post-synaptic potentials of the dendrites of the pyramidal neurons of the cortex
- The amplitude of the signal depends on the degree of synchronization of these neurons

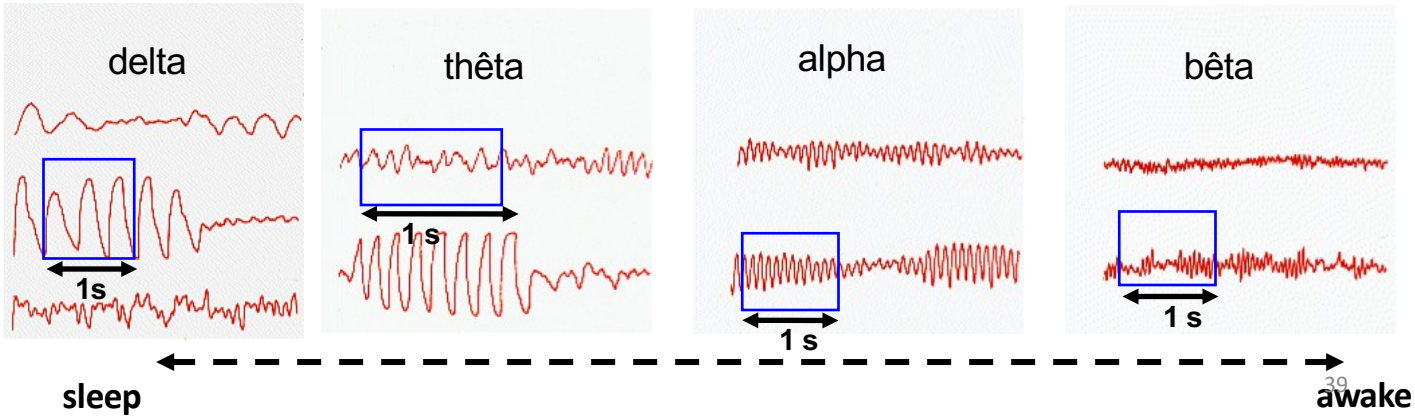
EEG - Definitions - (awake and sleep)

- ✓ Oscillatory activity 1000 times smaller than ECG → ampli
- ✓ We measure the sommation of thousands of neurons of a specific region
- ✓ Basic activity is defined by its frequency



+ sleep figures and reactivity

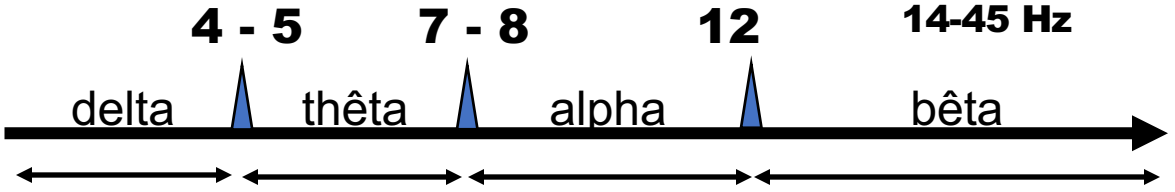


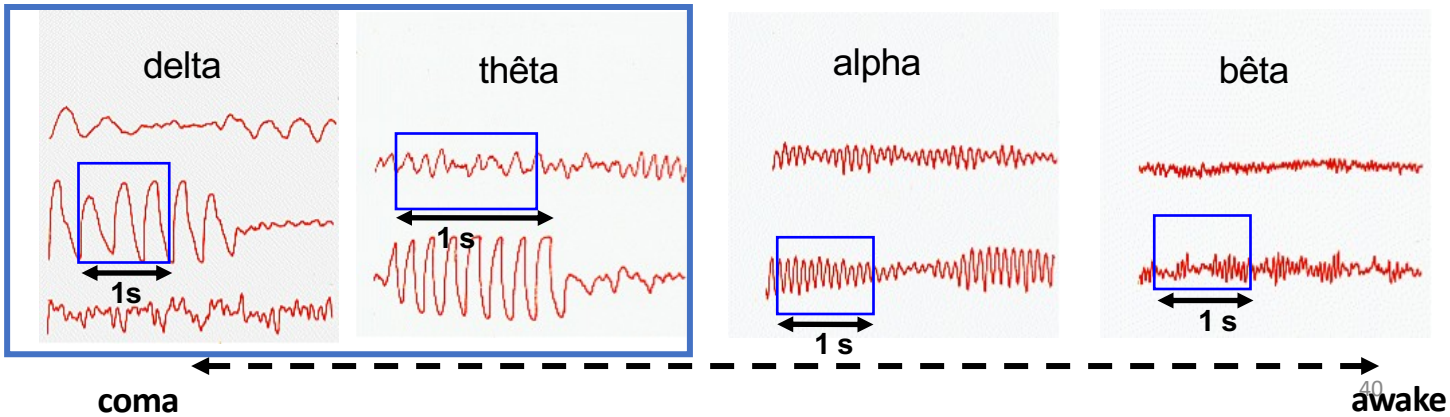


EEG - Definitions - (coma)

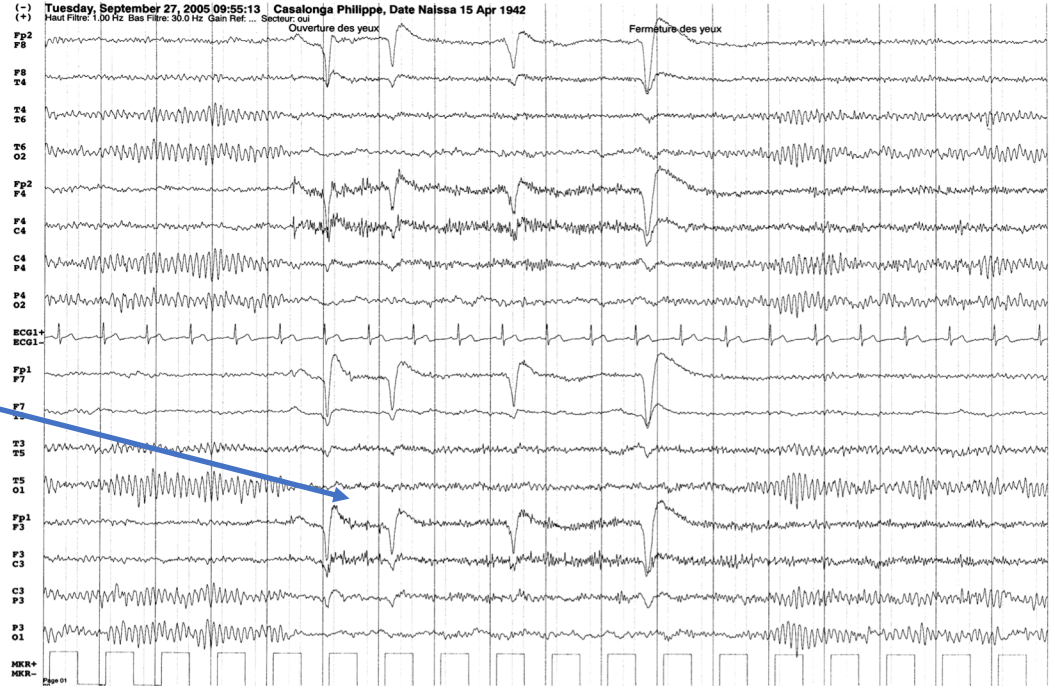
± reactivity

- ✓ Oscillatory activity 1000 times smaller than ECG → ampli
- ✓ We measure the sommation of thousands of neurons of a specific region
- ✓ Basic activity is defined by its frequency



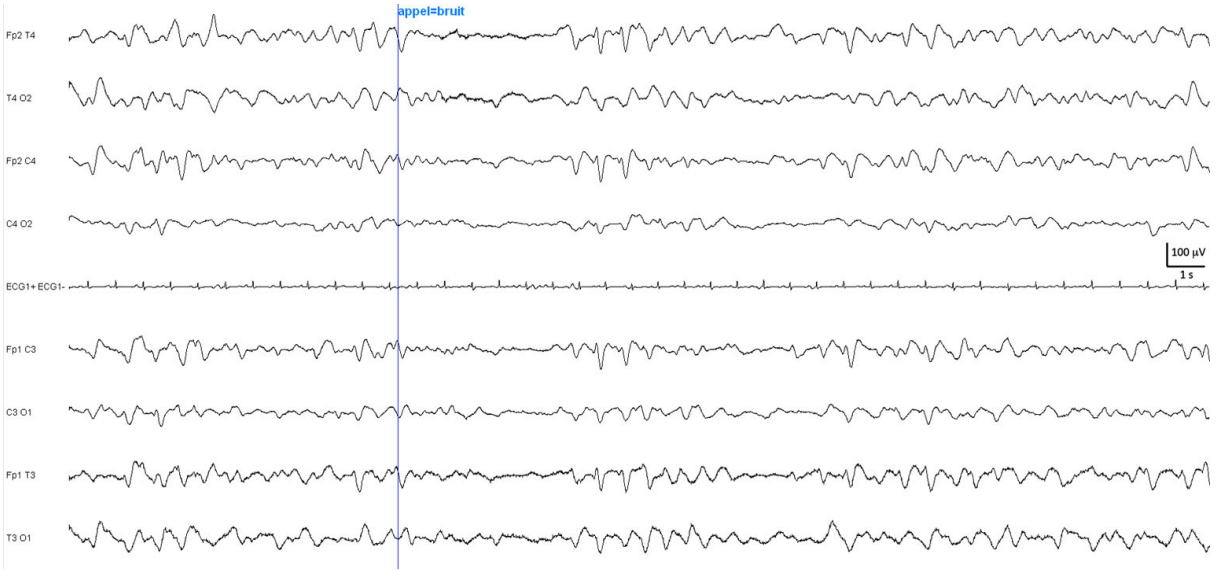


- O/C eyes (*deep breath, intermittent photic stimulation*)
- Quiet, eyes closed:
  - alpha rythm 8-12 c/s,
  - posterior,
  - symetrical,
  - vanishing at eyes opening *(reactive),*
  - without modification induced by deep breath and intermittent photic stimulation

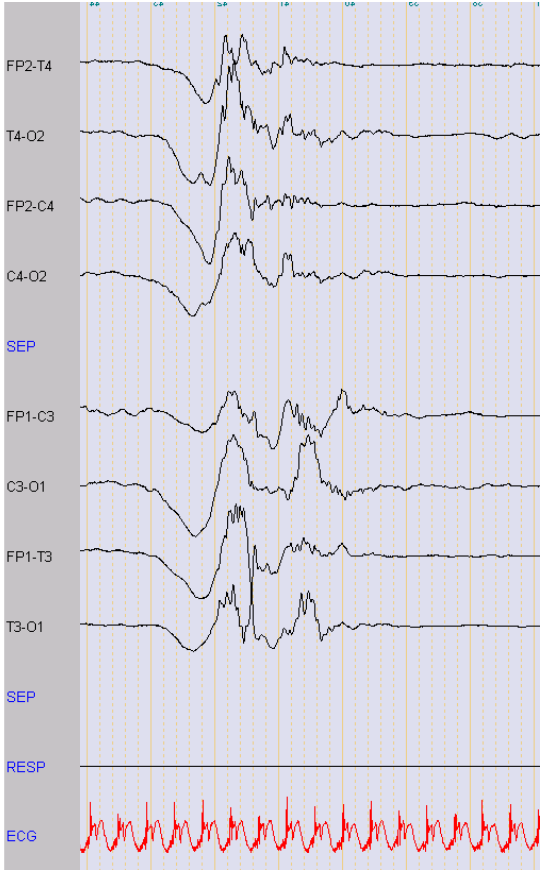




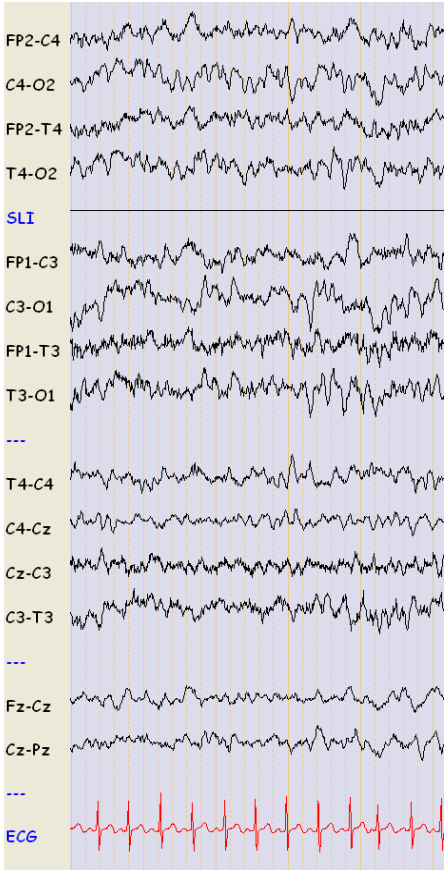
- First name and name calling, hands clap, painful stimulations when the patient does not follow verbal command
  - Clinical and EEG reactivity (smaller and faster amplitude)
  - Paradoxical reactivity: increasing of slow background activity /SIRPID
  - No reactivity
  - Good prognosis in coma: fluctuating background activity



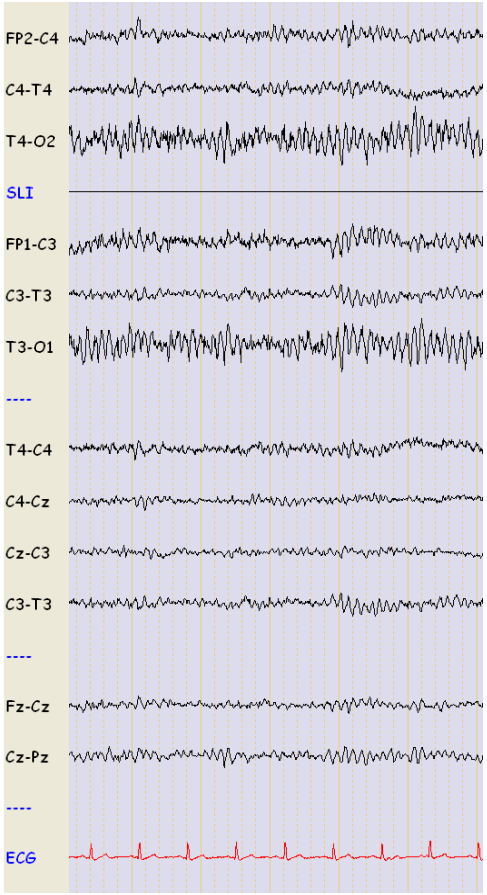
EEG matures with development



Premature new born 30 weeks



18 months year old child



adult

Auditory evoked potentials

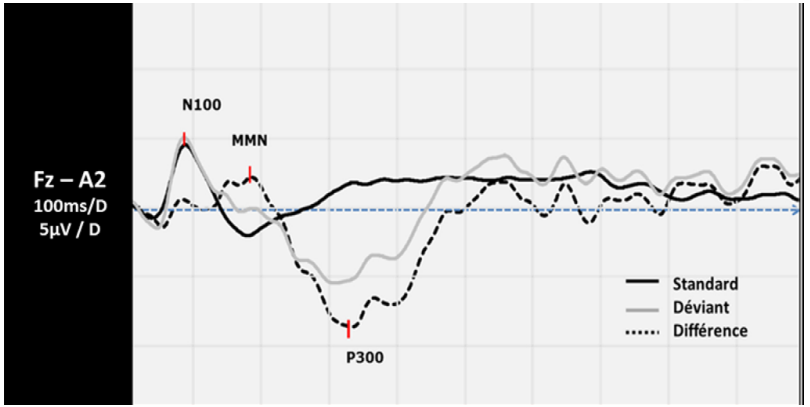
- General principle of EP: « to measure the sommation of electrical activity in a given area after repetitive sensory stimulation »
- Auditory earphones with consecutive sounds

  X X X X Y = there is automatic detection of novelty
- A series of regulary sounds that follow a global rule that the patient must pay attention to:

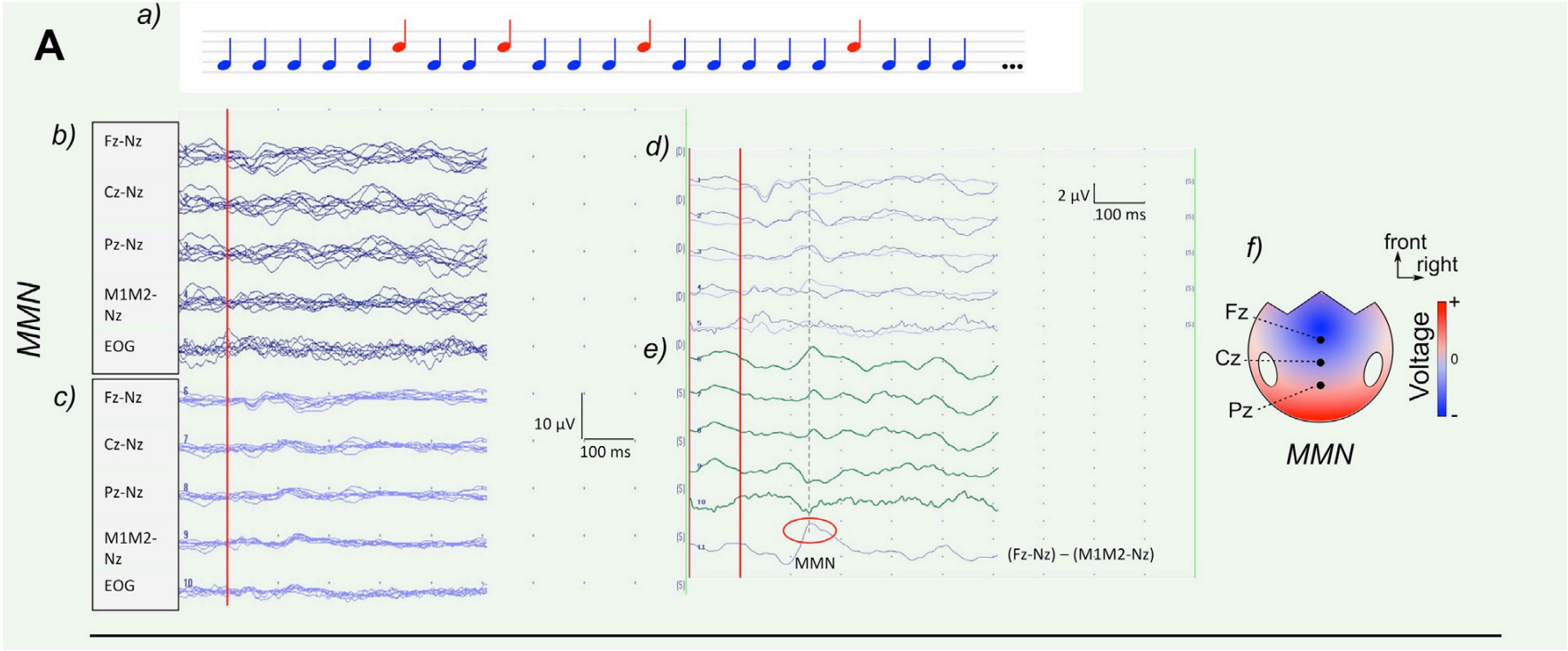
  XXXXY XXXXY XXXXY XXXXY XXXXY
- A series of sounds in which a modification of the rule occurs randomly:

  XXXXY XXXXY XXXXX XXXXY XXXXY





Azabou E med int rea 2017



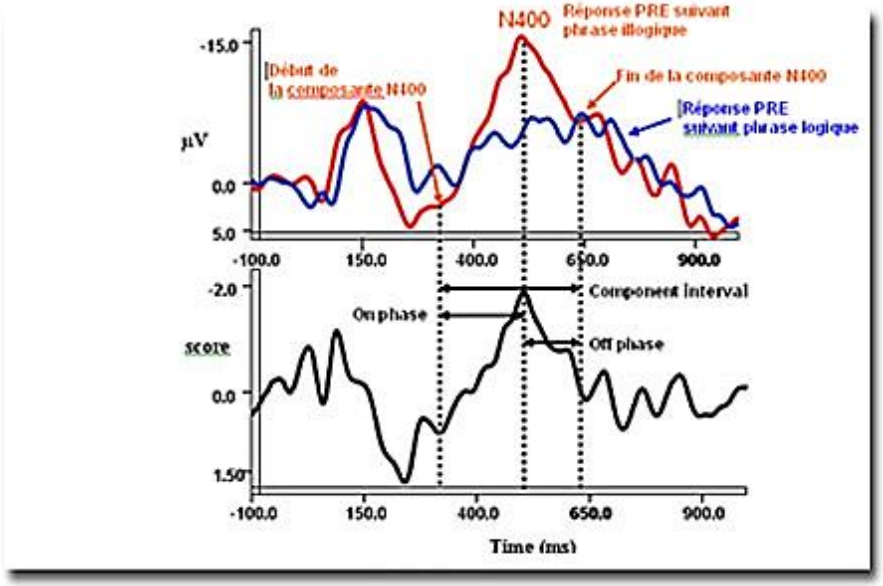
A. The oddball paradigm (a) consists of delivering rare sounds (in red) during a sequence of frequent sounds (in blue). Trials obtained from rare (b) and frequent (c) sounds are averaged (d) showing the P1/N1 complex followed by a voltage difference between both conditions peaking around 200 ms, which is the mismatch negativity (MMN). The plot of the subtraction trace can help in identifying the MMN (e). The MMN is usually maximal in Fc or Cz as represented in a topo-plot of the subtracted voltages (f).

Andre-Obadia N, Clin Neurophysiol 2018

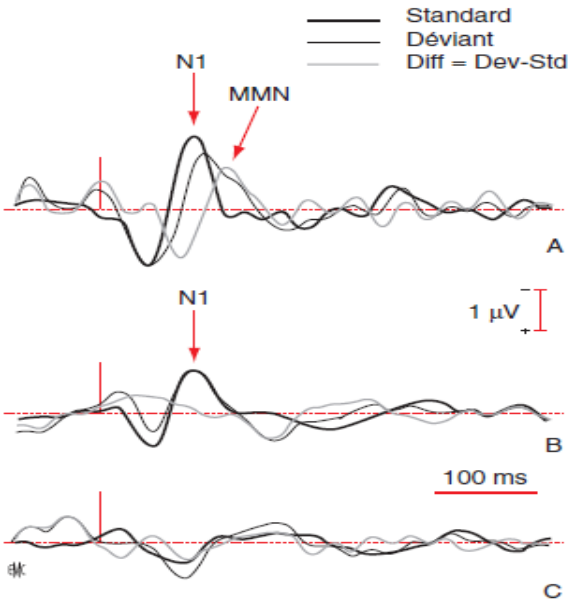
Auditory evoked potentials

N400, *sensitive to language*

« Recorded » when the last word of the sentence is not congruent with the begining of the sentence: « I'm going to go for a swim…. on the highway »



Auditory evoked potentials



Mauguière F EMC 2007

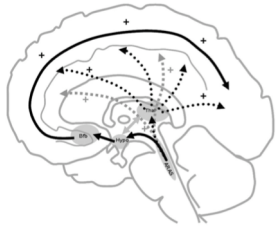
Good prognosis when present (specificity 90-100%) (does not rule out a severe disability including MCS)

No significance when absent…..

Coma Definition



- Clinical
  - ✓gr. *kôma*, deep sleep (≅)
  - ✓ Vigilance disorder little or not reversible under the influnce of stimulation (*Plum* & *Posner)*



- EEG
  - ✓« sleep » EEG but not responding to various types of stimulations
  - ✓Depth of coma
  - ✓± specific abnormalities in relation to the cause

Brain injury in critical illness



Neurologic illness

- Traumatic brain injury
- Stroke
- Cardiac arrest
- Status epilepticus
- Encephalitis / meningitis

Non-neurologic illness

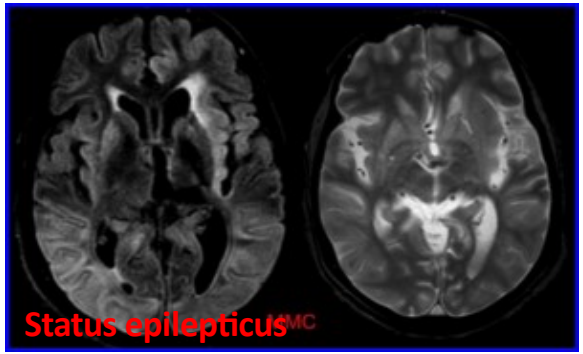
- Acute respiratory distress syndrome
- Sepsis
- Shock
- Major (cardiac) surgery

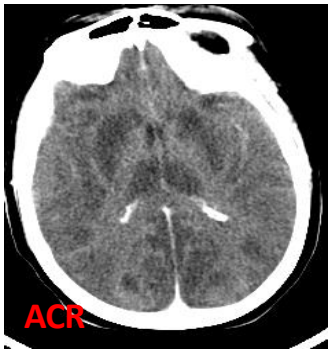
- Clinical question: how to evaluate coma prognosis?

Brain injury in critical illness

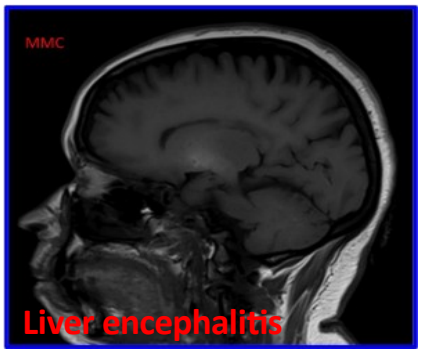




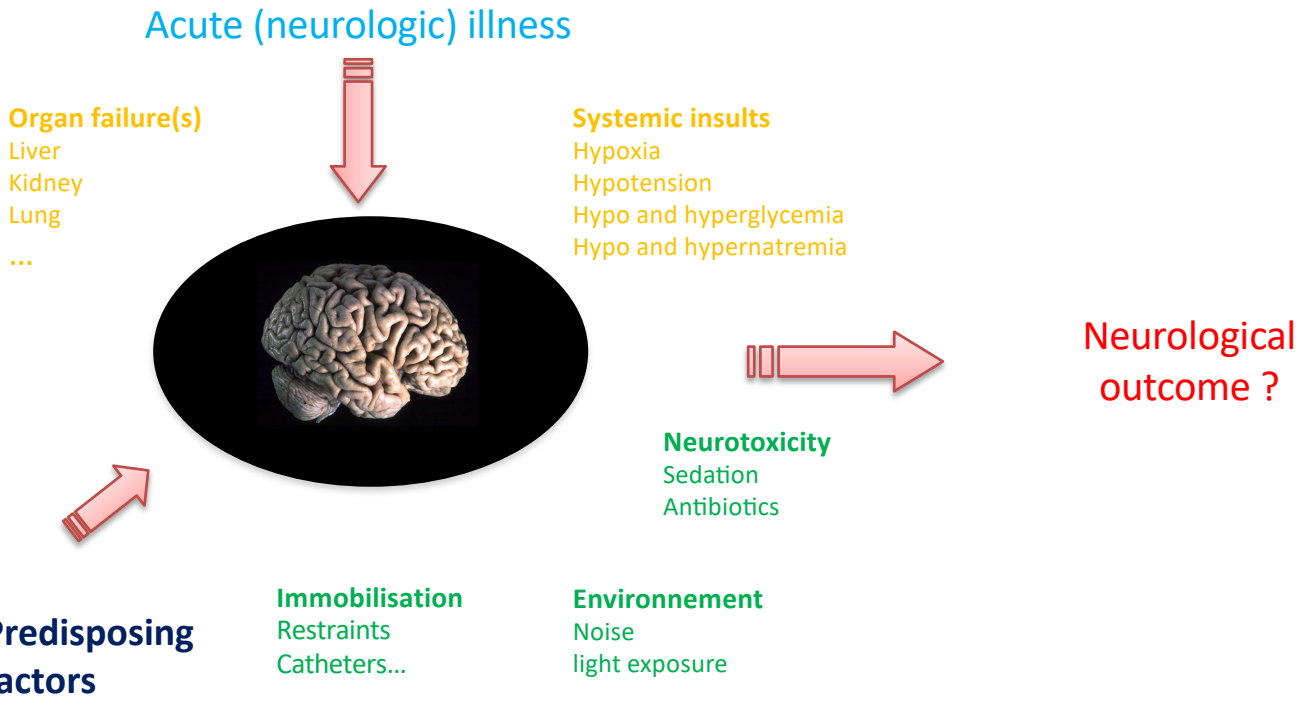






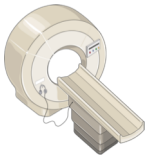


Factors impacting coma prognosis

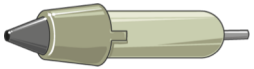


From Romain Sonneville

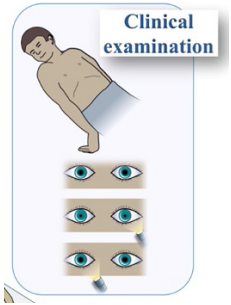
- Clinical question: how to evaluate coma prognosis?

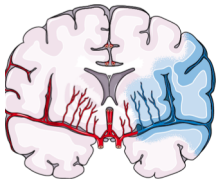


MRI
PET scan



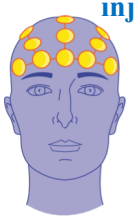
Transcranial
Doppler



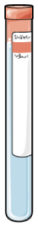


Brain
injury





EEG
Evoked potentials



Blood
Biomarkers
(NSE, S100B, NFL ..)

Long term
outcomes



Quality of life
EQ-5D, SF36



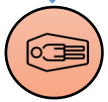
Mental health
HAD, IES-revised



Cognition
MMS-E, MOCA
RBANS



Functional disability
Rankin, GOS-E

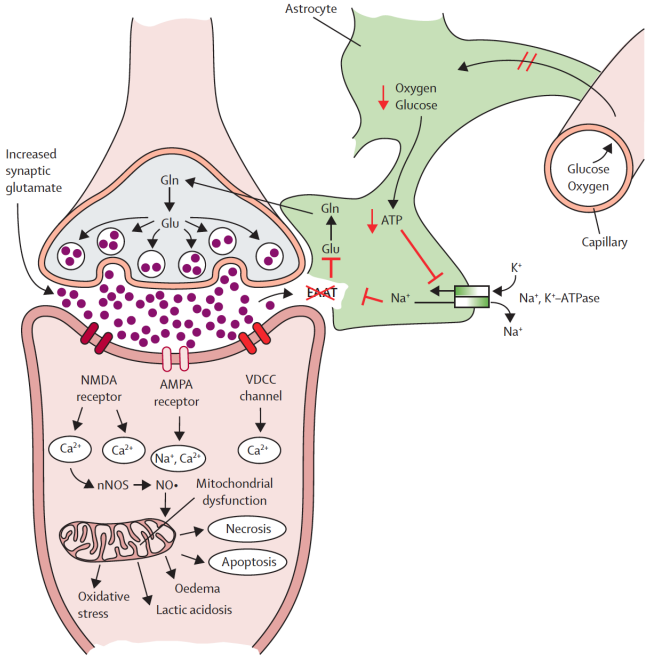


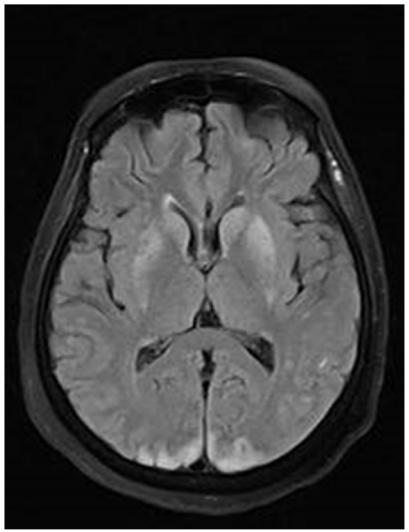
Mortality

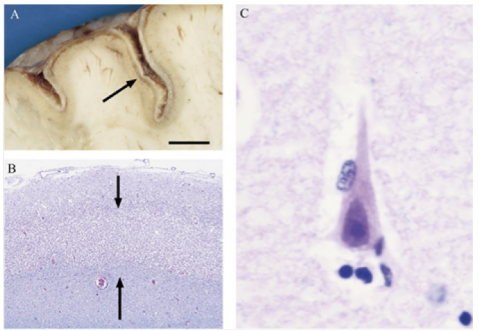
From Romain Sonneville

- Clinical question: how to evaluate coma prognosis?

Cellular mechanisms (Excito-oxidative Cascade of Events that Mediate Hypoxic-Ischemic Brain Injury)



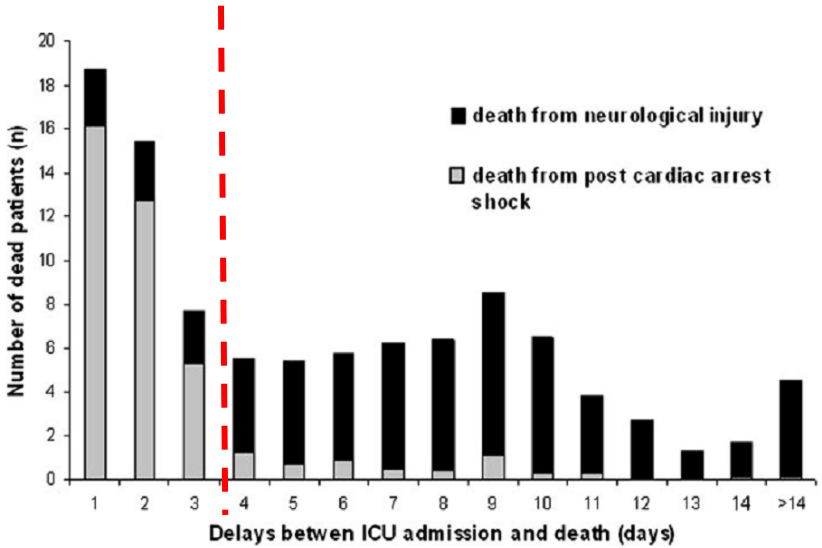




From Romain Sonneville

- Clinical question: how to evaluate coma prognosis?

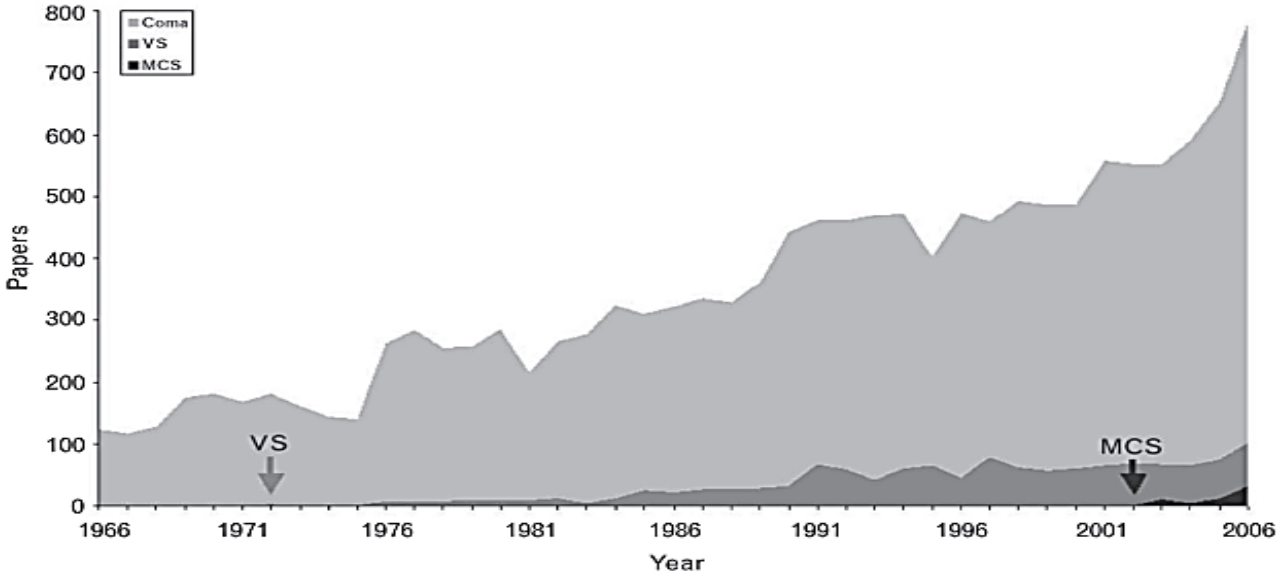
- **> 50% of patients** after cardiac arrest are still comatose D3-D5 after admission in the intensive care unit
- 2/3 of these patients die of a neurological cause



n =1150

Lemiale V et al, Intensive Care Med 2013; 39: 1972–80

« Silent epidemic »



The issue is to be alive…without being disabled

Laureys Cur Op Neurol 2006

- Clinical question: how to evaluate coma prognosis?

WHY ?

- To inform relatives as early as possible
- To avoid to maintain useless therapeutics in hopeless patients

- Clinical question: how to evaluate coma prognosis?

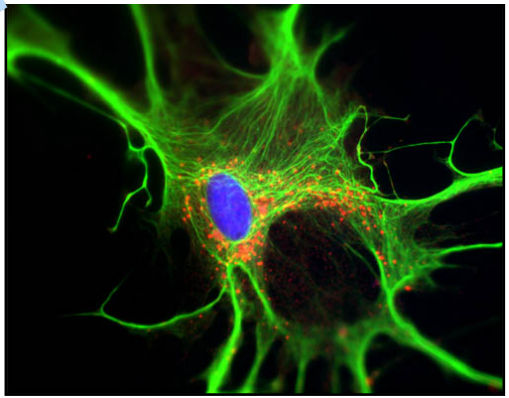
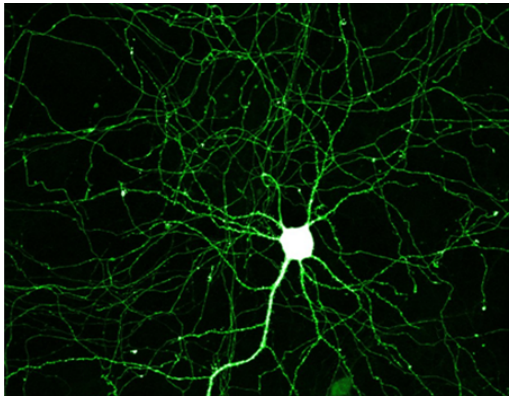
IN WHOM?

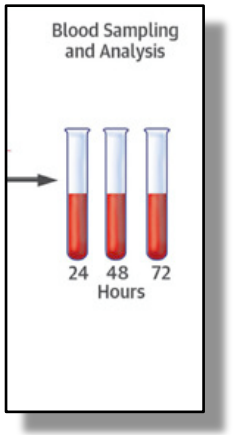
- In post-cardiac arrest patients
- **In patients still in coma** at 48h-72h
- Without adaptive response after stimulation à stimulation (GCS motor = 1-2)
- Taking into account any confounding bias…

- Clinical question: how to evaluate coma prognosis?

Example of biological biomarkers correlated to neurological outcome

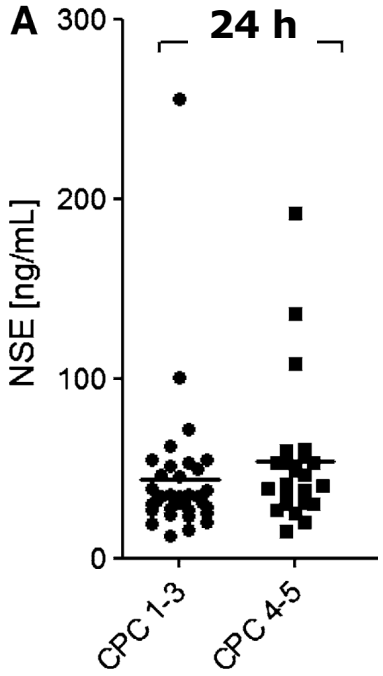
WHICH ONE?

Astrocyte	Neuron
	
• S100beta • astrocytes, BM, fat, skeletal muscle • Rise <24h after brain insult	• NSE, Neuron specific enolase • neurons, platelets, red blood cells, tumors • Rise <6h after brain insult



- Clinical question: how to evaluate coma prognosis?

$n = 73$ pts



Huntgeburth et al., Neurocrit Care 2014; 20: 358-66

In summary

- NSE : high values (> 50-60 µg ▪ L^{-1}) and increase at 48h-72h post CA

→ **Bad prognosis**

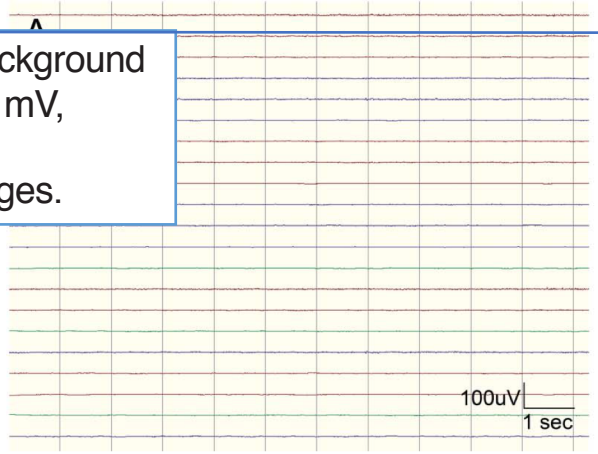
- Repeated measures +++

- False positive

Examples of grades of EEG correlated to neurological outcome

- Clinical question: how to evaluate coma prognosis?

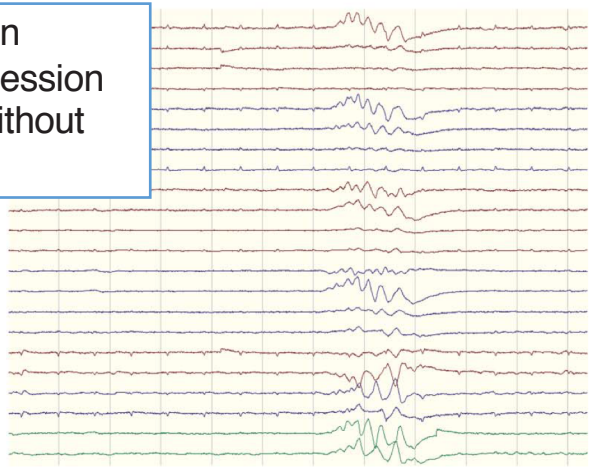
Suppressed background (amplitude <10 mV, 100% of REC) without discharges.





Suppressed background with superimposed continuous periodic discharges.

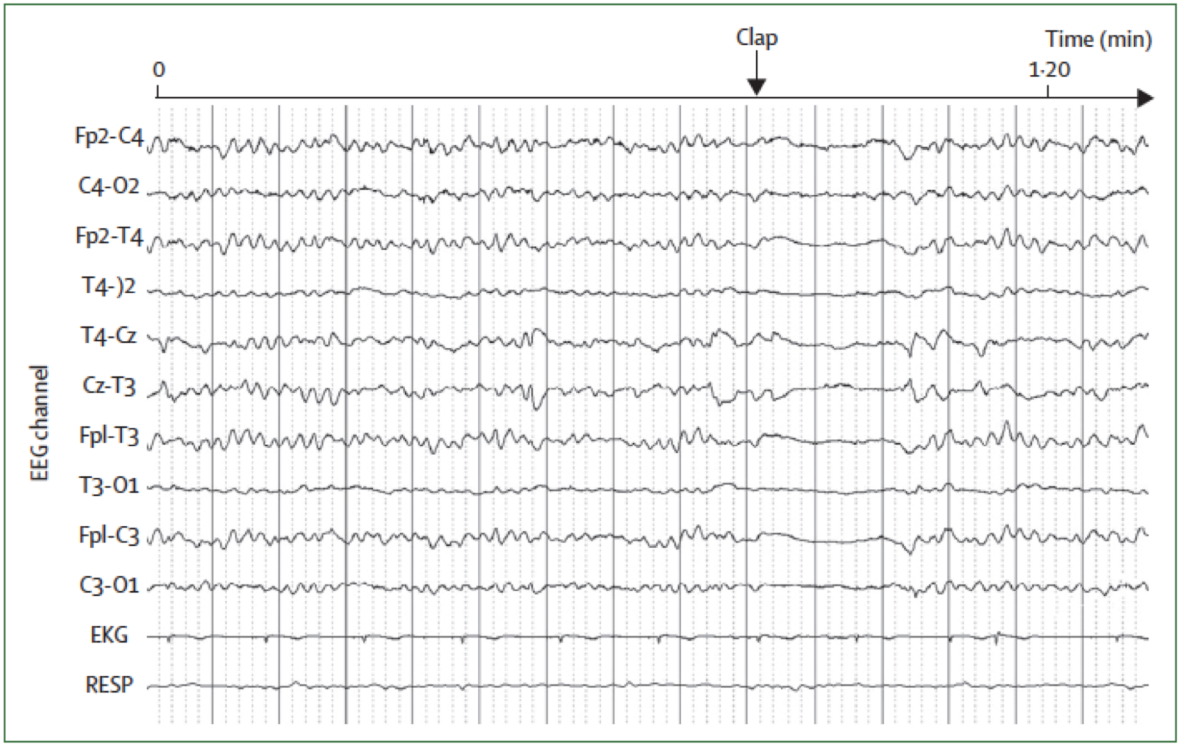
Burst-suppression (periods of suppression >50% of REC) without discharges.





Burst-suppression with superimposed discharges.

Example of EEG reactivity correlated to neurological outcome

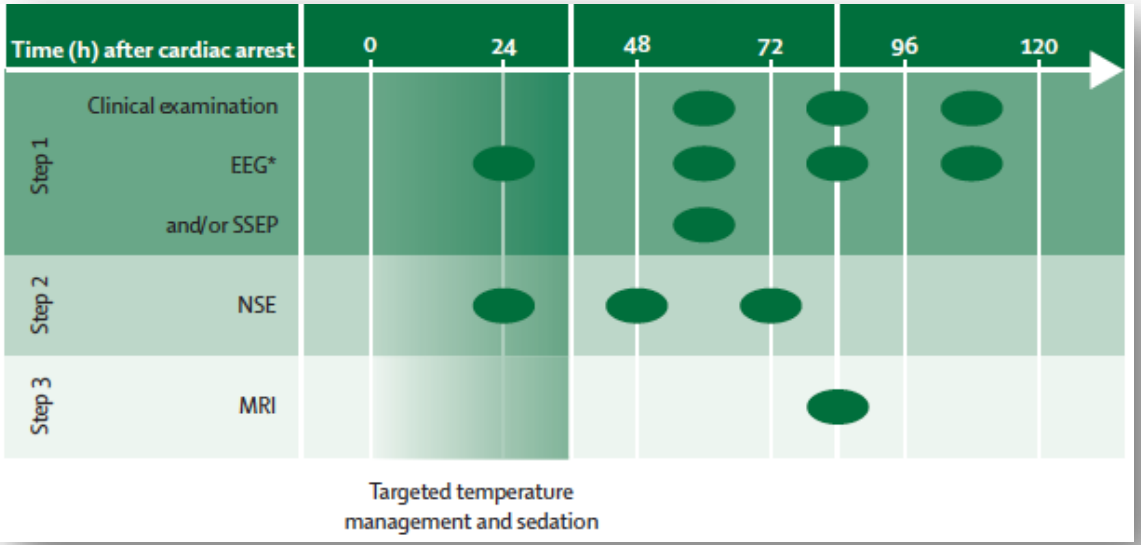


Rossetti A, Lancet Neurology 2016

- Clinical question: how to evaluate coma prognosis?

Neurological prognostication of outcome in patients in coma after cardiac arrest

Andrea O Rossetti, Alejandro A Rabinstein, Mauro Oddo



Lancet Neurology 2016

- Clinical question: how to evaluate coma prognosis?

Very good



Very bad

A mathematical solution to a clinical issue

- Electrophysiological expertise is rare and time consuming
- Often difficult to interpret in the intensive care unit setting (artefacts, electrical environment)
- Combined assessment remains unsatisfactory with a gray zone for many patients

→ *Aim*: a tool easy to handle which does not demand any neurophysiological expertize with high accuracy



- *Hypothesis*: to take into account the whole amount of data generated by cortical activity and classify patients according to reasonable fluctuation using EEG and AEP
- *Aim* : to generate a probabilist classifier

- Clinical question: how to evaluate coma prognosis?

A mathematical solution to a clinical issue

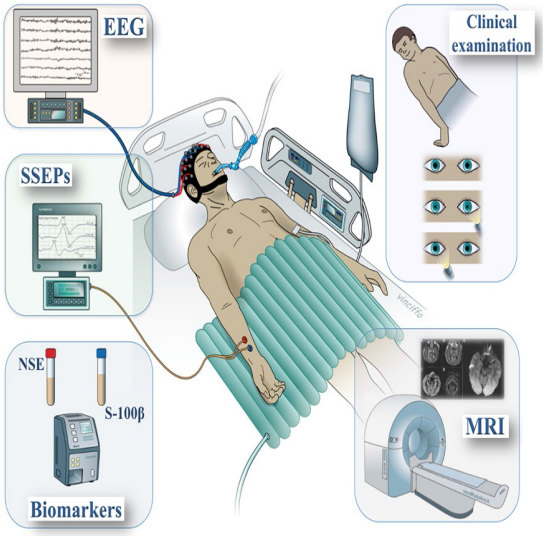
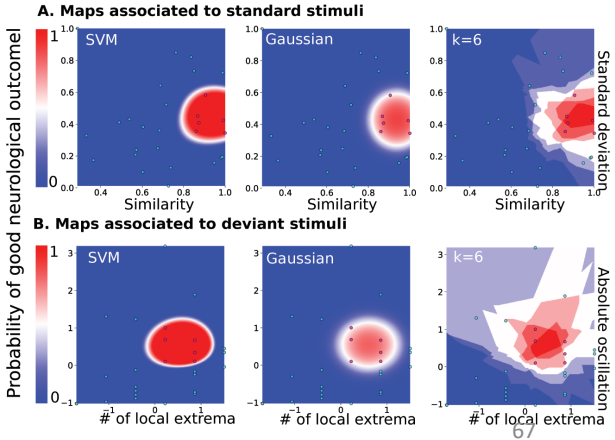


Figure 1 Multimodal approach to assess prognosis in comatose survivors after cardiac arrest treated with hypothermia. The multimodal approach to assess prognosis in comatose survivors after cardiac arrest treated with hypothermia should ideally include neurological examination combined with the use of electroencephalography (EEG) and somatosensory evoked potentials (SSEPs), the measurement of biomarkers (neuron-specific enolase (NSE) and S-100β protein) and magnetic resonance imaging (MRI).

Brevet FR 1852473 (22 mars 2018)

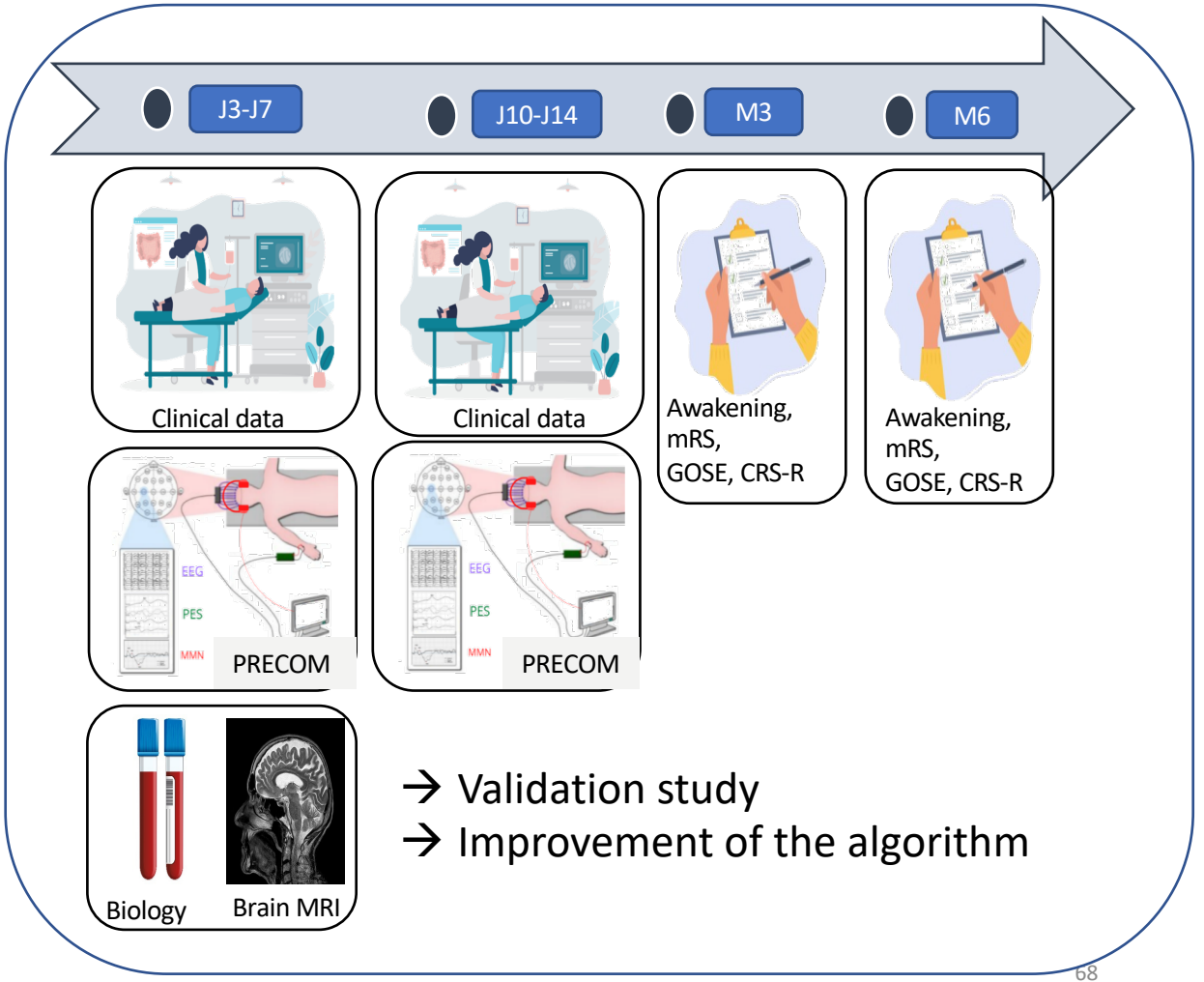
- In 29 patients post CA (D3-D7)
- From electrical signals recorded from AEP (taking the whole amount of data and not only the temporal window of MMN)
- Development of an algorithme predictive of neurological prognosis at the discharge of the ICU – on Cz



Floyrac et al, Frontiers in Neuroscience 2023

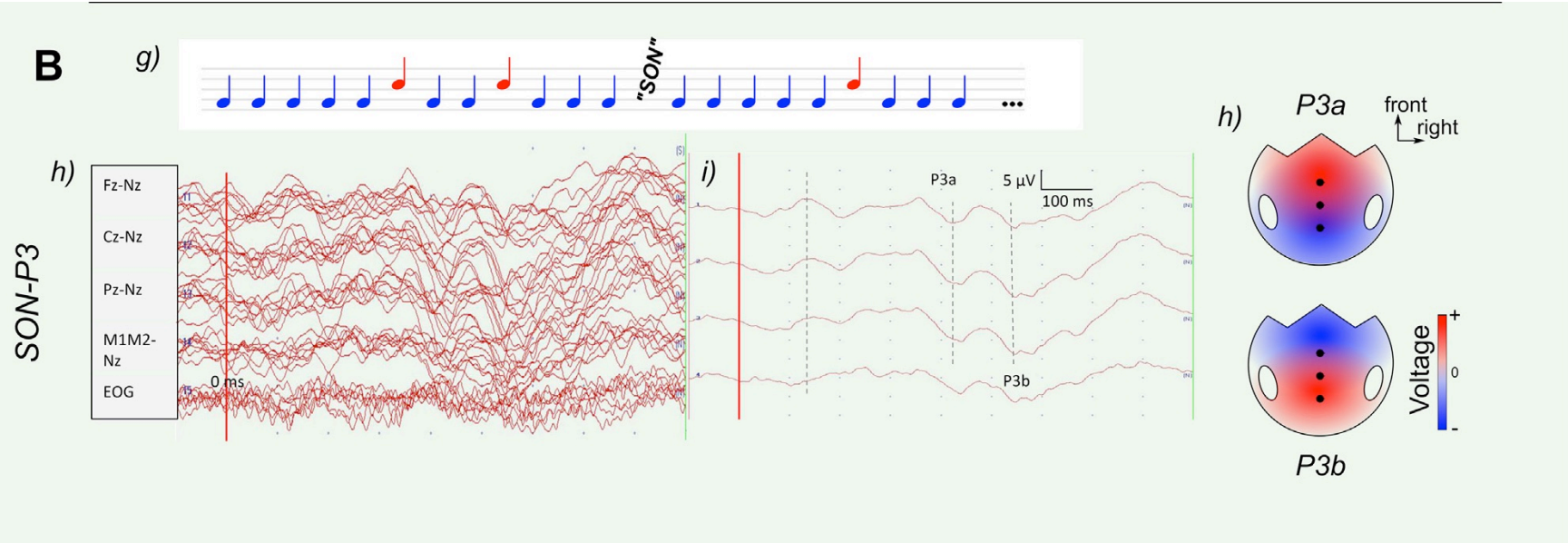
PRECOM (PHRC grant)

- **Multicentre clinical trial**
- **100 patients**





Perspectives



B. The subject's own name paradigm (SON) consists in delivering the SON during a sequence of sounds similar to the oddball paradigm (g). Trials obtained from the SON (h) are averaged (i) showing two consecutive positivities peaking around 420 ms and 530 ms, called P3a and P3b, respectively. Usually, it is difficult to disentangle these two components of the P300. In addition to their latencies, their topographies are different (h) with a more posterior P3b and a more anterior P3a. *To help to distinguish between VS and MCS*.

Andre-Obadia N, Clin Neurophysiol 2018

Journal of Neuroscience Methods 342 (2020) 108812

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

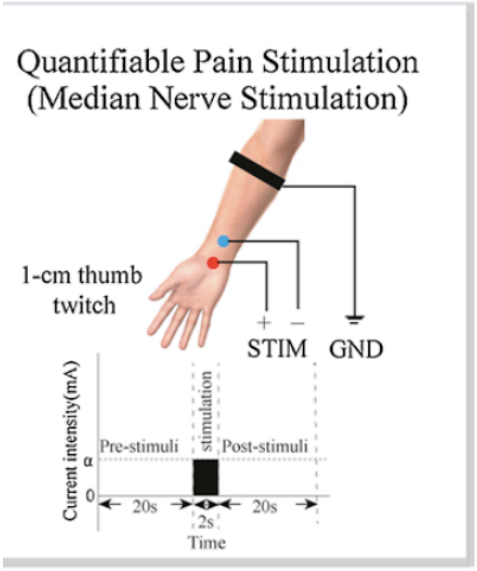
journal homepage: www.elsevier.com/locate/jneumeth

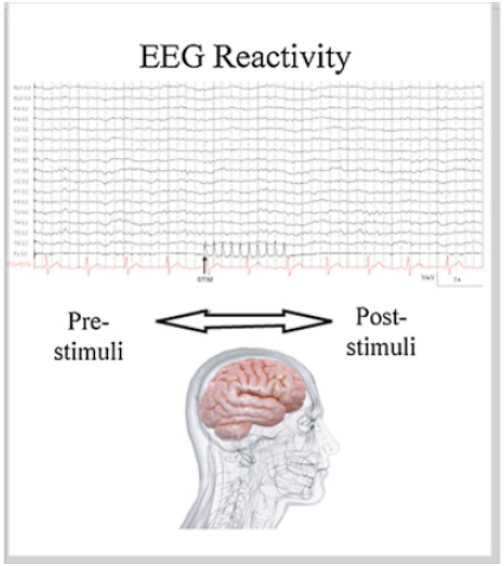
Connectivity studies

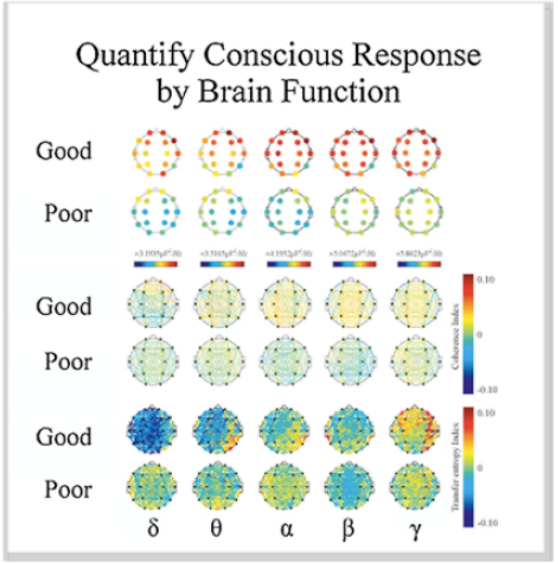
EEG signal varies with different outcomes in comatose patients: A quantitative method of electroencephalography reactivity

Weibi Chen[a,1], Gang Liu[a,1], Yingying Su[a,**], Yan Zhang[a], Yicong Lin[a], Mengdi Jiang[a], Huijin Huang[a], Guoping Ren[b], Jiaqing Yan[c,*]

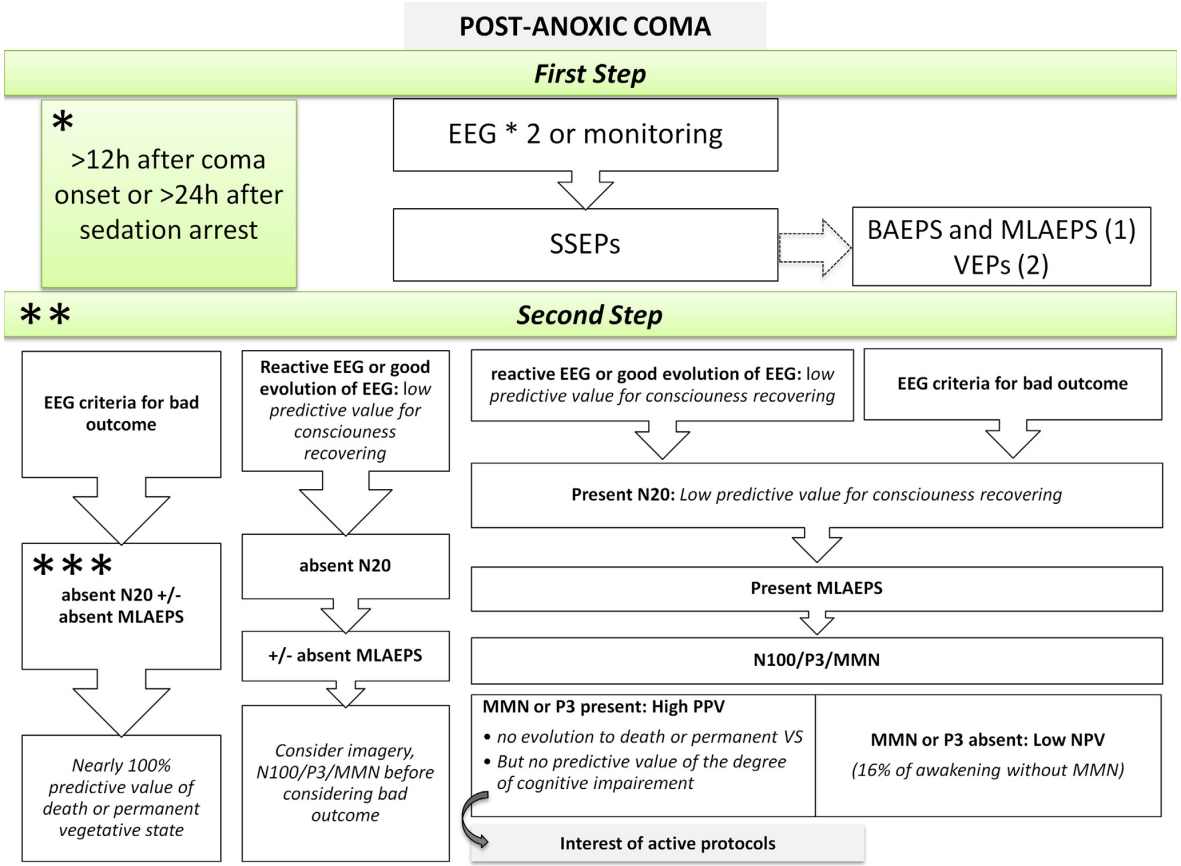
$$(\text{Reactivity} = \text{Signal}_{\text{post-stim}} - \text{Signal}_{\text{pre-stim}}).$$







Towards the development of step by step decisions trees….or IA algorithms



Andre-Obadia N, Clin Neurophysiol 2018

Take Home Messages

