



COMA BIOLOGY

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Outlines

- Definitions
- Classification and Major Causes
- Arousal Systems (Reticular Activating System)
- Relationship of Coma and Sleep
- Cerebral Hemispheres and Conscious Behavior
- Structural Lesions



Poor Neurological Outcomes After Brain Injury

- Death
- Coma
- Vegetative State
- Minimally conscious state (MCS)
- Severe disability with chronic dependence



Definition of Coma

- Loss of consciousness
 - State of complete unresponsiveness to external or internal stimuli, and is characterized by a failure of arousal renders it impossible to test awareness
- Complete loss of both
 - **Arousal (or Wakefulness)**
 - process of waking or becoming more vigilant
 - can occur in response to external or internal stimuli
 - intact subcortical and brainstem function
 - Intact Reticular Activating System (RAS) and Diencephalon
 - **Awareness**
 - intact cortical function
 - cerebral cortex of both hemispheres
- Similar to **General Anesthesia**



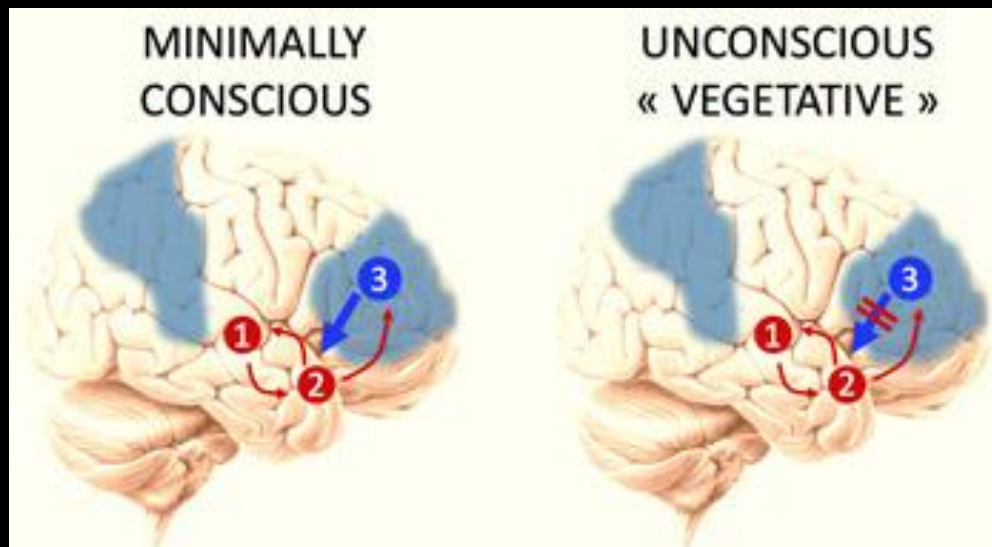
Poor Neurological Outcomes After Brain Injury

- Vegetative State
 - **Periodic** episodes of spontaneous arousal,
 - **Arouse to external stimuli**,
 - All other components of consciousness and cognition are absent .
 - Arousal occurs in the absence of consciousness because awareness is absent.
 - Extensive bilateral cortical, subcortical white matter, or thalamic injuries, with **relative sparing of the brainstem**, which accounts for preservation of arousal mechanisms.
 - **Transitional state** from the unarousable unresponsiveness of a coma to a partially responsive state.

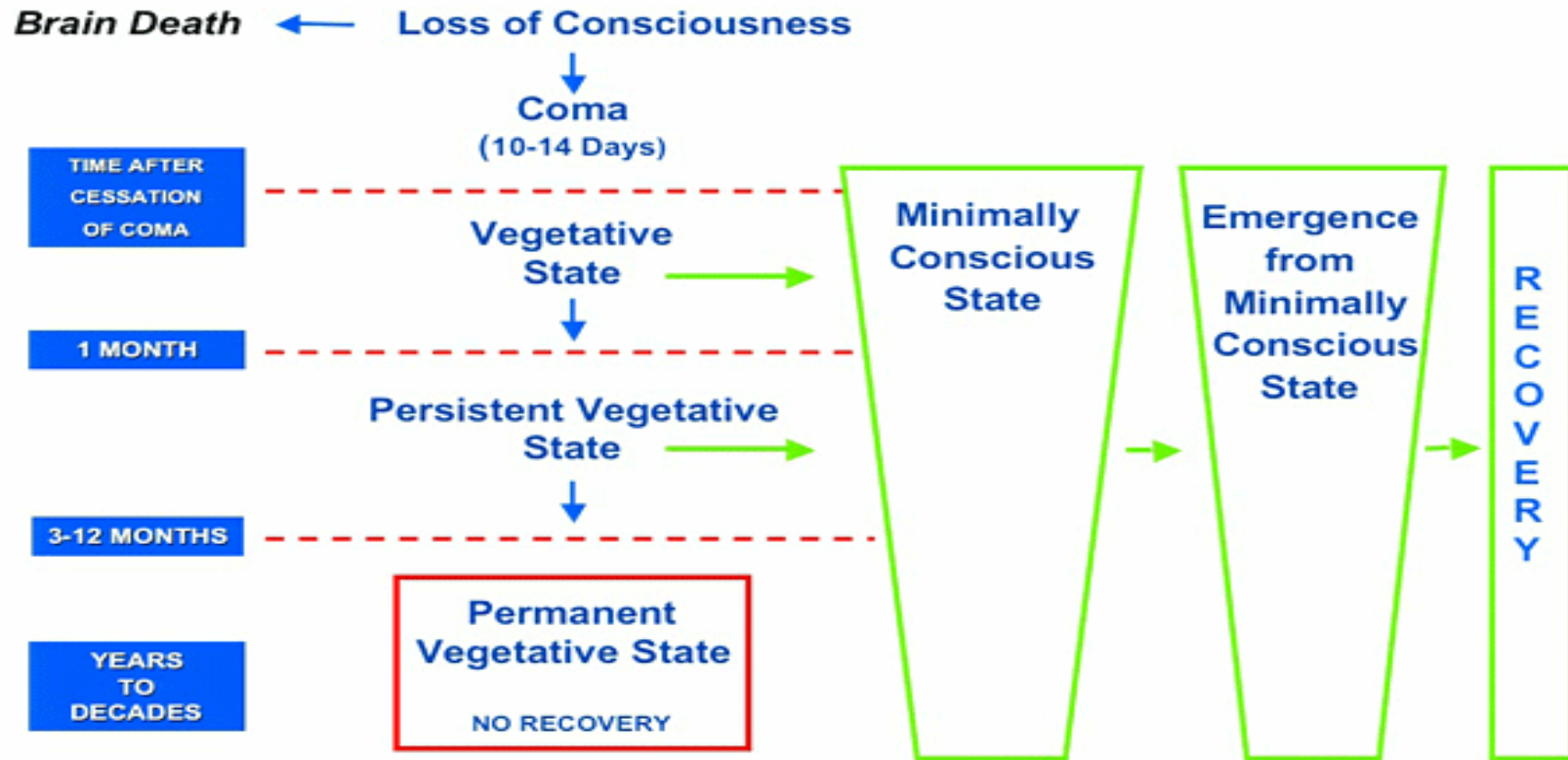


Poor Neurological Outcomes After Brain Injury

- Minimally conscious state (MCS)
 - Responses to environmental and internal stimuli present,
 - Differs from VS → **intermittent, inconsistent** behavioral evidence of consciousness is discernible, **suggesting awareness**
- Severe disability with chronic dependence
 - **Arousability and Awareness Intact**



Poor Neurological Outcomes After Brain Injury



Fins Am J Bioethics, 2008



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Classification and Major Causes of Coma

- Brain injury from global cerebral ischemia
 - Cardiac arrest (Prolonged hypoxia)
 - Metabolic-endocrine derangement
 - Traumatic head injury
 - Intoxication (including illicit and legal drugs),
- Results in damage to the
 - Cerebral hemispheres
 - Brainstem
 - Thalamus



Classification and Major Causes of Coma

- **Unilateral Hemisphere (with displacement)**

- Intraparenchymal hematoma
- Middle cerebral artery occlusion
- Hemorrhagic contusion
- Cerebral abscess
- Brain tumor

- **Bilateral Hemisphere**

- Penetrating traumatic brain injury
- Multiple traumatic brain injuries
- Anoxic-ischemic encephalopathy
- Aneurysmal subarachnoid hemorrhage

- **Bilateral Hemisphere**

- Multiple cerebral infarcts
- Bilateral thalamic infarcts
- Cerebral venous thrombosis
- Lymphoma
- Encephalitis
- Gliomatosis
- Acute disseminated encephalomyelitis
- Cerebral edema
- Multiple brain metastases
- Acute hydrocephalus
- Acute leukodystrophy



Classification and Major Causes of Coma

- **Brainstem**
 - Pontine hemorrhage
 - Basilar artery occlusion
 - Central pontine myelinolysis
 - Brainstem hemorrhagic contusion
- **Cerebellum (with displacement of brainstem)**
 - Cerebellar infarct
 - Cerebellar hematoma
 - Cerebellar abscess
 - Cerebellar glioma
- **Psychogenic unresponsiveness**
 - Hysterical
 - Malingering
- **Acute metabolic-endocrine derangement**
 - Hypoglycemia
 - Hyperglycemia (nonketotic hyperosmolar)
 - Hyponatremia
 - Hypernatremia
 - Hyperbilirubinemia
 - Hypercapnia
- **Diffuse physiologic brain dysfunction**
 - Generalized tonic-clonic seizures
 - Poisoning, illicit drug use
 - Hypothermia
 - Gas inhalation



Recent research has generated considerable hope for better chances of recovery following global ischemia

- **Therapeutic Hypothermia (TH)**

- Significantly improve neurological outcomes in approximately one of every six patients

- **Deep Brain Stimulation**

(stimulation of central thalamic nuclei)

- Improve arousal in a patient who had MCS after traumatic brain injury



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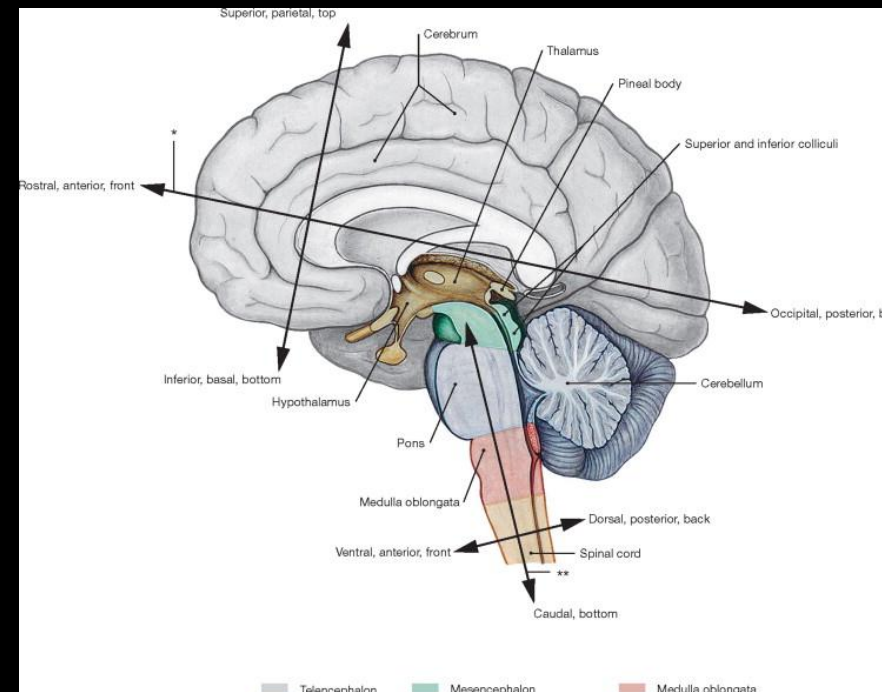


Arousal Systems

- Arousal or vigilance is mediated by a complex interaction of cortical and subcortical networks.
- Cortical activation is required for arousal, but anatomic and physiological data suggest that the cortex does not contain an intrinsic mechanism for the generation and maintenance of arousal

- Subcortical Networks
(Reticular Activating System)

- the brainstem
- the thalamus
- the basal forebrain
- the hypothalamus



Arousal Systems

- The most convincing body of evidence was first assembled by **Baron Constantin von Economo** (Viennese neurologist)
 - A unique disorder, **Encephalitis Lethargica**
 - in the years surrounding World War I
 - Most victims of encephalitis lethargica were very sleepy, spending **20 or more hours per day asleep**, and awakening only briefly to eat.
 - When awakened, they could interact in a relatively unimpaired fashion with the examiner, but soon fell asleep if not continuously stimulated.
 - When they died, they were found to have lesions involving the **reticular formation of the midbrain** at the junction with the diencephalon.



Arousal Systems

- The most convincing body of evidence was first assembled by **Baron Constantin von Economo** (Viennese neurologist)
 - Other patients during the same epidemic developed **prolonged wakefulness**, sleeping at most a few hours per day. Movement disorders were also common.
 - Von Economo identified the causative **lesion in the hypothalamus** and extending laterally into the basal ganglia
- Von Economo **suggested that there was specific brainstem circuitry** that causes arousal or wakefulness of the forebrain, and that the hypothalamus contains circuitry for inhibiting this system to induce sleep.



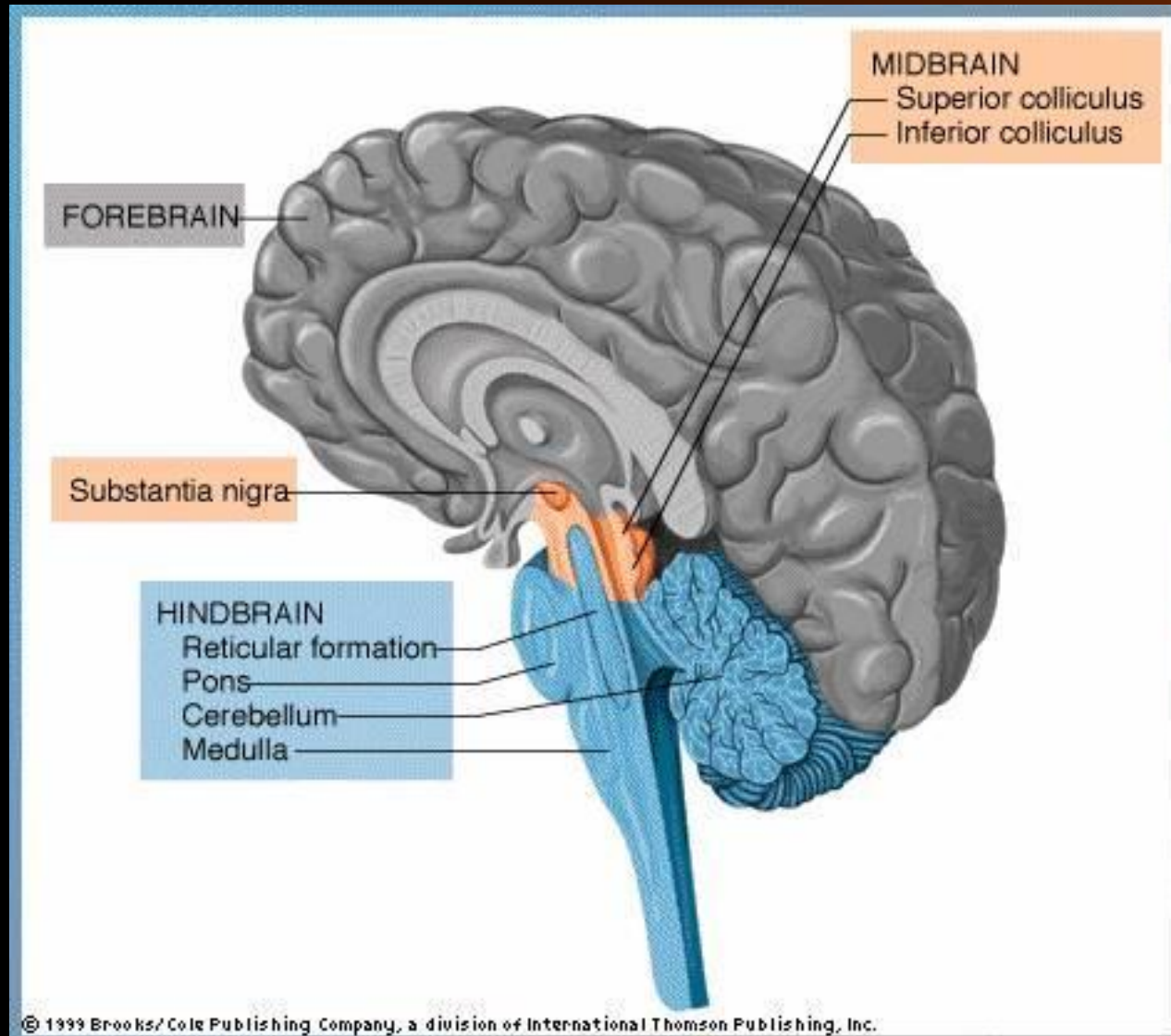
Arousal Systems

- In 1929, Hans Berger, (Swiss psychiatrist) reported a technologic innovation, the electroencephalogram (EEG)
 - He noted that the **waveform pattern** recorded from the scalps of his patients was generally **sinusoidal**, and that the **amplitude and frequency** of the waves in the EEG correlated closely with the **level of consciousness of the patient**.
- In 1935, Frederic Bremer (Belgian neurophysiologist) examined the **EEG waveforms in cats** into which he had placed lesions of the **brainstem**.
 - Transection between the medulla and the spinal cord
 - EEG pattern appeared to be fully awake
 - Transection between the superior and inferior colliculus
 - EEG pattern appeared to be indicative of deep sleep and the animals were behaviorally unresponsive



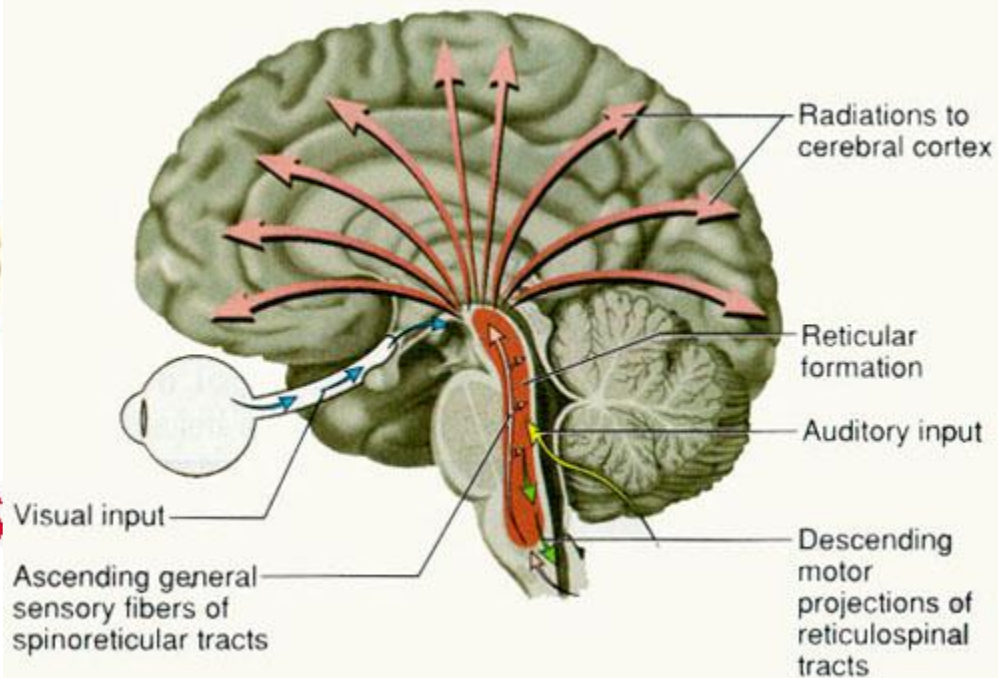
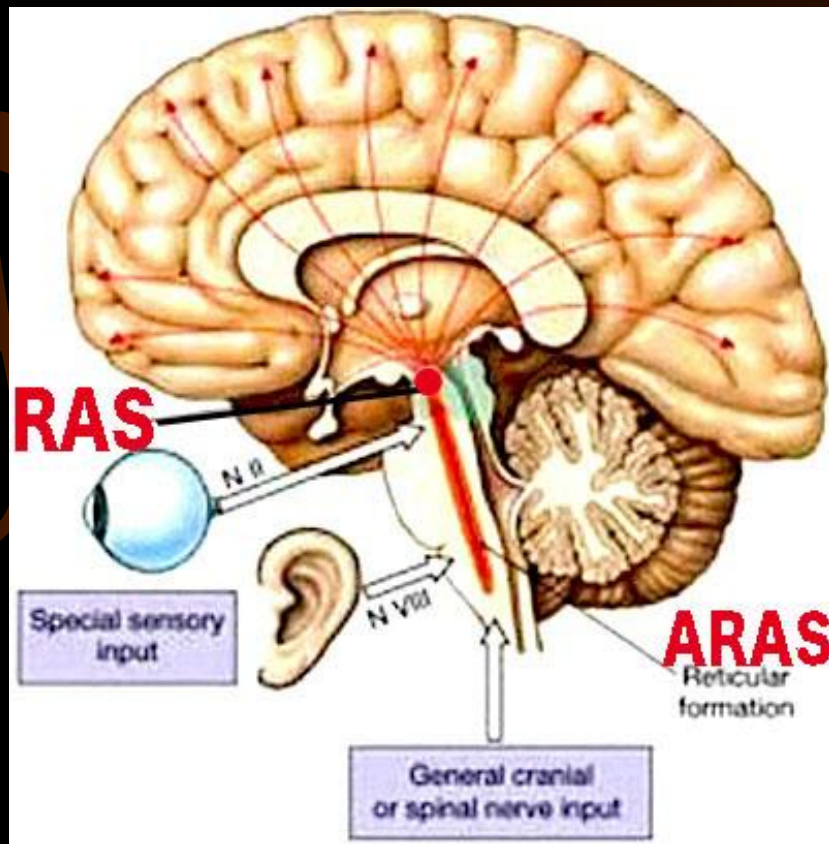
Arousal Systems

Reticular Activating System (RAS)



Arousal Systems

Reticular Activating System (RAS)



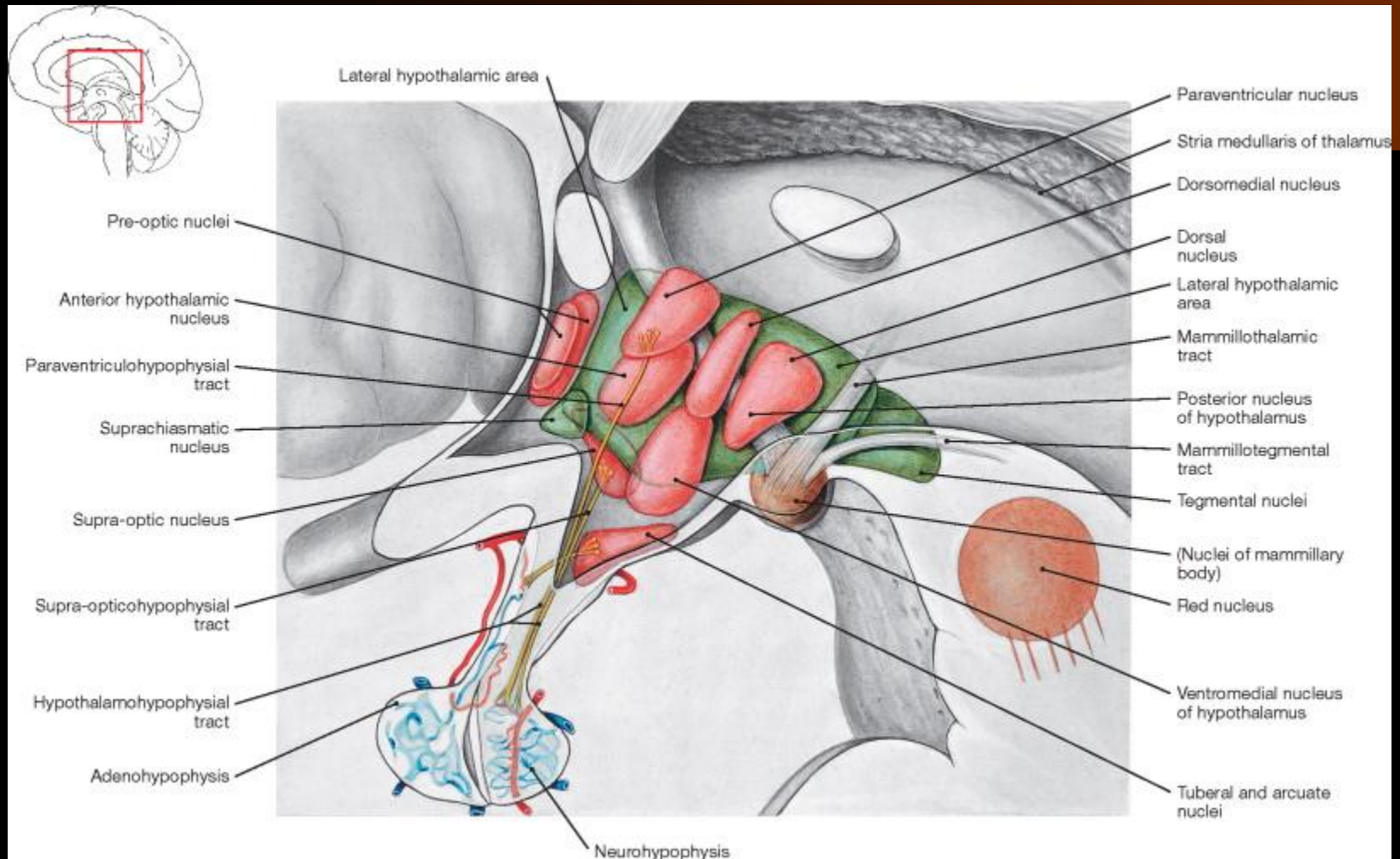
Arousal Systems

Reticular Activating System (RAS)

- Reticular Activating System (RAS)
 - Pedunculo pontine tegmental and laterodorsal nuclei (PPT/LDT)
 - Locus ceruleus (LC)
 - Substantia nigra pars compacta and ventral tegmental area (SNPC-VTA)
 - Raphe nucleus (RN)

These Nuclei May Serve as Centries for the Arousal System

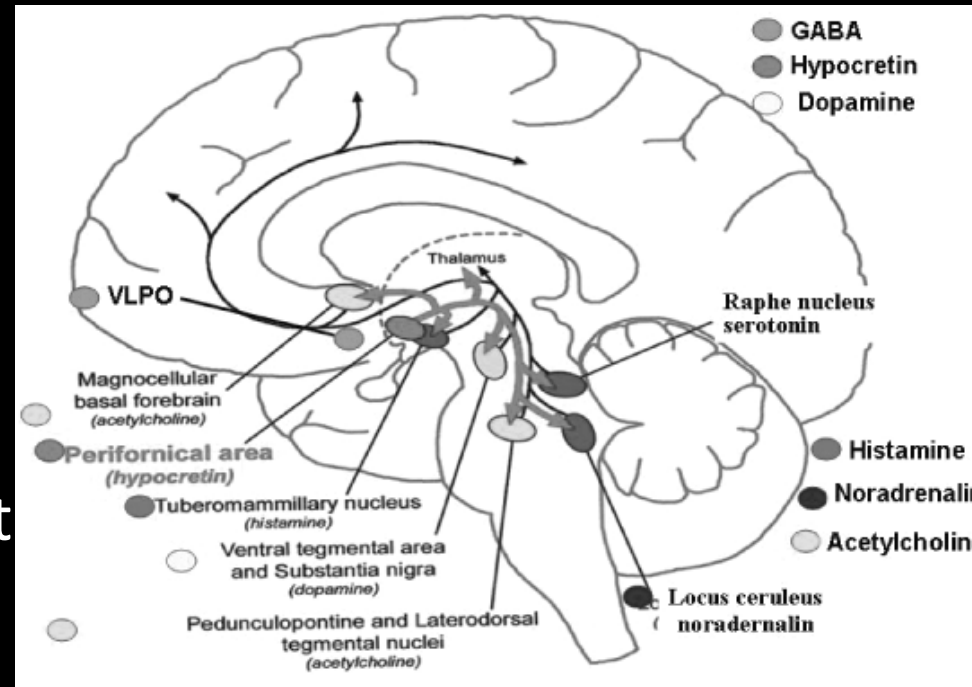




Arousal Systems

Reticular Activating System (RAS)

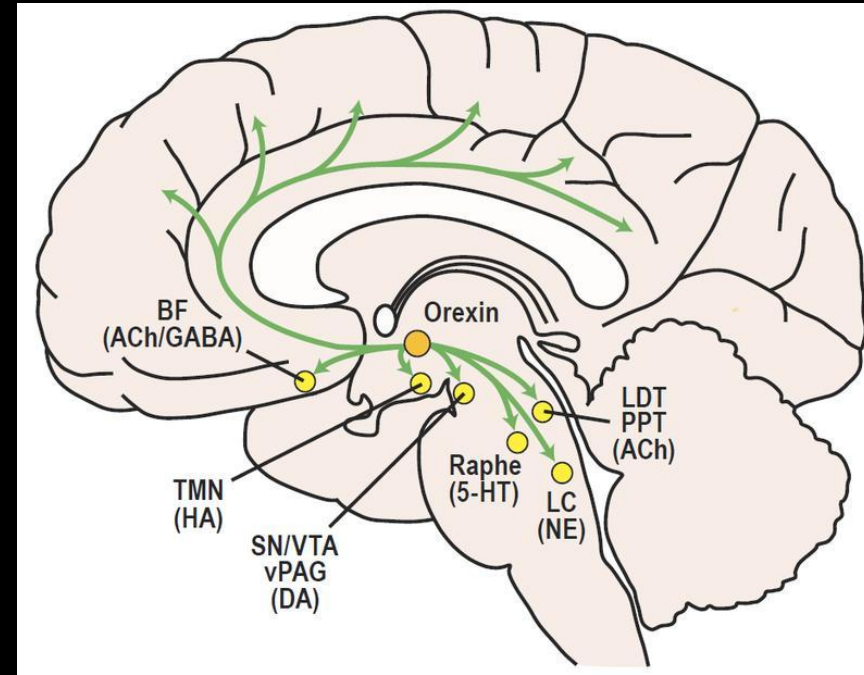
- Integrate information wide variety of sources,
- Sensory input from
 - visual,
 - somatosensory,
 - auditory
 - vestibular systems,
- Sensory and motor output
 - cerebral cortex,
 - thalamus
 - basal ganglia



Arousal Systems

Reticular Activating System (RAS)

- Critical role in arousal,
- Tasks such as the regulation of muscle tone
- Integration of afferent pain signals
- Efferent signals to the spinal cord
 - Cholinergic (ACh)
 - Gamma-AminoButyric Acid (GABA)
 - Norepinephrine
 - Dopaminergic
 - Serotonergic
 - Histaminergic
 - Orexin



Arousal Systems

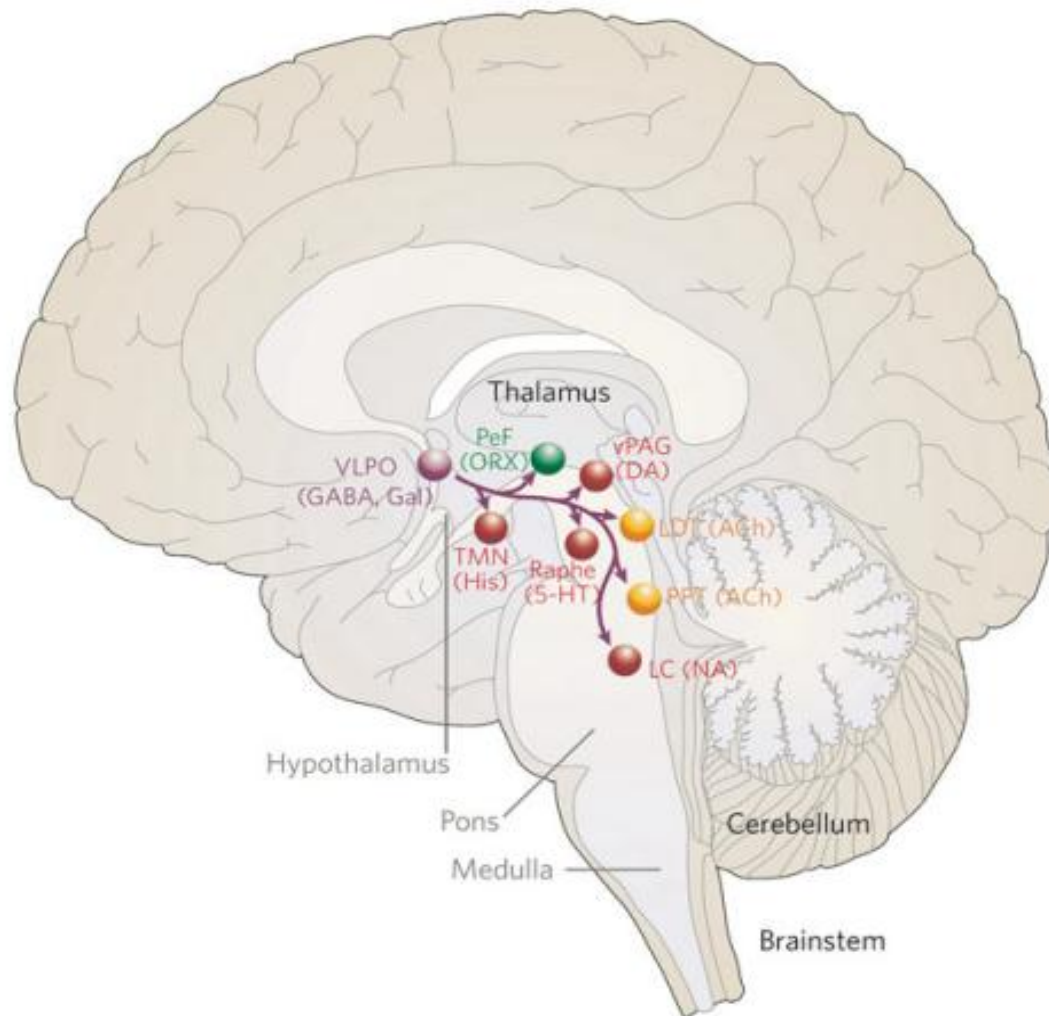
Reticular Activating System (RAS)

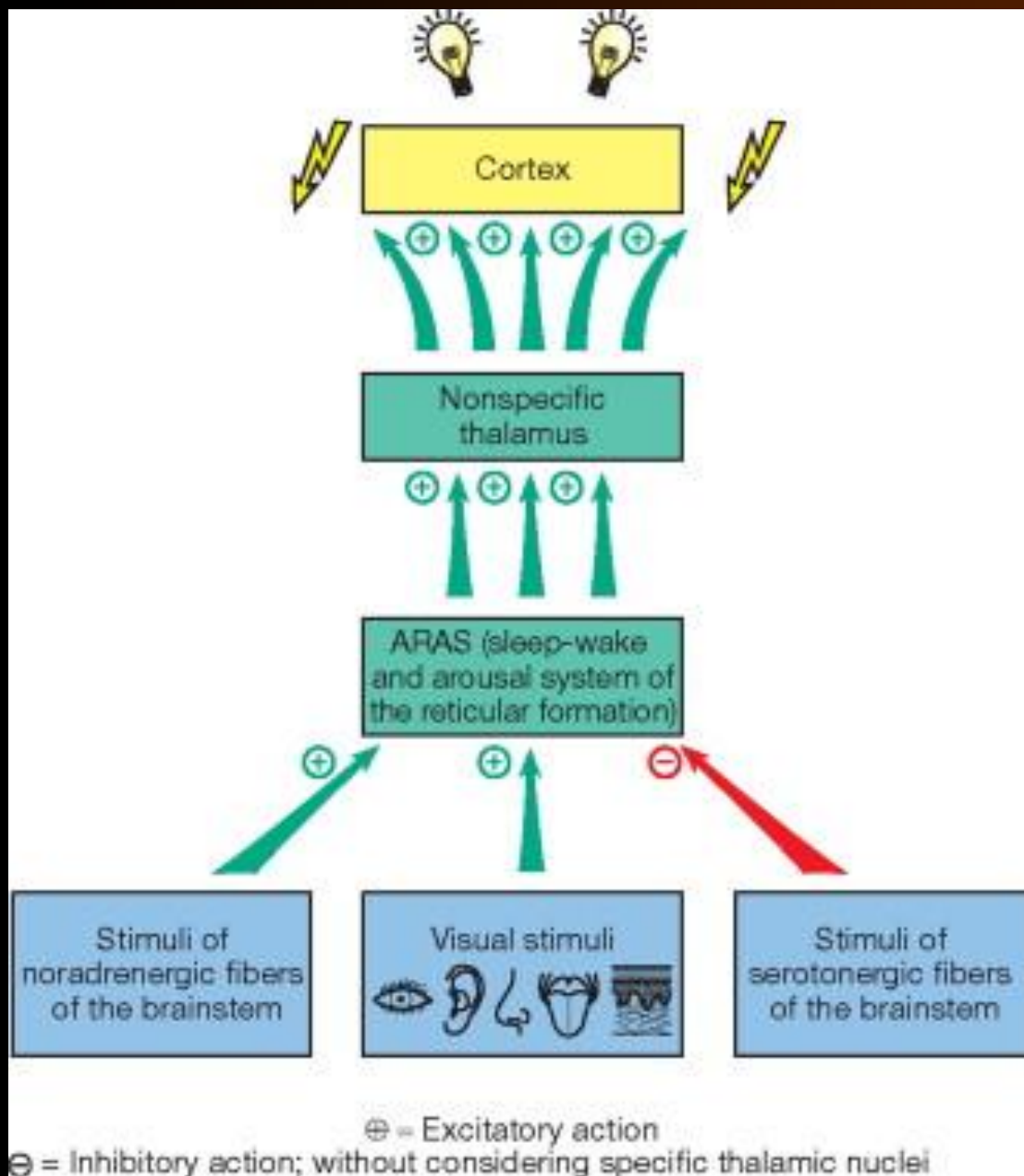
- Cholinergic synapses are **excitatory**, (stimulation of PPT/LDT nuclei leads to **cortical activation and arousal**)
- LC activation associated with **heightened arousal**, LC lesions, associated with **hypersomnolence**,
- Lesions of midbrain dopaminergic nuclei associated with **akinetic state** (failure to arouse)
- Serotonergic neurons during sleep, firing rate drops and in the setting of heightened arousal, the firing rate can increase by up to 50%



Arousal Systems

Reticular Activating System (RAS)





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Relationship of Coma and Sleep

- Both impaired states of consciousness and NREM sleep are characterized by
 - **Same EEG patterns**
 - **Lack of activity by the ascending arousal system.**
- In sleep:
 - **Intrinsically regulated** inhibition of the arousal system
 - **The subject can be aroused** from it to wakefulness
 - Subjects undergo a variety of **postural adjustments**, including yawning, stretching, and turning
 - **Charecteristic cycling** of NREM and REM sleep during night and day



Relationship of Coma and Sleep

- In coma:
 - **Damage** to the arousal system or
 - **Diffuse dysfunction** of its' diencephalic or forebrain targets.
 - Comatose patients **may not be arousable**
 - **Postural adjustments not seen** in comatose patients
 - **Lack of cycling** between NREM and REM sleep in comatose patients



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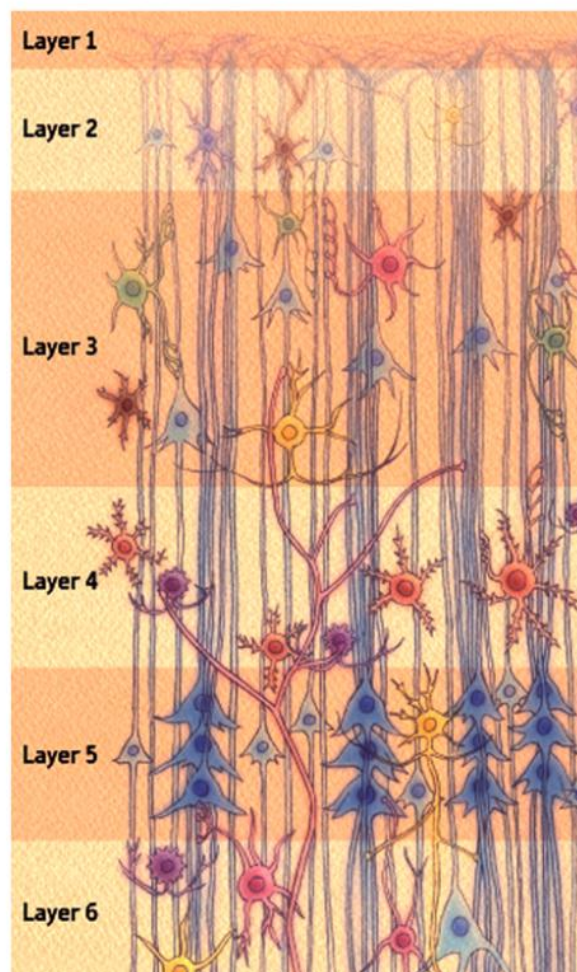
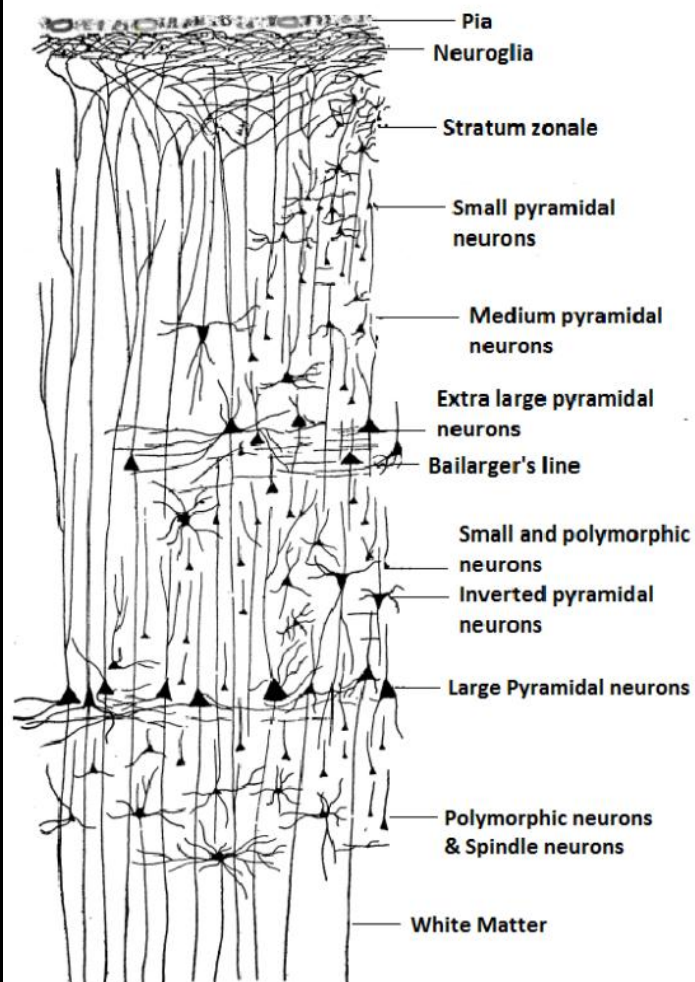


Cerebral Hemispheres and Conscious Behavior

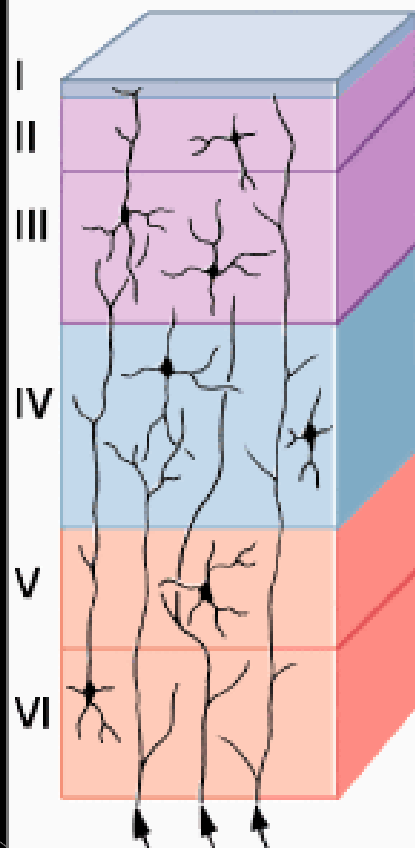
- The cerebral cortex **acts like a massive processor**
- The cerebral neocortex of mammals, from rodents to humans, consists of a **sheet of neurons** divided into six layers.
- Inputs and Outputs
 - Thalamic nuclei
 - Cortical areas
 - Brainstem and Spinal Cord
- Organizational scheme predicts many of the properties of consciousness



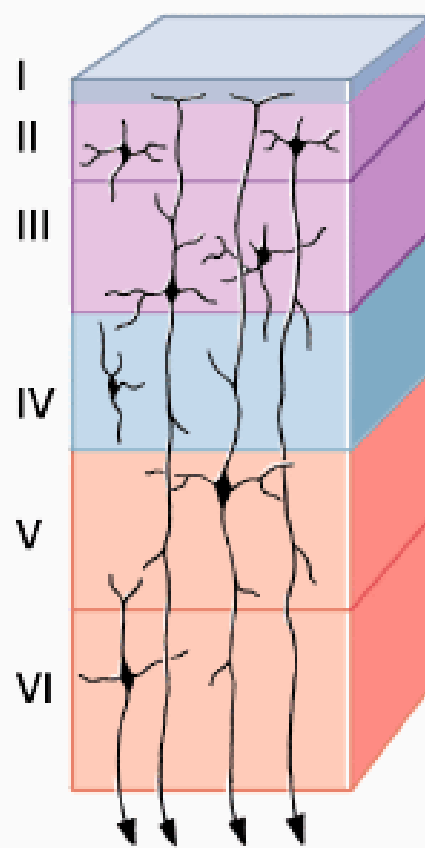
Histological Structure of the Cerebral Cortex



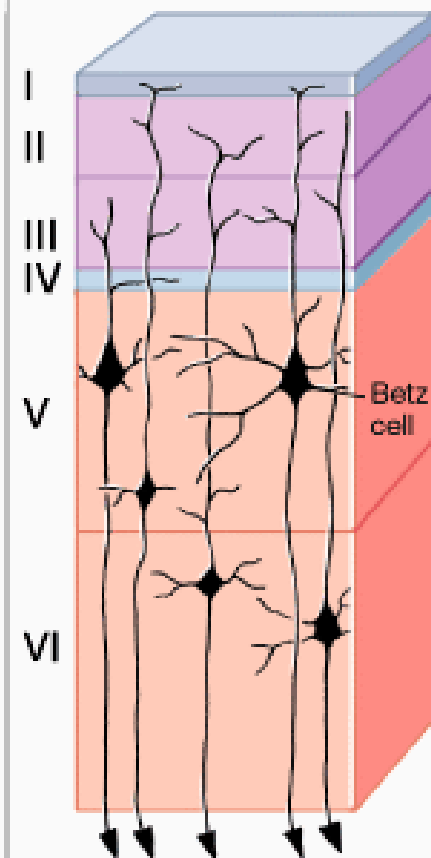
Primary sensory cortex



Association cortex



Primary motor cortex



Cerebral Hemispheres and Conscious Behavior

- Neurons in successive layers of cerebral cortex
 - Line perpendicular to the pial surface and
 - All tend to be concerned with similar sensory or motor processes.
 - These neurons form columns, (~ 0.3 to 0.5 mm in width)
 - Incoming signals in a vertically integrated manner



Cerebral Hemispheres and Conscious Behavior

- For example in visual cortex
 - Columns of neurons send information to one another and to higher order association areas via projection cells in layer III and layer V
 - Primary visual cortical area → primarily concerned with simple lines, edges, and corners → integrating their inputs → higher order visual association area → respond only to a complex shape (hand – brush)



Cerebral Hemispheres and Conscious Behavior

- Primates → → → → → → → Mammals
 - Number of **cortical columns** ↑
 - Neurons in different areas of the cerebral cortex specialize in **certain types of operations**
- In a young brain (before school age)
 - Cortical functions to **reorganize themselves** to an astonishing degree if one area of cortex is damaged
- By aging
 - **Plasticity decrease** but **improved efficiency of processing**
 - A large right parietal lobe tumor who ate only the food on the right side of her plate



Cerebral Hemispheres and Conscious Behavior

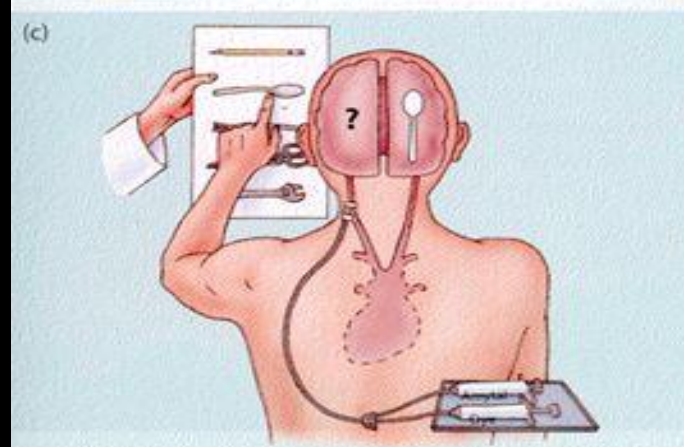
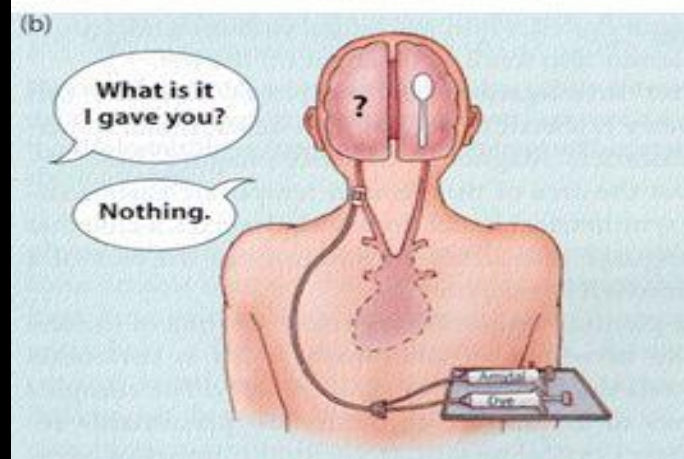
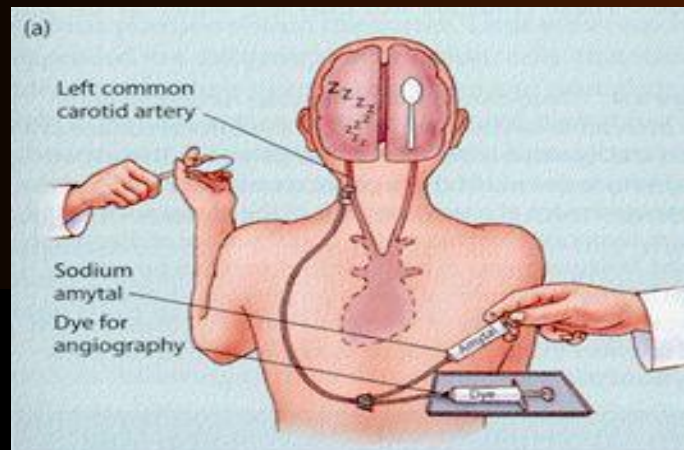
- This concept of **fractional loss of consciousness** is critical because it explains confusional states caused by focal cortical lesions.
- Cerebral cortex damaged in **multiple locations** (multifocal disorder), it can eventually cease to function as a whole, producing a state of severe cognitive impairment



Cerebral Hemispheres and Conscious Behavior

- In Wada Test:
 - Short-acting barbiturate into the carotid artery to anesthetize one hemisphere
 - Language can be assessed prior to cortical surgery
 - Left hemisphere injection → absence of language skills
 - Right hemisphere injection → unable to orient to his or her surroundings, but can answer simple questions





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Cerebral Hemispheres and Conscious Behavior

- The patient generally does **not appear to be unconscious**
 - One hemisphere is acutely anesthetized.
 - Lesion confined to a single hemisphere
 - Acute infarct of one hemisphere
- A very large space-occupying lesion
 - Simultaneously damage both hemispheres
 - Compress the diencephalon,

causing impairment of consciousness

- Consciousness conceived by **integrated activity of the two cerebral hemispheres** and not in need of a separate physical manifestation



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Structural Lesions That Cause Altered Consciousness in Humans

- To produce stupor or coma in humans,
 - Disorder must damage or depress the function:
 - **Both cerebral hemispheres** or
 - **Brainstem arousal system,**
 - Paramedian region of the upper brainstem or
 - The diencephalon on both sides of the brain.
- Conversely, **unilateral hemispheric lesions, or lesions of the brainstem at the level of the midpons or below,** do not cause coma



Bilateral Hemispheric Damage

- **Bilateral and extensive damage**
 - **Hypoxic-ischemic insult**
 - **Brain Trauma.**
- Initial response includes loss of consciousness.



Bilateral Hemispheric Damage

- Even if blood flow or oxygenation is restored after 5 or more minutes, even in the absence of frank infarction, there may be
 - **Widespread cortical injury and**
 - **Neuronal loss**
- Less extreme cortical hypoxia,
 - **Lucid interval** $\Rightarrow$ Recover $\rightarrow$ Subsequent Deterioration.



Diencephalic Injury

- **Nuclei of the thalamus** provide the largest ascending source of input to the cerebral cortex
- If thalamic lesions sufficiently extensive can produce the same result as bilateral cortical injury.
 - **“Tip Of The Basilar” Syndrome** → occlusion of the perforating arteries of the posterior cerebral arteries → bilateral thalamic infarction
 - **Primarily thalamic hemorrhage,**
 - **Local thalamic infiltrating tumors,**
 - **Diencephalic inflammatory lesions** (Behçet’s syndrome)
- Ischemic lesions of the **hypothalamus** rare, (encircled by the main vessels of the circle of Willis)



Upper Brainstem Injury

- **Midbrain and Pontine Area** critical to consciousness
- Numerous cases are on record of **small lesions** + **bilaterally** profound loss of consciousness
- Loss of consciousness usually not seen with lesions confined to
 - **Medulla or**
 - **Caudal pons**



THANK YOU

QUESTIONS ????
CONTRIBUTIONS ????

