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# Neuroscience Fundamentals

## Notes

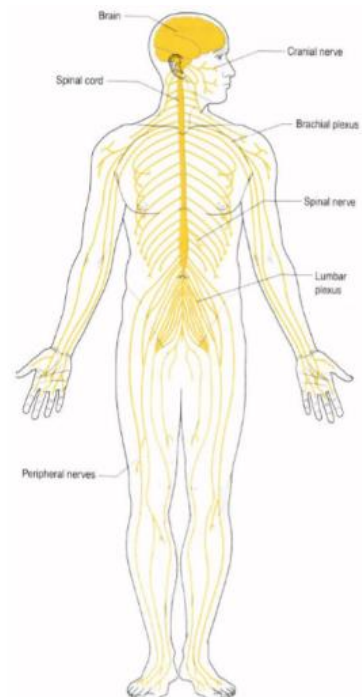
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### Neurotrauma

- ▶Lecture 1: CNS Anatomy
- ▶Lecture 2: Overview & Neurotrauma Types
- ▶Lecture 3: Vascular & Hypoxic Neurotrauma
- ▶Lecture 4: Mechanical Neurotrauma

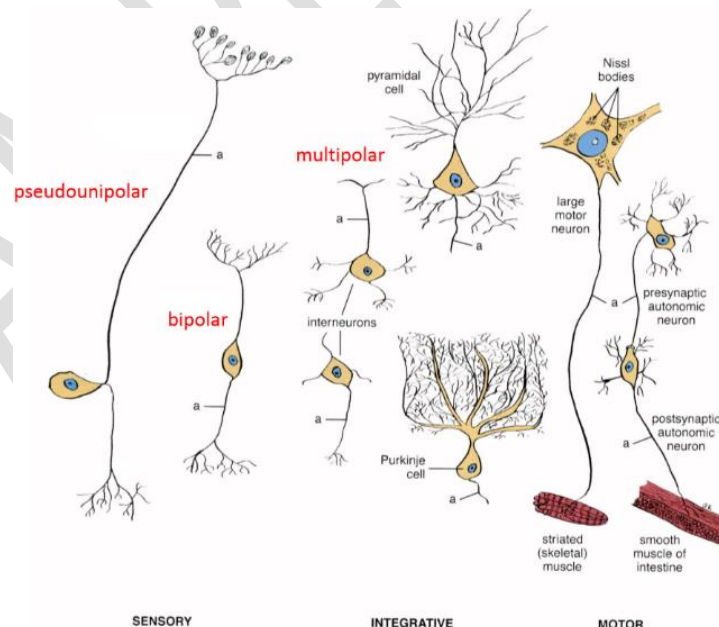
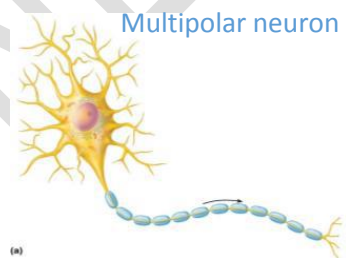
### CNS Anatomy

- The nervous system can be broadly classified in two categories:
  - **Central Nervous System (CNS)** →
    - Brain
    - Spinal Cord
  - **Peripheral Nervous System (PNS)** → links the CNS with structures in the periphery of the body from which it receives sensory information and to which it sends controlling impulses; also is the only nervous system area where axon regrowth occurs (regeneration).
- A **neuron** is the smallest functional unit of the nervous system and is **highly polarised, terminally differential** to other cells.
  - Neurons or “nerve cells” transmit information
  - On average, the human brain has 86 billion neurons – stretching 160,000km end-to-end.
    - **Soma (cell body)** – protects the nucleus and cell contents; the phospholipid bilayer maintains the negative (-ve) charge within the cell.
    - **Dendrites** – branch-like structures “neurites” that conduct information towards the cell body [**RECEIVING**].
    - **Axon** – a long nerve fibre which conducts the electrical signals from the cell body [**DELIVERING**].
    - **Axon hillock** – processes transmission “gate-keeper”; graded potentials are summed up to determine whether an action potential will be fired.



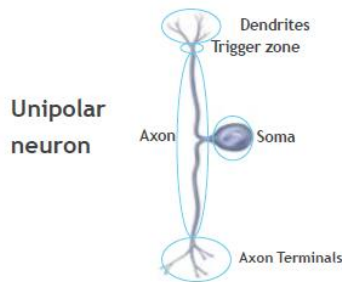
- **Nucleus** – the “engine room” of the cell, contains all the genetic material and acts in the production of neurotransmitters.
- **Synapse** – cell-to-cell connections between neurons and other neurons as well as between neurons and non-neuronal cells (such as muscle cells); information between cells is transferred via neurotransmitters.
- **Nissl granules** – also ‘Nissl substance’ is an irregularly shaped mass of basophilic material, scattered throughout the cytoplasm of the cell body and the dendrites but absent from axons; reflects the rough endoplasmic reticulum (which all cells have, but is the Nissl substance in neurons).
- **Myelin sheath** – a coating that insulates the axon which enables faster signalling (produced by Schwann cells).
- **Nodes of Ranvier** – bare parts of the axon that are exposed and unshielded by the sheath, allowing transmission to continue down the axon.
- **Axon terminals/ terminal buttons** – chemical messages are sent from these terminals and are pre-synaptic.

- Axon hillock free of Nissl granules, typically will only find the rough endoplasmic reticulum in the dendritic compartment.
- There is a clear distinction between the axonal and dendritic compartments.
- Neurons can be: **pseudo-unipolar, bipolar, multipolar.**
- Dorsal root ganglion a typical example of a pseudo-unipolar branching neuron – with the emerging branch divided into a central branch and peripheral branch.

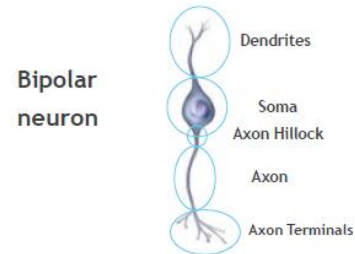


- Bipolar neurons –
- Multipolar neurons – consist of the retinal ganglion cell (eye), Purkinje cells (only found in the cerebellum), pyramidal cells (cerebral cortex), among others. These multipolar neurons are stained using a Golgi stain → gives silver, unspecified regions.

## Neuron classification - Type

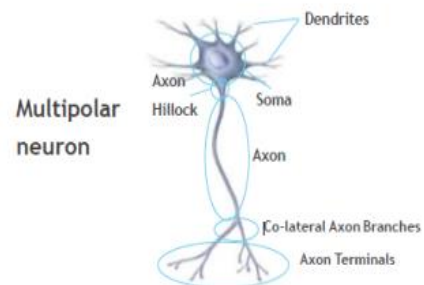


## Neuron classification - Type

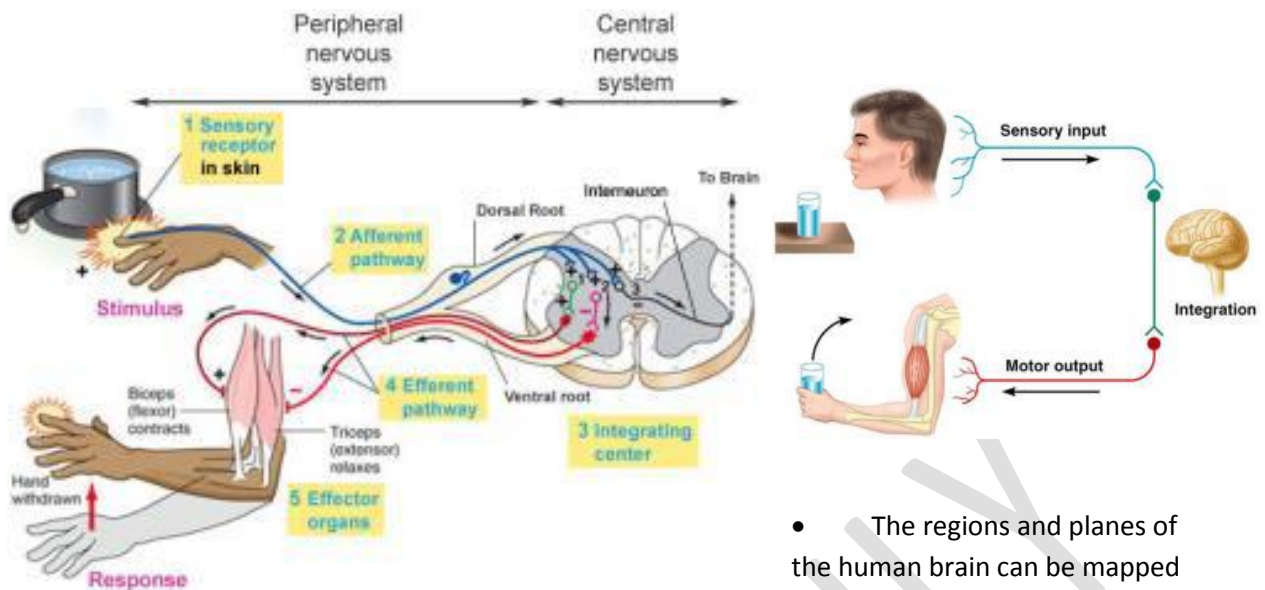


- These can be further classified by function: SENSORY neurons, MOTOR neurons, INTER-neurons.

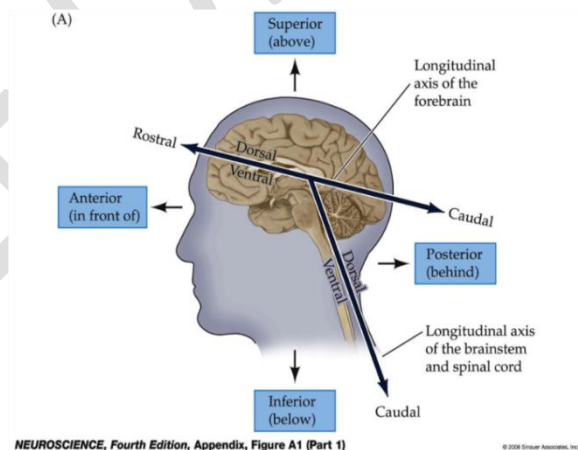
## Neuron classification - Type



- **SENSORY** → Activated by sensory input e.g. vision (photoreceptors: *light*), somatic (mechanoreceptors: *touch/ pressure/ temp*), auditory (stereocilia *vibrations*). Tends to be unipolar or bipolar neurons. Sends info to the brain from periphery signals (afferent signals)
- **MOTOR** → Cell body located IN the spinal cord. Axon projects to the periphery control muscles; tends to be multipolar neurons. Sends info from the brain (motor cortex or brain stem) to the periphery (efferent signal)
- **INTER** → Neurons within the brain. Neurons that only connect to other neurons (i.e. NOT sensory or motor signals). Tend to be multipolar neurons. Involved in higher order processing e.g. memory and cognition

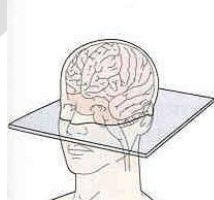


- The regions and planes of the human brain can be mapped specifically
- Three (3) directional planes exist in the brain: **rostral/caudal**, **dorsal/ventral**, and **medial/lateral**.
- When sectioning (cutting or slicing) the brain, the planes that will be visible for examination is determined by the type of section [performed].
  - In the **sagittal section** (which is made parallel to the midline) the rostral/caudal and dorsal/ventral planes can be seen.
  - In the **coronal or cross section** (made perpendicular to the midline) the medial/lateral and dorsal/ventral planes can be seen.
  - In the **axial section** (distinguished horizontally cross sectioning the midline) the "" planes can be seen

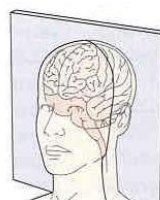


The images below show the 3 different planes in which the brain can be sectioned:

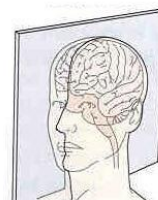
**Axial**



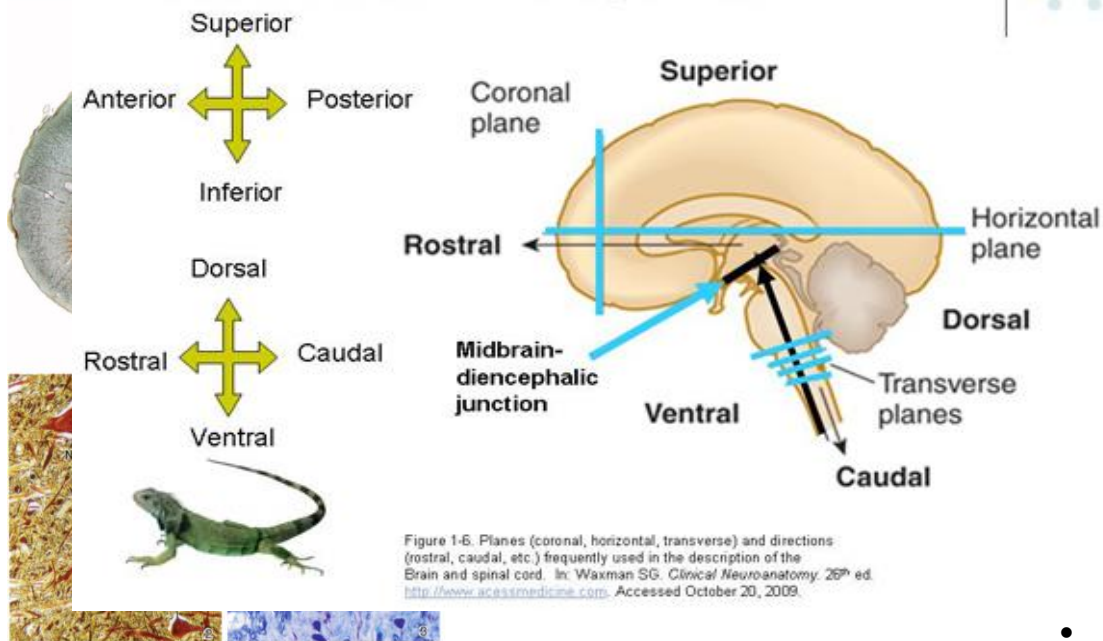
**Coronal**



**Sagittal**

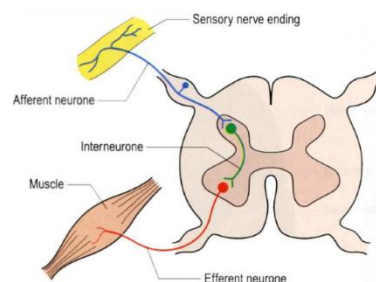


# Orientation and Planes of the Central Nervous System



components and neural connectivity of the spinal cord:

- The

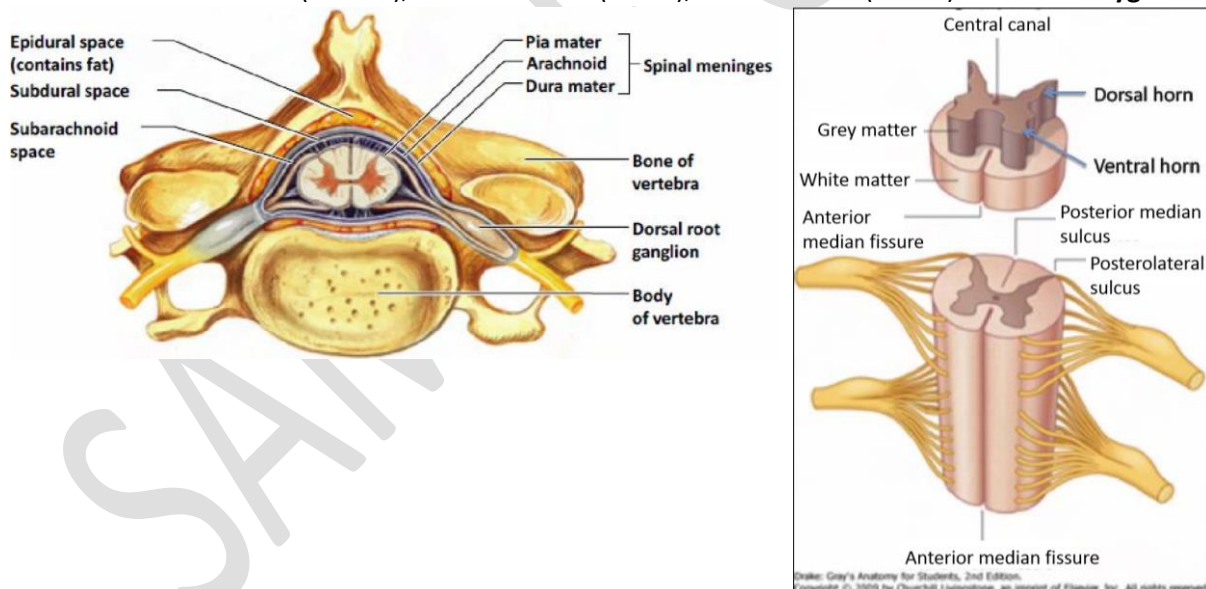




- The spinal cord itself consists of many layers of structural formation.
  - These parts of the cross-sectional spinal cord can be defined as the:
    - **Epidural space** – outer region within the spine (contains lipid layer)
    - **Subdural space**
    - **Subarachnoid space**
    - **Bone of vertebra**
    - **Dorsal ganglion root**
    - **Spinal meninges** – further comprised of:
      - **Pia mater** – inner-most meninges; soft and cushiony for pliability
      - **Arachnoid** – flexible, folded layer of the meninges
      - **Dura mater** – outer most meninges; toughest and for protection

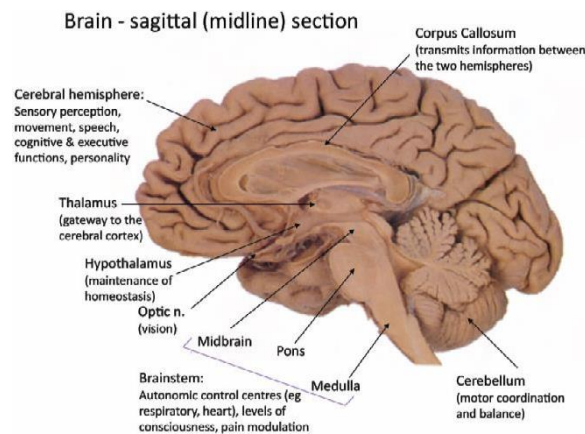
Grey matter contains:	White matter contains
Mainly cell bodies	Myelinated axons
Dorsal horn → sensory information processing interneurons	Ascending and descending processes, delivering information to the brain
Ventral horn → motor neurons	Simultaneously sending information into the periphery

- The spinal cord regions can be split into sections/ further regions → **cervical nerves** (C<sub>1</sub> – C<sub>8</sub>), **thoracic nerves** (T<sub>1</sub> – T<sub>12</sub>), **lumbar nerves** (L<sub>1</sub> – L<sub>5</sub>), **sacral nerves** (S<sub>1</sub> – S<sub>5</sub>) and the **coccygeal n.**

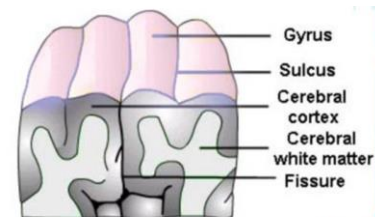


- The brain contains specified regions responsible for performing tasks involving memory, executive thought, problem-solving/ analysis, endocrine and homeostatic responses as well as balance and relaying neural transmission.
  - The components of the CNS – the brain as follows
    - **Cerebral Hemisphere** – sensory perception
    - **Thalamus** – gateway to the cerebral cortex
    - **Hypothalamus** – maintenance of homeostasis and governing of endocrine system
    - **Hippocampus** – important in memory formation and storage of LTM

- **Brainstem** – autonomic control centre (e.g. respiratory system and cardiovascular/ heart), levels of consciousness and pain modulation
  - **Midbrain** – control over eye movements/ auditory and unconscious processes.
  - **Pons** – relay signals/ respiration/ cranial nerve integration
  - **Medulla** – autonomic centre for heart rate and blood pressure/ consists of cranial nerve input
- **Cerebellum** – motor co-ordination and spatial awareness; also responsible for balance in response with the vestibular organ in the inner ear region
- **Corpus Callosum** – relays information and the site of neural transmission between left and right hemispheres

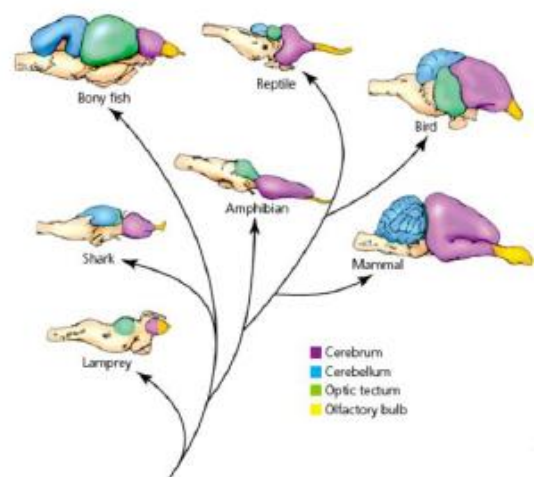


- Gyri, Sulci and Fissures
  - Gyrus → a ridge on the cerebral cortex
  - Sulcus → a depression in the cerebral cortex
  - Fissure → a deeper groove in the cerebral cortex

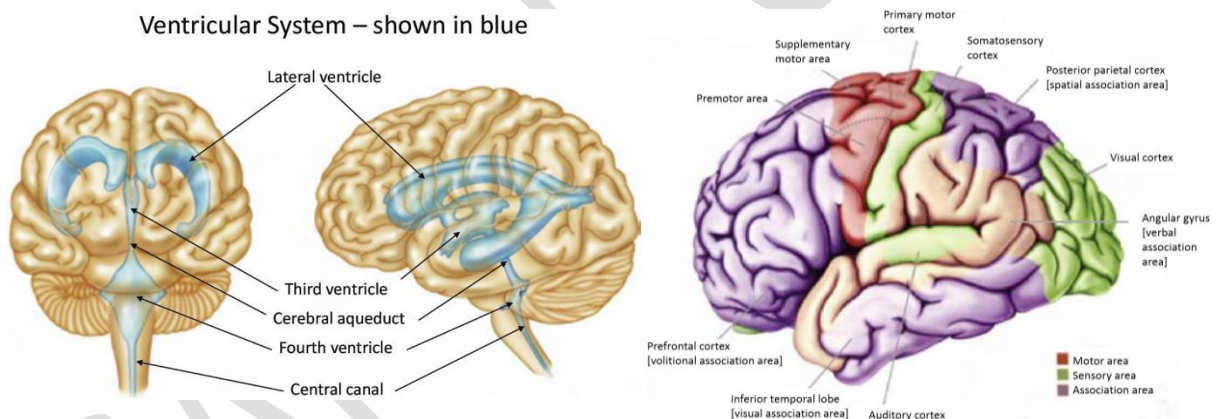


- Brain evolution has occurred over hundreds of millions of years
- Evolutionary patterns indicate similar hindbrain/midbrain to ancestors
- However there has been a markedly altered and improved fore frontal region of the brain.

- **Hindbrain** → control of vital functions
- **Midbrain** → relay station
- **Forebrain** → everything else (higher order/conscious thoughts & processes)
- **Hindbrain** comprised of: MEDULLA, PONS and CEREBELLUM
  - **MEDULLA** → automatic centre for heart rate and blood pressure; also consists of cranial nerve input
  - **PONS** → relay signals; respiration; cranial nerve integration



- **CEREBELLUM** → fine motor control (cerebellum ataxia occurs with damage to the cerebellum)
- **Midbrain** comprised of: TECTUM and TEGMENTUM
  - **TECTUM** → visual processing and control over eye movements (superior colliculus); auditory processing (inferior colliculus)
  - **TEGMENTUM** → unconscious processes; wider/broader/more general movement
- **Forebrain** comprised of: HYPOTHALAMUS, THALAMUS, AMYGDALA, HIPPOCAMPUS and CEREBRAL CORTEX
  - **HYPOTHALAMUS** → master controller of almost the entire endocrine system (adjacent to the pituitary gland); ensures homeostasis
  - **THALAMUS** → relay sensory signals to the cerebral cortex; important filter in conveyance process of sensory communication
  - **AMYGDALA** → involved in emotion; heavily orients fear responses
  - **HIPPOCAMPUS** → involved in the formation and storage of new memories (not responsible for working and procedural memory); contains water maze for learning (also known as the seahorse).
  - **CEREBRAL CORTEX** → executive function abstract thinking, problem solving, implicating logic, impulse control/ social skills (motor cortex & Phineas Gage)



- The **fourth ventricle** is a notable structure as it is easy to see when viewing histological sections and specimens. Located near the cerebellum, it is also important in determining the direction of the flow of the **central spinal fluid (CSF)**.
  - The major **functional regions** of the brain can be classified into lobes of the brain.
    - **Frontal lobe**
    - **Parietal lobe**
    - **Occipital lobe**



- Temporal lobe

- ▶ Each sense has a primary cortex
- ▶ There are also association areas

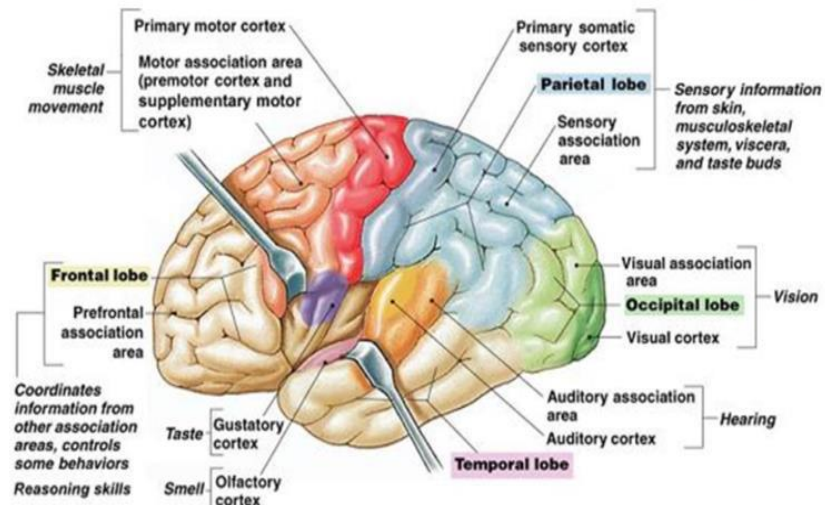
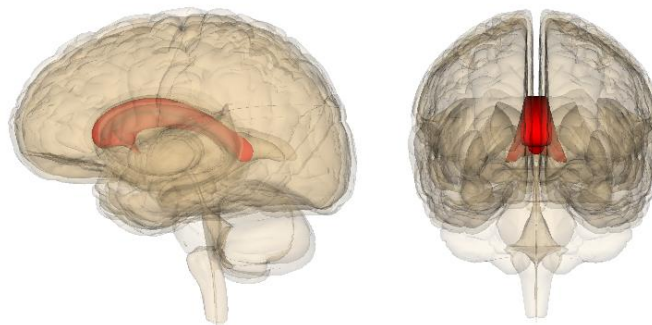


FIG. 9.15

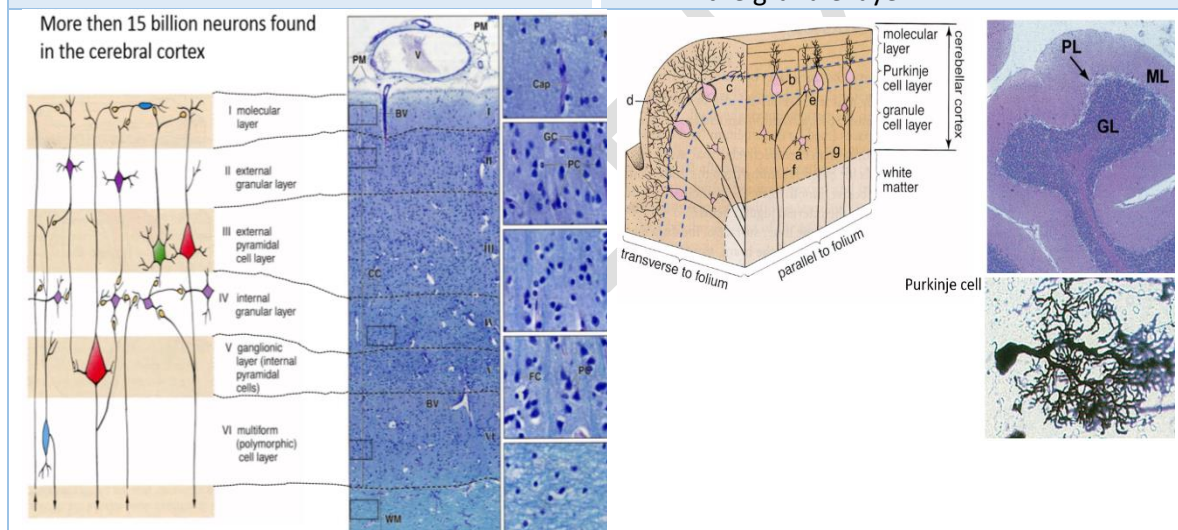


### Organisation of Brain Regions into Layers – THE CORTEX

- **Organised into horizontal layers** → laminated appearance
- **Generally 6 ill-defined layers** → which differentiate in neuronal populations
- **5 types of cortical neurons exist** → with pyramidal and stellate cells being the most numerous
- **Triangular-shaped pyramidal cell bodies range from 10-50µm in diameter (quite large)** → projecting a dendrite apically and a single axon towards the deeper cortical layers

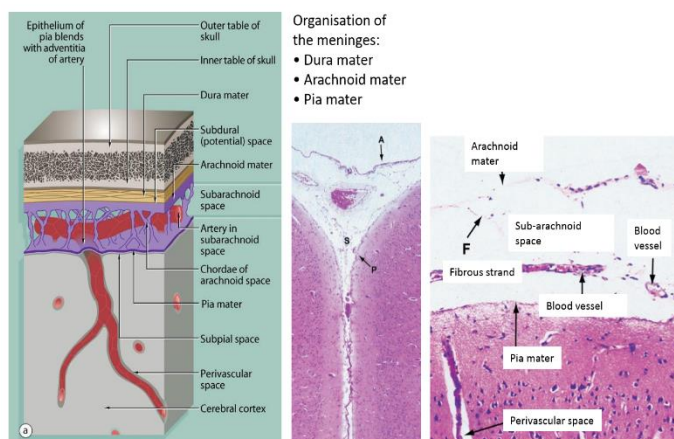
### Organisation of Brain Regions into Layers – THE CEREBELLUM

- **Uniform tri-laminar organisation** → and three fourths (75%) the size of the cerebral cortex
- **Outer molecular layer:** pale stained zone with relatively few neuron bodies; contains a network of branching dendrites of Purkinje cells (neuropil)
- **Inner granule cell layer:** densely packed, small neurons; only nucleus is visible as there is only very little cytoplasm; several short dendrites on each cell and one axon extending into the molecular layer; axons establish multiple synaptic contacts with dendritic spines of Purkinje cells
- **Middle monolayer of Purkinje cells:** single row of uniformly arranged, large neuron bodies on the outer surface of the granule layer



### The outer covering of the brain and spinal cord – the meninges

- One overall difference in the structure of the meninges b/w the spinal cord and brain
  - Spinal cord → white matter outside, with the butterfly-shaped inner layer composed of grey matter
  - Brain → inverted organisation, with the outside being grey matter & inside white matter.

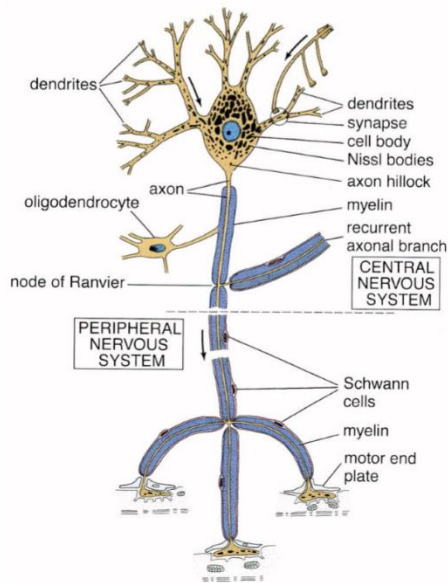


- The importance of non-neuronal cells in the nervous system:

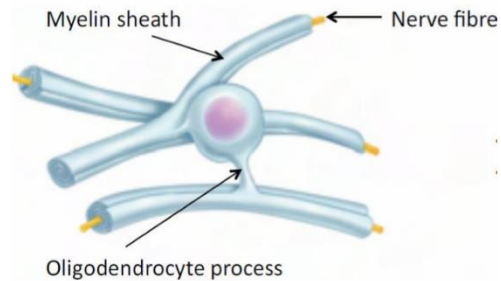
<p><b><u>GLIAL CELLS</u></b></p> <ul style="list-style-type: none"> <li>• <b>Non-conductive cells</b> with diverse structural, protective and nutritive roles.</li> <li>• Glia control the <b>extracellular environment</b> of the brain.</li> <li>• Also <b>buffer biochemical processes</b> which occur in neurons.</li> <li>• <b>Process energy sources</b> for neurons and are involved in the reprocessing and 'clean up' of neurotransmitters at EVERY synapse.</li> <li>• <b>GLIAL CELL TYPES:</b> Ependymal Cells, Astrocytes, Oligodendrocytes/ Schwann Cells and Microglia</li> </ul>	<p><b><u>EPENDYMAL CELLS</u></b></p> <ul style="list-style-type: none"> <li>• Remnants of <b>embryonic neuro-epithelium</b>.</li> <li>• Formation of a closely packed <b>cuboidal</b> or <b>columnar epithelium</b>, lining the <b>ventricles of the BRAIN</b> and the <b>central canal of the SPINAL CORD</b>.</li> <li>• <b>Luminal surface</b> directly in contact with the CEREbrospinal FLUID (CSF).</li> <li>• Cells possess <b>apical microvilli</b> (for ↑ surface area for diffusion) and most also possess motile cilia (to ↑ movement of the CSF).</li> <li>• Possess <b>structural</b> and <b>enzymatic</b> characteristics <b>for scavenging</b> and <b>detoxifying</b> substances in the CSF.</li> </ul>
<p><b><u>ASTROCYTES</u></b></p> <ul style="list-style-type: none"> <li>• Derived from the <b>neural ectoderm</b>.</li> <li>• Appear <b>stellate</b> in shape.</li> <li>• NOT part of the <b>blood-brain barrier</b>, but help ependymal cells in the building of the blood-brain barrier.</li> <li>• Important in the <b>maintenance of homeostasis</b>.</li> <li>• <b>Cytoplasm</b> contains tightly packed <b>intermediate filaments</b> unique to glial cells → <b>glial fibrillary acidic protein (GFAP)</b>.</li> <li>• Form a structural <b>syncytium</b> in the CNS via <b>gap junctions</b>.</li> <li>• They control the <b>ionic milieu</b> by taking up <b>potassium ions (K<sup>+</sup>)</b> and they <b>regulate GABA</b> and <b>inactivate neurotransmitters</b> such as glutamate.</li> <li>• Undergo <b>mitosis</b> in response to <b>CNS injury</b> → 'gliosis'.</li> </ul>	<p><b><u>OLIGODENDROCYTES (CNS)</u></b></p> <ul style="list-style-type: none"> <li>• Provide <b>support for nerve fibres</b> and <b>produce myelin sheaths</b> (rich in lipids) that insulate the nerves.</li> <li>• <b>Modulation of nerve conduction</b> by ↑ the conduction velocity of nerve fibres → <b>rapid salutatory conduction</b> (impulses jumping from one Node of Ranvier to another).</li> <li>• Myelin sheaths also contain <b>neurokeratin</b> as a non-lipid component.</li> <li>• Myelinate by wrapping around numerous (up to 60) axons.</li> <li>• DO NOT contain ANY <b>intermediate filaments</b> in their cytoplasm → being the ONLY cell type that does this.</li> <li>• Controls the <b>extracellular pH</b> in the CNS.</li> </ul>
<p><b><u>SCHWANN CELLS (PNS)</u></b></p> <ul style="list-style-type: none"> <li>• Can occur in <b>myelinating</b> and <b>non-myelinating forms</b>.</li> <li>• Non-myelinating cells → collectively ensheath <b>groups of several small axons</b>.</li> <li>• Myelinating cells → collectively ensheath a <b>single large axon</b>.</li> <li>• Help to <b>remove cell debris</b> and <b>guides for regenerating axons</b> after injury.</li> </ul>	<p><b><u>MICROGLIAL CELLS</u></b></p> <ul style="list-style-type: none"> <li>• Originate from <b>blood monocytes</b>.</li> <li>• The smallest glial cell type.</li> <li>• Act as <b>phagocytes</b> and remove CNS debris.</li> <li>• Constitute the <b>brain's immune system</b>.</li> </ul>



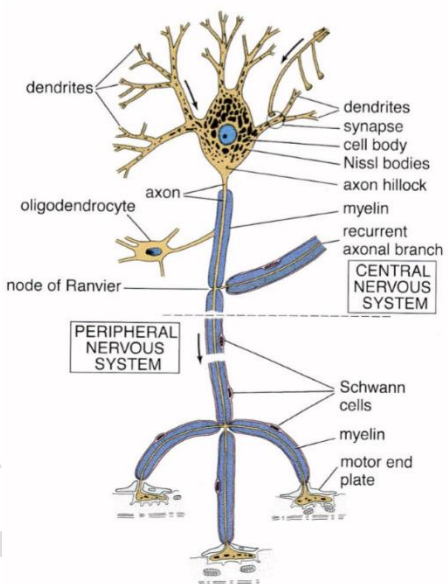
## Myelinisation of axons by oligodendrocytes and Schwann cells



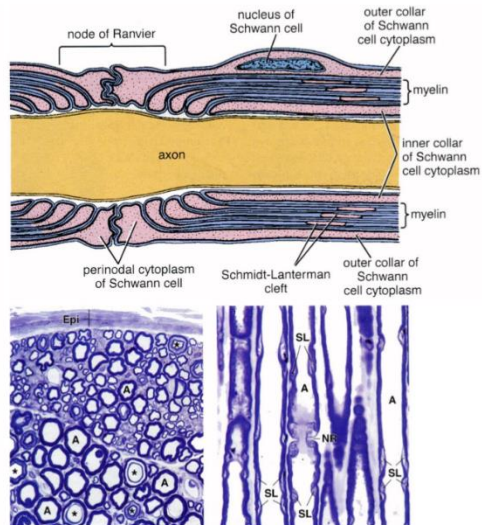
### oligodendrocytes



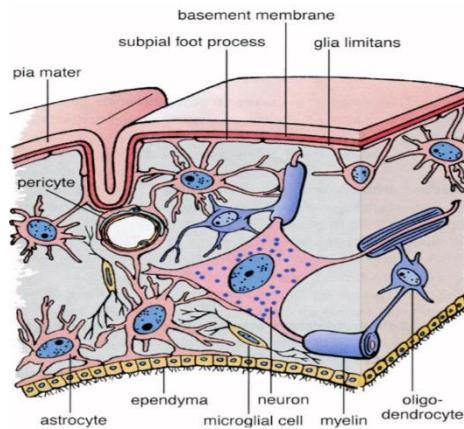
## Myelinisation of axons by oligodendrocytes and Schwann cells



### Schwann cells



Speed of conduction in unmyelinated axons: 0.2-2 m/s  
Speed of conduction in myelinated axons: 5-10 m/s



## Overview & Neurotrauma Types

- **Neurotrauma** refers to injury to a nerve, especially part of the CNS (brain and spinal cord).
- An injury resulting from external forces leading to central nervous system deficits, including motor and/or sensory dysfunction, cognitive impairment, emotional difficulties, or behavioural problems.
  - A **concussion** is a violent jarring or shaking that results in a disturbance of brain function.
- The neurology of neurotrauma can include the primary symptoms associated with the various types. These may include:
  - Neurology – Symptoms
  - Neuroimaging – Visualisation
  - Neurosurgery – Repair

### NEUROLOGY

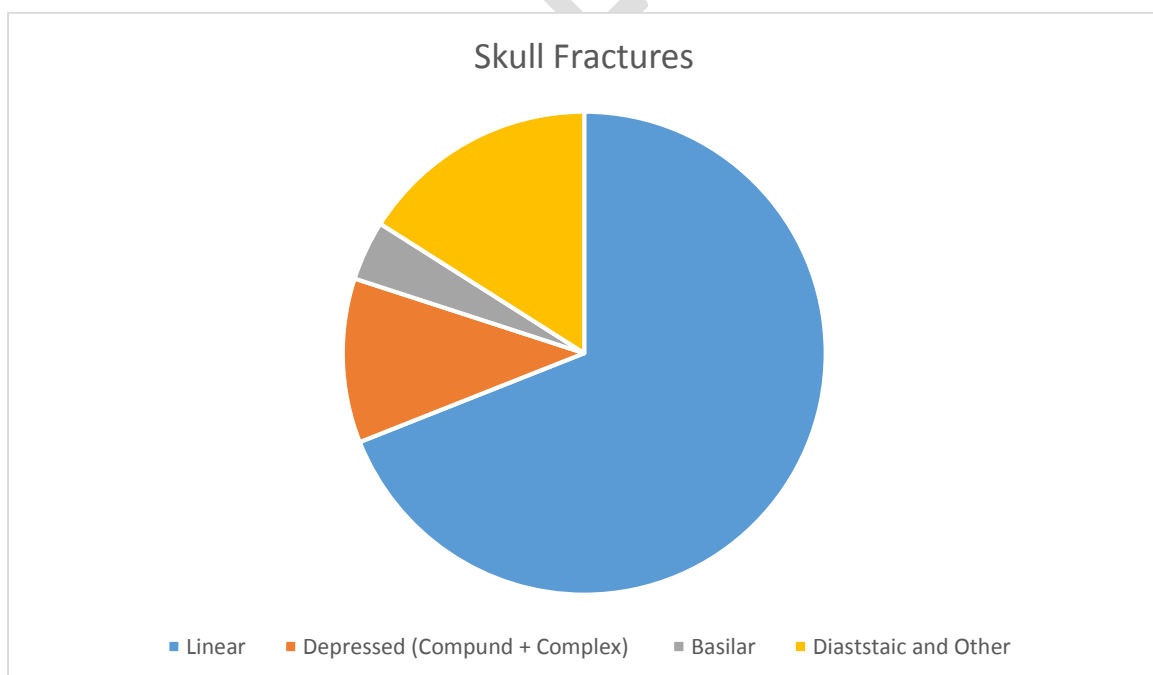
Symptom	Affects	Brain Area
<b>Hemiplegia</b>	Movement → paralysis of arm, leg and trunk on same side of the body. Paralysis on opposite side of injury (i.e. injury right side of the brain, means left side of the body is affected).	Frontal lobe
<b>Aphasia</b>	Language → <b>expressive</b> aphasia (Broca's aphasia) and <b>receptive</b> aphasia (Wernicke's).	Broca's – medial insular cortex Wernicke's – temporal lobe
<b>Ataxia</b>	Co-ordination	Cerebellum
<b>Apraxia</b>	Motor planning and execution	Parietal lobe
	Short-term memory	Temporal lobe
	Vision	Occipital lobe

### NEUROIMAGING

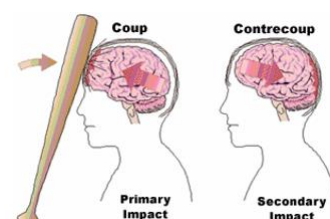
- **CT – Computed Tomography (X-Rays)**
  - Fast
  - Acute care
  - Bone = white, Soft Tissue = grey
- **MRI – Magnetic Resonance Imaging**
  - More detailed, high resolution
  - Dense areas = white
- **PET – Positron Emission Tomography**
  - Functional reflection
  - Radio-nucleotides or tracers are required to obtain read-out
- Causes of neurotrauma:
  - Head Injury
    - Stroke
    - Car accidents
    - Gunshot/ Missiles
    - Blow to the Head
    - Fall
  - Spinal Cord Injury
    - Car accident
    - Fall
    - Sports
    - Diving
    - Assault



- Assault
- Disease
- Tumour
- Infection
- SEQUENCE of neurotrauma: some traumatic event (direct injury to the brain tissue via penetration, infection or removal) → mechanical distortion of the tissue → **primary injury**.
  - Mechanical distortion can occur without a violent, penetrative rupture of the tissue, but can ALSO be caused by movement of or within the skull cavity.
  - Primary injury usually include:
    - Bone (skull/ spinal column) fractures
    - Lacerations (irregular tear-like wounds)
    - Contusions (closed wound)
    - Haemorrhage (bleeding) or hematoma
    - Axonal Injury
  - **Haemorrhage** is the bleeding and release of blood from the blood vessels, becomes a **hematoma** if the blood is released into a cavity → a cavity that holds the haemorrhage together
    - For example, the space between the skull and the dura mater or dura mater and the arachnoid mater or any other closely defined space in the brain (neurotrauma); but can also be a joint cavity. ANY AREA that the blood from the haemorrhage is RESTRICTED.

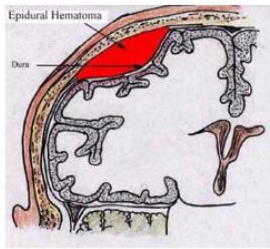


- Coup = at the site of impact
- Contrecoup = opposite/ remote from the site of impact



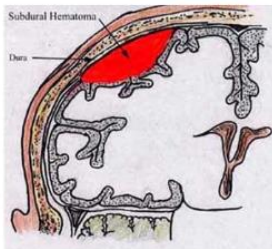
## Hematoma

### Epidural



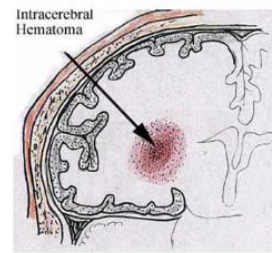
**Epidural hematoma:** A hematoma between the cranium (skull) and the dura. Epidural hematoma is usually caused by a full-on blow to the head, and is often associated with a skull fracture. Treatment is by trepanation: drilling through the skull to drain the excess blood.

### Subdural

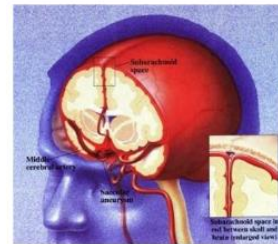


Bleeding into the space between the dura (the brain cover) and the brain itself. If the hematoma puts increased pressure on the brain, neurological abnormalities including slurred speech, impaired gait, and dizziness may result and progress to coma and even death.

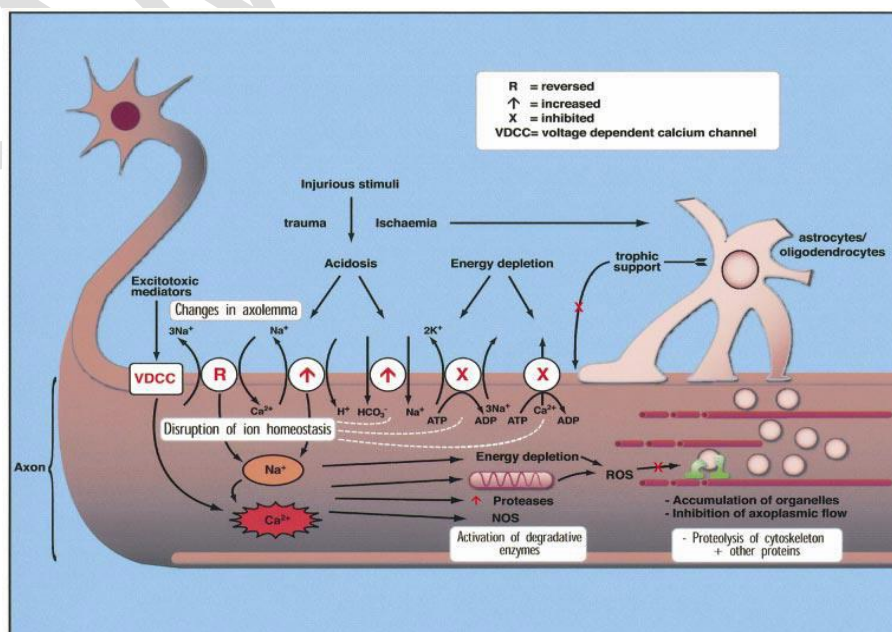
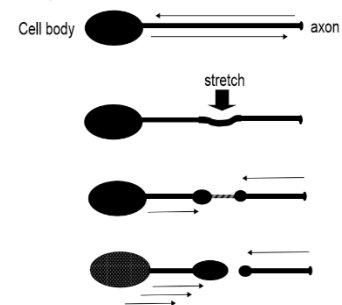
### Intracerebral



### Sub-arachnoid



- **Trephination:** surgical intervention in which a hole is drilled or scraped into the human skull, exposing the dura mater, in order to treat health problems related to intracranial diseases.
  - It is often used to relieve pressure beneath a surface.
- **Diffuse Axonal Injury (DAI):** disruption to the axons of the nerves; typically caused by shearing forces but without complete tearing (also axonal degeneration) e.g. motor vehicle accidents
  - Regardless of injury mode, axonal injury is associated with a broadly similar pattern of disruption:
    - increased axonal membrane permeability** with excess  $\text{Na}^+$  and/or  $\text{Ca}^{2+}$  ions influx into the axon →
    - deleterious cascades involving activation of **intracellular proteases**, failure of the **mitochondria** and **cytoskeleton breakdown** →
    - disturbance of axonal transport** and possibly degeneration.

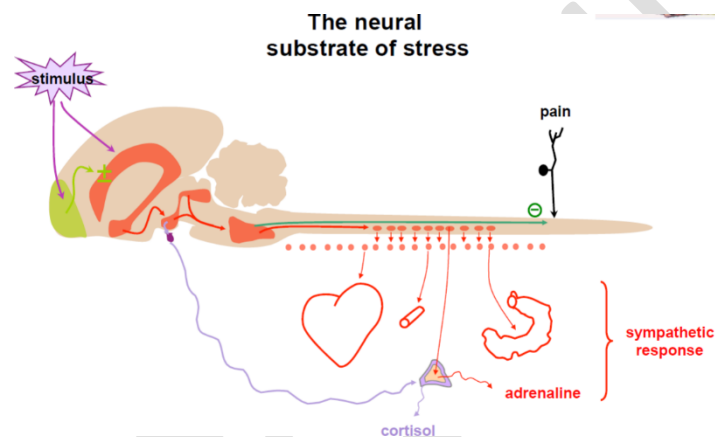


## Stress

- ▶Lecture 1: Peripheral Nervous System & Stress
- ▶Lecture 2: Central Nervous System & Stress
- ▶Lecture 3: Psychology of Stress
- ▶Lecture 4: Available Treatments & Management

### Psychology of Stress

- The stress system is among the most fundamental systems detecting and mediating coping strategies and has been conserved across a long period of evolutionary history.
  - **Stressor**: any challenge to the body (maybe be physical or psychological) that causes some form of discomfort.
  - **Stress**: integrated and adaptive nervous and endocrine system response to that challenge.



- The **hypothalamic-pituitary-adrenal axis** (HPA axis) is a sequential axis termed by Selye, describing the specialised neurons in the paraventricular nucleus of the hypothalamus, called **corticotrophs** which make the corticotropin-releasing hormone.
  - This then binds to receptors in the pituitary gland which synthesise ACTH → ACTH binds to receptor on the adrenal gland to cause synthesis and release of glucocorticoids. CRH → ACTH → adrenal glands release cortisol (glucocorticoid) → hypothalamus signals medullas to release epinephrine (A) and norepinephrine (NA).

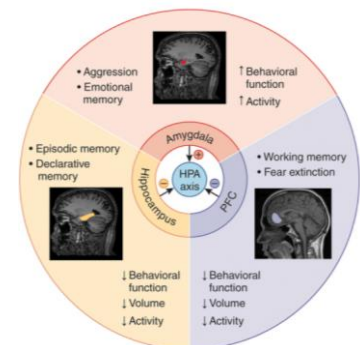
- **Glucocorticoids** mobilise glucose from storage sites to increase available energy.

- Effects on the liver → defend blood-glucose levels
- Effects on the heart → promote ↑ cardiovascular tone
- Modulate, ↓ and suppress immune system
- ↑ vigilance or bias attention towards environmental stimuli
- Enhance certain forms of learning and memory, particularly emotional memory.

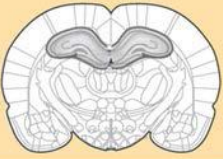
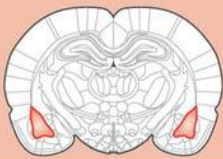
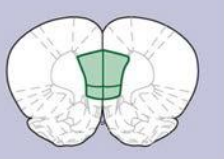




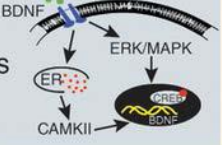
- Glucocorticoids readily cross the **blood-brain-barrier** and bind to either one of 2 receptors:

- Synaptic feedback → actions at these receptors terminates the HPA axis response
  - Glucocorticoid receptor (GR)
  - Mineralocorticoid receptor (MR)

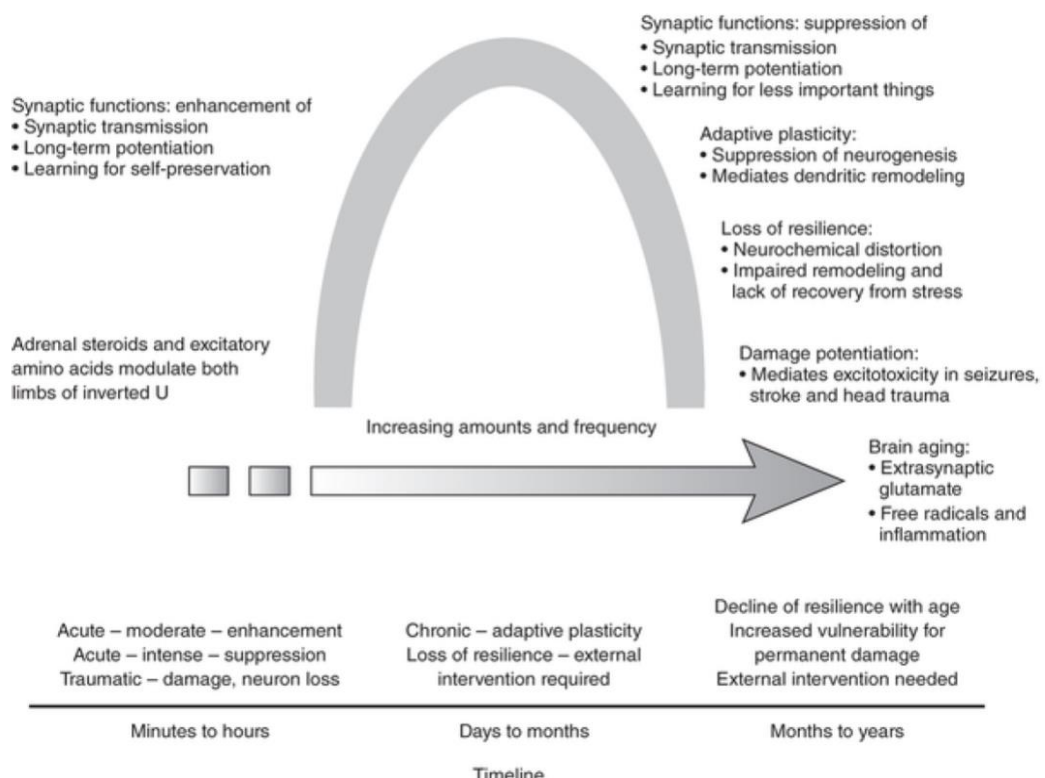
### Neural circuits of stress



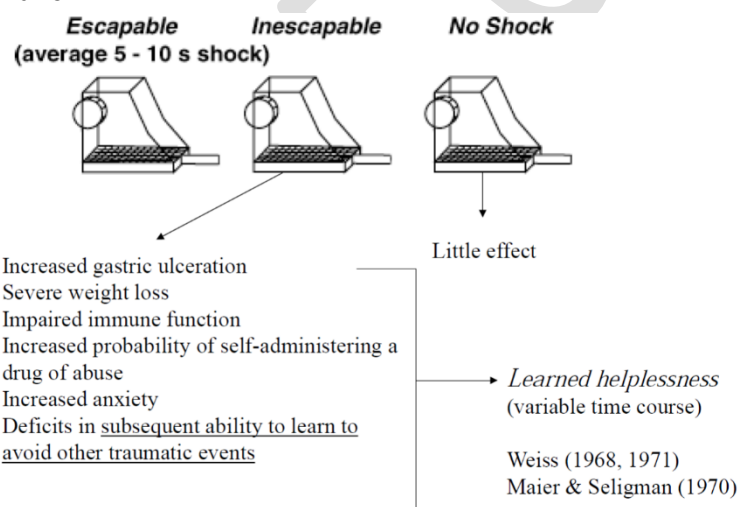
a

	Hippocampus	Amygdala	mPFC
			
Behavior 	↓ Spatial memory ↓ Spatial navigation	↑ Fear memory ↑ Anxiety	↓ Working memory ↓ Fear extinction
Networks 	↓ Auditory-evoked potential ↓ Place cell	↑ Auditory-evoked potential	?
Neurons 	↓ Dendrites	↑ Dendrites	↓ Dendrites
Synapses 	↓ Spines ↓ LTP ↑ LTD	↑ Spines ↑ LTP	↓ Spines ↓ LTP
Molecules 	↓ BDNF	↑ BDNF	?

Effects of acute and chronic stress, mediated in part by glutamate and glucocorticoids



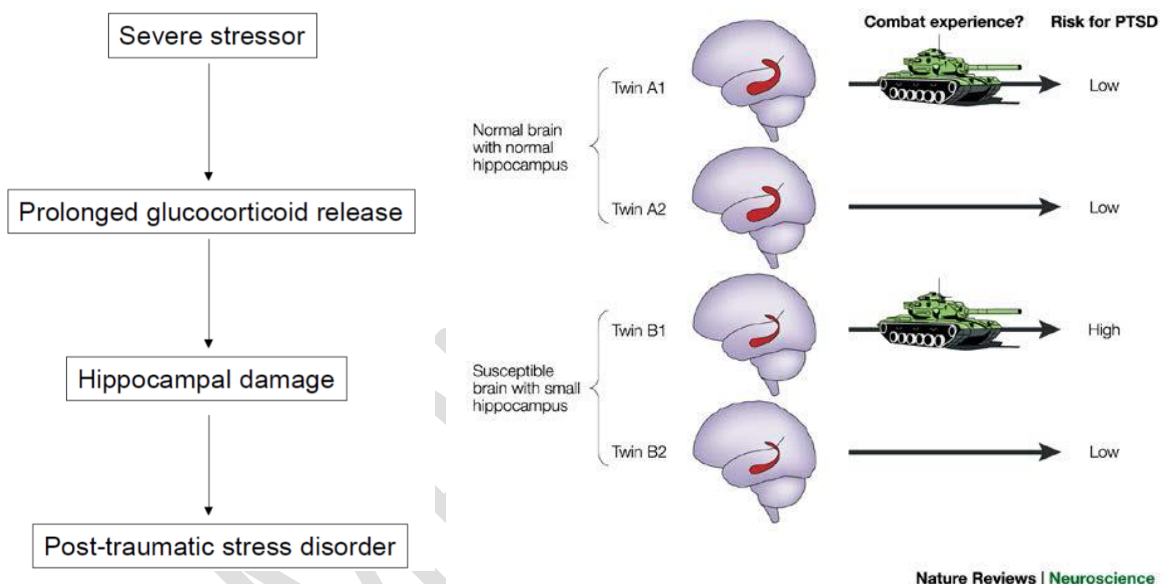
- There are marked individual differences in stress responding and HPA axis function.
  - Due to genetics and differences in environment – unique or shared.
- Animal studies have clearly shown that one important environmental factor governing individual differences in HPA axis function is in levels of **maternal care**.
  - In rats, there is naturally occurring variation in maternal care and HPA axis development.
  - Liu et al. (1997) Examined the relationship between naturally occurring variations in maternal care and stress responding of their offspring – High versus low levels of licking and grooming of pups (LG) – High versus low levels of “arched back” nursing (ABN)
  - Results taken from structural scans fMRI and other testing indicated a decrease in everything (except IRI - Affective).
  - Lower cognitive empathy, reduced skin conductance levels (SCL), under-aroused, whole brain volume reduced, as with regions of the brain.
- Another environmental factor for distinct differences in HPA axis is exposure to and phenomenon of **‘learned helplessness’** in learning.
  - Triadic design of controllable = escapable group, uncontrollable = inescapable group and none group.
  - Both escapable and inescapable (exposed to electrical shocks) showed no difference in **corticosterone** responses to the stressor → subsequent loss of negative control of HPA axis



- Learned helplessness and Depression
  - Similar endocrine manifestations
  - Similar neural mechanisms and behaviour manifestations
  - Similar sensitivity to antidepressants
- Learned helplessness might be a useful animal model of some aspects of depression in humans:
  - As there is evidence for heritability of HPA axis function and stress responsivity
  - As there is evidence for environmental influences on HPA axis and stress responsivity.
  - As there is evidence for a contribution of learning and ‘learned helplessness’ to HPA axis and responsivity



- PTSD is an anxiety disorder emerging from the experience of severe trauma or stressors from the past that elicits intense fear, helplessness or horror.
  - To be diagnosed as suffering from PTSD
    - Re-experience of the trauma (through nightmares or intrusive thoughts)
    - Avoidance and emotional numbing
    - Increased arousal (difficulty sleeping, hypervigilance, exaggerated or intensified startle response) → DSM IV
  - Approximately 50-60% of the adult population experience severe stressor/ trauma, yet only around 5-10% develop PTSD.
  - Predictors of PTSD include: prior trauma, prior psychological adjustment, family history of psychological problems, perceived life threat, feelings of detachment at time of trauma.
- Significant and strong negative correlations have been found between hippocampal volume and psychological disorders arising from failures of adaptation to the stressors.



- Smaller hippocampal volumes (~10% reduction) are NOT a consequence of experiencing the traumatic stress of combat.
- There are pre-existing factors that appear to predict the development of PTSD
- Familial (environment or genetic) vulnerability factor for PTSD.
- The HPA axis is a key biological mechanism for detecting and responding to changes in the environment.
- HPA axis IS NOT static, and differences in HPA axis function are associated with pronounced individual differences in stress reactivity.
  - These individual differences can be due to one or more interactions between:
    - Genetics
    - Environmental factors (including early post-natal environment) e.g. caring
    - Learning e.g. 'learned helplessness'
- This flexibility enables the body to adjust to current environmental demands but can also have adverse effects on physical and physiological well-being.

### Available Treatments & Management

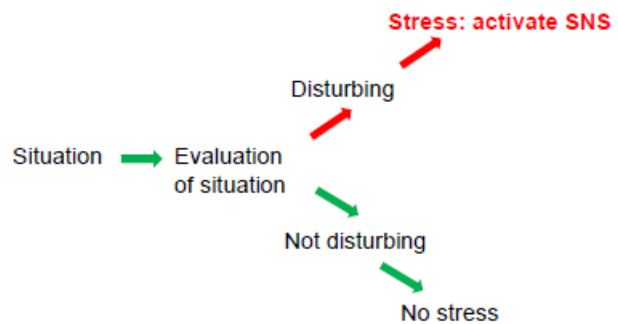
- The **sympathetic** pathway → “**energy expenditure**” → prepares the body for “fight or flight” and other stress related behaviours (↑ HR, breathing, blood pressure, sweating).
- The **parasympathetic** pathway → “**energy conservation**” → preps the body “rest & digest” and supports the non-emergency functions (↓ HR, breathing, restfulness, digestion).
- Stress and fear mainly activate the sympathetic pathway, but may also involve some parasympathetic activities (i.e., being frightened can cause an individual to lose bowel or bladder control).
- Mental reactions to stressors may vary according to the situation and the individual. These may include: tension, frustration, anger and/ or anxiety.
- Prolonged stress can induce a **chronic state of hyper-sympathetic activity** and/or **suppressed parasympathetic** response.
  - Due to weakening of immune system, if chronic, can also trigger numerous disease processes to occur: inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), peptic ulceration, chronic fatigues system, gastroesophageal reflux disease, etc
  - Prolonged stress may also lead to life-threatening illnesses: hypertension, stroke, etc
- **SIGNS & SYMPTOMS OF STRESS**
  - **Physical Symptoms:**
    - Headaches
    - Increased HR
    - Increased muscle tension (esp. neck and shoulders)
    - Higher levels of perspiration/ sweating
    - Insomnia
    - Feelings of exhaustion/ lethargy/ lassitude
    - Shakiness or tremors
    - Recent loss of interest in sex
    - Restlessness
  - **Behavioural Symptoms:**
    - Putting off work
    - Increased reliance on drugs and alcohol/ smoking
    - Dieting and eating disorders/ changes (usually worse food choices)
    - Withdrawal from others
    - Rumination (of stressful situations)
  - **Emotional Symptoms:**
    - Poor concentration
    - Indecisiveness
    - Strong mood fluctuations
    - Quick to anger (outbursts/ impatience)
    - Depression
    - Difficulty remembering things/ feelings of helplessness
- The Holmes-Rahe Stress Scale is a list of 43 stressful life events that can contribute to illness due to stress. Each event, called a life change unit (LCU), has a different “weighting” for stress → the more events added up → the higher the score → more likely to become ill.

- Story: Between a Rock and a Hard Place  
also known as the film 127 Hours

### Coping with Stress- Aron's Story

- The Stressor: arm was trapped by a huge rock
- Stress responses: anxiety
- Coping Strategies:
  - "time to relax. The adrenaline is not going to get you out of here...I need to be calm".
  - "I'll get out. I mean, if I don't get out, I'm going to lose more than my hand. I have to get out!"
  - ".....There's a bigger issue. Stressing over the superficial problem will only consume my resources. Right now, I need to focus on gathering more information. With that decision made, a feeling of acceptance settles over me..."

## Coping with Stress



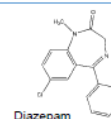
- Effectively dealing with stress involves:
  - **Problem Focused** → efforts to change circumstances
  - **Emotion Focused** → changing interpretation of circumstances to make them less threatening/ unpleasant (rationalising the “bigger picture”)
- Coping is a dynamic process and can be adjusted according to the situation and effectiveness
  - The **TARP** method is a widely used technique to control response to stress
    - **Tune In** – be aware of early signs of stress or stressors
    - **Analyse** – think about the source or cause of the stress
    - **Respond** – deal with the cause and minimise the its potential adverse effects
    - **Prevent** – develop good stress-reduction habits/ strategies for healthier lifestyle and the future.

NON-PHARMACOLOGICAL MANAGEMENT	PHARMACOLOGICAL MANAGEMENT
<b>Hyperventilation control</b> e.g. slow and controlled breathing, walking	<b>Anxiolytic drugs – benzodiazepines, tricyclis, etc</b> Modulate neurotransmission of GABA, serotonin
<b>Problem solving</b> e.g. mental distractions	<b>5-HTP</b> A derivation from the amino acid L-tryptophan Precursor of serotonin. Found in dairy, lean meat
<b>Relaxation techniques</b> e.g. tai chi, yoga, meditation	<b>Beta-blockers – <math>\beta</math>-Adrenergic recept. antagonist</b> Manage excessive sympathetic stimulation by targeting the excessive release of <b>catecholamine</b>
<b>Psychotherapy</b>	<b>St. John's Wart</b> The active chemicals in SJW = <b>hyperforin</b> and <b>hypericin</b> ; inhibit reuptake of monoamines to maintain balance of serotonin, noradrenaline, dopamine and GABA in the brain

- **Benzodiazepines** are highly effective against panic disorder, anxiety, insomnia
  - Sedative and induces sleep
  - Usually start with low doses, gradually increasing until anxiety is controlled.
  - Used for short periods (2-4 wks) as long-term use can lead to dependence/ withdrawal reactions.

### Benzodiazepines

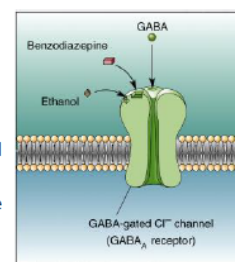
- Many possible compound  
e.g. **diazepam**, **nitrazepam**, **lormetazepam**



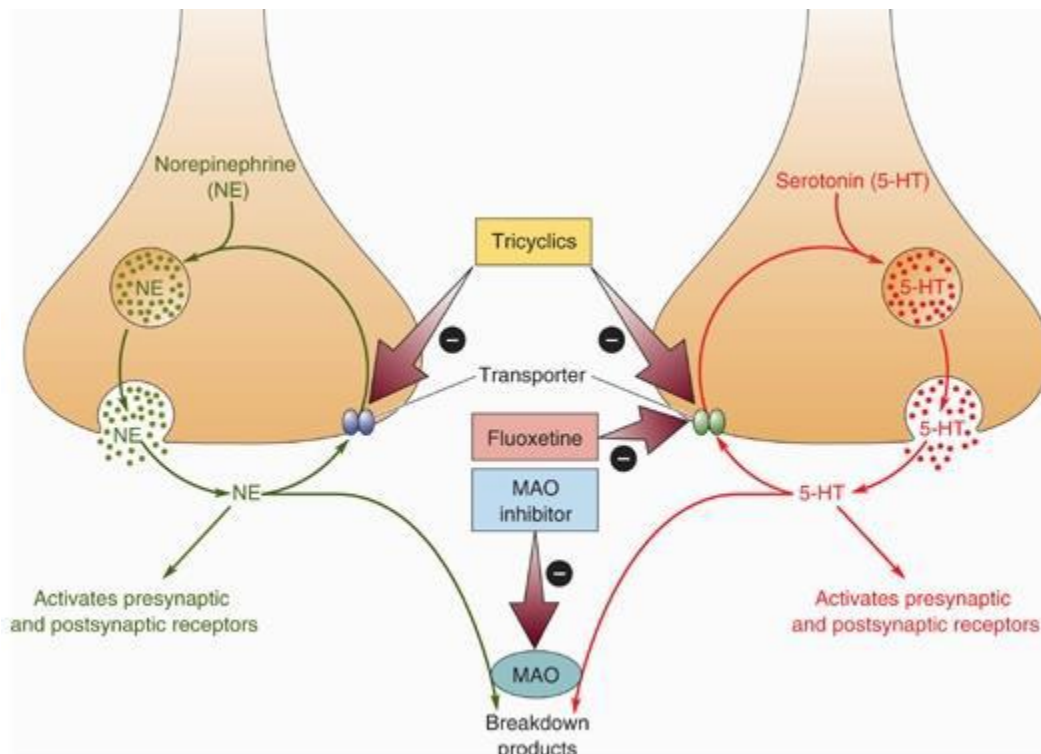
### Mechanisms of action

- Bind to regulatory site on receptor, distinct from GABA binding site
- Facilitate opening of GABA activated  $\text{Cl}^-$  channels ( $\text{GABA}_A$  receptor)
- Increase the affinity of GABA for the receptor

Thus **potentiate** inhibitory effects of GABA throughout CNS

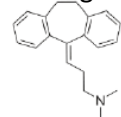


Bear et al. Neuroscience

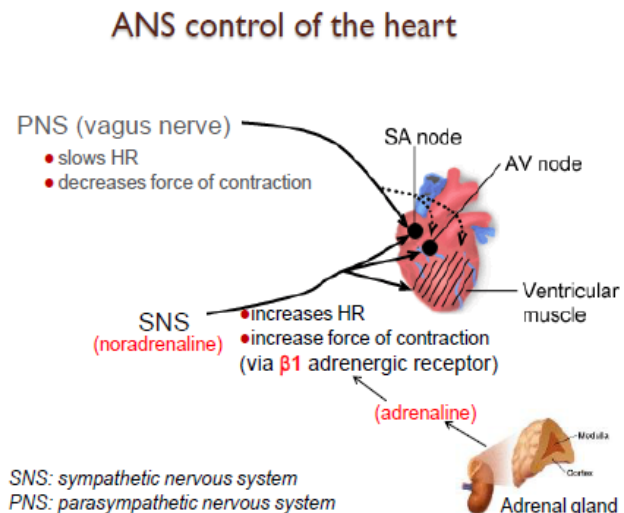


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- **Selective Serotonin Reuptake Inhibitors (SSRIs)** like fluoxetine (Prozac) inhibit the reuptake of serotonin which means it is still present in the synaptic cleft → physiologically causing sustained feeling of well-being and happiness (alertness).
  - Widely used as antidepressants and are also used in the treatment of panic disorder and OCD
  - **Common side-effects include:** nausea, sexual difficulties and nervousness.
- **Tricyclics (TCAs)** are non-addictive medications used to treat depression, mood and eating disorders, anxiety, and panic attacks.
  - Name comes from the 3 benzene(o) rings
  - Amitriptyline is one of many available TCA compounds
  - Help maintain neurotransmitters at normal levels → very helpful in treating both PTSD and OCD
  - **Common side effects include:** weight gain, also highly dangerous if overdosed.
- **Monoamine Oxidase Inhibitors (MAOIs)**, such as Selegiline, are rarely used as first line of treatment and are only used if the other pharmacological treatments have not worked.
  - May be used in the treatment of panic disorder, PTSD and social phobia.
  - **Common side effects include:** high withdrawal, addiction as it is very strong.
- **B-Adrenergic Receptor Antagonists (Beta-Blockers)** are used to target stress symptoms by blocking the beta adrenergic receptors which lower the physiological tremor (tachycardia, nervous sweating, blushing, etc.) caused by excessive sympathetic stimulation.
  - Targets the excessive release of catecholamine
  - Excessive catecholamine release further exacerbates anxiety, establishing a vicious cycle.



- Examples of beta-blockers(-ol):
  - **Propranolol** (non-selective)
  - **Atenolol** ( $\beta_1$  selective)
- Block **adrenaline (A)/ noradrenaline (NA)** to access to beta receptors, thus a reduced heart rate and ↓ “fight or flight” reaction.
- Reduce symptoms associated with sympathetic activation: e.g. palpitation (rapid heartbeat), tremor (shaking), blushing, and nervous sweating.



- Fast acting and non-habit forming but NOT FDA approved anxiolytics, but are commonly prescribed “off-label” for anxiety and panic, especially social or performance anxiety.
  - The National Institute of Mental Health (NIMH) has indicated that “a doctor may prescribe a beta-blocker to keep physical symptoms of anxiety under control.”
  - Contraindications: asthma, congestive heart failure, diabetes, vascular diseases, hyperthyroidism and angina. “The musicians underground drug”.
- Suggestions that the beta-blocker, propranolol, **reverses the stress-induced cognitive problems AND promotes the ability to think flexibly** under stressful conditions.
- Drug target: CRH receptors
  - Stress: Corticotropin-releasing hormone (CRH) → adrenocorticotrophic hormone (ACTH) → cortisol
  - Animal studies using antisense oligodeoxynucleotides directed against the mRNA of CRH receptor subtypes suggest CRH1 receptor as the mediator of the anxiogenic effects of CRH
    - CRH1 KO mice are less anxious than wild-type mice when experimentally stressed.
    - CRH1 receptor antagonist are the drug development target for anxiety, stress and depression treatment
  - Results taken from structural scans fMRI and other testing indicated a decrease in everything (except IRI - Affective).
  - Lower cognitive empathy, reduced skin conductance levels (SCL), under-arousal, and whole brain volume reduced, as with regions of the brain.