Week 2: Brain Function Disorders

Hypoxia

- Inadequate supply of oxygen to the tissues
- Causes ATP depletion or "power failure"
    - Cells cannot respire, reduced resources, no signals
- Aerobic metabolism stops → less ATP is produced
    - Na+/K+ ATPase cannot run fast enough
    - Cell become hypervolemic, swell up with water + eventually burst due to ↑ internal pressure
        - Serious problem in non-degenerative neurons
- Anaerobic metabolism used → lactic acid produced
    - Prolonged and excess production = cannot be cleared = build-up = ↓ pH
    - Acid denatures proteins + damages cell membranes, intracellular structures, and DNA

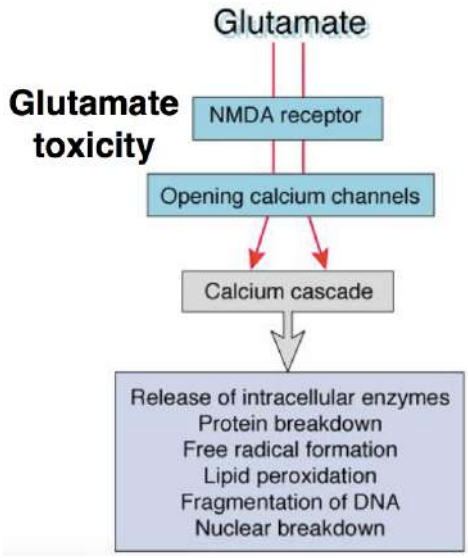
Ischaemia

- Decreased blood supply due to constriction or obstruction of a blood vessel
- Interferes with:
    - Delivery of energy stores (e.g. glucose)
        - Needed for respiration
    - Damage to blood vessels
        - Vasomotor paralysis due to lack of oxygen, glucose and Ca2+ needed for muscle contraction
        - Vasoconstriction
- Blood flow inadequate to meet the metabolic needs of the brain
- Changes in blood that can cause ischaemia:
    - Desaturation or changes in ionic concentrations
    - Clotting
        - E.g. deep vein thrombosis, atherosclerosis
    - Sludging
        - Changes in blood viscosity → blood stays 'liquid' to keep moving with ease
        - ↑ Viscosity = difficult to pump + damages blood vessels

Calcium Cascade/Excitotoxicity

- Excitotoxicity = pathological process by which neurons are damaged and killed by the overactivations of receptors for the excitatory neurotransmitter glutamate e.g. NMDA and AMPA receptors
- In neurologic disorders, neuron injury may be caused by:
    - Excitatory amino acids incl. glutamate
    - Catecholamines, nitric oxide, free radicals, inflammatory cells, apoptosis, & intracellular proteases
- Ischaemia becomes toxic through the calcium cascade
    - Lack of resource at one point means build up of recourses at another point
    - E.g. blockage of artery = one side has lack and other has build up
- During prolonged ischemia, extracellular glutamate accumulates
    - Bc intracellular glutamate released from hypoxic, lysed, damaged cells
    - Usually released into bloodstream but accumulates bc lack of blood flow
- Excites neurons and allows high levels of calcium ions to enter the cell
    - Calcium influx = activates enzymes = damage cell structures

- Ischemia → depolarisation
- Depolarisation → glutamate release causes opening of NMDA receptor channels
- Glutamate → intracellular calcium cascade → releases enzymes and cell-damaging molecules
- Calcium influx → depolarisation
- Neuron firing releases glutamate
- Causes neighboring neurons to fire
- Intracellular calcium cascade triggers apoptosis → releases more glutamate
    - Enough glutamate accumulation = cell death = more glutamate release, and so on
        - ∴ Spreading/propagating injury across the ischemic area



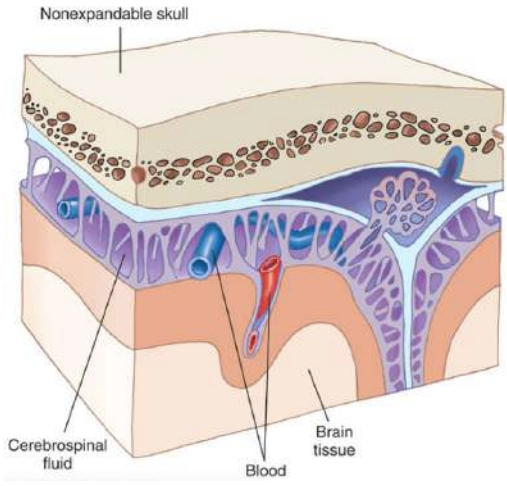
- Neuroprotectant drugs being developed to interfere with calcium cascade to avoid depolarisations and damaging processes = reduce permanent brain cell injury
    - E.g. calcium-channel blockers

Intracranial Pressure (ICP)

- Within skull:
    - 1. Brain tissue and interstitial fluid (80%)
    - 2. Blood (10%)
    - 3. CSF (10%)
- Compartment syndrome in the skull
    - Compartment syndrome = increased pressure within a body's compartment
    - ICP greater than arterial blood pressure = crushes BVs = arteries collapse = ↓ BV diameter = blood flow to brain cut off = insufficient blood supply
- ↑ ICP = brain swelling
    - Vasogenic → extracellular fluid
    - Cytotoxic → intracellular fluid

Cerebrospinal Fluid (CSF)

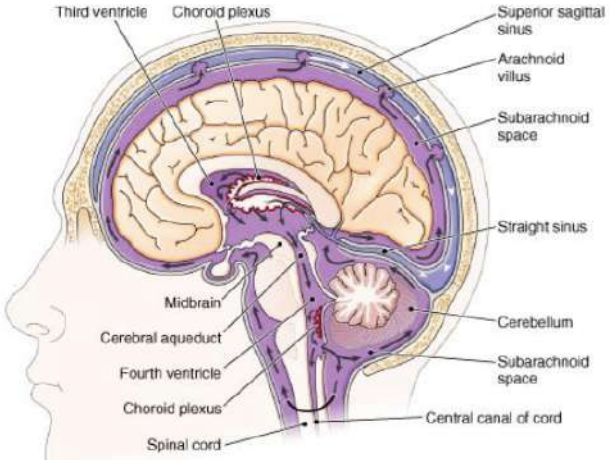
- Supports nervous tissue, cushions from shock + trauma
- Carries nutrients to cells + transports waste products from cells
- Produced in ventricles:
    - Choroid plexus
    - Lateral ventricles
    - Foramina
    - Cerebral aqueduct



Flow of CSF

- Black arrows show the flow of CSF from the choroid plexuses and back to the blood in dural sinuses

- White arrows show the flow of blood
- Interruption of CSF flow at any point is detrimental bc one way flow + only exit are dural sinuses
- The actual passageways through which the CSF flows are narrower than those shown here, which have been enlarged for visibility



Hydrocephalus

- Abnormal CSF accumulation within brain
    - Due to over production or impaired drainage of CSF
- Hypertensive hydrocephalus = increase in BP
    - Further swelling, further blockage of blood flow = hypoxia and ischaemia
- Normotensive hydrocephalus = accumulation of CSF in brain with no change in pressure, drainage is slightly compensating
- Causes:
    - Congenital malformation, tumour, inflammation, haemorrhage
- Mounting pressure can squeeze brain against skull and destroy brain tissue
    - Cortex/outer portion of brain = important functions but damaged first
        - ∴ V severe issues are common
- More common in infants
    - Skulls fontanels have not closed = more room for brain to expand
- Adult skulls have fully ossified = no room for cranial enlargement
    - ∴ Fluid increase leads to rapid increase in ICP
- Treatment → creation of a shunt (bypass) to drain excess CSF from the brain

Normal vs. Abnormal EEG

- Large bursts of activity are easy to identify
    - E.g. epilepsy, barbiturate poisoning
- Conditions associated with loss of activity are more difficult to identify
    - Haematoma and embolism = slow down due to cellular damage
        - Look like theta waves → light sleep

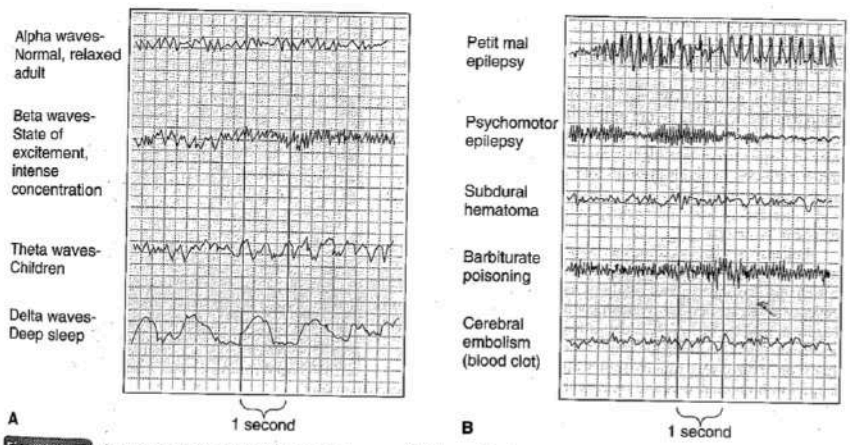
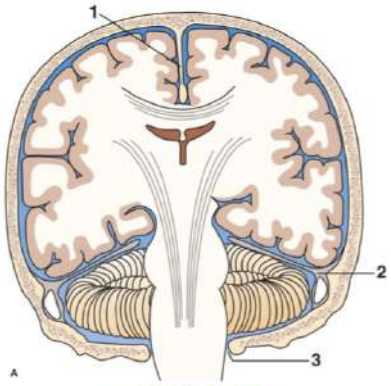


Figure 10-13 **Electroencephalography. (A)** Normal brain waves. **(B)** Abnormal brain waves.

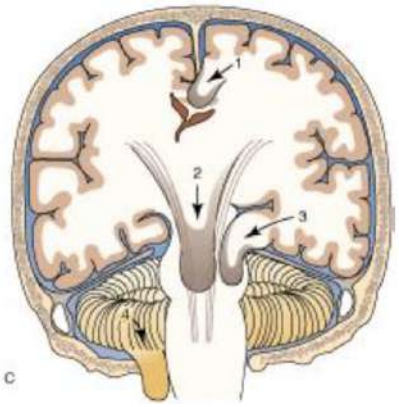
Brain Herniation

- Associated with increased ICP = pushes the brain out of position
- Brain tissue is compressed into the:
    - Center of the brain (2)
        - Lose ventricular space = ↑ pressure
    - Against bone (4)
    - Against rigid folds of the dura mater (1, 3) esp. concerning the brainstem
        - Compression of the occulomotor nerve is an early sign
            - Manifests via erratic or lacking eye motor responses
        - Can also compress other cranial nerves

1. The falx cerebri = extension of dura separating the cerebral hemispheres
2. Tentorium cerebelli = extension of dura between the cerebellum and occipital lobe
3. Foramen magnum = hole at the base of the skull through which the spinal cord passes



1. Herniation of cingulate gyrus under falx cerebri
2. Central or transtentorial herniation
3. Uncal herniation of the temporal lobe into the tentorial notch
4. Infratentorial herniation of the cerebellar tonsils



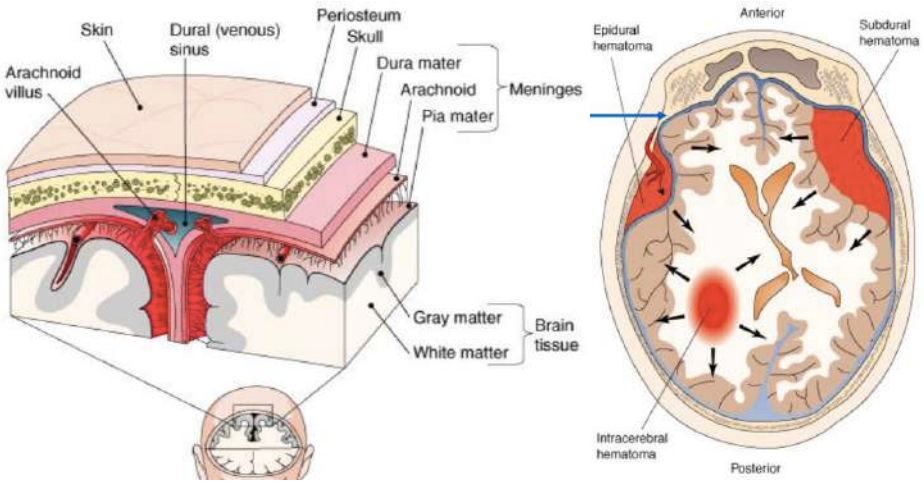
Traumatic Brain Injury

- <u>Primary injuries</u> → damage due to impact
    - Microscopic damage: concussion, diffuse axonal injury
    - Less common than secondary injuries in adults, more common in teenagers

- Secondary injuries → damage due to:
    - Haemorrhage
    - Ischaemia
        - Ischaemia and haemorrhage = related to age and cardiovascular risk
    - Infection (meningitis, encephalitis)
        - Common in children
    - Increased intracranial pressure
- Traumatic brain injury = brain bounces against skull = contusion
- Damage = natural inflammatory response = more damage than good
    - Endogenous cytokines = inflammation = phagocytic uptake of astrocytes and glial cells that do not regenerate = detrimental
    - "Protective" inflammatory mechanisms do the damage
    - Treatment can involve hypothermic procedures to slow down inflammatory pathways and slow damage
- Cerebral concussion → due to blow to the head or sudden movement of brain against the skull as in violent shaking
- Head trauma can lead to injury within skull

Haematoma

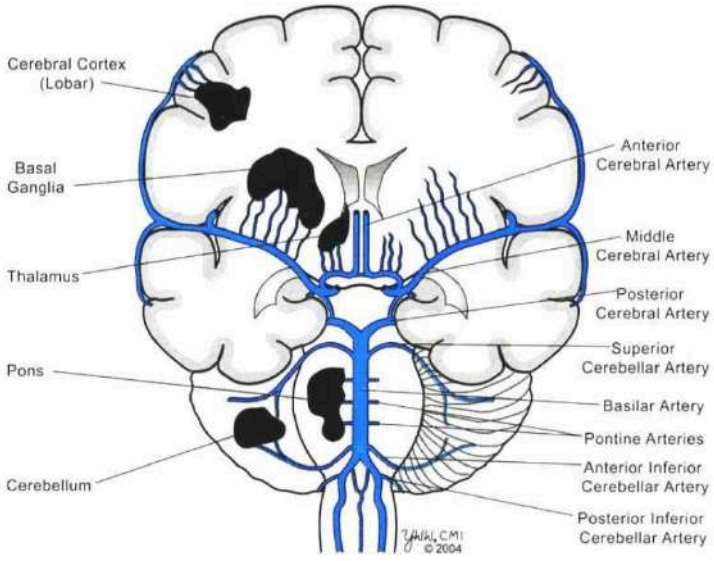
- Increase ICP can lead to hydrocephalus but also internal blood loss
- Haematoma → solid swelling of clotted blood within the tissues, outside the BVs
- Categorised based on localisation
- Epidural hematoma → bleeding between dura mater and skull
    - Epidural space = meningeal arteries = BVs that carry blood to and from meninges
    - Rapid bleeding in the brain = unconsciousness
        - May be followed by brief lucid period
- Subdural hematoma → tear in the wall of the dural sinuses ∴ between dura and brain tissue
    - Subdural space = between dura and arachnoid
    - Result of a tear in small bridging veins that contact veins on cortical surface to dural sinuses
    - These veins readily broken in head injury
    - Bleeding can occur between dura and subarachnoid (subdural hematoma) or into CSF-filled subarachnoid space (subarachnoid hematoma)
    - Slower bleeding = gradual development over days or weeks bc damage to smaller BVs or tissue itself ∴ blood accumulates
- Intracerebral hematoma → bleeding into the brain tissues



Stroke (Cerebrovascular Accident/"Brain attack")

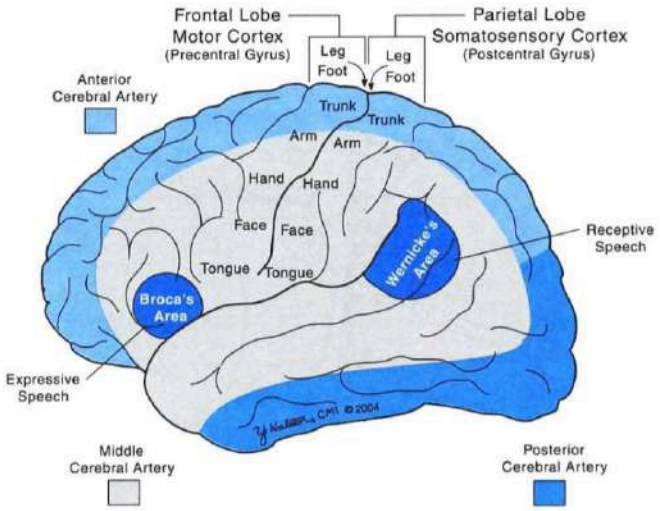
- Ischemic stroke
    - Caused by interruption of blood flow in a cerebral vessel (more common)
    - Large vessel (thrombotic) → artherosclerotic disease
    - Small vessel or penetrating artery disease
        - Lacunar infarct → small vessel stroke in deeper parts of brain or in the brainstem
        - Difficult to locate but obvious symptoms bc target primitive areas
    - Cardiogenic embolic → peripherally clotted blood/other elements that obstruct brain circulation
- Hemorrhagic stroke
    - Caused by bleeding into brain tissues due to hypertension, aneurysm (outpouching or dilation in BV wall), head injury, arteriovenous malformation, blood dyscrasias
    - Lack of blood supply to tissue supplied by disrupted blood flow
- Transient ischemic attacks ("brain angina") → mini-stroke
    - Reflects a temporary disturbance in focal cerebral blood flow, which reverses before infarction occurs
    - Associated with stroke history or prognostic in likelihood of stroke
- Causes:
    - Common cause is a blood clot that blocks blood flow to an area of the brain
    - Rupture of BV resulting in cerebral haemorrhage + brain tissue destruction
- Common in those > 40 yrs, those with arterial wall damage, diabetes, hypertension
- Smoking and excess alcohol intake increase risk of stroke
- Localisation in brain corresponds to symptomology
    - E.g. damage to Broca's area = Broca's aphasia, damage to basal ganglia = Parkinsonian syndrome
    - Damage to internal capsule's white matter in inferior part of cerebrum may cause paralysis of the side opposite the affected area
- Treatment:
    - Restore blood flow by surgical removal of clot or using clot-dissolving medication
- If damage has already occurred, intervention tries to prevent another one either pharmacologically or lifestyle changes

Common Sites of Intracerebral Haemorrhage



Cerebral Ischaemia

- Cerebral ischaemia in arteries that supply blood to major areas
    - Determine what area is ischemic based on patient's symptom presentation



Cerebral ischemia: location and distribution of major arteries

Epileptic Syndromes

- Increase in synchronisation in the brain = switches on and off
- Generalised seizures = involve both hemispheres
- Partial seizures = begin in one cerebral hemisphere
    - Localisation of seizure characterises symptoms
        - E.g. occipital = flashing lights, temporal = sensory hallucinations
    - Mostly maintain consciousness
- Secondarily generalised seizures = begin in one hemisphere and spread to other
- Generalised + 2° generalised = unconsciousness
- Seizures can interrupt clearance pathways of metabolic wastes = other types of toxicity
- Seizure types:
    - Absence (petit mal) → disturbances in consciousness
    - Atonic → loss of muscle tone
    - Myoclonic → muscles contract rapidly, possible loss of consciousness
    - Tonic-clonic (grand mal) → muscle contraction and loss of consciousness
        - "Hollywood" seizures, periods of muscle contraction and relaxation
    - Generalised convulsive status epilepticus → seizure ongoing beyond 2 minutes or seizures continuing without recovery between them
- Loss of consciousness + muscle tone = risk of falling + subsequent head injuries

Dementia

- Category of neurodegenerative diseases with various subtypes
- Cognitive decline caused by damage to association areas of the cerebral hemispheres or subcortical areas linked to memory and learning
- Many dementias are associated with abnormal inclusions in the brain
    - Can be structural deformation in the brain
- <u>Alzheimer disease</u>
    - Amyloid plaques + neurofibrillary tangles cause signalling pathway deficits
- <u>Pick disease</u>
    - Frontotemporal dementia

    - Atrophy of frontal and anterior temporal lobes of the brain = cognitive deficits
        - With normally aging, brain matter is lost. Loss of brain matter beyond what is normally seen for person of that age
- Prion diseases or Creutzfeldt-Jakob disease
    - Caused by prion = an infective protein agent
    - Causes degeneration of pyramidal and extrapyramidal systems
    - Gross and fine motor control affected
- Almost all untreatable bc brain matter is non-degenerative, possibly removed amyloid plaques in animals
- Multi-infarct dementia → brain damage from chronic ischemia such as those caused by a series of small strokes
- Wernicke-Korsakoff syndrome
    - Results from chronic alcoholism, malnutrition, gastric surgeries
    - Caused by vitamin B12 (thiamine) deficiency which interferes with glucose metabolism, the brain's main nutrient = brain cannot respire = cells die
    - Easily treatable!
- Inherited atrophy of brain structure: Huntington disease
    - GABA, GABA receptors and acetylcholine are found to be reduced
    - Dopamine pathway preserved
    - Dopamine + Ach work reciprocally ∴ imbalance of ACh pathway may contribute to the manifestations of the disease
    - Treat with restoring balance of neurotransmitters

Alzheimer's Disease

- Brain disorder due to degeneration of cerebral cortex + hippocampus → cerebrum
    - Cerebellum and motor functions intact
- Causes intellectual impairment, mood changes, confusion, memory loss
- Change in the brain:
    - Amyloid-beta protein-forming plaques
    - Neurofibrillary tangles involving protein tau prevents communication between cells and kills neurons and the brain shrinks → atrophy
        - Esp. hippocampus + basal forebrain involved in thinking + memory
    - Decreased acetylcholine production due to loss of neurons in basal forebrain
- Disease stages (DSM stage classification):
    1. Short-term memory loss
    2. Confusional stage
        - Disorientation, lack of insight, impaired hygiene and language use
        - Sundown syndrome = increased confusion and restlessness
    3. Incontinence, inability to recognise family and friends
        - Loss of bodily functions as well as cognitive