NEUROSCIENCE NOTES

L1 – WHY HAVE A NS?

WHAT DO WE KNOW ABOUT THE NS?

- That we are thinking is the only thing we know for sure
- Cogito ergo sum = I think, therefore I exist (Descarte)
- Being aware of our thoughts makes us recognize our mental experience
- Thought is a private experience (our thoughts are part of our definition of ourselves)
- We have a mental experience of our existence
- What else are we aware of?
    - We're in a universe, in which we are embedded as actors
    - A variety of attributes about ourselves (internal state/how we are feeling)
    - A capacity for action
- These properties/attributes of the mind are a product of the operation of the NS
- If we compromise the NS, we compromise our awareness

HOW DO WE KNOW WHAT WE KNOW ABOUT THE NS?

What we now recognize as the action of the NS, was thought of as the conscious properties of the mind, and was not always attributed to the brain's function.

Ancient Egypt	• Believed health of the body and mind, like viability of the land related to flow of fluid • Health or mind problems would result from too much or too little flow (like with the Nile and land viability) • The heart was believed to be the centre of the mind as it was the centre of flow in the body
Ancient Greece	• Hippocrates: 'from nothing else but the brain comes joy, delights, laughter and sports, and sorrows, griefs despondency and lamentations'
Roman Empire Galen	• Accepted the classical explanation of bodily fluids being important in health • Brain was thought to be important in intellect • Liver was thought to have animalistic/instinctive functions • Heart was thought to have strong passion and growing and living • Tripartite soul = brain, liver, heart • Galen synthesized a corpus of anatomy, and described a '3rd system', which was the NS, supply tissues and connecting them to the brain and spinal cord
Renaissance	• Fluid flow as being a mechanistic explanation of the mind • Spaces of CSF in the brain proved this

WHY ISN'T THE BRAIN THE SEAT OF REASON AND EXPERIENCE?

- Aristotle held a cardio-centric view of the mind
- Why the heart and not the brain?
    - The heart moves, the brain doesn't
    - Simple animals move and react, but have no brain
    - Warmth (symbolic of life) emanates from the body's core (the heart)
    - All known civilizations thought the heart was the centre of conscious being
- Observation of sophisticated animals with larger, more convoluted brains, showed they ran hotter → more heat is generated by the heart, so more cooling of the blood is needed
- Language contains ample references to the heart being the locus of our mental experience

DESCARTE'S VIEW OF BRAIN FUNCTION

- The brain's function was reliant on fluid and tubes, and the pineal gland
- Fluid in ventricles was pumped down to muscles, initiating movement
- Fluid was transmitted from sense organs to ventricles of the brain

NEUROLOGY

- Neurology = studying what happens when people damage their brains
- The study from neurology advanced us from a mechanistic brain model to a modern brain model
- Paul Broca studied the relationship between brain damage and the resulting functional consequences
- Patients with damage to the right temporal lobe had difficulty producing speech, but could hear and understand speech

GENOME AND THE NS

- An animal's genome doesn't give much information about its NS
- Arabidopsis thaliana is a complex organism with 27,000 genes, but no NS, and hence cannot move
- Humans have 21,000 genes and a very complex NS, with a huge area dedicated to motor control
- Corynactic californica is a simple, sessile invertebrate with a NS comprising a simple network of nerve cells

EGO-CENTRIC EXTERNAL UNIVERSE

- Action of the NS reveals the universe to ourselves
- We tend to think the external/real world has properties which we perceive
- However, these properties are the conscious experiences generated by the NS
- The NS generates our experiences of ourselves and the external world

L2 – CELLULAR BASIS OF NEURAL FUNCTION

HOW DO NEURONS AND THE NS WORK?

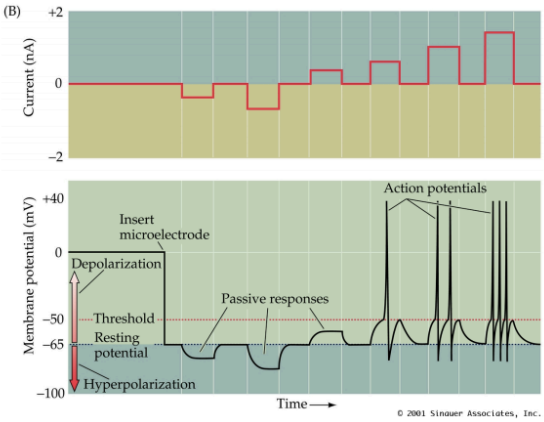
- The NS doesn't seem as though it's made of cells
- '3 repugnant ideas' of how the NS worked (1700s):
    - Spirits running through hollow nerve fibres, conveying impressions to the brain and activating muscles
    - Mini explosions caused by fermentation from the missing of fluid in nerve cells with blood, which activated muscles
    - Vibrations, with light of different energies transferring vibrations to nerves, conveying sensations to the brain
- Experimentation revealed problems with these 3 theories:
    - Limbs don't increase volume when muscles are activated
    - Nerves cut underwater didn't result in bubbling ferment
    - Ligation of nerves didn't cause accumulation of fluid
    - Fluid couldn't move fast enough to explain the speed of the NS

ELECTRICITY

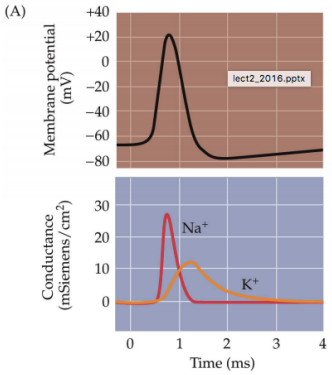
- In the 1700s, it was through that perhaps the NS might work by electricity, but how is electricity contained within nerves
- Luigi Galvani demonstrated that nerves convey 'animal electricity', by which they activate muscles
- A spark jumping from a scalpel to a nerve will cause muscle contraction
- Electricity is needed to cause a muscle contraction
- Galvani concluded that the spark must've activated the natural process by which nerves activated muscles
- Aldini managed to activate facial muscles by stimulating the brain of severed heads
- These studies however lacked cellular resolution

CELLS IN THE NS

- Cells in the NS are specialized for transmission of electrical signals
- Electricity in neurons arises from differences in charge across its cell membrane
- Can be measured using small electrodes formed from hollow glass tubes
- Recording of the electrical potential difference across the membrane of a neuron during electrical stimulation:
    - Injecting negative current causes hyperpolarization
    - Injecting positive current causes depolarization
    - At a certain level of positive current being injected, an AP is initiated



- Electricity in neurons is created by selective movement of ions across the cell membrane
    - Ion transporters move ions against their concentration gradients (electrogenic pump)
    - Ion channels allow ions to diffuse down their concentration gradients



- Electrical impulse travels along the neuron as a result of voltage gated ion channels opening and activating adjacent voltage gated ion channels
- Myelination increases conduction velocity → salutatory conduction, where the electrical impulse jumps from node to node

MECHANISMS OF NEURAL TISSUE

Neurons

- Nerve tissue is excitable (generate electrical events/impulses)
- Cell theory, although being broadly accepted, was not initially applied to the NS
- In the late 1800s, improvements in microscopes and histological methods allowed us to see that the NS is composed of nerve cells, and how these cells are organized in the NS
- Neural tissue was believed to be a reticular network, not composed of individual cells
- Purkinje was the first to suggest the NS was composed of discrete cells
- Purkinje preserved, sectioned and viewed parts of the brain, and in doing so described a large neural cell type in the cerebellum
- Silver staining of single nerve cells in tissue showed their long, irregular shape
- Cyto-architecture showed different brain regions to have different neuronal organisations
- By the end of the 1800s, the neuron was found to be the anatomical and functional unit of the NS

- Terms neuron, axon and dendrites were introduced

Neural Connectivity

- The nature of neuronal connectivity was still unknown
- If neurons are discrete cells, how does an electrical impulse in 1 neuron affect another neuron
- A spark jumping from neuron to neuron was established with the electrical nature of the NS, however, how could we test this and are there other mechanisms?
- Neuromuscular junction suggested that fusion is not necessary for signal transmission, as motor neurons terminate at muscle fibres
- Some saw this as evidence proving that fusion doesn't occur, others saw the point of contact between neurons and muscle fibres as fusion

Autonomic NS

- Knowledge of neural connection came from the autonomic NS
- Different divisions of the ANS innervate the same organ, often with opposing effects
- Stimulation of the parasympathetic vagus nerve slowed HR, but stimulation of the sympathetic nerve increased HR
- How could a spark from a nerve, which is supposedly 'fused' to the heart, do both opposing actions?
- We now know that synaptic transmission is initiated by electrical events but itself is a chemical event, allowing for this differentiation

L3 – NEURAL COMMUNICATION AND PLASTICITY

Neural communication was believed to either arise from:

- Neurons that are connected/fused
- Gaps between neurons, which the signal must pass through

CAJAL

- Cajal used superior staining in developing neural tissue
- He discovered growth cones of neurons which provided evidence of the dynamic morphology of growing neurons
- This raised the question of how fixed the neuronal structure in the brain is?

SHERRINGTON

- Sherrington believed some form of functional junction must exist between neurons, based on several observations:
    - His studies of degeneration of the NS always resulted in a discrete, demarcated pattern of loss, rather than diffuse loss (neuronal death only caused death of a single neuron, not the entire network)
    - The reflex responses he studied were slower than expected by the speed of nerve conduction (there was a delay somewhere)
    - Something makes reflex conduction unidirectional
- Sherrington and Cajal proposed there must be a junction between neurons, and termed it the synapsis (later becoming synapse)
- The synapse was purely hypothetical at this point (we only were able to see the synapse in the 1950s when the electron microscope was invented)

INFORMATION PROCESSING

- Solid state switches can be likened to the brain and neuronal networks
- A transistor has 3 connections; voltage in 1 determines current flow through the other 2
- This allows transistors to act as switches
- Switches can be combined to make logical elements/gates

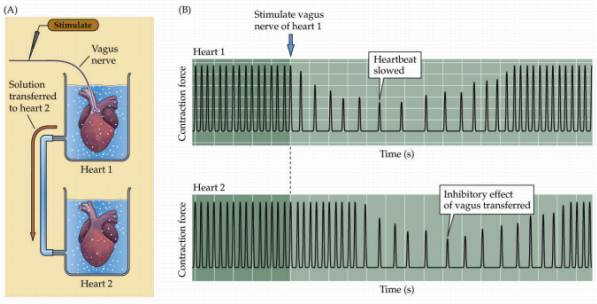
- Switches can be used to represent logic because we can encode ideas into switches
- Gates can perform Boolean (true or false) logic → this is the basis of all machine computation

SYNAPTIC TRANSMISSION

- Neurons must transmit signals, integrate, process and store information
- Connections between neurons (synapse) act as points of control over information transmission
- Synaptic transmission involves synaptic vesicles docking and releasing NT into the synaptic cleft
- NT diffuses across the synaptic cleft and binds with receptors on the post-synaptic neuron

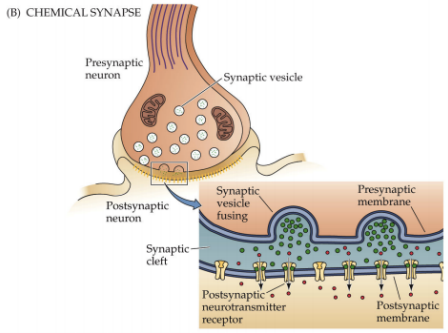
How did we come to learn how synaptic transmission worked?

- Until the end of the 1800s, it was thought that synaptic transmission was electrical
- George Oliver and Hendry Dale conducted experiments with plants and fungi which mimicked the effects of nerve stimulation on peripheral structures
- Chemicals affected the NS and signal transmission in the NS, demonstrating that synaptic transmission was chemical, not electrical
- Applying crushed up adrenal glands to blood vessels caused vasoconstriction → this substance is endogenous, so the body can synthesize product which act on tissues like the NS does
- Chemicals such as adrenaline which mimicked the effect of stimulating a nerve raised the question of whether synaptic transmission naturally involved a chemical step
- Otto Lowei demonstrated the chemical nature of synaptic transmission
    - Vagus nerve to the heart stimulated
    - Heart submerged in fluid
    - Chemical released upon stimulation collected in this fluid
    - Fluid applied to a secondary heart
    - Both direct nervous stimulation and indirect chemical stimulation caused slowing of HR



CHEMICAL SYNAPSES

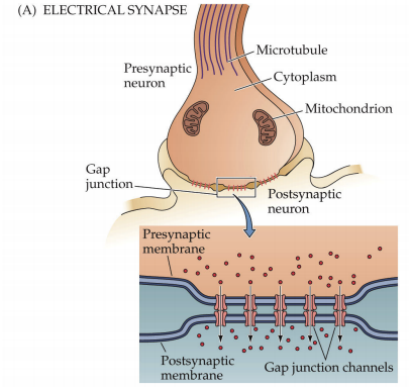
- Have huge variety (over 100 NTs with many receptors)
- Involve energy dependent processes such as synthesis, release and reuptake
- Slow due to complex energy dependent release machinery, diffusion and post-synaptic receptor activation
- Delay in time is mostly due to the release machinery, not diffusion of NT across the synapse



ELECTRICAL SYNAPSES

- Gap junctions between neurons which carry on the AP
- Excitation is the only possible effect on the post-synaptic cell
- Passive transmission → no complex energy dependent release machinery

- Fast → no long latency due to release machinery, diffusion and post-synaptic receptor activation
- Useful for synchronization of neuronal groups (e.g. respiratory neurons)
- Bi-directional
- Seen in foetal and embryonic development, and are eventually replaced by chemical synapses

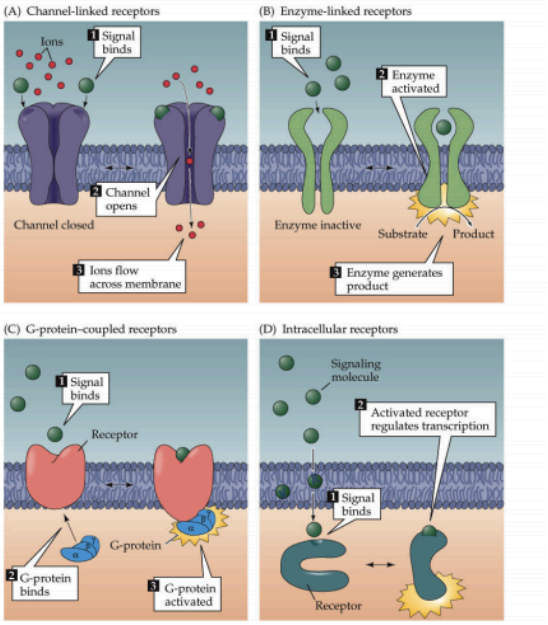


NEUROTRANSMITTERS

- Defining a NT:
  - Stored in neurons terminals (in vesicles), or able to be rapidly synthesized and transported to the terminals
  - Released into the synapse when AP arrives at terminals (Ca2+ mediated process)
  - Short acting, therefore there must be a mechanism for stopping the NT's action (degrading it or taking it back up)
- Very small molecules
- Can be amino acids, purines, biogenic amines and peptides
- Nothing can be inferred about the post-synaptic effect of a NT from its chemical nature/structure
- NTs simply activate a post-synaptic receptor
- It's the receptor which has the effect on the post-synaptic neuron

RECEPTORS

Channel Linked Receptors	• NT binds to receptor and opens an ion channel • Ions move in/out causing hyperpolarization/depolarization • Voltage gated channels are found at dendrites, axon and terminals • Ligand gated channels are found at dendrites (post-synaptic membrane)
Enzyme Linked Receptors	• NT binds to receptor, causing catalysis carried out by the receptor itself
G-Protein Coupled Receptors	• NT binds to receptor, activating a G-protein • G-protein goes on to effect the cell
Receptor Tyrosine Kinases	• NT binds to receptor, causing phosphorylation downstream
Intracellular Receptors	• NT moves into cell and activates a receptor inside the cell (not on the surface)



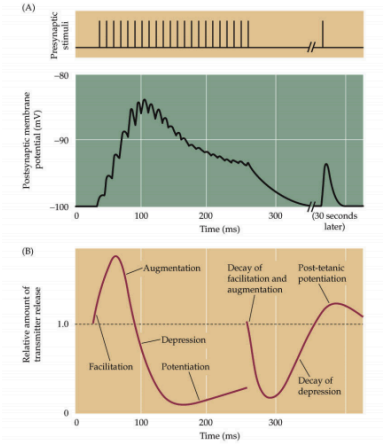
LONG TERM POTENTIATION AND PLASTICITY

Short-term vs Long-term

- Neuronal connectivity can be changed and is plastic
- Short-term changes in the size of the effect on the post-synaptic neuron are due to changes in the amount of NT released
- However, some changes to synapses last longer, as a result of molecular signaling pathways in the post-synaptic neuron, which affects intracellular processes (protein function, gene expression etc.)

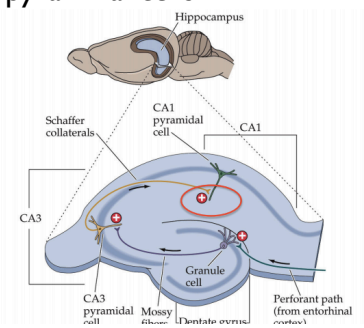
NMJ

- At the NMJ, repeated stimulation causes an exaggerated response, as responses summate and the cell reaches tetanus
- Following this repeated stimulation, the muscle cell will give a larger response to the same stimulus

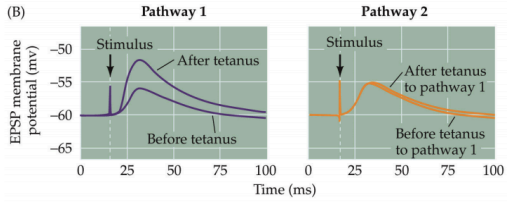


Hippocampus

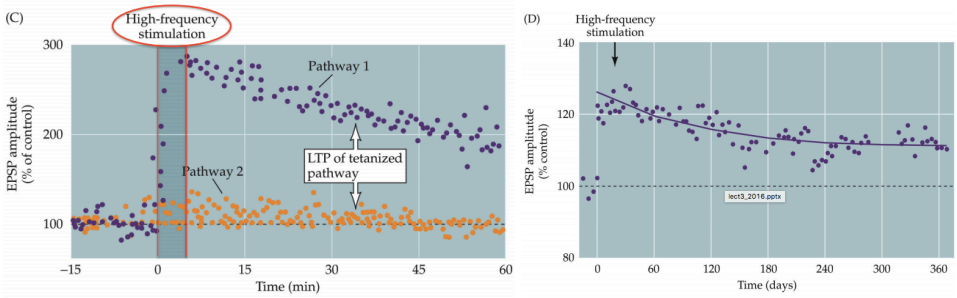
- Inputs from the perforant pathway excite granule cells
- Granule cells excite CA3 pyramidal cells
- CA3 pyramidal cells excite CA1 pyramidal cells



- Inputs from CA3 cells to CA1 neurons display LTP
- Stimulating CA1 cells tetanically resulted in the CA1 cell being more responsive than CA1 cells that were not stimulated tetanically

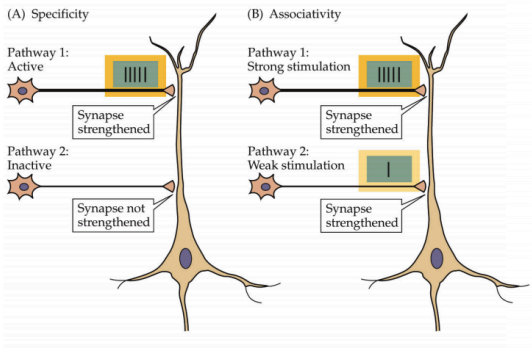


- Even after hours, tetanically stimulated CA1 cells were more responsive and more efficacious



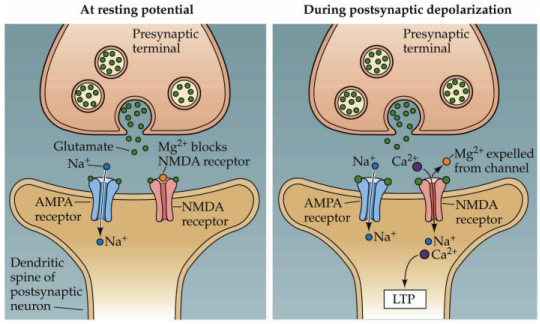
Specific Plasticity vs Associative Plasticity

Specific Plasticity	• Continuous stimulation of 1 synapse strengthens that synaptic connection • No other synaptic connections on that post-synaptic neuron are strengthened
Associative Plasticity	• Continuous stimulation of 1 synapse strengthens that synaptic connection • Other synaptic connections on that post-synaptic neuron are also strengthened



Receptors in LTP

- LTP is mediated by the type of receptor activated
- AMPA glutamate receptor = ligand gated Na+ channel, which causes depolarization when activated
- NMDA glutamate receptor
    - Ligand and voltage gated cation channel
    - At rest, the pore is blocked by Mg2+
    - Glutamate binds, but the receptor cannot conduct
    - Depolarization from AMPA receptor causes Mg2+ to be expelled from the pore
    - Na+ and Ca2+ influx
    - Ca2+ causes intracellular changes and LTP:
        - Ca2+ in the cell can increase the number of AMPA receptors, making the cell more excitable
        - Ca2+ can alter gene expression, changing the structure of the synapse



Protein Synthesis and LTP

- LTP is dependent on protein synthesis
- Protein synthesis is needed to change the structure of the synapse and respond to inputs
- Blocking protein synthesis blocks LTP