

Neuroscience Notes

Neural organisation-presumed prior knowledge

- We should know the terms for anatomical orientation, definition of the CNS and PNS, terminology used to describe the cells of the nervous system, major features of the brain spinal cord including an understanding of the organisation of grey and white matter and the ventricular system, major division of the brain stem (**midbrain**, **pons** and **medulla**) and important features of the **forebrain** and major sub-cortical structures (**basal ganglia**, **amygdala**, **hippocampus** and **thalamus**).
- For the brain there is the **rostral** (anterior) and **caudal** (posterior) axis and the **dorsal** (superior) and **ventral** (inferior) axis while the spinal cord has the **rostral** (superior) and **caudal** (inferior) axis as well as the **dorsal** (posterior) and **ventral** (anterior) axis. There is also the medial-lateral plane where medial is in the middle (corpus callosum) while the lateral is out towards the periphery. There are 3 planes that can be taken, there is a **horizontal** cross section (chop the top off), and a **coronal** cross section (chop the front off) and the **sagittal** cross section (chop a side off).
- The **cerebrum** is the major part of the brain with the **diencephalon** underneath, which has the **midbrain** at the top of the brain stem, the **pons** as the middle dilated part of the brain stem and the **medulla** as a lower region in the brain stem. The **cerebellum** sits behind the brain stem.
- The spinal cord is divided into different sections with from most superior there is the **12 cervical nerves**, **12 thoracic nerves**, **5 lumbar nerves**, **5 sacral nerves** and **1 coccygeal nerve**. We see an enlargement of the spinal cord in the cervical and lumbar regions as well as seeing the **cauda equina** which is where a bunch of the lower spinal nerves protrude from.
- The brain is composed of **grey matter** (neurons and neuropil and astrocytes, oligodendrocytes and microglia) and **white matter** (myelinated and unmyelinated axons, astrocytes, lots of oligodendrocytes and microglia). There are also **ventricles** in the brain which are **CSF** (cerebrospinal fluid) filled cavities in the brain and is where CSF is produced. There are 4 ventricles in the brain, two of which are the lateral ventricles, the third is central and leads inferiorly down towards the fourth ventricle.
- The CNS is mainly divided into the **cerebrum**, **diencephalon** (thalamus and hypothalamus), **cerebellum**, brain stem (midbrain, pons and medulla) and the spinal cord.
- The **dorsal root ganglia** receive stimulation from the periphery and send information into the spinal cord via the **dorsal roots** (afferent fibres) which go towards the brain and various controlling centres. In response to the stimuli, efferents are sent out to the periphery by **ventral roots**.
- The brain stem sits below the **thalamus** with the brain stem having the midbrain, then the pons and then the medulla. The spinal cord extends the brain stem and sits below the medulla.
- The cerebrum consists of the **left** and **right cerebral hemisphere**. It consists of the **frontal lobe**, **parietal lobe** (sits near the top of the cerebrum separated from the frontal by the **central sulcus**), the **occipital lobe** (sits at the back above the cerebellum) and the **temporal lobe** (sits below frontal and parietal lobes and above the brain stem). The **Sylvian fissure** separates the temporal lobe from the two lobes above it.
- The **basal ganglia** (functions in control of voluntary motor movements, procedural learning and routine behaviours or habits and emotion) sit in the cerebrum lateral to the thalamus and medial to the **amygdala** (functions in memory, decision making and emotional reactions and is part of the **limbic system**).
- The **hippocampus** also sits in the forebrain and functions in the consolidation of memory for short and long term memory and in spatial memory that enables navigation.
- The cellular components of neural tissue include neurons, microglia and **macroglia** (astrocytes and oligodendrocytes).
- The **oligodendrocytes** (CNS) and **Schwann** cells (PNS) are glial cells that provide insulation to nerve axons. The lipid bilayers of the oligodendrocyte cell membrane forms an insulation (myelin sheath) giving the axonal bundles a white appearance and hence fibre tracts in the brain and spinal cord are called white matter.

- Axons in the periphery cluster together to form nerves (Collections of thousands of individual axons within a common external connective tissue sheath-**epineurium**). Within the nerve, axons are sub-grouped into fascicles surrounded by a **perineural sheath (perineurium)**. Surrounding a single nerve fibre is the **endoneurium**.
- The **astroglia** (astrocytes) have numerous functions including the recycling of neurotransmitters and maintaining the ionic composition of the ECF. The microglial cells are innate immune cells that are related to macrophages.
- Neurons are excitable cells that utilise a transmembrane electrochemical gradient to generate electrical signals. The action potential is a transmembrane electrical event that propagates along axons. It's produced by precisely controlled passage of sodium and potassium across the membrane via voltage-gated channels. Signals are passed between neurons by synapses, the vast majority of synapses in the nervous system utilise chemical neurotransmission. Chemical neurotransmission involves complex molecular synthetic and transport mechanisms. Neurotransmitter released from the postsynaptic terminal diffuses across the synaptic cleft and interacts with neurotransmitter receptors on the postsynaptic membrane which can initiate a variety of events, depending on the nature of the receptor and the biochemical processes it activates.

Lecture 1:

- The only thing that we know for sure is that we are thinking. That is we recognise our mental existence- I think therefore I am. We are aware of a universe in which we are embedded actors with a variety of attributes about ourselves in what we may call our internal state or how we are feeling and we are also aware of having a capacity for action.
- The ancient Egyptians thought that the health of the body and the mind like the viability of the land was concerned with the flow of fluids and problems occur when there is too much or too little flow. The centre of flow in the body is the heart.
- Galen, a Roman surgeon admired Hippocrates and accepted the brain as the seat of the intellect and also accepted the classical explanation of humours of the body. Animalistic and instinctive functions were assigned to the liver, the strong passions and the “growing and living” to the heart. Much was learnt about the brain from treating injured gladiators as the Romans permitted themselves direct observation and investigation through dissection of corpses and animals. Galen made numerous discoveries and synthesised a corpus of anatomy including the most complete description of the “third system” to supply the tissues (the nerves) and their connections to the brain and spinal cord. The Renaissance reinstated the importance of detailed observation and questioning of doctrine, but the primacy of the humours as mechanistic explanation prevailed.
- The brain was not considered to be the seat of reason and experience as Aristotle held a cardio-centric view of the mind contrary to Hippocrates and the growing acceptance of the brain as the seat of the mind. The heart was chosen as it moves unlike the brain and simple animals move and react despite having no brain. It was also chosen as it provides warmth and all known civilisations held the heart to be the centre of the conscious being.
- The left **temporal lobe** functions to produce speech. Professor Paul Broca found this due to a patient that could only respond with “Tan” to anything, despite being able to understand what people were telling him.
- The organism *Arabidopsis thaliana* is a distant relative of ours and has more genes than us despite not having a nervous system. *Corynactis californica* is a simple sessile invertebrate animal that has very little tissue specialisation and a nervous system comprising a network of nerve cells.
- The brain regions associated with action include the **motor areas** of the cerebral cortex, the **basal ganglia** which are subcortical structures, the **cerebellum** (has about as many cells as in the cortex- just highly convoluted) and the **brain stem motor nuclei**. Further out the **motor neurons** receive the signals from the brain and lead to movement.
- The world that we see is predominantly light- electromagnetic radiation- what is actually there may in fact be different to what we experience. Alfred North Whitehead states that nature is a dull affair, soundless, scentless, and colourless and merely the hurrying of material- it is what we give it. We think that the external or real world has the properties that we perceive, but these properties are the conscious experiences generated by the actions of the nervous system. So one of the things our nervous system does is generate our experiences of ourselves and the external world.
- Compared to other animals (where most of the brain is dedicated to motor or sensory function), a small proportion of the primary areas (where input stimuli comes in for detection and reception) of the brain is taken up for sensory or motor function. Most of the rest of the human brain is for construction of abstract things based on sensory information.
- The nervous system reveals the universe and ourselves in it, provides a capacity for action and controls the **milieu interieur**- homeostatic regulation (physiological properties).
- Everything that has or ever will exist is only known to us through the action of our nervous system.
- All of sweating, experiencing loneliness, dreaming and feeling exhausted are associated with specific activation of the nervous system. The colours we perceive are only there as that’s what our brains perceive.
- William Harvey deduced that the heart was like a pump and thus this helped us decide that the heart wasn’t like a furnace that contained our spirits and emotions but rather functioned just as a pump.

Lecture 2: The cellular basis of neural function.

- In the early 1700s we had three main ideas on how the nervous system works but simple experimentation was all that was required in order to disprove the theories. Nerves can't be rigid as they need to be flexible and floppy for movement. When electricity was discovered a solution to this issue was found.
- Luigi Galvani conducted a large number of experiments demonstrating that nerves convey electricity in animals in order to activate muscles in doing so he demonstrated that nerves have the capacity to transmit an electrical signal.
- The form of the cells in the nervous system suggests that their function is specialised for transmission of electrical signals. This can be measured by microelectrodes which can penetrate a neuron to stimulate the neuron, where the electrode measures the potential difference between the ICF and ECF such that the resting membrane potential is determined to be -70mV.
- The **graded potentials** causes slight changes to the RMP be it positive or negative, but a large enough positive increasing in the RMP to that of the threshold will stimulate an action potential to be generated which is of a constant magnitude and when we add more electrical stimulation we are only changing the frequency of the action potential rather than the magnitude of the action potentials.
- Cells set up an **electrochemical equilibrium** where the movement of ions is determined by both the concentration and electrical gradients such that even if there is a concentration drive of potassium out of the cell, the negative charge inside the cell draws potassium in leading to this equilibrium forming.
- We have **ion transporters** which move ions against the concentration gradient (Na⁺/K⁺ ATPase) for long term maintenance of the membrane potential which are **electrogenic** while **ion channels** allow ions to diffuse down their electrochemical gradient for the action potential to be generated. There is voltage gated (for action potential) and passive leak channels (for RMP). The Na⁺ and K⁺ ion channels are voltage gated and are key to creating the nerve impulse. The Na⁺ channels open quicker and have a larger conductance than the K⁺ channels that take longer to open and have a lower conductance but are open for a longer period of time.
- Upon threshold potential being released, there is an input of Na⁺ to the area leading to a local depolarisation, such that there is an opening of the Na⁺ channel for Na⁺ to run in (increasing the membrane potential-rising phase of action potential). There is then a spread of depolarisation for the AP to occur where only a relatively small amount of Na⁺ needs to rush in for there to be a change to the membrane potential. After a certain period of time the Na⁺ channels close and at approximately the same time the K⁺ channels will open allowing K⁺ to leave the axon (this process of K⁺ opening takes longer despite being initiated at threshold).
- The **myelin sheath** is made by glial cells in order to ensure that the spread of depolarisation occurs at the nodes (action potential jumps from node to node) such that it leads to a greater current density (more ions moving to the node) and thus increasing the speed of conduction down the axon.
- Neural tissue was determined to be excitable but it wasn't known how neurons communicated with each other. Prior to the discovery of neurons, most of neuroscience dealt primarily with brain function (Broca- localised functioning of parts of the brain). This was because cell theory had not been developed yet and microscope technology was still relatively primitive, so structures such as the synapse or dendrite had not been discovered.
- The **silver stain** was improved by **Cajal** and is still used today to examine the fine details of neurons. The stain allows us to stain the neurons giving us an ability to see them- it stains only 1% of the neurons such that we can differentiate between the neurons and pick them out rather than it being a big blob.
- After this staining technique was discovered the reticular theory (all neural tissue acts together in compartments) was replaced by the neuron doctrine (neurons act as discrete cells and we can tell it was discrete as other cells around an injured one may work fine and the area being innervated would still remain functional). It was concluded that the neuron was the anatomical and functional unit of the nervous system.

- There was an idea that neurons were fused together in order to transmit signals from one neuron to the other but there were significant arguments against it such as the evidence behind there being signal transmission at the neuromuscular junction. The motor neurons terminate at muscle fibres in a number of branches with club-like terminations (leading to discourse over whether this was fusion or not).
- Much of the knowledge about neural interaction came from examination of peripheral innervation, the innervation of skeletal muscle and the autonomic nervous system. It was recognised that different divisions innervated the same organ, with in many cases the effects of stimulation being opposite- stimulation of the parasympathetic **vagus nerve** slowed the heart while stimulation of the sympathetic neurons increased heart rate (hence nerves that were supposedly fused did opposing actions, disproving fusion).

Lecture 3: Neural communication and plasticity

- Cajal's recognition of superior staining in developing tissue led him to discover growth cones (growth of neurons in developing brain) and the evidence of the dynamic morphology of growing neurons (neuroplasticity). This led to Cajal's evidence leading to the destruction of the reticular theory (that neurons are static and all act together like a net) with **Charles Sherrington** postulating that functional junctions existed between neurons based on the observations that studies showed degeneration of the nervous system always resulted in a discrete, demarcated pattern of loss (rather than diffuse), reflex response were much slower than explicable by the speed of nerve conduction (must be some delay from first neuron to effector organ) and that reflex conduction was unidirectional. This led to the proposition that there must be a junction between neurons (a **synapse**). The synapse was hypothetical until electron microscopes were invented. As well as transmission of signals, the cells of the nervous system must also integrate, process and store information. The points of control over information transmission are the connections between neurons (the synapse).
- The scientist **Otto Loewi** was able to mimic the effects of sympathetic and parasympathetic nerve stimulation by applying the fluid collected during the stimulation to another non-stimulated heart. That is, he electrically stimulated the vagus nerve connected to a heart in solution and then transferred the solution to a non-stimulated heart and saw the inhibitory effect of the vagus nerve on both hearts such that there must have been neurotransmitter transfer (acetylcholine was discovered).
- A neurotransmitter is stored in axon terminals within vesicles or rapidly made in demand. It is released upon the action potential reaching the terminal and there are neurotransmitter specific receptors on the postsynaptic cell which are able to recognise and initiate the next step of transmission on the post-synaptic cell.
- There are **chemical synapses** (various types- over 100 neurotransmitters with a huge variety of receptors). There are 100,000 billion synapses in the human body. The chemical synapses have energy dependent processes occurring at them such as synthesis, release and reuptake and thus the transfer of an impulse across a chemical synapse is slow, due to the complex energy-dependent release, machinery, diffusion (across synaptic cleft-20nm-quick relative to the other actions occurring in the synapse) and post-synaptic receptor activation. Usually the neurotransmitters binding onto the postsynaptic neurotransmitter receptor causes a nerve impulse on the next nerve via depolarisation.
- The **electrical synapses** show a direct electrical connection between neurons which is seen in invertebrates mainly (at gap junctions- transfer of ions) but is also seen in humans in respiratory control (rare in humans though) so that all our functional cells of respiration are acting at around the same time (like how the ventricles of the heart pump at same time). The electrical synapses can only cause excitation (can't choose whether to be excitatory or inhibitory) on the postsynaptic cell and is a passive transmission (passing of current) with no complex energy-dependent release machinery. It's a fast transmission with no latency due to lack of complex energy-dependent release machinery, diffusion or post-synaptic receptor activation. Electrical synapses are good for synchronisation of neuronal groups (respiratory group) and are typically bi-directional with effects depending on recent or concurrent activity.

- A **vesicle** is a bundle of membrane containing neurotransmitter. There are proteins on the vesicle for sequestering neurotransmitter into the vesicle, transporting into the vesicle, transport around the terminal or docking of the vesicle under the right conditions and removal of the vesicle from the synaptic membrane (so it doesn't enlarge and stays a constant length).
- Receptors are large multimeric structures in comparison to the small sizes of neurotransmitter. The effect a neurotransmitter has on a system is defined by the receptor it binds with, which can be **channel-linked receptors, enzyme-linked receptors, GPCRs or intracellular receptors**.
- Neurons communicate through the release of neurotransmitters at synapses for either a directly or indirectly excitatory/inhibitory effect. Synaptic connectivity determines the pattern of activity in the nervous system but it's not static but rather it is dynamic (changeable), there is **neuroplasticity**. Short term changes in the size of the effect a synapse will have on the post-synaptic neuron are due to changes in the amount of neurotransmitter released. Some changes in synaptic efficacy last much longer (minutes, hours, days or years) with these changes involving the activities of molecular signalling pathways in the post-synaptic neuron that effect various intracellular processes from short-term changes in protein function to long term changes in gene expression.
- The rodent **hippocampus** (important in memory) is a nice preparation to study synaptic connections as the entire circuit can be seen in one plane and can therefore be tested quite easily in vitro. It is divided into different sections such as the **dentate gyrus** which leads to the **CA3 region** and then leads to the **CA1 region**. We can see **long term potentiation** (increase of strength in nervous pathways that have been previously used) is seen in the **Schaffer collaterals** (axons of CA3 going to CA1). To see this potentiation we record the **EPSP** (excitatory post-synaptic potential) in the CA1 neurons. It was observed that after we give a large amount of stimulus (to reach **tetanus**- can't transmit signal any faster- high frequency stimulation) and then give a single stimulus to the same neuron, an exaggerated response will be produced in the post-synaptic cell as a result of the burst of high frequency stimulation (tetanic pathway). The post-synaptic cell therefore became more excitable after the tetanic stimulation (more neurotransmitter released and more neurotransmitter picked up by the post-synaptic cell) such that there was a larger response.
- Potentiation can include **specificity** where only the synapse at which the strong stimulation occurs is strengthened or it can be shown through **associativity** where the synapse that received the strong stimulation is not the only one that is strengthened (pathways downstream are also strengthened).
- A mechanism for long-term potentiation is seen with glutamate and the **AMPA and NMDA receptors**. At a resting potential, there is some glutamate released from the presynaptic terminal which then binds to the AMPA receptor (Na^+ flows in) but not the NMDA receptor (as blocked by Mg^{2+}). The release of the glutamate occurs when there is an increase in ICF $[\text{Ca}^{2+}]$ in the presynaptic cells which is normally low as sequestered by cells, but increases through voltage-gated calcium channels. When a big voltage difference occurs across the postsynaptic cell then the Mg^{2+} is expelled from the NMDA receptor such that Ca^{2+} can flow into the postsynaptic cell and causes long term potentiation as there will be a larger EPSP. Tetanic stimulation keeps the NMDA channel open such that Na^+ and Ca^{2+} (Mg^{2+} is expelled from NMDA receptor) can come in and Ca^{2+} can alter biochemical pathways such as protein synthesis (plasticity of the neuron). The calcium coming in makes the synapse more excitable over time as Ca^{2+} causes more receptors to be produced and may stay activating the receptor for an extended period of time. Protein synthesis in the cell is increased as more Ca^{2+} comes in through as a result of action at the NMDA receptor. Protein synthesis hence plays a large role in the maintenance of LTP.
- Real neurons receive thousands of synaptic inputs and makes hundreds or thousands of synaptic contacts with other neurons (massive convergence and divergence is a fundamental feature of neuronal connectivity) unlike an electrical circuit. The synapses aren't binary but rather are **quantal** (variable) but essentially analogue (continuously variable-slight differences) in operation.
- When plastic change occurs we can question whether the changes are purely functional or macro-molecular changes or structural changes. We can also question whether the connections that control excitability being solid state.