Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory and cognition

Topic 3
The effects of activity, experience and deprivation on the nervous system
– Part 1 of 5

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Slide 3:
Hello, my name is Sam Cooke. I'm a lecturer, here, at King's College London and I work on learning and memory, the processes by which sensory experience and deprivation modify the brain to store information which can later be retrieved in the appropriate context. This work is important not just for increasing our understanding of how the brain works, but as you'll see at the end of this lecture, it's also highly relevant to understanding what goes wrong in disorders of the nervous system and for identifying potential treatments.

In this lecture, we will delve into how neural activity and sensory experience and deprivation can shape brain function. We will start with a quick refresher on synaptic plasticity, focusing on Hebbian synaptic plasticity which you will have already covered in a lecture by Professor Peter Geza. We will then apply this knowledge to start thinking about how the selective responses of neurons in the brain to neural activity or to sensory input, which – as we will see – are not necessarily the same thing, can be shaped through Hebbian synaptic plasticity to both segregate and integrate inputs.

For the purposes of this lecture, we will focus mostly on the visual system. As this is an important sensory modality for humans, it's intuitive to understand and it is probably the sensory modality that we have the deepest understanding of. However, it's also important to note that most of the concepts that we described are relevant to the postnatal development of other sensory modalities, such as auditory or somatosensory systems and to higher order functions, such as the development of language faculties or executive function.

Slide 4:
Okay, so let's briefly revisit Hebbian plasticity in order to make sure that we have a command of the key characteristics which will then enable understanding of how activity and experience can shape functional properties of the nervous system.

Slide 5:
Donald Hebb was a Canadian psychologist who used his knowledge of animal learning to identify some important theoretical criteria for the biological mechanisms that must support this critical faculty. In his famous text, *The Organization of Behavior*, Hebb describes many theories that remain influential to this day. Perhaps his most famous theory describes the process of Hebbian synaptic plasticity:

> 'When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that the efficiency of A, as one of the cells firing B, is increased'.

This somewhat wordy postulate is depicted pictorially here. The key concept to get hold of here is that existing chemical synapses on any one neuron arise from many different sources and are independently modifiable in strength based on the pattern of activity between the two connected cells. This fact would allow the synapse to serve as the major unit of information storage in the brain and reflect the history of activity at that synapse.

Although Hebb never discussed bidirectional modification, it is also important – for the purposes of this lecture – to appreciate that synapses can be strengthened or weakened, depending on whether pre- and post-synaptic cells are correlated in their activity or uncorrelated in activity respectively. Many of you may have come across the phrase, 'fire together, wire together', which was coined as a mnemonic device to understand and remember the key aspects of Hebbian plasticity.

I would like to point out that, while you may find it useful in some way, this slogan misses the mark and does not really describe Hebbian plasticity, because it implies that this plasticity is occurring between cells that are not already connected. A critical component of Hebbian theory is that synaptic plasticity allows experience to shape connections that already exist by increasing or decreasing their efficacy.

There are certain examples of rewiring that occur in the nervous system that may actually be critical for recovery of function after brain damage, or perhaps even aspects of learning and memory, but they are very different phenomenon from Hebbian plasticity.

Slide 6:
These processes of Hebbian plasticity are commonly studied experimentally using high frequency trains of electrical stimulation, known as a 'tetanus', which is applied to axonal pathways that are afferent to a population of neurons, whose activity can be recorded using methods known as electrophysiology.

This stimulation allows experimenters to guarantee electrical activation of pre-synaptic terminals at the same time as producing activation of post-synaptic neurons. The precise conditions that Hebb described as being necessary for the strengthening of synapses. Some experimental preparations also allow for the isolation of separate axonal inputs to the same cell, allowing experimenters to test the Hebbian theory that synaptic plasticity can occur at one synapse without affecting its neighbour – an important property, known as 'input specificity'.

Slide 7:
The most commonly studied form of Hebbian plasticity, known as 'long-term potentiation' or 'LTP', relies upon these electrophysiological stimulations and recording techniques. This very well studied phenomenon was originally discovered and characterised by British neuroscientist, Tim Bliss, and his Norwegian colleague, Terje

Lømo, in the hippocampus of anaesthetised rabbits. LTP is now commonly studied in surgically excised tissue, which helps greatly with positioning, stimulating and recording electrodes and for washing drugs on and off to determine underlying mechanisms.

Here is a slice of human hippocampus, which has been removed from a patient with otherwise intractable epilepsy as an emergency treatment. The neurons in this transverse hippocampus slice can be kept alive by maintaining it at the correct temperature in carefully oxygenated solutions that contain all the required ionic concentrations

and metabolites. Visualisation of the slice, under a microscope, allows precise positioning of recording electrodes by the cell bodies of hippocampal neurons and, in this case, the granule cells of the dentate gyrus – where LTP was first recorded by Bliss and Lømo in the early 70s. Two stimulating electrodes are positioned on either side of these cells to stimulate different afferent pathways, each of which evokes a response in the post-synaptic cells, demonstrating independent synaptic inputs.

On the right is a graph showing the strength of the synaptic response to electrical pulses delivered to each of these pathways at a test frequency, which is delivered at one pulse every minute, and it does not induce plasticity. After a half hour baseline, to ensure stability, a high frequency tetanus of 100 Hz is delivered to just one of these pathways – which is depicted with black circles – while the other pathway continues to receive the very low frequency test pulses. As you can see, the tetanised pathway undergoes potentiation which then lasts for at least an hour without the control pathway being affected. This is the famous phenomenon of LTP which is an input-specific, long-lasting Hebbian form of synaptic plasticity.

Slide 8:
Since LTP was discovered, many considered it a theoretical imperative that the reverse phenomenon, 'long-term depression' or 'LTD', must exist at synapses since activity-dependent potentiation would quickly saturate synaptic strength and lead to hyperexcitability in the nervous system.

After many years of trying it, it was discovered that low frequency tetanus of 1 Hz, still much higher in frequency than the test pulses that don't induce plasticity at all, would produce the reverse effect of LTD – in contrast to the 100 Hz tetanus that induces LTP. Importantly, both forms of plasticity could be observed longitudinally at the same synapses.

On the right is a modification curve, which is a graph mapping the effects of different stimulus frequencies on the strength of synapses. As you can see, a range of low frequency stimuli will induce LTD while higher frequencies induce LTP. There's also a frequency of around 10 Hz that induces no change at all, which is known as the modification threshold.

Much work has been conducted to show that the frequencies which result in LTP do so by ensuring strongly correlated pre- and post-synaptic activity, just as Hebb had originally described, while the lower frequency stimuli that induce LTD do so by ensuring explicitly uncorrelated activity between pre- and post-synaptic cells.

As we shall see later in the lecture, this bidirectional plasticity, the direction of which reflects the recent history of activity at the synapse, is a perfect system to shape the functional response of neurons in the brain to activity and to sensory input.

Slide 9:
The phenomena of LTP and LTD have been observed at most synapses throughout the nervous system. This slide shows work in ex vivo slices taken from rat hippocampus, rat visual cortex and cat visual cortex. All showing very similar degrees of LTP and LTD when assessed with electrophysiology. This fact will be highly relevant to most of the remainder of this topic, which will focus on activity-dependent plasticity in the primary visual cortex.

Slide 10:
Critical mechanisms, at the heart of many forms of LTP and LTD, are the AMPA and NMDA subclasses of ionotropic glutamate receptors. One of these receptors, the AMPA receptor, is opened by glutamate and is an ion channel that allows the flow of positively charged ions, mostly sodium ions, into a neuron. This receptor carries the majority of synaptic current and is responsible for much excitatory fast synaptic transmission. Changes in the properties or number of AMPA receptors are a major expression mechanism of both LTP and LTD. The NMDA receptor is also an ion channel that allows positively charged ions to flow into neurons.

However, it's more complex than the AMPA receptor because, as well as glutamate-binding, it is also voltage-dependent. Meaning that the channel will only open when glutamate is bound and the post-synaptic neuron is also depolarised, or active. This property arises from a magnesium ion that blocks the channel pore unless the post-synaptic membrane is depolarised.

The NMDA receptor, therefore, has the ideal properties to serve as a critical coincidence detector for the Hebbian criterion of pre- and post-synaptic coactivity. And the key ions that flow through the NMDA receptor, and indicates that Hebbian conditions have been met, are calcium ions.

Slide 11:
This slide shows the original experimental evidence that AP5 (or APV), the specific NMDA receptor antagonist, blocks the induction of both LTP and LTD. This was ground-breaking work as it demonstrated how biology serves Hebb's theory. This experiment also demonstrates an invaluable experimental advantage of the ex vivo slice – which not only allows drugs to be washed on at the appropriate time but also washed off to demonstrate the synapses are not irreparably altered by drug delivery and the LTP can still be induced subsequent to washout.

Slide 12:
How can it be that the same receptor serves opposing directions of synaptic change? The answer is in the conduction of calcium ions through the NMDA receptor. Because of the different dynamics of post-synaptic activation, produced by high- and low-frequency stimulation, the concentration of post-synaptic calcium is very different – as it summates to high concentrations for high-frequency stimulation while remaining elevated, but considerably lower in concentration, as a result of pulsatile, non-summating increases in calcium ion concentration.

This result in activation of different types of calcium-sensing enzymes, some kinases that will phosphorylate targets – such as AMPA receptors – to change their properties and some phosphatases which dephosphorylate and have the reverse effect. We will not go into the details of the particular signalling systems that play, as Professor Peter Geza has already discussed this to some degree previously, but it is important to understand how LTP and LTD can coexist at the same synapses and share many key mechanisms.

Slide 13:
So, to summarise this brief overview of Hebbian plasticity, Hebbian plasticity is an activity-dependent strengthening of synapses between coactive neurons or a weakening of synapses between neurons with uncorrelated activity.

Hebbian plasticity is modelled experimentally in vitro and in vivo through electrical stimulation to produce long-term potentiation, LTP or long-term depression, LTD which respectively strengthen or weaken synapses. The frequency of stimulation is a major determinant of the direction of change – high for LTP and low for LTD. LTP and LTD occur at most synapses in the nervous system.

Hebbian plasticity is input-specific, as it occurs only at synapses that have undergone activity and does not occur at neighbouring inactive synapses on the same neuron. It is also long-lasting.

The NMDA subclass of glutamate receptor is often a key mechanism in the induction of LTP as it is an ion channel that conveys calcium ions only when two coincident events occur: glutamate-binding and post-synaptic depolarisation. Thus, it serves as the detector of the defining events in Hebbian LTP: correlated pre- and post-synaptic activity. It's also a key mechanism for many forms of Hebbian LTD.

Hebbian plasticity is not accurately described by the statement 'fire together, wire together'. Hebbian plasticity can only change existing synapses. It does not involve the formation of new synapses.