# Module:
# Biological Foundations of Mental Health

## Week 4
## Biological basis of learning, memory and cognition

### Topic 2
### From the dynamic synapse to synaptopathies – Part 1 of 4

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Slide 3:
Hello, and welcome to this lecture entitled, 'From the dynamics synapse to synaptopathies'. My name is Deepak Srivastava and I am the head of the neuronal circuitry and neurodevelopmental disorders research group here at the Institute of Psychiatry, Psychology and Neuroscience, King's College London.

In this lecture, we will focus on understanding the function of synapses in the healthy brain. In particular, we will focus on tiny dendritic protrusions that decorate dendrites, which are known as 'dendritic spines'. Dendritic spines are the site for the majority of excitatory synapses in the mammalian brain. We'll explore the basic function of these structures, as well as the overall structure and what they contain.

We will go on to examine how dendritic spines make synaptic connections and how these synaptic connections can be fine-tuned by a number of physiological stimuli. Finally, we'll explore the evidence that indicates that abnormal dendritic spine function is connected with mental illnesses and how studying genetic risk factors associated with mental illnesses can tell us how dendritic spine dysfunction may contribute to the emergence of disease.

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In this part of the lecture, we'll explore the basic function of synapses, the structure and content of dendritic spines, and talk about two processes known as 'spinogenesis' and 'synaptogenesis'.

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Synapses are the site where synaptic communication occurs by the transfer of chemical messages between cells within the central nervous system. The importance of correct synaptic communication lies in the knowledge of the important functions that synaptic communication is responsible for. This includes cognitive function, including executive and more complex functions such as social behaviours, personality, learning and memory, motor behaviours amongst others. Synaptic communication can occur between sensory organs and neurons, between neurons and neurons, as well as from neurons to target organs.

Typically, the flow of information occurs only in one direction – from the pre-synaptic neuron to the post-synaptic neuron. And, finally, there is increasing evidence that disruption of synapse number, and/or function is strongly linked with brain dysfunction.

In the diagram here, we can see a cartoon of a post-synaptic neuron in grey. You can see its cell body – or 'soma' – and its dendrites, that emerge out of it. The dendrites are where this neuron will receive information and, thus, dictates the receptive field of the post-synaptic neuron. That is, the size of the dendritic arbor is critical in determining how many pre-synaptic cells it can connect with.

We can also see several bundles of blue axons, which are part of the pre-synaptic neuron – the arrow shows the direction of information flow. Basically, information flows along the axons until they reach the synapse. The information is then transferred across the synapse to the post-synaptic neuron. This neuron then collates the information and then decides whether or not to send this information to the next neuron through the generation of an action potential that is sent along its axon.

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Within the mammalian brain, synapses can be classified in three different ways. You have axodendritic or axospino synapses. This is where the axon of the pre-synaptic neuron synapses with the post-synaptic cell along its dendrite or on dendritic protrusions known as dendritic spines. These synapses account for the vast majority of synapses in the brain and can be excitatory, inhibitory or neuromodulatory.

You also have axosomatic synapses. These are synapses that occur on the cell body, or 'soma', of the post-synaptic cell. These are typically inhibitory or neuromodulatory. Finally, you have axoaxonic synopses. This is where the pre-synaptic axon synapses directly on the axon of a post-synaptic cell and, thereby, controls the amount of information flow along the axon of the post-synaptic neuron. For the remainder of this lecture, we will focus on axodendritic or axospino synapses.

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As previously mentioned, a lot of synapses occur on highly specialised dendritic protrusions, known as 'dendritic spines'. Here, on the right, we have an example of a pyramidal neuron located in layer 5 of the mouse frontal cortex. You can see that it has a very typified morphology. There is a cell body, or soma, at the bottom and, then, projecting to the top of the cortex – or the pia of the cortex – you can see a primary dendrite. It is this typified structure that is quintessential of pyramidal neurons that are found within the cortex.

If we now zoom into the dendrite of one of these neurons, we can see that it is decorated by these funny little protrusions that come off the dendrites. These protrusions are known as dendritic spines. And what we do know is that dendritic spines form the post-synaptic compartment of synapses and that they are the site where the majority of excitatory synapses occur within the mammalian forebrain.

In this cartoon of an excitatory synapse, we can see in the pre-synaptic terminal where the synaptic vesicles containing neurotransmitters reside. Once an action potential arrives at the pre-synaptic terminal, the synaptic vesicles move to the synaptic membrane, fuse with the membrane and release their neurotransmitter into the synaptic cleft.

On the other side of the synaptic cleft, we have a dendritic spine, which is typified by its spine neck and spine head. Within the spine head, you have the post-synaptic density – or PSD for short – which contains a large number of proteins, including the neurotransmitter receptors. It is these receptors that receive the information

from the pre-synaptic neuron, in the form of neurotransmitters, and then translates these signals into a response in the post-synaptic cell.

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One question you may have is, 'why have dendritic spines?' Firstly, as these structures are where the majority of excitatory synapses occur, they increase the surface area and thus the potential number of synaptic connections a post-synaptic neuron can make. Secondly, it is emerging that dendritic spines can compartmentalise, both electrical and biochemical signals from the rest of the cell. What this means is that dendritic spines can filter – or even amplify – signals, both biochemical as well as electrical, before allowing them to pass into the rest of the cell and, thus, influence the output of the neuron.

In order to do this, dendritic spines have developed their specialised shapes, but they also contain a vast number of proteins. These include receptors – such as glutamate receptors; adhesion proteins – that physically connect pre- and post-synapses together; scaffold proteins – such as PSD95, that organises the PSD and proteins within dendritic spines. A major component of dendritic spines is F-actin – it is the rearrangement of F-actin that allows dendritic spines to change shape. We'll explore this concept in more detail later.

It should also be noted that dendritic spines have a number of organelles within them, such as the endoplasmic reticulum and polyribosomes – these are required for the production of new proteins. They also contain mitochondria, which provide the fuel needed for many processes.

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Over recent years, we have really begun to develop an appreciation of the important role that dendritic spines play in normal brain function. For example, during early brain development, dendritic spines can be seen to emerge out of dendrites and to search at the surrounding neuropil for an appropriate pre-synaptic partner. Once it finds the appropriate pre-synaptic partner, it can make a synaptic connection. It is thought to be one of the ways that neural circuits or neural networks can be formed, and it is the basis by which wiring within the brain occurs.

Interestingly, a number of signals, including synaptic activity as well as neuromodulating signals, can also cause dendritic spines to change shape and size as well as to increase or decrease in number. In this cartoon, we can see that synaptic activity – such as long-term potentiation – seen here in red, causes the existing dendritic spine to increase in its size, but also causes a new dendritic spine to emerge. This spine has the potential to form a synapse. And, overall, this has led us to the emerging theme that synaptic connectivity within neural circuits – or neural networks – can be remodelled and, thus, that wiring within the brain can be refined. Importantly, the changes in synaptic connectivity can occur in a bi-directional manner.

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Here, again, we just have a cartoon of a neural circuit or neural network. And, simply put, a physiological stimulus – such as synaptic activity – can cause either a change in the number or the shape of dendritic spines. This can either lead to an increase or decrease in either the number or the strength of synaptic connections. Moreover, it is these changes and synaptic connectivity – driven in part by changes in dendritic spine, shape or number– that are thought to be essential for normal brain function.

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So, how do neurons make synapses? There have been several different models by which synapses can be formed. The prevailing model that is used is dependent on the time of development as well as the region of the

brain where this process is occurring. I would like to focus on one model of synapse formation that is thought to be the prevalent mechanism that occurs during development and within the adult forebrain. This model, known as the Filopodial model, can be easily broken down into two events: 'spinogenesis' and 'synaptogenesis'.

In this model, the axon and dendrites of the pre- and post-synaptic neurons have already been established. At this point, you can see a pre-synaptic terminal on the axon. In this model, the dendrite creates a dendritic protrusion known as a filopodia. This is a very long protrusion that is very dynamic – that is, it moves around the surrounding neuropil very quickly and can appear and disappear very quickly. Filipodia do not have a discernible head structure and do not contain the proteins necessary to create a synaptic connection. For example, these protrusions do not have a post-synaptic density – or 'PSD' – and they do not contain neurotransmitter receptors. The Filipodia then searches the surrounding neuropil looking for an appropriate pre-synaptic partner – which is known as 'target selection'.

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Once a pre- and post-synaptic cell have identified each other as partners, the next stage is known as 'synaptogenesis'. The initial step of this is known as 'synapse assembly'. Here, several key synaptic proteins are recruited to the nascent dendritic protrusion. These proteins include NMDA receptors, the scaffold protein, 'PSD95', and a number of adhesion proteins. One of the main roles of the adhesion proteins is to physically connect the pre- and post-synaptic side of the synapse together. It is the recruitment of these synaptic proteins that signals the change of the filipodia into a dendritic spine.

At this stage, the nascent dendritic spine has a defined head with a PSD and contains the key elements, like NMDA receptors, that would allow synaptic communication to occur. However, these connections are weak and considered to be unstable. The next step is known as synapse stabilisation. This is where synaptic activity induces the recruitment of more adhesion molecules to further stabilise the dendritic spines, as well as NMDA receptors and other synaptic proteins to establish these pre- and post-synaptic structures as fully functional synaptic connections.