# Module:
# Biological Foundations of Mental Health

## Week 1
## Introduction to brain anatomy

## Topic 3
## Microanatomy of the nervous system – Part 2 of 3

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In Part 2, we'll be learning about cell structures and function.

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Neuronal morphology, or shape, is refined during development to fit the function of neurons and is, therefore, highly variable. The extent of dendritic arborisation, or branching, reflects the level of input that a neuron requires – as dendrites are the main sites of neuronal input. For example, cerebellar Purkinje cells are highly branched, as they receive many inputs and are the only input of the entire cerebellar cortex.

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Axonal length can also vary widely, determining the distance of output in the network. The longest axon in the body is from the lower motor neurons, which is one meter in length, which is quite incredible for a single cell. To give you an equivalent – if the cell body was the size of a ping pong ball, the axon would be 380 meters long, just under four football fields in length.

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Neurons also have microstructures called dendritic spines. These are small protrusions from dendrites which form the postsynaptic side of a synapse with axon tunnels from other neurons. Dendritic spines come in different forms, from long and thin to mushroom shaped. Their shape and size will affect how they receive and transmit input. Those with a larger surface area provide more space capacity for neurotransmitter receptors and, thus, generally form stronger, more stable synapses rather than the more transient, filopodial types. Spines are also plastic and can increase in size during learning and memory.

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Glial cells also vary in morphology. Here, microglia change morphology when they become activated, or 'reactive', with increasing numbers of processes and progressively become more round and phagocytic. Reactive microglial release more cytokines to attract more microglia to the site of a perceived injury. In phagocytic mode, they engulf any perceived debris, which can include synapses. Thus, microglial morphology can be used to score and infer neuroinflammation. Here, we show an example of the scoring system in a mouse brain from a model of frontotemporal dementia stained with a microglial marker, 'Iba1'. You can see the scoring system goes from '1', ramified – which is normal; through '2', reactive; '3', ameboid; to '4', phagocytic. This has then been used to show progressive neuroinflammation in this model, compared to a non-transgenic mouse control.

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Astrocytic morphology is highly heterogeneous even under normal conditions. Therefore, instead of morphology, activation is often inferred from increased numbers of cells in a given location – this is often called 'astrocytosis'. An increased number of cells may be due to local recruitment or enhanced proliferation of astrocytes. In the same mouse model of frontotemporal dementia as before, an increase in the number of astrocytes is quantified by the percentage of the total area that is stained for the astrocytic marker, 'GFAP'. In this case, progressive astrocytosis is observed from 12 months of age, panel 'E', and quantification below.

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Inside a neuron, the majority of specialised organelles are very similar to a standard eukaryotic cell, including the following: the nucleus – where all genetic information is stored; the endoplasmic reticulum – where some new proteins are produced, sorted and processed for delivery to their required location; the Golgi apparatus – where additional sorting and processing occurs; mitochondria – are the energy generator of the cell and also have key roles in calcium buffering and cell signaling; lysosomes – are enzyme-filled vesicles for the degradation of proteins and other organelles when faulty; and the cell membrane – is a lipid bilayer containing receptors for cellular communication. You can see a great video introduction to some of these concepts with this link provided [https://www.youtube.com/watch?v=URUJD5NEXC8].

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Neurons do, however, have some unique features that relate to their highly specialised function. The first of these is that they have an unusually high energy demand. In a human, the brain comprises only 2% of body mass yet it uses about 20% of the oxygen consumed by the rest of the body. The majority of this is used to maintain the electrical equilibrium of the neuronal cell membrane by the sodium-potassium ATP pump which, as its name suggests, consumes ATP. Other main energy demands include the recycling of neurotransmitters and calcium buffering.

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Due to their extended morphology, including both axons and dendrites, neurons also need to transport cargo along very long distances. Although some proteins are made locally, the vast majority of proteins – and mitochondria – are produced next to the nucleus. But they are often required at distant sites, such as synapses. Cargo, therefore, needs to be transported out to synapses and back to the soma for recycling or signalling. Cargo is mainly transported along microtubules, one of the key cytoskeletal components of the cell. This can be away from the nucleus – 'anterograde' – or towards the nucleus – 'retrograde'.

## Slide 11

As for the majority of processes in neurons, neuronal transport lies in a delicate balance – where even a slight imbalance can lead to dysfunction. This is notable in most neurons, probably due to their really long axons. For example, a slight impairment in retrograde transport can lead to a build-up of dysfunctional components at synapses and a reduction in the supply of recycled components, blocking normal synaptic function.

## Slide 12

The last key feature of a neuron is due to the fact that we have limited capacity to generate new neurons during adulthood and that neurons are post-mitotic and cannot undergo cell division for growth or repair. Thus, neurons become vulnerable with age – as cell components deteriorate and, thus, have a reduced resistance to cell stress. The key processes that often become dysfunctional with ageing are protein clearance, DNA repair and mitochondrial function. Selective neuronal vulnerability in disease is probably due to the varying vulnerability of specific neuronal populations to different cell and networks stresses.