## Week 1

### Types of neuroscience

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| **Cognitive** | Understanding higher level (human) thought processing<br>- MRI scan on Hippocampus and Amygdala where the redder the area is, the higher the craving for cocaine is |
| **Behavioural** | Biopsychology, why and how we produce certain behaviours<br>- Elevated plus maze to measure anxiety in laboratory animals |
| **Systems** | How does this brain control body systems, how do body systems provide information to the brain?<br>- Modify brain systems (microinject chemicals into discrete brain areas) and see how this effects behaviour, blood pressure, respiration and renal – usually done in freely moving animals or anaesthetized animals |
| **Cellular** | How do neurons and/or glia work? Signalling in cells<br>- Immunohistochemistry, electrophysiology, connectome |
| **Molecular** | How do molecules or chemicals work in brain cells to communicate, grow, change?<br>- Proteomics, immunohistochemistry, neuroinflammatory markers, HPLC, epigenetics |

### Epigenetics: study of heritable changes in gene function that cannot be explained by changes in DNA sequence

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| **Chromatin** | DNA/protein complex<br>- DNA is packaged around histone proteins<br>- The tightness of the association between DNA and histone influence the accessibility of a DNA sequence for transcription enzymes<br>The pattern of gene expression is influenced by the accessibility of a gene sequence to transcription machinery |
| **Histone modification** | Changing how tightly DNA sticks to histone proteins<br><u>Four important classes</u><br>1. Acetylation<br>2. Methylation<br>3. Ubiquitination<br>4. Phosphorylation |
| **Histone acetylation** | Addition of acetyl groups to lysine amino acids within the histone protein<br>- Catalysed by histone acetyltransferases (HATs)<br>- Neutralises the positive charge of the histone<br>- Weakens association with DNA – **exposes DNA for transcription** |
| **Histone deacetylation** | - Catalysed by histone deacetylate (HDACs)<br>- Increases positive charge of the histone<br>- Strengthens association with DNA – **reduces likelihood of transcription** |
| **Histone methylation** | Addition (HMT) or removal (HDM) of methyl groups to lysine residues<br>- Methylation can either enhance or silence transcription |
| **DNA methylation** | Sticking methyl groups onto the DNA chain<br>- DNA methyltransferase enzymes (DNMTs) catalyse the addition of methyl groups to Cytosine/Guanine nucleotide pairs (CGs) within a DNA strand<br>- Maintenance DNMTs restore methyl groups after DNA replication<br>- De Novo DNMTs add new methyl tags to DNA<br>**DNA methylation reduces gene transcription** – silences gene<br>- Methyl groups physically interfere with binding of RNA polymerase, inhibits transcription |

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| | **DNA demethylation encourages transcription**<br>- Converts 5-methylcytosine to 5-hydroxmethylcytosine (5HmC)<br>- 5HmC promotes transcription of a gene |
| **microRNAs** | Blocking the translation of mRNA into protein with microRNAs (miRNA) |
| **Neuroepigenetics** | The role of epigenetic systems as regulators of neuronal function to influence the output of neuronal circuits |

**Alzheimer's Disease: memory loss, slowly progressing dementia**

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| **Neurodegeneration** | Selective death of Acetylcholine (Ach) cells<br>- Neurodegenerative disease characterised by protein accumulation in and around neurons: intracellular neurofibrillary tangles and extracellular amyloid plaques<br>- Amyloid plaques occur before neurofibrillary tangles |
| **Apraxia (movement)** | Loss of ability to co-ordinate movements |
| **Aphasia (comprehension)** | Loss of ability to articulate ideas and comprehend written/spoken word |
| **Agnosia (sensory)** | Cannot interpret sensory stimuli |
| **Amyloid precursor protein** | Cleave to make secretory products used in learning and memory storage<br>- 90% of the time making AB40 which is used in learning and memory storage but 10% of the time AB42 which is a by-product of the whole process causing plaques and the brain clears this way – bamyloid plaques<br>In Alzheimer's Disease – APP cleavage has shifted (genetic, environment?)<br>- 10% of the time making AB40 and 90% of the time making AB42<br>- Bamyloid protein may be responsible for starting cell death cascades |
| **Neurofibrillary tangles** | Abnormal cluster of hyper-phosphorylated tau protein<br>- Tau protein helps to maintain axon shape and transport molecules from the cell body to the terminals (microtubules) |
| **Genetic** | **apoE gene -** Apolipoprotein E-4 (apoE-4) may predispose to plaque deposits<br>**A2M gene** - Usually clears plaque deposits, mutant form doesn't<br>- Role of genetic risk factors is increasingly less related to developing late-onset AD: environmental influences are greater |
| **Environment** | Triggers include<br>- Nutrition<br>- Exposure to metal or pesticides<br>- Stress<br>- Social factors<br>- Vascular risk factors<br>- Brain trauma |
| **AD: Histone Modification** | In discordant twins<br>- Increased H3K9 trimethylation in hippocampus and temporal cortex<br>In AD<br>- Increased 4-hydro (HNE) – thought to alter histone-DNA interactions making DNA more vulnerable to oxidative damage<br>- HDAC changes may differ across disease progression |
| **AD: DNA Methylation** | Hypomethylation of APP or APP promotor: association with increased deposition of bamyloid production<br>- Exposure to lead may reduce activity of DNMTs |
| **AD with mouse model** | Neuron loss in the forebrain, Bamyloid accumulation and Tau pathology and memory loss – AD is most likely a product of gene x environment (epigenetic) interactions |