Pruning and refining of synapses

Factors determining amount of synapses in the brain involved genetic and environmental.

- Genetics: Individuals with mutations such as neurexin mutants have defects in synapse formation, e.g. Autism
- Environmental: Enriched environment with cognitive stimulation lead to synaptogenesis and increased complexity.
    - E.g. social interaction, exercise, music, visual, creativity, lead to increased BDNF release and increased synaptogenesis.

Pruning: elimination of synapses based on activity.

- Blocking of all synaptic transmission —> no synapse are eliminated. Shows acivity based elimination
- Conserved mechanism across species, peak number of synapses in juvenile stage followed by pruning in adolescent.
- Two modesl of elimination:
    - Sequential model: Growth phase followed by elimination phase in sequential manner
    - Concurrent model: Synaptogenesis while pruning occur, supported by **live imaging in Xenopus RGCs.**

Neuronal activity regulates:

- Neurotrophic factor release:
    - BDNF is released upon stimulation, bind to TrkB tyrosine kinase receptors, regulate neuronal proliferation, differentiation, synaptic plasticity.
    - Neurotrophic factor release can be constitutive or activity dependent.
        - Activity dependent neurotrophic factor release could be attribute to astrocytes or other neurons sensing the synaptic activity and releasing neurotrophic factors. This can promote additional branching or stronger synapse formation
        - **GFP-tagged presynaptic markers increase with BDNF addition, showing greater arborisation**

- Synapse dynamics:
    - Dendritic spines receives primarily excitatory inputs, its formation and elimination is a dynamic process.
    - Maintainence of dendritic spine is an outcome of synaptic plasticity: Strengthening & weakening of synapse responding to external environment
    - Long term potentiation: Increase in spine number and spine size following high frequency stimulation
    - Long term depression: Decrease in spine number and spine size following low frequency stimulation.

- Regulation of synapses:
    - Excitatory activity induce increase in localisation of glutamatergic receptors (AMPA, NMDA), and neurotrophic factor receptors (TrkB)
    - Neuronal activity increase localisation of β-neurexin at to the synaptic membrane. Stabilising both excitatory or inhibitory synapses
        - **TTX blocking synaptic activity decreases Neurexin turnover rate**
    - Wnt signalling elevated following high frequency stimulation, promoting synapse formation:
        - **Fluorescent tagging - increased Wnt7 intensity hence concentration following HFS**
        - **Fluorescent tagging - dendritic spine number and size did not change is Wnt antagonist added with HFS**
    - Localisation of Wnt7 pathway receptors:
        - **Increased proportion of synapses with Frz-5 following HFS**
        - **Blocking of Frz-5 with HFS lead to decrease in synapse number and size**

- Cadherin-catenin complex: Trans-membrane cadherin binds with intracellular α/β-catenin, regulate downstream signals
  - **Decrease in synapse activity with TTX lead to decrease in α-catenin**
  - **Increase in synapse activity with bucucullin lead to increase in both α/β-catenin.**