Divergent trajectories of cortical development regulated by differential NMDA receptor populations

Supervisory team:
Main supervisor: Dr Michael Ashby (University of Bristol)
Second supervisor: Dr Paul Anastasiades (University of Bristol)

Host institution: University of Bristol

Project description:
Maturation of the prefrontal cortex (PFC) early in life is key to the higher cognitive functions of mammalian brain, such as complex and emotional decision making. As such, abnormal development of PFC is linked to cognitive disorders such as schizophrenia.

PFC structure appears to be broadly similar to other cortical areas, but its maturation is delayed – indeed, prefrontal synapses and circuits only gain adult-like properties during late adolescence. We do not understand why PFC maturation is delayed despite sharing many similar characteristics with other cortical regions. One suggestion is that prefrontal synapses are different, causing them to retain plasticity later in brain development. In this project, we will compare the development of prefrontal with the whisker barrel cortex of the mouse to reveal the mechanisms that control their differential developmental trajectories.

In the Ashby lab, we have shown that barrel cortex formation occurs sequentially, with an initial circuit template that is subsequently refined by activity and synaptic plasticity. Prefrontal cortex also undergoes activity-dependent developmental plasticity, but this occurs much later, during adolescence. NMDA receptors (NMDARs) are key regulators of activity dependent plasticity. We will therefore test the hypothesis that differences in the maturation of NMDAR subunits in prefrontal with barrel cortex contributes to their distinct developmental trajectories. To test this, we will measure changes in NMDAR expression at specific cells and synapses. We will use RNAscope, a new technique recently established in PFC by Dr Anastasiades, to image and quantify the expression and spatial location of multiple NMDAR mRNAs within intact brain tissue. Building on these findings, the student will then learn single cell photostimulation and electrophysiology in brain slices, which was pioneered by Dr Ashby, to measure NMDAR characteristics at specific synapses. To relate NMDAR maturation to circuit development, they will then apply photostimulation-based circuit mapping, in which Dr Anastasiades is expert, to define connectivity between individual layers of the cortex is established in the two regions. Having determined common and divergent developmental patterns in PFC and S1BF, we will then link this to NMDAR expression by genetically deleting NMDAR subunits using transgenic mice. These cutting-edge experiments, based on bringing together established expertise within the two host labs, will define how and when early differences in NMDAR-based neuronal communication controls the timing of cortical maturation in different regions of the cortex. These findings will therefore provide insight into why prefrontal synapses may be highly sensitive to perturbations during adolescence.