Functional roles of cholinergic signalling in the retrosplenial cortex

Supervisory team:
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Project description:
Prioritising the right behaviours at the right time is crucial for survival. This is enabled by neuromodulation, which fine tunes the functional properties of brain circuits to meet behavioural demands. Acetylcholine (ACh) is a neuromodulator that promotes behaviours related to cognitive processes such as learning and memory, planning and decision making. Disrupted ACh signalling is associated with several neurological diseases in which these functions are impaired, most notably Alzheimer's disease (AD).

Retrosplenial cortex (RSC) is a region of the brain's neocortex that is involved in the processing of spatial learning and memory. Interestingly, AD patients have decreased activity in RSC before other brain areas, suggesting that RSC dysfunction may be a cause of cognitive deficits in AD.

RSC is richly supplied by cholinergic (i.e. ACh releasing) synapses, and contains muscarinic and nicotinic ACh receptors which are known to support learning and memory. However, almost nothing is known about how ACh regulates RSC at the circuit level. This study will use new technologies to reveal how and when ACh is acting to control the processing of spatial information in RSC.

The specific aims of the project are to (i) define the cellular anatomy of the cholinergic input to RSC, (ii) determine the cellular and synaptic mechanisms by which ACh regulates the activity of neurons in RSC, and (iii) determine how spatial navigation and memory drives the activation of cholinergic fibres in RSC.

You will work between the Witton and Randall labs in Exeter and Mellor lab in Bristol, using a range of advanced in vitro and in vivo techniques that take advantage of genetic tools to label and manipulate cholinergic neurons in mice. You will use viral-genetic neural circuit tracing to address aim (i), optogenetics and patch clamp electrophysiology to address aim (ii) and a combination of in vivo two-photon brain imaging and behavioural analysis to address aim (iii). You will also develop skills in computer programming by writing novel algorithms to analyse in vivo imaging data.

Through this project you will establish a new foundation for understanding how ACh regulates the processing of spatial cognition in RSC. This will help to understand how impaired cholinergic signalling disrupts cognition in diseases such as AD, and how ACh boosting drugs used for symptomatic treatment of AD (e.g. Donepezil) are working in patients.