Understanding pattern separation in the hippocampal dentate gyrus: a pathway to preserving memory

Project ID: 221

Supervisory team

Main supervisor: Prof Denize Atan (University of Bristol)
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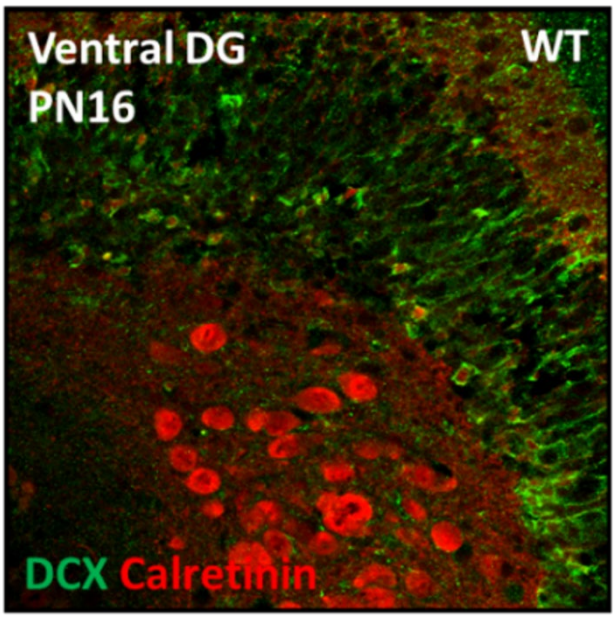
Collaborators: Prof Helen Scharfman (New York University)

Host institution: University of Bristol



Project description: How do we remember where we placed our car keys today versus yesterday? This ability hinges on a cognitive process known as pattern separation—the brain's mechanism for distinguishing between similar experiences. Pattern separation is one of the earliest memory functions to decline with age, making it a critical focus in neuroscience research.At the heart of pattern separation lies the dentate gyrus (DG), a specialized subregion of the hippocampus. Our experimental data, supported by computational modeling, reveal that mossy cells play a pivotal role in regulating the balance between excitation and inhibition within this circuitry. These cells orchestrate memory encoding by recruiting various classes of GABAergic interneurons, which suppress background activity—or "noise"—across the DG network. This dampening effect reduces interference between overlapping memory traces, each represented by distinct spatiotemporal patterns of neuronal activity.The DG contains three principal classes of interneurons—parvalbumin (PV), cholecystokinin (CCK), and somatostatin (SST)—each with unique physiological properties and response kinetics. These differences suggest that each class may exert frequency-dependent inhibitory effects, yet their specific contributions to pattern separation remain largely unexplored.This project will focus on CCK-interneurons, a relatively understudied population within the DG. Notably, CCK-interneurons express endocannabinoid receptors, which are known to modulate DG network activity. This receptor profile positions them as potential key players in pattern separation, both in healthy cognition and in neurological disease.The selected student will join a vibrant, interdisciplinary team with expertise in electrophysiology, pharmacology, optogenetics (P. Anastasiades, Z. Bashir), and advanced genetic and imaging techniques (D. Atan, M. Ashby). Together, we will manipulate and monitor CCK-interneuron activity to uncover their functional role in DG circuitry. These findings will inform and refine our computational model (M. Goodfellow), integrating interneuron-specific properties—such as ion channel dynamics and receptor expression—to simulate the spatiotemporal behavior of the DG and predict pharmacological outcomes.Simulations will be developed in Python and executed on the University's high-performance computing platforms, Blue Crystal and AI-Isambard. For instance, given the widespread use of cannabinoids in epilepsy treatment and the known expression of endocannabinoid receptors in the DG, our model predicts that cannabinoid agonists may impair

pattern separation, potentially affecting memory precision.Ultimately, this project aims to deepen our understanding of DG microcircuitry and identify novel therapeutic targets to combat memory decline associated with ageing and neurological disorders.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.