Project outline

1. Project outline describing the scientific rationale of the project (max 4,000 characters incl. spaces and returns)

The prefrontal cortex (PFC) is critical for optimising behavioural outcomes by prioritising choices relevant to an animal’s well-being. It does so by integrating a diverse set of sensory and interoceptive information that influences the flow of activity from brain regions signalling the animal’s needs, the significance of surrounding stimuli, and the motor repertoire for their integration. The hypothalamus is a brain region important for sensing interoceptive signals that relate to the energy requirements of an organism. Discrete hypothalamic circuits, in particular those expressing melanin-concentrating hormone (MCH) can robustly drive eating and food-seeking behaviour. Interestingly, the medial PFC sends projections to the lateral hypothalamus (LH) revealing an anatomical substrate for top-down influences on bottom-up signalling for maintaining energy homeostasis.

Animal studies have demonstrated that direct activation of the PFC can reduce instinctive behaviour such as fear, habits as well as aggression. Such results translate well clinically as there is much evidence indicating that PFC dysfunction is associated with disruptions in cognition where patients lack control over their impulses or emotions. In the case of eating disorders, such as binge-eating disorder and Anorexia Nervosa, one model posits that over- and under-eating can potentially result from PFC hypo- or hyper-activity, respectively, imparting diminished or excessive control over the drive to eat. Whether or not the cognitive control over eating may result from interactions between the PFC and the hypothalamus, specifically the melanin-concentrating hormone (MCH) system, is unclear and the main question to be investigated in this PhD proposal.

Implementing advanced imaging techniques (fibre photometry) together with a rodent eating disorder model that promotes under- and over-eating we aim to determine the response dynamics of MCH neurons during distinct feeding bouts. Specifically, by consisting of two phases, one where animals restrict their food intake, the other where they over-consume food, this behavioural paradigm will allow us to monitor and relate changes in MCH activity across phases where animals exhibit different feeding patterns. Optogenetic circuit-mapping strategies will next be implemented to determine the influence of PFC neurons on MCH activity. Finally, we will attempt to normalise this under/over-eating by manipulating PFC inputs to the LH, thus determining a causal role for this circuit in influencing eating. In addition to linking executive circuits with feeding circuits this project aims to provide insight into the neural mechanisms underlying eating behaviour.
Often enough eating is independent of our energy needs thus necessitating a new framework for understanding the regulatory mechanisms over the drive to eat. To shed light on the neural circuits that impose control over eating behaviour our aim is to relate the connectivity between executive brain regions that impose control over instinctive behaviour and ones that respond to energy deficiencies for executing appropriate food seeking behaviour. Together with local collaborating labs my lab is in an optimal position having the resources and expertise to take a multi-disciplinary approach in understanding the link between brain circuits and behaviour. By mapping out the anatomical and synaptic relationship between regions and revealing the unique activity signatures of specific hypothalamic cell populations during distinct feeding behaviour we can begin to design physiologically-relevant activity patterns for revealing causal relationships between activity, circuits, and behaviour. Such a multimodal approach will not only contribute to a better understanding of the underlying circuits mediating the top-down control over eating but also provide insight into the mechanisms disrupted during maladaptive eating behaviour and its metabolic consequences.

Techniques that will be undertaken during the project

Implementing advanced imaging techniques (fibre photometry) together with a rodent eating disorder model that promotes under- and over-eating we aim to determine the response dynamics of MCH neurons during distinct feeding bouts. Optogenetic circuit-mapping strategies will next be implemented to determine the influence of PFC neurons on MCH activity. Finally, we will attempt to normalise this under/over-eating by manipulating PFC inputs to the LH, thus determining a causal role for this circuit in influencing eating. The combination of these techniques is designed to not only map out the functional connectivity between areas known to be important for the decision to eat but also to use advanced imaging approaches to find relationships between the activity of specific cell populations and over/under-eating. In the final stage we will attempt to find causal relationships between this circuit and regulation over eating behaviour by manipulating these circuits in freely behaving animals. Together we hope this multi-disciplinary approach will provide knowledge for better understanding the circuits and cell types involved in maladaptive eating.