The cellular and synaptic mechanisms for the effects of psychedelics on flexible memory representations in the hippocampus

Supervisory team:
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Project description:
Psychedelic therapies offer a potentially paradigm-shifting approach to the treatment of many mental health conditions including depression, anxiety, addiction and post-traumatic stress disorder. However, the mechanism of action of psychedelics remains poorly understood, and this has led to new investment and interest in not only studying the clinical effects of psychedelics, but also their fundamental biology. The heterogeneity of psychological disorders which apparently benefit from psychedelic therapy presents a challenge to understanding underlying mechanisms and highlights the importance of studying mechanisms which are transdiagnostic (shared across different diagnostic groups). Furthermore, psychedelics typically exhibit complex pharmacological profiles, and interact with many different receptor populations.

Current understanding of the mechanism of action of psychedelics, such as psilocybin, emphasises its ability to act as an agonist at the 5-HT2A receptor and cause an enhancement of both synaptic plasticity and cognitive flexibility. These acute effects may enable changes in the memory representations that maintain states of poor mental health. The mechanisms by which psychedelics affect neural plasticity are not completely known, and importantly its functional importance for mediating change in cognition and behaviour is poorly characterised. In this project we aim to address these unknowns by investigating the effects of psychedelics on representations of memory in the hippocampus, integrating expertise in rodent behaviour, in vivo imaging and brain slice electrophysiology.

We have developed a method to directly measure cognitive memory representations in the neural activity of the rodent hippocampus using 2-photon imaging to monitor hippocampal CA1 place cell activity in mice as they navigate in virtual reality. We and others have shown that hippocampal place cell representations adapt to defined changes in the environment, particularly for salient features such as reward locations and that these adaptations are crucial for guiding learned behaviour. Through our collaboration with COMPASS Pathways, we will explore the effects of COMP360 (a synthetic formulation of psilocybin used in ongoing clinical trials) on memory representations and resulting behaviour by analysing the speed and extent of place cell adaptations in response to precise manipulations of the virtual reality environment, incorporating varying levels of uncertainty. In vivo work will be complemented by further testing the effects of psilocybin on synaptic plasticity in hippocampal slices using paradigms that closely model the in vivo situation by stimulating dendritic calcium signalling events. We will test the effects of psilocybin on calcium events and synaptic plasticity using a combination of electrophysiology and 2-photon imaging.

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.