New BBSRC Fellows

Dr Asaph Zybertal

BBSRC Discovery Fellow

Research Associate, Neuroscience, Physiology and Pharmacology, Division of Biosciences, UCL

Title: ***Matter of context: Revealing the circuit architecture of internal brain state influence on behaviour***

Summary:

My aim is to understand how ongoing internal activity patterns within the brain shape the way it processes information and controls behaviour. Human and animal behaviour is not merely a set of 'automatic' reflexes. Rather, the way we respond to sensory inputs such as the sight of food or the sound of a phone ringing depends on multiple contextual factors such as emotional state, time of day and how satiated or alert we are. Modern neuroscience has made important progress towards understanding the brain systems that report these factors. For instance, the dopaminergic and serotonergic systems that signal reward have been extensively studied due to their importance in shaping normal behaviour as well as psychiatric disorders.

However, major challenges remain in terms of understanding how multiple brain pathways act together to modulate sensory processing and behaviour. To a large extent this is due to the size and complexity of the brain which precludes simultaneous measurement of the many brain cells involved. By establishing a new research programme in the Department of Neuroscience, Physiology & Pharmacology at UCL, I plan to take a novel approach to tackle this problem. My strategy combines state-of-the-art imaging in an experimentally advantageous model organism - the larval zebrafish - with data-driven biology and computational modelling: key research avenues identified by the BBSRC.

Zebrafish larvae are particularly well suited for simultaneously tracking activity in multiple brain structures. This tiny animal (3.5 mm long) is almost perfectly transparent, allowing its small brain to be monitored non-invasively using fluorescent microscopy while the fish performs a range of recognizable behaviours such as hunting and avoidance. Importantly, many of these behaviours are influenced by contextual factors such as hunger or alertness, by virtue of brain circuits fish share with all other vertebrates, including humans.

To study how distributed brain networks work together to shape behaviour, I will use cutting-edge "light-sheet microscopy" to individually track the activity of each of the zebrafish's 80,000 neurons. While doing so, I will alter environmental factors to manipulate satiety, alertness and other contextual elements. Deciphering the resulting dataset will be a complex endeavour, comparable to extracting insights into market dynamics by simultaneously listening to each and every one of the 100,000 finance employees in the City of London. The potential for valuable insights is enormous, but so is the challenge in making sense of the massive amount of data and finding the most informative sources. To meet this challenge, I will use recurrent neural networks - a modern machine-learning algorithm akin to the one that powers automated speech recognition. It will enable me to identify neurons that can predict if the animal is likely to respond to a specific visual cue, even before the stimulus is presented. Such cells are good candidates for signalling contextual information and my computational modelling will resolve how they work together to collectively influence behaviour. To test my hypotheses, I will use advanced "optogenetic methods" to directly control brain activity using light and examine the resulting effects on activity elsewhere in the brain and on the behaviour of the fish.

Ultimately, these findings will shed new light on how neural activity related to context and experience combine to influence fundamental brain function. Because all vertebrates possess the same basic brain plan, my experimental findings are likely to reveal principles that apply to many species, including humans. Thus, in line with the BBSRC's priority of supporting world-class basic bioscience for health, this project will provide a major advance in our understanding of how the healthy brain produces behaviour. In the longer term, this could underpin greater understanding of how brain function is disrupted during disease.

New BBSRC Fellows

Dr Ryan McDonald

BBSRC David Phillips Fellow

Joining the Institute of Ophthalmology, UCL from the University of Sheffield where he is JG Graves Medical Research Fellow in department of Infection, Immunity and Cardiovascular Disease

Title: ***Support for synapses: the role of cell adhesion molecules in glial morphogenesis***

Summary:

The central nervous system (CNS) consists of the brain, spinal cord and retina (eye). It controls most functions of the body and mind. Despite the importance of these tissues are made up of only two major cell types: neurons and glia. Most researchers focus on neurons because they are the electrical wires passing signals to perform daily functions. However, glial cells outnumber neurons in the CNS and they support neurons to make sure they are healthy and function properly. To make up the CNS, neurons and glia need to meet during development and make specific partnerships that last a lifetime. Glial cells have special shapes so that they can connect to the neurons. Changes in glial shape can make neurons sick and potentially lead to disease. So it is important to understand how glial cells get their shape in the first place so we can make sure they keep it and support the neurons throughout the lifespan. We don't know how glial cells get their shape and meet their neuronal partners. We also don't know exactly what happens to neurons if glial cells don't make these connections in the first place. I want to explore these really important fundamental questions.

In order to really understand how glia get their shapes and support neurons the best way is to watch it happen in a living animal during their development. I am an expert in studying glial cells in the retina of the zebrafish using genetics and microscopy techniques. The retina is a really simple CNS tissue, if compared to the brain. I will use the zebrafish to study this very interesting problem as we can see inside it during early development, its retina has neurons and glia just like humans, and we can follow individual cells using fluorescent proteins. Thus, using microscopy I can watch how neurons and glia behave to meet and make their connections in a living fish. I have found that glia are active and change their shapes very quickly to find and contact specific neurons. We don't know what molecules are controlling the glia to find their neuronal partners. To identify molecules I carried out a genetic screen looking for glial cells with shape defects. This identified the cell adhesion molecules, which are important molecules for cell connections in many different tissues, including the retina and brain. However, we don't know how these particular ones work in the glia to control their shapes during development. To find out why these genes are important and how they help the glia find their partners I will delete them in zebrafish and observe how retina development goes wrong in animals without these genes. To achieve this I will use microscopy to watch glia and neurons in retinas that grow abnormally. Finally, I have shown before that if you don't have any glia in the zebrafish retina then it doesn't function properly. So I will test the vision of fish that still have glia but only their shapes, and connections to neurons, are affected. I will test this by using visual behavioral tests and stimulation with specific light patterns, these are experiments that can easily be done and something myself and other experts will work on together to accomplish.

My research programme will tell us how glia find their partner neurons, which cell adhesion molecules are important for glia to get their shapes and how they make sure our CNS function normally. These answers will be very important for understanding how our retinas and brains are built in the first place. If we understand how glia shape is set up then maybe it will be the same molecules to maintain the connections, so this will also be very important for keeping each part of the CNS healthy as we age. Finally, these behaviors and molecules might help with discovering drugs and treatments to change glial shape and make sure they connect to neurons and support them again. This will be very important for patients with neurodegenerative diseases, like Alzheimers, or retina degeneration (major cause of blindness).