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Co-supervisor: Dr Jaime McCutcheon

**PhD project title:** The dopaminergic basis of behaviour

University of Registration: University of Leicester

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**Project outline**

1. Project outline describing the scientific rationale of the project

The neurotransmitter dopamine has an important behavioural role in the vertebrate brain, modulating locomotion, aggression, feeding and reward. Our laboratory has recently established fast-scan cyclic voltammetry (FSCV) in zebrafish, a technique that permits the release- and reuptake of neurotransmitters to be measured at the synapse. In this project we will establish a protocol to perform FSCV in the intact larval zebrafish brain and couple this to optic flow – a virtual reality simulation of behaviour. These experiments will permit us to investigate neurotransmitter release in awake freely behaving animals.

Research in our laboratory investigates the genetic, neurological and pharmacological basis of behaviour. Zebrafish are an ideal model for neuroscience since their genes and neurotransmitter signalling pathways are highly conserved with other vertebrates. We combine measurements of behaviour with techniques to examine the brain such as high precision liquid chromatography (HPLC), fast-scan cyclic voltammetry (FSCV), in situ hybridisation (ISH) and immunohistochemistry. For example, our laboratory has shown that *fibroblast growth factor receptor 1a* mutants exhibit increased aggression and a malformation of the hypothalamus demonstrating the power of this model to connect behaviour and neurobiology.

In a recent project, we used FSCV to show that electrical stimulation of the adult telencephalon triggers the release of dopamine and histamine coupled to a change in pH. These experiments, the first demonstration of FSCV in zebrafish, were performed on sagittal sections of the brain cultured in artificial cerebrospinal fluid. In this project we will develop a setup to measure neurotransmitter release in awake behaving animals. Importantly, we have access to several zebrafish lines that will enable us to complete this research:

- Tg(VMAT2:GFP) transgenic fish that label monoaminergic neurons in the brain with green fluorescent protein.
- *slc6a4a/dat* mutant fish that lack the function of the dopamine transporter in the brain and so are hyperdopaminergic.

We will investigate 3 objectives:

1) Establish an FSCV protocol to measure dopamine release in the intact larval (6 day-old) forebrain. We will use Tg(VMAT2:GFP) to accurately target dopamine neurons.

2) Build an optic flow setup to stimulate behaviour in larval fish. The setup will use a flat screen computer to play films to larvae. Fish will be restrained in agarose using a preparation that permits the eyes and tail to move freely. Films played on the screen
will stimulate behaviour: for example, a looming shadow will elicit an escape response, whereas small bite-sized stimuli will trigger hunting and feeding.

3) Measure the release of neurotransmitters in real-time by combining FSCV with optic flow. Tail movements will be recorded to show the reaction to behavioural stimulation. If dopamine release or reuptake correlates with the behavioural reaction to optical stimulation we will then manipulate dopaminergic signalling. We will either genetically alter dopamine levels using the slc6a4/dat mutant line that has heightened dopamine levels in the brain, or use drugs that selectively target dopaminergic receptors.

In summary, this project combines state-of-the-art techniques to investigate the contribution of dopaminergic signalling to behaviour by measuring the release of neurotransmitters in the intact vertebrate brain.


**Relevant BBSRC Strategic Research Priority:** World-class bioscience

Techniques that will be undertaken during the project.

- Fast-scan cyclic voltammetry
- Behavioural analysis
- Neuroanatomy
- Characterisation of mutant lines
- Pharmacological manipulation
- Zebrafish husbandry and care

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