Project Details	
Project Code	MRC22NMHBr Mosienko
Title	Regulation of stress response by astrocytes
Research Theme	Neuroscience & Mental Health
Summary	Exposure to chronically stressful situations is a major risk factor for clinically diagnosed depression. However, some individuals are less susceptible to stress and resilient to developing serious mental health illness. This project will investigate how non-neuronal brain cells, called astrocytes, fine-tune responses to stress and discover novel molecular and cellular determinants of stress resilience.
Description	Depression is the most common mental health illness affecting 1 in 4 people in the UK. It costs England an estimated £7.5 billion a year spent on services, treatments and lost employment. Exposure to chronically stressful situations is a major risk factor for clinically diagnosed depression. However, some individuals are more susceptible to stress than others. To respond to stress, the brain first integrates signals in the brainstem and the limbic system which includes the prefrontal cortex, amygdala and hippocampus. These in turn activate signalling networks in the hypothalamus and pituitary gland and lead to glucocorticoid release from the adrenal gland into the blood. Glucocorticoids feed back to the limbic system to regulate the strength of the stress response and to restore the system to baseline level after stress. Understanding the cellular and molecular basis of response and resilience to stress will lay the foundation for the development of drugs that might prevent extreme stress responses and possess antidepressant properties. Astrocytes are the most abundant type of brain glial cells. They integrate various physiological signals through modulation of synaptic transmission. Lactate has been recently identified as a novel gliotransmitter released specifically by astrocytes (Mosienko et al., Neuroglia 2018; Tang et al., NatCommunications 2014). During periods of increased local brain activity, astrocytes elevate their release of lactate to support a wide range of brain area-dependent functions, including memory (hippocampus and cortex), decision making (amygdala and anterior cingulate cortex) and attention (brainstem). Our ongoing work shows that astrocytic lactate in amygdala also drives the response to acute stress (Mosienko et al., in preparation), and hippocampal astrocytic lactate reinforces the acute response to novel stimuli (Vaccari Cardoso et al., Glia 2021). Building on our current work, this project will investigate limbic lactate pathways that regulate and predict responses to chronic stress. Using cutting edge technologies including lactate amperometry and 2-photon imaging in behaving animals, and cell-type specific next generation sequencing this project will address the following main questions: 1. How does stress affect lactate metabolism in the limbic brain areas? 2. Can differences in lactate metabolism within the limbic system predict responsiveness to stress? 3. What are the underlying genetic determinants of stress resistance in astrocytes? The prospective student will employ in vivo biosensors in behaving animals to discover how chronic stress affects extracellular brain lactate metabolism. To monitor changes to intracellular lactate metabolism specifically in astrocyte, stereotaxically injected viral vectors encoding a lactate biosensor in combination with in

	vivo 2-photon imaging will be used. Throughout the stress paradigm motivation, aversive and social behaviours of mice will be assessed. To discover astrocyte molecular pathways underlying stress resistance and responsiveness the student will analyse profiling changes in gene expression in astrocytes isolated from animals undergoing chronic stress, and perform live-cell imaging of astrocyte calcium signalling, metabolic state and gliotransmitter release. The student will join a well-funded lab and vibrant Neuroscience community at the University of Exeter and will be supported throughout the PhD by the excellent team of researchers in Exeter and at the University of Bristol. The project will provide a unique chance to receive training in in vivo physiology and 2-photon imaging, live-cell calcium imaging, big data analysis and bioinformatics by a collaborative research team with an outstanding track-record in cellular, system and behavioural neuroscience, and genetics.
Supervisory Team	
Lead Supervisor	
Name	Dr Valentina Mosienko
Affiliation	Bristol
College/Faculty	College of Medicine and Health
Department/School	Neuroscience and Mental Health
Email Address	v.mosienko@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Michael Ashby
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology and Neuroscience
Co-Supervisor 2	
Name	Professor Katie Lunnon
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Neuroscience and Mental Health
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	