

Cumulative effects of stress across the lifespan on behaviour and mitochondrial function in the brain

Project Reference: TRG-PD-JD26

Supervisor: Professor Jeff Dalley (jwd20@cam.ac.uk)

Department/Institute: Psychology

Website: <https://www.neuroscience.cam.ac.uk/directory/profile.php?jwd20>

Collaborating co-supervisor: Professor Andrew Murray (PDN)

Main BBSRC strategic theme: Bioscience for an integrated understanding of health

Secondary BBSRC strategic theme: n/a

Project outline:

Depression and anxiety in adolescents often result from early-life adverse experiences such as trauma or abuse. However, the brain mechanisms linking early-life stress (ELS) to psychopathology in adulthood remain poorly understood. Recent research in the Dalley and Murray labs has implicated cellular and molecular substrates of mitochondrial function as mediators of stress outcomes and behaviour. The high energetic demands of the brain make it particularly vulnerable to mitochondrial impairments, particularly in the prefrontal cortex – a region critical for emotional regulation and decision-making. However, the cell-type specificity of these effects and their potential relationship to behavioural phenotypes have not been well investigated. This project will investigate the enduring effects of repeated maternal separation stress, a rodent model of neglect in early life, to characterise cell-type specific mitochondrial dysfunction in the prefrontal cortex, hippocampus, and amygdala. The specific aims of this projects are: (1). To validate previous behavioural and mitochondrial respirometry findings by performing transcriptomics and proteomic analysis of rodent brain tissue; (2) To assess behavioural correlates using touchscreen-based cognitive tasks such as the ambiguous cue and probabilistic reversal learning tasks to evaluate decision-making; (3). To explore the sex dependency of stress on mitochondrial function; (4). To identify molecular targets and signalling pathways involved in stress-induced mitochondrial impairments by focusing on uncoupling proteins, biogenesis transcripts (SIRT1, PGC-1 α), and mitochondrial antioxidant activity (SOD, CAT). This innovative programme of research aims to provide novel insights into stress-mitochondria interactions and identify translationally relevant biomarkers and therapeutic targets for precision medicine approaches in mental health.