Project Details	
Project Code	MRCNMH24Br Montgomery
Title	Maturation of expanded learning and memory circuits
Research Theme	Neuroscience & Mental Health
Summary	How do the billions of neurons in your brain change as you mature? How do they grow and form connections? Establishing the right neural morphologies and connectivity is essential for healthy development. This project aims to understand the basic biological mechanisms that determine interactions between neuron number, plasticity and longevity during circuit maturation, in a novel, emerging insect model of neurodevelopment.
Description	Learning and memory circuits are by necessity environmentally sensitive. The imprint of memories on behavioural circuits can involve multiple mechanisms including changes in protein expression, neuronal growth processes, and connectivity. Understanding how these processes play out across the lifespan is a central challenge of behavioural neuroscience, and disruption of these processes underpins many neurodevelopmental disorders in humans. Invertebrate models have been at the forefront of research into learning and memory circuits. Drosophila is the predominant insect model for neurogenetics, but other insect species provide phenotypic traits that more closely parallel those observed in our own species. Human brains have uniquely expanded neuron numbers, increased neurodevelopmental plasticity, and are required to function over elongated lifespans. Many neurodevelopmental disorders may arise directly as a consequence of these derived traits. As such, developing tractable model systems that reflect these conditions can be used to understand the basic biological mechanisms that determine interactions between neuron number, plasticity and longevity. Focusing on the primary site of insect associative memories, the mushroom bodies, as a model to understand the circuit maturation, this project will develop a unique model system. Heliconius butterflies display an extreme enlargement of the mushroom bodies, with 8-fold increase in intrinsic neuron number, accompanied by a specific expansion of visual processing areas and a prolonged adult lifespan (Couto et al. Nat Comms 2023). The increase in learning and memory circuits coincides with enhanced performance in multiple cognitive assays and increased environment-dependent synaptic pruning (Young et al. BioRxiv 2023). Enhanced cognitive ability in Heliconius therefore arose through expansion and specialization of learning and memory circuits, allied with increased environmental sensitivity and elongated neural longevities, providing an insect parallel of human brain evolution and development. Using this model we will ask: 1. How do processes of circuit maturation scale with network size? We will pioneer the use of high throughput NanoCT imaging of heavy-metal stained brains, allied with electron microscopy of synaptic structure, to reconstruct individual neural morphologies and projectomes across the adult lifespan in Heliconius and related genera with smaller mushroom bodies. This will allow us to understand how individual neural morphologies and circuit architectures change during adult maturation. 2. What molecular processes facilitate plasticity and stabilize long term memories? Identifying cell groups involved in learning is critical for

understanding how these systems are organised. We will use molecular markers of neural activation to link performance under specific cognitive tasks to molecularly and morphologically defined cell types. We will then test how neural activation under different learning tasks corresponds to observed changes in neural morphologies, and the molecular response to neural activation. By comparing data across species with stable and unstable long-term memories, and performing perturbation experiments, we can link changes in molecular and cellular processes to increased memory fidelity. 3. How is functional longevity maintained as neural lifespan is increased? Increased developmental plasticity and longevity of neural cells likely has an intrinsic energetic cost which must be matched by mitochondrial activity. Across humans and animals, neuronal health is linked to the balance of mitochondrial biogenesis and death. Preliminary electron microscopy data suggests an increased abundance of mitochondria in Heliconius dendrites. Combining confocal and electron microscopy we will changes in mitochondria abundance and location across the adult maturation of the mushroom body, and link these to synaptic pruning and preservation during memory formation.

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