Project Details	
Project Code	MRCNMH24Ex Ryu
Title	In vivo analysis of stress system dynamics
Research Theme	Neuroscience & Mental Health
Summary	Dysregulated activity in the stress system is linked to early life stress, chronic stress and depression. To understand how this dysregulation occurs, we need to know how the multiple parts of the system coordinate their activity. This is challenging in mammals as the system's parts are anatomically distant. We will overcome this issue using zebrafish, which will enable us to perform live imaging of the system's multiple parts in an intact animal for the first time.
Description	The hypothalamic-pituitary-adrenal (HPA) axis is a key regulatory system for homeostasis, highly conserved throughout evolution. It is a multisystem axis that culminates in the regulated output of glucocorticoid hormones (GCs) with widespread targets throughout the body. It regulates basal tones of metabolic, cardiovascular, cognitive and immune systems and prepares these systems for adaptive responses in case of stress exposure. A critical feature of the HPA axis, necessary for achieving its diverse roles, is its dynamic pattern of activity. In mammals, GCs are released in a pulsatile manner following both a circadian and an ultradian pattern. HPA dynamics are altered in a myriad of diseased states including trauma, cushing's syndrome and depression. Pulsatile GC production arises through the interplay between the pituitary and adrenal glands. How is the coordination between pituitary and adrenal gland established and regulated? Despite the importance of understanding pituitary-adrenal interactions, it has been difficult to experimentally tackle this question as these two glands are far away from each other. Thus, cell activity from each gland cannot be recorded simultaneously in mammalian models. The overall goal of this project is to address the establishment and regulation of the coordinated activity of pituitary and adrenal glands using a small vertebrate model, the zebrafish larva. Zebrafish show significant homology with other vertebrates, but are much smaller and easier to breed. Larval zebrafish are transparent and develop externally, making them amenable to experimental observation. Importantly, as a vertebrate, zebrafish possess Hypothalamo-Pituitary-Interrenal (HPI) axis with high degree of conservation to the mammalian HPA axis. The Ryu lab is a pioneer in studying HPI axis development and function in zebrafish and has generated cell-type specific transgenic animals that specifically label corticotroph cells in the anterior pituitary and cortisol-producing cells in interrenal gland. Utilizing the same approach, transgenics fish that express the activity sensor GCaMP6 in both corticotroph and steroidogenic cells will be generated by the start of the project. Using this double transgenic zebrafish line, we propose, for the first time, to image pituitary and adrenal gland activities simultaneously in an intact animal. This will enable the PhD student to ask the following fundamental questions in stress biology: 1. What is the Pituitary-Interrenal (P-I) temporal coordination at basal state, and how does it change with time of day? By imaging Ca2+ variations, simultaneously in the corticotroph and interrenal populations, the student will determine whether these activities are pulsatile as in rodents. Further, the student

	can adapt a mathematical model of pituitary-adrenal interactions, originally developed by Walker, to explain the observed P-I interactions. 2. When does normal P-I coordination emerge during development? Establishing this will enable future studies about how early life stress impacts HPI dynamics and future animal behaviour. Additionally, the student may choose to zoom in on the pituitary corticotroph population and analyze functional connectivity (correlations) among corticotroph cells at different stages of development. 3. How is the P-I coordination altered under stressful conditions? The student will determine how the P-I activity coordination changes dynamically in response to a stressor. If the student is most interested in this question, the student will be trained to generate transgenic fish that express the light-sensitive channel rhodopsin in pituitary corticotroph cells. Light stimulation will be used to excite the corticotroph population to either induce a stress response or to affect the response to a stressor (assessed by imaging interrenal population activity). This will establish what key dynamical aspects that are necessary/sufficient to mediate a stress response.
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