Project Details	
Project Code	MRCNMH24Ca Triantafilou
Title	Deciphering how NLRP3 inflammasome- and STING-driven inflammatory pathways are linked to mental health disorders
Research Theme	Neuroscience & Mental Health
Summary	There is an interaction between activation of the innate immune system, pro-inflammatory cytokines and changes in the brain relating to mood and behaviour. Innate immune pathways, such as the Inflammasome and STING can detect diverse danger signals and trigger inflammatory reactions. According to our hypothesis, these innate pathways are central mediators by which psychological stressors can contribute to the development of depression and psychiatric disorders.
Description	The inflammatory response is a tightly controlled response of the host innate immune system to exogenous and endogenous threats. Accumulating evidence indicates that in addition to its role in precipitating autoimmune disorders, disturbances in the systemic inflammatory response can also disrupt neuronal function resulting in mental health disorders like depression and accelerated age-related cognitive decline. Although a number of innate immune pathways, such as the Nod-like receptor pyrin containing 3 inflammasome (NLRP3)(1) and the cGAS-STING pathway(2) appear to be linked to the pathogenesis of psychiatric disorders, questions still remain as to exactly which innate immune (NLRs, RLRs, etc) and metabolic (glycolysis, mitochondrial etc) pathways are involved and how they relate to observed changes in discrete brain areas (prefrontal cortex, hippocampus, etc) and behaviour (impaired mood, fatigue, etc). We will utilize transcriptomics and metabolomics data from individuals that have been immune challenged, to identify the innate immune pathways that are activated in depression in different age groups. In addition, we will utilize mendelian randomization analyses of NRLP3 and STING biomarkers using genetic variants to analyse the relationship between the innate immune system and psychiatric disorders. The findings from this study could lead to the identification of novel therapeutic targets for psychiatric disorders in the future as well as in drug repurposing, an effective approach to complement traditional drug discovery by reducing the time and monetary-related costs. To address this, the student will have access to: 1) Paired serum and paxgene samples from 40 healthy young participants before and 5 hours after intravenous lipopolysaccharide (1ng/Kg) and placebo (saline); 2) paired serum and RNASeq data from 30 young and older participants 5 hours after Interferon-beta injection. Repeat physiological (blood-pressure, temperature etc), heart-rate variability, cognitive (POMS, fVAS, KSS, reward/punishment learning) and MRI data (T1 structural, resting-state-fMRI, diffusion-weighted spectroscopy) is available on all participants. The PhD will address the following questions: 1) Which innate immune pathways (Toll-like receptors, inflammasomes, STING, etc) are activated following interferon-beta and lipopolysaccharide injection (Bio-informatics analysis of RNASeq datasets) 2) What is the causal relevance of NLRP3 & STING in psychiatric disorders (Mendelian randomization analyses) 3) What is the cytokine profile of each individual using MSD & ELISA assays 4) How do these “immunological profiles” relate to inter-

	individual differences in A) subjective response to inflammation (e.g. reduction in mood or experience of fatigue)? And B) observed in brain imaging? References: 1. Kaufmann, F.N. et al. NLRP3 inflammasome-driven pathways in depression: Clinical and preclinical findings. Brain Behav Immun 64, 367-383 (2017). 2. Duan, N. et al. Therapeutic targeting of STING-TBK1-IRF3 signalling ameliorates chronic stress induced depression-like behaviours by modulating neuroinflammation and microglia phagocytosis. Neurobiol Dis 169, 105739 (2022).
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