HOW DO MATERNAL INFECTIONS DURING PREGNANCY INCREASE THE CHILD'S RISK FOR DEVELOPING SCHIZOPHRENIA?

The detrimental effects of smoking, drinking, or excessive stress during pregnancy on the unborn child are now well-documented and widely known to the public. However, the effect of maternal *infections* during pregnancy on fetal brain development are less well known, until they recently reached the headlines in the aftermath of the recent Zika virus outbreaks. Images of children born with abnormally small heads (microcehpaly) and developmental problems circulated the news, putting the research area of *maternal immune activation* (MIA) into the public eye.

In reality, earlier outbreaks of viruses, including the 1957 Asian influenza epidemic, provided scientists with the basis of MIA research. A few decades after the 1957 epidemic, it was observed that people who were fetuses during this period were at a much higher risk of developing neurodevelopmental disorders, such as schizophrenia in later life. Schizophrenia is a debilitating psychiatric disorder, affecting around 1% of the population, and characterised by a range of cognitive symptoms. Recently, research has focused on developing animal models of MIA to identify the mechanisms by which prenatal infection leads to cognitive deficits in the adult offspring. Critically, understanding the biology behind the MIA theory of schizophrenia will allow the identification of novel therapeutic targets in schizophrenia, ultimately leading to the development of new treatments for this devastating condition.

It is now known that the maternal inflammatory response to MIA, through the production of pro-inflammatory proteins called *cytokines*, rather than the specific pathogen, is one such mechanism (see Figure 1). It has been estimated that 14-21% of schizophrenia cases are linked to exposure to MIA *in utero*, but the mechanisms behind this are poorly understood. The research presented here aims to understand the role of the maternal environment, both prenatally and postnatally, in a rat model of MIA, and identify molecular biomarkers of behavioural dysfunction in the offspring.

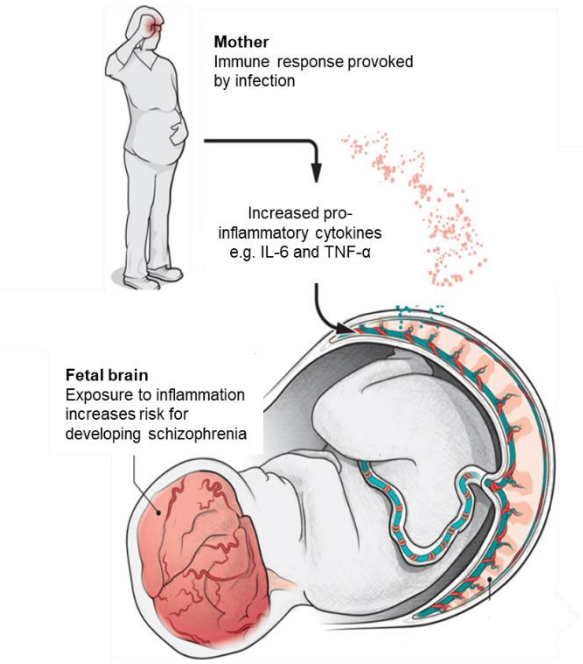

Figure 1: the maternal immune activation (MIA) hypothesis of schizophrenia. Adapted from Estes and McAllister 2016.

Pregnant rats were injected with a clinically-relevant dose of viral genetic material, called *poly I:C*, which is known to cause an inflammatory response similar to that of a virus. The production of pro-inflammatory cytokines were measured 3 hours after this treatment. During early life (6-14 days old), the behavioural interaction between mother and offspring were recorded, as well as the vocalisations of the offspring. During adulthood, the offspring were tested on a range of cognitive tasks. Expression of genes and proteins relevant to the pathogenesis of schizophrenia were measured in the offspring's brains.

We show that MIA reduces the amount of time mothers spend engaging in particular maternal behaviours and causes offspring to vocalise more than their control counterparts. In adulthood, offspring exposed to MIA prenatally exhibit deficits in cognitive flexibility, but surprisingly display increased pro-social behaviours with other rats. We show that these behaviours are programmed prenatally, and may be related to the severity of the maternal inflammatory response to MIA. Investigations into the molecular changes in the offspring brain are ongoing, but we predict to see a reduction in specific proteins related to schizophrenia expressed in neurons in the offspring brain.