The prenatal maternal response to immune activation predicts offspring cognitive dysfunction in a rat model of schizophrenia

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Converging evidence from epidemiological studies and animal models implicates maternal immune activation (mIA) as a risk factor for neurodevelopmental disorders such as schizophrenia in the adult offspring. The transient increase in maternal pro-inflammatory cytokines following mIA is thought to perturb fetal neurodevelopment and results in cognitive deficits. Here, we employed a split-litter cross-fostering design to investigate how the prenatal and postnatal maternal environments interact to predict offspring cognitive deficits in a rodent model of mIA.

20 female Wistar rats were timed-mated and treated with a single intraperitoneal injection of 10mg/kg bodyweight polyinosinic-polycytidylic acid (poly I:C; low-molecular weight, InvivoGen) or vehicle (endotoxin-free 0.9% saline) on gestational day 15 (GD15). Offspring were culled to 10 pups/litter on postnatal day 1 (PD1) and either crossed to a dam in the opposite treatment group or remained in their home litter. Offspring ultrasonic vocalisations (USVs) were recorded on PD6, 10, and 14 and analysed using the open-source MATLAB script MUPET. Offspring were tested on the attentional set-shifting task (ASST) in adulthood. Global DNA methylation in the frontal cortices of offspring at a prenatal (GD21) and postnatal (PD21) time-point were measured by ELISA (Enzo Life Sciences). Statistical analyses were carried out in SPSS using General Linear Mixed Models (GLMM).

Prenatal exposure to poly I:C significantly increased the number of syllables emitted by female (GLMM, $F_{1,19}$=6.26, p=0.022, n=24-28) and male (GLMM, $F_{1,20}$=8.87, p=0.008, n=25-31) pups with no effect of cross-fostering. In adulthood, offspring exposed to poly I:C showed a deficit in the ASST as evidenced by a significant increase in the intra-extra dimensional shift, regardless of sex (GLMM, $F_{1,49}$=7.42, p=0.009, n=5-7). Poly I:C caused a significant and sex-specific increase in global DNA methylation in males only at GD21 (GLMM, $F_{1,8}$=18.97, p=0.002), but increased DNA methylation in females only at PD21 (GLMM, $F_{1,8}$=6.39, p=0.035).

Our data suggests that the prenatal maternal response to poly I:C, rather than the postnatal maternal environment, is critical for the developmental programming of behavioural and cognitive deficits associated with schizophrenia in a rat model of mIA. Using a split-litter cross-fostering design we show that mIA by poly I:C on GD15 causes an increase in number and duration of vocalisations in early postnatal life followed by a clinically-relevant deficit in cognitive flexibility in adulthood, regardless of sex or the postnatal maternal environment. mIA may induce these developmental changes through an epigenetically-regulated mechanism which acts in a sex- and age-specific manner.