Combined prenatal immune activation and peri-pubertal stress alters the neurochemical profile in the mouse cortex but not hippocampus

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TARGET AUDIENCE – Scientists and clinical researchers with interest in neurochemistry and developmental disorders.

PURPOSE – Both genetic and environmental factors are determinant for the emergency of schizophrenia and susceptibility for psychopathology can be potentiated by the co-incidence of multiple environmental risk factors, including prenatal maternal infection and peri-pubertal psychological stress [1]. Immunological insults in pregnant mice revealed that mechanisms underlying aberrant behaviour in adulthood include alterations to dopaminergic, GABAergic and glutamatergic systems [2-6] and neuroinflamation but not astrogliosis [7]. Nonetheless, severe developmental brain disorders are rare in the offspring of mothers exposed to infection during pregnancy, and thus other factors are required to trigger psychopathology, which could be either genetic predispositions [8] or environmental challenges [7]. We tested the hypothesis that peri-pubertal stress after asymptomatic maternal infection leads to development of neurochemical alterations that are characteristic of neurodevelopmental brain disorders.

METHODS – Prenatal immune activation and peri-pubertal stress exposure was performed in C57BL/6 mice as in Giovanolli *et al.* (2013) [7]. Briefly, maternal immune activation was induced by the viral mimetic polyriboinosinic-polyribocytidilic acid (poly(I:C), 1 mg/kg, i.v. on gestation day 9). Offspring were then exposed to variable and unpredictable stress, namely 5 distinct stressors on alternate days, from P30 to P40, a maturational period known to be highly sensitive to disrupting effects of traumatizing events. Behavioural analyses including spatial recognition memory in the Y-maze and discrimination reversal learning in the water T-maze were performed in adulthood. MRS under isoflurane anaesthesia was carried out at P90 in a 14.1 T magnet with a quadrature surface coil. After FAST(EST)MAP shimming, ^{1}H spectra were acquired from hippocampus or anterior cortex using SPECIAL [9] with TE=2.8 ms and TR=4 s, and then analysed with LCModel.

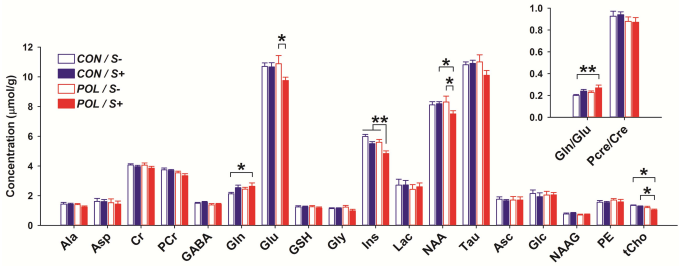

Figure 1. Cortical neurochemical profile. *p<0.05, **p<0.01 based on Fisher's LSD comparison after ANOVA (n=7-9). Experimental groups: CON, prenatal control vehicle treatment; POL, prenatal poly(I:C) treatment; S-, no pubertal stress; S+, pubertal stress exposure.

RESULTS – Stress or immune activation were devoid of effects on the neurochemical profiles. Only the combination of the two environmental factors induced alterations in the cortex (fig.1). Namely, prenatal immune activation followed by peri-pubertal stress resulted in increased concentration of glutamine (P<0.05 *vs.* control, +24%) and reduced concentration of glutamate (P<0.05 *vs.* Poly(I:C)-treated without stress, -10%), *myo*-inositol (P<0.01 *vs.* remaining groups: -19% to -12%), NAA (P<0.05 *vs.* Poly(I:C)-treated without stress and *vs.* vehicle-treated with stress, -10% to -8%) and choline-containing compounds (P<0.05 *vs.* vehicle-treated with or without stress, -19% to -23%). Gln/Glu was affected by the combined exposure of stress and immune activation (P<0.05 *vs.* control, +35±4%). Single or combined exposure to immune activation and stress were devoid of metabolic alterations in the hippocampus, in agreement with normal hippocampal-dependent spatial recognition memory in the Y-maze. In contrast, prefrontal-associated reversal learning of right-left discrimination in the T-maze was strongly affected by the combination of prenatal immune activation and peri-pubertal exposure to unpredictable stress.

DISCUSSION/CONCLUSION – Peri-pubertal stress unmasked latent vulnerability to psychopathology in mice exposed to the prenatal immune challenge with poly(I:C). In particular, the combination of the two environmental stressors induced increased concentration of glutamine and caused a reduction of glutmate, NAA, *myo*-inositol, and choline-containing compounds in the frontal cortex, relative to untreated, undisturbed mice. These modifications were not patent in the hippocampus. Accordingly, prefrontal-associated discrimination reversal learning was strongly affected by the combination of prenatal immune activation and peri-pubertal stress exposure, while hippocampal-dependent spatial learning was fully preserved.

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