Voxel-based morphometry using DARTEL in the mouse reveals differential impact of early and late prenatal inflammation on adult brain.

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Introduction

Exposure to maternal inflammation in response to infection is associated with an increased risk for neurodevelopmental disorders such as schizophrenia and autism [1,2]. In adults patients with schizophrenia, the levels of inflammatory cytokine in maternal serum during prenatal life have been shown to correlate with lower volumes in limbic-temporo-striatal circuits [3]. However there are limitations in interpreting the direction of causal relationships in correlational analyses. Animal models offer the opportunity to directly explore the impact of prenatal inflammation on adult brain maturation and exposure of pregnant mice to the viral analogue PolyIC causes a transient increase in inflammatory cytokines and is agreed to precipitate post-natal behavioural changes relevant to neurodevelopmental disorders. However the exact phenotype depends upon the time window of exposure, with debate surrounding whether early exposure elicits 'worse' [4] or distinct [5,6,7] outcomes and the extent to which changes mirror features of autism or schizophrenia [5,6,7]. Therefore we investigated the impact of early or late prenatal inflammation on post-natal brain morphometry in the mouse.

Methods

Following previous methods [6], PolyIC (5mg/5ml/kg) or saline (control) was administered to pregnant C57/B6 mice via tail vein in early (gestation day 9) or late gestation (day 17). These days are equivalent to mid 1st and mid 2nd trimester of human pregnancy respectively. Mice were scanned at 12 weeks i*n-vivo* in a 7 T small animal scanner (maximum gradient 360 mT/m; 70/16 PharmaScan, Bruker Biospoin GmbH, Germany) with 23mm quadrature RF coil. Axial images were acquired over less than 1 hour per animal [T2 – weighted: Effective TE = 38.71ms, TR = 4614.566ms, No of Average = 6, Rare Factor =8, Acquisition Matrix = 256 °— 256, FOV = 25 °—25mm, Slice thickness = 0.25mm, Scan Time = 11m4s]. Final numbers were: controls n=8, PolyI:C n=14 (PolyI:C, GD9 n=8, GD17 n=6). Group differences in volumes across whole brain were analysed using a diffeomorphic framework for registering images, DARTEL [8]. Statistical analysis in Statistical Parametric Mapping 8 software used "Single-subject: conditions & covariates" to compare tissue volume between different groups. Results were thresholded at p<.001 with a cluster extent of 30 voxels.

Results

As shown in Figure 1 early prenatal exposure to PolyIC caused lower volumes in hippocampal, subicular and striatal brain regions compared to saline exposed controls. This was accompanied by increased volumes in the mid-brain and expansion of the lateral ventricles. In contrast, Figure 2 shows that mice exposed to later prenatal inflammation had more extensive volumetric differences in cerebellar regions, with mainly lower volumes compared to controls. In addition these animals had lower volumes in hippocampal regions and lateral ventricles with greater volumes around the amygdala and mid-brain regions.

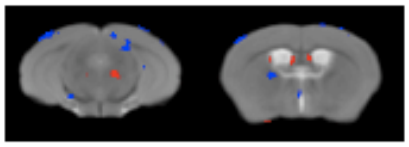

Figure 1: Early prenatal inflammation

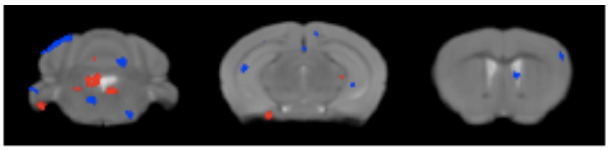

Figure 2: Late prenatal inflammation

Figures 1 and 2 show representative coronal sections through mouse brain, normalized to a customized template and co-registered to a publicly available mouse template [9]. Blue = lower volumes relative to control; Red = higher volumes.

Discussion

Neurodevelopmental disorders such as schizophrenia and autism, while diagnostically distinct, share a number of features. They have their origins in fetal life and share genetic and environmental risk factors. They impact upon cognition and cause theory of mind and executive function difficulties. Thus these conditions can be considered to reflect a common brain vulnerability to brain dysmaturation [7]. Our work suggests that the timing of prenatal insult results in distinct post-natal differences in brain morphology. Increased lateral ventricular volume together with lower limbic-striatal volumes observed in the early exposed mice is consistent with similar anatomical features in schizophrenia [10]. In contrast, cerebellar dysmorphology and smaller lateral ventricles as found in the late exposed mice, have been reported in autism [11,12]. Thus we speculate that periods of vulnerability in prenatal brain development are an important component of the aetiological mechanisms at play in disorders affecting neurodevelopment with developmental changes during an early pregnancy window associated with schizophrenia spectrum outcomes [1] and those in a later window with autism spectrum outcome [7].

References

1. Brown AS (2006) Schizophr Bull 32: 200-202; **2.** Libbey et al. (2005) J Neurovirol 11: 1-10; **3.** Ellman et al. (2010) Schizophr Res; **4.** Meyer et al. (2007) Neuroscientist 13: 241-256; **5.** Li et al.. (2010) Neuroimage 52: 1-8; **6.** Li et al. (2009) PLoS One 4: e6354; **7.** McAlonan et al., (2010) NeuroSignals in press; **8.** Ashburner (2007) Neuroimage 38: 95-113; **9.** Chan et al. (2007) Neuroscience 144: 604-615.**10.** Chua et al. (2007) Schizophr Res 89: 12-21; **11.** Vidal et al. (2008) Psychiatry Res 163: 106-115; **12.** Courchesne (1999) Neurology 52: 1106-1107.