Brain Development and Effects of Chronic Fetal Hypoxia in Neonatal Guinea Pigs: DTI, T2 and Volumetric MRI at 9.4T

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INTRODUCTION Fetal hypoxia is one of the common pregnancy complications that lead to fetal neuro-developmental abnormalities [1]. The CNS injury to the developing fetal brain can cause functional and behavioral disorders in later life including cerebral palsy, epilepsy and schizophrenia. However, the impact of fetal hypoxia to the brain development from neonates to young adulthood has not been well described. In this study, we characterized the physiological, morphological and structural changes during brain development and the effect of fetal hypoxia to the brain maturation processes on postnatal guinea pigs in a longitudinal manner using *in vivo* MRI of T_2 mapping, DTI and brain volume measurements.

METHODS: *In vivo* MRI experiments were performed at a 9.4 T Varian system (Agilent Technologies, Santa Clara, CA). A quadrature surface RF coil consisting of two geometrically decoupled loops was placed on the animal head for transmitting and receiving at 400 MHz proton frequency. The T_2 data set was acquired using a multi-slice spin echo sequence with FOV = 2.5x2.5 cm^2, matrix = 128x128, TR = 1 s, TE = 12/24/36/48/60 ms, NEX = 2, thk = 1 mm. MR parameters for DTI were FOV = 2.5x2.5 cm^2, matrix = 128x128, TR/TE = 1000/23 ms. Diffusion gradients were applied along six different orientations with b = 832 s/mm^2, NEX = 2, thk = 1 mm. High resolution T_2-weighted (T_2w) images were acquired with a rapid acquisition with a relaxation enhancement (RARE) sequence, FOV = 3.0x3.0 cm^2, matrix = 256x256, TR/TE = 4000/72 ms, NEX = 2, thk = 1mm, echo train length = 8, echo spacing = 18 ms. DTI and T_2 data were acquired at 4 time-points: postnatal day 1 (P1), day 7 (P7), day 28 (P28) and day 42 (P42), and T_2w data at nine time-points (P1, P7, P14, P21, P42, P56, P70, P84) from 7 hypoxic (HPX) and 7 normoxic (NMX) guinea pigs. Image analysis was performed using FSL [3] and ImageJ [4].

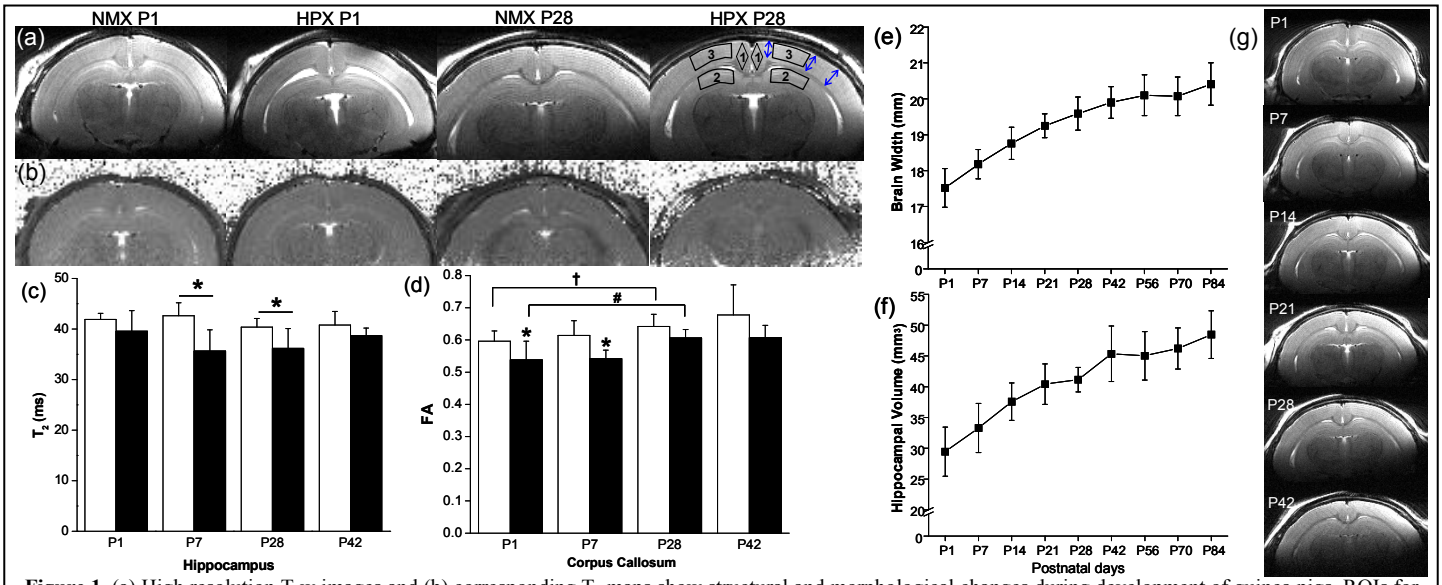

Figure 1. (a) High resolution T_2w images and (b) corresponding T_2 maps show structural and morphological changes during development of guinea pigs. ROIs for the T_2 values (1. cingulate, 2. hippocampus, 3. cortex) and arrows for the cortical thickness are indicated in Fig. 1 (a) right. Comparisons of T_2 values in the hippocampus (c) and FA in the corpus callosum (CC) (d) of NMX (□) and HPX (■) groups at postnatal days P1, P7, P28 and P42 (* $p < 0.05$ comparison between HPX and NMX at each age; # $p < 0.05$ comparison between P1 & P28 of HPX; † $p < 0.05$ comparison between P1 & P28 of NMX). Structural changes of NMX guinea pigs from birth (P1) to P84: (e) brain width (f) hippocampal volume changes and (g) corresponding T_2w images.

RESULTS AND DISCUSSION: The HPX group showed lower T_2 values in the hippocampus (HPC) compared to the NMX group at P7 ($p < 0.01$) and P28 ($p < 0.02$) (Fig. 1c). Both cortex and cingulate did not show any significant differences in T_2 values. FA values in the corpus callosum (CC) of HPX were lower than those in NMX (P1: $p < 0.05$ and P7: $p < 0.02$) (Fig. 1d). Significant structural changes were observed during development such as increases in brain size and hippocampal volume over 6 weeks of NMX guinea pigs (Fig. 1e, 1f). Although statistically not significant, the overall brain sizes as well as hippocampal volumes of HPX animals were consistently smaller than those of NMX animals.

Lower T_2 values in HPC of HPX guinea pigs suggest that fetal hypoxia affects tissue maturation process, particularly in the hippocampus, which is critical in learning and memory functions. Lower T_2 values in the hippocampus from P7 to P28 in HPX than in NMX suggest possible CNS damage due to fetal hypoxia and persistently slower tissue maturation. Increases of FA values in the CC in both NMX and HPX animals are consistent with the axonal myelination during development [5]. Lower FA values in HPX guinea pigs suggest that fetal hypoxia affects brain development, especially white matter maturation in the CC. This study demonstrated the feasibility of quantitative noninvasive measurement of postnatal brain development of guinea pig neonates in a longitudinal manner using DTI and T_2 mapping.

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