Neurobehavioral consequences of preterm birth in a rabbit model

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Background: Preterm birth is the most significant problem in obstetrics accounting for 5-18\% of all deliveries. Encephalopathy of prematurity encompasses the multifaceted diffuse brain injury resulting from preterm birth. Current animal models exploring the underlying pathophysiology of encephalopathy of prematurity employ significant insults to generate gross central nervous system abnormalities. To date the exclusive effect of prematurity was only modeled in a non-human primate model.

Objectives: We aimed to develop a representative encephalopathy of prematurity small animal model only dependent on preterm birth.

Methods: Time mated New-Zealand white rabbit does were either delivered on 28 (pre-term) or 31 (term) postconceptional days by caesarean section. Neonatal rabbits underwent neurobehavioral evaluation on 32 days post conception and then were transcardially perfuse fixed. Neuropathological assessments for neuron and oligodendrocyte quantification, astrogliosis, apoptosis and cellular proliferation were done. Lastly, ex-vivo high-resolution Magnetic Resonance Imaging was performed to calculate T1 volumetric and Diffusion Tensor Imaging derived fractional anisotropy and mean diffusivity.

Results: Preterm birth was associated with a motoric (posture instability, abnormal gait and decreased locomotion) and partial sensory (less pain responsiveness and
failing righting reflex) deficit that coincided with global lower neuron densities, less oligodendrocyte precursors, increased apoptosis and less proliferation. These region-specific histological changes corresponded with Magnetic Resonance Diffusion Tensor Imaging differences. The most significant differences were seen in the hippocampus, caudate nucleus and thalamus of the preterm rabbits.

**Conclusions:** In this model, preterm birth in the absence of any other contributory events, resulted in measurable neurobehavioral deficit that related with brain structural and Magnetic Resonance Diffusion Tensor Imaging findings.

![Figure 1](image1.png)  
**Figure 1.** New-born rabbit survival, body weight, brain biometrics and neurobehavioral assessment on postconceptional day 20. Term rabbits = 16, preterm rabbits = 20. Data displayed as median and IQR with significance as $^*$p < 0.05, $^*$p < 0.01, $^*$p < 0.001.

![Figure 2](image2.png)  
**Figure 2.** Neuron quantification in selected regions of interest. Representative fields from main regions of interest. Scale bar 50µm. Data displayed as median and IQR with significance as $^*$p < 0.05, $^*$p < 0.01, $^*$p < 0.001.

![Figure 3](image3.png)  
**Figure 3.** MRI derived data per region of interest. (A) T1 relative volumes (B) DTI fractional anisotropy (C) DTI mean diffusivity. Data displayed as median and IQR with significance as $^*$p < 0.05, $^*$p < 0.01, $^*$p < 0.001.