In-utero localized diffusion MRI of the embryonic mouse brain microstructure and injury

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Target audience: scientists who are interested in imaging live embryonic mouse brain microstructure and injury.

Rationale: *In-utero* MRI of the embryonic mouse brain is important for longitudinal monitoring of early brain development and understanding the links between fetal neuropathology and MRI signals through various mouse models. It, however, remains extremely challenging due to motion and limited resolution. Only recently, Turnbull and colleagues demonstrated successful *in-utero* T_1-weighted MRI of live mouse embryos [1]. Diffusion MRI (dMRI), while offering superb contrasts for characterization of embryonic brain microstructures and injuries [2-3], has not been utilized to examine live mouse embryos due to these challenges. In this study, we explored the feasibility of *in-utero* dMRI of the embryonic mouse brain using selective excitation and advanced motion correction, taking advantage of the fact that individual mouse brain occupies only a small portion of the abdomen (Fig. 1A) and fetal motions are relatively sporadic and spatially limited.

Methods: Pregnant CD-1 mice with an average litter size of eleven pups at embryonic day 17 (E17) were used in this study. Spatially selective excitation pulses were designed based on a linear class of large tip-angle excitation pulses [4] and implemented to target selected embryonic mouse brains using a 72 mm quadrature transmitter coil on an 11.7T horizontal MRI system. The pulses were integrated with a 3D diffusion-weighted gradient-spin echo (DW-GRASE) sequence [5,6] with twin-navigator echoes [7]. DTI of normal E17 mice (n=10, one per pregnant dam) were acquired using a 15mm plannar surface coil: TE/TR = 21/500 ms; two averages; four b_0 images and 30 diffusion directions; b = 1000 s/mm^2; FOV = 12.8 x 12.8 x 8 mm^3; and 0.2 mm isotropic resolution in 72 mins. Co-registered T_2-weighted images (TE/TR = 30/1000 ms) were acquired at 0.13 mm isotropic resolution in 10 mins. Five normal pregnant mice received i.p. injection of Gd-DTPA at a dose of 0.4 mMol/kg before imaging to improve SNR and tissue contrast. Another three pregnant dams were subjected to a model of intrauterine inflammation [7] and imaged at 6 hrs after injury. DWI of the injured E17 mice (n=9, three per dam) were acquired using an 8-channel rat-body phased array coil for full body coverage: TE/TR = 21/1000 ms; two b_0 images and six diffusion directions, b = 800s/mm^2; and 0.2 mm isotropic resolution in 34 min. Motions were monitored and corrected by the twin navigators and rigid registration, and images acquired during large fetal motions were rejected.

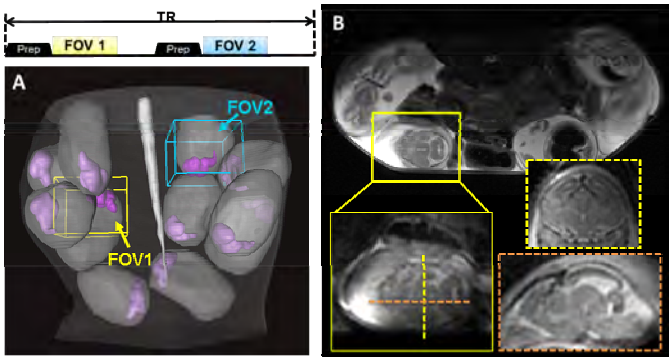

Fig. 1 (A) Anatomy of a mouse uterus with 12 embryos and the concept of localized imaging targeting individual or multiple embryos for fast imaging. (B) Localized high-resolution 3D T_2-weighted images of an E17 mouse brain (selected based on the whole-body multislice T_2 MRI).

Results and discussions: Localized T_2-weighted image of the E17 brains (Fig. 1B) (SNR = 26.1±4.3) showed clearly-defined ventricles and overall brain morphology (Fig. 1B). Major white and gray matter structures in the E17 mouse brains could be delineated in 30 direction DTI data acquired at 0.2 mm isotropic resolution (Fig. 2A), and several fiber tracts could be reconstructed in 3D (Fig. 2B). The average movement of mouse embryo during DTI acquisition was 0.18 ± 0.09 mm (n=5). Comparison between the *in vivo* and *ex vivo* DTI revealed significant differences in ADC values and relatively consistent FA values. The imaging throughput can be further increased by simultaneously imaging multiple embryos using separate fields of excitation (FOE) and interleaved acquisition (Fig. 1A). Application of this technique in a mouse model of fetal inflammatory injury revealed cortical and subcortical lesions at 6hrs after the insult (Fig. 3), characterized by reduced T_2 signals and ADC values (0.26±0.08 x 10^{-3} mm^2/s, about 1/3 of the normal ADC). Histology showed shrunken neurons and disruptions in neuronal processes and organelles (Fig. 3B). In summary, we demonstrated the feasibility of *in-utero* dMRI of the embryonic mouse brain for the first time, which is an important step toward non-invasive examination of key developmental processes, and injury progression in live mouse embryos.

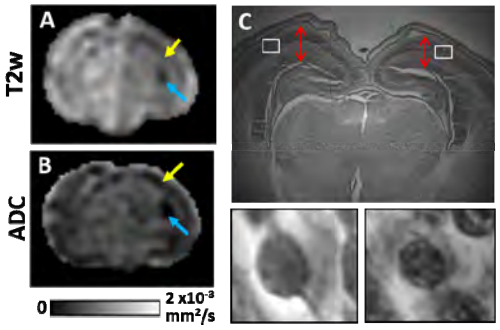

Fig. 3 A-B) T2-weighted and ADC images of an E17 brain at 6hrs after inflammatory injury showed cortical and subcortical lesions. Nissl stained section (C) showed cortical shrinkage and cellular injury in the same regions.

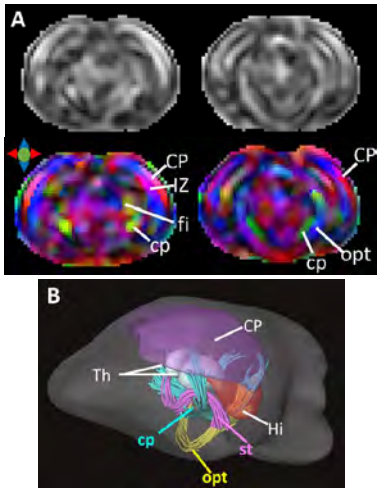

Fig. 3 (A) FA and DTI colormaps of the E17 brain at 24hrs at 0.2 mm isotropic resolution. (B) Tracking of major fibers in the E17 brain. cp-cerebral peduncle, st-stria terminalis, CP-cortical plate, Th-thalamus, Hi-hippocampus.

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