Diffusion tensor imaging studies of morphological changes in developing cerebral cortex and white matter of the early postnatal ferret

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Introduction Diffusion tensor imaging (DTI) is a valuable technique for studying brain development [1]. Two stages of morphological change give rise to characteristic DTI patterns. In the first, cerebral cortical diffusion anisotropy decreases with maturation as pyramidal cells differentiate [2, 3]. Subsequently, diffusion anisotropy increases within developing white matter as axon tracts mature and become myelinated (though anisotropy is detectable in white matter prior to full myelination) [4]. Despite considerable variation in gestational/postnatal timing of these events, their relative order is highly conserved across species. Studies of potential cause-and-effect relationships between these morphological changes using traditional histological methods are challenging because they involve terminal experimental designs. In order to observe this developmental chain, we have undertaken DTI studies of ferret development. Ferrets are naturally born at an immature stage of brain development (approximately equivalent to a mid-gestation human). Here we determine the postnatal ages in which major DTI changes are observed.

We utilize two computational tools to complement standard DTI procedures for specifically studying brain maturation. First, cortical surface models are utilized to compare cortical diffusion anisotropy changes and systematically define regions of interest for tractography. Second, a deterministic scale factor is defined that specifies connectivity between arbitrary voxel pairs in the image data set using the DTI data as input.

Methods Female ferrets ranging in age from P4 to adulthood were perfused intracardially with 4% phosphate-buffered paraformaldehyde. Single-turn solenoidal MRI coils matched in size to each brain were fabricated and used to acquire DTI data using published procedures [5]. Image resolution ranged from 0.2 to 0.35 mm-sided cubic voxels. Diffusion anisotropy was measured using 25 (P4-P31) or 22 (P59-adult) direction sampling schemes. Caret software (http://brainmap.wustl.edu/caret) was used to generate and deform cortical surface models to an adult brain "atlas" model. For voxels in selected regions, connectivity measures were calculated along paths to all other voxels in the image data set. Paths were chosen by maximizing the projection onto the diffusion ellipsoid at each inter-voxel step, and the connectivity measure is the average projection of diffusion ellipsoids onto the series of neighboring inter-voxel vectors.

Results Figure 1 shows how regions of interest are selected. Thalamic nuclei are manually traced, and primary sensory areas are obtained from cortical surface registrations to an adult atlas. Figure 2 shows early postnatal anisotropy changes in the ferret cerebral cortex. Relative anisotropy [6] in the primary visual cortex over the first month resembles primate development during the second half of gestation (Figure 1B). Thalamo-cortical connectivity to the auditory thalamic nucleus is shown for surface voxels in Figure 3.

Discussion Ferret brain development in the first postnatal month resembles primate brain development throughout the second half of gestation. This animal model therefore enables the study of early development by DTI independent of confounds related to *in utero* manipulations or preterm birth. Cortical surface modeling procedures can be combined with a deterministic connectivity analysis to design studies of both cortical and white matter development. DTI applications using this animal model can potentially be of use in determining relationships between morphological changes in cortex and white matter.

References 1. Mori, S., et al., Magn Reson Med, 2001. 46(1): p. 18-23. **2.** McKinstry, R.C., et al., Cereb Cortex, 2002. 12: p. 1237-1243. **3.** Neil, J.J., et al., Radiology, 1998. 209: p. 57-66. **4.** Wimberger, D.M., et al., J. Comput. Assist. Tomogr., 1995. 19: p. 28-33. **5.** Kroenke, C.D., et al., NeuroImage, 2005. 25: p. 1205-1213. **6.** Basser, P.J. and C. Pierpaoli, J. Mag. Reson., Ser. B, 1996. 111: p. 209-219.

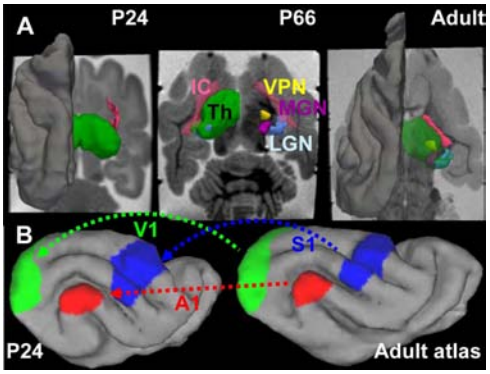

Figure 1. Specification of regions of interest. (A) Surface models of manually-traced thalamic nuclei and the internal capsule for P24, P66, and adult brains. (B) Cortical surface models are registered to the adult atlas surface. This procedure permits an objective definition of cortical area boundaries, as exemplified here for the P24 cortcical surface. Abbreviations: IC, internal capsule; Th, thalamus; VPN, ventroposterior nucleus; MGN, medial geniculate nucleus; LGN, lateral geniculate nucleus; V1, primary visual cortex; S1, primary somatosensory cortex; A1, primary auditory cortex.

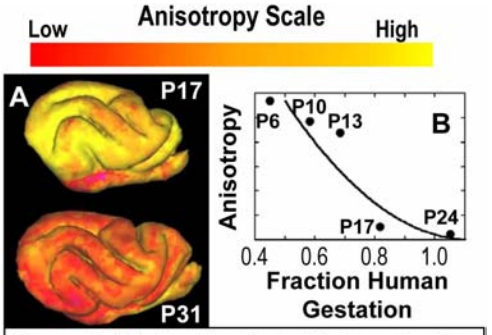

Figure 2. (A) Ferret cortical diffusion anisotropy rendered on cortical surface models (B) Cortical diffusion anisotropy in the ferret primary visual cortex (filled circles, labeled according to postnatal age) is comparable to human prenatal cortical development (McKinstry *et al.* [2] data are represented by a solid line).

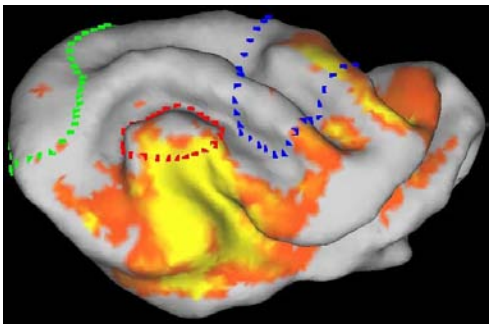

Figure 3. The low/high color scale shown in Figure 2 is used here to relay connectivity to the auditory thalamus (MGN). The color specifies the connectivity index to MGN divided by the mean connectivity to the thalamus. Surface borders are as in Figure 1B. Significant connectivity to primary auditory cortex (red border) is observed.