Longitudinal in utero characterization of cerebral cortical surface area, curvature and fractional anisotropy in the rhesus monkey

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Introduction By the beginning of the second half of rhesus monkey gestation, most of the cerebral cortical neurons have migrated to their final destinations and have initiated the process of mophological differentiation [1]. As a consequece of the rapid increase in volume fraction of the neuropil, the cerebral cortical surface (SA) increases. At the same time, gyral and sulcal folding takes place. Previous diffusion tensor imaging (DTI) studies have revealed that the fractional anisotropy (FA) of water diffusion whithin cerebral cortical gray matter decreases over this time as well. Our hypothesis is that the decrease in FA shares the same cellular bases as those that underlie macroscopic transformations such as SA and curvature changes. However, until now it has been impossible to test this hypothesis because longitudinal FA and surface data have not been available on the same individuals. Here we report *in utero* MRI analysis of anatomical and DTI data from three rhesus macaques that were imaged at gestation days (G)85, G110, and G135.

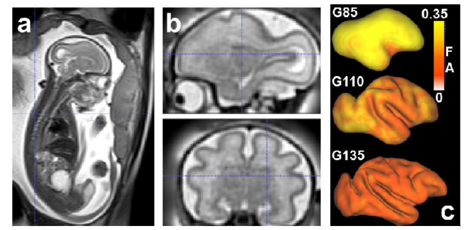

Fig.1. A raw T2W image of an entire G110 fetus is shown in (a). A reconstructed high-resolution T2W volume is shown in sagittal (b, top) and coronal (b, bottom) views. FA values were mapped onto surfaces generated from T2W volumes for each hemisphere. A representative surface color-coded with FA values is shown at G85, G110, and G135 (c).

Methods Time-mated pregnant rhesus macaques underwent MRI examination at G85, G110, and G135 using a Siemens 3T Tim Trio system. Turbo spin-echo (TSE) was used to acquire T2-weighted (T2W) images (TR/TE=5000/97ms). Multiple stacks with an in-plane resolution of 0.67mm and thickness of 1mm were acquired along axial, sagittal and coronal axes to provide complementary resolution. An EPI-based diffusion weighted (DW) pulse sequence was used to acquire one b0 volume and 20 volumes with b=0.5ms/μm^2. Likewise, the diffusion-weighted stacks were acquired along 3 orthogonal axes at an in-plane resolution of 1.13mm and thickness of 3mm. Three sets per each axis with 1mm offset were collected. T2W and FA volumes were reconstructed at isotropic resolutions of 0.5mm and 0.75mm, respectively, following recently-described procedures [2]. Fetal brains were manually segmented on the reconstructed T2W volumes using ITK-SNAP (http://www.itksnap.org). Using CARET software (http://brainvis.wustl.edu), cerebral cortical surfaces were generated and then cortical FA was mapped onto these surfaces. Seven cortical regions (Fig.2a) were manually drawn on each of the six hemisphere surfaces. Cortical FA, SA, and normalized curvature, K* (absolute mean curvature normalized by characteristic length, defined in [3]) were computed for each cortical region per hemisphere.

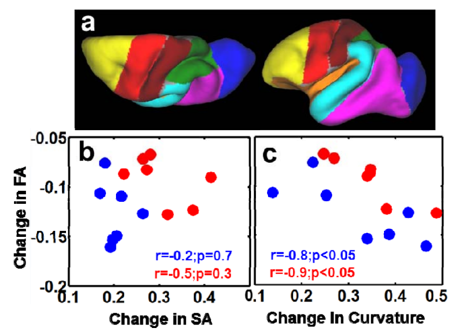

Fig.2 One hemisphere color-coded with different cortical regions is shown in dorsal (a, left) and lateral (a, right) view. Yellow: prefrontal, red: primary motor, maroon: somatosensory, green: non-primary parietal, cyan: auditory, magenta: non-primary temporal, blue: occipital. Changes in FA values of each cortical region averaged over 6 hemispheres are plotted against changes in SA (b) and changes in curvature (c).

Results As shown in Fig. 1c for one hemisphere of a representative animal, at G85 the cerebral cortex possesses high FA, and is devoid of folds (K* is low). With gestation age, the cerebral cortex expands rapidly and folds significantly, resulting increased SA and K*. Simultaneously, cerebral cortical FA decreases. To assess the correspondences between FA reductions and changes in SA and K*, averaged values for each of the 3 measures were calculated for 7 cortical regions (Fig. 2a), and SA and K* were expressed as ratios of the values they attain at adulthood, determined from a cerebral cortical surface constructed from the INIA19 rhesus macaque brain atlas [4]. Changes in FA were compared to changes in SA (Fig. 2b) and K* (Fig. 2c) between G85 and G110 (blue data points) and between G110 and G135 (red data points). Each data point in Figs. 2b and 2c represent the average of the 6 hemispheres for each cortical region. Significant negative correlations are observed between FA changes and cerebral cortical curvature, but not between FA and SA.

Conclusion Fetal T2W and diffusion-MRI facilitate a combined analysis of changes in cerebral cortical FA, surface area, and surface curvature. We find evidence that morphological differentiation of cerebral cortical neurons, thought to underlie FA changes, correlates with changes in cortical curvature but not surface area. These results suggest FA and curvature share similar biological bases, but these factors do not influence surface area expansion to the same extent.

References 1. Rakic et al., Trends Neurosci., 1995,18: 383-388. 2. Studholme et al., Ann. Rev. Biomed. Eng., 2011,13: 345-368. 3. Knutsen et al., Cereb. Cortex, 2013, 23: 488-498. 4. Rohlfing et al., Front. Neuroinform., 2012, 6:1-15.