In vivo diffusion tensor imaging of the neonatal rat brain development

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Purpose: The human brain undergoes active grey and white matter development during the late fetal and neonatal periods. Diffusion tensor imaging (DTI) is increasingly recognized as a sensitive tool for studying the mechanisms of brain maturation and injuries during these critical periods. The unique tissue contrasts provided by DTI reflect microstructural properties and allow structural delineation in the neonatal brain, which is often difficult in conventional MRI. It is therefore important to investigate the relationships between DTI based markers and microstructural changes in the developing brain and apply the knowledge to gain deeper understanding on brain maturation. To achieve these goals, it is necessary to use DTI to study brain development in animal models. In this study, high resolution in vivo DTI data were used to characterize neonatal rat brain development from P2 to P10, which provide parallels to near-term human brain development in several aspects [1,2].

Methods: Healthy neonatal Wistar rats were randomly chosen for MRI at P2, P4, P6, P8, and P10 (n = 6 for each time point). In vivo DTI experiments were performed on a Bruker horizontal 11.7T system using a 72 mm diameter quadrature transmit volume coil and a 4-channel phase array receive coil. Data were acquired using a three-dimensional (3D) diffusion weighted gradient and spin echo sequence with the following parameters: TE/TR = 26/600 ms, 9 diffusion directions, b = 1000 s/mm^2, resolution = 0.125 x 0.125 x 0.2 mm^3. The total imaging time was 2 hours. After MRI, the rats were sacrificed for histology. Histological staining included Nissl, GFAP, Nestin, Neurofilament, DAPI, and MBP. Diffusion tensor images were reconstructed using the Log-linear fitting method. A group average image was generated at each time point using iterative methods based on Large Deformation Diffeomorphic Metric Mapping (LDDMM), and mappings between average images at consecutive time points were also constructed [3]. All images were then normalized to the P6 average rat brain image, in which voxel wise statistical analysis was performed to identify regions with significant time related changes in fractional anisotropy (FA), apparent diffusion coefficient (ADC) and local tissue volume (as measured by Log-Jacobian). The rates of changes in these parameters over time were estimated at each pixel assuming simple linear relationships.

Results: The 3D high resolution DTI allowed delineation of major structures in the neonatal rat brain. Group average images from P2 to P10 (Fig. 1A) showed dramatic changes in both structural morphology and DTI derived parameters. For example, the thickness of the cortex increased and FA values in various cortical areas declined (Fig. 1B) during this period. Voxel based analysis showed significant time-related changes in FA, ADC, and local tissue volume throughout the brain. The estimated daily changes in these parameters (Fig. 1C) showed that the cortical regions had the most rapid decline of FA but with relatively small changes in ADC. Major white matter tracts showed relatively small increases in FA and moderate increases in ADC (Fig. 1B and 1C). During this period, the neocortex, striatum, and part of the thalamus showed more rapid expansion in volume than other regions. We are currently processing the histological data to correlate with these DTI findings.

Discussion and conclusion: Compared to previous studies on postmortem brain specimens, in vivo DTI data collected in this study reflect microscopic tissue properties under physiological conditions, without artifacts associated with death and fixation. The declines in FA observed in the neonatal cortex agree with previous ex vivo MRI based studies [4]. It is interesting to note that the ADC values of the cortex showed initial increases from P2 to P6 and then slight declines from P6 to P10 (Fig. 1B). These changes may reflect underlying dendritic growth or myelination, as myelination in the rodent brain starts at approximately P7.

References: [1] Johnston MV. Lancet 2003;361(9359):713-4. [2] Martin LJ et al. J Comp Neurol. 1997;377(2):262-85. [3] Chunag N et al. Neuroimage 2011;54(1):80-9. [4] Huang H et al. J Neurosci. 2008;28(6):1427-33.

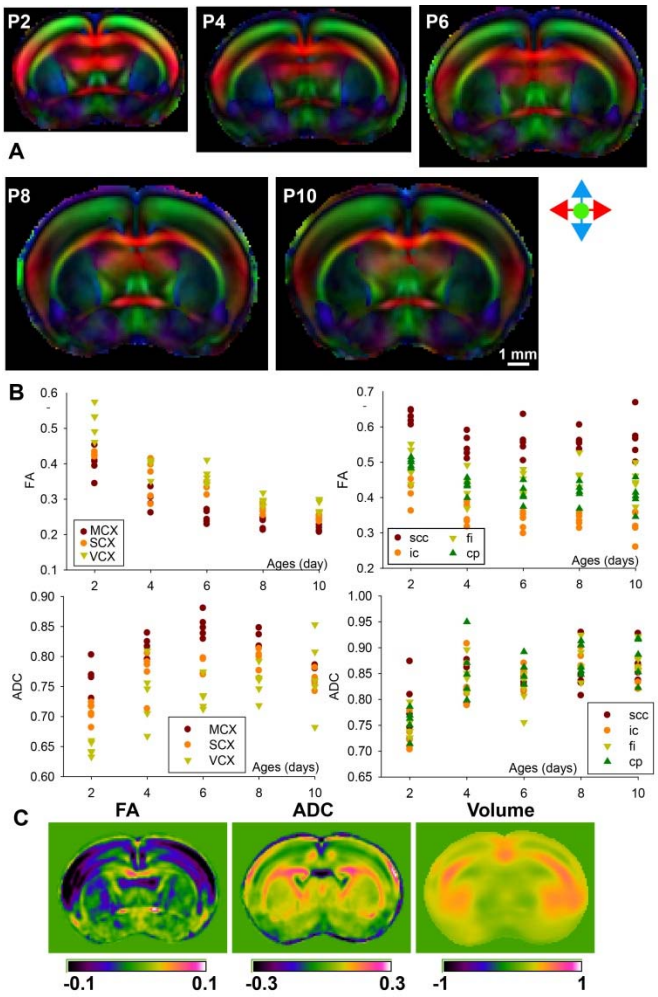

Fig. 1: A) *Average DTI colormap images of neonatal rat from P2 to P10.* ***B)*** *Time related FA changes in selected cortical and white matter structures. Abbreviations are: MCX: motor cortex; SCX: sensory cortex; VCX: visual cortex; scc: splenium of the corpus callosum; ic: internal capsule; fi: fimbria; cp: cerebral peduncle.* ***C)*** *Estimated daily changes in FA, ADC, and local volume (measured by Log-Jacobian) from P2 to P10 in the same section as in Fig. 1. The unit of the ADC is 10^{-3} mm^2/s.*