DTI of Adult Visual Pathways after Severe Neonatal Hypoxic-ischemic Cerebral Injury

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INTRODUCTION: Neonatal hypoxic-ischemic (HI) encephalopathy is a major cause of brain damage in infants, and may result in periventricular white matter injury and chronic neurological dysfunctions (1,2). Although infants with HI injuries frequently present cerebral visual impairments upon unilateral posterior cerebral lesions (3), our previous functional MRI (fMRI) study demonstrated the residual visual functions in the subcortical adult rat brain of both hemispheres after severe neonatal HI injury to the entire ipsilesional visual cortex (4). In order to understand the structural-functional relationship of such visual deficit and plasticity, this study employed diffusion tensor imaging (DTI) to determine the long-term outcomes of microstructural integrity along the visual pathways after severe neonatal HI injury.

MATERIALS AND METHODS: Animal Preparation: Sprague-Dawley rats (12-16 g, N=14) were divided into two groups. In the HI group (n=7), the ipsilesional visual cortex was damaged after unilateral ligation of the left common carotid artery at postnatal day (P) 7, followed by hypoxia at 36-37ºC for 2 hours. The other 7 animals were untreated and acted as controls. T1WI, T2WI and DTI were performed to all animals at P60. **MRI Protocol:** All MRI measurements were acquired utilizing a 7 T Bruker scanner. T1WI and T2WI were acquired using 2D RARE pulse sequences. For DTI, 4-shot SE-EPI diffusion weighted images were acquired with FOV = 32x32 mm^2, MTX = 128 x 128, slice thickness = 1 mm, number of slices = 15, TR/TE = 3000/28 ms, b = 0 and 1000 s/mm^2 and 30 diffusion directions. **Data Analysis:** DTI parameters, including FA, $\lambda_{//}$, $\lambda_{\perp}$ and diffusion trace value were obtained using DTIStudio v2.30 after co-registration. As more than 98.5% of the axons of rat retinal ganglion cells decussate to the contralateral posterior visual components at the optic chiasm (5), DTI parameters along the visual pathway projected from the ipsilateral eye (ipsilateral optic nerve, and contralateral anterior and posterior optic tract) were compared to the contralateral eye (contralateral optic nerve, and ipsilateral anterior and posterior optic tract) in the same group. DTI parameters on the same sides were also compared between groups.

RESULTS: In Figure 1, a porencephalic cyst was presented in the HI-injured animals by hyperintensity in diffusion trace map covering the ipsilesional hemisphere, including the visual cortex. The HI group exhibited a reduced FA in the ipsilesional prechiasmatic optic nerve (solid arrows) and the contralesional anterior (dashed arrows) and posterior (arrowheads) optic tracts, whereby the ipsilesional posterior optic tract (open arrows) appeared to be displaced by the porencephalic cyst (asterisks), and was identified as a dorsoventrally-oriented fiber bundle in the color-encoded FA directionality map. Quantitative analyses in Figure 2 showed that, compared to age-matched normal brains, a significantly lower FA but higher $\lambda_{//}$, $\lambda_{\perp}$ and diffusion trace value was observed in the ipsilesional posterior optic tract in the HI brains, whereas significantly lower FA but mildly lower $\lambda_{//}$ and higher $\lambda_{\perp}$ and trace was observed in the ipsilesional prechiasmatic optic nerve and contralesional anterior and posterior optic tracts. Along the visual pathway projected from the ipsilesional eye, the differences in DTI metrics between normal and HI brains were the largest in the ipsilesional optic nerve and the smallest in the contralesional posterior optic tract, whereas along the pathway from the contralesional eye, such differences were the largest in the ipsilesional posterior optic tract and the smallest in the contralesional optic nerve. The maximum decrease in FA along the visual pathway projected from the ipsilesional eye (44.6% in ipsilesional prechiasmatic optic nerve) was also larger than the contralateral one (24.1% in ipsilesional posterior optic tract).

DISCUSSION AND CONCLUSION: The larger maximum decrease in FA along the visual pathway projected from the ipsilesional eye than the contralateral one was in parallel with the larger reduction in BOLD signal increase in the contralesional superior colliculus than the ipsilesional one in the same groups of animals in our previous fMRI study (4), indicative of smaller hemodynamic responses in more disorganized tissues. On the other hand, it is believed that the ipsilateral posterior optic tract experienced primary white matter lesion, which was known for FA reduction, increased average diffusivity, and increased $\lambda_{//}$ relative to secondary fiber loss resulted from decrease in FA and $\lambda_{//}$, and increase in $\lambda_{\perp}$ and trace in the ipsilesional optic nerve and contralesional anterior and posterior optic tracts (6). Previous studies showed that visual cortex damage caused trans-synaptic degeneration of the thalamus and the retinal ganglion cells. However, the survivors continued to transmit visual information via the remaining routes to the superior colliculus of the midbrain (7), which could be enhanced as the result of extensive training (8). Our results on the long-term outcome of the remaining visual pathways after neonatal brain injury are potentially important in determining and improving the functional consequences of brain lesions after most compensatory and reparative phases have been passed.

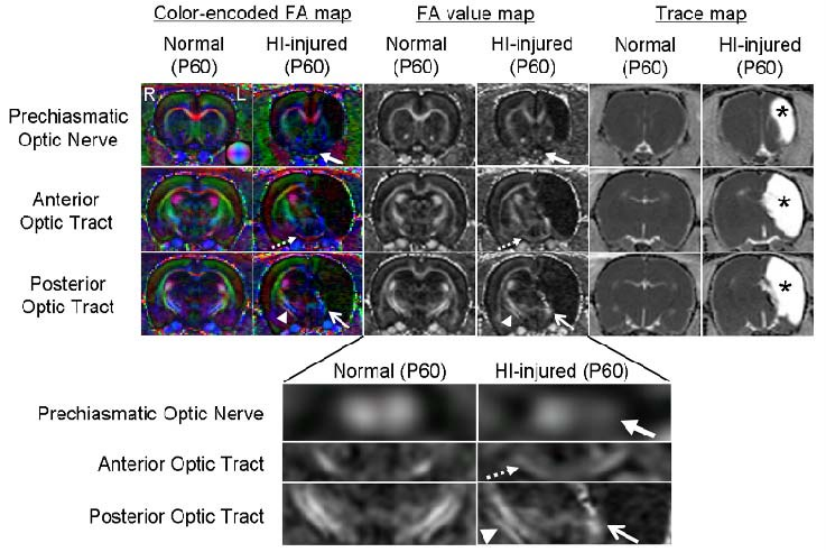

Fig. 1: Color-encoded FA directionality, FA value and diffusion trace maps of a normal rat and an HI-injured rat at P60 at the level of the prechiasmatic optic nerves, and anterior and posterior optic tracts. The expanded views of optic nerves and tracts in the FA value map are shown at the bottom. (Representative colors for different directions in color-encoded FA directionality map: blue, caudal-rostral; red, left-right; and green, dorsal-ventral.)

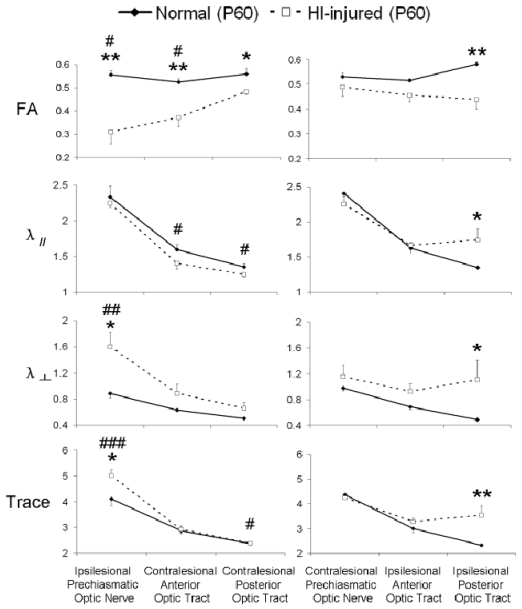

Fig. 2: Comparisons of DTI parametric values along the visual pathways projected from the ipsilesional left eye (left column) and contralesional right eye (right column) in normal and HI-injured groups at P60. (Units for $\lambda_{//}$, $\lambda_{\perp}$ and trace: $x10^{-3}$ mm^2/s) (Two-tailed unpaired t-tests between normal and HI-injured groups: *p<0.05, **p<0.01, ***p<0.001; Two-tailed paired t-tests between ipsi- and contra-lesional hemispheres in the HI-injured group: # p<0.05; ## p<0.01; ### p<0.001 in the left column)

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