Alterations of Temporal and Prefrontal White Matter in Adult Macaques with Neonatal Hippocampal Lesion

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TARGET AUDIENCE Neuroscientists, clinicians, psychiatrists and MRI physicists.

INTODUCTION A recent DTI study demonstrated that excitotoxic hippocampal lesions in adult macaques alter white matter tracts of the hippocampal projection systems, a finding consistent with the notion that hippocampal damage results in altered interactions with multiple memory-related brain regions, including the ventromedial prefrontal cortex[1–3]. In the present study, we used diffusion tensor imaging (DTI) to examine whether similar changes of white matter tracts in temporal and frontal lobes will also be found in adult macaque monkeys that had received similar selective hippocampal (Neo-H) lesions in infancy. Given the persistent memory impairment reported in animals with Neo-H lesions[4], we predicted significant alterations in the white matter of the temporal stem (TS) and ventromedial prefrontal cortex (VM).

METHODS Adult macaque monkeys with Neo-H lesion and sham-operated control (8-10 years old, n = 5 in each group) were used. Hippocampal lesions were induced using ibotenic acid (5.0 µl) bilaterally at 10–12 days after birth[5]. DTI images were collected on a Siemens 3T Trio scanner using a dual spin-echo EPI sequence with following imaging parameters : b values = 0, 1000 s/mm^2, TE/TR = 96 ms/5700 ms, isotropic spatial resolution = 1.3 mm, 60 gradient directions with the phase-reversal acquisition. High-resolution T_1-weighed images were also acquired. Data were processed with FSL (FMRIB, Oxford) and MATLAB (Mathworks, Natick, MA) scripts. Using TBSS toolbox in FSL, maps of fractional anisotropy (FA), mean diffusivity (MD), axial (D_a) and radial diffusivity (D_r) were nonlinearly registered to a population-specific FA template, and then skeletonised to produce white matter pathways for the DTI parameters maps. The diffusivity values in the skeleton of VM and TS were calculated[6] (Fig. 1). Two-way ANOVA with group (control and lesion) as the between-subject factor and hemisphere (left or L, and right or R) as the within-subject factor, followed by *post-hoc* univariate test, were performed. Pearson's correlation analysis was used to test the relation between DTI variables and hippocampus volumes measured at 18 months[5]. P-values less than 0.05 were considered statistically significant.

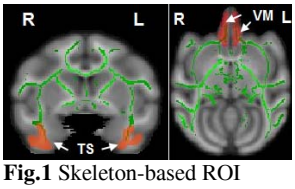

Fig.1 Skeleton-based ROI analysis in temporal stem (TS) and ventromedial prefrontal cortex (VM) (red color). FA, MD, D_a, or D_r in each ROI was averaged from the correspondent skeletonised map (green color). L, R: left or right hemisphere.

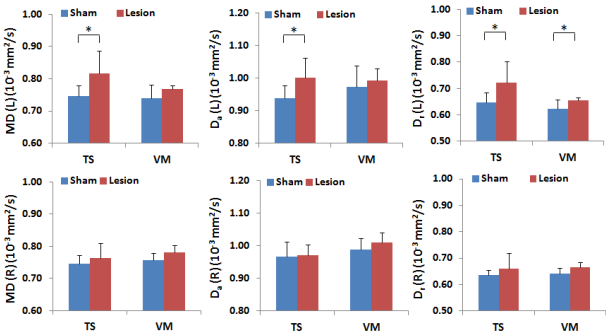

Fig. 2 Comparisons of DTI variables in temporal stem (TS) and ventromedial prefrontal cortex (VM) between groups, in the left (L, top row) and right (R, bottom row) hemispheres (* $p < 0.05$).

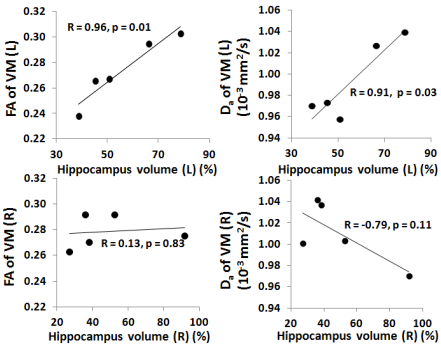

Fig. 3 Correlations between hippocampal volume and FA or D_a of VM in the left (top row) and the right (bottom row) hemispheres in the lesion group.

RESULTS Significant increase of diffusivities was observed in TS (MD, D_a, and D_r) and VM (D_r) in the left hemisphere of the Neo-H animals as compared to the sham-operated controls (Fig. 2). In contrast, no significant changes were observed in the right hemisphere. In addition, FA and D_a of VM were positively correlated with hippocampal volume in the left hemisphere, but not with that in the right hemisphere (Fig. 3).

DISCUSSION AND CONCLUSION The data indicated that Neo-H lesions results in connectivity alteration in the left TS and VM white matter. In addition, the diffusivities of the left VM significantly decreased as Neo-H lesions were more complete. Increase of diffusion measures (MD, D_a and D_r) after Neo-H lesions may be due to a lack of functional hippocampal inputs to the prefrontal cortex from early development stage[7]. Interestingly, the hemispheric difference found in VM white matter changes is consistent with recent evidence showing that VM [2,3], especially the left VM [3,8], is involved in memory consolidation and working memory retrieval, two memory processes that were impaired in the animals with Neo-H lesions [4,5].

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