Impaired Functional Connectivity between the Hippocampus and Dorsolateral Prefrontal Cortex in a Neonatal Hippocampal Lesion Macaque Model

Chunxia Li[1], Zhihao Li[2], Xiaoping Hu[2], Jocelyne Bachevalier[3], and Xiaodong Zhang[1,4]

[1]*Yerkes Imaging Center, Yerkes National Primate Research Center, Emory University, Atlanta, Georgia, United States,* [2]*Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia, United States,* [3]*Yerkes National Primate Research Center and Department of Psychology, Emory University, Atlanta, Georgia, United States,* [4]*Division of Neuropharmacology and Neurologic Disease, Yerkes National Primate Research Center, Emory University, Atlanta, Georgia, United States*

Introduction: Earlier studies have shown that neonatal damage to the hippocampus (HP) in monkeys yields not only impaired episodic memory [1], known to depend on HP integrity, but also impaired working memory processes mediated by the dorsolateral prefrontal cortex (DLPFC) [2]. These behavioral findings suggested that early dysfunction of HP may have altered the functioning of the DLPFC, a finding similar to the abnormal functional HP-DLPFC connectivity reported in schizophrenic (SZ) patients [3]. In this study, we used *in vivo* neuroimaging technique (resting-state functional MRI) to more directly investigate the functional integrity of HP-DLPFC connectivity in monkeys with neonatal HP lesions.

Method: Four adult rhesus monkeys with neonatal hippocampal lesions and one sham-operated monkey were used. Hippocampal lesions were performed using injection of the neurotoxin, ibotenic acid (5.0 µl of ibotenic acid bilaterally) at 10–12 days old [1]. At the age of 8-10 years, animals were anesthetized and maintained under ~1% isoflurane mixed with O_2, and their head was secured into a stereotaxic apparatus in a sphinx position. MR images were collected using a Siemens 3T scanner. Et-CO_2, inhaled CO_2, O_2 saturation, blood pressure, heart rate, respiration rate, and body temperature were monitored continuously. Functional MRI images were collected using a gradient echo EPI sequence (TR/TE = 2190 ms/25 ms, FOV= 96 mm × 96 mm, Data matrix = 64 × 64, thickness= 1.5 mm) with 150 volumes acquired per scan. The corresponding field map and high-resolution T1-weighted images were acquired for correction of image distortion and co-registration respectively with FSL (FMRIB Software Library). AFNI (National Institutes of Mental Health, Bethesda, Maryland) was utilized for analysis of functional connectivity with the seed regions of interest (ROI) defined in the bilateral HP (Fig.1, right) and DLPFC (Fig.1, left). Fisher *Z* transformation was applied to the correlation maps of each subject. Correlation analyses (Spearman) were subsequently made between the functional connection of DLPFC-HP and the bilateral HP lesion volume measured at the 18 months old [3]. P-values less than 0.05 were considered statistically significant.

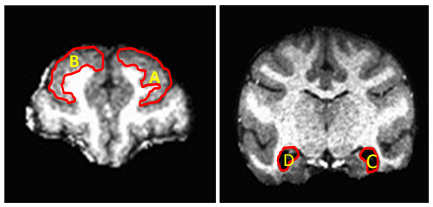

Fig.1 Representive slices show seed regions of interest from one monkey: (A) left and (B) right dorsolateral prefrontal cortex; (C) left and (D) right hippocampus; (C) and D) also indicate enlarged ventricles due to loss of hippocampal tissue.

Result: All animals with neonatal HP lesions showed weaker HP-DLPFC connectivity than the sham-operated controls. Also, the connection strength (*z* score) of the left HP-DLPFC was significantly anti-correlated with the volume of left HP lesion (Fig. 2, p = 0.037). This correlation remained significant even when the sham-operated control was removed (r = 0.94, P < 0.05). In contrast, the connections of left HP to right DLPFC, and the right HP to either DLPFC did not significantly correlate with the volume of either left or right HP lesions.

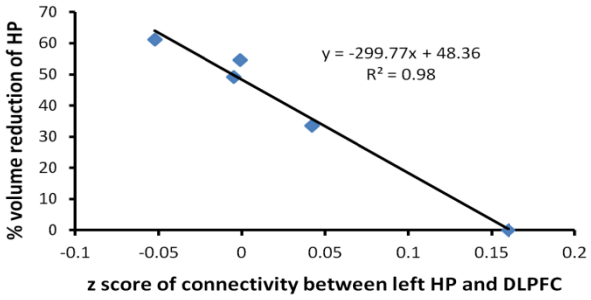

Fig.2 The correlation between *z* score of left DLPFC and left HP connectivity of the monkeys with neonatal hippocampal lesions.

Discussion and conclusion:

Our results indicate altered functional connectivity between HP and DLPFC after neonatal HP lesions in monkeys. Interestingly, not only did this abnormal connectivity between the two regions correlated with the extent of HP lesions, but it was also predominantly seen in the left hemisphere. The data thus parallel some recent findings in humans demonstrating that the dominance of left DLPFC in the development of SZ given that abnormal memory deficits correlate with left DLPFC dysfunction in SZ patients [4, 5]. The present findings suggest that, as the monkeys, early dysfunction of the HP (especially left HP lesion) in SZ might induce maldevelopment of the DLPFC. Although these preliminary findings need confirmation with the inclusion of additional sham-operated animals, the data indicate that macaques with neonatal hippocampal lesions may represent an ideal model for studying the mechanism of the connectivity deficits seen in SZ [2].

Reference: [1] Zeamer et al Journal of Neuroscience (2010); [2] Heuer E et al, Behav Neurosci (2011); [3] Zhou et al., Schizophrenia Research (2008); [4] Nicoletta M.J. van Veelen et al, Schizophrenia Research (2010); [5] Choi JW et al, Psychiatry Investig (2008)

Acknowledgments: This work was supported by NIH/NIMH RO1 MH058846 and NIH/NCRR RR0000165