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# Decreased functional connectivity in dorsolateral prefrontal cortical networks in adult macaques with neonatal hippocampal lesions: Relations to visual working memory deficits

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ABSTRACT

Neonatal hippocampal lesions in monkeys impairs normal performance on both relational and working memory tasks, suggesting that the early lesions have impacted the normal development of prefrontal–hippocampal functional interactions necessary for normal performance on these tasks. Given that working memory processes engage distributed neuronal networks associated with the prefrontal cortex, it is critical to explore the integrity of distributed neural networks of dorsolateral prefrontal cortex (dlPFC) following neonatal hippocampal lesions in monkeys. We used resting-state functional MRI to assess functional connectivity of dlPFC networks in monkeys with neonatal neurotoxic hippocampal lesion (Neo-Hibo, $n = 4$) and sham-operated control animals (Neo-C, $n = 4$). Significant differences in the patterns of dlPFC functional networks were found between Groups Neo-Hibo and Neo-C. The within-group maps and the between-group comparisons yielded a highly coherent picture showing altered interactions of core regions of the working memory network (medial prefrontal cortex and posterior parietal cortex) as well as the dorsal (fundus of superior temporal area and superior temporal cortex) and ventral (V4 and infero-temporal cortex) visual processing areas in animals with Neo-Hibo lesions. Correlations between functional connectivity changes and working memory impairment in the same animals were found only between the dlPFC and visual cortical areas (V4 and infero-temporal cortex). Thus, the impact of the neonatal hippocampal lesions extends to multiple cortical areas interconnected with the dlPFC.



## 1. Introduction

Working memory, an ability of temporally holding or manipulating information maintained in memory buffer (Baddeley, 1992), is closely associated with interactive activity in the prefrontal, parietal and medial temporal lobes, especially the hippocampus (Constantinidis & Procyk, 2004; Petrides, 1996). Earlier lesions and electrophysiological studies in monkeys revealed that the dorsolateral prefrontal cortex (areas 8, 46) is reciprocally connected with the dorsal visual stream via the parietal cortex, whereas the ventral visual stream (areas 12, 45) is associated with the inferior temporal cortex (Goldman-Rakic, 1988). This conceptual functional network has been largely confirmed by more recent neuroimaging studies (PET and fMRI) in humans, demonstrating concurrent activation of multiple brain areas when subjects are engaged in working memory tasks (Courtney, Ungerleider, Keil, & Haxby, 1997; Jonides et al., 1993; Owen, 2000; Petrides, 1995a; Ungerleider, Courtney, & Haxby, 1998). In clinical studies, changes in functional networks associated with the dorsolateral prefrontal cortex were reported in patients with mental illnesses, notably with developmental neuropsychiatric disorders such as schizophrenia (Callicott et al., 2000; Kraguljac, Srivastava, & Lahti, 2013; Kyriakopoulos et al., 2012; Zhou et al., 2007). Although earlier studies assigned working and episodic memory deficits in schizophrenics to dysfunction of specific neural structures, such as dorsolateral prefrontal cortex and hippocampus, respectively (Kraguljac et al., 2013), more recent fMRI studies have revealed large scale changes in prefrontal cortex functional networks associated with these memory deficits (Baker et al., 2014; Henseler, Falkai, & Gruber, 2010; Kang, Sponheim, Chafee, & MacDonald, 2011).

The high similarity of anatomical connections and functional organizations of brain in nonhuman primates, especially the macaque monkeys, and humans makes it possible to mirror human

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brain pathology with more controllable primate models in which invasive techniques can be applied (Nakahara, Adachi, Osada, & Miyashita, 2007; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). On the evidence that neonatal ventral hippocampal lesions in rodents mimic certain aspects of the positive symptoms of schizophrenia, including working and spatial memory deficits (O'Donnell, 2012; Tseng, Chambers, & Lipska, 2009), we investigated memory performance of monkeys that had received neonatal hippocampal lesions in the first two weeks of life. These neonatal lesions yielded severe loss of object recognition memory and episodic-like (relational) memory (Blue, Kazama, & Bachevalier, 2013; Glavis-Bloom, Alvarado, & Bachevalier, 2013; Zeamer, Heuer, & Bache valier, 2010; Zeamer & Bachevalier, 2013) as well as deficits in working memory related to impaired monitoring processes rather than maintenance processes (Heuer & Bachevalier, 2011, 2013). These data suggested that neonatal hippocampal lesions impacted the normal development of prefrontal–hippocampal functional associations necessary for normal performance on both episodic and working memory tasks. Given the assumption that working memory processes engage distributed neuronal networks associated with the prefrontal cortex instead of sole brain areas (McIntosh, 1999), it becomes critical to explore the integrity of distributed neural networks of dorsolateral prefrontal cortex following neonatal hippocampal lesions in monkeys. Findings from such studies may provide a greater understanding of the functional alterations in this primate model and provide valuable information for identifying the neural correlates of memory impairments reported in schizophrenic patients as well as in other developmental brain disorders, such as developmental amnesia resulting in hippocampal atrophy from ischemic episode.

Using Diffusion Tensor Imaging (DTI), we recently revealed significant and enduring alterations of white matter integrity in the hippocampal projection systems after neonatal hippocampal lesions. These white matter changes were observed not only in the fornix and ventromedial prefrontal cortex, but also the temporal stem and optic radiations (Meng, Payne, Hu, Bachevalier, & Zhang, 2013; Meng et al., 2014). To further explore the distributed neural networks that have been impacted by these neonatal lesions, resting state functional MRI was used in the present study to assess functional connectivity of dorsolateral prefrontal cortex networks in adult monkeys with neonatal hippocampal lesion and sham-operated control animals. Resting state functional MRI detects the intrinsic functional connectivity between brain areas regardless of stimulation (Ralchle & Snyder, 2007). During rest, blood oxygen level-dependent (BOLD) signal often measured by correlation in low frequency fluctuations (LFF) (<0.1 Hz) can reflect the metabolic level of the brain in the absence of extrinsic stimulation in the default mode functional network. Changes of the default mode network provide valuable insights regarding the integrity and functional alteration in normal subjects or patients (Lee, Smyser, & Shimony, 2013), and also in anaesthetized monkeys (Vincent et al., 2007). By calculating the correlation of the time courses of the acquired signal between the dorsolateral prefrontal cortex and other areas, functional connectivity of macaque monkeys in both groups was compared on a voxel-by-voxel basis. More importantly, to explore whether the altered functional networks were associated with the episodic and working memory deficits found in the same animals, correlations were also performed between functional changes in neural networks and working and episodic memory performance.

## 2. Methods

### 2.1. Animals

All procedures were carried out and used in full compliance with the Institutional Animal Care and Use Committees of Emory University (IACUC). Four infant macaque monkeys had received sham lesions (Neo-C), and the other four had received neurotoxic lesions of the hippocampus (Neo-Hibo) via bilateral infusion of ibotenic acid (5.0 μl) at the age of about two weeks. Details of the surgical procedures and descriptions of the extent of hippocampal lesions can be found in previous studies using the same animals (Heuer & Bachevalier, 2011; Zeamer et al., 2010).

When this MR imaging study was performed, animals were 8–10 years old. They were initially sedated with ketamine (5–10 mg/kg, IM) and then intubated for anesthesia with 1.0–1.5% isoflurane. An IV catheter was placed for delivering lactated ringers solution (3.5–10 ml/kg/h) during the entire scanning procedure. Animals' heads were immobilized in a custom-made head holder. During the acquisition of the MRI scans, they were spontaneously breathing under isoflurane at ~1.0% end-tidal inspiratory concentration, mixed with 100% $O_2$. Physiological parameters were maintained in normal ranges (Li, Patel, Auerbach, & Zhang, 2013) as follows: end-tidal $PCO_2$ = 38–42 mmHg, end-tidal $PO_2$ = 25–35 mmHg, end-tidal $O_2$ saturation = 95–100%, respiration rate = 3 0–45 breaths/min, heart rate = 110–140 beats/min, body temperature = 37.5 °C maintained by a feedback-regulated circulating warm-water blanket.

### 2.2. MRI experiments

All MRI scans were acquired on a Siemens 3T Trio scanner. Resting-state fMRI data were obtained with a Siemens 8-channel phase-array volume coil and a single-shot echo planar imaging (EPI) sequence and following imaging parameters: TE = 25 ms, TR = 2.2 s, data matrix = 64 × 64, voxel size = 1.5 mm × 1.5 mm, slice thickness = 1.5 mm, 34 slices to cover the whole brain, and 300 repetitions done within around 10 min. $T_1$-weighted images were acquired by using a 3D MPRage sequence with GRAPPA ($R$ = 2) and following parameters: inversion time = 0.95 s, TE/TR = 3.5 ms/3 s, voxel size = 0.5 mm × 0.5 mm and slice thickness = 0.5 mm, to build the anatomical macaque template for the image registration. Whole brain field maps were acquired using a gradient echo sequence with TE = 6.24 and 8.7 ms, TR = 500 ms, FOV = 96 mm × 96 mm, voxel size = 1.3 mm × 1.3 mm, and slice thickness = 1.3 mm.

### 2.3. Data processing

Data were processed with FSL (FMRIB, Oxford) and home-made MATLAB (Mathworks, Natick, MA) scripts. For resting-state fMRI data, image distortion was corrected based on an acquired field map. For each dataset, initial 10 time points were removed to eliminate the instability at the start of scanning, followed by motion correction and slice timing correction for the fact that a functional volume is covered with a series of successively measured 2D slices, and spatial smoothing with FWHM 3 mm. High-pass temporal filtering (Gaussian-weighted least-squares straight line fitting with sigma = 100 s) were applied. Dorsolateral prefrontal cortex (dlPFC), including Brodmann areas 8, 9 and 46 d, was selected as the seed in the template derived from the high-spatial resolution $T_1$-weighted anatomical images built from the Neo-C animals (see Fig. 1). The dlPFC areas from the template were registered (12 DOF linear affine transformation) to individual BOLD maps for Neo-C and Neo-Hibo animals. Individual functional connectivity maps were obtained by voxelwise calculation of the correlation coefficients between the time series of the gray matter of each whole brain and the averaged time series of the BOLD signal in the seed dlPFC, followed by a Fisher $r$-to-$z$ transform to normalize the distribution of the correlation coefficients. The correlation coefficient maps of subjects were then registered to the $T_1$-weighted anatomical template map. Significant activations were determined voxel-by-voxel