# Decreased Resting-state Functional Connectivity in Dorsolateral Prefrontal Cortical Networks Correlates with Deficient Visual Working Memory Performance in Adult Macaques with Neonatal Hippocampal Lesion

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**TARGET AUDIENCE** Neuroscientists, clinicians and MRI physicists.

**INTRODUCTION** Previous studies have shown that visual working memory dependent on dorsolateral prefrontal cortex (dlPFC) was impaired in adult rhesus macaques with neonatal hippocampal lesions (Neo-H) [1]. To further explore the dysfunction of the dorsolateral prefrontal cortex after neonatal hippocampal lesions, we used resting-state functional MRI (rsfMRI) to investigate the integrity of the whole functional network of dlPFC in adult monkeys with Neo-H.

**METHODS** Neo-H lesions were performed via injection of 5.0 µl ibotenic acid bilaterally at 10–12 days after birth [1]. fMRI acquisitions was performed on animals with Neo-H lesions and sham-operated controls (Neo-C) ($n$ = 4 in each group, 8-10 years old) on a Siemens 3T Trio scanner, with a single-shot EPI sequence (TE/TR = 25 ms/2.2 s, FOV = 96 mm × 96 mm, data matrix = 64 × 64, voxel size = 1.5 mm × 1.5 mm, slice thickness = 1.5 mm, total time = 5 minutes). Data were processed with FSL (FMRIB, Oxford) and custom-made MATLAB (Mathworks, Natick, MA) scripts. Image distortion correction was applied based on the acquired field map. For each dataset, initial 10 time points were removed to eliminate the instability at the beginning of acquisition, followed by intra-modal motion correction and slice timing correction, spatial smoothing with FWHM 3 mm, and removal of linear trend due to baseline drift in fMRI data. High-pass temporal filtering (Gaussian-weighted least-squares straight line fitting with sigma = 100 s) and low-pass temporal filtering (HWHM=2.8 s, Gaussian filter) were applied. A monkey brain template was derived from the high-spatial resolution $T_1$-weighted anatomical images from Neo-C animals. The dlPFC ROI was determined from the template and registered (12 DOF linear affine transformation) to individual fMRI raw data for each animal. Then, the individual functional connectivity map was obtained by voxelwisely calculating the correlation coefficients between the time series of the grey matter voxels in the brain and the averaged time series of the dlPFC ROI, followed by a Fisher r-to-z transform for the normality of the correlation coefficients. The correlation coefficient maps of the subjects were then registered to the monkey brain template. Significant activations were determined voxelwisely by applying a two-sample t-test with a threshold of $p < 0.05$ and corrected with Gaussian random field theory and cluster size > 5. To test the correlations between the functional networks with significant group difference and the working memory performance, Pearson's correlation analysis was conducted with the Fisher Z-scores between the dlPFC ROI and the rest areas in Neo-H group and the behavioral measures in an object self-order working memory task performed at 6-8 years of age [1].

**RESULTS** Group comparisons showed reduced functional connectivity between dlPFC and other regions like medial prefontal cortex (mPFC), inferotemporal cortex (IT), fundus of superior temporal area (FST), parietal cortex (PC) and visual area V4 (Fig. 1). Details of results are shown in Table 1. Also, the number of errors in the object self-order working memory task was significantly negatively correlated with functional connectivity between dlPFC and IT (r = -0.91) and V4 (r = -0.92). For the other areas, the functional connectivity decreased with the behavioral measures (r < 0), though the correlations did not reach significant.

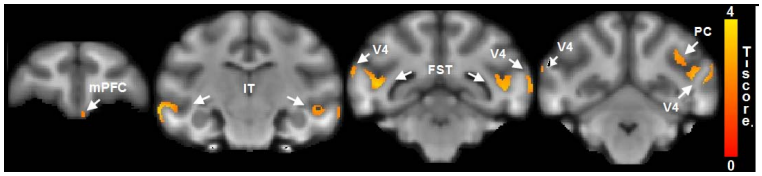


**Fig. 1** Areas with significant connectivity decreases in the dlPFC networks of macaques with Neo-H are illustrated.

**Table 1** Details of areas in Fig.1 and the correlations between the connectivity and the behavioral measures ($^*p < 0.05$).

| Areas | Voxels | Max. T-score | r | p |
|---|---|---|---|---|
| mPFC | 23 | 2.05 | -0.50 | 0.25 |
| IT | 2223 | 3.84 | -0.91 | **0.04**$^*$ |
| FST | 1242 | 3.77 | -0.53 | 0.24 |
| PC | 357 | 2.57 | -0.27 | 0.36 |
| V4 | 427 | 3.40 | -0.92 | **0.04**$^*$ |

**DISCUSSIONS AND CONCLUSIONS**

It is well known that working memory, especially the visual monitoring working memory depends on dorsolateral prefrontal cortex [2]. Also, inferotemporal cortex is responsible for visual working memory [3], especially for the maintenance of visual information [4]. The disruption of prefrontal and inferotemporal cortices can impair the performance of visual associative recall [5]. In the present study, reduced functional connectivity in mPFC, IT, FST, PC, and V4 was observed, indicating the impact of the neonatal hippocampal lesions on these regions. In particular, the visual monitoring of information in working memory of monkeys with Neo-H was significantly correlated with the decreased functional connectivity between dorsolateral prefrontal cortex and inferotemporal cortex and between dorsolateral prefrontal cortex and visual cortex V4, respectively. These MRI findings suggest that the neonatal hippocampus lesion has a profound impact on the functionality of dorsolateral prefrontal cortex network.

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