Functional MRI of Visual Responses in the Late Stage of Neonatal Hypoxic-Ischemic Encephalopathy

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INTRODUCTION:

Hypoxic-ischemic encephalopathy (HIE) is an important cause of permanent damage to neuronal cells that may result in neonatal death or be manifested later as cerebral palsy or impaired cognition. Although the neonatal brain undergoes massive cell death and atrophy the first week after injury, it retains the potential to generate new oligodendrocytes up to 4 weeks after injury within and surrounding the infarct (1). However, the long-term changes in brain development after neonatal injury remains largely unclear (2,3). In this study, functional magnetic resonance imaging (fMRI) was employed using blood oxygenation level–dependent (BOLD) contrast to study the visual responses in both sides of the rat superior colliculi in the late stage after unilateral neonatal HIE.

MATERIALS AND METHODS:

Animal Preparation: Sprague-Dawley rats (12-16 g, N=13) were prepared and were divided into 2 groups. The HIE group (n=7) underwent unilateral ligation of the left common carotid artery at postnatal day (P) 7 under isoflurane anaesthesia, followed by hypoxia in 8% oxygen and 92% nitrogen at 36-37ºC for 2 hours. The normal group (n=6) was untreated and served as a control. At the age of 2 months, T1WI, T2WI and BOLD-fMRI were performed to all animals.

Visual Stimulation Paradigm: Fiber optic cables with 2 green light-emitting diodes (LEDs) were placed bilaterally at about 1 cm away from each eye of the rats. The LEDs were flashed at a frequency of 1 Hz and a pulse width of 50 ms to each eye. A standard block-design visual stimulation protocol of 40 s of rest followed by stimulation for 20 s repeated for 3 blocks was used. The rats were allowed to rest for few minutes between stimulation sets, and 3-6 sets of data were recorded from each eye for each rat.

MRI Protocol: All MRI measurements were acquired utilizing a 7 T Bruker scanner. Under inhaled isoflurane anaesthesia (3% induction and 1% maintenance), animals were kept warm under circulating water at 37ºC and were imaged using a receive-only surface coil. T1WI and T2WI were acquired using the 2D RARE pulse sequences. Single-shot SE-EPI sequence was acquired with TR/TE = 2000/21ms, FOV = 3.2 x 2.4 cm^2 and matrix resolution = 64 x 48 (zero-filled to 64 x 64), slice thickness = 1.5 mm, and number of slices = 6.

Data Analysis: All the fMRI data analyses were performed using the STIMULATE software package (STIMULATE, Center for Magnetic Resonance Research, University of Minnesota). Correlation threshold was set at 0.15. Time profiles of BOLD signals were collected from each side of the rat superior colliculus. Percentage changes of BOLD signals were calculated and averaged among animals from the same groups.

RESULTS:

The HIE animals exhibited a significantly delayed time of eyelid opening at P23.7±3.3 compared to the normal group at P14.5±0.5 (unpaired t-tests, $p<0.001$). At 2 months after HI injury, T2WIs showed the involvement of the cyst formation at the ipsilesional visual cortex in all animals of the HIE group (Fig. 1), whereas shrinkage of the ipsilesional optic nerve was observed in some animals of the HIE group. The averaged stimulus-induced percentage signal change in the right superior colliculus was significantly lower in the HIE group than the normal group by 44.8% upon left eye stimulation (unpaired t-tests, $p<0.05$) (Fig. 2), whereas in the left superior colliculus upon right eye stimulation, the percentage signal change in the HIE group was smaller than the normal group by 31.0% with marginal significance ($p=0.06$).

DISCUSSIONS AND CONCLUSION:

Several previous studies have demonstrated the functional impact of visual cortical damage on subcortical target structures in the thalamus and midbrain (4,5). Our results presented here constitute the first fMRI report in evaluating the visual responses of the rat superior colliculus upon neonatal HI insults. These can be potentially useful in establishing the links between the changes related to the visual sensory development after neonatal injury. It has been shown that the cerebral cortex has the ability to adapt to altered sensory inputs and can undergo massive restructuring of neuronal circuits during functional reorganization. While the present study showed occasional activations of the visual cortex upon the current stimulation and scanning parameters, further experiments will be performed to understand the functional reorganization of the visual cortex in the same model.

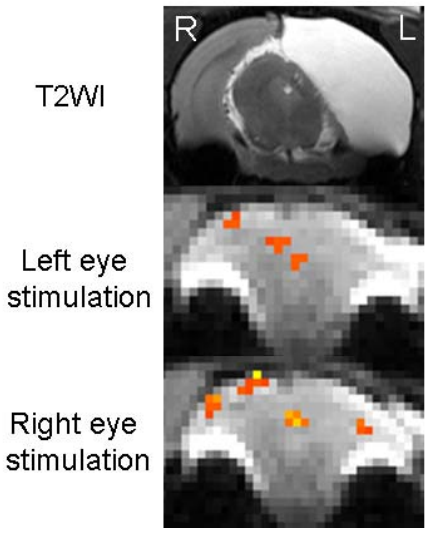

Fig 1: (Top) T2WI showing the large cyst formation in the ipsilesional hemisphere; (Middle and bottom) Activation maps overlaid on EPI images at the superior colliculi upon left (middle) and right (bottom) eye stimulation.

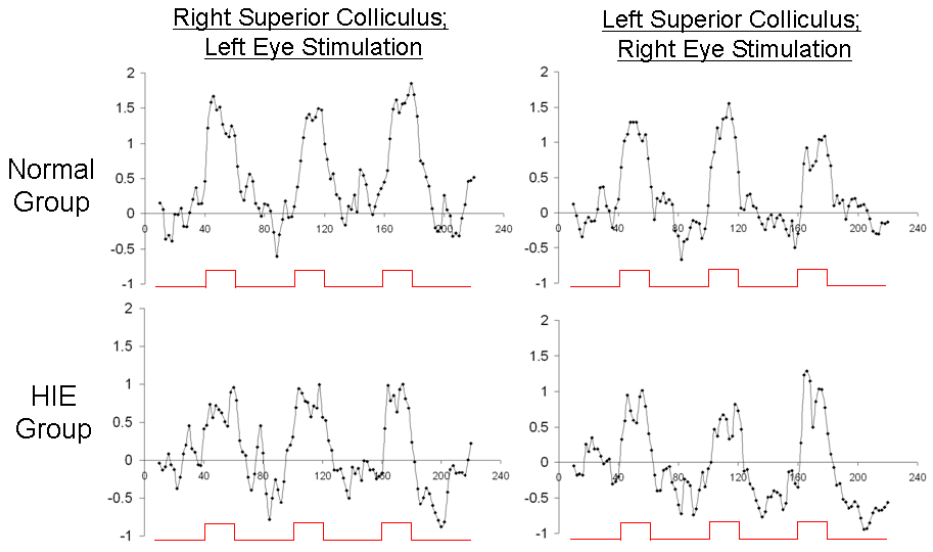

Fig. 2: Population-averaged BOLD responses to visual stimulation. Mean time courses were computed from activated voxels in superior colliculus averaged across all animals in the same group. A smaller BOLD signal amplitude increase was observed in the HIE group in the stimulation period ('on' period in red lines).

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