Neuroplasticity for spontaneous functional recovery after neonatal hypoxic ischemic injury

Won Beom Jung[1,2], Geun Ho Im[1,2], Sun Young Chae[3], Yong Hee Han[1,2], and Jung Hee Lee[1,3]

[1]*Department of Radiology Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea,* [2]*Center for Molecular and Cellular Imaging Samsung Biomedical Research Institute, Seoul, Korea,* [3]*Samsung Advanced Institute of Health Science and Technology Sungkyunkwan University, Seoul, Korea*

Purpose

Recovery from brain injury is fast for infants and children compared to adults by the ability in developing brain to compensate for loss of function through reorganization of neural networks and/or recruitment of new areas[1]. Perinatal hypoxic-ischemia (HI), which occurs as a result of birth asphyxia, causes a major brain injury in the newborn, leading to encephalopathy associated with cognitive and behavioral deficits later in life[2]. Spontaneous recovery seems to be a major mechanism for the HI injured brains occurred at the neonatal stage, however, the exact mechanism has not been fully understood. In this work, we investigate the brain plasticity of the HI injured rat brain using magnetic resonance imaging techniques with the behavioral tests.

Methods

Hypoxic ischemic brain damage was induced to postnatal day 7 (p7) Sprague-Dawley rats (weight, 16–18g, n=6) according to Rice-Vannucci HI-model[3]. The rat pups underwent right carotid artery occlusion under anesthesia followed by 150 minutes of hypoxic condition in a chamber supplied with 8% O_2 and 92% of N_2. Sham operation includes only incision under anesthesia (n=6). The MRI data were obtained 9 weeks (p63) after including HI brain injury with a 7.0 Tesla MRI scanner (Bruker Biospin GmbH, Ettlingen, Germany). T2 weighted imaging (TR/TE=3000/60ms, in-plane resolution=120×120μm^2, slice thickness=1.5mm) and DTI (TR/TE=4500/37ms, resolution=156×156μm^2, slice thickness=0.75mm, gradient direction=30, b-values=1000s/mm^2) were acquired to visualize the hypoxic-ischemic damage and to estimate the anatomical connectivity, respectively. We derived electrical stimulus pulses at a frequency of 12 Hz with two needle-electrodes inserted into a forepaw of the rat. Each stimulus run consisted of a 20 sec pre-stimulus, 20 sec stimulus, and 40 sec post-stimulus period. BOLD-fMRI was performed using a single-shot gradient-echo EPI sequence (TR/TE=1000/60ms, resolution=469×469μm^2, slice thickness=1.5mm, number of repetition=80). For resting state fMRI (rs-fMRI) data, 300 EPI volumes were acquired using the same BOLD-fMRI parameters without stimulation. The brain activation responding to stimulation was identified using AFNI and FSL packages. The preprocessing steps were involved to improve the detection of signal activation. After activation map was generated from a voxel-wise cross-correlation between the signal time course and boxcar reference convolved with a canonical hemodynamic response function, one-sample t-test and independent two-sample t-test between HIE and sham were performed to identify the group patterns. The DTI analysis was performed with tractography and TBSS to estimate the anatomical connectivity. The fiber tracks were extracted by placing seed point within the anterior corpus callosum and then the number of tracks passing through one voxel was mapped into volume space as track density in a given voxel. The track density was scaled between 0 and 1, and then TBSS was performed for the alignment-invariant voxel-wise comparison. To confirm the coherent functional connectivity patterns, the group ICA was implemented with MELODIC and then dual regression was followed. We also performed the adhesive removal test to assess somatosensory and sensorimotor ability (time to touch/remove a tape) before MRI.

Results

Under normal condition, BOLD response to forepaw stimulation was prominently localized to the contralateral S1FL and M1 (Figure 1.A & C); whereas, in HI rats (Figure 1.B & C), diffusely distributed activations in the contralateral cortex were detected in response to stimulation of intact right forepaw and the brain activated areas for left forepaw stimulation were also largely distributed in contralesional cortex with week significance and low signal amplitude (% increase < 1%). In the group statistics on right forepaw stimulation (Figure 1.C.a & c), increased brain activation were exhibited in left M1 and M2 areas in HI rats with respect to sham-operated rats (Figure 2.A, uncorrected $p < 0.005$). The DTI data also showed the enhanced intra-hemispheric track density in HI rats (Figure 2.B, uncorrected $p < 0.005$). In the visual inspection on functional connectivity, sham control was observed with inter-hemispheric communication in each component but HI rats only show the internal networks in intact hemisphere (Figure 2.b). However, intra-connectivity of cingulate cortex was increased in HI rats compared with sham controls (TFCE corrected $p < 0.05$)

Discussion and conclusion

In this study, we show the functional and anatomical changes in HI-induced developing rat brains using BOLD-fMRI, DTI and rsfMRI. Our main findings are the the widespread sensory-motor related areas on intact forelimb, weakly evoked brain activation on impaired forelimb, intra-hemispheric track rewiring and enhanced intra-connectivity in cingulate cortex areas in HIE rats. In addition, the left fowpaw contralateral to brain damage exhibit the behavioral outcome, but not fully working. Thus, we may speculate that the intra-hemispheric modulation showed in HIE are from neuralplasticity for spontaneous recovery to compensate for functional loss and to manage the both forepaws consequetly.

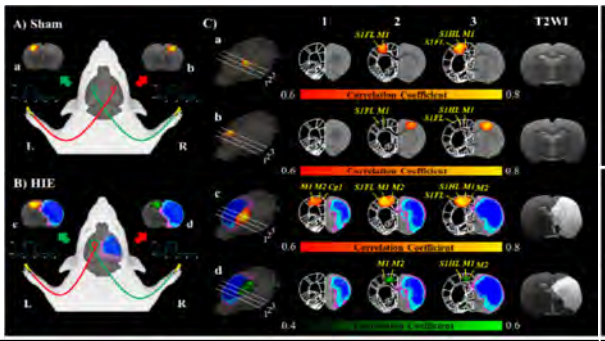

Figure 1. Overview of cerebral BOLD response to electrical forepaw stimulation on sham-operated and HI-injured rats

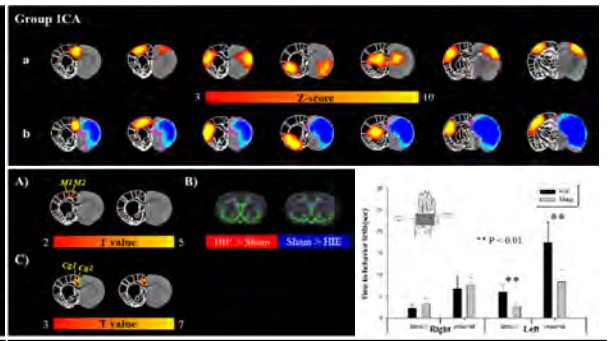

Figure 2. Functional connectivity maps resulting from 15 components ICA (upper), group voxel-wise comparison statistics (bottom left, A: BOLD, B: DTI, C: rsfMRI) and behavioral test data (bottom right)

References

[1] Johnston MV. Dev Disail Res Rev 2009;15:94-101 [2] Johnston MV et al. Pediatr Res 2001;49:735-741 [3] Rice Je 3rd et al. *Ann Neurol*. 1981;9:131-141