Functional MRI detection of cortical plasticity in the rodent brain following peripheral nerve injury

G. Pelled[1], S. J. Dodd[1], A. P. Koretsky[1]

[1]Labratory of Functional and Molecular Imaging, National Institute of Health, Bethesda, MD, United States

Introduction: High resolution functional MRI (fMRI) has emerged as a great tool to study brain plasticity in humans and rodents (1-3). Brain plasticity occurs during development and learning as well as during brain diseases and as a response to nerve injury. However, the different mechanisms by which the brain rewires and reorganizes are not fully understood. Plasticity processes are extremely important in order to gain more understanding of brain function, as well as to explore the future possibility of guiding plasticity to be able to treat a variety of neurological disorders such as stroke, head trauma, nerve injury, as well as brain dysfunction in newborns and children. An exciting recent result from studies examining plasticity after damage to the cortex in humans and rodents indicates that there may be a great deal of long range, interhemispheric plasticity (1-3). The goal of this study was to use functional imaging to examine plasticity in the rodent brain after peripheral nerve injury.

Peripheral nerve injury is known to cause local changes in cortical representations, there has been no work examining longer range plasticity. Sciatic nerve injury in rodents has been demonstrated previously to serve as an appropriate model to study both long and short term plasticity mechanisms. Therefore we have applied the sciatic and saphanous nerves injury in a rat model in order to study cortical reorganization following peripheral nerve injury. At different time points after surgery, fMRI was performed on the injured rats as well as on two control groups for the assessment of brain reorganization. Electrical stimulation of the healthy hindpaw resulted only in activation of contra-lateral somatosensory cortex (SI) activation in the control groups. Rats that had both the sciatic and saphenous nerves injured demonstrated both contra- and ipsilateral cortical activation, in response to stimulation of the healthy paw. These results suggest that brain reorganization following peripheral nerve injury is not restricted to cortex contralateral to the injured paw, but involves ipsi-lateral neuronal changes that may involve major interhemispheric pathways, such as the corpus callosum.

Methods: Sciatic and saphanous nerve injury: Sprague-Dawley Rats (70-90 g**,** 4 weeks old) were anesthetized with 2% Isoflurane, and the right sciatic nerve (which innervates more then 85% of the hindpaw) and the right saphanous nerves were exposed. A 3 mm long cut was made in the sciatic (n=5) or both the sciatic and saphenous nerves (n=8). A long cut was made in order to prevent future regeneration of the nerves. For the sham-operated control group, the nerves were exposed but were not truncated (n=5). The skin was sutured and the rats were allowed to recover for between 3 and 30 days prior to MR imaging. Rats were fed with a special soy diet which has been shown previously to reduce post-operative pain, and were treated with pain analgesics for a week following the surgeries.

Animal preparation for functional MRI: Rats were initially anesthetized with 2% Isoflurane during surgical procedures. Rats were orally intubated and placed on a mechanical ventilator. The femoral artery and the femoral vein were catheterized for sampling blood and infusing drugs. Two short stimulation electrodes were inserted in each hindpaw. After surgery, anesthesia was maintained with a constant α-chloralose infusion. Each animal was secured in a head holder with ear bars and a bite bar to prevent head motion and was strapped to a plastic cradle. End-tidal CO_2, rectal temperature, tidal pressure of ventilation, heart rate, arterial blood pressure and arterial blood gases were monitored during the experiment.

Image Acquisition: All images were acquired with an 11.7 T / 31 cm horizontal bore magnet (Magnex), interfaced to an AVANCE console (Bruker) and equipped with a 9-cm gradient set, capable of providing 64 G/cm with a rise time of 80 μs. A 2 cm diameter surface coil that was attached to a head holder was used to transmit and receive the MR signal. A single-shot, spin-echo EPI sequence with a 64 × 64 matrix was run with the following parameters: effective echo time (TE) 30 ms, repetition time (TR) 1.0-1.5 sec, bandwidth 200 kHz, field of view 2.64 × 2.64 cm. Brain coverage was obtained with 5 2-mm thick slices, spaced 0.2 mm apart (4). 190 images were acquired for a total experiment time of 4 min.

Somatosensory Stimulation Paradigm: A World Precision Instruments stimulator supplied 2 mA, 300 μs pulses repeated at 3 Hz to both forepaws upon demand. The paradigm consists of 40 scans during rest, 10 scans during hindpaw stimulation, which was repeated 4 times.

Data Analysis: Analysis of the time series was performed using STIMULATE. A correlation coefficient was calculated from cross-correlation of the unfiltered time series with a boxcar waveform representing the stimulation period. The activation threshold was set at 0.22-0.4, and only groups that include at least four activated pixels were considered significant.

Results and Discussion: The BOLD fMRI response was measured after stimulating the healthy hindpaw and after stimulating the injured hindpaw. In all the time points measured (3 to 30 days following surgery) the sham-operated rats exhibit normal SI activation when the intact (Figure 1, left column) or the sham-lesioned hindpaw were stimulated. As expected, the injured rats did not exhibit any cortical or sub-cortical activation in response to stimulation of the injured hindpaw. In rats where only the sciatic nerve was truncated, stimulation of the intact hindpaw resulted in contralateral SI activation (figure 1, middle column). However, as soon as 3 days following the deafferentiation of both the saphanous and the sciatic nerve, stimulation of the healthy hindpaw yielded ipsilateral SI activation as well as contralateral SI activation (Figure 1, right column). The average number of pixels that were activated above the determined cross correlation threshold (>0.22) in response to hindpaw stimulation in each of the three groups is shown in Figure 2.

To the best of our knowledge this is the first of interhemispheric plasticity in a peripheral nerve injury model. The brain reorganization that was detected within three days following the deafferentiation procedure suggests that long-term plasticity mechanisms underlie the cortical reorganization of the deprived cortical area. Due to the increased responsiveness of the reorganized cortical region to ipsilateral sensory stimulation, the plasticity mechanisms associated with this phenomenon might involve modifications of interhemispheric connections.

Understanding the cellular and the network mechanisms that underlie the induction and the maintenance of plasticity in pathological brain conditions might aid in developing new ways to increase or decrease the rate of specific neuronal processes in order to improve one's quality of life following brain trauma, brain lesions, stroke and peripheral nerve injury.

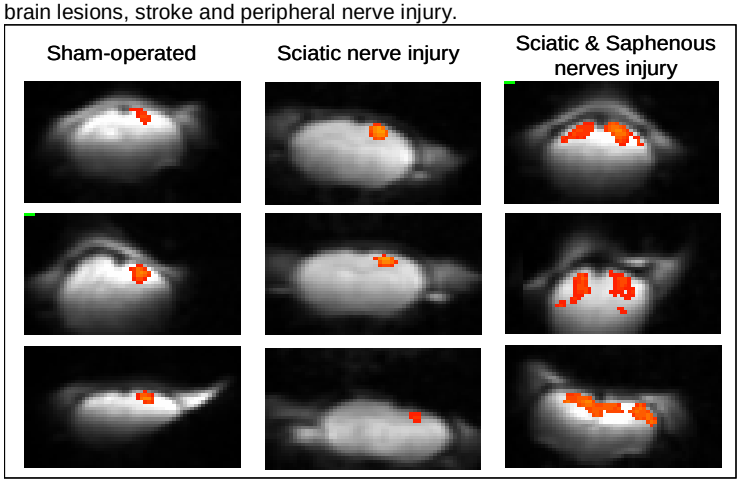

Figure 1. Representative BOLD cross correlation (>0.22) activation maps from three different rats overlaid on an EPI spin echo image are shown. Sensory stimulation of the healthy hindpaw resulted in contra-lateral somatosensory cortical activation in the sham-operated (left column) and sciatic nerve injury rats groups (middle column). Sensory stimulation of the healthy hindpaw in the sciatic & saphanous nerve cut rats resulted in both contra- and ipsi-lateral cortical activation (right column).

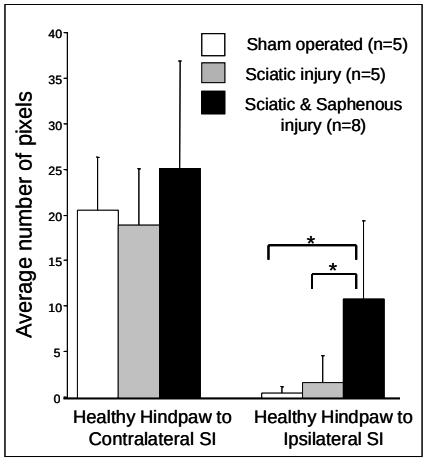

Figure 2. Averaged number of pixels (+ SD) activated above 0.22 cross-correlation threshold following intact hindpaw sensory stimulation in the sham-operated, sciatic nerve injury and sciatic and saphenous nerve injury rats' groups. P values were determined using a Two-Tail student T-test performed between groups.

References:

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