The Utility of fMRI in Measuring Brain Plasticity Following Peripheral Nerve Injury

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Purpose: To demonstrate the feasibility of using functional magnetic resonance imaging (fMRI) to track brain reorganization. This was done in the context of brain changes in response to peripheral nerve injury and repair in rat. Historically cortical plasticity has been measured using electrophysiology (1). Blood oxygen-level dependent (BOLD) fMRI has many advantages over electrophysiology including greater spatial coverage. FMRI is also a noninvasive technique. The noninvasive nature of fMRI lends itself to longitudinal survival studies; and the use of a high field animal scanner can provide spatial resolution in the brain similar to the limits of conventional electrophysiological electrode spacing. Peripheral nerve injury and repair have been demonstrated to cause significant brain changes over time (2). These factors have driven the development of a rat model of brain plasticity that uses manipulation of the peripheral nerves to drive brain reorganization.

Materials and Methods: Sixty rats were first divided into two groups of thirty rats. One group was assigned as an experimental group and the second as a control group. The two groups of thirty rats were further subdivided into groups of six which were each assigned a specific time-point (0, 2, 4, 8, 12 weeks). The experimental group received a complete transection of the forearm median nerve followed by immediate repair using standard microsurgical techniques. The control group received a surgical procedure that mimicked the experimental group approach without any median nerve transection or repair. The subject rats were then allowed to recover for their assigned time point. A stimulating electrode was surgically implanted directly on the median nerve distal to the site of the repair or sham protocol on the day on imaging. This stimulation method provides both orthodromic and antidromic nerve excitation and has been described previously in the fMRI literature (3). The animals were imaged in a Bruker 9.4T animal scanner equipped with a Bruker linear transmit coil (T10325) and Bruker surface receive coil (T9208). Medetomidine was infused through a femoral vein catheter at a continuous rate of 100 µg/kg/hr during the imaging session. The median nerve was stimulated at 1 mA D/C amplitude, 1 ms pulse-width, and 5 Hz frequency in a standard fMRI boxcar sequence using 40 sec off/20 sec on/40 sec off for a total of three blocks. Gradient echo scans (single shot EPI, TE = 18.76 ms, TR = 2 s, matrix size 128 x 128, FOV = 3.5 cm, number of repetitions = 110, 10 contiguous interleaved 1 mm slices, acquisition time = 3 min 40 s) were acquired.

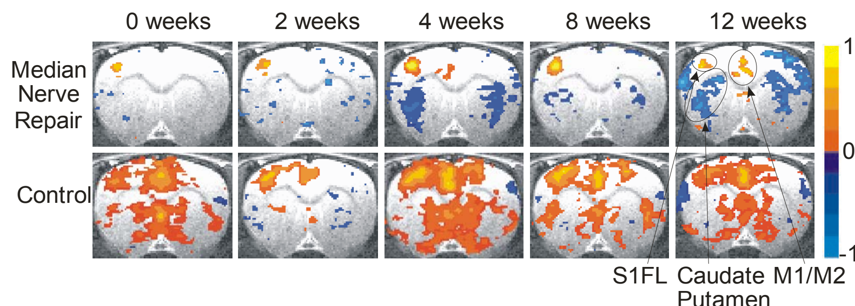

Figure 1. Images 0.6 mm from the bregma obtained at 0, 2, 4, 8, and 12 weeks after median nerve repair or sham control surgery. For all images, stimulation parameters were 1 ms, 5 Hz, 1 mA.

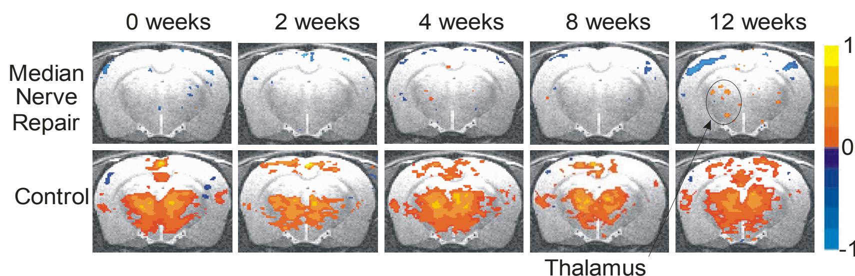

Figure 2. Images -3.36mm from the bregma obtained at 0, 2, 4, 8, and 12 weeks after median nerve repair or sham control surgery. For all images, stimulation parameters were 1 ms, 5Hz, 1mA.

Results: Figures 1 and 2 display fMRI activation maps to direct median nerve stimulation. Figure 1 is a slice located over the primary sensory forelimb region (S1FL) and figure 2 is a slice located over the VPM region of the thalamus. Both the experimental nerve repair group (Top) and sham control group (Bottom) are displayed. Progression in time is from left to right and the five time-points (0,2,4,8,12 wks) are included. Average activation maps across all six rats are overlaid over anatomical images and correlate to the colorbar to the right of the figures. Large regions of both positive (red) and negative (blue) are evident. Figure 3 is a bar graph depicting the number of BOLD activated voxels in the S1FL region at each of the five time-points.

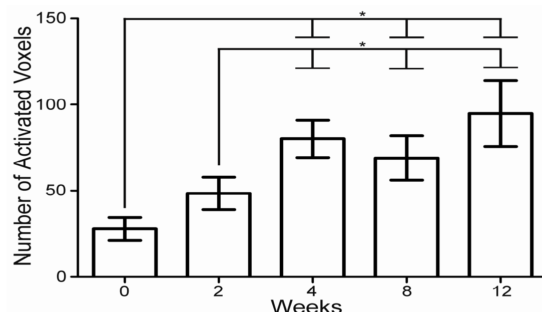

Figure 3. S1FL activation following median nerve repair. * statistical significance (t-test)

Discussion: The brain networks activated by direct median nerve stimulation are different between the groups that underwent nerve repair or the sham procedure. The networks remain relatively constant in the control group but are evolving in the experimental group. There is a greater amount of negative BOLD response to stimulation over time in the repair group. This may be due to release of inhibitory influence on brain interneurons following peripheral nerve injury (4). Notice the thalamic return after a 12 week recovery period in the repair group (Fig.2). Activation in S1FL progresses slowly (Fig 3) demonstrating a slow return of sensory innervation over time. These results demonstrate the utility of using fMRI as a biomarker of brain plasticity and reveal how fMRI can be used as a replacement for conventional electrophysiology. **References:** 1.) Neuroscience, 1983. 10(3): p. 639-65. 2.) Prog Neurobiol, 2007 82(4): p. 163-201. 3.) MRM, 2007. 58: p. 901-909. 4.) Neuroimage. 2009 Epub. Sept 28.