Cortical Plasticity of the Brain after Median Nerve Transection using fMRI at 9.4T by Direct Nerve Stimulation

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Abstract: Peripheral nerve surgeons often see patients who have suffered traumatic nerve transections days to weeks after the trauma has occurred. When a patient presents immediately after a suspected median nerve transection, the loss of the known median nerve sensory distribution will support the diagnosis. One interesting observation is that when these patients present to a clinic two weeks after the transection, they have slight but noticeable sensory recovery in the median nerve sensory distribution. For example, after two weeks, the patient may have sensation over the entire ring finger, not just the ulnar portion of the ring finger as initially observed. It is theorized that the sensory recovery minimally advances from the border nerve distributions. Obviously, without median nerve repair, we would not see the increased sensory recovery of the median nerve months to years down the road, but the partial recovery after two weeks cannot be explained by the typical axonal ingrowth of primarily repaired nerves of one millimeter per day. This observed clinical phenomenon provided a starting point for generating a study with dual roles of examining the brain plasticity in peripheral nerve injuries and providing clinical correlates.

Methods: Five Sprague Daley rats were used in a pilot study of acute plasticity. The median nerve was transected on the right side and an electrode was placed on the proximal end. The left side served as an internal control and the left side brachial plexus was exposed and an electrode was placed on the left median nerve (intact).

Three Sprague Daley rats were used a pilot study of *sub-acute* (1-30 days) plasticity. In a sterile fashion, the median nerve of the right forepaw of the rat was dissected, isolated, and cut. Fourteen days following the right median nerve transection, the rat underwent surgical placement of four electrodes. The left forepaw again served as an internal control. The electrodes were placed on the intact left ulnar and median nerves, intact right ulnar nerve, and the proximal end of the cut right median nerve.

Two separate electrical stimulation protocols were used. Each of the nerve stimulation sequences began with an OFF period of 40 s followed by three repetitions of ON for 20 s and OFF for 40 S (total scan time = 3 min 40 s). A rapid acquisition with relaxation enhancement (RARE) anatomical image was acquired with a 256 x 256 matrix, TE = 12.5 ms, TR = 2.5 s, and the same slice geometry as the echo planar imaging (EPI) sequence. Gradient echo scans (single shot EPI, TE = 18.76 ms, TR = 2 s, matrix size 128 x 128, FOV = 4cm, number of repetitions = 110, 10 contiguous interleaved 1 mm slices, acquisition time = 3 min 40 s) were acquired using a Bruker AVANCE MRI scanner with a 30 cm bore. Two sets of gradient echo images were acquired for each stimulation protocol. Images were acquired using a Bruker receiving surface coil (T9208) and a linear transmit coil (T10325).

Results: Fig. 1a displays the representation of the BOLD signal we observed when the right transected median nerve was stimulated proximal to the cut immediately after the cut was made. Compared to stimulation of the intact side (Fig. 1b), we see that there is no signal in the sensory (S1FL) region on the contralateral side. Notice the motor system region Caudate Putamen (CP) is unchanged.

When the proximal end of the cut nerve is stimulated 2 weeks later the cortical BOLD signal response (Fig. 1c) is noticeably less than the left intact median nerve (control) (Fig. 1d). Possibly the lack of afferent input to the brain from the cut median nerve over the two week recovery period resulted in the complete loss of cortical representation of this nerve.

The BOLD signal responses from left side nerve stimulation (control) show an expected signal in the right cortex corresponding to the sensory of the rat left forepaw (Fig. 1d). These were considered normal and closely resemble the signal we see when developing the cortical map using direct nerve stimulation(1).

There is an increase in the cortical representation of the right **ulnar** nerve with stimulation (Fig. 1e) 2 weeks after the right **median** nerve was cut. As expected, the signal is stronger and more extensive when compared to the representation of the contralateral intact ulnar nerve (control) (Fig. 1f).

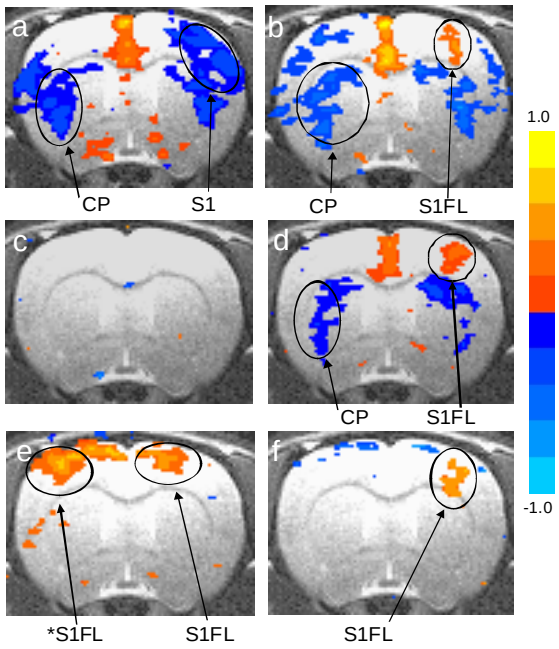

Figure 1: a) Acute: right median nerve stimulation (cut side) (1 ms, 10 Hz, 0.5 mA); b) acute: left median nerve stimulation (uncut side) (1 ms, 10 Hz, 0.5 mA); c) after two weeks: right median nerve stimulation (1 ms, 10 Hz, 0.5 mA); d) after two weeks: left median nerve stimulation (1 ms, 10 Hz, 0.5 mA); e) after two weeks: right ulnar nerve stimulation (1 ms, 10 Hz, 0.5 mA); and f) after two weeks: left ulnar nerve stimulation (1 ms, 10 Hz, 0.5 mA).

Discussion:

The absence of signal in the SiFL region with stimulation of the proximal end of the cut median nerve is an astonishing result demonstrating a form of immediate plasticity. We hypothesize two possibilities. After acute nerve transection, the earlier disappearance of the fMRI sensory signal compared to the fMRI motor signal may be due to earlier chromatolysis of the sensory dorsal root ganglia cells compared to the motor neurons. It is also possible that peripheral sensory de-afferentation somehow disrupts the ability of the CNS to produce surround inhibition, which is more important in enhancing CNS somatosensory signaling, when compared to motor signaling. Since we saw a dramatic difference in the signal when the right median nerve was transected and stimulated immediately, we questioned whether there would be a difference in the signal after the median nerve was transected and stimulated *sub-acutely*. At two weeks, we expected a normal cortical BOLD signal distribution from stimulation of the left intact forepaw nerves. We also expected an increased cortical BOLD signal area from stimulation of the intact right ulnar nerve and a decrease in the cortical BOLD signal area from the proximal cut right median nerve. It appears the brain compensates for the median nerve deficit and an expansion of the representation of the ulnar nerve occurs. This finding supports the observed clinical phenomenon of creeping sensory borders with a single nerve transection. The intact ulnar nerve, in this case, has an increased cortical response to stimulation and in theory requires a larger cortical representation as it tries to compensate for the lack of sensory input coming from the median nerve. We intend to closely compare this data with the cortical mapping experiments (1) to delineate specifically the cortical areas involved in the observed brain plasticity.

1. Magn. Reson. Med. 58: 901-909, 2007.