

Functional MRI detection of acute and chronic brain plasticity following median and ulnar nerve transection using direct nerve stimulation at 9.4T

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Introduction

Brain plasticity that occurs after peripheral nerve injury has been studied by numerous groups. Borsook showed that removal of a sensory input can cause major cortical reorganization (1). Koretsky demonstrated that total denervation of a forepaw or a hindlimb leads to inter-hemispheric reorganization in the rodent primary somatosensory cortex. This kind of bilateral fMRI activation was only detected when all of the nerves innervating the forepaw or hindpaw were cut. The healthy cortex was essential for the inter-hemispheric cortical reorganization (2). In fact, most of the peripheral nerves are mixed, which means that they also contain motor components. Clinically, the sensory and motor nerves heal in different ways after nerve injury, which suggests that there might be different patterns of brain plasticity following different kinds of nerve injury. This study has four novel aspects. First, we show that pure motor nerve activation in the rat central nervous system can be demonstrated using fMRI. Given the fact that peripheral nerves are mixed, it has previously been considered impossible to activate the pure motor nerve component and detect its CNS representation by fMRI in the past. Second, it has been found that the motor nerve is less sensitive to injury than the sensory nerve. Third, our experiment showed that inter-hemispheric brain plasticity occurs in the motor and sensory areas even if more than one nerve of the brachial plexus is intact. Finally, the thalamus and caudate putamen (CP) were activated in different ways in acute and chronic brain plasticity, which suggests that they may also play an important role in brain reorganization.

Method

Animal preparation: Eight Sprague Dawley rats were used in this study, divided into two groups. In group 1 (acute plasticity group), the brachial plexus was exposed on both sides. The median and ulnar nerves on the right side were surgically transected as a pair. A 150- μ m diameter stainless-steel bipolar electrode (AISI 304, Plastics1, Roanoke, Virginia) was attached to the proximal end of the transected nerve on the right side and a second electrode was placed on the intact nerve trunk on the left side. Similarly, in group 2 (chronic plasticity group), the right median and ulnar nerves were transected and a 3 mm section was removed. After surgery, the site was closed, and the rats were allowed to recover from anesthesia; they were monitored for 2 h before returned to MCW's Biomedical Resource Center. Two weeks after the initial surgery, the brachial plexus on both sides of the rat was exposed. At that time, an electrode was attached to the proximal end of the transected nerves and a second electrode on the left median and ulnar nerves. Brain image distortion associated with the electrodes was not apparent at 9.4T. **Anesthesia:** Isoflurane (1.4%) was administered during the surgical portion of the procedure. Once the rat was transferred to the scanner, the isoflurane was turned off. A continuous infusion of pancuronium bromide (2 mg/kg/hr) and Domitor (0.1 mg/kg/hr) was used during the fMRI acquisition. **Stimulation protocol:** Two separate protocols (10 Hz, 0.5 mA, and 5 Hz, 1 mA) with a constant duration of 1 ms were used. Each stimulation sequence 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 minutes 40 seconds). There was a four-minute resting time between two stimulations for rats to recover. **MRI parameter:** Gradient echo scans (single shot EPI, TE = 18.4 ms, TR = 2 ms, matrix 128 x 128, FOV = 4 cm, number of repetitions = 110, 10 contiguous 1 mm scans) were acquired on a 9.4T/30 cm Bruker MRI scanner. Physiologic monitoring included arterial blood gases, pulse oximetry, pulse, temperature, respiratory rate, and inspired/expired O₂ and CO₂. **Data analysis:** A RARE anatomical image was acquired with a 256 x 256 matrix with the same slice geometry as the EPI images. Two sets of gradient echo images were acquired for each stimulation protocol. The EPI scans were registered to an ideal anatomy using FLIRT software. The images for each nerve and stimulation protocol were averaged (3Dcalc) using AFNI software. The averaged data for each nerve and stimulation level was then masked (3DAutomask) using AFNI. Activation was determined by an F test (3DDeconvolve) with a P-value threshold of 0.005 using AFNI.

Results

Figure 1 shows the average (of four rats) of the acute and chronic brain activation induced by combined median and ulnar nerve stimulation. (A) The sensory component of the mixed nerve representation in the cortex is no longer activated, while pure motor area activation in the M1/M2 region can be seen. In comparison to the control side (C), the thalamus in the latter slices was slightly activated, and there was an enhanced negative BOLD signal that can be detected in the caudate putamen in the first few slices. This suggests that the caudate putamen and thalamus might play important roles in brain acute plasticity. Figure (A) shows that motor cortex reacts more slowly to the damage of the peripheral nerve than the sensory cortex.

From Fig. 1 (B), it was found that two weeks after nerve injury, when stimulating the proximal end of a transected nerve, there was no activation in the brain in either the sensory or motor areas, and the neural-activity in the thalamus and caudate putamen was also abolished. There was no activation in the brain during stimulation. On the other hand, there was a diffused activation in the S1FL, S2, and M1/M2 regions when nerves on the left were stimulated, as demonstrated in Fig. 1 (D). The activation also could be detected on the ipsilateral side of the brain, which suggests that inter-hemispheric plasticity occurs in both the sensory and motor areas. No negative BOLD can be detected in the caudate putamen, and there was an enhanced thalamic activation in the latter slices.

Comparing Fig. (C) with Fig. (D), it was found that two weeks after nerve transection, when acute brain plasticity progressed into chronic plasticity, there was a huge change in the caudate putamen and thalamus. This suggests that these two structures might also be essential in chronic brain plasticity.

Conclusion and Discussion

From the experiment, it can be seen that pure motor area activation in the brain can be obtained by nerve transection and direct nerve stimulation. Acute brain plasticity can be detected by fMRI using direct nerve stimulation following nerve injury. Chronic brain plasticity can be detected two weeks after nerve transection, and inter-hemispheric brain plasticity occurs even if more than one major nerve remains in the rat's forelimb. The caudate putamen and thalamus might be essential in both acute and chronic brain plasticity.

Anatomically, the median and ulnar nerves are in charge of forepaw flexation, and the radial nerve is in charge of forepaw extension. By cutting off both the median and ulnar nerves, the flexation function of the forelimb is completely removed, and potentially larger brain reorganization can be induced, which may be easier to detect.

References

1. Borsook, D et al. Acute plasticity in the human somatosensory cortex following amputation. *NeuroReport* 9, 1998. 1013–1017.
2. Koretsky, AP et al. Functional MRI detection of bilateral cortical reorganization in the rodent brain following peripheral nerve deafferentation. *Neuroimage*. 2007 Aug 1;37(1):262-73.

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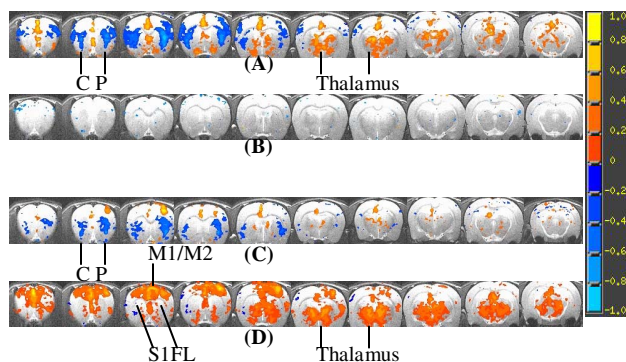


Fig 1. F test images of acute and chronic brain activation induced by median and ulnar nerve stimulation at 10Hz/1ms/0.5mA (n=4 in each group).

- (A) acute group right median and ulnar stimulation
- (B) chronic group right median and ulnar stimulation
- (C) acute group left median and ulnar stimulation
- (D) chronic group left median and ulnar stimulation