The Role of Cortico-Cortical Connections in Intercortical Plasticity Following Peripheral Nerve Injury

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Introduction:

Peripheral nerve injury has been demonstrated previously to cause remarkable brain organization in the somatosensory area in humans and in animal models (1). Although the cellular level of this type of reorganization is being studied extensively using electrophysiological methods, little is known about the changes that the network level undergoes under these circumstances. Functional MRI (fMRI) methods has a great potential to contribute significantly to the understanding of the cascade of events that leads to brain reorganization, and therefore was applied in our study (2,3).

The sciatic and saphenous nerve injury model in rats was used and the reorganization of the somatosensory regions was followed by fMRI. In control (sham-operated) rats, sensory stimulation of the healthy hindpaw led to contralateral somatosensory activation. Surprisingly, sensory stimulation of the healthy hindpaw in the hindpaw lesioned rats, led to both ipsi- and contra-lateral somatosensory activation, 2 weeks following the surgery. In order to test the anatomical origin of this type of brain reorganization, we stereotaxically lesioned the healthy somatosensory cortex of the hindpaw representation in both control and hindpaw lesioned rats. In these rats, sensory stimulation of the healthy hindpaw (contralateral to the lesioned cortex) did not yield any brain activation, suggesting that the healthy somatosensory cortex was mediating the reorganization of the deprived cortical area.

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 both the sciatic and saphenous nerves (n=8). 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 2 weeks prior to MR imaging.

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 and forepaw. 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.

Cortical lesions: A week following the hindpaw nerves cut, rats were placed in a stereotaxic head holder, and a small electrode was inserted to the hindpaw representation of the cortical somatosensory area. A continues 1 mA current was delivered for 1 minute. At the end of the procedure, the head was sutured and the rats were allowed to recover for a week prior to the MR imaging (for a total of 2 weeks following the initial hindpaw nerves cut).

Image Acquisition: All images were acquired with an 11.7 T / 31 cm horizontal bore magnet (Magnex), interfaced to an AVANCE console (Bruker).A 2 cm diameter surface coil that was attached to a head holder was used to transmit and receive the MR signal. For fMRI experiments, a single-shot, spin-echo EPI sequence with a 64 × 64 matrix was run with the following parameters: TE 30 ms, TR 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 WPI stimulator supplied 2 mA, 300 μs pulses repeated at 3 Hz to both hindpaws and forepaws upon demand. The paradigm consists of 40 scans during rest, 10 scans during hindpaw stimulation, which was repeated 4 times.

Data Analysis: For fMRI group statistics analysis, all images were spatially normalized to the brain of a control rat using 2D affine transform. Images were smoothed by Gaussian filter with full-at-half-maximum (FWAHM) of 3 pixels. The group *t*-score maps were calculated using a fixed-effects analysis and threshold at $p<10^{-5}$ (corrected for multiple comparison with Bonferroni correction).

Results & Discussion:

Figure 1 shows group average fMRI data demonstrating inter-cortical plasticity after peripheral nerve damage. Using fMRI we were able to observed reorganization of the somatosensory cortex and to identify one of the major pathways by which this type of brain reorganization is being mediated through. Sham operated (a) and sciatic nerve deafferentiated maps (b) activated the normal hindpaw somatosenory representation. Interestingly sciatic and saphenous nerve lesions (c) led to activation in both contralateral and ipsalateral cortex. Activation of both contralateral and ipsalateral also occurred after sciatic and saphenous nerve deafferentation and sham cortical lesion surgery (f). Cortical lesions in hindpaw somatosensory region in either control (d) or sciatic and saphenouse nerve deafferentation (e) abolished activation in both the contralateral (from the healthy limb) and ipsilateral cortex. These results support the model that the intercortical plasticity that occurs after sciatic and saphenous nerve deafferentation occurs due to cortical-cortical interactions. In conclusion, these results demonstrate that there is intercortical plasticity after peripheral nerve damage and that his occurs via manipulation of inter-hemispheric brain communication, mainly through the corpus callosum. This interaction may serve as a target region to enhance brain recovery following traumatic events.

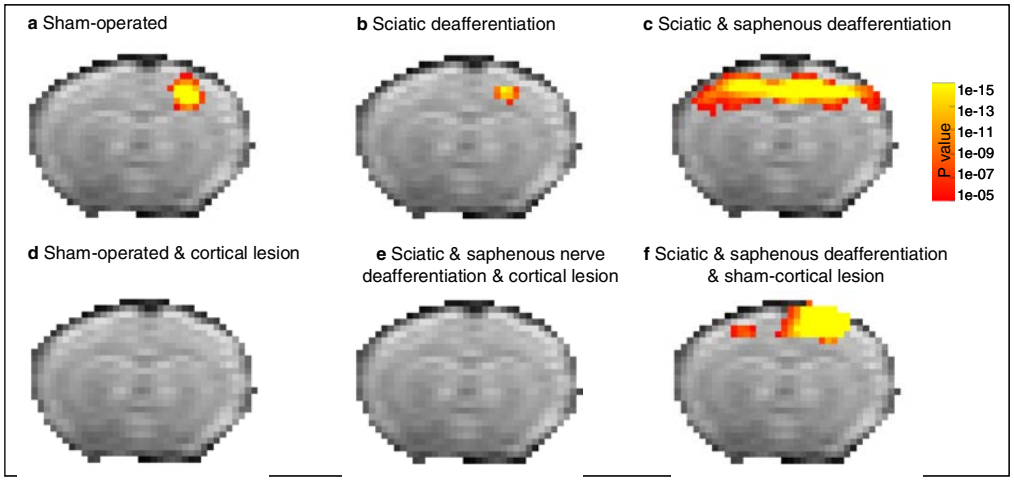

Figure 1: **Group activation t-test maps.** Group t-test maps ($p<10^{-5}$, corrected for multiple comparison) overlaid on the EPI template image for the (**a**) Sham-operated rats (n=5), (**b**) Sciatic nerve deafferentiated rats (n=5), (**c**) Sciatic and saphenous nerves deafferentiated rats (n=8). In addition group t-test maps are shown for (**d**) Sham-operated with cortical lesion rats (n=5), (**e**) Sciatic and saphanous nerve deffaretiated rats with cortical lesions (n=5) and (**f**) Sciatic and saphenous nerves deafferentiation with sham-cortical lesions (n=5). All somatosensory ablations were positioned in the hindpaw representation contralateral to the healthy hindpaw.

References:

1. Merzenich *et al.*, 1983, *Neuroscience*
2. Abo *et al.*, 2001, *Neuroreport*
3. Dijkhuizen *et al.*, 2001, *PNAS*