Changes In Central Nervous System Activity After Peripheral Nerve Injury: A Functional MRI Study


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Introduction: Peripheral nerve injury stems from various causes, including trauma and inflammation, and causes motor and sensory dysfunction. In addition, patients sometimes suffer from chronic pain such as hyperalgesia or allodynia after injury. The mechanisms by which chronic pain develops are currently being clarified. Some investigations have suggested that the development of chronic pain is affected by the alteration of pathways of pain or emotional factors (1, 2). Non-steroidal anti-inflammatory drugs, opioid analgesics, pregabalin (3) and antidepressants (4), alone or in combination, are usually used to treat chronic pain, but there remains no established method of therapy. In order to identify the most effective form of treatment, we must first reveal the mechanisms by which chronic pain develops.

The aim of this study is to investigate the mechanisms underlying chronic pain development in a rat peripheral nerve injury model using functional magnetic resonance imaging (fMRI).

Methods: All experiments were carried out in accordance with the National Institute on Health Guide for the Care and Use of Laboratory Animals. Six male Sprague Dawley rats weighing 250 - 300g were used in the experiments. All rats were deeply anesthetized before the right sciatic nerve was exposed and ligated using a Yasargil aneurysm clip to produce a crush injury. Serial functional MR images of each rat’s brain were taken before the operation and at 1, 3, 6 and 9 weeks after the crush injury. A high magnetic field MRI system (Varian MRI system 7.04T, Agilent, Santa Clara, CA, USA) was used throughout the MR imaging study. To emphasize the changes in blood perfusion in the MR images, iron MR imaging contrast agents (Molday ION, Bio PAL, Worcester, MA, USA) were administered. A needle electrode was inserted under the plantar skin of each rat’s right foot to provide electronic stimulation. Changes in signal intensity in the brain evoked by electrical stimulation were analyzed. Statistic t-value maps were made by processing the MR images acquired at the various time points.

Results: Longitudinal statistic t-value maps were generated from data taken after sciatic nerve crush injury (Fig.1). In these maps, colored areas indicate significant gains in blood perfusion, that is, brain areas that were significantly activated by electric stimulation to the plantar surface of the foot. Before injury, a significant change in signal intensity was observed at the left thalamus. One week after injury, various parts of the brain were activated by electric stimulation of the injury site. The anterior cingulate and the insula cortex on the right side were activated particularly strongly. At three and six weeks after injury, however, these activated areas were becoming smaller and fewer. Activation in the right amygdala was observed nine weeks after injury.
**Discussion:** This study investigated changes in activation in the brain after peripheral nerve injury as visualized using fMRI. We observed changes in the CNS throughout the acute and chronic phases. The anterior cingulate and insula cortex were activated in the acute phase. Furthermore, at nine weeks after injury, in the chronic phase of nerve regeneration, the amygdala was activated by stimuli. These areas are not directly included in the pathway of pain. Rather, the anterior cingulate and the insula cortex are parts of the limbic system, involved in consciousness and emotion about pain. The insula cortex projects to the amygdala and participates in the pain memory. Past histological studies have revealed that the amygdala greatly affects the development of chronic pain (5). This study demonstrates that real-time activation of the amygdala occurs during the chronic phase of peripheral nerve injury. This result supports the involvement of the amygdala in the development of chronic pain.

**Significance:** This study demonstrates real-time activation in elements of the limbic system, including the anterior cingulate cortex, insula cortex and amygdala, after peripheral nerve injury. The results of this study shed some light on the mechanisms underlying the development of chronic pain.

![Functional MRI images](image-url)

*Fig. 1*

Functional MRI images acquired before and at 1, 3, 6, and 9 weeks after sciatic nerve injury. The color chart indicates the natural logarithm of the P value, calculated according to the t-test at each time point.

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