



# Functional Reorganization in the Primary Somatosensory Cortex of Rat Following Hind-Paw Amputation: A Study of Functional Imaging with 1.5 Tesla MRI

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## ABSTRACT

**AIM:** To learn how rat primary somatosensory cortex (pSSC) responses to the loss of inputs from hind-paw, using fMRI of an inferior magnetic power (1.5 Tesla) with special designed high-powered rat coil.

**MATERIAL and METHODS:** Ten adult male Sprague-Dawley rats were enrolled in this study. The rats were anesthetized with ketamine injection. Xylazine was intraperitoneally injected for analgesia and muscle relaxation with careful maintenance of spontaneous respiration. Either right or left hind-paws were amputated under aseptic conditions according to predefined random allocation of the rats. A 12-channel rat surface coil developed for proper image resolution in 1.5 Tesla MR was used. Functional magnetic resonance imaging was obtained before hind-paw amputation; 2, 15 and 30 days after the amputation.

**RESULTS:** Activation signals were detected in 5 rats' contralateral pSSC before the hind-paw amputation with regression and cessation of the signal after the amputation. Signal re-appeared in the contralateral pSSC of only one rat (rat 9) 30 days after the amputation.

**CONCLUSION:** This study showed that functional plasticity might occur in the pSSC following hind-paw amputation of rats. Further studies are necessary to understand the true nature of the plasticity observed in pSSC, with new and novel measurement techniques on cellular basis rather than gross anatomical one.

**KEYWORDS:** Amputation, Somatosensory cortex, Plasticity, Functional imaging

## INTRODUCTION

Limb amputations, which could be caused by illness and traumatic events, increase mortality and medical costs, and decrease the quality of life (23). Trauma is one of the

most common reasons for morbidity and mortality in children older than 1 year of age. Traumatic limb amputation is more common in children compared to adults (13). Lawn mower and motor vehicle injuries are leading causes of limb amputation

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in children, whereas trauma and diabetes with concomitant vascular pathologies are leading causes of limb amputation in adults (8,13,22). Functionality following amputation procedures is very important for social re-integration of the patients.

Morphological and functional changes in the primary somatosensory cortex (pSSC) following limb amputation are still unclear. In the last 50 years, many animal and human studies began with histological analysis and ended up with functional magnetic resonance imaging (fMRI). Limb amputated rats have been good to study the morphological and/or functional changes in the pSSC (5,16,17,26-28,33,34,36).

Topographical organization of the hind-paw in pSSC is present in S-I cortex of normal rats. The mean area of rat pSSC associated with hind-paw innervation is 0.94 mm<sup>2</sup> (34). Sciatic and saphenous nerves innervate the hind-paw skin in rats. Sciatic nerve dominates (85%) over saphenous nerve (15%) in means of representative area of the hind-paw skin in pSSC. Hind-paw skin area innervated by sciatic nerve is represented in a more rostral and medial location in the pSSC compared to that innervated by the saphenous nerve. Medial and lateral sides of hind-paw are represented contrarily in the pSSC. Similarly, distal plantar and hairy skin surfaces convey signals to more anterior; proximal skin surfaces convey signals to caudal sides of representative area in the pSSC (34).

Previous studies regarding pSSC plasticity were mostly on histological or neurophysiological basis (5,34). However, neurophysiological studies are limited in means of spatial resolution due to the dimension of electrodes, precision of electrode positioning, and distribution of local field potential (36). Blood-oxygen-level dependent (BOLD) fMRI studies have gained attention to study the pSSC plasticity in both animal and human models, in the past 20 years (3,4,7,9,10,19,24,26-28,30,31,33,36,39-41).

In this study, we aimed to learn how rat pSSC responses to the loss of inputs from hind-paw, using fMRI of an inferior magnetic power (1.5 Tesla) with special designed high-powered rat coil.

## ■ MATERIAL and METHODS

We conducted a prospective laboratory study. Local Ethics Committee for Animal Research of Marmara University approved the study protocol (33.2013.mar). Ten adult male Sprague-Dawley rats were enrolled in this study. The rats were anesthetized with ketamine injection. Xylazine was intraperitoneally injected for analgesia and muscle relaxation with careful maintenance of spontaneous respiration. Onset of anesthesia effect was checked with absence of the cornea reflex and spontaneous limb retraction. Either right (rats 1-4, 7) or left hind-paws (rats 5-6, 8-10) were amputated under aseptic conditions according to predefined random allocation of the rats. The rats were daily observed for any sign of infection at the site of the cut surface.

A 12-channel rat surface coil developed by Bilkent University, National Magnetic Resonance Research Center (UMRAM, Ankara, Turkey) was used for proper image resolution in

1.5 Tesla MRI (Magnetom Espree, Siemens, Germany). Anatomical references were shown using 3D T1-weighted (3D-T1W) images. Repetition time (TR) was 1300 msec, echo time (TE) was 3.2 msec, FOV read was 120 mm, slice thickness was 1 mm, and image matrix was 115x192 for these 3D-T1W images. The technical features for functional imaging (gradient-echo BOLD imaging) were as follows; TR/TE: 3000/30, number of slices: 35, slice thickness 3.0 mm, FOV: 145x145 mm, matrix size: 64x64, and flip angle: 90°. Different runs of the experiment were averaged to improve signal-to-noise ratio.

Functional magnetic resonance imaging was obtained before hind-paw amputation, 2, 15 and 30 days after the amputation. The rats were positioned supine on fMRI. Each fMRI session took 2 minutes 48 seconds at 10 phases of passive and active points. Active points were done as standard hind-limb motion of flexion-extension in the same manner each time applied by the same author (AA).

## ■ RESULTS

Intense activation signal was observed at the junction of the left cingulate gyrus and the left medial thalamus before the hind-paw amputation in rat 1. A decreased activation signal was seen in the cingulate gyrus 2 days after the amputation. No activation signal was detected on the 15<sup>th</sup> and 30<sup>th</sup> days of the amputation.

No activation signal was present in the left pSSC of rat 2 at any time point. An intense activation signal was observed in the right cingulate gyrus at pre-amputation era. It turned into a slight activation signal at the lateral border of the right pSSC 2 days after the amputation, at the inferior border of the left medial thalamus 15 days after the amputation and in the right pSSC at the final follow-up.

No activation signal was present in the left pSSC of rat 3. An intense activation signal was detected in the right medial thalamus before hind-paw amputation. Activation signal in the left medial thalamus was intense 2 days after the amputation and slight 15 days after the amputation. It faded away 30 days after the amputation.

An intense activation signal was observed at the junction of the left cingulate gyrus and the medial border of the left pSSC before hind-paw amputation in rat 4. Intensity of this activation signal decreased 2 days after the amputation (Figure 1, rat 4; a, b). Activation signals totally disappeared on the 15<sup>th</sup> day of the amputation, and never reappeared thereafter (Figure 1, rat 4; c, d).

An intense activation signal was present in the right cingulate gyrus and at the border of the right cingulate gyrus and the right pSSC before hind-paw amputation in rat 5 (Figure 1, rat 5; a). Activation signals totally regressed following the amputation (Figure 1, rat 5; b-d).

An intense activation signal was observed in the right medial thalamus before hind-paw amputation in rat 6. The activation signals faded away and never turned back following the amputation. However, no signal was detected in the pSSC at any time point.

An intense activation signal was seen in the left pSSC of rat 7, yet the signal decreased in intensity on the 2<sup>nd</sup> day and disappeared on the 15<sup>th</sup> day of the amputation (Figure 1, rat 7; a-d).

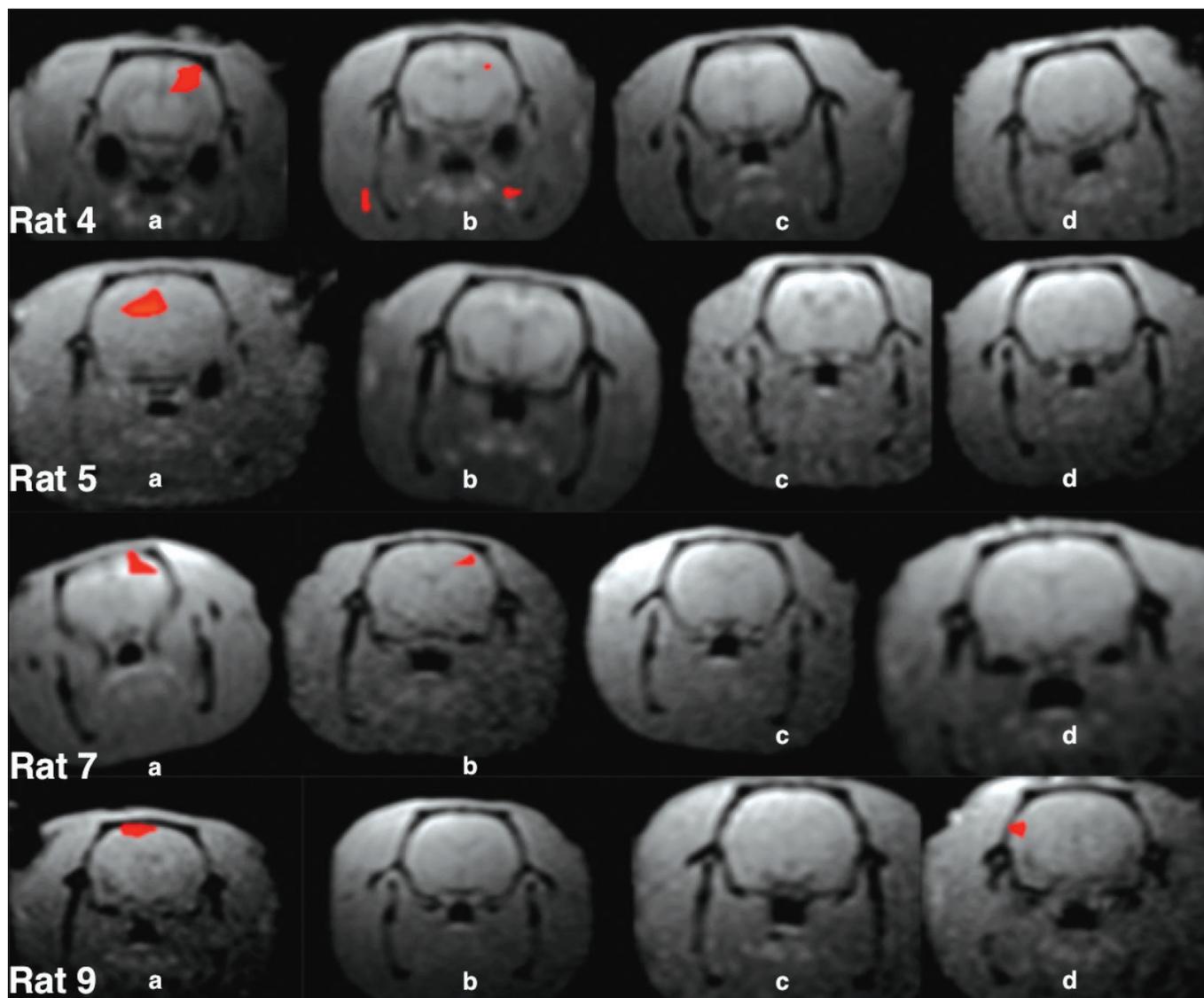
A slight activation signal was present in the left cingulate gyrus before hind-paw amputation in rat 8. Intense activation signals were detected in the right pSSC area 2 days after the amputation, and in the right cingulate gyrus 15 days after the amputation. No activation signal was seen at the final follow-up.

An intense activation signal was observed at the medial border of the right pSSC of rat 9, which disappeared after the amputation. A new slight activation signal re-appeared at the lateral border of the right pSSC on the 30<sup>th</sup> day of amputation (Figure 1, rat 9; a-d).

An intense activation signal was detected in the right pSSC before the amputation in rat 10. The signal intensity decreased following the amputation. However, it was still visible in the same location until the final follow-up, and then it disappeared. The study results have been summarized in Table I.

## ■ DISCUSSION

Trauma and diabetes with concomitant vascular pathologies are leading causes of limb amputations (8,13,22). Functionality following amputation procedures is very important for social re-integration of the patients. It was shown that the loss of upper limb in non-human primates changed functions in somato-sensory and motor areas of the brain. This phenomenon corresponds to phantom limb sensation/pain seen in human amputees (32). Thus, understanding brain plasticity will help us manage the process with improved functionality.



**Figure 1:** Somatosensory cortex (SSC) activation patterns detected in rats 4, 5, 7, and 9. Rats 4 and 7 underwent right hind-paw amputation. Rats 5 and 9 underwent left hind-paw amputation.

**Table I:** Side of Hind-Paw Amputation and Response of the Somatosensory Cortex at Pre-Amputation and Post-Amputation Follow-ups

Rat #	Side of amputation	Pre-amputation	Post-amputation day 2	Post-amputation day 15	Post-amputation day 30
1	R	N	N	N	N
2	R	N	N	N	N
3	R	N	N	N	N
4	<b>R</b>	<b>I</b>	<b>S</b>	<b>N</b>	<b>N</b>
5	<b>L</b>	<b>I</b>	<b>N</b>	<b>N</b>	<b>N</b>
6	L	N	N	N	N
7	<b>R</b>	<b>I</b>	<b>S</b>	<b>N</b>	<b>N</b>
8	L	N	I	N	N
9	<b>L</b>	<b>I</b>	<b>N</b>	<b>N</b>	<b>S</b>
10	<b>L</b>	<b>I</b>	<b>S</b>	<b>S</b>	<b>N</b>

#: Number, **R**: right, **L**: left, **I**: intense activation signal, **S**: slight activation signal, **N**: no activation signal.

Functional MRI has developed a view of functionality in the human brain. Stimulation of the pSSC increases neuronal activity, induces extracellular ATP release and increases intracellular calcium concentration in astrocytes. Hence, these changes facilitate the release of vasoactive metabolites from astrocytes contributing to neurovascular coupling, which makes up BOLD fMRI. Neurovascular coupling is still unclear and requires further studies in this field (15,25,35,36). There are some drawbacks of BOLD fMRI such as the large vein effect, the signal-to-noise ratio, and the vascular point spread function that could intervene with understanding of neural function in cortical columns or layers (14,18). However, BOLD fMRI has been used many times in high field power MRI studies (3T-11.7T) (3,4,7,9,10,19,24,26-28,30,31,33,36,39-41). In this study, we aimed to learn how rat pSSC responses to the loss of inputs from hind-paw, using fMRI of an inferior magnetic power (1.5 Tesla) with special designed high-powered rat coil.

The first topographical analysis between a peripheral organ and the somato sensory cortex was done in a mouse model, between large mystacial vibrissae and group of cells termed as 'barrels' in the fourth layer of the mouse pSSC (38). Mammalian pSSC has representation areas of the body parts according to the distribution and density of the receptors in that body parts such that head composing 67%, fore-limb composing 15%, trunk composing 14% and hind-limb composing 4% of the rat pSSC (37). The representation of hind-paw in the pSSC lays posterior to the representation of fore-paw, and is formed by anterior and posterior portions. The anterior portion is composed of three- or four-elongated clusters aligned in an anteromedial-posterolateral orientation, which correspond to hind-paw digits. The posterior portion is composed of smaller and round clusters representing the palm pads. Overall proportions of these areas are similar in rats (5).

Peripheral organ or nerve injuries may result in changes in the rat pSSC anatomy, if these injuries occur before the 5<sup>th</sup>

postnatal day (5). In the present study, we observed functional changes in the adult life of rats. We also found that the rats were affected in different patterns, even though the injuries and follow-up images were done on a regular pre-designed pattern. This was previously depicted by Dawson and Killackey (5). As a limitation of our study, we did not evaluate the brains histologically to identify whether functional changes correlated with the morphological ones.

Representation of the hind-paw area in the pSSC is mostly fed up by the sciatic nerve (85%) and less by the saphenous nerve (15%). In case of sciatic nerve injury, representation of sciatic nerve supplied area in the pSSC is replaced partly by saphenous nerve (the area represented by saphenous nerve increases 3-fold) (34). This expansion takes place in 1-2 days following sciatic nerve injury, yet it could not enlarge to the whole representation of the hind-paw area in pSSC. No further neurophysiological recovery could be seen in the representation of hind-paw area innervated by the sciatic nerve 5 months after de-afferentation of the nerve itself (34). Similar expansions in the pSSC have been reported in an fMRI study of fore-paw digit amputation in rats (36). In the present study, a slight functional recovery was observed in rat 9 at the final follow-up. The recovery we observed in rat 9 could be explained by regain of the cortical area by skin proximal to the amputation, which is termed as peripheral adjacency. Peripheral adjacency, the intact skin innervation surrounding the sacrificed skin area, has been reported to be the main source of re-afferentation in the pSSC (17,20,21,34). The re-afferentation by this peripheral adjacency occurs with a limited efficiency (34), as we observed in the present study. Another factor that could explain recovery in the pSSC area could be the interference with motor signals that overlap with sensory signals in the S-I representation of the rat hind-paw (6,11,29). The other possible explanation for the re-afferentation could be plasticity of the pre-existing yet inactive neuronal circuits that have been re-activated by the peripheral feedback (1,2,12).

As a limitation of our study, we gave stimulations as standardized movements of the limb by the same author (AA) instead of electrical stimulation. However, not all frequencies of electrical stimulation are successful in raising fMRI responses in the corresponding pSSC area in rats (36). Besides, phantom expansion in pSSC area of corresponding body part has been observed due to electrical stimulation itself (16). We were successful to observe activation signals in 5 out of 10 rats' pSSC in the pre-amputation era. This difference in results could be due to different hemodynamic responsiveness of the rats. Besides, BOLD fMRI results are affected by signals disseminated from vessels neighboring the cortical field of interest. Thus, this explains different zones of signal activation other than pSSC observed in the remaining five rats at pre-amputation period. One other limitation was lower magnetic power of the MRI (1.5 Tesla), which could have missed some signals from other five rats. So, further studies with higher settings should be conducted to make more clear statements about this topic.

## ■ CONCLUSION

This study showed us that pSSC functional plasticity might occur following hind-paw amputation in a rat model. Further studies are necessary to understand true nature of plasticity observed in pSSC following limb amputation, with new and novel measurement techniques on cellular basis rather than gross anatomical one.

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