

# Characterization of somatosensory BOLD response deficit and recovery after traumatic brain injury in rat

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## INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability worldwide with an estimated 10 million people affected annually [1]. Initial mechanical damage to the brain causes immediate brain damage and triggers a cascade of secondary damage and recovery processes which typically last from few weeks to even years. In a previous fMRI study [2], we detected functional deficit and subsequent recovery in the BOLD response of rat primary somatosensory cortex (SI) following fluid percussion induced TBI (Fig. 1), although SI is far from the injury site and appeared normal in structural T<sub>2</sub>-w. MRI. The aim of this study was to further investigate the previously observed functional deficit and recovery in the rat SI after TBI using simultaneous local field potential (LFP)/fMRI measurements and histology.

## METHODS

Adult male Sprague-Dawley rats (n=10) were used. Moderate TBI was induced for 8 animals using the lateral fluid percussion method [3] while the remaining 2 animals were sham operated and used as controls. MRI experiments were performed in a 4.7 T horizontal scanner interfaced with a Varian UNITY Inova console. Half of the animals (4 TBI and 1 control) were imaged at 2 days after TBI while the other half was imaged at 35 days after TBI. One animal in the 2 days after TBI group had to be discarded due to technical difficulties. LFP electrodes (50 µm diameter tungsten wire) were inserted in the right and left primary somatosensory cortices. Femoral artery was cannulated for monitoring blood gases and pH during the experiment and needle electrodes were placed in the forepaws for electrical stimulation. After placing the animals into the magnet, the isoflurane anesthesia was switched to medetomidine sedation (0.05 mg/kg bolus and 0.1 mg/kg/h infusion, s.c.). The functional imaging slice was positioned axially to the somatosensory cortex at 1 mm posterior from bregma. fMRI data were acquired using a single-shot spin-echo EPI sequence (TR 2 s, TE 60 ms, slice thickness 1.5 mm, FOV 2.5 x 2.5 cm, 64 x 64 matrix) during electric stimulation (electrical pulses of 0.3 ms duration, 2.0 mA, repeated at 9 Hz frequency) of the right and left forepaws separately in randomized order. The stimulus paradigm consisted of 30 images of baseline, 15 images of activation, repeated three times with 30 images of baseline at the end. Anatomic T<sub>2</sub>-weighted images were acquired using a multislice spin-echo sequence (TR 2.5 s, TE 60 ms, 256 x 256, FOV 5 x 5 cm, slice thickness 1.5 mm). LFP signal was recorded simultaneously with fMRI using a BrainAmp MR plus MRI compatible biosignal amplifier. Breathing rate was monitored throughout the experiment. Immediately after the MRI experiments the animals were deeply anesthetized and perfused transcardially. Brains were removed, sectioned and stained for thionin (Nissl), which was used to identify the cytoarchitectonic boundaries and neuronal damage as well as the distribution and severity of the neuronal damage. All data analyses were conducted using Matlab. The fMRI data were analyzed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>). LFP signal was analyzed using in-house made Matlab routines. All errors are presented as standard deviations.

## RESULTS

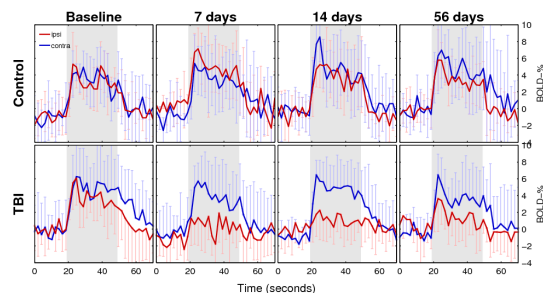
The BOLD activation in the ipsilateral SI was lost in all animals at 2 days after TBI. This functional deficit was also observed in the simultaneously recorded LFP responses as lowered amplitude (Fig. 2B). The average LFP response amplitudes in the ipsilateral SI (-0.37±0.24 mV) were statistically significantly lower ( $p<0.04$ , paired t-test) compared to contralateral amplitudes (-1.50±0.74 mV) at 2 days after TBI. However, at 35 days after TBI half of the animals (2) showed BOLD activation also in the ipsilateral SI (Fig. 2D). Furthermore, the ipsilateral LFP response amplitudes of these animals were roughly equal to the contralateral responses (Fig. 2, C-D). No statistically significant differences in the average LFP response amplitudes between ipsilateral (-0.28±0.31 mV) and contralateral (-0.77±0.60 mV) SI were detected at 35 days after TBI. Histological (Nissl) analysis of SI did not show any cell loss or neuronal damage. However, gliosis and neuronal loss were observed in the ipsilateral ventral posterolateral (VPL) thalamic nucleus (Fig. 3, A and C).

## DISCUSSION

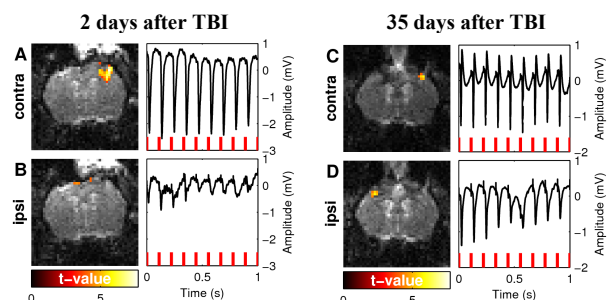
Our results show that the functional deficit detected by fMRI in the rat SI following TBI is accompanied by reduced firing of the neurons in SI, indicating that coupling between the hemodynamic and neuronal response is preserved. However, histological analysis of Nissl stained sections did not show any evident damage in the SI. Further histological investigation revealed gliosis and neuronal loss in the ipsilateral thalamic VPL, which is known to mediate signals to the ipsilateral SI [4]. The neurodegeneration in the thalamic VPL could offer an explanation for the observed functional deficit in the ipsilateral SI after TBI. However, the thalamic changes fail to explain the detected recovery of the ipsilateral responses in fMRI and LFP in some animals 35 days after TBI. The recovery of the somatosensory function could be caused by damage induced plasticity reorganizing the SI signaling pathways in response to the thalamic VPL damage.

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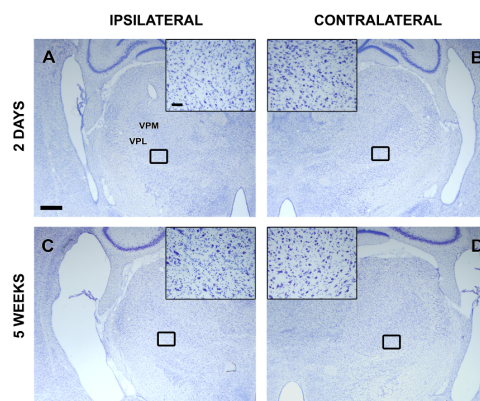
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**Fig. 1:** Group average fMRI time series of 6 sham operated controls and 10 TBI rats before TBI (baseline) and 7, 14 and 56 days after TBI from 2x2 ROIs in ipsilateral (red) and contralateral (blue) SI (taken from a previous longitudinal study [2]). The functional deficit of the somatosensory response is clearly seen in the ipsilateral time series of TBI animals at 7 and 14 days. However, partial recovery of the functional response can be seen at 56 days.



**Fig. 2:** fMRI activation maps and simultaneously measured LFP responses from SI in response to electrical forepaw stimulation for two representative animals at 2 days (A-B) and 35 days (C-D) after TBI. The red lines denote stimulation events.



**Fig. 3:** Photomicrographs of Nissl-stained sections of 2 trauma animals at 2 days (A, B) and 35 days (C, D) after injury. High magnification photomicrographs were taken to show up neuronal loss and gliosis in ipsilateral VPL (black squares). Scale bars: 500 µm (low magnification view) and 50 µm (high magnification view).