Evaluation of functional deficit and recovery in the rat somatosensory cortex after moderate traumatic brain injury using fMRI

J-P. Niskanen[1,2], A. Airaksinen[1], J. Nissinen[1], A. Pitkänen[1], and O. Gröhn[1]

[1]Department of Neurobiology, A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland, [2]Department of Physics, University of Kuopio, Kuopio, Finland

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. During this period, neuroprotective treatments and/or rehabilitation could have great potential for improving patient outcome. However, for planning optimal treatment protocols, objective measurements of the functional defect and recovery are required. The aim of this study was to evaluate the feasibility of longitudinal functional magnetic resonance imaging (fMRI) in detecting functional deficit and recovery after moderate TBI in the rat primary somatosensory cortex (SI).

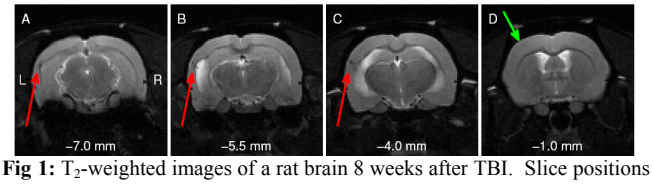

Fig 1: T_2-weighted images of a rat brain 8 weeks after TBI. Slice positions are given as distance from bregma. The lesion is visible in the posterior slices (A-C, red arrow), but the primary somatosensory cortex appears normal (D, green arrow).

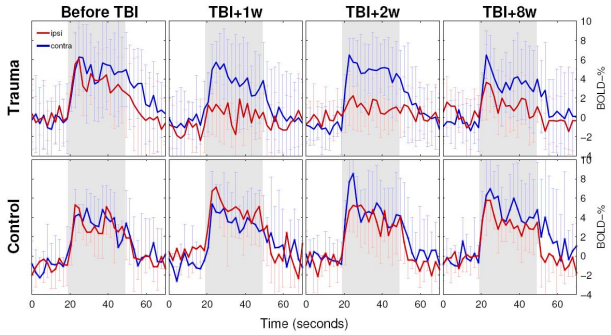

Fig 2: Average fMRI time series of one stimulus block taken from a 2 x 2 pixel ROIs in the ipsilateral (red) and contralateral (blue) primary somatosensory cortices of trauma and control rats. The functional deficit of the somatosensory response is clearly seen in the ipsilateral time series of trauma animals 1 and 2 weeks after TBI. However, partial recovery of the functional response can be seen 8 weeks after TBI.

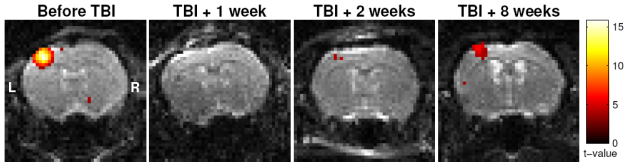

Fig 3: From left to right: fMRI activation maps in response to electrical stimulation of the right forepaw for a representative trauma rat before TBI and 1, 2 and 8 weeks after TBI. No voxels survive the threshold ($p < 0.05$, FDR corrected) 1 week after TBI. However, partial recovery of the somatosensory function can be observed 8 weeks after TBI.

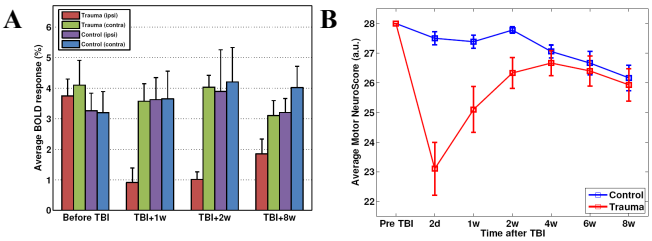

Fig 4: (A) Average BOLD responses relative to baseline. Statistically significant ($p<0.02$, one-tailed paired t-test) recovery of the ipsilateral somatosensory function is observed in the trauma animals. (B) Average motor NeuroScore results for trauma and control animals.

METHODS

Adult male Sprague-Dawley rats (n=16) initially weighing 293-322 g were used. Moderate TBI was induced for 10 animals using the lateral fluid percussion method [2] while the remaining 6 animals were sham operated and used as controls. MRI experiments were performed using a 4.7 T horizontal scanner (Magnex Scientific Ltd., Oxfordshire, UK) interfaced with a Varian ^{Unity}Inova console. The animals were first anesthetized with isoflurane 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 0.01 mg/kg/h infusion, *s.c.*). The functional imaging slice was positioned axially to the somatosensory cortex at 1 mm posterior from bregma. Functional MR 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 and adding 30 images of baseline at the end. Anatomic T_2-weighted images were acquired using a multislice spin-echo sequence (TR 2.5 s, TE 60 ms, 256 × 256, FOV 5 x 5 cm, slice thickness 1.5 mm). Breathing rate was monitored throughout the experiment. After the MRI experiments the rats were given 2.0 ml of glucose and 0.1 mg/kg of atipamezole hydrochloride (AntiSedan®) *i.p.* for reversing the medetomidine sedation. The MRI experiments were conducted for every rat before TBI and 1, 2 and 8 weeks after TBI. Behavioral motor testing (composite neuroscore [1,3]) was also conducted for all animals before TBI and 2 days, 1, 2, 4, 6 and 8 weeks after TBI.

All data analyses were conducted using Matlab R2007b (MathWorks, Natick, MA). The fMRI data sets were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, University College London, UK). Average fMRI time series were extracted from 2 x 2 voxel ROIs in the ipsi- and contralateral primary somatosensory cortices. The strength of the BOLD response was estimated by fitting the stimulus paradigm convolved with a hemodynamic response to the somatosensory fMRI time series. All errors are presented as standard errors of the mean.

RESULTS

A lesion is clearly visible in T_2-weighted MRI 8 weeks after moderate TBI near the trauma site (Fig. 1, A-C) but the more anterior primary somatosensory cortex appears as normal tissue (Fig. 1D). However, a statistically significant ($p<3*10^{-5}$, one-tailed paired t-test) functional deficit is observed in the ipsilateral SI 1 week after TBI (Fig. 2, Fig. 3, Fig. 4A). Partial recovery of the somatosensory function (Fig. 2, Fig. 3, Fig. 4A) is detected 8 weeks after TBI ($p<0.02$, one-tailed paired t-test) whereas the behavioral motor function recovers faster and cannot be distinguished from controls 4 weeks after TBI (Fig. 4B).

DISCUSSION

The results show that fMRI with forepaw stimulation is able to reveal functional deficit after TBI in the area that appears normal in structural T_2-weighted MRI. This indicates that functionally compromised tissue may extend over a significantly larger area than appears to be affected in conventional MRI. Importantly, fMRI was also able to detect delayed partial sensory recovery 8 weeks after TBI. However, the observed sensory recovery was slower than behavioral motor recovery, which suggests that fMRI provides complementary information to behavioral testing and could serve as a non-invasive user independent tool to evaluate functional recovery after TBI. Since similar methodology can also be applied in patients, fMRI could be utilized as a powerful tool in developing new drugs for delayed damage after TBI.

ACKNOWLEDGEMENTS

Academy of Finland (grant #123579), Orion-Farmos Research Foundation

REFERENCES

[1] Hyder AA *et al.* NeuroRehabilitation, 22(5):341-53, 2007. [2] McIntosh TK *et al.* Neuroscience, 28(1):233-44, 1989. [3] Fujimoto ST *et al.* Neurosci Biobehav Rev, 28(4):365-78, 2004.