# A long-term MRI assessment of head trauma induced tissue damage in rat brain

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## Introduction

The MRI investigation of spatio-temporal changes in morphology and tissue water-homeostasis in traumatic brain injury (TBI) may clarify the mechanisms of TBI and provide an insight into long-term consequences leading to e.g. development of epilepsy in ~50 % of patients with penetrating head trauma. In the present study the evolution of quantitative MRI parameters in different brain regions were studied in fluid percussion induced TBI model for six months.

## Methods

TBI was induced to 14 Spraque Dawley –rats by fluid percussion as previously described [1]. 5 sham operated and 4 intact rats served as controls. MRI data were acquired in 4.7T Magnex magnet interfaced to Varian Inova console. Quadratur half volume rf-coil was used in transmit/receive –mode. Rats were anaesthetised with 1% halothane and MRI was performed 3 hours, 3 days, 9 days, 23 days, 2 months, 3 months and 6 months after induction of TBI. *Volumetric changes* were detected using $T_2$-wt adiabatic spin echo multi-slice sequence (TE=70ms, TR=3s, 128*256pts, FOV 3*3cm$^2$, thk=0.75mm, 19 slices covering rat cerebrum). *$T_2$, $T_{1\rho}$ and the 1/3 of the trace of diffusion tensor ($D_{av}$)* were quantified from a single slice using a fast-spin-echo sequence (TR=3.0s, echo spacing=10ms, 16 echoes, 128*256pts, FOV=3*3cm$^2$, thk=1.5mm; T2: TE=20, 38, 52, 76ms; T1ρ: spin lock times=18, 38, 58, 78ms, $B1_{SL}$=0.8G; diffusion: b-values=90, 496,1014s/mm²). *Gradient echo* –sequence (TE=5ms, 15ms, TR=0.7s, flip angle=20°) was used to detect intracerebral hemorrhage. Histological assessment of neuronal damage will be performed from Nissl stained sections corresponding to MRI slice.

## Results

*Volumetric changes*: progression of the damage was evident from the increasing cortical lesion or/and the increased size of ipsilateral ventricle and the decreased size of hippocampus (Figs 1 and 2). There was a significant variation between individual animals and for initial analysis, rats were divided into 3 groups according to 23-day lesion+ventricle volume: 'severe' > 30 mm$^3$ > 'moderate' > 10 mm$^3$ > 'mild' (Fig.1). *Hemorrhage*: Most of the animals (11/14) had intracerebral hemorrhage in between ipsilateral cortex and hippocampus in acute phase, 3 hours after trauma, (Fig.2), and this seems to be related to development of lesion and/or severe atrophy (Fig.3).

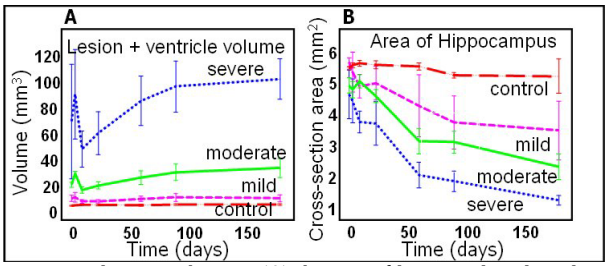



Fig. 1: Volumetric changes: (A) the sum of lesion and ipsilateral ventricle volumes and (B) the cross-section area of ipsilateral hippocampus.

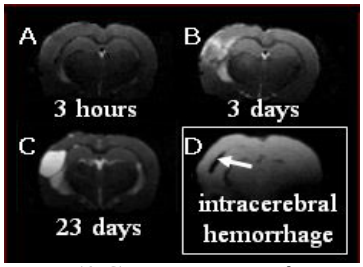



Fig 2. (A-C) $T_2$-wt images showing progression of lesion in severe group and (D) a $T_2$*-wt image demonstrating intracerebral hemorrhage.

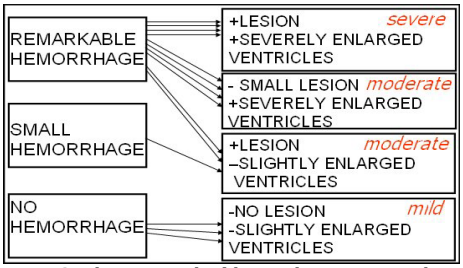


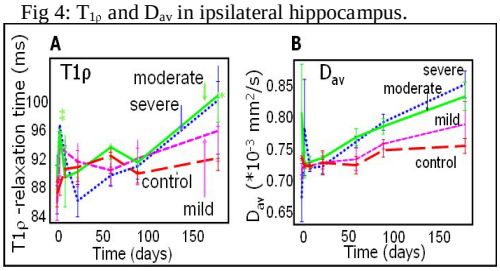

Fig.3: The intracerebral hemorrhage in acute phase and its correlation with the severity of lesion. Each arrow represents an individual animal.

***Cortical lesion area***: All trauma animals displayed decreased $D_{av}$ in the ipsilateral cortical area at 3hrs (severe group 22%, moderate-group 9% and mild group 6% decrease compared to the sham operated controls, Table 1). This initial diffusion drop was followed by normalization and/or an increase of $D_{av}$ after day 9 to the level that was >300%, 25% or 0% of the control in severe, moderate and mild groups respectively. At 3 hours, $T_{1\rho}$ was elevated by 15%, 8% and 2% and $T_2$ 20%, 12% and 4% in severe, moderate and mild groups respectively. During subsequent weeks-months relaxation values in the severe-group dramatically increased being > 10 times higher than in controls from 2 months timepoint onwards. Relaxation times in moderate group peaked at day 3 ($T_{1\rho}$ 26% and $T_2$ 21% increase) stabilising to lower level ($T_{1\rho}$ +12% and $T_2$ to +3%) in later timepoints ***Hippocampus:*** Both $T_{1\rho}$- and $T_2$-times were elevated on day 3 in ipsilateral hippocampus ($T_{1\rho}$ 8%, 8% and 5%; $T_2$ 6%, 4% and 0% for severe, moderate and mild-groups, respectively). In subsequent measurements at days 9-23 relaxation times returned to the control level ($T_{1\rho}$) or slightly below ($T_2$). Interestingly, relaxation times showed secondary increase after 3 months. In $T_2$ this secondary increase levelled of at 5% above the control-level, but $T_{1\rho}$ gradually increased throughout the rest of the 6-months observation period. In hippocampus $D_{av}$ showed no changes in acute or subacute phase but became elevated after 2 months.

Table 1: Quantitative diffusion and relaxation values from ipsilateral cortex and hippocampus in moderate-group,(n=7, Mean ± SEM)

| | Cortex | | | Hippocampus | | |
|---|---|---|---|---|---|---|
| | **$D_{av}$**(*10$^{-3}$mm$^2$/s) | **T2** (ms) | **T1ρ** (ms) | **$D_{av}$**(*10$^{-3}$mm$^2$/s) | **T2** (ms) | **T1ρ** (ms) |
| Ctrl | 0.739±0.002 | 56.4±0.1 | 82.0±0.4 | 0.718±0.002 | 62.0±0.1 | 87.8±10.4 |
| 3hours | 0.65±0.02** | 63.8±1.0** | 89.0±2.1* | 0.81±0.09 | 63.7±0.5** | 88.3±1.7 |
| 3 days | 0.76±0.02** | 71.2±1.6** | 107.3±2.1** | 0.72±0.03 | 64.7±0.2** | 94.3±1.3** |
| 9 days | 0.91±0.05** | 66.4±2.5** | 104.7±7.5** | 0.72±0.01 | 61.1±0.3 | 88.7±4.7 |
| 23 days | 0.98±0.05** | 65.3±1.9** | 107.0±4.5** | 0.73±0.01 | 62.1±0.3 | 89.8±0.8 |
| 2 months | 1.02±0.06** | 61.1±1.3** | 104.0±4.3** | 0.77±0.01** | 63.1±0.5 | 92.5±1.0** |
| 3 months | 1.00±0.08** | 59.8±1.3* | 98.0±5.3** | 0.78±0.01** | 63.6±0.7* | 90.8±1.2 |
| 6 months | 0.93±0.05** | 58.3±1.5 | 98.5±3.9** | 0.82±0.02** | 63.4±1.1 | 97.9±1.9* |

Fig 4: $T_{1\rho}$ and $D_{av}$ in ipsilateral hippocampus.




## Conclusion

Current data indicate that a subpopulation of animals develops cortical and/or hippocampal damage that continues to progress several months after TBI and is detectable with quantitative MRI. In acute phase, the initial diffusion drop and hemorrhage as detected by $T_2$* seem to best predict the severity of the subsequent lesion. Elevated diffusion reveals progressive changes, and furthermore, $T_{1\rho}$ shows higher sensitivity to long-term post-traumatic changes than $T_2$, resembling the high sensitivity of this parameter to neuronal damage in experimental stroke studies [2]. It remains to be studied whether quantitative MRI may predict the histologically determined cellular damage.

**References**: [1] Kharatisvili et al [2003] *Epilepsy*, 44, suppl. 8, [2] Gröhn et al [1999] *MRM* 42, 268