Quantitative T_2 but not lesion volume correlates with functional outcome after traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is a major public health problem that affects approximately 1 million people each year in the United States. TBI can lead to variety of symptoms, such as loss of consciousness, headache, seizures, weakness or numbness in the extremities, loss of coordination and increased confusion, depending on the extent of the damage to the brain. In experimental models of TBI, inter animal variety is generally large and not necessarily directly related to strength of the impact, which is a significant limitation in eg. pre-clinical drug testing. The aim of this study was to test if simple MRI examination including quantitative T_2 and lesion volume measurements correlates with the functional outcome measured using behavioural tests: Morris Water Maze (MWM), Neuroscore and Beam Balance (BB).

Methods

The TBI was induced by lateral fluid-percussion injury to 35 Sprague-Dawley male rats (350-400 g) while 11 sham operated rats were used as controls. The TBI animals were divided into two groups according to the impact pressure: moderate trauma injury (mTBI) (n=20; 2 atm) and severe trauma injury (sTBI) (n=15; 3 atm) (Kharatishvili et al., 2006). MRI data were acquired 3 days after induction of trauma in a 4.7 T horizontal magnet interfaced to a Varian Inova console using an actively decoupled volume transmission coil and quadrature surface receiver coil. T_2 maps were measured with a spin echo sequence from 15 slices (TR=2 s, TE=20, 40, 60 ms, thk=1 mm, FOV=3.5*3.5 cm) and T_2* weighted images with gradient echo sequence (TE=15 ms, TR=700 ms, flip = 50º). For the ROI analysis, the central part (2 slices) of the septal hippocampus and the whole lesion were outlined. T_2* weighted images were used to detect hemorrhage. MWM was performed 8-10 days after injury to test spatial learning and memory. The parameter we measured was the latency to find the hidden platform in a pool (average from 10 trials at the second testing day). Neuroscore, which measures motor impairment and reflexes, was performed 2 days before and after the injury. BB is sensory-motor test sensitive to motor cortical insults and it was performed 3 days before and after the injury. The differences between groups were assessed (Mann-Whitney post hoc test after Kruskal Wallis) and the behavioural test performance was compared with MRI data including control, mTBI and sTBI animals (bivariate correlations; r is correlation coeficient; *P<0.05, **P<0.01). The results are shown as mean±SD.

Results

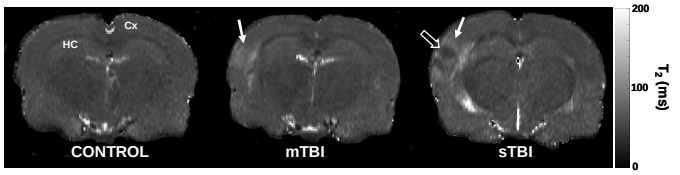

***Figure 1**: Representative T_2 maps from a control, a moderate TBI (mTBI) and a severe TBI (sTBI) animal. The lesion is indicated by a white arrow and hemorrhage inside with a black arrow (hippocampus, HC; contralateral cortex, Cx).*

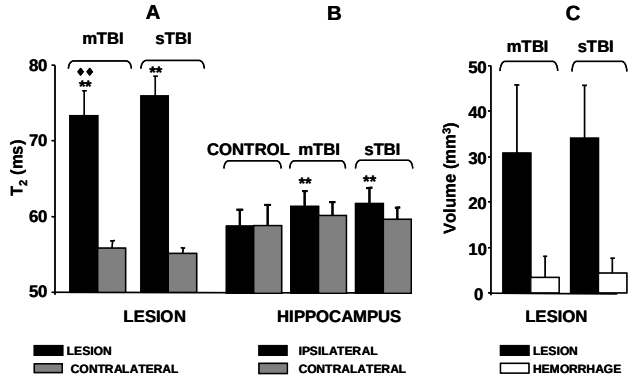

***Figure 2**: (A) T_2 values in the lesion, contralateral cortex and hemorrhage area, (B) T_2 values in ipsi- and contralateral hippocampus and (C) the volume of the lesion and hemorrhage in mTBI and sTBI animals. * indicates differences compared to controls (**P<0.01) and ♦ comparing between mTBI and sTBI (♦♦P<0.01). The lesion volume did not differ between mTBI and sTBI groups, but the T_2 in the lesion area did. T_2 values of the hippocampus ipsilateral to the lesion are increased in TBI animals compared to control animals (**P<0.01).*

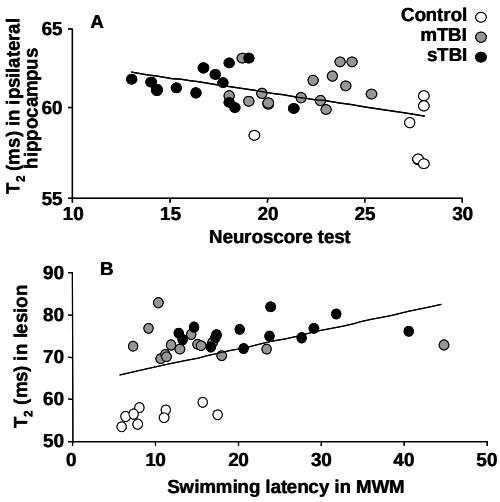

***Figure 3**: Correlation between the T_2 in the ipsilateral hippocampus and the neuroscore test (A), and correlations between the T_2 in the lesion and the swimming latency in MWM (B). (White: control; Gray: moderate TBI; Black: severe TBI).*

Latency in MWM test correlated positively with T_2 values in the lesion (r=0.510**; P=0.001) (Figure 3B), T_2 values in the ipsilateral hippocampus (r=0.333*; P=0.044), and volume of the lesion (r=0.468*; P=0.010). Furthermore, both BB and neuroscore showed negative correlations with T_2 values of the lesion (r=-0.582**; P<0.001 and r=-0.682**; P<0.001, respectively). In addition, neuroscore correlated negatively with T_2 in the ipsilateral hippocampus (r=-0.381*; P=0.020). Lesion volume did not show any correlations with BB or neuroscore results. There was hemorrhage inside the lesion in many of the TBI animals, but there was no difference in the amount of hemorrhage between mTBI and sTBI groups. The volume of the hemorrhage inside the lesion showed only correlation with MWM (r=0.573**; P=0.007).

Discussion

MRI data were acquird three days after onset of TBI when edema typically peaks in the primary lesion area in this animal models. Quantitative T_2 measurement is a sensitive indicator of edema and was correlated with BB and neuroscore tests, which represent cortical funcion. More subtle T_2 changes were detected in the hippocampus, which is outside the primary lesion area. Interestingly, these changes correlated with MWM, which measures the hippocampal function of spatial learning. It should be noted that neither lesion size nor visual inspection of the T_2 weighted images were able to reveal differences between animals with different functional outcome. These findings suggest that simple quantitative T_2 mapping in lesion and hippocampus 3 days after TBI is an indicator of the functional impairment and has potential both as a clinical marker for severity of post traumatic tissue damage and an aid in selecting homogenous animal populations for preclinical drug studies.

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