MEMRI of Mild Traumatic Brain Injury

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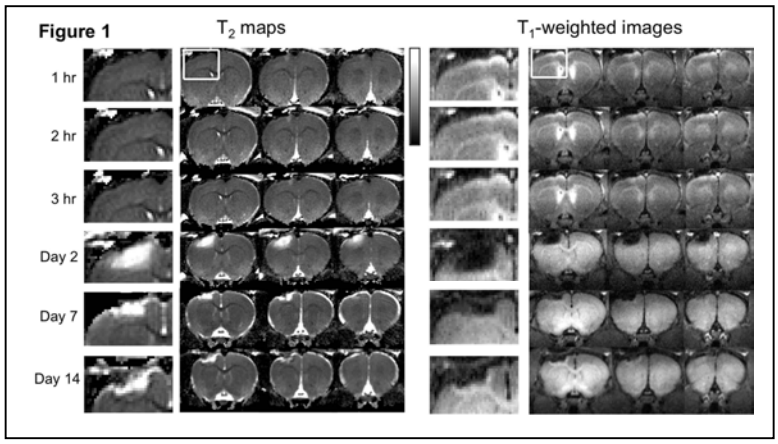
Target Audience: Researchers in experimental traumatic brain injury and MEMRI

Purpose: Traumatic brain injury is the leading cause of death and disability for people under the age of 45 years [1]. Manganese enhanced MRI (MEMRI) offers unique MRI contrast in a number of neurological disorders because manganese is a calcium analog and T1 contrast agent [2]. The purpose of this study was to explore MEMRI of mild TBI in a rat model with correlation by histology.

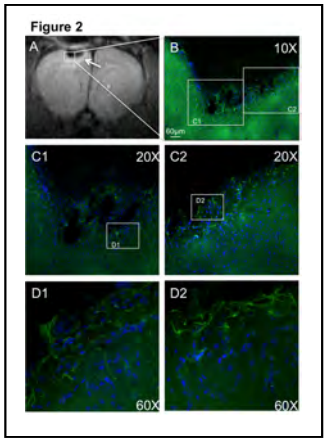
Methods: Vehicle (n=6) or Mn^{2+} (29 mg $MnCl_2$*$4H_2O$ per kg, n = 6) was administered 1 hr prior to TBI (day 0), and again one before MRI on day 2, 7 and 14. For TBI, a 6mm craniotomy was created over the left forelimb somatosensory cortex. The intact dura matter was impacted with a Ø3mm tip (5.0m/s, 250μs dwell time, 1mm depth). MRI was performed 1-3hrs, 1, 2, 7 and 14 days after TBI on a 7T Bruker scanner. T_2 map was acquired using fast spin echo RARE sequence with four echo times (18, 54, 90 and 126ms). Inversion recovery RARE (IR-RARE) sequence with TR=3s and inversion delay (TI) = 1s, FOV = 25.6x25.6 mm, matrix size = 128x128, seven 1-mm thick coronal images. Sensorimotor function was assessed using the asymmetry forelimb placement (cylinder) test and foot-fault test longitudinally before MRI. Glial fibrillary acidic protein (GFAP) staining was performed on day 14.

Results and Discussion: Forelimb asymmetry and foot-fault scores of both groups were normal before TBI, worst on day 2, and improved significantly on day 14. Behavioral scores were not statistically different between vehicle and Mn group, suggesting the low Mn used didn't affect functional outcome. Similarly, lesion volumes of Mn and vehicle group were not statistically different between the two groups (15.2±3.4, and 17.3±4.4 mm^3) on day 2. These findings are consistent with those reported previous [3].

Representative time-series T_2 maps and T_1-weighted images of Mn injected animals at 2 hrs and again on 2, 7, and 14 days post TBI from one animal are shown in **Figure 1**. At 1-3 hrs, little or no apparent T_2 changes were visible in the tissue immediately below the impact, whereas hyper- and hypo-intensities were detected in T_1-weighted images in and around the impact area. On day 2, T_2 map indicated hyperintense areas within the impact area, whereas MEMRI reversed from hyperintensity on day 0 to hypointensity with heterogeneous contrasts. On day 7, T_2 contrast reversed and became mostly hypointense, likely due to T_2 reduction by Mn^{2+}, with some hyperintensity on the cortical surface. By comparison, T_1-weighted MRI showed a large signal void immediately beneath the impact area. On day 14, the T_2 maps remained hyperintense (albeit less). By comparison, T_1-weighted images showed a signal void immediately below the impact area and a crescent-shaped hyperintensity surrounding the signal void on day 14.



To investigate the strong crescent-shaped T_1-weighted signal enhancement surrounding the impact region on day 14, immunohistochemistry for GFAP was performed after MRI on day 14 (**Figure 2**). Below the impact area, a pronounced lesion devoid of GFAP staining was observed, suggesting tissue cavitation. At the border surrounding the void, there was enhanced GFAP staining. The expanded views showed astrocytic processes interdigitated along the lesion border, suggesting the formation of a "wall" or scar. These findings indicated that the crescent-shaped T_1-weighted signal enhancement surrounding the impact region was likely due to reactive gliosis.



For controls, animals injected with vehicle showed no significant T_1-weighted enhancement in the cortex below the impact area and no signal void on T_1-weighted MRI.

Conclusions: The major findings were: *(i)* MEMRI was hyperintense in the impact area at 1-3hrs, hypointense on day 2, and markedly hypointense in the impact core with a hyperintense area surrounding the core on days 7 and/or 14, *(ii)* T_2 MRI showed little contrast in the area below the impact at 2hrs, was hyperintense on day 2 (vasogenic edema), hyperintense in some animals and pseudo-normalized in others on day 7 and/or 14, *(iii)* in the hyperacute phase, area of hyperintense T_1-weighted MEMRI was larger than that of T_2 MRI, which was particularly hyperintense along the superficial cortex, and *(iv)* histology revealed that the MEMRI signal void in the area below the impact and the hyperintense area surrounding the core on day 7 and/or 14 corresponded to tissue cavitation and reactive gliosis, respectively. In conclusion, MEMRI offers novel contrast for detecting mild TBI.

References: 1) Coronado 2012 J Safety Res 43, 299. 2) Silva 2004 NMR Biomed 17, 532. 3) Watts 2014 J of Neurotrauma.