Preliminary Multimodal MR Imaging Evaluation in Blast-induced Traumatic Brain Injury Rat Model

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Target Audience: MRI scientists and researchers interested in brain resting state functional MRI and pre-clinical TBI model studies.

Purpose: Blast-induced traumatic brain injury (bTBI) is of particular relevance to the military battles and urban terrorist attacks and has increasingly gained serious public attention. Proper animal bTBI models and noninvasive neuroimaging tools are essential for early diagnosis, neuropathology progression monitor and treatment efficacy evaluation. In the present study, we performed multiple MRI measures using a new bTBI rat model to explore potential neuroimaging biomarkers for bTBI and to better understand its underlying neuropathology.

Materials and Methods: The bTBI rats were generated by delivering 5 shockwave (SW) pulses at 24kV with 60 Hz to the right frontal cortex using a SW lithotripsy[1] machine (STS-T system, Medstone International, Inc., Austin, TX). During MRI experiments, the bTBI rats were maintained with 1.8% isoflurane, a typical anesthesia state characterized with a well-documented burst-suppressed (BS) electroencephalogram (EEG) pattern. Five bTBI rats were scanned on day 1 and another ten rats were scanned on day 3 after the induction of trauma. Some of them were repeated at 7 days or 30 days after the injury. MRI measurements were performed using a 9.4T/31cm magnet interfaced with VNMRJ consoles (Varian) and a ^{1}H surface coil. Resting-state fMRI (rs-fMRI) data were acquired using multiple-slice gradient-echo (GE)-EPI (TE=17ms; TR=612ms; FOV=3.2×3.2cm; matrix=64×64; thickness=1 mm; 500 volumes for each rs-fMRI run). GE-EPI images were spatially smoothed with a Gaussian filter and the initial 20 image volumes were discarded to avoid the transient BOLD signals at the beginning of the acquisition. The time course of each image pixel was normalized by its mean and then band-pass (0.005--0.1 Hz) filtered to remove the DC component, linear drift and high frequency noise. A 2×2 pixel region located in the left/right S1FL cortical region was selected as the reference region and the BOLD time courses of all image pixels were then cross correlated (Pearson's correlation) with the reference time course to generate a correlation coefficient (CC) map for each rs-fMRI run. In addition, images for T_2-weighted, cerebral blood flow (CBF), apparent diffusion coefficient (ADC), saturation recovery (SR)-T_1, cerebrovascular reactivity (CVR) based on arterial spin labeling (ASL) CBF approach induced with 6% CO_2 inhalation were also assessed for comparison.

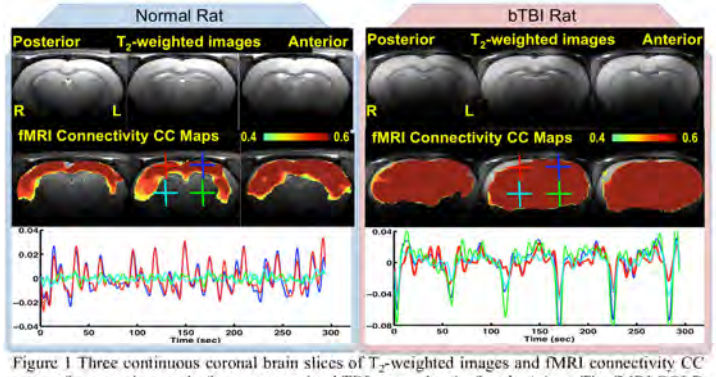

Figure 1 Three continuous coronal brain slices of T_2-weighted images and fMRI connectivity CC maps of a normal rat and of a representative bTBI rat on day 1 after the injury. The fMRI BOLD time courses were extracted from four different regions (indicated by different color cross-marks, two from S1FL and two from caudate putamen) displayed in the middle slice of CC maps. BOLD time courses from different regions were indicated by corresponding colored lines.

Results: Figure 1 shows three continuous slices of T_2-weighted coronal images and corresponding rs-fMRI connectivity CC maps of a normal rat and a representative bTBI rat at 1 day after the injury. For this bTBI rat, no obvious lesion was found in its T_2-weighted images. Interestingly, the fMRI CC maps show a highly synchronized spatiotemporal correlation cross the entire brain including both cortical and sub-cortical regions. In contrast, the CC maps of normal rat show coherent pattern mainly in the cortical regions with a weak connection to sub-cortical areas. Moreover, the high-amplitude BOLD signals fluctuation (reflecting the underlying burst EEG activity) appeared much less frequent as compared to the control rat (see Fig. 1). Figure 2 illustrates T_2-weighted images and corresponding rs-fMRI CC maps from another bTBI rat scanned at 3 days after the injury. For this particular rat, large lesion areas at the right sub-cortical region showing hetero-intensity were observed on the T_2-weighted images. A strongly correlated and widely distributed network (whole brain except the severely damaged sub-cortical region) was also detected even with a very high CC threshold of ≥0.8.

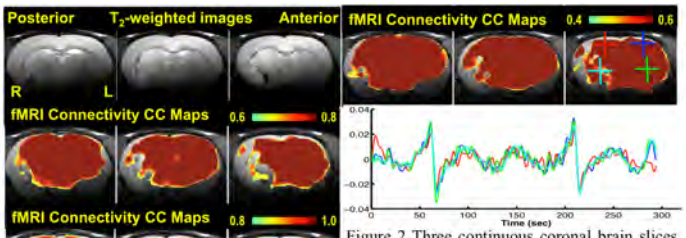

Figure 2 Three continuous coronal brain slices of T_2-weighted images and fMRI connectivity CC maps with increased CC display scales of another representative bTBI rat on day 3 after the injury. The fMRI BOLD time courses were extracted from four different regions (indicated by different color cross-marks, two from S1FL and two from caudate putamen) displayed in CC maps. BOLD time courses from different regions were indicated by corresponding colored lines.

Discussion and Conclusion: This study presents an intriguing phenomenon of abnormal rs-fMRI connectivity in the bTBI rats. It has shown that the rs-fMRI BOLD signal fluctuations reflect the spontaneous neuron activity associated with the unique burst-suppression pattern under the 1.8% isoflurane anesthesia[2]. The distinct rs-fMRI CC maps observed in the bTBI rat model under the same isoflurane anesthesia level suggest that the underlying neuronal activity was strikingly synchronized or unified almost as a whole. This special pattern was not observed in normal rats within a wide range of isoflurane level from 1.0 to 3.0 including 1.8% that was used in the present study. The observed abnormal connectivity pattern indicates a complete loss of specificity in the functional connectivity[2] caused by the bTBI. Moreover, the highly coherent BOLD spontaneous fluctuation pattern can be detected in brains with or without macroscopic lesion (see Figs. 1 and 2), suggesting that a normal appearing anatomic structure does not necessarily guarantee an intact and normal neuronal network, and it does not rule out long-term functional declines. Furthermore, large variation in the resting-state CBF (hypo-, normo-, or hyper-perfusion), normal ADC and reduced CVR (data not shown herein) were observed in the bTBI rats accompany with highly synchronized BOLD pattern. These results suggest that CBF may not be an accurate biomarker for assessing bTBI as compared to the rs-fMRI connectivity; and this notion is supported by a study of acute MCA stroke rat model[3]. The observed extremely strong synchronization pattern might be related to unbalanced brain functional segregation, disrupted neural excitation and/or inhibition and compensatory neural processes caused by the bTBI. Elevated spontaneous brain activity has also been reported in conscious human TBI patients, resulting in an increased connectivity strength of default mode network (DMN)[4-6]; enhanced working memory network strength during the recovery[7], and a higher level of resting-state spontaneous brain activity associated with a low level of unconsciousness[8]. The large global coherent pattern was observed in one out of five 1-day and four out of ten 3-day bTBI rats after the injury. Nevertheless, the abnormal connectivity pattern was repeatedly observed in the same rats on the subsequent scans at 7-day and 30-day post-bTBI, suggesting that the observations/phenomenon are reliable and consistent. The inter-rats differences might reflect the variation of bTBI severity, brain function and behavior impairments (currently under investigation). I*n vivo* oxidative metabolism[9] and adenosine triphosphate (ATP) metabolic rate[10] studies, as well as intracranial EEG monitoring should add great value to better understand the underlying mechanism of the abnormal connectivity observed in this study. In summary, we found a strong and highly synchronized rs-fMRI connectivity pattern without functional specificity in the bTBI brains. The rs-fMRI can serve as a sensitive neuroimaging biomarker for investigating the bTBI rat model and better understanding the underlying neuropathology mechanisms. The findings and outcomes should have a constructive impact for clinical translation specific to TBI patients.

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References: 1. Nakagawa et al. *Endoscopy*, 2011; 2. Liu et al. *Cerebral cortex*, 2011; 3. Wang et.al., *ISMRM Proceedings*, 4752, 2014; 4. Bonnelle et. al. *PNAS*, 2012; 5**.** Hillary et.al *International Journal of Psychophysiology*, 2011; 6. Stevens et.al., *Brain Imaging and Behavior*, 2012; 7. Nakamura et.al *PLoS ONE, 2009*; 8. Scheibel et.al *J Neurotrauma*, 2009; 9. Zhu et.al *JCBFM*, 2007; 10. Du et. al., *PNAS*, 2008.