Neuro-Imaging Assessments as Translational Pathophysiological Outcome Measures in TBI

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Introduction

TBI is considered a major public health problem worldwide and is a leading cause of death and disability in developed countries. The failure of numerous Phase 3 clinical trials in TBI has prompted a re-thinking of our animal model design in order to provide better translations to human clinical studies and therapeutic trials. In preclinical TBI research and testing of experimental therapeutic in such models, the most commonly used outcome endpoints are lesion volume/size, neuronal cell preservation and behavioral functional outcome measures. While these measures are clearly useful – they lack the ability to inform on the underlying distinct pathophysiological mechanisms relevant in human TBI. Consistent with the vision of the Translational Outcomes Project in Neurotrauma (TOP-NT) RFA, here we propose to evaluate MRI-neuroimaging biomarker assessment, which can readily transition into clinical TBI studies and can address a range of clinically relevant TBI pathological mechanistic subphenotypes including axonal injury, contusion/tissue necrosis, white matter integrity, microvascular injury and inflammation and help define location, temporal profile and relative contribution of these subphenotypes in a particular TBI model .

Methods

Two rat TBI models were used: controlled cortical injury (CCI) and fluid percussion injury (FPI). Live vivo imaging will be assessed at 2 days and 4 weeks on the same animals with 4.7T or 11T MRI (UF AMRIS). MR protocols included (i) Diffusion Tensor Imaging (DTI) to monitor brain water diffusion across compromised tissue compartments after TBI to assess fiber track, grey matter and tissue edema, (ii) blood oxygenation level dependent (BOLD) signal resting state functional MRI (rs-fMRI), (iii) susceptibility weighted imaging (SWI) to detect microvascular injury such as microbleeding. (iv) T2/T2* to address bleeding and edema.

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Results and Discussion

In this set of study, imaging data were collected from 4-6 animals per group. Images from FPI rats were obtained from 4.7T scanner while CCI rats were scanned by 11T scanner. We compared image qualities between both scanners and found out 11T show better quality of SWI, while the other protocols worked well on both scanners. As indicated in Figure 1, CCI animal were scanned using 11T scanner and the lesion was significant at 2 days post injury. But unexpectedly, the lesion was reduced at 30 days post injury. Similar results were found in FPI model (data not shown). Although the lesion seemed to get recovery, whether the tissues have functions is still unclear.

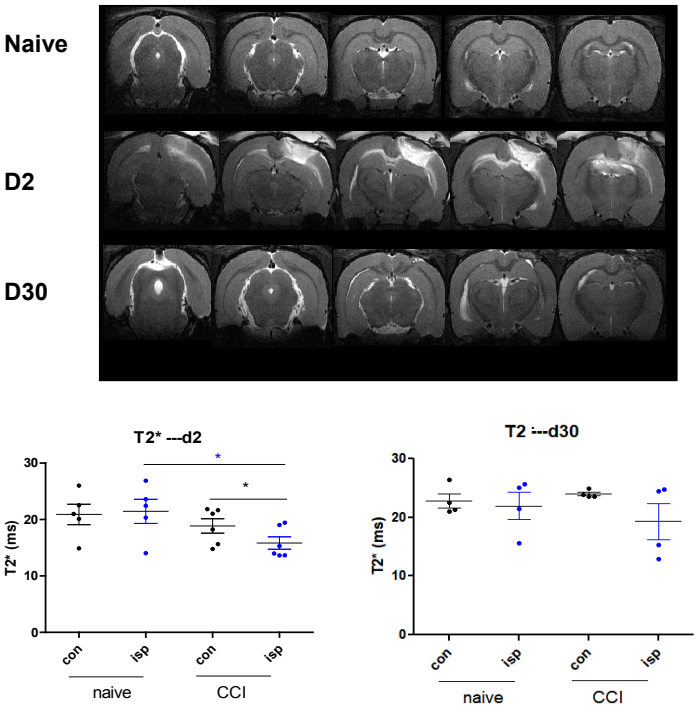

Fig. 1 T2 map shows lesion at D2 post TBI in a CCI model. The lesion area reduces after 30 days of recovery.

Conclusions

At this time, we are processing diffusion MRI and functional MRI data sets, which we collected using a multi shell sequence in order to determine TBI pathology on neurite orientation dispersion and density, as well as free water, and to address the brain lesion activities. These studies are currently under way.

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