Random forests analysis of DTI metrics and histology measures in a mouse model of traumatic brain injury

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Introduction:
Imaging markers provide crucial insight and important clinical tools for human brain injury. However, the relationship between imaging markers and pathomechanisms remains unclear. This study examines the sensitivity of diffusion tensor imaging (DTI) and quantitative histology measures to detect microstructural damage following experimental traumatic brain injury (TBI) in mice using random forest analysis (RFA) to identify the important regions and metrics affected by injury.

Method:
Paraformaldehyde fixed brain specimens were obtained from sham mice (n=5) and mice that were exposed to repetitive CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) injuries (n=5).
Diffusion MRI data were acquired on a 14T Bruker system with a 3D echo-planar imaging acquisition with b-values= 250 to 3800 s/mm^2. The TORTOISE pipeline was used for image correction and tensor fitting. All diffusion tensors were registered to a common space using the DR-TAMAS registration algorithm. Diffusion parameters such as fractional anisotropy (FA), trace (TR), axial and radial diffusivity (AD, RD), Westin's linear and planar (WL, WP) were computed. In addition, quantitative histology values of percent area were measured in the same specimen with ImageJ to detect: axonal damage (APP), myelin damage (MBP), astrocytes (GFAP), and microgliosis (IBA-1). DTI metrics and quantitative histology measures for regions of interest (ROI) were used as input to RFA to classify injured tissue.

Results:
Using histology metrics, RFA was able to predict correct classification of all the injured animals, but wrongly classified one of the shams as injured, reaching an overall classification accuracy of 90%. Using a different combinations of DTI metrics (FA/TR, AD/RD, and WL/WP/TR), the same sham was consistently misclassified as injured and one injured sample was misclassified as sham reaching an overall classification accuracy of 80%.
Multiple DTI metrics as well as GFAP and IBA-1 of the optic tract and brachium of superior colliculus were consistently ranked as important for classification. Hippocampus was also ranked as an important ROI for classification using DTI metrics.

Discussion:
The study revealed that ex-vivo DTI abnormalities are evident post injury and RFA identified regions and metrics that can serve as potential imaging biomarkers. Multiple histological measures were affected in injured tissue indicating that multiple cellular processes affected DTI metrics. Nonetheless, RFA of DTI measures has proved to be a valuable tool for identifying injured regions and potential biomarkers for TBI.