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**Diffusion weighted imaging acquired at 30-days post injury is most sensitive for PTE classification in rodent preclinical model of traumatic brain injury**

**Rationale**: Post-traumatic epilepsy (PTE), a consequence of traumatic brain injury (TBI), is a debilitating neurological disorder that drastically decreases quality of life. PTE is characterized by the occurrence of 2+ unprovoked seizures at least one week after TBI. PTE cases are highly heterogeneous and symptoms may appear years after the initial injury, making it difficult to study the pathophysiology of PTE. Consequently, the management and prognosis of patients after injury is a challenge. Given the severity and incidence of PTE, there is an urgent need to identify clinical biomarkers for PTE. The goal of this pilot study was to utilize machine learning tools in conjunction with diffusion weighted imaging (DWI) to characterize PTE and identify the most sensitive time period to detect microstructural changes associated with PTE in a rodent model.

**Methods**: A subset of data for 32 rodents from the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy collected at the University of Eastern Finland at Kuopio was used. TBI was induced with temporal lobe fluid percussion injury and imaged with in vivo structural MRI at four time points (two days, nine days, 30 days and 150 days post-TBI). Microstructural data was captured using magnetization prepared multi-echo-gradient sequence and diffusion tensor imaging (DTI). Animals were continuously monitored with intracortical, intrahippocampal and contralateral cortical epidural electrodes post-TBI to diagnose epilepsy development. The final sample consisted of nine rats that developed PTE and 23 rats that did not develop PTE post-TBI. Tractrophy-based analysis was performed using the Quantitative Imaging Toolkit to extract mean fractional anisotropy (FA) values from 48 white matter bundles. Next a classification analysis was performed to classify non-PTE TBI vs. PTE from FA features using elastic net regression with leave-one-out-cross-validation.

**Results**: The elastic net regression classified non-PTE TBI vs. PTE with an accuracy of 56% (sensitivity: 0.22; specificity: 0.69) for FA features at two days post-TBI , 59% (sensitivity: 0.33; specificity: 0.69) at nine days post-TBI, 75% (sensitivity: 0.66; specificity: 0.78) at 30 days post-TBI, and 62% (sensitivity: 0.33; specificity: 0.73) at five months post-TBI. The analysis results are summarised in Table 1.

**Conclusion**: This pilot study employed an elastic net regression model in conjunction with DWI to characterize seizure outcomes in rodents across various time points post-TBI. Our results indicate that the model displayed the highest accuracy and sensitivity to detect PTE with features extracted imaging 30 days post-TBI. Consistent with previous findings, our results suggest that the most robust progression of pathologies is seen during the first month post-TBI. Future studies should focus analysis at this time point post-injury and will also focus on conducting a multimodal approach based on functional and structural neuroimaging measures to further improve the classification performance.

Table 1. Classification results for FA features for the various time points. Performance assessed are reported in terms of accuracy, sensitivity, and specificity.

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| **Time Point** | **Accuracy** | **Sensitivity** | **Specificity** |
| 2 days | 56% | 0.22 | 0.69 |
| 9 days | 59% | 0.33 | 0.69 |
| 30 days | 75% | 0.66 | 0.78 |
| 150 days | 62% | 0.33 | 0.73 |