The role of tau and other pathologies in an animal model of repetitive mild traumatic brain injury.

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The Chronic Effects of Neurotrauma Consortium or CENC is dedicated to understanding the chronic sequelae associated with neurotrauma, primarily focused on mild TBI (mTBI)/concussion incurred by U.S. service personnel. However, little is known about the timeline and sequence in which tau is processed following TBI, nor about the relationship with other TBI-dependent neuropathologies such as neuroinflammation and cerebrovascular changes. This study is evaluating tau alterations and accompanying neuropathologies over time after r-mTBI in hTau transgenic mice. hTau mice aged either 8-12 weeks will receive either r-mTBI or r-sham in order to control for effects of repeated anesthesia. Mice will be euthanized for neuropathological, genomic and biochemical analyses at 24hrs, 5, 10 and 15 days, 3, 6 and 12 months after last mTBI/anesthesia. For the 15 day and 3, 6 and 12 month time points post injury mice will undergo a battery of neurobehavioral test in the 2 weeks immediately prior to euthanasia. The entire paradigm is being replicated in hTau mice aged 12 months at the time of injury, to study the effects of age at time of injury. r-mTBI in the young cohort shows learning impairment post injury that progressively worsens from 2 weeks to 12 months. To date, Tau IHC and ELISA results suggest that r-mTBI is associated with a transient injury dependent increase in p-tau accumulation with greater dendritic and membranous staining in the cerebral cortex beneath the impact site without neurofibrillary tangles. While a trend for an increase in aggregated tau at 12 months post injury was observed, r-mTBI was not associated with elevated brain levels of abnormal soluble tau phosphorylation. This study is ongoing and will take several years to complete; our previous data suggest that neuroinflammatory pathology is key in this model and that TBI-dependent tau pathology will be evident in the older mouse models where tau pathology already exists.