

**LIMBIC-CENC Clinical Care Monograph Version 2**

**F. TBI, Biomarkers, and Neuroimaging**

from LIMBIC-CENC Knowledge Translation Center (LIMBICTM)

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**Key Findings**

1. **TBI and Serum Exosomal Proteins**. Blood levels of exosomal proteins, especially neuronal proteins (i.e., Neurofilament light or NfL, p-tau, tau) and neuroinflammatory proteins (IL-6 and IL-10) have drawn interest as mTBI biomarkers of dementia risk and other suboptimal outcomes. In LIMBIC-CENC research studies: (a) NfL has been elevated in Service Members and Veterans with mTBI compared to those without TBI,1-5 with 3 or more mTBIs,1-3 chronic neurobehavioral symptoms,1, 2 cognitive impairment,2, 4, 5 and poor sleep/obstructive sleep apnea;2, 4 (b) tau has been elevated in chronic neurobehavioral symptoms1, 3  and poor sleep/obstructive sleep apnea;5 and (c) p-tau, IL-6 and IL-10 are elevated in mTBI and chronic neurobehavioral sysptoms.1
2. **TBI and Exosomal micro-RNAs (miRNAs)**. In LIMBIC-CENC research, miRNAs, which are mediators of intercellular communication, have been shown to be dysregulated in Service Members and Veterans with 3 or more mTBIs and 1-2 mTBI compared to no TBI,5 and chronic neurobehavioral symptoms;5 mTBI blast exposure group, which correlated with inflammatory, neurodegenerative, and androgen receptor pathways;6 and extracellular vesicles (EV) levels of proteins and miRNAs that correlated with PTSD symptom levels.7
3. **TBI and Imaging-based Advanced Brain Age.** Brain age, based on MRI data, was noted to be associated with history of deployment-related mTBI, depression, PTSD, and alcohol misuse.8,9 Males with a history of deployment-related mTBI showed advanced brain age compared to those without deployment mTBI, while females did not. 8 In follow-up analyses of male participants, severity of PTSD, depression symptoms, and alcohol misuse were also associated with advanced brain age.9, 10
4. **Functional Neuroimaging and EEG Research.** Functional neuroimaging suggests that there are distinct patterns of resting-state functional connectivity in the middle frontal gyrus of the frontoparietal region, in which connectivity is increased in mTBI and decreased in PTSD.11 Executive function complaints, poorer cognitive performance, and higher psychological distress.12

**Clinical Impact**

* **NfL and Tau as mTBI Dementia Biomarkers**. Five LIMBIC-CENC studies found small effect sizes that extend the current research literature on the potential value of NfL and tau as markers of neuro-axonal damage in the mTBI population. In early discovery studies, exosomal proteins emerged as potential diagnostic or prognostic biomarkers of late effects of mild TBI, especially for repetitive (≥3), mild TBI. LIMBIC-CENC research is in development to examine the potential use of biomarkers in mTBI phenotype development.
* **Potential Role of Exosomal miRNAs in Chronic mTBI**. LIMBIC-CENC researchers are among the first to examine exosomal miRNAs in remote TBI and early findings provide novel insights into the potential underlying pathobiology in chronic TBI symptom persistence. Levels of proteins and miRNAs that correlated with PTSD symptom levels may provide insights into signaling pathways linked to persistent PTSD symptoms after mTBI and the biological mechanisms underlying susceptibility to PTSD. Study results suggest a possible role for axonal degeneration and neurodegenerative changes in the development of persistent or later-in-life PTSD symptoms.
* **LIMBIC-CENC Research Reveals Novel Imaging Finding.** LIMBIC-CENC PLS research identified opposing patterns of connectivity in the lateral Prefrontal Cortexthat increased in mTBI and decreased in PTSD. These opposite patterns highlight the potential for a biomarker that could differentiate mTBI and PTSD pathophysiology and symptoms.
* **TBI, Sleep and Neurodegeneration**. LIMBIC-CENC PLS findings from a number of biomarker, neuroimaging, and medical condition studies provide strong evidentiary support for implementing validated sleep measures in both longitudinal studies investigating pathobiological mechanisms of TBI related neurodegeneration and comprehensive clinical evaluations.

**Primary Knowledge Translation Projects**

* LIMBIC-CENC provides a repository of information on [TBI and Pathophysiology for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/pathophysiology-and-tbi-clinicians/) and [TBI and Diagnostics for Researchers](https://www.limbic-cenc.org/for-tbi-researchers/diagnostic-researchers/).
* Kenney K, Werner JK, Gill J. Chapter 7: Genetic, Epigenetic and Proteomic Biomarkers. In: Brain Injury Medicine: Board Review. Blessen Eapen, David Cifu editors. 1st edition: Elsevier Press; 2020.

**TBI, Biomarkers, and Neuroimaging References**

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