Neurocognitive and Psychological Health Outcomes

Chronic Effects of Neurotrauma Consortium 1: The Chronic Effects of Neurotrauma Consortium Addresses Long-Term Effects of Brain Injury in Military Personnel

The Chronic Effects of Neurotrauma Consortium (CENC) is a joint Department of Defense and U.S. Department of Veterans Affairs (VA) effort addressing the long-term consequences of mild traumatic brain injury (mTBI) in Service members and Veterans. The CENC is centered at the Virginia Commonwealth University (Richmond, Virginia) and involves 10 studies and five integrated research cores across more than 30 participating institutions. The CENC seeks to understand the association (onset, prevalence, and severity) of the chronic effects of mTBI and comorbidities, and probe for correlations to neurodegenerative disease. Most studies are focused on human subjects recruited from Veteran, active duty Service members, Reserve, and National Guard populations, and include individuals with exposure to blast. CENC studies examine chronic TBI and comorbidities associated with mTBI; sensory deficits (visual, auditory, vestibular), movement disorders, pain (including headache), cognitive, and neuroendocrine deficits (*Davenport et al. 2016, Eapen and Cifu 2017, Gattu et al. 2016, Jurick et al. 2016, Lejbman et al. 2016, Lynch et al. 2016, Mac Donald, Barber, Andre, et al. 2017, Mac Donald, Barber, Jordan, et al. 2017, Mac Donald, Johnson, et al. 2017, Mufson et al. 2016, Ojo et al. 2016, Pugh et al. 2016, Schneider et al. 2017, Seal et al. 2017, Stone et al. 2016, Swan, Nelson, Swiger, et al. 2017, Tzekov et al. 2016, Uchendu et al. 2016, Walker et al. 2016, Wilde et al. 2016*).

> Characterization of the sequelae of chronic mTBI in Service members and Veterans can be used to establish risk factors for long term TBI-related disease such as neurodegeneration, cognitive decline, and neurosensory dysfunction.

The largest CENC study is an observational study with a large volume of controlled, prospective longitudinal data from Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn Service members and Veterans to understand the late functional and biological effects of mTBI. This study will help determine potential risk factors for long-term comorbidities and associated dementia in individuals with military mTBI. The study has reached target enrollment and continues to follow up subjects for the duration of the consortium period of performance. The recruited population leverages other large research efforts such as the VA's Million Veteran Program.

In FY17, the CENC was the focus of a special edition of the journal, Brain Injury, which included methodological, basic science, epidemiological, and clinical research topics (*Davenport et al. 2016, Gattu et al. 2016, Jurick et al. 2016, Lejbman et al. 2016, Lynch et al. 2016, Mufson et al. 2016, Pugh et al. 2016, Stone et al. 2016, Tzekov et al. 2016, Walker et al. 2016, Wilde et al. 2016*). One article described work from a basic-science study examining mTBI in a transgenic mouse that expresses the human

variant of the protein Tau, which is implicated in TBI-associated neurodegenerative disease (*Lynch et al. 2016*). The study correlates findings in the animal model with post-mortem human brain tissue with known TBI histories to inform on linkages between TBI and potential progressive neurodegeneration. Alterations in cerebrovascular function, such as decreased cerebral blood flow are often observed in neurodegenerative disease. Animals with repetitive mTBI demonstrated persistent impaired cognitive function, reduced cerebral blood flow and down-regulation of cerebrovascular-associated markers.

Investigators in the CENC neuroimaging core have developed enhanced data analysis methodologies, including open-source pipelines, which have been implemented in non-CENC efforts (*Schneider et al. 2017, Stone et al. 2016, Wilde et al. 2016*). In addition, CENC investigators have developed an expandable, 4 module diffusion tensor imaging (DTI) phantom which enables temporal, location, vendor standardization, and comparability of neuroimaging. The Quantitative Imaging Biomarkers Alliance®, organized by the Radiological Society of North America, has chosen the CENC-developed product as the base magnetic resonance imaging and DTI measurement standard, which will have a significant impact on the use of DTI in Food and Drug Administration-regulated studies.

More information on the CENC can be found at https://cenc.rti.org.

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