Chronic Effects of Neurotrauma Consortium

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The **Chronic Effects of Neurotrauma Consortium** (CENC; www.cenc.rti.org) is a response to the federal National Research Action Project (NRAP)[1] initiated by President Obama in August 2013. CENC is a dually-funded, $62.175M Department of Defense (DoD) and Department of Veterans Affairs (VHA) project intended to investigate the short and long term consequences associated with mild traumatic brain injury (mTBI = concussion), to develop scientifically valid, confirmatory diagnostics, and to test innovative interventions for both mTBI and the multiple co-morbidities that frequently accompany it.

After three highly competitive, peer-reviewed selection rounds that considered over 300 proposals, CENC leadership selected and funded 10 independent research studies, while simultaneously establishing five research support cores: biostatistics, neuroimaging, biorepository, study and data management and neuropathology. Presently, CENC is comprised of 30 academic universities, 15 Veterans Affairs medical centers (VAMC), 2 non-profit research institutions, and 7 military medical centers. Additionally, a scientific advisory board, a consumer advisory board, a data safety committee, a research coordination committee, and a scientific publication committee serve as advisory and support mechanisms. In October 2016, CENC passed the 3-year mark in the current five-year funding cycle and is planning on additional funding of key elements of the program. The overall CENC is administered by Virginia Commonwealth University, led by principal investigator David Cifu, MD, and is governed by a government steering committee (GSC) comprised of DoD, VHA and other relevant government representatives. The GSC has the final authority in CENC's overall operation.

RESEARCH INVESTIGATIONS

CENC is currently supporting 7 clinical investigations, 1 epidemiologic database project, 1 basic science study and an MRI standardization and calibration project.

A **Longitudinal, Observational Study** that utilizes a wide array of measures, including neuropsychological instruments, laboratory and biophysical samples, electrophysiological measures and neuroimaging to evaluate a cohort (projected n = 880) of U.S. Operation Enduring Freedom (OIF - Afghanistan), Operation Iraqi Freedom (OIF) and Operation New Dawn (OND – Entire Gulf region after 9/1/2010) combatants who have had at least one mTBI and a control group of participants (projected n = 220) who have experienced combat, but have not had a mTBI. Each participant is assessed annually (in person or via telephone), with the goal of following the cohort for as long as funding is continued. Presently, there are 8 study sites and that have consented over 700 participants. One of the emerging benefits of this study has been the development of standardized and validated interview technique that identifies potential concussive events and any mTBI that may have resulted, which may help remediate a long-standing weakness in unwitnessed mTBI research methods. In addition, this study is utilizing the NIH Toolbox and will be able to validate these measures with older, established neuropsychological instruments.

An **Epidemiology Study** that to aims to integrate and analyze existing VA and DoD healthcare data to study the chronic effects of mild traumatic brain injury (mTBI) on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI, in Veterans and Service Members over time. Presently, this study includes 9 VA and DoD datasets with more than 2 million unique subjects, and has been successful in accessing, coordinating and harmonizing numerous

other databases to combine the analytical power available.

A Tau Modification Study that examines one of the few known biological changes seen in mTBI, massive intraneuronal accumulation of the Tau-protein in very specific and recognizable patterns in the human brain. The consequences of repeated mTBI (r-mTBI) over a prolonged period have not been well studied, and the factors and mechanisms that contribute to the long-term consequences of r-mTBI are still poorly understood. The goal of this study is to develop an animal model of r-mTBI model that will allow the tracking of these progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, fluorescent in situ hybridization, and gene expression signatures. The model could then be used to assess the effects of interventions. The observations made in the animal model will be tested for agreement in soldiers who have died after sustaining r-mTBI. Exploitation of such a model will have great translational significance by providing seminal data needed to develop new and better treatments for our military personnel with mTBI. More than 220 experimental animals have been tested to date.

An Otolith Dysfunction Study that examines the importance of abnormal otolith organ (an inner ear balance organ that senses gravity and contribute to maintaining upright posture or balance) function in the evaluation of concussed individuals suffering from dizziness and imbalance. Although newer otolith organ tests are available, horizontal canal tests are still most commonly used, in part because it is unclear if abnormal otolith organ function has a direct negative affect on balance and participation in activities of everyday living. There is recent evidence to suggest that otolith organ dysfunction can occur in participants with mild traumatic brain injury (TBI) or blast exposure, which is important because symptoms of dizziness and imbalance resulting from mTBI can last six months or longer; far longer than recovery from other types of inner ear balance disturbances would be expected. If the dizziness and imbalance symptoms that occur following head injury or blast exposure are related to injury to the otolith organs rather the horizontal semicircular canal, then new treatment approaches may be necessary to focus on otolith organ pathway recovery rather than horizontal canal recovery. In addition, these research findings may direct the development of new clinical protocols to better assess individuals with dizziness and balance problems. More than 95 subjects have been consented.

A Novel White Matter Study that recognizes that since traditional structural neuroimaging techniques are largely insensitive to the subtle damage resulting from mTBI and even newer magnetic resonance imaging (MRI) acquisition methods, such as Diffusion Tensor Imaging (DTI) have shown more promise in identifying changes in white matter integrity following mTBI, even this advanced technology produces equivocal results, and lacks the sensitivity or specificity to identify the underlying cause of any white matter changes. To address these limitations, this study incorporates a new approach for specifically assessing myelin abnormalities through multicomponent-driven equilibrium single-pulse observation of T1 and T2 (McDESPOT), which calculates myelin volume. For this study subjects with a history of combat-associated mTBI, PTSD, or both are included. More than 35 subjects have been consented.

The **ADAPT Study** is investigating acute and long-term advanced MR imaging and clinical outcome measures of concussive TBI in military personnel injured during deployment. As part of previous collaborative efforts, the investigators completed early prospective, longitudinal studies enrolling active-duty US military at 0-7 days, 0-30 days, and 0-90 days post-injury both with and without mTBI. Early MR imaging and clinical information was collected and then at 6-12 months, MR imaging was repeated and a battery of neurological, neuropsychological and psychiatric evaluations were repeated. In total, 591 subjects were enrolled through these initial efforts; 54% TBI and 46% control. This study re-examines a subset of these subjects at 3-5 years post-injury, comparing their current clinical and imaging presentation to acute and 1 year data. The study has been completed (n = 94) and data analysis is underway.

A **Structural And Functional Neurobiology Study** that is investigating the microstructural nature and functional effect of diffuse heterogeneous white matter abnormalities present in post-deployment Veterans and Service Members exposed only to primary blast, without exposure to other mechanisms likely to injure the brain. This study aims to characterize white matter abnormalities present, examine how history of primary blast exposure and mild TBI are related to the presence of white matter abnormalities, and characterize the clinical sequelae of white matter abnormalities, including effects on brain function, cognitive processes, and symptom presentation. More than 100 subjects have been consented.

A **DTI Phantom Diffusion Study** that capitalizes on the fact that Diffusion Tensor Imaging (DTI) holds particular promise for evaluation of individuals who have experienced TBI, because damage to white matter pathways is considered to be an important component in the causation of the many types of neurocognitive impairment that can result. If diffusion imaging is to be developed as a means to evaluate individuals with suspected TBI, a uniform type of image acquisition is needed across the different types of imaging systems available within hospital and research networks. This study uses diffusion imaging phantoms to evaluate differences between and within scanners, with the goal of providing acquisition techniques that will allow data to be compared across different participant groups and combined into large data collections.

A **Clinical and Neuroimaging Study** that seeks to improve the characterization of long-term, ongoing damage associated with mTBI among active duty service members and Veterans, thereby, reducing clinical costs and improving long-term health outcomes. This study tests several psychological and biological measures for utility as markers of mTBI-related neurodegeneration, and characterizes the utility and limitations of self-report measures in the context of mTBI and comorbid psychopathology. The results of this research may have implications for the assessment and documentation of mTBI during deployment, education of soldiers and military medical providers, long-term monitoring of individuals who sustain mTBI, and enable more efficient provision of long-term care. More than 55 subjects have been consented.

A **Visual Sensory Study** that capitalizes on the fact that although visual symptoms are a common sequelae of TBI, very little is known about the chronic visual consequences of mild TBI, its progression, and its correlation with other central nervous system deficits. Additionally, it is unknown if neuronal loss in the retina and brain after mTBI continue to progress over time. Closing this knowledge gap is important for understanding and treating TBI-related visual symptoms and for establishing whether ocular biomarkers can be used to predict risk of CNS dysfunction and its progression over

time. The purpose of this study is to identify the spectrum of visual sensory disturbances after mTBI by utilizing detailed tests of visual function and ocular motility, and newer structural analyses of optical coherence tomography (OCT) in combination with functional MRI imaging of visual pathways and volume analysis of corresponding grey and white matter locations. More than 65 subjects have been consented.

SUMMARY

In only three years after inception, the CENC has initiated and put into place a fully matured research leadership and infrastructure system, and its researchers have initiated 10 peer-reviewed research investigations that have consented more than 1,100 Veteran and Service Member subjects, published 27 peer-reviewed scientific publications, delivered 39 scientific presentations and displayed 54 poster presentations. CENC's nationwide team of scientific experts in combat-associated concussion have begun the long and complex journey towards an evidence-influenced understanding of the longitudinal nature of self-report symptoms, clinical findings, neurophysiologic findings, neuroimaging, and biomarkers after injury.

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David Cifu, MD is Chairman and the Herman J. Flax, MD Endowed Professor (tenured) of the Department of PM&R at the Virginia Commonwealth University (VCU) School of Medicine in Richmond, Virginia. He is also Chief of PM&R Services of the VCU Health System and Founding Director of the VCU-Center for Rehabilitation Sciences and Engineering (CERSE). He is the Senior TBI Specialist for the U.S. Department of Veterans Affairs. He has been funded on 42 research grants for over $135 million, including Principal Investigator of the VA/DoD $62.2 million Chronic Effects of Neurotrauma Consortium (CENC). He has published more than 215 scientific articles and 65 abstracts, and co-authored or edited 30 books and book chapters. He is Past President of the American Academy of PM&R (2007-8).

William Carne, PhD is an Associate Professor in VCU's Department of PM&R with over 35 years of clinical experience in private, public and academic settings. He has supervised over three dozen psychology interns, residents and fellows in a variety of outpatient and in-patient settings. Dr. Carne is the co-author of a graduate level text on writing psychological reports as well as a book chapter on Parkinson's disease. He has published over 30 peer reviewed scientific articles. In addition to his private practice, he consults at the Richmond Veterans Affairs Medical Center. Additionally, he is a co-principle investigator in the jointly funded ($62.3M) VA/DoD Chronic Effects of Neurotrauma Consortium (CENC) designed to investigate the long term effects of mild traumatic brain injury.