OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND READINESS

13 JUN 2019

The Honorable James M. Inhofe
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report is in response to House Report 115–676, page 128, accompanying H.R. 5515, the John S. McCain National Defense Authorization Act for Fiscal Year (FY) 2019 on Chronic Traumatic Encephalopathy (CTE). The report summarizes key knowledge gaps between CTE and traumatic brain injury (TBI), and outlines CTE-relevant initiatives pursued through research collaborations across Government agencies, academia, and leading research institutions.

During FYs 2013-2017, total expenditures for CTE-relevant research were $90,937,066.53. This research consisted of 47 projects within the National Research Action Plan Portfolio. The potential relationship between CTE and multiple sub-concussive events, or more substantial head injuries such as blast-related TBI, remains an important area of study for the Department of Defense.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the Chairman of the House Armed Services Committee.

Sincerely,

James N. Stewart
Assistant Secretary of Defense for Manpower and Reserve Affairs, Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Jack Reed
Ranking Member

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND READINESS

The Honorable Adam Smith
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

13 JUN 2019

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Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the Chairman of the Senate Armed Services Committee.

Sincerely,

James N. Stewart
Assistant Secretary of Defense for Manpower and Reserve Affairs, Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable William M. "Mac" Thornberry
Ranking Member

Report to Congressional Armed Services Committees

Chronic Traumatic Encephalopathy Research in the Military

June 2019

In Response To: House Report 115-676, page 128, accompanying H.R. 5515, the John S. McCain National Defense Authorization Act for Fiscal Year 2019

The estimated cost of this report for the Department of Defense (DoD) is approximately $4,500.00 for the 2019 fiscal year. This includes $1,500.00 in expenses and $3,000.00 in DoD labor.

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I. PURPOSE

This report is in response to House Report 115–676, page 128, accompanying H.R. 5515, the John S. McCain National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2019, which requests the Secretary of Defense, in consultation with the Secretaries of the Military Departments, submit a report to the Committees on Armed Services of the House of Representatives and the Senate, no later than April 1, 2019 on Chronic Traumatic Encephalopathy (CTE) research in the military.

II. BACKGROUND: Assessment of Gaps between CTE and Traumatic Brain Injury (TBI) Research

CTE is a progressive neurodegenerative disease that is suspected to be associated with repeated brain trauma. Currently a CTE diagnosis can only be made through a neuropathological examination post-mortem. Although post-morbid manifestations attributed to CTE are similar to those of Alzheimer's Disease (AD), CTE appears to be a pathologically distinct entity. The potential relationship between CTE and multiple sub-concussive events or more substantial head injuries, including blast-related TBI, is an important area of study for the DoD. Accordingly, in 2015, the DoD Blast Injury Research Program Coordinating Office organized a State-of-the-Science Meeting on CTE.[1] This meeting brought together subject matter experts from the DoD, other Federal agencies, academia, industry, international partners, and the sports community and identified clinical and research knowledge gaps. Beyond this meeting, CTE-related research published in peer reviewed journals and ongoing work presented at major scientific meetings has further delineated key knowledge gaps regarding the relationship between CTE and TBI. These gaps are summarized as follows:

- The incidence and prevalence of CTE, including in Service members and veterans, are currently unknown.
- At present, CTE is diagnosed via post-mortem neuropathological examination and no reliable means exists to diagnose CTE prior to death. In addition, there is little consensus on the neuropathological abnormalities that distinguish CTE from other neurodegenerative diseases, such as AD. Development of fluid and imaging biomarkers, including positron emission tomography (PET) ligands for tau and other aberrant proteins associated with CTE, are needed for the pre-mortem diagnosis of CTE and subsequent treatment of those diagnosed with CTE.
- The most commonly cited peer-reviewed publication on CTE is a case series limited by methodological biases, pathological inconsistencies, insufficient clinical data, and a reliance on postmortem data.[2]
- With the possible exception of head trauma, substantiated risk factors for CTE are unknown due to the absence of any longitudinal or prospective studies with broad recruitment strategies, reliable diagnostics, and a robust neuropathological component.

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[1] Brix, K.A, Brody, D.B., Grimes, J.B., Yitzhak, A., and Working Group Members. (2017). Military blast exposure and chronic neurodegeneration: Summary of working groups and expert panel findings and recommendations. *Journal of Neurotrauma*, *34*(S1):S18-S25.

[2] Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., ... & Cormier, K. A. (2017). Clinicopathological evaluation of Chronic Traumatic Encephalopathy in players of American football. *Jama*, *318*(4), 360-370.

- Clear and standardized clinical criteria for CTE are lacking: There are currently no consensus-based clinical diagnostic criteria for CTE, and no prospective study has linked CTE to specific symptoms and behaviors in living persons.
- Symptoms and mood disorders that have been attributed to CTE are non-specific. For example, aggressive behaviors, depression, or suicide, often linked to CTE, have also been attributed to narcotics and alcohol abuse and behavioral health disorders without evidence of CTE.
- It remains unknown whether there exists a dose response relationship between CTE and brain trauma. For example, evidence is unavailable regarding the potential for CTE following prolonged exposure to a large number of sub-concussive blows (e.g., repetitive low level blasts) versus the potential after sustaining a single or multiple symptomatic mild TBIs.
- There is a lack of blast-exposed clinical tissue, with well annotated medical and blast exposure histories, available for neuropathological analysis.

III. FYS 2013-2017 FUNDING LEVELS FOR CTE/TBI

According to the funding level data reported at the National Research Action Plan (NRAP) Review and Analysis (R&A) in October 2018, the total FYs 2013-2017 expenditures for CTE-relevant research is $90,937,066.53 across 47 funded projects, all part of the NRAP portfolio. The NRAP was published in August 2013, in response to a White House Directive for the DoD, and the Departments of Veterans Affairs (VA), Health and Human Services (HHS), and Education to outline coordinated research efforts focused on the causes and mechanisms underlying TBI, post-traumatic stress disorder (PTSD), and other co-occurring conditions. To address the objectives outlined in the NRAP, the National Institutes of Health (NIH), VA, and DoD have many joint initiatives, including research targeting the acute and chronic effects of neurotrauma and the relationship of CTE and TBI. Details of the ongoing efforts related to CTE and TBI research are included in the following lists of projects, each separated by the primary funding source.

A. Combat Casualty Care Research Program (CCCRP)/Joint Program Committee 6 (JPC-6)

The neurotrauma portfolio (NTP) of the CCCRP is focused on closing military relevant gaps across a broad range of research areas to improve the prevention, diagnosis, management, and treatment of TBI and related sequelae from point-of-injury through recovery. In consultation with the Services, VA, and HHS, JPC-6 gathers and submits data for the annual NRAP R&A. Table 1 provides a summary of the JPC-6/CCCRP FYs 2013-2017 investments in CTE-related research totaling $25,670,731.19 (*indicates funds also received from the VA and JPC-8).

Table 1 JPC-6 supported CTE research

NRAP Category	Study Title	Lead site	Total Funded Amount
Foundational Science/Etiology	The Role of Inflammation in Development of AD Following Repetitive Head Trauma	Indiana University School of Medicine	658,533.00

Foundational Science/Etiology	Mechanism and Biomarkers of Degenerative Conditions After Repeated Mild TBI	Uniformed Services University of the Health Sciences (USUHS)	759,562.00
Prevention and Screening	Early Recognition of CTE Through FDDNP PET Imaging	Cleveland Clinic Foundation	746,068.00
Prevention and Screening	Tau Imaging Of CTE	Brigham and Women's Hospital, Inc.	992,585.00
Prevention and Screening	In Vivo Neuroimaging Biomarker Panel For CTE	University of Pittsburgh	631,733.00
Prevention and Screening	PET Ligands For Measuring Tau In The Brains Of Combatants After TBI	University of California, San Francisco	2,863,058.00
Foundational Science/Etiology	Tau Accumulation In TBI: Mechanisms And Treatment	University of Pennsylvania	2,769,876.19
Treatment	Novel Mechanism for Reducing Acute and Chronic Neurodegeneration After TBI	University of California Davis	763,916.00
Prevention and Screening	Development of in Vivo Biomarkers for Progressive Tau Pathology after TBI	Washington University	2,985,400.00
Treatment	Chronic Effects of Neurotrauma Consortium	Virginia Commonwealth University	12,500,000.00*

*indicates funds also received from the VA and JPC-8

B. The VA

The VA Health Services Research and Development (HSR&D) portfolio is focused on veterans' needs. CTE research reported for the VA HSR&D portfolio includes VA collaborations with academic institutions or other Federal agencies, including the DoD. Table 2 provides a summary of the total of this $1,158,990.96 VA investment in CTE-related research.

Table 2 VA supported CTE research

NRAP Category	Study Title	Lead site	Total Funded Amount
Foundational Science/Etiology	CTE: Role Of Astrocytes	Miami, FL	599,390.96
Prevention and Screening	Diagnosing Combat-Related TBI Using Magnetoencephalography	Naval Medical Center San Diego	559,600.00*

*indicates funds also received from DoD

C. The NIH

Two key goals of the NIH are to foster fundamental creative discoveries and to develop resources to ensure the capability to prevent disease. Aligning with this mission, the NIH actively supports CTE-relevant research: Table 3 provides a summary of the CTE-related research supported by the NIH for a total of $28,386,543.00.

Table 3 NIH supported CTE research

NRAP Category	Study Title	Lead site	Total Funded Amount
Foundational Science/Etiology	Magnetic Resonance Spectroscopy As A Biomarker For CTE	Boston University Medical Campus	117,501.00
Foundational Science/Etiology	In Vitro Tauopathy Model For TBI	University of Minnesota	402,148.00
Prevention and Screening	CTE: Detection, Diagnosis, Course, And Risk Factors	Boston University Medical Campus	10,080.00
Treatment	Taurine Treatment For TBI In Aging	University of Kansas Medical Center	606,984.00
Foundational Science/Etiology	The Role Of Microglia In Acute Pathology Of Repeated Concussion And CTE Development	University of Kentucky	61,246.00
Foundational Science/Etiology	CTE And Posttraumatic Neurodegeneration: Neuropathology And Ex Vivo Imaging	Boston University Medical Campus	6,064,240.00
Foundational Science/Etiology	The Role Of Monocytes And Microglia In TBI-Induced Tauopathies	Cleveland Clinic Lerner	433,893.00
Foundational Science/Etiology	Frontal Lobe Neuroimaging As A Biomarker Of CTE	Boston University Medical Campus	37,814.00
Foundational Science/Etiology	CTE: Clinical Presentation And Biomarkers	Boston University Medical Campus	1,413,234.00
Foundational Science/Etiology	Mechanisms Underlying Tauopathy Following TBI	Washington University	6,086,710.00
Foundational Science/Etiology	Magnetoencephalography And Neurobehavioral Outcome Of Pediatric TBI	University of California, San Diego	669,983.00
Foundational Science/Etiology	Tau Pathology In CTE vs. Alzheimer's Disease: Microvasculopathy And Neuroinflammation	Boston University Medical Campus	4,071,754.00
Foundational Science/Etiology	Neuropathological Characterization Of CTE	University of Pennsylvania	1,260,965.00

Foundational Science/Etiology	Neuropathology Of CTE And Delayed Effects Of TBI: Toward In-Vivo Diagnostics	Icahn School of Medicine at Mount Sinai	6,086,710.00
Foundational Science/Etiology	Investigating RNA Splicing Factor Aggregations In Alzheimer's Disease And CTE	Emory University	181,440.00
Prevention and Screening	Development of PET Radioligands for Imaging Tau Aggregates	National Institute of Mental Health	429,725.00
Prevention and Screening	PET Imaging Of Tau Aggregates	National Institute of Mental Health	452,116.00

D. Office of Naval Research (ONR)

The ONR was established by law as the U.S. Government's first permanent agency devoted to funding civilian scientific research during peacetime. It manages and funds basic and applied science and advanced technology development with an array of partners in academia, industry, and government in the U.S. and around the world. Table 4 provides a summary of the CTE-related research supported by ONR that totals $447,673.00.

Table 4 ONR supported CTE research

NRAP Category	Study Title	Lead site	Total Funded Amount
Prevention and Screening	Correlating Blast Exposure In Humans With Injury Using Reconstructed Blast Gauge Data Project	Naval Medical Research Center	21,831.00
Foundational Science/Etiology	Detection And Characterization Of Micro-Cavitation Generation In Surrogate Forms By Simulated Underwater Blast Events	Naval Submarine Medical Research Laboratory	105,000.00
Foundational Science/Etiology	Characterizing The Neuroprotective Effects Of Hypothermia As A Potential Therapeutic For TBI	Brown University	320,842.00

E. The Peer Reviewed Alzheimer's Disease Research Program (PRARP)

The PRARP, a congressionally directed medical research program, was initiated in 2011 to address the long-term consequences of TBI as they pertain to AD. In FY 2016, the program was expanded to include AD-related dementias research as it pertains to TBI. Consistent with this mission, the PRARP has invested a total of $7,549,406.38 in CTE-related research projects (Table 5).

Table 5 PRARP supported CTE research

NRAP Category	Study Title	Lead site	Total Funded Amount
Foundational Science/Etiology	The Impact Of Perk On Posttraumatic Tauopathy In Alzheimer's Disease	University of Kentucky	762,493.00
Foundational Science/Etiology	Mouse And Human Models For Investigating Influences Of Tau On Progression Of Alzheimer's Disease Following Traumatic Neuronal Injury	University of California San Diego	582,222.00
Foundational Science/Etiology	Mechanisms Of Tau Structural Changes And Aggregation Upon Tau Hyperphosphorylation	University of Delaware	757,600.00
Foundational Science/Etiology	Role Of Non-neuronal Cells In Tauopathies After Brain Injury	University of California, Los Angeles	629,525.00
Foundational Science/Etiology	Defining The Pathophysiological Role Of Tau In Experimental TBI	University of Pennsylvania	725,110.00
Foundational Science/Etiology	Molecular & Genetic Investigation Of Tau In CTE	Icahn School of Medicine at Mount Sinai	515,534.00
Foundational Science/Etiology	Tau And Beta-Amyloid Deposition, Microhemorrhage And Brain Function After TBI In War Veterans	University of Melbourne	738,421.38
Foundational Science/Etiology	N-Terminal Tau Fragments As Biomarkers For Alzheimer's Disease And Neurotrauma	University of Massachusetts, Lowell	447,820.00
Foundational Science/Etiology	Is Failure of Glymphatic Tau Clearance a Critical Pathophysiological Event in CTE?	University of Rochester	769,000.00
Foundational Science/Etiology	Application of Proteomics and Electrophysiology to Identify Biomarkers and Targets for CTE Therapeutics	Emory University	779,883.00
Foundational Science/Etiology	Measuring Glial Metabolism in Repetitive Brain Trauma and Alzheimer's Disease	Brigham and Women's Hospital, Inc.	841,798.00

F. Uniformed Services University of the Health Sciences (USUHS)

As part of the mission of USUHS to educate, train, and prepare uniformed services health professionals and scientists to support the Military Health System and the readiness of the Uniformed Services, USUHS supports CTE research that is innovative and relevant to the DoD. Specifically, the USUHS has invested $27,723,722.00 in support of CTE-related research projects (Table 6).

Table 6 USUHS supported CTE projects

NRAP Category	Study Title	Lead site	Total Funded Amount
Foundational Science/Etiology	Repetitive mTBI-Induced Neurobehavioral Changes And CTE-Like Proteinopathy	Gainesville, FL	1,099,092.00
Treatment	UCSF/USUHS Partnership To Develop Tau Prion Therapeutics For CTE	USUHS; University of California, San Francisco	24,801,029.00
Foundational Science/Etiology	Pre-Clinical Modeling Of Tau Expression Following Repeated Closed Head Impact Injury And Simulated Blast	USUHS	1,559,961.00
Foundational Science/Etiology	Characterizing Mitochondrial Ca+2 Homeostasis And The Effects Of Oxidative Damage	USUHS	263,640.00

IV. CTE-RELATED INITIATIVES TO TRACK AND MONITOR SERVICE MEMBERS

Currently, the state of the science has not established clear relationships between particular causes and clinical manifestations of CTE. No pre-morbid diagnostic tools to identify or track progression of potential CTE-like pathology yet exist. The relationship between CTE and the mechanism of injury, pre-morbid clinical deterioration, or pre-disposing factors can only be firmly established through large brain tissue repositories that include complete and comprehensive clinical records of the donors. The Veterans Administration-Boston University-Concussion Legacy Foundation (VA-BU-CLF) Brain Bank and the Center for Neuroscience and Regenerative Medicine (CNRM) Brain Tissue Repository are two existing brain tissue repository programs; both programs emphasize outreach to ensure public awareness of the brain tissue repositories, and sufficient staffing and technology to facilitate rapid access to the fresh tissue and medical records. Deputy Secretary of Defense Memorandum, "Comprehensive Strategy and Action Plan for Warfighter Brain Health," dated October 1, 2018, directs the Under Secretary of Defense for Personnel and Readiness to develop a comprehensive strategy and plan of action focused on promoting warfighter brain health and countering TBI. On February 1, 2019 the strategy was expanded by the Acting Deputy Assistant Secretary of Defense for Health Readiness Policy and Oversight to specify six lines of effort (LOEs). Of particular relevance to CTE, LOE 5 focuses on the long term effects of TBI and awareness and support for the CNRM Brain Tissue Repository. Below, each brain tissue repository initiative is further described:

- The VA-BU-CLF Brain Bank, established in 2009, is focused on understanding any

potential relationship between brain trauma and CTE (http://www.bu.edu/cte/our-research/brain-bank/). The VA-BU-CLF Brain Bank contains more than 600 brains, of which over 325 brains (including those of veterans) have been diagnosed with CTE according to the NINDS criteria. Bio specimens are acquired via a brain donor registry and hotline, with standardized protocols in place to ensure that tissue and data are acquired and readily available to investigators. Beyond brain tissue, comprehensive retrospective clinical data (e.g., clinical symptoms, history of TBI, history of substance abuse) are available.

- In 2011, the USUHS established the CNRM Brain Tissue Repository to better understand the potential causes and risk factors for CTE in the military. (http://www.researchbraininjury.org/our-team/). The CNRM Brain Tissue Repository currently contains brain specimens of about 100 Service members or veterans who were suspected of having CTE before they died. An outreach awareness program has also been developed to build a registry for individuals interested in brain donation. Two large epidemiological studies are tracking the long-term effects of TBI in Service members and veterans who served in post-9/11 military conflicts, including working with the above mentioned brain tissue repositories to better understand the natural history of TBI.

- The Chronic Effects of Neurotrauma Consortium was funded in 2013 to conduct a longitudinal multi-center observational study designed to comprehensively evaluate a large cohort of U.S. veterans and Service members. The study aims to better understand possible chronic and late-life effects of military-related mild TBI, including effects that may stem from neurodegeneration. Outcome assessments include structured interviews, questionnaires, neuropsychological testing, motor, sensory and vestibular functions, neuroimaging, electrophysiology, genotypes and biomarkers. As of January 2019, more than 1,600 participants have been enrolled and over 300 in person follow-up evaluations have been completed.

- In response to section 721 of the NDAA for FY 2007, the 15 Year Longitudinal Studies, comprised of the Natural History Study and the Caregiver Study, examine long-term physical and mental health effects of all TBI severity in Service members and veterans; health care, mental health care, rehabilitation and service needs; and the impact of TBI on the family. As of February 2019, over 2,800 baseline and follow-up evaluations have been conducted on Service members and veterans enrolled in the 15 Year Natural History Study to assess health care utilization; medical, mental health, and TBI history; neurobehavioral and neurocognitive outcomes; neuroimaging scans; sensory/motor functioning; and a blood draw for blood-biomarker and genetic analyses.

V. ONGOING COLLABORATIVE RESEARCH EFFORTS WITH THE NIH, EXECUTIVE AGENCIES AND CIVILIAN ACADEMIC AND RESEARCH ORGANIZATIONS

- As listed in Section III, Federal agencies continue to invest in clinical research programs relevant to CTE and TBI, with many of these programs being rich collaborations across Federal and non-Federal organizations. For example, University of California, San Francisco and USUHS have partnered, with funding from USUHS, to develop tau prion therapeutics for CTE, and improved PET ligands for measuring tau in the brains of combatants after TBI. Another example comes from the NIH- and PRARP-funded collaboration on the neuropathology of CTE and late effects of TBI examining individuals with TBI from numerous centers including the Brain Injury Research Center at Mount Sinai, the University of Texas Southwestern, and the National Football League.

- In 2018, the DoD and the VA committed up to $10 million per year for five years to fund a program entitled "The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC)." The intention of this program is to support a consortium of clinical sites conducting a large longitudinal study and associated sub-studies of Service members and veterans who sustained a TBI or are otherwise at risk for chronic TBI related health issues. The knowledge gained through the proposed studies will inform TBI pathways of care and illuminate specific target areas to improve TBI care. Candidate applications for this award are currently being evaluated, and the successful applicant is expected to be announced in mid to late 2019.

- Federal agencies remain committed to visibility on research as well as access to data. The DoD is continuing to upload DoD-funded research information on an annual basis to the Federal Reporter to enable transparent flow of information with the public and across Federal funding agencies. This enhanced visibility mitigates unnecessary redundancy. In addition, selected DoD and NIH-funded studies upload TBI research data to the Federal Interagency Traumatic Brain Injury Registry (FITBIR). The FITBIR system, physically located on the NIH campus, was developed to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms. It includes common data definitions and standards, as well as comprehensive and coherent informatics approaches which facilitate investigations that require large datasets.

VI. CONCLUSION

The DoD is committed to continued research on CTE to address the outlined gaps between CTE and TBI research and ultimately assist Service members and their families.