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# Introduction

# International State-of-the-Science Meeting Exploring the Potential Relationship between Blast-Related Trauma and the Development of Chronic Traumatic Encephalopathy

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Blast injuries have emerged as one of the most pressing military medical challenges because of the increased use of improvised explosive devices by terrorists and insurgents in Iraq and Afghanistan. Recent estimates indicate blasts were responsible for approximately 75% of United States (US) combat casualties in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).[1] The survival rate for those injured in OIF and OEF is much higher than in past conflicts in part because of advanced in-theater medical care, rapid evacuation, and improved personal protective equipment. For example, there were 7.5 wounded service members per fatality in Afghanistan and 7.2 in Iraq compared with 3.2 in Vietnam, 3.1 in Korea, 2.3 in World War II, and 3.8 in World War I.[2] As the survival rate increased, so too has the number of service members living with milder short-term, intermediate length, and life-long effects of their injuries.

Blast-related mild traumatic brain injury (mTBI) not only affects the resilience and in-theater performance of troops, but also may result in long-term health effects. More than 300,000 US Service Members have received a diagnosis of TBI since 2000, with most (84%) being of mTBI.[3] While approximately 80–85% of those who sustain mTBI recover fully within one month,[4–6] the remainder show persistent symptoms that may last several weeks, years, or may not resolve within their lifetime.[7] Blast-related TBI represents a spectrum disorder that appears to be associated with chronic traumatic encephalopathy (CTE), a progressive tau protein-linked neurodegenerative disease associated with repetitive concussive injury.[8–11] These neuropathological findings have led to the following question: Is there an association between blast-related TBI and CTE?

CTE potentially represents a major public health issue and is a subject of intense interest to the Department of Defense (DoD). The concerns of the DoD have a widely publicized parallel in the sports community, which has also been concerned about possible links between repeated concussions and the development of CTE in athletes. The DoD, together with the Veterans Affairs, academia, and the sports community, have made considerable investments in establishing multi-institutional and multi-disciplinary collaborative research programs for the purposes of finding consensus on the existence of, and diagnostic criteria for, CTE.[12–16] This work is ongoing and promises to evaluate further the association of brain injury and chronic effects.

To explore the potential links between blast-related mTBI and CTE, the DoD Blast Injury Research Program Coordinating Office (PCO) hosted the International State-of-the-Science (SoS) Meeting titled ''Does Repeated Blast-related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?'' on November 3–5, 2015 in McLean, VA. More than 120 attendees from the DoD, other Federal agencies, academia, industry, foreign allies, and the sports community came together to review and summarize the current knowledge base, identify knowledge gaps, and formulate recommendations for medical research to close the knowledge gaps and enable the timely delivery of effective blast injury prevention, mitigation, and treatment strategies to service members.

To inform the SoS Meeting, the DoD Blast Injury Research PCO prepared and disseminated a literature review to address specific research questions before the meeting. A summary of the research questions and findings of the literature review are included in Table 1 and the complete literature review is included in this Supplement.

During the opening plenary and general sessions, keynote, topical, and research presentations identified requirements, defined the scope of the problem, addressed policy issues, and summarized the state of the science. On the last two days of the meeting, attendees divided into working groups, with each working group made up of a representative subset of the multi-disciplinary meeting attendees. The working groups discussed and developed responses to the following research questions:

1. What are the definitive pathological characteristics of neurodegeneration from repeated blast-induced trauma?
2. What risk factors, both traumatic and nontraumatic, are predictive of CTE?
3. What research is needed to explore the putative spatiotemporal development of CTE resulting from repeated blast exposure?
4. What approaches can be used to detect early stages of blast-related neurodegeneration and evaluate the progression to

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Table 1. Literature Review Research Questions and Findings

| *Research questions* | *Findings* |
|---|---|
| **What is the current evidence describing the pathophysiological basis of CTE?**<br>• What biological processes following head injury are associated with the development of CTE?<br>• What advances in neuroimaging or biomarkers of CTE may lead to the development of diagnostic tools or therapeutic strategies? | • An initial consensus has recently identified a specific neuropathology thought to be required for a diagnosis of CTE.<br>• Ongoing biomarker development, including neuroimaging and biospecimen-based modalities, may enable identification and study of CTE neuropathology in living persons.<br>• Treatment of CTE has not been established; therefore, current mitigation strategies focus on prevention. |
| **What associations are known between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE?**<br>• Does the frequency of exposure to head injury correlate with the development of CTE?<br>• Are there any known distinctions between how impact injury, nonimpact injury, and blast-induced injury are associated with the development of CTE? | • Largely because of limitations in clinical data collection, associations between CTE development and 1) frequency of head injury or 2) type of head injury cannot be determined. |

CTE, chronic traumatic encephalopathy.

CTE to support the screening, detection, diagnosis, prognosis, assessment of therapeutic interventions, and determination of return to duty status?

5. What are the strategies that can be used to prevent, mitigate, or treat neurodegeneration following repeated blast exposure?

Following the meeting, a six-member expert panel convened to highlight the major themes from the meeting, synthesize the relevant findings, identify knowledge gaps, and make recommendations. This process took into account the major discussion points and key ideas that emerged from the focused working group sessions, the literature review, the keynote, topical, and research presentations, and the poster sessions.

## SoS Expert Panel Findings and Recommendations

The overarching finding is that existing scientific evidence is insufficient to link blast-related TBI with CTE. The expert panel acknowledged that this was, in part, because of a paucity of tissue samples from those with well-annotated medical and blast exposure histories. They concluded that without access to blast-exposed tissue samples, a deeper exploration of potential associations between blast exposure and the development of CTE, including non-blast risk factors, such as genetic susceptibility, age, and gender, as well as co-morbidities such as drug, alcohol abuse, and cardiovascular disease, is not possible.

The expert panel addressed this gap by calling for the creation of a coordinated brain bank within the DoD to accept brain tissue donations from deceased service members and ensure that these tissue samples would be accessible to the broader research community. This brain bank would stand to complement and benefit from efforts already under way, such as the Brain Tissue Repository that was established at the Center for Neuroscience and Regenerative Medicine. To maximize participation, the expert panel recommended that an education program be developed to teach researchers strategies to address social and logistical barriers of brain donation within the confines of regulatory, legal, and ethical frameworks that govern tissue donation. A robust brain donation repository that can be shared between DoD and academic researchers is essential to determine whether there are distinct pathological features of CTE and whether these features are a result of blast-related TBI.

The expert panel also acknowledged that a major impediment to definitive studies of CTE is a lack of validated diagnostic and screening tools, including fluid biomarker and neuroimaging approaches based on standardized clinical criteria. The only way to identify CTE is through post-mortem autopsy of affected brains using neuropathological criteria that are only just beginning to achieve consensus.[17,18] Therefore, to facilitate the development of ante-mortem diagnosis and screening approaches, the expert panel recommended the establishment of an independent panel to assess current biomarkers and provide recommendations for future development of technologies, protocols, and analytics of next-generation biomarkers. Noninvasive biomarkers would enable diagnosis not only in living subjects but could also be used to detect potential neuroanatomical characteristics specific to CTE. A longer-term component of the strategy called for the development of high spatial resolution molecular imaging technologies that would enable imaging of discreet brain locations and their function.

A complementary and important component recommended by the expert panel was for increasing research efforts toward the development and validation of animal models clinically relevant to blast-related TBI and chronic neurodegeneration. They emphasized that animal models would likely accelerate the discovery of diagnostics and treatments and may represent the key to unlocking a greater understanding of the pathophysiological mechanisms of CTE. The expert panel stressed the importance of developing clinically relevant models with standardized protocols that are shared across the research community.

In light of the research challenges faced and what little is known about CTE, the expert panel recommended that an independent panel be convened to determine whether ongoing longitudinal studies could be leveraged to explore whether there is a spatio-temporal development of CTE and candidate risk factors. These studies could include the Defense and Veterans Brain Injury Center's 15-year longitudinal study on TBI, the Traumatic Brain Injury Model Systems study, the Chronic Effects of Neurotrauma Consortium study, or the National Collegiate Athletic Association Concussion Assessment, Research and Education Consortium study. The panel would identify ways to strengthen these studies

and maximize their usefulness for shedding light on CTE. This could include, for example, identifying gaps in the studies that could be filled by a neuropathological component or using the ongoing studies to explore nonblast CTE risk factors.

The expert panel noted that additional large prospective longitudinal clinical studies of service members with, or at risk of, combat-related blast injury may still be needed, and should be initiated, to adequately characterize the association between repeated blast exposure and CTE. They recommended that these studies collect detailed medical histories on at-risk populations such as breachers or gunners who have more predictable and reliable blast exposures histories (e.g., frequency, magnitude) when compared with other study populations. To complement these efforts, the expert panel called for the continuous monitoring of at-risk populations to help establish a dose-response relationship between blast intensity, frequency, and resulting injury severity with improved sensor technology. Outcomes of these studies would inform efforts to establish standardized clinical diagnostic criteria, the lack of which is a major gap.

Given the current state of the science regarding the relationship between blast-related TBI and CTE, it is important to implement prevention and mitigation strategies of blast-related TBI. Some of these strategies include modifying training protocols to reduce blast exposure (e.g., breacher training, weapon systems training) and educating military instructors about long-term exposure risks. Improving personal protective equipment and limiting blast exposure are perhaps the most promising areas for preventing blast-induced TBI. The expert panel also emphasized the importance of implementing current return-to-duty guidelines after blast exposure, but also questioned their basis in evidence and recommended that the extent to which the guidelines minimize the risk of blast-related TBI be evaluated.

The articles presented in this Supplement represent a sampling of the work presented at the meeting and exemplify the multidisciplinary approaches that are under way to elucidate the pathophysiological basis of CTE, identify whether there is a link with repeated blast-related TBI, and determine the long-term implications of blast-related TBI. This knowledge base is crucial for the development of effective prevention, mitigation, and treatment strategies for service members and veterans who have been exposed to blast or have endured blast-related TBI.

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