Optimizing Brain Health of United States Special Operations Forces

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ABSTRACT

United States Special Operations Forces (SOF) personnel are frequently exposed to explosive blasts in training and combat. However, the effects of repeated blast exposure on the human brain are incompletely understood. Moreover, there is currently no diagnostic test to detect repeated blast brain injury (rBBI). In this "Human Performance Optimization" article, we discuss how the development and implementation of a reliable diagnostic test for rBBI has the potential to promote SOF brain health, combat readiness, and quality of life.

KEYWORDS: *blast overpressure; brain injury; special operations forces; sof; human performance optimization*

Introduction

United States (U.S.) Special Operations Forces (SOF) personnel experience high levels of blast exposure during training and combat.[1] The cumulative effects of repeated blast exposure (RBE) on SOF brain health and performance are not fully understood.[2,3] Consequently, there is no diagnostic test to identify brain injury resulting from RBE, which we refer to as repeated blast brain injury (rBBI). In this "Human Performance Optimization" article, we discuss why the development of a diagnostic test for rBBI is essential for optimizing SOF brain health. We first review the state of the science in blast-related brain injury, with a focus on biomechanical, pathological, and neuroimaging data. Second, we discuss current technical, scientific, logistical, and social barriers to developing and disseminating a diagnostic test for rBBI and propose strategies to overcome them. Third, we consider how the extraordinary cognitive and physical demands of training and combat impact access to diagnostic testing and the delivery of medical care for SOF personnel. Finally, we propose an operational definition for rBBI, which is distinct from mild traumatic brain injury (mTBI) and traumatic encephalopathy syndrome.[4,5]

State of the Science

The effects of repeated blast exposure on the human brain are not fully understood. Current studies are limited by incomplete surveillance of blast exposure frequency and magnitude, an inability to distinguish between the effects of blast and blunt trauma, and inadequate baseline (i.e., pre-exposure) assessments.[6-8] Without comprehensive baseline data on Operators at the time of selection, longitudinal measurements of blast-related changes in brain structure and function are not possible.[6]

There are also fundamental gaps in knowledge about the mechanisms by which RBE may cause brain injury. Biomechanical, computational, and animal models have begun to reveal how blast waves penetrate the skull and affect underlying brain tissue.[9-19] These studies suggest that, depending on the head's orientation with respect to the blast, overpressure waves may enter the intracranial vault via the ear canals, orbits, nasal sinuses, and foramen magnum, injuring the nearby cerebellum, orbitofrontal lobes, temporal lobes, and brainstem.[9,20,21] Focal injury within these regions may explain several symptoms reported by military personnel with RBE, which include dizziness (cerebellum), behavioral dysregulation and aggression (orbitofrontal lobes), memory loss (temporal lobes), autonomic dysfunction, and insomnia (brainstem).[22] The proposed mechanism of focal blast-induced brain injury is supported by advanced neuroimaging studies, which have identified structural brain abnormalities in close proximity to openings in the skull.[23]

Several lines of evidence suggest that blast overpressure also causes diffuse brain injury. Biomechanical studies indicate that blast overpressure waves penetrate the helmet and dynamically deform the skull, creating pressure gradients that sweep through the brain (Figure 1).[12,24,25] Consistent with biomechanical evidence for diffuse brain injury, recent histopathology and neuroimaging studies in individuals with blast exposure have revealed lesions throughout the thalamus, hypothalamus, basal forebrain, and cerebral cortex at tissue interfaces such as the grey-white matter junction.[13,19,23,26,27] Blast overpressure may cause compression and shearing of neurons and glia at these interfaces, where there is a change in brain tissue density.[28,29] Radiologic-pathologic correlation studies of military personnel exposed to blasts indicate that astroglial scarring at the grey-white junction is associated with rBBI and may

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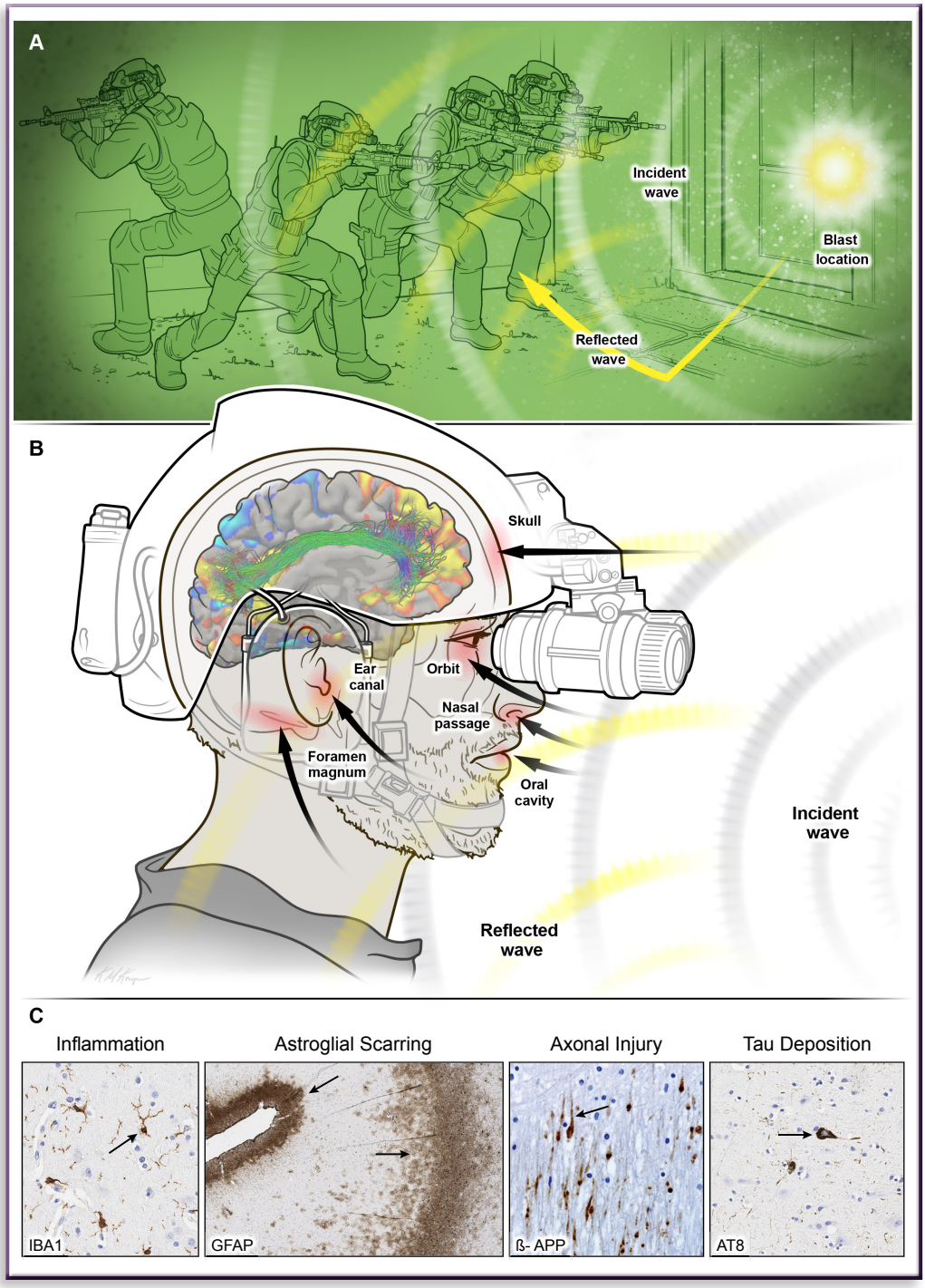
FIGURE 1 *Mechanisms of blast injury in the human brain.*



Artwork in Panels A and B by Kimberly Main Knoper.

(A) Four Operators breach a door using an explosive during a combat mission. The Operators are exposed to overpressure waves that emerge directly from the blast location (incident waves indicated by curved white lines) and overpressure waves that rebound off the ground and other surfaces (reflected waves indicated by the yellow arrow and yellow curved lines). **(B)** A zoomed-in view of an Operator (third from right in the stack formation) demonstrates the mechanisms by which overpressure waves are believed to penetrate the skull. Waves may penetrate the openings in the skull—which include the orbits, nasal passages, oral cavity, ear canals, and foramen magnum—resulting in focal brain injury. Overpressure waves may also penetrate the helmet and skull, causing diffuse brain injury. The left hemisphere of the Operator's brain is shown in the sagittal plane, with the right hemisphere not shown so that the medial surface of the left hemisphere can be visualized. Default mode network functional connectivity is displayed in yellow/orange, and executive control network connectivity is shown in blue. The cingulum bundle, which connects the core midline nodes of the default mode network, is shown using standard color-coding for diffusion magnetic resonance imaging (MRI) tractography (green = anterior-posterior; red = medial-lateral; blue = superior-inferior). Functional and structural connectivity data are superimposed on a T1-weighted MRI scan from an Operator enrolled in the ReBlast study. Functional MRI data were acquired on a 7 Tesla scanner, while the diffusion and T1-weighted MRI data were acquired on the 3 Tesla Connectome scanner at the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging in Boston, MA. Data were processed and analyzed using previously published methods.[71] **(C)** Representative pathology (arrows) detected by immunohistochemistry in the brains of military personnel exposed to repeated blasts includes inflammation, astroglial scarring, axonal injury, and tau deposition.

AT8 = anti-phospho-tau; ß-APP = beta-amyloid precursor protein; GFAP = glial fibrillary acidic protein; IBA1 = ionized calcium binding adaptor molecule 1.

be detectable by advanced magnetic resonance imaging (MRI) techniques.[26,30] Astroglial scarring is rarely seen in cases of pure chronic traumatic encephalopathy (CTE), which has been described primarily in athletes with repetitive blunt head trauma.[31,32] Whereas CTE has been described as a tauopathy (i.e., a neurodegenerative disorder characterized by accumulation of phosphorylated tau protein within neurons), rBBI may be more aptly described as a polyproteinopathy (i.e., a process characterized by accumulation of multiple abnormal proteins in the brain).[32-35]

While the precise contributions of focal and diffuse pathophysiologic mechanisms to rBBI are unknown, it is likely that heterogeneous forces are exerted on the brain during thousands of blast exposures.[36] A single exposure to overpressure may not be sufficient to alter brain structure or function or cause long-term symptoms. However, years of cumulative exposure may contribute to a broad spectrum of cognitive symptoms such as memory loss and inattention, physical symptoms such as headache and dizziness, and psychological symptoms related or similar to post-traumatic stress disorder (PTSD) and depression.[3,8,37] Each of these sequelae—alone or in concert—has been reported by SOF personnel with high levels of blast exposure.[38-41]

It is also unknown whether the pathophysiology of rBBI differs from that of a single blast-induced mTBI (Table 1).[42] In other words, do multiple subconcussive exposures to blast overpressure cause the same type of brain injury as a single mTBI from blast overpressure? We can approach this question from the perspective of civilian head trauma, in which the pathology of multiple subconcussive blunt traumas (i.e., repetitive head impacts) appears to differ from that of a single blunt mTBI.[43,44,45] By extension, we might expect rBBI to cause brain pathology that is distinct from that of a single blast-induced mTBI, but this reasoning awaits further evidence.

In summary, the mechanisms underlying rBBI are complex, heterogenous, and incompletely understood. Similarly, the pathological distinctions between rBBI and a single blast-induced mTBI have not been fully elucidated, in part because it is difficult to isolate "pure" blast exposure from concurrent blunt head trauma exposure in training and combat. Given current gaps in knowledge, translating findings from the laboratory to the war theater is an exceedingly complex and multidimensional challenge. A diagnostic test for rBBI must not only detect the multitude of focal and diffuse effects of blasts on the human brain but also distinguish rBBI from brain injury caused by other exposures.

Barriers to the Development of a Diagnostic Test

Scientific Barrier – Measuring the Magnitude and Frequency of Blast Exposure

There are no validated tools that accurately measure the strength and number of blasts experienced by an Operator. Studies using blast gauges to measure pounds per square inch suggest that four pounds per square inch is a threshold at which a blast adversely affects the human brain.[46] However, these studies are limited by gauge placement (typically on the back of the helmet, chest, and one shoulder), which precludes measurement of the exact amount of overpressure that reaches the brain. Given that placement of an intracranial blast gauge is not ethical and that placement of blast gauges at sites of skull entry (e.g., the orbits and ear canals) could interfere with vision and communication, the options for blast gauge placement are inherently limited. Gauges may also malfunction in the harsh environments in which SOF personnel operate, or they may fail to detect rounds from a weapon with a rapid firing speed. Blast gauges thus may not provide a measurement of the ground truth (i.e., the true magnitude and number of blasts an Operator experienced).

Using subjective self-report questionnaires, in which Operators are asked to provide a cumulative count of blast exposure from various weapons systems, is a complementary approach to objective data gathered through blast gauges.[6] This approach is currently the only method of eliciting exposures that were not otherwise measured, witnessed, or treated. However, important limitations include recall bias and lack of validation against blast gauge or alternative measurements. Furthermore, self-report assessments are unlikely to account for variations in Operator positioning with respect to the blast, physical barriers between the Operator and the blast, and reverberations of blast waves off nearby objects and surfaces—all of which influence the amount of overpressure that reaches the brain.[24]

A recently published measure, the Generalized Blast Exposure Value, asks respondents to self-report average lifetime exposure to five categories of blast ranging from small- and medium-sized arms to large explosives or targeted explosives in close range.[36] Other measures like the Blast Ordnance and Occupational Exposure Measure incorporate information about recent exposures as well as history of breacher training courses attended and taught, during which exposures are especially frequent.[47] These measures assess cumulative blast exposure (i.e., over months to years), rather than incremental changes in exposure, which would be required to measure the relationship between increasing blast exposure and changes in neuroimaging or blood-based biomarkers. In summary, though a variety of sensors and self-report questionnaires have been designed to measure blast exposure, precise, reliable, and longitudinal measurements remain elusive.

Scientific Barrier – Accounting for Resilience

Additional barriers to development of a diagnostic test for rBBI include the unique characteristics of Operators themselves. Within the military, the SOF community may be both the most exposed and the most resilient to the effects of blasts.[48,49] With respect to resilience – the ability to withstand or quickly recover from difficult situations – SOF personnel may possess characteristics that affect brain structure and function in unique ways.[50] For example, the cognitive and physical capabilities that enable them to withstand the grueling selection process and that are further refined during training and combat missions (which require continuous high performance) may promote faster recovery from brain injury.[49,51,52] Resilience has also been associated with more robust physiologic health, as measured by cerebral blood flow velocity, and with cognitive reserve, which is the brain's resistance to damage.[53-55] Cognitive reserve can develop over a lifetime of pursuing mentally challenging tasks such as educational and occupational specialization and training.[56]

Scientific Barrier – Accounting for Additional Exposures

The broad spectrum of additional harmful exposures that SOF personnel may experience poses a related challenge in isolating blast effects on the brain. Many SOF personnel experience

TABLE 1 *Comparison of Mild Traumatic Brain Injury, Traumatic Encephalopathy Syndrome, and Repeated Blast Brain Injury*

Diagnosis	Exposure	Pathophysiology	Diagnostic criteria	Symptoms	Treatment
mTBI	Single external force (blunt contact, rotational acceleration/ deceleration, or blast overpressure)	Diffuse axonal injury; contusion; subarachnoid, subdural, or epidural hemorrhage; cerebral edema; and/or skull fracture[93]	Traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that leads to at least one new or worsening clinical symptom immediately following the event (e.g., loss of consciousness ≤30 minutes, post-traumatic amnesia ≤24 hours, or focal neurological deficits), with normal conventional brain imaging[4,94]	Headache, confusion, dyscoordination, memory loss, nausea, vomiting, dizziness, ringing in the ears, sleepiness, excessive fatigue, irritability, disinhibition, and emotional lability[94,95]	Rest, treat individual symptoms, prevention of secondary injury[95,96]
TES (proposed)	Repeated exposure to multiple blunt force impacts to the head and/ or rotational acceleration/ deceleration events that do not meet mTBI diagnostic criteria, such as those sustained in American-style football*	Current evidence suggests that RHI is associated with CTE, in which hyperphosphorylated tau protein forms neurofibrillary tangles and astrocytic tangles along small cortical blood vessels, particularly in the sulcal depths.[32,33] However, CTE can only be confirmed after death if brain autopsy reveals the pathognomonic pattern of tau protein deposition.[5,97]	Proposed diagnostic criteria for TES are 1) substantial exposure to RHI, the threshold for which has not yet been determined; 2) cognitive impairment and/or neurobehavioral dysregulation; 3) progressive worsening of these symptoms over at least one year in the absence of continued exposure to RHI; and 4) clinical symptoms are not fully accounted for by another neurologic, psychiatric or medical condition[5]	Cognitive impairment in the domains of episodic memory and/ or executive function; decreased regulation of emotions and/or behavior, including explosiveness, impulsivity, rage, violent outbursts, having a short fuse, or emotional lability[5]	Unknown; treat individual symptoms[96]
rBBI (proposed)	Repeated exposure to blast overpressure events that do not meet mTBI diagnostic criteria, such as those sustained during explosive breaching	Current evidence suggests that RBE may lead to astroglial scarring[26]	Proposed diagnostic criteria for rBBI are 1) a quantitative change in a blood or neuroimaging biomarker that exceeds the reliable change index[87] for that biomarker; and 2) the biomarker change occurs during a period of RBE	Individuals may be asymptomatic or may experience dizziness, dyscoordination, vision and hearing problems, sensitivity to light and noise, numbness, tingling, change in taste/ smell, inattention, forgetfulness, difficulty with decision-making, slowed thinking, fatigue, sleep difficulty, irritability, and/or poor frustration tolerance[36]	Unknown; treat individual symptoms[96]

*Recent histopathological evidence has called into question the pathophysiologic link between RBE and CTE.[31] Thus, we do not include RBE as a risk factor for TES, and these histopathological data are a primary motivation for distinguishing rBBI from TES. The diagnostic criteria that distinguish rBBI from TES are as follows: exposure to multiple blast overpressure events is required for rBBI; there must be a quantitative change in a blood or imaging biomarker that is associated with increased exposure to blast overpressure for a diagnosis of rBBI; and rBBI can be asymptomatic, given that the diagnosis is based upon quantitative biomarker changes, not the onset of new symptoms. The requirement of a biomarker change for the diagnosis of rBBI is proposed to increase the specificity of the rBBI diagnosis, given that additional exposures (e.g., heavy metals) and other neuropsychiatric disorders (e.g., PTSD) are associated with similar constellations of symptoms. By proposing diagnostic criteria that include individuals with asymptomatic rBBI, we intend to facilitate early detection and timely intervention.

CTE =chronic traumatic encephalopathy; mTBI = mild traumatic brain injury; rBBI = repeated blast brain injury; RBE = repeated blast exposure; RHI = repetitive head impacts; TES = traumatic encephalopathy syndrome; PTSD = post-traumatic stress disorder.

both blast and blunt head trauma, which are often simultaneous (e.g., the head striking or being struck by a physical object in the setting of high explosive exposure), complicating efforts to distinguish the unique effects of blast versus blunt traumatic brain injury (TBI).[23] Exposure to blunt TBI may also occur pre-selection, particularly in Operators with a history of contact sport participation, further complicating efforts to identify a relationship between RBE and brain injury. For example, in a recent histopathological analysis of autopsied brain specimens from military personnel, only those with pre-existing participation in contact sports were found to have the characteristic pattern of phosphorylated tau deposition within their brains that defines the diagnostic lesion of CTE.[31]

During years of training with explosives, such as those used to breach buildings, Operators may also be exposed to aerosolized heavy metals, which can reach the central nervous system via inhalation, producing cognitive and motor deficits.[57] Similar exposures to heavy metals and other toxins are encountered on helicopters and fixed-wing planes, where Operators are exposed to fumes from artillery and rockets.[58] Though data are limited, high rates of headaches have been reported in SOF helicopter pilots.[59] Whether headaches and other symptoms are attributable to fume inhalation, blast exposure, or to some combination of these factors or others is unknown.

The extreme environmental conditions under which SOF personnel operate yield additional exposures, such as those associated with the high altitudes encountered during mountain warfare and by AC-130 and CV-22 Operators during air missions. Animal studies suggest that exposure to high altitudes may be associated with tau deposition, neuroinflammation, and myelin loss.[60] While this finding has not been replicated in humans, the potential implications need to be considered

when developing diagnostic tests for SOF personnel who are exposed to both blasts and high altitudes. Similarly, Navy SEALs, Air Force Special Tactics Teams, Green Beret Combat Dive Teams, and other Operators who perform combat diving, as well as Explosive Ordnance Disposal specialists who perform deep diving, may be at risk for a broad spectrum of neurological symptoms and electrophysiological alterations associated with diving.[61]

Additional exposures include vibrations and g-forces experienced by Special Operations Aviation elements, Air Force Combat Search and Rescue Operators, and Special Tactics Airmen, as well as rapid acceleration-deceleration forces experienced by Naval Special Warfare Combatant-craft Crewmen as they travel over various sea-state conditions at high speed.[62-64] Finally, the physical and emotional stress of repeated exposure to combat and the continuous threat of harm may lead to symptoms and brain alterations that resemble those related to blast exposure.[65-67] The current inability to differentiate the effects of these myriad exposures on the brain is a major motivation for the development of blast-specific diagnostic biomarkers.

Logistical Barrier – Deployment of Diagnostic Tests to Combat Zones

Diagnostic testing protocols for rBBI will need to be adaptable to the relative needs and conditions of training and combat. During training, utilization of state-of-the-art, large-scale infrastructure –such as MRI and positron emission tomography (PET) scanners – may be feasible. Hence, optimization of diagnostic test performance may involve leveraging these imaging technologies, which have shown promise in multiple observational studies over the past two decades.[23,68-70] The potential diagnostic utility of MRI and PET biomarkers in U.S. SOF personnel is being tested in the ReBlast Pilot study, which was designed to inform and accelerate efforts to develop a diagnostic test for rBBI.[71]

In combat, an essential requirement of a diagnostic test for rBBI is its deployability. To meet this requirement, a test must be portable, compact, rugged, and secure and provide real-time feedback. These stipulations rule out brain MRI and PET scans, which are not feasible to deploy in theater at scale. Technologies that could be deployable in theater include point-of-care blood tests, application-based cognitive performance tests, electronically delivered and scored symptom questionnaires, and targeted neurological examinations (i.e., mental status, cranial nerves, sensory/motor function, reflexes).[72-74] These tests are being assessed for their diagnostic utility in multiple ongoing studies of blast TBI in military personnel, which include EVOLVE, LETBI, LIMBIC-CENC, ENIGMA, ReBlast, and INVICTA.[71,75-79] It remains to be determined which tests, alone or in combination, will provide the greatest sensitivity and specificity for detecting rBBI in training and combat.

Social Barrier – Acknowledging Symptoms and Seeking Care in a Culture of Self-Sacrifice and Fortitude

Though empiric evidence about SOF attitudes toward their own health care is limited, public interviews with SOF personnel suggest that commitment to the team and mission is prioritized over personal health and safety.[22,80] It is therefore not surprising that many Operators are willing to train and deploy even when they are experiencing physical, cognitive, or psychological symptoms. Indeed, the ability to persevere and succeed despite pain and discomfort is an essential component of SOF selection.

Beyond the understandable reluctance of Operators to seek medical care that could lead to missing training or deployment is their potential hesitancy to call attention to symptoms that are perceived as mental rather than physical. The implications of the "invisible wounds of war" for individual Operators, and for the military more broadly, have been widely discussed in opinion articles and policy statements.[81] There have been extensive efforts by the U.S. Special Operations Command and the U.S. Department of Defense to raise awareness about these invisible wounds and to provide support for the millions of military personnel who have experienced TBI and PTSD.[82] The creation of centers of excellence that provide care for military personnel with TBI and PTSD is emblematic of these efforts.[83-85] However, most SOF personnel do not routinely seek these services early in their careers, when symptoms may have the best chance of responding to therapies.[86]

Development and Deployment of a New Diagnostic Test for SOF Personnel

Operational Definitions of rBBI and Recovery

A foundational step toward development of a diagnostic test for rBBI is to define rBBI itself. Despite recent efforts to standardize terminology describing blast exposure, there are currently no standardized criteria that define a brain injury resulting from RBE.[46] Conceptually, rBBI is a brain injury caused by the cumulative effects of multiple blast overpressure events, many of which do not meet the U.S. Department of Defense/Department of Veterans Affairs criteria for a TBI.[4] Operationally, we propose a definition of rBBI as a quantitative change in a blood *or* neuroimaging biomarker that exceeds the reliable change index for that biomarker *and* is associated with RBE during the same time period.[87]

Using this working definition of rBBI, a diagnostic test should classify individual Operators into one of four groups:

- **No rBBI**: No evidence of rBBI, regardless of the extent of blast exposure or the presence of new physical symptoms, cognitive deficits, or psychological health changes. We anticipate that symptoms observed in this group may be driven by comorbid psychological illness (e.g., PTSD), while acknowledging the potential for false negatives (e.g., currently available neuroimaging and blood biomarkers may lack sensitivity to detect rBBI in this group).
- **Asymptomatic rBBI**: Evidence of rBBI but absence of new physical symptoms, cognitive deficits, and psychological health changes. A lack of measurable symptoms in this group may represent "false negatives" (e.g., currently available self-reported and performance-based measures may lack sensitivity to detect subtle changes in symptoms, or Operators may under-report symptoms).
- **Symptomatic rBBI**: Evidence of rBBI and development of new physical symptoms, cognitive deficits, or psychological health changes.
- **Recovery from rBBI**: Evidence of rBBI and resolution of physical symptoms, cognitive deficits, or psychological health changes that were detected at an earlier assessment.

Accurate classification requires careful baselining to determine pre-exposure biomarker levels and serial assessment to

ensure early detection and treatment. Moreover, the proposed classification system does not account for the possibility that symptoms may emerge weeks to years after RBE, resulting in misattribution of symptoms to other sources. We therefore anticipate that this diagnostic classification system will require iterative revisions as more information about the temporal dynamics of rBBI becomes available and as new tools are developed to measure concurrent exposures.

Proposal for a Diagnostic Risk Assessment Matrix

Once individual Operators are classified into one of the above four groups, we advocate for the implementation of a Risk Assessment Matrix to guide symptom monitoring and treatment (Figure 2). This Risk Assessment Matrix is designed to facilitate the realization of two goals:

1. *Individualized care:* rBBI symptoms exist on a continuum and therefore require an individualized approach in which Operators are monitored with direct comparison to baseline assessments performed at the time of selection.
2. *Operational flexibility:* While Operators exposed to high numbers of blasts during training will have access to diagnostic monitoring protocols, Operators who experience rBBI while deployed may have limited access to medical care.

Thus, the Risk Assessment Matrix must provide guidance about optimal clinical management that accounts for these constraints. This Risk Assessment Matrix could provide an early clinical guide that will be refined as additional evidence becomes available.

FIGURE 2 *Repeated blast brain injury (rBBI) risk assessment matrix.*

	rBBI	No rBBI
Symptomatic	high (treat)	uncertain (monitor)
Asymptomatic	moderate (frequent monitoring)	low (monitor)

In this proposed Risk Assessment Matrix, medical care for Operators is individualized based on the presence or absence of cognitive, physical, and psychological symptoms, as well as on the presence or absence of objective changes in neuroimaging or blood biomarkers.

rBBI = repeated blast brain injury.

Clinical Management of rBBI

Once an Operator is diagnosed with rBBI, what is the appropriate clinical management to optimize brain healing? We propose four guiding principles, recognizing that it is premature to recommend specific clinical guidelines.

First, management strategies will likely differ depending on where the diagnosis is made. For Operators diagnosed with rBBI during training, it may be possible to reduce or eliminate further blast exposure for a period of time that allows the brain to heal, adapt, or compensate for the injury. For Operators diagnosed with rBBI after being exposed to repeated blasts during combat and other deployment settings, optimal management will depend upon the operational requirements of the mission and the potential risks to the mission if an Operator were to be temporarily sidelined.

Second, proof-of-principle evidence suggests that multidisciplinary treatment programs with individualized approaches to psychotherapy and cognitive rehabilitation may be effective in treating Operators with both blast-induced mTBI and chronic symptoms from RBE.[85] As we await disease-modifying therapies, these multidisciplinary treatment programs may currently be the most effective way to treat Operators who experience cognitive, psychological, and physical symptoms after blast exposure. However, randomized controlled trials in large numbers of SOF personnel have not yet been performed. Hence, multidisciplinary, individualized treatment programs require further evaluation before they can be endorsed by clinical guidelines.

Third, when assessing responses to therapy, there are likely to be differences in brain monitoring protocols that are eventually translated to clinical care for rBBI and single, blast-induced mTBI. For example, rBBI may be associated with a specific combination of blood biomarkers that are expressed chronically.[88,89] Studies of blunt TBI in civilians indicate that blood tau and neurofilament light are elevated in the subacute and chronic stages of injury, as compared to ubiquitin C-terminal hydrolase L1, which becomes elevated in the blood acutely, and glial fibrillary acidic protein, which is elevated acutely, declines subacutely, but may rise again starting six months post-injury.[90,91] Determining the temporal dynamics of these blood biomarkers is critically important for their clinical translation as measures of brain injury and brain healing.

Fourth, just as blunt TBI can cause chronic brain inflammation and contribute to neurodegeneration, the effects of rBBI may be long-lasting and progressive.[34,35,92] Early detection and treatment of rBBI, before it becomes irreversible, is a major motivation for developing a diagnostic test for rBBI. Regardless of how diagnostic information about rBBI is ultimately used to inform clinical care, a reliable diagnostic test will empower Operators, team leaders, commanders, and U.S. Special Operations Command leadership to make more informed decisions about combat readiness and capacity for peak performance.

Conclusions

Historically, a diagnostic test for rBBI has been elusive due to a variety of barriers, including the pathophysiologic complexity of blast overpressure, which exerts both focal and diffuse effects on brain structure and function. Moreover, SOF personnel experience a myriad of additional exposures during training and combat, such that rBBI symptoms may be difficult to distinguish from those related to blunt head trauma, combat stress, or exposure to heavy metals, high altitudes, diving, aircraft vibrations, and acceleration-deceleration forces on fast-moving Naval Special Warfare Combatant-craft Crewmen boats. To address this complex, multidimensional problem, we advocate for the development of a multimodal diagnostic battery that will integrate data from cognitive performance, psychological health, physical symptoms, blood measures, and brain imaging to detect and monitor the trajectory of rBBI throughout an Operator's career. Such a test must be specific for rBBI and deployable to combat zones. We propose that this diagnostic test will provide the foundation for a Risk Assessment Matrix to guide decision-making about symptom monitoring and treatment. A diagnostic testing battery will also provide new targets for therapies aimed at preventing or alleviating symptoms caused by rBBI. A reliable diagnostic test for rBBI will thus promote SOF brain health, combat readiness, and quality of life.

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Conflicts of Interest

The authors declare no conflicts of interest.

Disclaimer

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