Over the past decade, there has been increasing awareness of the central nervous system (CNS) effects of exposure to explosive blast. A key driver of that awareness has been the blast-related injuries suffered during combat operations in Iraq and Afghanistan. With the near cessation of U.S. combat operations in these regions, concern has grown over common, repetitive forms of blast exposure during military service that are, most often, unrelated to combat. Examples of these exposures include routine military training involving heavy weaponry, such as artillery, recoilless rifles and shoulder-held rocket launchers. These blast exposures are of a lower intensity than those causing acute combat-related injuries; however, repeated exposure may also have impacts on CNS structure, function, and development, as well as on the broader health of military service members.

The authors of this report review the relevant literature on the effects of repeated, military occupational blast (MOB) exposures; prioritize the key research and policy gaps related to repeated MOB exposure; and examine the projects and initiatives that attempt to address those research and policy gaps.
Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast

A Review of Scientific Literature

Molly M. Simmons, Charles C. Engel, Emily Hoch, Patrick Orr, Brent Anderson, Gulrez Shah Azhar

Prepared for the United States Army
Approved for public release; distribution unlimited
Preface

This report documents research and analysis conducted as part of a project entitled *Facilitating the Seventh Department of Defense State of the Science Meeting for Blast Injury Research*, sponsored by the U.S. Army Medical Research and Materiel Command. The purpose of the project was to facilitate the convening of the Seventh Department of Defense State-of-the-Science Meeting for Blast Injury.

This research was conducted within RAND Arroyo Center’s Personnel, Training, and Health Program. RAND Arroyo Center, part of the RAND Corporation, is a federally funded research and development center (FFRDC) sponsored by the United States Army.

RAND operates under a “Federal-Wide Assurance” (FWA00003425) and complies with the *Code of Federal Regulations for the Protection of Human Subjects Under United States Law* (45 CFR 46), also known as “the Common Rule,” as well as with the implementation guidance set forth in DoD Instruction 3216.02. As applicable, this compliance includes reviews and approvals by RAND’s Institutional Review Board (the Human Subjects Protection Committee) and by the U.S. Army. The views of sources utilized in this study are solely their own and do not represent the official policy or position of DoD or the U.S. Government.
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Summary

This report details the state of the science regarding the relationship between occupational exposure to low-level blasts and nervous system problems in military service members. This literature review was completed as part of the 2017 State of the Science (SoS) Meeting sponsored by the United States Department of Defense (DoD) Blast Injury Research Program Coordinating Office. The goal of the SoS and its associated processes is to identify what is known and not known pertaining to key blast injury–related topics and emerging issues. The topic of the 7th SoS as well as this supporting literature review is “The Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast: Implications for Health and Prevention.”

Over the past decade, awareness of the central nervous system (CNS) effects of explosive blast exposure has increased. A key driver of that awareness has been the blast-related injuries suffered by service members during combat operations in Iraq and Afghanistan. As U.S. combat operations in these regions have largely come to a close, there has been growing concern over repetitive forms of blast exposure during military service that is, most often, unrelated to combat. Examples of these forms of exposure include exposure to weapon systems, such as “recoilless” rifles and shoulder-launched rocket launchers (e.g., the Carl Gustav antitank weapon), that can produce more than one blast exposure per round. The repeated exposure to these low-level blasts raises new questions of effects on CNS structure and function and on the health of those service members who have been exposed to repeated discharges. The literature review that follows has targeted the scientific literature pertaining to the effects of repeated military occupational blast exposures, specifically exploring what is known regarding the broad nervous system consequences of these exposures. For this review, military occupational blast (MOB) was defined as low-level repeated blast exposures that do not result in immediate loss of consciousness (LoC) and often may not even involve acute alteration of consciousness (AoC), and that have potential neurological health implications. Either LoC or AoC are prerequisites for mild traumatic brain injury (mTBI) and therefore, this report is focused mainly on sub-mTBI (i.e., subconcussive) blast exposure. The literature review addressed the following research questions:

1. What is known about the occurrence of repeated low-level occupational blast exposure incurred during military service?
2. What is the scientific evidence relating to the potential neurological health effects of repeated low-level occupational blast exposure?
3. What are promising strategies for preventing the potential neurological effects of repeated low-level military occupational blast exposure?
4. What are promising early detection indicators for the potential neurological consequences of repeated low-level military occupational blast exposure?
Methods

We sought to review related studies to help us better understand short-, intermediate-, and long-term neurological outcomes associated with repeat low-level MOB exposure. Outcomes of importance that are considered in this review include functional status, physical and emotional symptoms, neuropsychological outcomes, theoretically plausible biomarkers, and clinical injuries and illnesses. Human studies to date largely address samples exposed to blast during combat, making it difficult to parse primary blast exposure effects of repeated low-level MOB (i.e., injury due to the blast overpressure wave) from secondary and tertiary blast injury effects (i.e., penetrating injury from blast fragments and blunt force injury when thrown by a blast, respectively). These studies were observational, with blast exposure assessed by self-report often months or years later. Animal studies offer the important advantages of experimental design for causal inference and the capacity to isolate some effects of blast overpressure exposure, so it was decided to include animal studies that evaluated primary blast exposures of 20 psi or less. The research team was aware of concerns regarding interspecies variation in blast effects, challenges correlating level of blast in animals to those in humans, limitations of evidence gleaned from laboratory paradigms designed to model concussive rather than subconcussive blast exposures in animals (i.e., “shock tube” methods), interlaboratory variation in procedures (e.g., position, single versus multiple exposures) and measurements, and variation as to whether exposure paradigms include multiple low-level blasts or a single blast exposure. However, to address questions of biological plausibility, it was decided to include appropriate experimental animal evidence.

A three-step process was used to develop search terms. First, potential search terms were identified from previous DoD Blast Injury Research State-of-the-Science (SoS) Literature Reviews, terms specifically relevant to the 7th SoS topic, and related National Library of Medicine Medical Subject Headings. Second, a preliminary literature search was performed and the results used to improve the search strategy. Third, the SoS Planning Committee, a group of experts from fields related to the 7th SoS topic, reviewed the search terms and recommended additional terms and search modifications. We then used a five-step process to produce this literature review: (1) definition of key questions, (2) literature search, (3) title and abstract and full text screening, (4) data abstraction, and (5) analysis. We searched peer-reviewed and gray literature that described the nature and effect of routinely incurring low-levels of MOB, including peer-reviewed scientific literature dating from 2007 to 2017, in PubMed, Web of Science, and PsycINFO, and research reports and proposals on the Defense Technical Information Center (DTIC). Additional relevant publications were identified from bibliographies of identified articles, targeted searches, and planning committee recommendations. Eligible studies included related human and animal studies and bioengineering models. This search yielded 369 full-text articles, of which 74 met inclusion criteria and were included in this review. Of these 74 articles, 28 were animal studies, 25 were human studies, and the remainder were reviews, bioengineering simulations, or medical news reports.

Of the 53 human and animal studies, 23 were longitudinal (i.e., followed subjects for 24 hours or longer). Only six followed subjects for longer than three months (three animal studies and three human studies). There was wide variation within both animal and human studies in subjects sampled, the assessments and study methods employed, and the outcomes assessed, making it difficult to reliably identify any replicated studies.
Key Findings

Occurrence of Low-Level MOB Exposure
The research team identified no research on the overall military population frequency of low-level MOB exposure. Five published studies evaluated military breachers—personnel who use explosives in the operational or training environment to gain rapid entry into buildings or across hard walls or structures after repeated low-level blast exposure. None of those studies combined appropriate controls, procedures to account for potential confounding, or a significant positive relationship of low-level MOB exposure to an outcome. One study found microhemorrhages in the brains and meninges of rats and pigs after experimental exposure to shoulder-mounted artillery weapon— and howitzer launcher—generated blast overpressure. There are no identified guidelines or models from which to determine what constitutes a safe level of repeated MOB exposure for the low levels often incurred in training or analogous settings.

Potential Neurologic Effects of Low-Level MOB

Motor Effects
None of the human or animal studies identified specifically looked for or identified motor effects of repeated low-level MOB exposure.

Neurosensory Effects
None of the human studies specifically sought or revealed neurosensory effects of repeated low-level MOB exposure. One study of rats exposed to low-level blast found increased expression of the pain mediator transient receptor potential vanilloid 1 in corneal tissue.

Cognition Effects
We identified two human studies of repeated low-level MOB exposure, neither of which found cognitive effects. However, six animal studies looked for cognitive effects of low-level MOB exposure; all of those showed a positive relationship, which suggests the cognitive domain may be particularly sensitive to low-level blast exposure. In these animal studies, blast exposures ranging from three to ten psi were associated with reduced learning or cognition, with measurable effects persisting up to 30 days.

Neuropathologic Effects
None of the human studies addressed—based on our definition—specific neuropathology related to repeated low-level MOB exposure. Published studies have focused exclusively on combat samples with higher-level blast exposures. Ten of 11 studies in rodents (rats and mice) found evidence of neuropathological changes after low-level blast exposure. Findings from these studies include evidence of increased permeability of the blood-brain barrier on magnetic resonance imaging; increases in fractional anisotropy; decrease in radial diffusivity on diffusion tensor imaging; changes to the cortex and hippocampus; white-matter changes, including greater amyloid precursor protein immunoreactive cells; chronic microvascular changes; scattered pyknotic neurons; altered gene expression; dynamic microglial and macrophage responses; microdomains of brain microvessel dysfunction; and other findings.

Given the substantial interspecies neuroanatomical and cranial differences between rodents and humans, the extent to which such findings in rodents may be generalized to
humans is unclear. However, the findings provide evidence that neuropathology in humans related to repeated low-level MOB exposure is plausible. Future animal studies should assess for similar effects in large animals, including nonhuman primates.

**Behavioral and Emotional Effects**

Human studies, mainly cross-sectional, have suggested that behavioral and emotional symptoms following blast-related traumatic brain injury (TBI) may be largely explained by coexisting posttraumatic stress disorder (PTSD) and depression. Cross-sectional studies suggest that blast exposure may increase PTSD arousal symptoms (e.g., hypervigilance). The interplay between PTSD and TBI is complex. Blast exposure in anesthetized animals is associated with PTSD-like manifestations, leading some researchers to hypothesize that the primary injury is not psychological but instead due to direct blast exposure effects, resulting in reduced frontal lobe inhibition of the amygdala, a center of fear expression previously implicated in PTSD and the psychological threat response.

**Auditory and Vestibular Effects**

It has long been known that blast exposures during military service can lead to sensorineural hearing loss. Three human studies looked for an association between blast exposure and auditory or vestibular impairments and symptoms in combat-deployed service members. Not surprisingly, all were positive. One study of 573 previously deployed service members with mTBI found a dose-response link between member-reported blast exposures and member-reported hearing loss and tinnitus. A crossover study found that low-level blast exposure from small-caliber arms fire, even while wearing fitted earplugs (adherence to earplug use was not described), affected middle-ear function and was associated with transient tinnitus. No related animal studies were identified.

**Visual Effects**

Closed-globe eye injuries are known to occur from combat-related blast exposure, although these injuries typically occur at higher blast-exposure levels than those that are the focus of this review. No human studies assessing or revealing eye effects of low-level MOB exposure were identified. A single animal study assessed the eye effects of single and repeated low-level blast exposures and found increased pain and inflammation in corneal tissue.

**Early Exposure Indicators**

Studies in animals and humans have examined a variety of different biomarkers with inconsistent findings to date. Preliminary studies of biosensors to monitor troops for the concussive effects of blast exposure have so far proven disappointing, and we found no studies that used biosensor data to assess subconcussive blast.

**Potential Prevention Methods**

Several preventive methods are addressed, including barrier and non-barrier methods and safety guidelines. Research on barrier methods has included helmets, earplugs, and body armor. Helmets (e.g., Advanced Combat Helmet), are typically designed to protect the wearer from head
trauma due to projectiles rather than blast exposure and may sometimes even amplify blast exposure. Earplugs are the most effective barrier protection from hearing-related blast exposure injury. The limited research on non-barrier prevention methods suggest that education programs may increase the use of hearing protection.

Conclusions

**What Is Known About the Occurrence of Repeated Occupational Blast Exposure Incurred During Military Service?**

We found no published information regarding military service–specific frequencies of exposure to low-level MOB. The only available information pertains to higher levels of blast exposure that is encountered in combat settings.

**What Is the Scientific Evidence Relating to the Potential Neurological Health Effects of Repeated Occupational Blast Exposure?**

Experimental studies in animals suggest that persistent neurological effects from low-level blast exposure (i.e., under 10 psi) are plausible. However, interspecies differences in exposure susceptibility may be large, and there have been no experimental studies of low-level blast exposure effects in nonhuman primates. There remains significant uncertainty as to how low-level blast-exposure effects observed in animal studies translate to humans.

Epidemiological and clinical studies of military personnel provide sufficient evidence of an association between combat-related blast exposure without penetrating injury, postconcussive syndrome (PCS), and PTSD. However, these blast-exposure levels are higher than the subconcussive exposures of interest in this review, which are blast exposures of a level occurring during routine field training, breaching, artillery fire, and shoulder-mounted weapons discharge. Moreover, the precise nature of the relationship between PCS and PTSD remains unclear—it is possible that nonspecific symptoms of PTSD may explain apparent associations between mTBI and PCS. Similarly, mTBI may have effects on the amygdala that mimic PTSD-like symptoms or result in increased vulnerability to PTSD. However, the relevance of this discussion to repeated low-level MOB exposure is not known.

**What Are Promising Strategies for Preventing the Potential Neurological Effects of Repeated Military Occupational Blast Exposure?**

Prevention programs targeting health risks that do not exist or implementing preventive methods that are not effective are clearly an unnecessary waste of societal resources—resources that presumably can be put to more productive use. Therefore, the relevance of discussion regarding prevention strategies depends on the answers to the following key questions that, at present, remain largely unanswered:

- **Is repeated low-level MOB exposure a significant risk to current and future force health?** There should be consensus, ideally based on empirical data, that the threat of MOB to health is significant before resources are devoted to preventing the health effects of such exposure.
- **Are current preventive interventions safe and effective?** Even if the problem is substantial, ineffective primary prevention approaches will prove wasteful.
• Will preventive intervention benefits outweigh the harms? If a preventive intervention is effective but renders the population vulnerable to more-serious threats, then its implementation would be self-defeating.

• Is the preventive intervention timely and feasible? If the preventive intervention is perfectly effective but cannot be delivered in time, it is not useful. There are any number of related factors to consider here: the availability of relevant material and staffing, and the acceptability of the intervention for leaders, service members, and society at large.

Given the early state of research into repeated low-level MOB exposure as a problem distinct from blast-related TBI, we recommend a cautious approach that would complete research into the effects of preventive intervention development and testing before implementing aggressive surveillance and prevention programs specifically targeting low-level MOB exposure.

We are not suggesting the abandonment of current protective measures against high-intensity combat blast injuries (e.g., mild, moderate, and severe TBI). However, as it pertains to low-level MOB exposure, the state of the science is preliminary at best. Implementing aggressive preventive programs against this threat without adequate evidence of preventable injury risks the consumption of considerable resources without commensurate benefit and may have adverse, unanticipated, and unintended consequences.

What Are Promising Early Detection Indicators for the Potential Neurological Consequences of Repeated Military Occupational Blast Exposure?

The research team was unable to identify early detection biomarkers, a key type of early detection indicator, in humans. Even candidate biomarkers remain highly speculative and less than feasible, as they are almost exclusively the product of rat and mouse studies. Biosensors are a second key indicator, but we were similarly unable to identify published biosensor studies designed to assess the health effects of low-level MOB exposure. The development and validation of improved human biosensor systems and methods of using human biosensor data to model the physiologic and physical effects of low-level MOB exposure on human tissue should be prioritized and pursued. Biosensor data is a potentially low-burden method for modeling low-level MOB exposure for use in prospective cohort research designs.

Recommendations

Perhaps the most-striking finding from this review of the literature is how little research has been done to determine the organizational threat and service member health impact of low-level MOB exposure, in contrast with our rapidly improving empirical research base relating to blast-related traumatic (concussive) brain injury. The 2018 National Defense Authorization Act mandated the design, initiation, and completion of a prospective longitudinal cohort study of low-level MOB exposure in a population-based sample of service members, and this study is one opportunity to improve understanding of repeated low-level MOB exposure. Our recommendations center on the need to improve this understanding through a coordinated program of epidemiologic, etiologic, measurement, and preventive intervention research. Organization-wide efforts to implement population exposure surveillance are more likely to be ineffective if implemented before the neurological effects of low-level MOB exposure are better characterized.
Acknowledgments

We gratefully acknowledge Michael Leggieri, Raj Gupta, and Colonel Sidney Hinds of the Blast Injury Research Program Project Coordinating Office (PCO) for their comments, guidance, and support of this project. We also wish to recognize the extensive work that PCO had done prior to our involvement, refining the State-of-the-Science Meeting process from which this literature review has emerged, a process they have used to develop U.S. Department of Defense research policy and priorities related to blast injury since 2009.

We would also like to thank the stakeholders consulted on topic selection and the planning committee who provided invaluable guidance preparing for the 7th DoD State-of-the-Science Meeting and for this literature review.

At RAND, we wish to thank Jody Larkin and Elizabeth Hammes for their help with the literature search, Shanthi Nataraj for her thoughtful and timely consultation and support, and Kristin Sereyko for her hard work and project assistance.

We appreciate the valuable insights we received from our technical reviewers: Melinda Moore of RAND, and Gregory Elder of the James J. Peters VA Medical Center. We addressed their constructive critiques as part of RAND’s rigorous quality assurance process to improve the quality of this report.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACH</td>
<td>Advanced Combat Helmet</td>
</tr>
<tr>
<td>ANAM</td>
<td>Automated Neuropsychological Assessment Metrics</td>
</tr>
<tr>
<td>AoC</td>
<td>alteration of consciousness</td>
</tr>
<tr>
<td>BBB</td>
<td>blood-brain barrier</td>
</tr>
<tr>
<td>CGRP</td>
<td>calcitonin gene-related peptide</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DoD</td>
<td>U.S. Department of Defense</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>DTIC</td>
<td>Defense Technical Information Center</td>
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<tr>
<td>ET-1</td>
<td>endothelin-1</td>
</tr>
<tr>
<td>FA</td>
<td>fractional anisotropy</td>
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<tr>
<td>LoC</td>
<td>loss of consciousness</td>
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<tr>
<td>MOB</td>
<td>Military Occupational Blast</td>
</tr>
<tr>
<td>mTBI</td>
<td>Mild Traumatic Brain Injury</td>
</tr>
<tr>
<td>OEF</td>
<td>Operation Enduring Freedom</td>
</tr>
<tr>
<td>OIF</td>
<td>Operation Iraqi Freedom</td>
</tr>
<tr>
<td>OND</td>
<td>Operation New Dawn</td>
</tr>
<tr>
<td>PCO</td>
<td>Blast Injury Research Program Coordinating Office</td>
</tr>
<tr>
<td>PCS</td>
<td>postconcussive syndrome</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
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<tr>
<td>SoS</td>
<td>State of the Science</td>
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<tr>
<td>SP</td>
<td>Substance P</td>
</tr>
<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
</tr>
<tr>
<td>TRPV1</td>
<td>transient receptor potential vanilloid 1</td>
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Over the past decade, there has been increasing awareness of the central nervous system (CNS) effects of exposure to explosive blast. A key driver of that awareness has been the blast-related injuries suffered during combat operations in Iraq and Afghanistan (Mac Donald et al., 2011; Miller, 2012). With the relative cessation of U.S. combat operations in these regions, concern has grown over common, repetitive forms of blast exposure during military service that are, most often, unrelated to combat. Examples of these exposures include heavy weapons, such as firing artillery, recoilless rifles, and shoulder-launched rocket launchers (e.g., the Carl Gustav antitank weapon) (Hamilton, 2017). These blast exposures are of much lower intensity than those causing recognized combat-related injuries; however, becoming proficient with these heavy weapon systems may require repeated exposure. Repeated exposure scenarios raise new questions concerning the potential for effects on CNS structure, function, and subsequent development, as well as on the broader health of the service members exposed.

As awareness of the potential effects of exposure to explosive blast increases, there has been extensive study and ongoing discussion of the neurological, neurocognitive, and emotional consequences of mild traumatic brain injury (mTBI) (Hoge et al., 2008; Walker et al., 2017), but the blast exposures of interest in this report are different in both magnitude and type. At the time of exposure, mTBI is marked either by brief alterations in consciousness (AoC) (seeing stars, having one’s “bell rung”) or a loss of consciousness (LoC), with the latter lasting up to 30 minutes (Management of Concussion-mild Traumatic Brain Injury Working Group, 2016). In contrast, the low-level blast exposures that are of interest in this report do not result in LoC and seldom cause AoC. Furthermore, most research on mTBI to date has focused on injury due to blunt-force trauma (i.e., a physical blow to the head) rather than to blast exposure, and research demonstrates that blast-induced brain injury may be different from blunt-force trauma (Fischer et al., 2014).

The literature review that follows has therefore targeted the scientific literature pertaining to the effects of repeated, military occupational blast exposures, specifically exploring what is known regarding the nervous system consequences of these exposures. For the purpose of this review, military occupational blast (MOB) is defined as low-level blasts that military members are exposed to through occupational situations that do not result in immediate LoC and may not involve acute AoC or apparent symptoms. Exposure to MOB has the potential to have health or safety implications.
Purpose of the Review

The purpose of this literature review is to support the U.S. Department of Defense (DoD) Blast Injury Research Program Coordinating Office (PCO)—sponsored Seventh DoD State-of-the-Science (SoS) Meeting. The goal of the SoS and its associated processes is to identify what is known and not known pertaining to key blast injury–related topics and emerging issues. The topic of the 7th SoS as well as this supporting literature review is “The Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast: Implications for Health and Prevention.”

To inform the 7th SoS, the PCO requested a literature review regarding the broad neurological and neurocognitive effects of repeated exposure to military occupational levels of blast and their implications for health and prevention. This review focuses on scientific evidence from medical, physiological, bioengineering, and health policy studies. In this review, our research team addressed the following questions:

1. What is known about the occurrence of repeated occupational blast exposure incurred during military service?
2. What is the scientific evidence relating to the potential neurological health effects of repeated occupational blast exposure?
3. What are promising strategies for preventing the potential neurological effects of repeated MOB exposure?
4. What are promising early detection indicators for the potential neurological consequences of repeated MOB exposure?

In reviewing the literature, we also sought to prioritize key research and policy gaps related to repeated MOB exposure, and examine the projects and initiatives that attempt to address them.

Blast Exposures of Interest

Blast exposures can cause injury via primary, secondary, tertiary, quaternary, or quinary mechanisms. Primary blast exposure injuries involve tissue damage that occurs directly from the shock of the overpressure wave colliding with the body. Secondary blast exposure injuries are those produced by fragments from the exploding device, or secondary projectiles from the environment (e.g., debris, vehicle fragments). Tertiary blast exposure injuries result from blast-related displacement of body parts that strike other objects, causing a variety of injury types (e.g., blunt, avulsion, crush). Quaternary and quinary blast exposure injuries result from other explosive products or the clinical consequences of environmental contaminants (e.g., biologicals, radiation, released fuels), respectively. The magnitude of the blast exposures of interest in this literature review are exposures that do not result in LoC or AoC.
Outcomes of Interest

We sought to review studies to help us better understand outcomes in the short (one day to three months following exposure), intermediate (three to nine months following exposure), and long terms (ten months or more after exposure). Outcomes of importance considered here included functional status, physical and emotional symptoms, neuropsychological outcomes, theoretically plausible biomarkers, and clinical injuries and illnesses.
We used a five-step process to conduct this literature review: (1) definition of key questions, (2) literature search, (3) title abstract and full text screening, (4) data abstraction, and (5) analysis.

**Key Questions**

The central review questions were: What are the neurological effects of repeated exposure to military occupational levels of blast? What are the implications for health and prevention? From these questions, our research team established the following four subquestions:

1. What is known about the occurrence of repeated occupational blast exposure incurred during military service?
2. What is the scientific evidence relating to the potential neurological health effects of repeated occupational blast exposure?
3. What are promising strategies for preventing the potential neurological effects of repeated military occupational blast exposure?
4. What are promising early detection indicators for the potential neurological consequences of repeated military occupational blast exposure?

**Literature Search**

We searched peer-reviewed and gray literature that described the nature and effect of routinely incurring low levels of blast exposures in training and in theater. We searched the peer-reviewed scientific literature on PubMed, Web of Science, and PsycINFO, and the DoD grey literature on Defense Technical Information Center (DTIC) dating back to 2007. This ten-year time horizon was selected for consistency with previous SoS literature-review search criteria.

A three-step process was used to develop search terms. First, with the help of a RAND Corporation Knowledge Services librarian, potential search terms were identified from previous SoS reports, terms specifically relevant to the 7th SoS topic, and related Medline medical subject headings. Second, a preliminary literature search was performed and its results used to improve the initial search strategy. Third, the SoS planning committee reviewed the search terms and recommended additional terms. Search terms are in Table 2.1.
<table>
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<th>Table 2.1</th>
<th>Search Terms</th>
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<tr>
<td><strong>Exposure</strong></td>
<td>Blast; brain; combat, battle; training, field training; low-level; psi; pressure, overpressure; shoulder-fired weapon; training; trauma; artillery, gun, cannon, rifle, howitzer, mortar, recoil, grenade, bomb, bazooka; Carl Gustaf / Carl Gustav</td>
</tr>
<tr>
<td><strong>Population and context</strong></td>
<td>Breachers; military, Army, Navy, Marine; occupational; deploy, deployed, deploying; infantry; Occupational Safety and Health Administration (OSHA); mining; field exercise, military exercise</td>
</tr>
<tr>
<td><strong>Strategies, interventions, and challenges</strong></td>
<td>Armor; helmet; Kevlar; goggles; detection; mitigation; prevention; protection, protective gear; mitigation; safety–field training, military, workplace, occupational; combat simulation, battle simulation</td>
</tr>
<tr>
<td><strong>Injury or outcomes</strong></td>
<td>Concuss*; disability; functional status; memory; central nervous system; ocular; auditory; headache; neuro*; lung; cerebrospinal; mental health; traumatic brain injury, mTBI; biomarker; seizure; epilepsy; posttraumatic stress disorder (PTSD); cognitive deficits; axonal injury; white matter; EEG (electroencephalogram); working memory; neuroendocrine; neuroinflammation; neurovascular; neurocognitive; neuronal</td>
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</table>
Our search yielded 3,892 citations for initial title and abstract screening. Two teams of two reviewers each screened article abstracts for human or animal research examining low-level blast exposure and its relationship to neurologic health, including hearing and vision. To achieve reliability, reviewer teams compared results, and then discussed any discordant codes between themselves and with the review team and principal investigator.

Title and abstract screening yielded 255 citations. Reference lists were screened and the SoS planning committee consulted. Targeted research team searches yielded an additional 114 full text articles (studies, clinical and safety guidelines, policy documents, other relevant grey literature, past DoD Blast Injury Research SoS Meeting literature reviews and reports). The resulting 369 full-text articles were carefully read, and prespecified inclusion and exclusion criteria were applied (see Table 3.1 and Figure 3.1). Full-text review and abstraction was completed to categorize articles by their type, target population, research design, and length of follow-up (if longitudinal information was provided). We excluded (1) human or animal studies that did not provide information regarding a blast exposure injury or a blast exposure assessment; (2) human studies that evaluated only severe blast exposure injuries (e.g., moderate or severe traumatic brain injury (TBI); mTBI but with no comparisons that excluded individuals with LoC); (3) animal studies with no experimental group receiving less than 20 psi blast exposure (see following section, Defining Low Level Blast Exposure); or (4) studies focused on pathologies outside of the scope of the review (e.g., psychiatric conditions in the absence of blast exposure injury assessments). After full text review, 74 articles met these final inclusion and exclusion criteria. Of these 74 studies, 28 were animal studies and 25 were human studies. The remainder were reviews ($n = 7$), bioengineering simulations ($n = 10$) or medical news reports ($n = 4$).

<table>
<thead>
<tr>
<th>Table 3.1</th>
<th>Literature Review Search Criteria</th>
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<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>English language articles only</td>
<td>Articles not directly addressing research questions</td>
</tr>
<tr>
<td>Articles published between 2007 and 2017 (inclusive)*</td>
<td>DTIC documents not approved for public release</td>
</tr>
<tr>
<td>Clinical and animal model studies</td>
<td></td>
</tr>
<tr>
<td>DTIC documents assigned Distribution A: Approved for public release: distribution unlimited</td>
<td></td>
</tr>
</tbody>
</table>

*Older publications were included when they were potentially critical to addressing the research questions or understanding the topic.
Of the 53 human and animal studies, 23 were longitudinal. Of the longitudinal studies, 16 studied animals (Baalman et al., 2013; Elder, Dorr, et al., 2012; Ewert et al., 2012; Gama Sosa, De Gasperi, Paulino, et al., 2013; Heldt et al., 2014; Kamnaksh et al., 2014; Luo et al., 2014; Park et al., 2011; Perez-Garcia, Gama Sosa, et al., 2016; Pun et al., 2011; Rodriguez et al., 2016; Rubovitch et al., 2011; Säljö, Bolouri, et al., 2010; Säljö, Mayorga, et al., 2011; Tweedie et al., 2013; Woods et al., 2013) and seven studied humans (Carr, Stone, et al., 2016; Haran et al., 2013; Parish et al., 2009; Shpak et al., 1993; Tate et al., 2013; Thiel, Dretsch, and Ahroon, 2015; Walker et al., 2017). Only six studies (Elder, Dorr, et al., 2012; Gama Sosa, De Gasperi, et al., 2014; Haran et al., 2013; Luo et al., 2014; Thiel, Dretsch, and Ahroon, 2015; Walker et al., 2017) followed subjects for longer than three months (three animal studies, three human studies) and only three followed subjects for longer than nine months, all of which were human studies (Haran et al., 2013; Thiel, Dretsch, and Ahroon, 2015; Walker et al., 2017). Among the longitudinal studies, both animal studies and human studies were noted to vary widely by sample, exposure methods, and assessments, as well as by outcome domains and assessments. As a result, it was difficult to clearly identify any replicated findings.

Defining Low-Level Blast Exposure

A full discussion of the biophysics of blast exposure is beyond the scope of this review. The interested reader can find a frequently cited and informative introduction in the Institute of Medicine report, *Gulf War and Health, Vol. 7: Long-Term Consequences of Traumatic Brain Injury* (Committee on Gulf War and Health, 2008). The direct physical effects of blast exposure are complex and depend on the intensity and duration of the blast, distance of an exposed object from the originating blast, and the presence of reflective barriers (e.g., nearby hard sur-
faces or enclosures) that may serve to amplify the exposure effects of a single blast event. There are important interspecies differences in the brain effects of blast exposure (Elder, Stone, and Ahlers, 2014; Säljö, Bolouri, et al., 2010). In humans, a blast exposure of 100 psi is widely considered lethal, and between 60 and 80 psi is potentially fatal. Anterograde memory deficits without neurological impairment or gross neuropathological or neurohistological changes are produced in rodents after a 5.3 to 10.8 psi shock-tube blast exposure (Säljö, Bolouri, et al., 2010). This finding is consistent with other studies suggesting that, in rats, blast exposures of up to 10.8 psi are consistent with low-level blast exposure (Ahlers et al., 2012). In contrast, blast exposures of 17 psi produced subdural hemorrhages and cortical contusions in rats (Ahlers et al., 2012), a level of neuropathology more severe that is found in neuroimaging studies of humans with mTBI. A summary of this information is shown in Table 3.2.

Therefore, in an effort to be maximally inclusive of available research evidence relevant to low-level MOB exposure, we included animal studies that assessed the effects of blast exposures up to 20 psi. It is important to note, however, that there is substantial variation across studies with regard to exposure paradigms, exposure thresholds, other blast characteristics (e.g., multiple versus single), animal species, pressure sensors, position of the animal at the time of exposure, and other laboratory-related factors that can affect blast-related exposure outcomes. However, given the inability to use experimental research designs in humans and the small number of human studies addressing low-level MOB exposures, the research team opted to include appropriate experimental animal evidence to inform questions of biological plausibility.

## Magnitude of the Problem

The research team found no generalizable military-wide or service-specific population data (or ongoing studies) from which to estimate the occurrence of repeated, low-level MOB exposure or its potential health consequences.

<table>
<thead>
<tr>
<th>Level of Blast</th>
<th>Impact on Animals or Humans</th>
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</thead>
<tbody>
<tr>
<td>3.3 psi</td>
<td>Sustained intracranial pressure increases in pigs exposed to firing of military weapons</td>
</tr>
<tr>
<td>4.4 psi</td>
<td>Sustained intracranial pressure increases detected in rats</td>
</tr>
<tr>
<td>5.1 psi</td>
<td>Positional transmission to rat brain</td>
</tr>
<tr>
<td>5.3–10.8 psi</td>
<td>Resulted in anterograde memory deficits without neuropathological or histological changes in rats</td>
</tr>
<tr>
<td>17 psi</td>
<td>Produced subdural hemorrhages and cortical contusions in rats</td>
</tr>
<tr>
<td>60 – 80 psi</td>
<td>Potentially fatal blast exposure in humans</td>
</tr>
<tr>
<td>100 psi</td>
<td>Lethal blast exposure in humans</td>
</tr>
</tbody>
</table>

SOURCES: Ahlers et al., 2012; Budde et al., 2013; Chavko et al., 2011; Säljö, Arrhéen, et al., 2008; Säljö, Bolouri, et al., 2010; Säljö, Mayorga, et al., 2011.
Incidence and Prevalence of Blast Exposure

According to the Defense Veterans Brain Injury Center, blast exposure injuries have been responsible for over 65 percent of the casualties in the ongoing conflicts in Iraq and Afghanistan (Wojcik et al., 2010). However, injury prediction models (e.g., the Bowen survivability curve) used by DoD are limited to blasts more powerful than those incurred during training. Consequently, there has been little research and few (if any) guidelines or models from which to determine what may constitute a safe number or level for the low levels of blast exposure often incurred in training or analogous settings (Teland, 2012). We identified no research on the overall frequency with which low-level MOB exposure occurs. However, there have been several studies of potentially high-risk populations, such as explosive breachers, shoulder mounted artillery operators, and military service members deployed and in training.

Studies of Breachers

Military breachers are personnel who use explosives in the operational or training environment to gain rapid entry into buildings or across hard walls or structures. Breachers are regularly exposed to subconcussive levels of blast. There have been anecdotal reports of breachers who have experienced cognitive problems and other symptoms after extensive exposure to low-level MOB. We identified five studies that investigated this issue, none of which combined appropriate controls, attempted accounting for potential confounding, and a significant positive relationship of low-level MOB exposure to an outcome. A conference abstract described a pre-post study of 31 Marine breachers without a control group for comparison. After two weeks of follow-up, most cognitive indicators showed improvements from the pre-exposure baseline, which the authors attributed to probable learning effects (Parish et al., 2009). There were no significant declines in cognitive function. Thiel and colleagues (2015) studied 12 Marine breacher trainers and compared them with a control group of 28 unexposed breacher engineers. Ten of the breachers were followed for two years—the researchers found no association between cumulative subconcussive blast exposure from routine breacher training results and persistent neurological manifestations (Thiel, Dretsch, and Ahroon, 2015).

In another study, a surveys of symptoms was administered to 135 breachers and 49 non-breachers, finding significantly higher numbers and severity of self-report symptoms among the breachers. However, results were not adjusted for important and potentially confounding variables, such as TBI history (Carr, Polejaeva, et al. 2015; Carr, Stone, et al., 2016). Yet another study compared five breacher instructors with 26 breacher students after breacher training and seven Marine controls on a broad battery of standard neurocognitive tests: the Automated Neuropsychological Assessment Metrics (ANAM) TBI battery, self-report measures (e.g., blast exposure, anxiety, depression, PTSD), and functional magnetic resonance imaging. The results did not yield clear evidence of neurological impairment in breachers or instructors (Carr, Stone, et al., 2016). Another study of 21 New Zealand breacher trainees attempted to link a number of experimental serum biomarkers of possible TBI to neurocognitive performance and self-reported symptoms before, during, and after a two-week breacher training course (Tate et al., 2013). Some biomarkers were indeed associated with symptoms, but there was no direct measurement of exposure provided from which we could link to either biomarkers or symptoms, and no control group of unexposed individuals for comparison (Tate et al., 2013). In sum, the breacher studies to date have involved small samples, resulting in limited power to detect potentially important differences and in limitations to generalizability. Carefully designed large, longitudinal studies that assess potential confounders, achieve
high follow-up rates, and use validated outcome measures are needed to better understand and describe the neurocognitive, functional, and symptom outcomes associated with this potentially high-risk occupation.

**Studies of Shoulder-Mounted Artillery Operators**

Shoulder-mounted weapons have become an increasingly powerful and important combat weapon. The blast generated from the Carl Gustav and shoulder-launched multipurpose assault weapon (SMAW) has not been quantified (Wiri et al., 2017). A single round from the Carl Gustav can weigh nearly ten pounds and is powerful enough to destroy a tank (Hamilton, 2017).

We found one study in this category. Investigators at the Swedish Sahlgrenska Academy found microhemorrhages in the brains and meninges of rats and pigs after exposure to experimental Carl Gustav– and howitzer launcher–generated blast overpressure. Subsequently, the Swedish Armed Forces are said to have restricted the number of rounds that service members can be exposed to daily (Säljö, Arrhén, et al., 2008; “Blast Overpressure Is Generated from the Firing of Weapons, and May Cause Brain Injury,” 2009). However, we found neither experimental animal studies replicating these findings nor descriptive or analytic epidemiologic studies to suggest human effects of these or similar weapons systems, and the current status of the Swedish Armed Forces policy is uncertain.

**Combat Settings**

Combat-related health issues have been described expansively in the literature. However, our research team found no data regarding repeated combat exposures to low-level MOB. Studies have shown that combat exposure to concussive blast is associated with sensory symptoms, including complaints of hearing loss and tinnitus (Reid et al., 2014) and poorer cognitive performance (Haran et al., 2013). However, we did not identify any epidemiologic studies that specifically evaluated the health effects of low-level MOB exposures during combat.

**Other Occupations or Informative Analogues**

The research team expanded its search from military and biomedical resources to include occupational safety, labor, physics, and engineering literature. We sought to learn from the mining and construction industries, which interact with small blast ordnances on a routine basis. While there are likely many parallels, the literature reviewed in this section emphasized pulmonary, dermatologic, and other morbidities associated with inhalation of toxic particulates, instead of the cumulative neurological effects of blast exposure.

**Potential Neurological Consequences and Mechanisms**

**Motor Effects**

None of the human or animal studies identified specifically looked for or identified motor effects of repeated low-level MOB exposure.

**Neurosensory Effects**

None of the human studies specifically sought or revealed neurosensory effects of repeated low-level MOB exposure. One study of rat corneal tissue found that exposure to both single
and repeated low-level blast was associated with increased transient receptor potential vanilloid 1 (TRPV1) expression (Por, Choi, and Lund, 2016). TRPV1 has a role in mediating various types of pain, and it is expressed on small, unmyelinated sensory neurons in the trigeminal ganglia.

**Cognition Effects**

Two human studies evaluated neurocognitive effects of repeated low-level MOB exposure, both negative studies of breachers (Parish et al., 2009; Tate et al., 2013). Two other studies looked at cognitive effects in samples that contained service members with mixed concussive and subconcussive blast exposure. Haran and colleagues (2013) analyzed longitudinal ANAM test data from 169 recently deployed, highly combat-exposed marines. Many reported concussions, and concussion was associated with measurable decreases in cognitive performance 2–8 weeks after deployment. Following up with the subjects after eight months, postconcussive symptoms persisted, but measurable cognitive deficits had resolved (Haran et al., 2013). A review of the cognitive construct assessments from nine studies (12 groups) involving 1,154 participants with more severe repeated combat blast–related mTBI—50 percent reported associated LoC (Karr, Areshenkoff, and Garcia-Barrera, 2014) — found that executive function, verbal delayed memory, and processing speed were the most-sensitive cognitive domains to blast-related TBI, and that observed associations were not explained by PTSD symptom severity. All of the studies in this review were cross-sectional and received low quality ratings. The average participant was assessed an average of 3.8 years after the event (a factor plaguing the vast majority of military and veteran studies of mTBI from any cause to date). The findings, however, suggest that cognitive effects of low-level, repeated MOB exposure are plausible and may not be explainable by concurrent PTSD.

We identified six animal studies that investigated low-level blast exposure, all of which revealed positive findings. Studies exposing rats to repeated low-level blast have found anterograde memory deficits on a passive avoidance task at 10.8 psi, and transient learning deficits in a water-maze task after 5.3 psi blast exposures (Ahlers et al., 2012); memory deficits in a water maze persisting through to a 30-day follow-up after exposure to a single 14.5 psi blast (Budde et al., 2013); and impaired memory on a novel-object recognition task after a single exposure to 10.7 psi (Baalman et al., 2013). A study of mice found impaired object recognition after multiple 2-psi blast exposures paired with 100 decibel noise (Xie, Kuang, and Tsien, 2013); impaired memory on novel-object recognition and Y-maze for 30 days after a single 5.5-psi blast exposure (Rubovitch et al., 2011); and impaired memory on novel-object recognition but not Y-maze or passive avoidance at 30 days after a single 2.5-psi blast exposure (Tweedie et al., 2013). Though it is unclear how such findings may translate to humans, these studies suggest that it is plausible that there would be cognitive effects after repeated, low-level MOB exposure. Studies in large animals, with a longer period of follow-up, are needed.

**Neuropathology Effects**

None of the 25 human studies we reviewed looked for neuropathologic changes after low-level MOB exposure. However, eleven animal studies investigated neuropathological changes after exposure to low-level blast exposure, and all but one (Elder, Stone, and Ahlers, 2014) found changes. An anatomy-based region-of-interest analysis using diffusion tensor imaging (DTI) to study rat brains (Kamnakh et al., 2014) found significant interactions in axial and radial diffusivity in a number of subcortical structures after single and multiple 19.9-psi blast expo-
sures. Multiple (versus single) exposed rats were associated with thalamic (but not hippocampal) changes. In rats two weeks after a single 10.7-psi blast exposure, Baalman and colleagues (2013) found little or no changes in cerebral cortex, corpus callosum, and hippocampus injury markers, though in the blast-exposed animals there was significant shortening of axon initial segments in the hippocampus and cortex. Another study found evidence of white-matter damage and minimal cell death, localized mainly in the corpus callosum and periventricular regions in rats after a 1.7-psi blast exposure (Park et al., 2011). There was also evidence of shear lesions in rats, and chronic changes in the microvasculature were evident several months after exposure to both single and multiple 10.8-psi blasts (Gama Sosa, De Gasperi, et al., 2014). Another study found an increase of intracranial pressure several hours after low-level (4.4- or 8.7-psi) exposure to a single blast (Säljö, Bolouri, et al., 2010). Scattered pyknotic neurons have also been found in the rat cortex after exposure to two blasts of 2.9 psi (Moochhala et al., 2004; Pun et al. 2011). Altered gene expression in over 5,700 genes, as well as greater amyloid precursor protein immunoreactive cells in white matter, was also observed following a single low-level blast exposure (Pun et al., 2011). Finally, decreases in fractional anisotropy (FA) have also been observed in brains that were exposed to a single low-level blast exposure (Budde et al., 2013).

Among mouse models, one study found increased ganglioside and depleted ceramide in the hippocampus, thalamus, and hypothalamus associated with low-level blast exposure (Woods et al., 2013). Researchers also observed an increase in blood-brain barrier (BBB) permeability one-month post-single low-level blast exposure on MRI (Rubovitch et al., 2011). While DTI showed an increase in FA and a decrease in radial diffusivity, these changes may represent brain axonal and myelin abnormalities. Other studies using mouse models reported acute subcortical changes after mild blast-induced TBI, with both single and multiple blast exposures (Kamnaksh et al., 2014). Finally, a robust astrogliosis and increased p-Tau immunoreactivity was observed upon post-mortem pathological examinations of mice after low-level blast exposure (Luo et al., 2014). Interestingly, one mouse model explored the differences in blunt-force trauma mTBI and blast-related mTBI and found them to be distinct, in that pathways that lead to Alzheimer’s disease are up-regulated in blunt-force-trauma injury and down-regulated in blast injury (Tweedie et al., 2013). Finally, researchers found single low-level blast exposure caused dynamic microglial and macrophage responses and microdomains of brain microvessel dysfunction among mice (Huber et al., 2016). They also argue that mild blast exposure causes an evolving CNS insult that is initiated by discrete disturbances of vascular function. Both of these conditions set the stage for more-protracted and more-widespread neuroinflammatory responses.

Given substantial interspecies neuroanatomical and cranial differences between rodents and humans, the extent to which such findings in rodents may be generalized to humans is unclear. However, the findings provide evidence that neuropathology in humans, related to repeated low-level MOB exposure, is plausible. Future animal studies should assess for the neuropathological effects of low-level blast exposure in large animals, including nonhuman primates.

### Behavioral and Emotional Effects

Four human studies that we reviewed assessed behavioral and emotional issues related to mixed samples of concussive and other blast exposures. Studies of blast-related mTBI suggest that blast exposure may be associated with a myriad of symptoms, both behavioral and emotional
Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast (e.g., PTSD, depression, anxiety) and physical (including those symptoms we think of most classically as “neurological” symptoms, such as headache, dizziness, memory problems, confusion, and nausea) (Hoge et al., 2008; Wilk et al., 2012). These studies suggest that mental and physical symptoms are elevated in blast-related mTBI, though to a lesser degree, even in the absence of a precipitating head injury with LoC (Hoge et al., 2008; Wilk et al., 2012). A possibility that both of these studies raise is that postconcussive symptoms are epiphenomena of PTSD and depression. Macera et al. (2012), however, investigated the co-occurrence of mTBI and PTSD and found that blast-related TBIs worsen the self-report of symptoms that overlap with PTSD, such as irritability (Macera et al., 2012). Likewise, Toyinbo et al. (2017) conducted an online survey and found that blast exposure, not mTBI per se, was associated with greater PTSD arousal symptoms and tinnitus (Toyinbo et al., 2017) and mTBI diagnosis alone was not significantly associated with an increase in other PTSD symptoms (Toyinbo et al., 2017). Unfortunately, however, we identified no human studies that isolated the effects of low-level MOB exposure on behavioral and emotional problems.

While it is tempting to view blast-related TBI and PTSD as distinct disorders, Elder, Stone, and Ahlers (2014) have offered a provocative model in which blast exposure may unmask a vulnerability to PTSD-related symptoms. In this model, blast-related TBI may reduce frontal cortical inhibition of the amygdala, a center of fear expression thought to heighten responses to psychological threats, which is implicated in PTSD development. For example, the same research team found that a blast-exposed rat, many months after the blast exposure, develops new traits that weren’t there before the exposure when exposed to a predator scent (a psychological stressor). They argue that an initial blast exposure may predispose individuals to develop PTSD in response to a subsequent psychological stressor. This can be seen as further support for blast exposure affecting the biological substrates that underlie PTSD (Perez-Garcia, Gama Sosa, et al., 2016). In a separate study, the authors showed that these PTSD-related symptoms were often present many months after blast exposure, and that these symptoms could be reversed with the medication BCI-838, which is currently under review for use in humans for depression and suicidality, and has been shown to have antidepressant effects in animals (Perez-Garcia, De Gasperi, et al., 2018).

Studies of animals exposed to a low-level blast also offer valuable insight into the potential association of behavioral symptoms and low-level MOB exposure. We identified five animal studies that investigated this issue, all of which had positive results. Rat and mouse exposure to a single low-level blast was associated with a decreased preference for novel objects (Rubovitch et al., 2011; Baalman et al., 2013; Tweedie et al., 2013), and multiple and single exposures were associated with increased anxiety, enhanced learned-fear response, and intensified acoustic startle, though in most of these studies the animals are never aware of a blast-induced traumatic stressor because they are anesthetized (Elder, Dorr, et al., 2012; Heldt et al., 2014). This may lend support for Elder and colleagues’ frontal lobe-amygdala fear-disinhibition hypothesis.

Auditory and Vestibular Effects

It has long been known that military populations are exposed to a multitude of compounding risks for auditory impairment, potentially leading to inner-ear and cochlear injuries (e.g., blast wave and noise exposure), middle-ear injuries (e.g., tympanic membrane perforation, ossicular disruption), outer-ear injuries (e.g., burns, flying debris), and chronic tinnitus (“ringing of the ears”) (Fausti et al., 2009). We identified three studies of blast exposure on the auditory and vestibular system in humans, and perhaps not surprisingly, all of them yielded positive
findings. One study of 573 previously deployed service members with mTBI found a dose-response relationship between higher levels of service member–reported combat-blast exposure and service member–reported hearing loss and tinnitus (Reid et al., 2014). Using a crossover design, researchers found that exposure to repeated low-level blasts from small-caliber firearms affected middle-ear function and was associated with subsequent report of transient tinnitus, even when wearing fitted earplugs, though adherence to earplug use was not reported. They concluded that exposure to small-caliber firearms may play a role in the early stages of auditory fatigue and eventual hearing loss (Job et al., 2016). The vestibular system helps to maintain balance and postural stability and has the potential to be impacted by repeated exposure to low-level blasts, though these effects are not well understood. The third study described five Israeli soldiers exposed to blast but who did not experience head trauma, LoC, or amnesia. Three reported vertigo, four had hearing loss, four suffered from tinnitus, and one had otalgia (Shupak et al., 1993).

**Visual Effects**
There were no human studies found of eye effects of low-level MOB exposure. Closed-globe eye injuries are known to occur from combat-related blast exposure, though these injuries typically occur at higher blast-exposure levels than are the focus of this review. We found one animal study on the eye effects of low-level blast exposure and it yielded positive findings. Por and colleagues (2016) found that both single and repeated 9.9-psi blast exposures led to increased pain and inflammation markers in the corneal tissue of rats.

**Potential Early Indicators of Low-Level MOB Exposure**
There are significant disadvantages associated with measuring low-level MOB exposure. There are few currently available methods, and Table 3.3 describes their advantages and disadvantages. Most of these assessment methods involve a significant burden for service members or the military unit. None of the methods are supported by published assessments of validity, reliability, adherence, or feasibility for assessing low-level MOB exposure.

One promising way to detect low-level MOB exposure may be through biomarkers and sensors. An accurate, reliable, and lightweight biosensor could offer objective, real-time assessment of exposure with minimal distraction to service members and military units. We identified three biosensor studies, none of which suggested that biosensors were effective for their intended purpose. One of these was an unpublished study suggesting the biosensors were insufficiently sensitive or specific for surveillance of combat blast–related TBI (Department of Defense Blast Injury Research Program Coordinating Office, 2014). These preliminary data suggest that there may be insufficient standardization of available biosensors for assessing low-level MOB exposure.

The Defense Advanced Research Projects Agency (DARPA) funded the development of the Blast Gauge System, which is a three-piece sensor system designed to record overpressure exposure levels in the battlefield. While the sensor technology may be adequate, a major challenge in this field is the absence of a feasible way to link sensor data to blast exposure injury. Panzer et al. (2012) demonstrated that in individuals with severe non-MOB blast-induced TBI, injury tolerance decreased with each exposure. Individual differences in overpressure-exposure thresholds to injury may present difficulties in the development of a general guideline for over-
Neurological Effects of Repeated Exposure to Military Occupational Levels of Blast pressure exposure limit and frequency (Panzer et al. 2012). Second, Courtney and Courtney (2011) identified that such thresholds are subject to blast exposure conditions and that a blast exposure can induce brain injury through multiple simultaneous mechanisms. This indicates that how an exposure event occurred (blast-specific) affects injury, and that relationship may need to be quantified. Finally, McEntire et al. (2010) showed that helmet-mounted sensors do not measure the overpressure that the head experiences during a blast. Their experimental data revealed that the head may experience vastly different forces, despite similar helmet sensor readings (McEntire et al. 2010).

Work has also been done in the area of biomarkers. We identified four studies within this category, two of which had positive results. As mentioned above, Por et al. (2016) exposed rats to single, multiple, or zero (control) compressed-air blasts to determine the expression of the TRPV1 channel, calcitonin gene-related peptide (CGRP), substance P (SP), endothelin-1 (ET-1), neutrophil infiltration, and myeloperoxidase (Por et al., 2016). These were identified as associated with blast exposure and pain and inflammatory mediators following ocular trauma. Results showed an increased expression of TRPV1, CGRP, SP, ET-1, and neutrophil infiltration; therefore, these findings suggest activation of pain- and inflammation-signaling following blast exposure (Por et al., 2016). Another study by Tate and colleagues (2013) looked at biomarkers in New Zealand Defense Force members who are breachers. This study found higher concentrations of three biomarkers—ubiquitin C-terminal hydrolase-L1, aII-spectrin breakdown product, and glial fibrillary acidic protein—which were associated with significantly longer reaction times, fewer correct answers on neurocognitive performance tests, and increased symptom reporting (Tate et al., 2013). Unfortunately, the study did not directly measure low-level blast exposure or employ a control group differing in low-level blast exposure. Therefore, the study did not validate these biomarkers as indicators of low-level MOB exposure.

<table>
<thead>
<tr>
<th>Assessment Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Service member or buddy self-report</td>
<td>Simple</td>
<td>Significant unit workload</td>
</tr>
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<td></td>
<td>Low-cost</td>
<td>Significant service member workload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Easily gamed</td>
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<td></td>
<td></td>
<td>Requires ongoing quality control</td>
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<tr>
<td>Supervisor report</td>
<td>Accountable</td>
<td>Significant leader workload</td>
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<tr>
<td></td>
<td></td>
<td>Low priority under fire</td>
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<tr>
<td></td>
<td></td>
<td>Low feasibility</td>
</tr>
<tr>
<td>Independent research rater</td>
<td>Low unit workload</td>
<td>Challenge embedding in unit</td>
</tr>
<tr>
<td></td>
<td>Quality control-data gathering</td>
<td></td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Objective indicator</td>
<td>No agreement on best biomarker(s)</td>
</tr>
<tr>
<td></td>
<td>Harder to game</td>
<td>May require biological samples</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially costly sample storage and processing</td>
</tr>
<tr>
<td>Biosensor</td>
<td>Objective indicator</td>
<td>Device reliability and validity concerns</td>
</tr>
<tr>
<td></td>
<td>Low burden</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable to assessor</td>
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</table>
Blennow and colleagues (2011) completed three studies to assess the relationship of repeated low-level MOB exposures to various biomarkers. First, 21 Swedish military officers were asked to repeatedly fire a howitzer or bazooka; then the researchers obtained samples of their cerebrospinal fluid (CSF) and serum biomarkers. Second, another group of 32 officers fired high-explosive antitank grenades using Carl Gustaf–model bazookas; serum biomarkers were drawn the day before; 30 minutes after; and one, 12, and 24 hours after exposure. Third, seven officers were exposed to 100 charges of detonating explosives over ten days. Serum samples were drawn the day before exposure; days 8, 9 and 10 of the exposures; and then ten days after all exposures. Nineteen healthy, age-matched volunteers acted as comparison controls for all three exposed groups. CSF biomarkers for neuronal or axonal damage (tau and neurofilament protein), glial cell injury (glial fibrillary acidic protein and S-100 calcium-binding protein B), BBB damage (CSF and serum albumin ratio) and hemorrhages (hemoglobin and bilirubin) were unrelated to the blast exposures (Goverover and Chiaravalloti, 2014).

The magnitude of the biomarker challenge is perhaps best captured by Elder and colleagues, who point out, “there are no biomarkers that can distinguish cognitive, affective, and somatic symptoms induced by a psychological stressor from those induced by physical trauma” (Elder et al., 2014). All of these factors similarly complicate our ability to understand and analyze blast exposure sensor data. The development and use of improved sensors and biomarkers, along with in situ coordination of care, will be instrumental to addressing this knowledge gap.

**Prevention Strategies**

“Prevention is the best medicine” remains a pervasive truism and a widely held and largely unchallenged societal view. However, prevention programs targeting health risks that do not exist or implementing preventive methods that are not effective is clearly an unnecessary waste of societal resources, resources that presumably can be put to more productive use. Therefore, the relevance of the following discussion (and future discussions) of prevention strategies depends on the answers to several key questions that at present remain largely unanswered:

- **Is low-level MOB exposure a significant risk to current and future force health?** There should be general consensus, ideally based on empirical data, that the threat to health posed by MOB is both real and significant before we devote significant resources to preventing the health effects of an exposure.
- **Are current preventive interventions safe and effective?** Even if the problem is substantial, ineffective primary prevention approaches will prove wasteful.
- **Will preventive intervention benefits outweigh the harms?** If a preventive intervention is effective but causes more harm than good, then implementation is likely self-defeating.
- **Is the preventive intervention timely and feasible?** If the preventive intervention is perfectly effective but cannot be delivered in time or in the appropriate context, then it is not useful. There are any number of related factors to consider here, such as the availability of relevant material and staffing and acceptance of the intervention by leaders, service members, and the larger society.

While prevention of illness and injury associated with repeated exposure to low-level blasts is relatively underresearched, we can draw from the literature on prevention methods
for blast exposure injuries more generally to better understand prevention methods. The main types of prevention methods are barrier methods—for example, helmets, earplugs, and protective goggles.

Protection Methods
Research indicates that helmets that service members wear, such as the Advanced Combat Helmet (ACH), are traditionally designed to protect wearers from head trauma caused by projectiles. Unfortunately, they are not designed to protect wearers from blast overpressure exposure and resulting neurotrauma. Moreover, traditional helmets may even exacerbate blast-related injury (Grujicic, Bell, Pandurangan, and Glomski, 2011; Ganpule et al., 2012; Kulkarni et al., 2013; Moss, King, and Blackman, 2009). While some studies found that ACH provided some level of protection from blast-related injury (Grujicic, Bell, Pandurangan, and Glomski, 2011), others found that space between pads inside the helmet creates blast-pressure-wave access to the skull and brain. When wearers are exposed to blast overpressure waves, these spaces allow the blast waves under the helmet where they reverberate, occasionally amplifying them in excess of the external blast-pressure waves. This causes the skull to flex, producing potentially dangerous forces acting on brain tissue (Moss, King, and Blackman, 2009).

One promising solution is to produce helmets without gaps between pads. In models, this has been shown to greatly reduce the reverberation of the blast within the helmet (Moss, King, and Blackman, 2009; Ganpule et al., 2012). Other potential solutions include the use of polyurea foam, face shields, and earplugs. Polyurea foam, compared with standard foam paddings, reduces the peak load of the blast wave (Grujicic, Bell, Pandurangan, and He, 2010). A partial face shield may reduce stress intensity on the brain (Nyein et al., 2010). Earplugs are the most effective barrier against blast-related hearing loss (Helling, 2004; Schulz, 2004; Wilmington et al., 2009; Dougherty et al., 2013). The angle of the head in relation to a blast exposure plays a role in how explosive force may cause the skull to flex (Chavko et al., 2011) and should be considered in the design of weapon systems that could result in repeated low-level blast exposure and how these weapons are used during training.

Body armor also has the potential to protect against chronic damage as a result of exposure to blasts. Rodriguez et al. (2016) found that mice protected with a polycarbonate body shield during blast exposure experienced a lower degree of signal enhancement compared with mice lacking a body shield, suggesting that improved body armor could reduce risks associated with blast exposure.

Nonbarrier Methods
Nonbarrier prevention methods, such as education programs, may aid efforts to reduce low-level MOB exposure. Available studies primarily address hearing loss. Among carpenters, research has suggested that education programs can increase the usage of hearing protection methods (Stephenson and Stephenson, 2011). However, one study found that even though British soldiers knew the specifics of hearing protection policy and that their job could affect their hearing, several factors prevented proper protection usage: communication difficulties, discomfort, and impracticability of use in some situations. The investigators concluded that hearing conservation education programs should be uniquely tailored for military populations (Okpala, 2007). An experimental rat study found that the antioxidant 2,4-disulfonyl alphaphenyl tertiary butyl nitrone (HPN-07) combined with N-acetylcysteine (NAC) administered an hour after three consecutive 14-psi blast exposures enhanced recovery and prevented per-
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manent hearing loss (Ewert et al., 2012). While a promising lead, the work is preliminary (Oishi and Schacht, 2011).

**Ongoing Research**

The military is currently funding ongoing research regarding protection from occupational blast exposure. One study is led by Rong Gan at the University of Oklahoma. The objective of this study is “to determine middle ear protective mechanisms and develop the finite element (FE) model of the human ear for simulating blast exposure injury and assisting design/evaluation of [hearing protective devices] HPDs” (Gan, 2015). The study is entering its final year (as of this writing in 2019) and is attempting to validate HPDs using the FE model that the researchers have developed. Another ongoing project, led by Brittany Coats at the University of Utah, is studying “Temporal Progression of Visual Injury from Blast Exposure” (Coats and Shedd, 2016). This study found that when rats are exposed to shock tube blast, the stroma of the eye thickens after two weeks, then the epithelial layer thickens at five weeks, leading to eventual corneal scarring. Early identification of corneal thickening may provide a time window during which appropriate early intervention could prevent corneal scarring and resulting visual impairment.
This section starts with a general summary of central findings, using the four key questions outlined in Chapter One as guideposts. Then, for each question, we discuss and attempt to prioritize key research gaps and opportunities for further understanding related to low-level MOB exposure. The questions are

1. What is known about the occurrence of repeated occupational blast exposure incurred during military service?
2. What is the scientific evidence relating to potential neurological health effects of repeated occupational blast exposure?
3. What are promising strategies for preventing the potential neurological effects of repeated MOB exposure?
4. What are promising early detection indicators for the potential neurological consequences of repeated MOB exposure?

For the research questions, we did not identify any epidemiological studies of low-level MOB exposure to help us understand the potential magnitude of the issue. We explored such specific situations and assignments as breacher training, shoulder-mounted artillery operators, and military service members deployed and in training—however, none of this research offers a comprehensive understanding of the magnitude of low-level MOB and whether low-level MOB exposure constitutes a neurological risk.

**Research Opportunities and Gaps**

In this section, we discuss the research necessary to develop a strong understanding of the neurological effects of low-level MOB exposure. A full understanding of the potential short- and long-term outcomes of low-level MOB is challenging because there has been little research on this topic to date, and the research that does exist does not present a clear picture of the issue. Most research on the issue of blast-related brain injury is generally concerned with a magnitude of blast exposure that is stronger than low-level MOB exposure. And, while epidemiologic and clinical studies to date provide sufficient evidence of an association between combat-related blast exposure without penetrating injury and postconcussive syndrome (PCS) and PTSD, this is not the type of blast exposure that is the focus of this report. Furthermore, the nature of the relationship between PCS and PTSD remains unclear, and it is possible that nonspecific symptoms of PTSD explain the association between low-level MOB exposure and PCS. As such,
we cannot recommend specific strategies for mitigating the neurological effects of low-level MOB, because these effects have not yet been established. If, however, it is assumed that neurological effects of low-level MOB exposure are significant, successful intervention will require knowledge regarding effective prevention strategies. To target research in this area requires an understanding of the most-frequent intermediate- and long-term risks. It is clear that more research is needed to understand whether low-level MOB exposure is a risk to service members, the specific risks and outcomes involved, and how to determine the best candidates for emerging preventive measures. In the ensuing paragraphs, gaps in the literature are discussed and we make related recommendations.

Among animals, studies in mouse and rat models suggest it is plausible that low-level MOB exposure could result in neurological effects. It is uncertain how blast exposure levels tested in animal studies relate to exposure levels in humans. Furthermore, many of these studies only involve a single blast exposure; therefore, it is unknown if the results of these studies would vary should there be multiple exposures. If further animal testing is to be done to assess the neurological effects of low-level MOB exposure, it should be done in larger animals, ideally nonhuman primates. Additionally, the cumulative effect of low-level blast exposures also needs further exploration within any future animal testing. Furthermore, testing is needed on larger animal species to determine the level, or range of levels, of psi that constitute safe and acceptable MOB exposure levels, and which levels lead to adverse outcomes (e.g., persistent neurocognitive or neuropathological changes; mild, moderate, and severe TBI). This is not yet defined in the literature, a fact that complicated our efforts to appropriately scope this review.

Among humans, completing carefully designed prospective, longitudinal research is essential. These studies should include a representative sample of service members anticipated to have varying levels of exposure to low-level MOB (records should include the intensity of the blast and number of exposures), appropriate accounting of potential confounding variables (e.g., past TBI and PTSD), validated measures of low-level blast exposure and key outcomes of interest, and concerted efforts to maximize follow-up during and after military service. Further work is needed to validate measures of exposure. Wearable sensors have the potential to give a more complete, reliable, and valid measure of MOB exposure, and collecting the data from those monitors would be a minimal burden to the service members wearing them.

However, sensor technology will need further work to ensure that the sensors could offer the previously mentioned measurement features and would be durable enough for military use. To accomplish this, we first recommend a long-term data-collection effort to measure exposure levels from MOB events in training. This effort should last for a period of three to five years. This collection can be performed with existing blast-exposure sensors, such as the Blast Gauge system. Training data (e.g., the type of heavy weapons training that a service member undergoes, recording the number of heavy-weapon launches during the exposure period) and any mental health or neurological issues should also be recorded. Second, we recommend a modeling effort to improve or develop precise mathematical models that link sensor data to overpressure forces on the brain.

Once this research is complete, sensors can be used to measure exposure in a longitudinal study. At the conclusion of that study, further research can be performed to analyze the collected data, apply and improve mathematical modeling to convert sensor data into measurements of overpressure forces on human brain and other tissues, and link the effects of multiple, low-level MOB exposure events to neurological health. Sensors could be used as an early detection device to signal potentially harmful levels of MOB exposure.
Finally, there is evidence that improvements to helmets, enforcing adherence to hearing protection, and supplemental antioxidants may eventually serve to mitigate the neurological effects of blast exposure (Moss, King, and Blackman, 2009; Oishi and Schacht, 2011; Stephenson and Stephenson, 2011; Ganpule et al., 2012). However, these have only been tested at higher-intensity blast exposure levels, and more research is required to determine (1) whether protection from low-level MOB exposure is necessary and (2) if these approaches are effective for mitigating the neurological effects of low-level MOB exposure.

We are not suggesting the abandonment of current protective measures against high-intensity combat blast injuries (e.g., mild, moderate, and severe TBI). However, as it pertains to low-level MOB exposure, the state of the science is preliminary. Implementing aggressive preventive programs against this threat—without adequate evidence of preventable injury—risks unintended consequences and the consumption of considerable resources without commensurate benefit.

Overall Recommendations

Perhaps the most striking finding from this review of the literature is how little research has been completed to determine the organizational threat and service member health impact of low-level MOB exposure, in contrast with our rapidly improving empirical research base relating to blast-related traumatic (concussive) brain injury. A Center for New American Security review of low-level MOB exposures (Fish and Scharre, 2018), published as we were completing this review, came to similar conclusions regarding the level of scientific uncertainty that exists relating to the neurological effects of low-level MOB exposure and recommended aggressive, ongoing surveillance of both exposure and neurological outcomes. However, military service-wide efforts to implement population exposure surveillance are more likely to be ineffective if they are implemented before the neurological effects of low-level MOB exposure are better characterized.

Prior to rolling out population-based military surveillance efforts, epidemiologic and other research is needed to establish whether low-level MOB exposure poses neurological or other health risks to service members and what, if any, the specific risks are. Surveillance programs require specific information to ensure collection of appropriate data, information that does not appear to be known in sufficient detail yet. Additional research, prior to surveillance, can ensure that surveillance efforts are calibrated to assess the most-important aspects of blast exposure and related outcomes.

Currently, most data from human and animal studies address the effects of higher-level blast exposures that can lead to concussion and more severe TBI. These studies do not allow a parsing of low-level MOB exposure effects, and therefore cannot adequately inform understanding of the risk that low-level MOB exposure creates for service members. Therefore, our main recommendation is for research that advances understanding of the specific health effects of low-level MOB exposure. This should include epidemiological studies to determine the magnitude of the problem and longitudinal research to better characterize short-, intermediate-, and long-term health risks. Other studies can help to calibrate future surveillance efforts. For example, neuropsychological research should be completed to determine which assessments are best for early detection of the potential cognitive effects of repeated low-level MOB exposure. Similarly, animal research can help researchers to better conduct human studies. These
studies should include nonhuman primate research, so that results will more easily translate to humans. Other recommendations include the development and testing of preventive interventions and biomarker and biosensor validation studies suited for use with preventive materiel and strategies.


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Over the past decade, there has been increasing awareness of the central nervous system (CNS) effects of exposure to explosive blast. A key driver of that awareness has been the blast-related injuries suffered during combat operations in Iraq and Afghanistan. With the near cessation of U.S. combat operations in these regions, concern has grown over common, repetitive forms of blast exposure during military service that are, most often, unrelated to combat. An example of such an exposure is routine military training involving heavy weaponry, such as artillery, recoilless rifles and shoulder-held rocket launchers. These blast exposures are of a lower intensity than those causing acute combat-related injuries; however, repeated exposure may also have impacts on CNS structure, function, and development, as well as on the broader health of military service members.

The authors of this report review the relevant literature on the effects of repeated, military occupational blast (MOB) exposures; prioritize the key research and policy gaps related to repeated MOB exposure; and examine the projects and initiatives that attempt to address those research and policy gaps.