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Review Article

A Neuropathology Approach to Understanding of Explosive Blast TBI Seizure Risk

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Abstract

It is recognized that explosive blast Traumatic Brain Injury (TBI) may be a significant risk factor for seizure and consequently Post-Traumatic Epilepsy (PTE). This has importance clinically as the manifestation of seizures following a blast exposure may be the only objective clinical sign that a victim may have suffered cellular and structural brain injury. The mechanisms by which explosive blast damages brain remain unclear. Characterizing blast TBI neuropathology will provide the basis for a deeper understanding of this condition thereby facilitating development of meaningful therapies. The evidence to date reveals that explosive blast TBI leads to the neuropathological features of axonal injury as evidenced by focal and diffuse axonal degeneration and axonal swelling detected by silver staining and beta-Amyloid Precursor Protein (APP). Silver stained and immunfluorescent Fluoro-jade reactive neurons consistent with neuronal degeneration and apoptotic bodies of cell death are also observed. Electron microscopy reveals neuron cell body chromatolysis and pycnosis as evidences of neuronal cell degeneration as well as swollen degenerating nerve fibers. These findings are mainly distributed in long fiber tracts, such as the corticospinal tract and visual pathways (including the optic tract and its deep nuclear structures such as the lateral geniculate body and superior colliculus), cerebellar white matter structures, the hippocampus and the brainstem. The neuropathological features of neuronal cell degeneration and cell loss and astrogliosis, particularly in hippocampal structures, have been shown in other clinical conditions with seizures and PTE, which supports the risk of this disorder following explosive blast TBI.

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INTRODUCTION

From the Global War on Terror (GWOT), which includes both Operation Iraqi Freedom (OIF) and Operation Enduring Freedom in Afghanistan (OEF), the clinical experience reveals that explosive blast Traumatic Brain Injury (TBI) can lead to seizures and epilepsy. It is well known that seizures and epilepsy have profound impacts on patients' quality and duration of life. Suffering a Traumatic Brain Injury (TBI) increases the risk of acquiring this neurological condition. Any type of TBI can lead to Post-Traumatic Epilepsy (PTE). Explosive blast has only recently re-emerged as a leading combat casualty. Close to 300,000 U.S. service members having suffered TBI during their service in Iraq or Afghanistan with the majority being the result of explosive blast exposure, mainly from exposure to Improvised Explosive Devices (IED) [1-4].

To appropriately treat and prevent this condition, it is critical to characterize the neuropathology. It is from the pathology that disease mechanisms are elucidated. These mechanisms are the root cause of seizures, cognitive impairment, emotional disturbance and other clinical features of TBI. Preclinical models are used to provide scientific insight and be platforms for therapy discovery. However, to be relevant, models must accurately reproduce the injury state experienced in the human condition. For this reason, detailed neuropathological characterization of each preclinical TBI model is required.

The 2 major types of TBI are closed and penetrating head. Explosive blast may be a third type but this is not yet universally accepted. Closed head or blunt force TBI is from an event where the head comes to a sudden stop but the brain being suspended in fluid continues to move striking the inside of the boney calvarium. In these cases, the skull remains intact. Examples of closed head injury events are hitting the windshield of a motor vehicle during a collision, striking the ground when falling or a head-to-head contact during a sports play. Penetrating head TBI occurs when an object passes through the skull into the brain. If at high velocity, air will rush in from the vacuum created by object leading to brain cavitation, which will greatly enhance tissue damage. Explosive blast TBI is a putative third type and is

a result of exposure to an explosive blast. The leading hypothesis is that the pressure wave generated by the detonation impacts the head. The pressure wave forces are transferred into the brain tissue which becomes injured as a result.

Post-traumatic epilepsy (PTE) is a major long-term complication of all TBI types. The risk of PTE depends largely on the type of TBI. The highest risk is associated with penetrating TBI. From GWOT analysis by the Defense and Veterans Brain Injury Center (DVBIC), only 1.5% all combat related TBI are from penetrating injury [1]. The rest are closed head injuries. Explosive blast are included among the close head injuries but alone account for close to 70% of all TBIs incurred in battle [5].

From the experience of prior wars, it is expected that about 10-25% of patients with closed head TBI and over 50% of patients who have penetrating TBI will develop PTE [6,7]. Among GWOT veterans with non-penetrating, moderate to severe TBI with no visible lesions on CT or MRI, have a 5% risk for PTE. Those victims of mild TBI or concussion, also with normal CT or MRI neuroimaging, the estimated risk is between 1-5%. It must be emphasized that for mild TBI patients, the risk is a gross estimate as the epidemiological studies have not been completed. This is important as the vast majority of military TBI victims (82.5%) are those who have suffered mild TBI or concussion [1].

Temporal Lobe Epilepsy (TLE) predominates among PTE, even though any type of epilepsy can develop. Up to 62% of TBI patients suffer these. It is important for clinicians to be aware that there may be a delay for years in seizures becoming clinically apparent after the initial injury. In prior wars, up to 15% of TBI patients did not develop clinical seizures until 5 or more years after their injury [6]. Recognizing that this is likely true also for GWOT veterans, the Veterans Administration (VA) has established a national network of Centers of Excellence for Epilepsy to provide long term surveillance and care for these patients.

The highest risk period for developing PTE is within the first 2-3 years after the traumatic event. However, the risk remains elevated for many years after that. About 50% of patients who develop early post-traumatic seizures, i.e., within the first 7 days after injury, will lead to PTE. [7,8]. This even includes those with only mild TBI or concussion. Not surprisingly, the highest risk for developing seizures correlates directly with TBI severity. Patients with structural lesions such as intracranial hematomas will have an even greater PTE risk. The Vietnam head injury study reveals that cortical involvement, brain tissue loss and intracranial retained metal fragments are also high risk factors [9,10].

Besides PTE, these victims are also at risk for other neurological disorders ranging from subtle mild cognitive impairment, affecting the ability of a person to perform under demanding conditions, to severe disruption of brain function as serious as coma. Any and all of these may be temporary or chronic. If chronic, for decades, patients and their families may suffer serious emotional and economic costs that affect them and society. Thus, it is critical that brain injury be identified early so that appropriate medical and supportive interventions may be instituted to reduce the overall impact of this condition. As this is often a silent condition, seizures may be the first objective sign that a TBI has occurred.

HOW EXPLOSIVE BLAST INJURES BRAIN

There are 4 types of injury that may be caused by an exploding device. The first or primary is from the physical forces generated by the explosion, such as the pressure wave. The second is from being struck by flying debris or weapon case fragments. The third is a result of the victim being thrown through the air and then striking an object such as the ground or wall. The fourth is from any other reason not covered by the first three types such as being burned by the explosive fireball, toxic fumes, etc. This discussion will be limited to the primary injury only.

The pressure wave mechanism is the leading hypothesis for how an explosive blast leads to TBI, i.e., primary injury. In this hypothesis, the pressure or shock waves generated by the explosion move through the air, impact the victim's head and then transits through the brain causing its acceleration and deformation. The severity of tissue damage is related to the shape of the blast shock wave, its peak overpressure and pulse duration, and the tissues' natural resonant frequencies [4,11,12]. This blast shock wave is commonly depicted by the Friedlander curve [13]. Clinical and preclinical evidence supports this hypothesis as the most commonly injured organs are hollow air-filled viscera such as lung and gastrointestinal tract [14-22].

An alternative hypothesis suggests that the explosion generated shock waves impacting the torso are then transmitted to the brain via blood vessels [23-27]. Cernak at al proposes that, indirect transmission of kinetic energy from the blast shock wave is transferred to the blood contained in large abdominal and thoracic blood vessels. Oscillating waves created in this column of blood is conducted up into the brain resulting structural and functional damage. Evidence to date suggest that both hypotheses may be valid as direct [28] and indirect mechanisms [29] likely have contributing roles in the pathogenesis of blast TBI.

Different preclinical methods have been developed using either shock or explosive blast tubes or open-field blast [15,30,31]. From these efforts, the effects of blast shock wave on brain tissue and its functional consequences of cognitive and behavior changes, seizure and brain pathology are being elucidated.

In the following, the neuropathology evidence derived from the most commonly used experimental blast-induced TBI models is reviewed. In particular, a more detailed discussion is made summarizing gross and microscopic findings, tissue staining methods and relevant neuropathology.

BLAST TBI MODELS

Preclinical experimental animal methods are essential to characterize injuries and disorders of blast TBI. In order to be predictive of the human condition, these models must fully reproduce the neuropathology and salient clinical features of human blast TBI. To that end, experimentally tested and investigated predetermined aspects of the blast, e.g., shock wave overpressure and mechanical properties of the blast, should produce predictable and reproducible tissue injuries that are clinically relevant [24].

Various methods are used to model explosive blast. The most common experimental models are open field blasts, blast tubes

and shock tubes [24]. An open field blast model uses an explosive device detonating in an outdoor test area. The device may be suspended above or placed directly on the ground. Subjects are positioned a specific distance away from the device. As in IED blasts, the shock waves produced are complex as they include reflection off the ground and other surfaces. Of the available experiment blast models, this is considered the most accurate representation of the human condition. However, it should be noted that the fireball and debris cloud will also contribute to the injury. This makes it difficult to separate primary blast effects from secondary and quaternary effects using this approach. For that reason, tubes are used.

An explosive blast tube creates a blast wave (shock wave plus blast wind) through explosive charge detonation. Thus, this approach will produce blast intensities equivalent to open field blasts but with significantly smaller explosive charges. Moreover, the blast tube allows for the exposure of experimental subjects to a "pure" blast event without reflected shock fronts from the ground or other surfaces. A primary blast only mechanism is achieved by using uncased explosive (to prevent secondary mechanism), subject immobilization (to minimize tertiary mechanism), and placement of the subject beyond the detonation fireball (to avoid quaternary mechanism). Commonly used blast tubes are those developed by Parks used by Bauman et al. [32] and De Lanerolle et al. [33] to study blast-induced TBI in swine, and the Clemedson tube [34] used in Sweden to study the blast-induced TBI in rat [35,36].

Using explosives is the most accurate way to study explosive blast effects but there are a number of practical considerations when using these blast tubes. There are the need to use specific dedicated remotely located testing locations (usually, ranges), to employ personnel specifically trained in the safe use of explosives, and likely to obey various legal ordnances. In as explosive blasts are typically carried out outdoors, weather and other environmental conditions become contributing factors [37].

Shock tubes using compressed gas, such as helium, as alternatives to blast tubes. In comparison, they are safer, more cost effective and can be used indoors. High pressure is generated in the sealed driven section of the shock tube by gas which is separated from the driver section by a breakable diaphragm membrane. When the pressure in the driven section rises above a certain threshold, the membrane ruptures and the generated shock wave travels through the driver section where the exposed subject is placed. Changing the distance of the subject from the membrane, the thickness of the membrane, varying the nature of the gas and the shape of the closed end of the driver section can alter the characteristics of the generated shock wave. This allows wide variations depending on the specific goals of each experimental study. Moreover, certain shock tubes are specifically designed to expose only selected anatomical regions of the subject, such as the head or torso. Among others, shock tubes have been used at Johns Hopkins University, Walter Reed Army Institute of Research, Wayne State University, University of Kentucky, University of Toronto and the Florida Institute of Technology [29,38-42].

Shock tubes have their own drawbacks such as the unique physics of the gas driven shock wave, possible impact of diaphragm fragments on the subject and the physical load of multiple small fragments may affect the dynamics of body-head acceleration. Therefore, the produced injury pattern may not be comparable to the human condition. Jet stream effect at the tube exit alters pressure dynamics creating unrealistic measurements and pressure effects [41,42].

It is a challenging task to create an ideal Friedlander wave by using explosives or gas since real-life combat scenarios are far more complex mostly due to shock wave reflections and consequently, altered shock wave-subject interactions. In order to recreate those complex combat situations, investigators designed and used surrogates of military buildings, vehicles and bunkers. However, differences in methodology could potentially obstruct the generalization of results [32,37,43-45]. Moreover, anatomical and physiological differences among the species used in blast studies can contribute to the wide range of pathological and pathophysiological reports on experimental blast injuries [24,37].

Key neuropathological findings of blast-TBI

For TBI, the terms "primary" and "secondary" are used to define the neuropathology of the tissue response as well as the physical mechanisms leading to injury, which are separate and distinct. For neuropathology, "primary" refers to the immediate tissue damage caused by the physical force such as brain contusion from a blow to the head or brain shearing along the track of a penetrating projectile. Secondary injury of tissue refers to pathophysiological responses, such as inflammation, excitatory amino acid release or expression of reactive oxygen species.

Histopathological analyses of neural tissues from blast-exposed experimental animals reveal focal or diffuse axonal injury, neuronal cell damage, glial cell activation and inflammatory reactions, occasional intracranial hemorrhages, brain edema and vasospasm [2,46]. Besides standard Hematoxylin and Eosin (H&E) and cresyl-violet stains immunohistochemistry is the most widely used method to detect abnormal tissue morphology. Combining standard, special and immunostains investigators are able to detect various histopathological changes and explain underlying biomechanical and pathophysiological processes. For ultrastructural examinations at the subcellular level electron microscopy is the preferred method. Several studies investigated axonal injury use silver staining techniques. Although, in clinical settings axonal injury is usually detected by β-amyloid precursor protein (β-APP) Immunohistochemistry (IHC), in experimental blast studies silver staining methods have been proven very reliable [47-50].

The neuropathological consequences of blast TBI are heterogeneous but the most frequently reported pathology associated with explosive blast TBI is axonal injury and reactive astrocytosis. Bauman et al. using a swine explosive blast TBI model describes degenerating axons in the white matter and cerebellum detected by a modified Gallyas silver method, as made available by FD Neurotechnologies [32]. B-APP positive periventricular fiber tracts are observed in another explosive blast model using swine [33] and a non-human primate study reveals β-APP positive axons and neural perykarions in the

brain [45]. Activated glia cells are visible in the grey and white matter and in multiple layers of the hippocampus at various time points [32,33] detected by Glial Fibrillary Acidic Protein (GFAP) immunohistochemistry. Neuronal cell damage in the cortex, cerebellum and hippocampus is hypothesized occasionally by standard staining methods and by increased expression of Neuronal Nuclear Antigen (NeuN) and Neuron Specific Enolase (NSE) [32,44,45]. Neuroinflammation characterized by microglia cell activation is also seen by de Lanerolle mostly in the central white matter and the corpus callosum [33]. Apoptotic cells and increased astroglial and water channel markers are also detected following explosive blast injury [45] however, apoptosis appears to be more characteristic in non-explosive TBI [51-53].

In rats and mice, shock tube studies reveal various axonal injuries that are similar to those found in explosive blast models. Silver stained degenerating axons are described throughout all levels of the brain, including long fiber tracts [29,54,55], optical and auditory pathways [54,55], dentate gyrus of the hippocampus [55], the cerebellum and brainstem [54,55]. The histological appearance of axonal degeneration is varying but strongest at 2 weeks following blast exposure. Applying protective measures to the body can eliminate silver labeled axonal injury in animals exposed to lower blast intensities (~ 18 p.s.i.) which supports the theory of shock wave impacting the torso followed by a transmission via large vessels to the brain causing TBI [23-27]. Neuronal damage and cell loss is also observed in the brain at higher blast intensities (~ 21 p.s.i.) along with gliosis, axonal damage hemorrhage and necrosis [29,56,57]. Silver stained degenerating neurons are also detected in the CA1 pyramidal layer of the hippocampus and cerebellum mostly seen at 1-3 days after injury [55]. Axonal injury detected by β-APP, microglia reaction and astrogliosis are weak or not present at all. Evidence for breach of the Blood-Brain Barrier (BBB) is very limited, detected mostly at 24 hours after blast exposure by Immunoglobulin G (IgG) immunohistochemistry [55,58,59]. A study, conducted to examine the connection between blast-induced TBI and Chronic Traumatic Encephalopathy (CTE) [60], reports CTE-like changes in the mouse brain [61-64] such as tau protein immunoreactivity, phosphorylated tau proteinopathy, cortical and hippocampal neurodegeneration, permanent perivascular pathology with `dark neurons` in close proximity to abnormal capillaries, myelinated axonopathy and chronic neuroinflammation with astrocytosis and microgliosis. Only the unrestrained head is exposed to a single blast and the body is protected. Electron microscopy showed similar changes to the non-human primate explosive blast model [45] revealing persistent microvascular pathology and astrocyte end-feet swelling suggesting BBB compromise which in turn possibly plays a role in local hypoxic, inflammatory and neurodegenerative changes.

The neuropathology of non-blast versus blast TBI models

There is non-blast TBI that model injury patterns associated with either blunt impact to the head or a bullet that penetrates the skull. The most common blunt impact TBI animal models are Fluid Percussion Injury (FPI), Controlled Cortical Impact (CCI), and Weight Drop (WD). These create localized damage to brain as contusion, hematoma, tissue laceration and axonal destruction. The Penetrating Ballistic Brain Injury Model (PBBI) simulates a gunshot wound TBI. In this model, there is hemorrhage, shearing and laceration to the brain along the projectile path and also cavitation stretch damage as reproduced with a balloon. All produce, through distinct mechanisms, a damage normally to the lateral cortex or deep brain structures which depending on the severity may affect the underlying regions of the hippocampus, striatum, corpus callosum and thalamus [65-74].

FPI models produce subarachnoid hemorrhage and vascular injury, tissue necrosis, apoptosis and cell loss, parenchymal microhemorrhages, axonal injury, reactive astrogliosis and microglia activation [65,68,75-78]. The anatomical locations mostly involved are proximate to the impact site but abnormal histopathology is also reported in more distant regions such as the hippocampus and various cortical areas.

The CCI model generates a more focused injury in the brain mainly resulting in focal contusion and tissue loss with occasional SAH, brain edema and axonal injury close to the injury site. In both experimental models there are significant physiological (increased intracranial pressure and transient blood flow changes) and behavioral deficiencies. Spatial memory and conditioned fear reaction is impaired in LFP experiments due to the involvement of the hippocampus and amygdala. CCI mostly results in gait deficiencies [67,79]. PBBI produces more severe injury in the brain. Histopathology shows widespread parenchymal injury with intracerebral hemorrhage, tissue swelling and inflammatory response. Astrogliosis, microglia activation is present even at distant sites to the injury. The extent of the injury and involvement of different anatomical locations depend on the size of the inflated balloon. Sensorimotor deficits and seizure activity are the most prominent consequences of the injury [70]. WD models cause widespread, diffuse axonal injury in white matter tracts along with apoptotic and necrotic neuronal cell loss brain edema and BBB damage in the cortex and hippocampus, mainly in the CA1 sector. Motor and cognitive deficits, increased intracranial pressure and hemodynamic changes are the major consequences [73,79].

Similarly to the above summarized pathological changes in non-blast TBI animal models animal models of blast TBI show various types of morphological changes in the brain. The most frequent finding is axonal injury however, for detection, silver staining seems more useful than β-APP in blast studies. In CCI, LFP or PBBI models axonal swelling and retraction balls are more readily observable than in blast TBI models. Both experimental TBI approaches cause vascular changes and breach of the BBB resulting in edema and hemodynamic changes although, this finding in blast TBI models are subtle and limited and its detection requires immunohistochemistry or electron microscopy [45,55,60]. Astrocytosis and microglia activation are seen in most of the TBI models but acute or chronic cellular inflammatory response is more characteristic in direct impact TBI models. The anatomical distribution of tissue damage has a wide range, especially in blast TBI models, but there are overlapping pathological findings with other TBI models in areas such as the hippocampus, white matter and brainstem fiber tracts, optical pathways and cerebellum. Visible, gross morphological changes, such as contusion, hemorrhage or

brain swelling, are almost entirely absent in blast TBI models in contrast to other TBI models. Furthermore, many of the cellular and morphological findings develop in blast TBI are best visible at 7-14 posttraumatic days.

Post-traumatic epilepsy from blast vs nonblast TBI

Non-TBI related epilepsy is a common clinical disorder for which standard animal models exist. These methods use either chemical or electrical means by which to induce seizures. For PTE study, the previously describe preclinical non-blast TBI models will all lead to epilepsy [80-84].

The risk of seizures and epilepsy increases following acute TBI through hemorrhage, cell and axon damage [85,86]. Increased extracellular calcium, glutamate and reactive oxygen species, the release of aspartate and glutamate and activation of NMDA receptors all contribute to PTE development. Formation of toxic free radicals from hemoglobin and transferrin and fiber tract damage, resulting in anterograde transynaptic neuronal degeneration with the loss of inhibitory interneurons, can also lower seizure threshold [85,87-89].

Histopathological findings in experimental models of PTE show similar changes to those of human TLE. The main structures of the temporal lobe with epileptogenic potential – categorized under the name `mesial TLE group` - are the hippocampus and occasionally the amygdala and the entorhinal cortex [90,91]. Neuropathological studies on surgical specimens of hippocampal tissues from TBI patients with blunt head trauma or acceleration injury show similar cellular and structural changes compared to the pathology from non-trauma patients (i.e. drug-refractory) with TLE. Dissected tissue specimens from these patients show direct hippocampal contusion, progressive hippocampal sclerosis and neuronal cell loss in the CA1-CA4 sectors with relatively mild histological changes in CA2 and the dentate gyrus and occasionally, neural cell loss in all hippocampal pyramidal cell subfields [92-96]. Additional neuropathological finding from patients with TLE described granule cell dispersion and temporal lobe sclerosis [90]. BBB opening can lead to astrocyte activation detectable in TLE with increased expression of GFAP through albumin-mediated transforming growth factor β (TGFβ)-dependent signaling [97-99]. Further evidence support that the hippocampus is one of the primary sites in epileptogenesis as there is increased acetylcholinesterase staining in the outer portion of the molecular layer of the dentate gyrus in human temporal lobe seizure specimens [100]. TLE is also associated with less frequently affected regions of the brain including the thalamus, basal forebrain, cerebellum and brain stem [101,102].

CCI and FPI animal models demonstrate epidural hematoma, subdural hematoma, cell loss in the cortex, mossy fiber sprouting in the ipsilateral hippocampus in rats and mice causing concurrent late spontaneous posttraumatic seizures similar to human TLE [66,80,81]. Furthermore, loss of dentate hilar neurons and neurogenesis in the dentate gyrus is also described [103-106].

As discussed above, various experimental blast methods and studies exist to investigate brain injury but none of them have reported or investigated seizure activity. Interestingly, even though experimental blast TBI models causes brain injury through a different mechanism from non-blast TBI models, morphological changes in the brain, most specifically in the hippocampus, are similar among all TBI methods (blast or non-blast). There is evidence of neurodegeneration, axonal injury and astrocytosis in the molecular layer of the hippocampus and the dentate gyrus at various short and long-term survival times [32,42,45,55,60]. Nevertheless, it should be emphasized that explosive blast study is a relatively new area of neuroscience research and the studies to date are largely limited to characterizing the neuropathological and behavioral consequences of blast TBI and not PTE specifically. One aspect of these blast TBI preclinical studies is that the subjects may not be followed long enough for PTE to manifest. It is clear that more research is needed to study the relationship between blast TBI and PTE [92].

SUMMARY AND DISCUSSION

Seizures are an important clinical consequence of all TBI types. Although the precise impact of this clinical condition on explosive blast TBI recovery is still being elucidated, the finding that explosive blast leads to consistent neuropathological brain changes raises significant concern that seizures and epilepsy may be more prevalent than previously suspected. Fortunately, the Veterans' Administration is taking a comprehensive prospective longitudinal clinical approach to study PTE in blast TBI victims.

The preclinical neuropathological findings most consistently observed after explosive blast TBI are axonal damage (axonal swelling and degeneration), vascular damage and the disruption of the BBB resulting in intracranial hemorrhages and brain edema, reactive gliosis, cellular inflammatory response, neuronal cell degeneration and cell death. The anatomical distribution of these findings, especially axonal injury, are varied but mostly observed in the long white matter tracts including the corpus callosum, optic tract, corticospinal tract, brain stem tracts and hippocampus. Other notable, non-neurological blast-related injuries are blast lung injuries, tympanic membrane rupture and gastrointestinal tract injuries. These are similar to those seen after non-blast TBI for which PTE has been well described. Thus, it is reasonable to infer that PTE is a significant risk following explosive blast TBI.

It is a long held medical principle that knowing the pathology is necessary to fully understand a disease. This is true also for explosive blast TBI related PTE. It is through the neuropathological study that critical insights will be gained that can be used to develop rational therapeutic strategies for ameliorating PTE.

DISCLAIMER

The opinions and views expressed herein belong only to those of the authors. They are not of and should not be interpreted as being endorsed by the Uniformed Services University of the Health Sciences, Dept. of Defense or any other agency of the U.S. government.

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