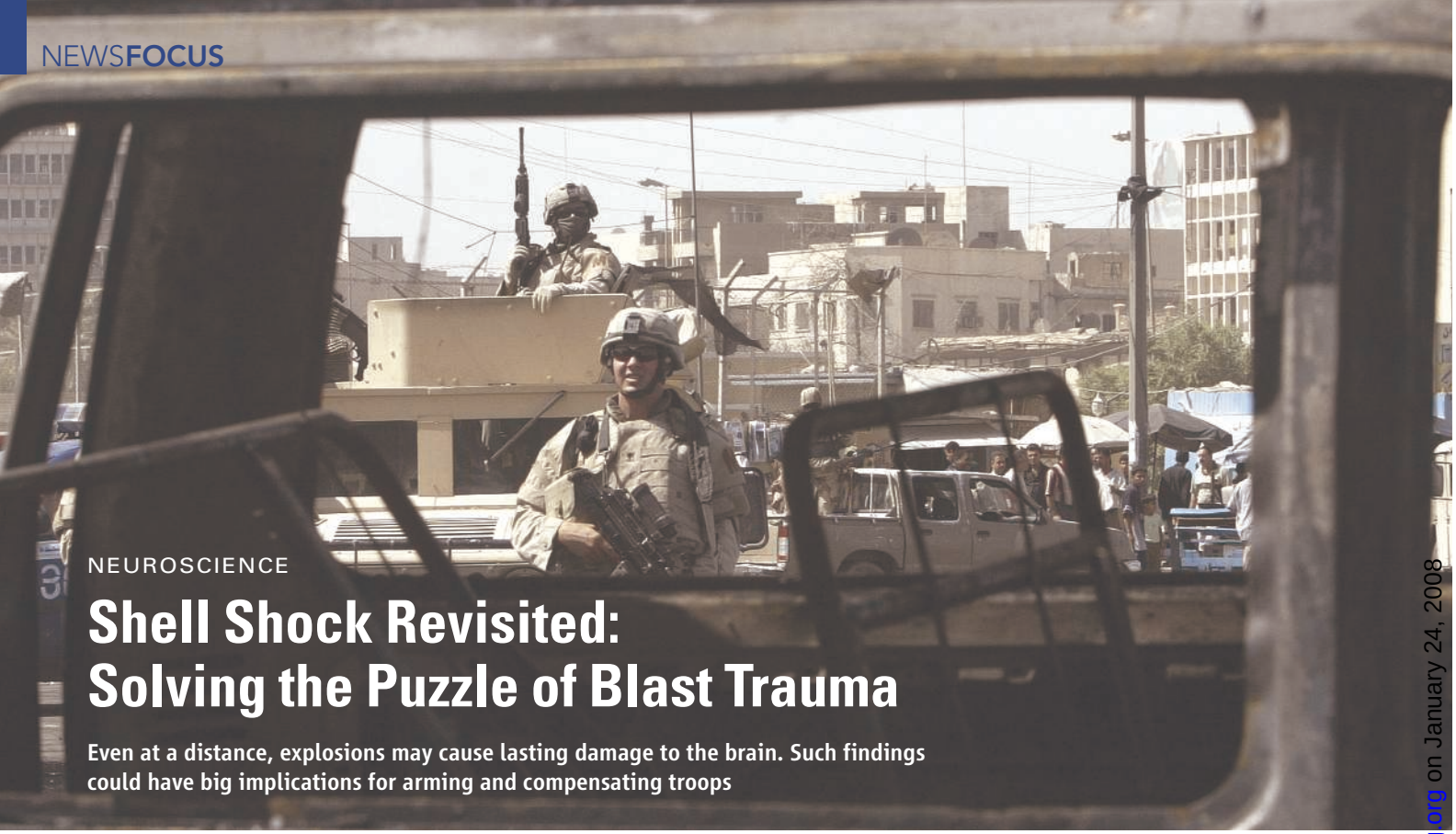

NEUROSCIENCE

Shell Shock Revisited: Solving the Puzzle of Blast Trauma

Even at a distance, explosions may cause lasting damage to the brain. Such findings could have big implications for arming and compensating troops

Working at the Military Hospital in Belgrade during the brutal Balkan war of the 1990s, neurologist Ibolja Cernak encountered a medical enigma. She saw soldier after soldier with memory deficits, dizziness, speech problems, and difficulties with decision-making—but no obvious injury. Cernak recalls one 19-year-old who went to a grocery store and began to weep after he couldn't remember how to get back home. When his mother brought him to the hospital a few days later, Cernak learned what later emerged as a common element in all these cases: The soldier had survived an explosion on the battlefield.

The strange thing was that most of these patients had not suffered a direct injury to the head. And yet, in computed tomography and magnetic resonance imaging scans, Cernak saw signs of internal damage. In some cases, the brain's ventricles—channels that carry cerebrospinal fluid—had become enlarged; and in some, there was evidence of minor bleeding. But when Cernak dug into the medical literature for an explanation, she came up empty. According to the available research, shock waves from an explosion injure mainly air-filled organs such as the lung and the bowel, not the brain.

With a small band of collaborators in Belgrade, China, and Sweden, Cernak undertook animal studies that eventually confirmed that blast waves can cause neuronal damage. The work drew little attention until 2 years ago when hundreds of U.S. and British soldiers began returning from Iraq with symptoms similar to those of Cernak's patients. As roadside explosions became more common, military doctors suspected that these symptoms were the likely result of mild traumatic brain injury (TBI) sustained in blasts. Seeing her observations borne out was as if "a myth had become reality," says Cernak, who is now a researcher at the Applied Physics Laboratory at Johns Hopkins University in Baltimore, Maryland.

How blasts affect the brain has since become an urgent question in military medicine. Last summer, the U.S. Congress gave $150 million to the Department of Defense (DOD) for the first year of research on TBI—both severe injuries that damage the skull and milder ones suspected of causing neurological deficits. The Defense Advanced Research Projects Agency (DARPA) has already launched a $9 million research program aimed specifically at understanding trauma caused by shock waves, heat, and electromagnetic radiation emanating from blasts. Another $14 million a year is going to the Defense and Veterans Brain Injury Center (DVBIC), a DOD-funded agency headquartered in Washington, D.C., for research and outreach on TBI.

This flurry of interest has focused a spotlight on Cernak's research. There is growing consensus that blasts can produce subtle injuries in the brain as suggested by Cernak several years ago. In fact, the Department of Veterans Affairs (VA) proposed a new rule this month acknowledging blast-related TBI as a special neurological condition whose symptoms may have gone undetected in the past. The proposed rule, published in the *Federal Register* on 3 January, would allow for greater disability compensation to victims than is granted currently.

But many researchers are skeptical of Cernak's ideas about how these injuries might occur. Cernak postulates that blast waves ripple through the victim's torso up into the brain through the major blood vessels, leading to neurological effects that can be slow to appear. Although she has evidence from animal experiments to back up that hypothesis, she admits that more research is needed. If the mechanism is confirmed by future studies, Cernak says, it would mean that helmets do not protect the brain against blast injury.

Besides raising questions about the protection of troops currently in combat, Cernak's suggestion that simply being exposed to an explosion might lead to long-lasting brain damage has opened a Pandora's box, particularly for veterans. It implies that some could be suffering from neurological deficits that went undiagnosed or were mistakenly attributed to posttraumatic stress disorder (PTSD). Indeed, since the

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government began putting out information about blast-related TBI, veterans have been trickling in to seek treatment for mental problems that some have lived with for decades. "It may well be that blast injuries follow the pattern of Agent Orange and Gulf War syndrome," says former VA psychiatrist David Trudeau, referring to ill-defined health problems that have lingered for years after battle.

Hidden trauma

If Cernak had been a doctor during World War I, she says, she might well have recognized mild TBI among the thousands of soldiers who suffered from what was simply called "shell shock." But during World War I, many doctors and military commanders viewed shell shock as a transient psychological phenomenon that affected soldiers who, in their opinion, were mentally weak.

Cernak discovered something very different: that soldiers' mental problems seemed to be driven by enduring physical changes in the brain. To test her hypothesis, she conducted a study of 1300 patients who had suffered penetrating wounds to the lower body but not the head. More than half had suffered injuries in a blast; the rest had been wounded by projectiles. Many of the blast victims complained of symptoms such as insomnia, vertigo, and memory deficits, and more than 36% in this group showed irregular patterns of electrical activity in the brain—as measured by electroencephalograms taken within 3 days of the injury—compared to only 12% in the other group. A year later, 30% of blast-injured patients still showed abnormal brain activity compared to 4% of the rest. Cernak says the findings, published in the *Journal of Trauma* in 1999, suggested that the mental problems of blast victims had a biological basis.

Her study wasn't the first to make that point. A year earlier, VA researchers had found that among veterans with PTSD, individuals with a history of blast exposure were much more likely than others to have abnormal brain activity as well as cognitive and behavioral problems. "Our evidence pointed to the possibility that blast injury was a long-lasting injury in combat veterans," says Trudeau, who retired in 2000. He says he was disappointed by the lack of follow-up to the study, published in the August 1998 *Journal of Neuropsychiatry*. "The reception we got was pretty lukewarm," he says.

For decades, Army researchers had been studying the effects of blast waves but with a different focus. They concentrated on how to protect the lungs and bowel because the pressure from an explosion is most likely to shear at the interface of these tissues, where densities differ. DOD was so confident that advanced body armor was protecting troops against lung and bowel injuries that it closed down this research program in 2003. "We thought, why spend more money on this when we've fixed the problem?" says Geoffrey Ling, a neurologist and a program manager at DARPA.

Then the bad news arrived. As blast survivors from Iraq were air-lifted to hospitals, U.S. Army doctors, including Ling, who was deployed in Iraq in late 2004, began to see patients whose brains had swelled markedly within hours of being close to a blast. Some had clear head injuries but many did not. Even in cases involving visible wounds, the extent of swelling was often much greater than expected, leading neurosurgeons to wonder whether blast waves had played a role in addition to penetrating shrapnel. Ling says the patterns of vascular enlargement seen across a range of patients showed a continuum of brain injury, suggesting that there could be milder versions that were less obvious.

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"What's happening in blast injury is that these inner structures [of the brain] are being affected."

—IBOLJA CERNAK, JOHNS HOPKINS UNIVERSITY

That suspicion has grown stronger with hundreds of soldiers returning from the war zone complaining of a common cluster of cognitive and behavioral problems. Army doctors say they have encountered many patients who are unable to perform simple addition and subtraction, read more than one sentence at a stretch, or recall simple things like what they had for lunch. "The majority are individuals who lost consciousness or were dazed after a blast but did not sustain overt head injuries," says Ronald Riechers, a neurologist at Walter Reed Army Medical Center in Washington, D.C. "Within a short time frame, they develop headaches and notice that their reaction time and concentration are not the same as before." Based on these evaluations, DVBIC estimates that 10% to 20% of all soldiers on duty in Iraq and Afghanistan have suffered some type of TBI.

Ling says the TBI numbers prompted DOD to restart its research on blast injury, this time with a focus on the brain. DARPA is funding two main projects as part of the first basic science effort on the topic. One will study the mechanical and cellular effects of blast waves in an animal model. Another will look at the consequences of repeated exposures to low-intensity explosions among military breachers, whose job is to blast holes into buildings using shoulder-launched weapons. "Once you know for certain what in a blast is really hurting the brain and how, you can use that to develop therapies and prevention strategies," says Ling.

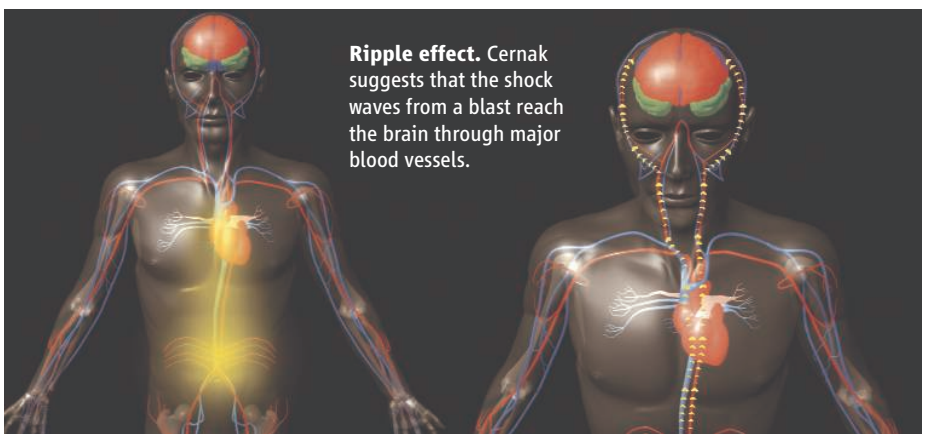
A tsunami in the brain

Although it is becoming accepted that blast waves can cause TBI, Cernak's theory about how the damage occurs is controversial, and it has implications for how best to protect troops. She hypothesizes that when blast waves strike the body, they transfer kinetic energy and cause pressure in the main blood vessels to oscillate rapidly. A pulse travels up through the neck into the brain, damaging axonal fibers and neurons in the hippocampus, brainstem, and other structures close to cerebral vessels. The shock can also injure cells farther out in the cortical regions.

That mechanism is entirely different from the more widely studied effects of acceleration or deceleration in a car crash. Researchers know that a crash impact can shake the brain so violently that axonal fibers are torn. Some say victims of explosions could be experiencing a similar whiplashing, in contrast to Cernak's view—which would mean that helmets designed to dampen that effect could help.

"I am very skeptical that kinetic energy could be transferred through the vascular system," says J. Clay Goodman, a neuropathologist at Baylor College of Medicine in Houston, Texas. "It is much more reasonable to consider the blast effects directly on the cranial vault and the brain."

Cernak says her findings show the vascular route to be more plausible. In experiments that exposed rats and rabbits to a simulated blast wave in a shock tube—a cylinder through which an air pulse is transmitted at high velocity—Cernak and her colleagues found that immobilizing the animal's head with steel plates to prevent whiplash effects did not protect against hippocampal cell damage, as they reported in the *Journal of Trauma* in 2001. Cernak says the vascular-transmission theory could explain the unique combination of symptoms in blast-induced TBI, as well as why neurological symptoms are seen in soldiers wearing helmets. For example, memory deficits hint at damage to the hippocampus, whereas problems in orientation reflect injuries to the cerebellum. "What's happening in blast injury is that these inner structures are being affected," Cernak says, in contrast to TBIs in traffic accidents and contact sports, where the cortex bears most of the brunt.



Ripple effect. Cernak suggests that the shock waves from a blast reach the brain through major blood vessels.

Cernak presented unpublished results last month at the Blast Injury Conference in Tampa, Florida, showing that exposure to blast waves can trigger neurodegeneration in rat brains, fragmenting the walls of neurons in the hippocampus and other regions. Similar findings have been published by Annette Säljö, a researcher at the University of Göteborg in Sweden and a collaborator of Cernak's. Säljö and her colleagues reported in the *Journal of Neurotrauma* in August 2000 that rats exposed to blasts showed a buildup of neurofilament proteins in the cortex and the hippocampus during the week following the injury. This suggests that the damage can worsen over time, like a "slow cooking under the surface," says Cernak: "One could think of it as a horribly accelerated aging of the brain."

If blast waves indeed cause injury by vascular transmission, new types of body armor may be needed. "We would need to develop materials that completely absorb or reflect the full range of blast-wave frequencies generated by an explosion," says Cernak, adding that current body armor only shields against some of a blast's kinetic energy.

Cernak has done pioneering work, says John Povlishock, a neuroanatomist at Virginia Commonwealth University in Richmond, adding that she may be right that a "rapid rise and fall in venous pressure" is what stamps the blast's signature on the brain. But more studies are needed to validate her ideas and translate the animal results into humans: "This is a topic with great economic, military, and social implications," he says, "and as of now, the literature is extremely limited."

Needed: A gold standard

As blast casualties from Iraq have mounted, the U.S. military has stepped up efforts to detect TBI among troops. In July 2006, the Army Surgeon General asked all unit commanders in Iraq to request TBI screening for soldiers displaying "poor marksmanship, delayed reaction times, decreased ability to concentrate, and inappropriate behavior." Troops who have been in a blast are evaluated by field medics using a short questionnaire that asks, among other things, if the person lost consciousness and had trouble remembering things from just before the explosion. Depending on the severity of the symptoms, they are asked to take a day off or see a neuropsychologist.

Some veterans groups believe a more aggressive screening policy is needed, especially because the symptoms of blast injury might not show up until later and because subtle injuries might not show up in standard brain scans. The ideal option, some say, would be to use a biomarker: "We'd like to be able to do a blood test to determine the injury," says Colonel Robert Labutta, a neurologist at the health affairs office at DOD. But until the science of blast injury is established, officials say, it does not make sense to bring home every soldier who has been in the vicinity of an explosion.

The costs of treating TBI victims from Iraq and Afghanistan could be astronomical. At last count, nearly 25,000 soldiers had been diagnosed with TBI. One estimate of the financial burden, calculated by Harvard researchers, puts the number at $14 billion over the next 20 years. But officials seem determined not to miss any cases among troops coming home: In April, VA mandated TBI screening for all Iraq and Afghanistan veterans who come to VA hospitals for any services, even if it's a dental exam.

The spotlight on mild TBI has drawn the attention of older combat veterans who were exposed to blasts but were never treated for neurological symptoms. Many were diagnosed with PTSD; some of the symptoms—such as depression, irritability, and attention deficit—overlap with those of mild TBI. These cases, some reaching back to the Vietnam War, could have significant legal and financial implications, says Edward Kim, a psychiatrist with Bristol-Myers Squibb in Plainsboro, New Jersey, and author of a recent report from the American Neuropsychiatric Association on the mental health effects of TBI. "I question whether DOD and the VA really want to open this can of worms," he says. For example, a veteran with Alzheimer's disease could make a claim pointing to research showing that TBI increases the risk of developing Alzheimer's disease.

Cernak says she has been receiving e-mails and phone calls from veterans thanking her for her research and seeking more information. Last month, she got a call from a 47-year-old woman who had served in the first Gulf War. The woman had been a teacher before she went to the combat zone, where she was exposed to repeated blasts. After she returned home, she had to stop teaching because she could not remember any facts. The story reminded Cernak why she had begun studying this obscure field 2 decades ago. "Soldiers anywhere are one of the most vulnerable populations in the world," she says. "It is a moral obligation to help them."

–YUDHIJIT BHATTACHARJEE

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