DAMAGE CONTROL

BY KRISTIN SAINANI

AS PUBLIC CONCERN INTENSIFIES, STANFORD BIOENGINEERS AND CLINICIANS JOIN FORCES IN A DRIVE TO UNDERSTAND AND PREVENT CONCUSSIONS.

ILLUSTRATION BY BRIAN STAUFFER

IN the fall of her freshman year, basketball standout Toni Kokenis was knocked to the floor during a layup, slid under the basket and—in a freak accident—hit her head on a photographer's camera. She shook it off and continued to play. But she awoke the next morning in a fog. She was barely able to get out of bed to see the team trainer, who diagnosed a concussion, her second. (The first happened in high school.) The Stanford starting guard recovered in a few weeks and went on to play on two Final Four teams, in 2011 and 2012.

The aftereffects of Kokenis's third concussion—caused by an elbow to her head during a pick-up game her sophomore spring—were worse and lasted longer. She was sensitive to light, had constant headaches, couldn't focus and felt like sleeping all the time. She also suffered disconcerting mood swings. "I would go from feeling fine to laughing hysterically to almost sobbing," says Kokenis, '14. "This was one of the hardest things for me to deal with, because I'm usually a pretty even-keeled person."

She battled symptoms well into her junior year. Though she was cleared to play basketball, Kokenis never felt like herself—on the court or off. "I felt withdrawn from everything. It was like I was there, but in slow motion," she says. "I didn't feel comfortable shooting three-pointers because I couldn't focus on the basket long enough to know that the ball was actually going to go near the hoop." When she suffered a fourth concussion that winter, she knew it was time to retire from the sport. Now a graduate student in sociology at Stanford, Kokenis still experiences residual effects if she pushes herself too hard.

Until recently, concussions received little public attention. Athletes brushed them off as insignificant dings to the head. Similarly, scientists dismissed them as "mild" brain injuries and focused on more life-threatening head traumas, such as those caused by car crashes or gunshot wounds. A widely cited 2006 Centers for Disease Control and Prevention report concludes that most of the estimated 1.6 million to 3.8 million sports- and recreation-related concussions that occur in the United States every year go unreported.

But in the past decade, there's been growing recognition of the severity of such injuries. Reports of concussion-related brain damage in professional football players and blast-exposed soldiers have made concussion a household word, and worried parents are holding their children out of contact sports. Scientists are paying attention.

Stanford investigators are at the forefront of concussion research, and they are using Stanford athletic fields as their laboratories. Partnering with teams from football to volleyball, they are tackling such fundamental questions as: What are the biomechanical forces that cause concussions, and how can we prevent them? What happens in the brain during and after a concussion? How can we objectively diagnose and monitor concussions?

The answers should help not only athletes, but also the many others who suffer concussions, and especially those who are prone to them, including soldiers, the elderly and young children.

HEAD-TURNING RESULTS

"There's an unmistakable sound that's two helmets hitting each other at high speed," says head football coach David Shaw, '94. That sound often foretells a concussion, he says.

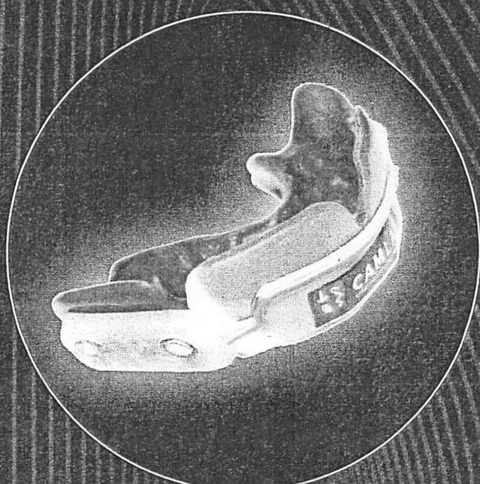
A concussion occurs when a blow to the head or body shakes the brain enough to cause neurological deficits. Although most first-time concussions resolve spontaneously, a small percent of sufferers have lasting impairments in cognition, memory or mood. Several studies show that subsequent concussions are more likely to cause persistent problems. Scientists have also begun to suspect that repeated subconcussive events (milder impacts that don't cause a full-blown concussion) harm the brain, although symptoms may take decades to manifest. The prospect of this slow, silent deterioration is perhaps most ominous.

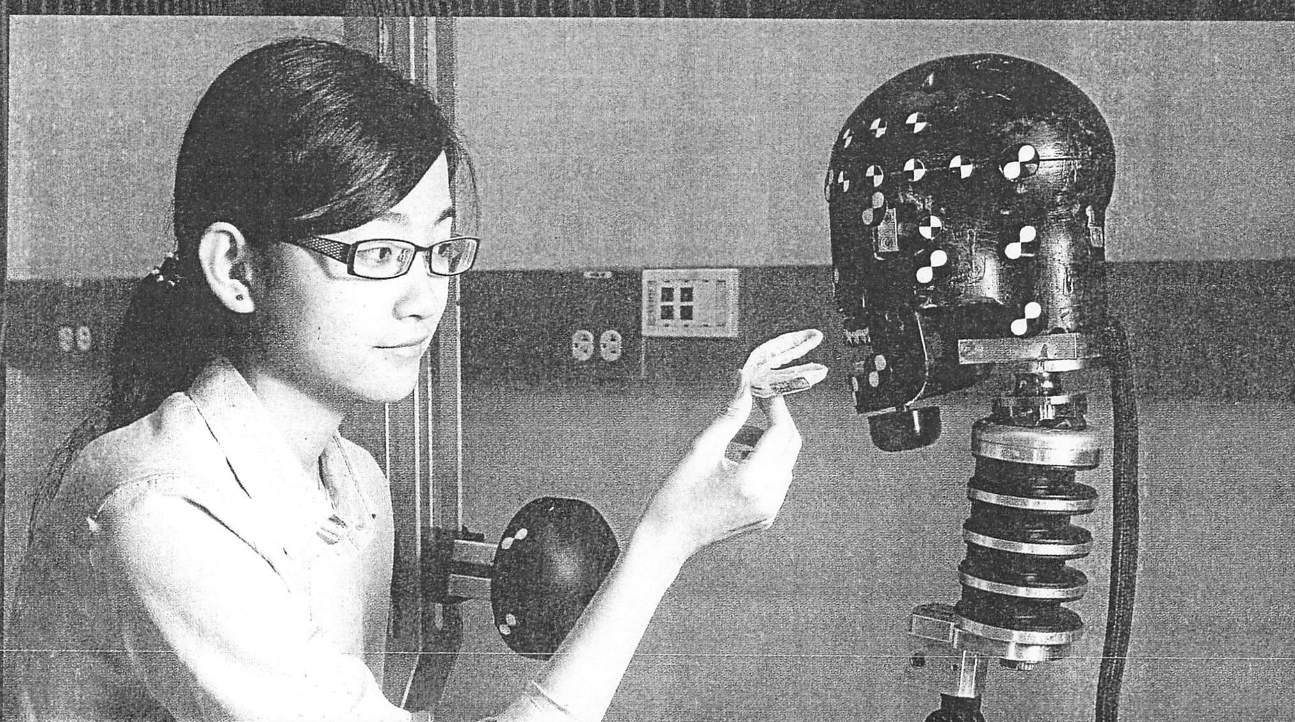
Unfortunately, after years of inattention, the science of concussions remains in its infancy. "We don't even know what a concussion is at a basic, biological level," says Mona Hicks, who oversaw traumatic brain injury research at the National Institutes of Health for nine years and is now chief scientific officer at One Mind, a nonprofit focused on brain disease. This scientific void creates uncertainty when it comes to addressing such controversies as how long to hold concussed athletes out of play, whether to ban heading in youth soccer and how much to change the game of football.

David Camarillo, assistant professor of bioengineering and a former football player at Princeton University, is studying the physics of such hits. His lab has outfitted most of Shaw's team with high-tech, data-gathering mouth guards that the players wear during games. Seattle-based X2Biosystems had developed prototypes for a commercial product; Camarillo's group customized the design for research use. The devices measure how violently a player's head gets tossed around during collisions, falls and other impacts.

"My long-term goal is to prevent concussions," Camarillo says. "The first step is to understand what causes them."

MAKING AN IMPACT: Camarillo (top), Wu and colleagues have pioneered mouth guards that measure and record the g-force of hits to athletes' heads.





CLOCKWISE FROM TOP: SAUL BROMBERGER AND SANDRA HOOVER; LINDA A. CICERO/STANFORD NEWS SERVICE; COURTESY CAMARILLO LAB IN BIOENGINEERING

'It's going to be accepted that you play the game as hard as you can, but you don't go after another man's head because the consequences in and out of the game are too severe for you and him.'

Camarillo's lab is on the second floor of the new Shriram building. The space is a tinkerer's heaven. Engineering students fabricate custom mouth guards on workbenches littered with magnifying glasses, welding equipment, discarded plastic and dental molds. The mouth guards contain tiny accelerometers and gyroscopes—the same sensors embedded in motion-aware smartphones. When deployed on the field, the devices record and store data on impacts that exceed 7 g's, or 7 times the force of gravity. (For comparison, a fighter pilot experiences 4 to 6 g's for longer durations during daredevil maneuvers.)

Most previous studies of head hits in football have focused on linear motion; that is, how fast the head is accelerating or decelerating in a single direction. Camarillo's mouth guards also measure rotational motion—how fast the head is turning—which is believed to play a key role in concussions. Although there are helmet-mounted sensors that measure rotational motion, mouth guards are designed to give more accurate readings, since they attach to the upper teeth and are more tightly coupled to the skull.

Our brains sit in our skulls surrounded by cerebrospinal fluid, Camarillo explains. "You've got this kind of gelatinous blob in a fluid floating in a sealed pressure vessel," he says. A concussion occurs when the brain is sloshed and bounced around in this fluid. Purely linear forces won't cause any sloshing, and thus can't cause a concussion. For example, if you put a head in a vise and tightened it, you'd crack the skull but wouldn't cause a concussion. Camarillo uses the analogy of a snow globe: If you push a snow globe in a straight line, no matter how fast or hard, "the snowflakes will stay perfectly still. They don't move at all," he says. However, the slightest rotation will cause a flurry.

To show what the brain looks like with just a tiny rotation, Camarillo plays a video of a person dropping her head by two centimeters in an MRI machine. "To me, it is astounding just how much the brain vibrates; it looks like clothes in a washing machine," he says.

Doctoral student Fidel Hernandez analyzed mouth guard data from 28 Stanford football players, as well as a handful of boxers and mixed martial arts athletes. His recent paper in the *Annals of Biomedical Engineering* reports that over the course of 19 competitions, the record showed 513 impacts, with an average linear acceleration of about 30 g's. Two athletes experienced concussions, including a football player who was knocked out cold for two minutes after a 106-g impact. But six hits with higher linear accelerations didn't cause concussions. A combination of linear and rotational measures best predicted the two concussive events, and rotational measures alone were moderately better predictors than linear ones. These results bear on preventive efforts. Helmets are designed to dampen linear forces, which prevents catastrophic events like skull fractures and brain bleeds, says doctoral student Lyndia Wu. However, helmets do little to reduce rotational forces, which means they are not optimized to prevent concussions (see sidebar). "A lot of the work we are doing here is trying to change the industry standards," she says.

If Camarillo's team can devise an algorithm that predicts which hits are most likely to cause concussions, then their mouth guards could be used to monitor athletes in real time. "The single largest risk factor for concussion is recent history of concussion," Camarillo says. Thus, pulling concussed athletes out of the game as quickly as possible can prevent further trauma and long-term damage. The mouthpieces, or similar technology, could also track the cumulative number and severity of impacts that an athlete sustains over time, alerting coaches and trainers when an athlete has reached a potentially dangerous threshold.

JIM SHORIN/STANFORDPHOTO.COM

BRAINSTORMING BRAIN STORMS

What happens when you shake the brain like a snow globe? Though no one knows for sure, a prevailing theory is that the brain's connective cables, or axons, get stretched to the point where they may fray or break. If enough of these wires are damaged, the resulting loss of connectivity may cause the symptoms of concussion, explains Michael Zeineh, assistant professor of radiology. Sub-concussive events may not injure enough axons at the same time to cause overt symptoms, but with hundreds or thousands of repeated blows to the head, the cumulative damage may prove to be significant.

Most concussed individuals have normal-looking brains on routine MRI and CT scans. This is why the underlying biology of concussion has been so hard to pinpoint. However, a newer imaging technique, diffusion tensor imaging, can detect axonal damage. DTI measures the movement of water molecules within and along axons. The flow of water is more irregular when axons are damaged than when they are healthy.

Researchers have documented DTI abnormalities in concussed athletes in soccer, ice hockey, rugby, wrestling, lacrosse, football and boxing. Plus, in recent studies of high school and college football players, non-concussed athletes had significant changes in DTI measures over the course of one season; these changes correlated with how often and how hard they were hit in the head. Finally, in a 2013 soccer study, heading the ball more than about 885 times per year was associated with DTI abnormalities, and doing so more than 1,800 times was associated with impairments in memory.

Adding to this body of literature, Zeineh's team will compare changes in the brains of Stanford athletes in high-contact sports and low-contact sports over two years. Besides looking at DTI data, they will search for other markers of harm, including thinning of the cortex (the outer layer of the brain) and iron deposition, an indication of inflammation. They plan to integrate their brain data with Camarillo's impact data.

Zeineh's work will shed light on the short-term effects of concussions and sub-concussions on the brain. But what about the long term? Are subtle changes on the

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MAKING HELMETS BETTER

In the late 1960s, nearly 20 football players died every year from high-impact hits that cracked their skulls or caused their brains to bleed. Scientists then introduced helmet safety standards aimed at dissipating direct forces to the skull. The standards were so successful at reducing fatalities that they remain in effect four decades later. However, they were never intended to reduce concussions—which result from off-center blows that rotate the head. "Despite what some people say, there's nothing on the market right now that will prevent a concussion. Nothing," says Stanford's head athletic trainer, Scott Anderson.

Scientists and entrepreneurs alike are rushing to fill this gap. Bioengineering professor David Camarillo's group has designed a

helmet that fastens to the chest and torso. "The head is small compared to the body. If you put a force on it, it will move fast. But if you can tie everything down, that might prevent rotational forces," he says. A shoulder-tethered helmet is already widely used in race-car driving. Camarillo is also partnering with a Swedish company that makes an airbag helmet for cyclists; the wearable collar inflates around the head during an accident. Compared with rigid helmets, this one substantially reduces impact forces. Another Swedish company makes a football helmet with a movable inner shell. During an impact, the head can slide under the padding, which prevents it from stopping short and jarring the brain.

It's unclear if any of these designs will work. The airbag helmet might even increase concussion risk if it causes the head to bounce too much, Camarillo notes. But many think that the next major advance in helmet technology is imminent. "I predict that there'll be a dramatic drop in the number of concussions in the next five to 10 years with the right equipment," says Jamshid Ghajar, director of the Stanford Concussion and Brain Performance Center.

brain scans of young athletes harbingers of more devastating brain damage to come?

A growing number of professional athletes—some of whom suffered evident mental declines or committed suicide—have been diagnosed posthumously with a neurodegenerative disease called chronic traumatic encephalopathy. Recognized in boxers in the 1920s, CTE was originally called "punch-drunk" syndrome or dementia pugilistica (boxer's dementia). The disease has been found in football, hockey, soccer and rugby players, as well as veterans exposed to explosions. And it's scary: Sufferers become increasingly confused, aggressive, depressed and lost, as their brains fill with the protein tangles that are CTE's calling card. Though CTE is relatively rare (and can only be diagnosed on autopsy), epidemiologic studies have also linked professional football with an elevated risk of more classic neurologic disorders, including Alzheimer's disease, Parkinson's disease and Lou Gehrig's disease.

GAME CHANGERS

It's unclear whether concussions and sub-concussions suffered in youth are risk factors for CTE and other neurologic diseases later in life. But when the stakes are so high, the specter of a link alone warrants attention from coaches, trainers and doctors. "Even in the absence of scientific evidence, we're obliged to act," says Stanford's head athletic trainer Scott Anderson. "We need to protect our kids until the science can catch up."

Gerald Grant, associate professor of neurosurgery and chief of pediatric neurosurgery, treats concussed patients at Stanford and works with Camarillo, providing neurocognitive testing of athletes. He can confirm that some patients never fully recover from one or more concussions: "They're never the same. Their personality is different. Their lives are totally changed."

Multiple studies show that athletes who return to play too soon after a concussion are more likely to sustain repeat injuries and irreversible damage, so prompt diagnosis and conservative management are critical. But concussions are vastly underdiagnosed: One study estimated that in the sport of ice hockey, only one in seven concussions is detected.

"There's very little incentive for the player or the soldier to report their symptoms because of the risk that they are going to be pulled out of the game or off the battlefield," says Grant, MD '94, who served as a neurosurgeon in the U.S. Air Force in Iraq in 2005. In his experience, "No soldier ever wanted to leave Iraq, ever. And athletes are the same."

Sideline neurologic tests, such as memory and balance checks, may miss subtle or early symptoms; and they can be fooled by athletes who deliberately underperform in preseason screening to distort the basis of comparison. But a new 30-second eye-tracking test may catch more injuries. "The concept is really exciting because you can't game the system," says research administrator Hicks.

Cameras embedded in portable gaming goggles track a person's eyes as they follow a dot moving in a circle. Healthy individuals can keep their eyes on the target with high fidelity, but concussed individuals can't focus—so they jitter on and off, explains Jamshid Ghajar, a clinical professor of neurosurgery who is director of the Stanford Concussion and Brain Performance Center and president of the Brain Trauma Foundation. Eye tracking can even distinguish concussed individuals from sleep-deprived ones, his team has found. They are now gathering participants, including Stanford athletes from a variety of sports, for a study that will establish normal values and assess eye tracking after a concussion. The crossover of Stanford athletes also participating in Camarillo's and Zeineh's studies will allow researchers to link head impacts and brain changes with eye-tracking deficits.

Eye tracking could also be useful to manage concussions. Athletes may feel fine a month post-injury, but if their eye tracking is still abnormal they may need more time to heal. Kokenis could have benefited from such a tool.

Grant is also developing objective tests to improve clinical care. Using stored blood from soldiers with a history of post-traumatic stress disorder or concussion, he is hunting for biomarkers that predict persistent symptoms. "If we could identify early on those people that are at risk for having complications, then we might be able to do something about it," Grant says.

Hicks says the last thing we want is for parents to hold their kids out of sports and recreation, but we have to make the games safer.

Forty-eight states have now adopted the Lystedt law, which formalizes the saying, "When in doubt, sit them out." Athletes under age 18 who are suspected of having had a concussion must be removed from play and cannot return to practices or games until they are cleared by a medical professional. College teams are also implementing strict return-to-play protocols after a concussion. Stanford was one of the first universities to put these policies in place, trainer Anderson says.

After coming under fire for ignoring the issue too long, the National Football League has recently begun to implement rule changes to protect athletes' heads and necks. The rules are controversial; some naysayers are forecasting the death of football as we know it. But Shaw is not worried. "The game is not going to go away," he says. "The game can still be played at a high level. It can still be played aggressively. It's still exciting.

"It's going to be accepted that you play this game as hard as you can, but you don't go after another man's head, because the consequences in and out of the game are too severe for you and him," Shaw predicts. Kokenis concurs. "I would have rather had any other injury." ■

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