Huge studies peer inside brain, blood to unlock mysteries of concussion

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LOS ANGELES ? An image of a concussed brain fills the computer screen, with shredded nerve cells lit up in red and orange. As Dr. Christopher Giza watches, the brain rotates. A time-lapse film shows the damaged cells cooling to green and blue as they slowly heal.

This advanced imaging technique offers a rare look inside a traumatized brain and its complex recovery.

Giza?s work is part of several ambitious efforts now underway across the nation that could redefine the science of concussion and fill many huge and frustrating gaps. There is still, for example, no definitive diagnostic test to show whether a brain has been concussed. Or how bad it is. Or when it has healed.

So the NCAA, the Pentagon, and the National Institutes of Health are spending tens of millions to enroll tens of thousands of college athletes, military cadets, and brain injury patients in studies that will track them in real time through their concussions and recoveries.

Through blood analysis, advanced brain imaging, genetic tests, cognitive screenings, and more, researchers will attempt to see what exactly happens to a concussed brain, how long it takes to recover, and if there is any way to speed healing. Some athletes will even wear helmets and other equipment rigged with sensors so researchers can track hits and directly correlate them with injuries.

Researchers hope the new studies will become the equivalent of the Framingham Heart Study, the landmark research that determined major cardiovascular risk factors by tracking
the health and habits of thousands of enrollees over a half-century.

There's hope, in time, for a simple blood test to help diagnose concussion, perhaps even administered on sidelines with a needle stick; for better imaging tools that can show exactly how much damage has occurred in a shaken brain; and even for treatments that could be administered right after injury, as with stroke patients, to keep brain cells alive and working.

Researchers also hope to find out why certain groups, such as women and people with learning or mood disorders, seem to be more prone to concussions, why some patients recover in days, while others suffer for months, and why some hits lead to long-term brain damage.

?These are the largest concussion studies ever conducted,? said Michael McCrea, a neuropsychologist at the Medical College of Wisconsin who has been studying concussions since 1994.

?In my first paper,? McCrea said, ?I think there were about a half-dozen concussions.? Now, he co-leads the $30 million NCAA and Defense Department study, the CARE Consortium [1], which has so far enrolled 17,582 athletes and cadets and recorded 689 concussions.

As is common in the field, many concussion researchers working on these new studies have ties to the NFL and sports world. McCrae sits on the NFL's Head, Neck, and Spine Committee, and Giza served on California's boxing commission and has received funding from a program sponsored by the NFL and General Electric.

While detractors liken the NCAA's study of concussion to tobacco companies studying smoking, Giza argues that sports leagues have a moral obligation to research head injuries. ?You could argue it's not ethical to let people participate in dangerous things and not try to make it safer,? he said.

Video on CTE [2]

Alex Hogan, Hyacinth Empinado/STAT

Concussions, or even more mild, repetitive head trauma, may lead to a degenerative brain disorder called Chronic Traumatic Encephalopathy.

An energy crisis in the brain

Giza's office at the University of California, Los Angeles is filled with reminders of his mission – a framed print of Robert De Niro in ?Raging Bull,? a jello-like molded brain, a stuffed toy shaped like a neuron. A pediatric neurologist, Giza directs UCLA's Steve Tisch BrainSPORT Program. He's worked with brain trauma not only in his clinic, but also as an advisor to the military in Afghanistan and as a member of Yosemite National Park's Search and Rescue team.

He has learned to see concussion not as an event, but as a process. A concussion, says Giza, sets off a cascade of events [3] ? both damaging and protective ? that change the brain by the minute, hour, and day.
When the brain shakes within the skull [4], axons — the long, slender projections of brain cells that carry messages — stretch and tear. This upsets the delicate balance of ions that allow neurons to transmit electrical signals, which may be the reason concussions can cause intense headaches and sensitivity.

In an effort to stem damage, the brain uses massive amounts of energy [5] to restore balance by redirecting ions. At the same time, because of the injury, blood flow to the brain slows, putting the brain into what Giza calls an energy crisis.?

It is during this energy crisis that the brain may be vulnerable to additional hits, even light ones, that can be far more damaging than the first. Giza’s work in rats with colleague Mayumi Prins shows that animals which suffer a second concussion soon after a first take far longer to recover and suffer from brain degeneration, while those given ample time to recover return to normal.

In humans, it’s just not clear when a concussed brain returns to normal. The symptoms may be gone, Giza said. But brain metabolism is still off.?

Recent brain imaging work — like that time-lapse video showing the tattered neurons slowly recovering over a month — shows that concussed brains often remain altered [6] long after the seven- to 10-day rest period many physicians advise, said Semyon Slobounov, who directs the Penn State Center for Sport Concussion and Service and recently joined a national consortium [7] hoping to use MRI work to improve concussion treatment.

?Maybe they are better after one, two, three, or four months, or maybe they never recover,? he said. But surely they are not better after only seven to 10 days.?

The quest for a blood test

Tests now in development could help determine just when — or if — it is safe to return to contact sports after a concussion or a hit. We have to understand the threshold, Slobounov said. How much is too much??

Because brain images can cost hundreds or more, Slobounov said it was unlikely they would be used routinely in concussion treatment. But he hopes researchers will be able to link damage found on brain images to markers in the blood.

Two biotech companies are working on exactly that; they hope to bring blood tests to market in the next few years.

But it’s still not entirely clear what a blood test should look for if it’s to help diagnose a concussion or determine its severity.

Dr. Linda Papa, an attending emergency physician at the Orlando Regional Medical Center, has been searching for a telltale marker in the blood for 15 years. When she looked at the literature, she found that scientists have proposed (and then, in many cases, discarded) no fewer than 99 different proteins as molecular signals that the brain has been concussed.

Two leading candidates at the moment are proteins called GFAP and UCH-L1. San Diego-based Banyan Biomarkers is hoping to commercialize a handheld test for concussion using
these markers within a few years, said Papa, who conducts clinical trials for Banyan but said she elected to receive no financial compensation to avoid conflicts of interest.

Another company, Quanterix of Lexington, Mass., is developing a test that can detect proteins with 1,000 times more sensitivity than a standard blood test, according to chief executive Kevin Hrusovsky. Important because only small amounts of brain proteins may leak past the blood-brain barrier during lesser injuries, such as the repeated subconcussive events that some think may lead to chronic traumatic encephalopathy.

“The real challenge is how do you get to the less severe cases,” said Hrusovsky.

Progress can’t come soon enough for those who treat concussion.

Dr. Geoffrey Manley, a professor of neurosurgery at the University of California, San Francisco leads an NIH study called Track TBI that is obtaining blood samples and brain images from 3,000 patients. The field lags 40 years behind heart disease and cancer, he said. We haven’t had any new treatments in 100 years.

Correction: A previous version of this story misspelled Michael McCrea’s name.

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