the fearful eye

USING VIRTUAL REALITY TO HACK FRIGHT

I STOOD, EXPOSED, AT THE PROW OF AN UNDERWATER VESSEL AND WATCHED A GREAT WHITE SHARK COME TOWARD ME, ITS ROWS of gleaming, pointy teeth headed for my throat.

The shark got within about 2 feet of me, hung a U and smoothly swam away. Another approached. I was stuck in the middle of a whole school of them.

A guilty source of comfort was the knowledge that a couple of the other divers were way more exposed than I was. I wouldn't want to be in their fins.

Most calming of all, I knew that none of this was real — or, at least, the conscious part of my brain did. Had I been convinced I was really 100 feet underwater and surrounded by these bionic buzz saws, my fear levels would have been registering on the Richter scale. I would be freaking out.

In actual fact I was standing in a small room immersed in sensory inputs, mostly visual, telling me that I was below the surface of the waters off Guadalupe, an island 150 miles west of Baja California — dodging the serial swim-bys of a few dozen great white sharks.

BY BRUCE GOLDMAN

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Vision's role in fear

Andrew Huberman, PhD, an associate professor of neurobiology at Stanford, doesn't know the meaning of fear — literally. You probably don't, either, although we all know it when we feel it: Our heartbeat speeds up, our limbs tingle, our breathing becomes shallow and rapid, our muscles pulse with multiples of their normal strength and time seems to slow down.

But there's more to fear than a constellation of peripheral bodily signals, Huberman says. It's a state of mind as well, a holding pattern designed to maintain heightened arousal while you figure out what to do next. To neuroscientists that means it's also a state of the brain, shaped by eons of evolutionary trial and error during which the punishment for failure to respond appropriately and quickly was often death, not to mention fewer viable offspring.

Huberman wants to learn more about fear by identifying the neural circuitry underlying it, and pinpointing the component circuits' settings during episodes of fear. In the long run, Huberman also hopes to help people gain more control over irrational fear, a response that can get tripped off so often or so severely it hampers healthy coping.

To study fear, one must induce it. This Huberman is doing. Having spent the last 20 years or so studying the neurobiology of vision, he's taking a mainly visual approach, with the help of a virtual-reality chamber his team created from scratch.

Vision is our dominant mode of sensation, says Huberman.

"Nearly 40 percent of the human brain is dedicated to processing visual information," he says. So it stands to reason that visual information about a real or imagined threat gets VIP treatment in the brain.

But very little has been done in charting the flow of information from visual input through the deeper centers in the brain where fear is generated, processed, acted on and overcome, Huberman adds. "There's still so much we just don't know."

We do know that images landing on the retina trigger signals in nerve-cell relays that, after numerous processing steps, yield a conscious perception of what we see. But we've also evolved specialized, faster forms of response to visual threats. Faced with a poisonous snake or a hungry beast, you don't want to wait until you've been devoured or injected with a lethal toxin before you get around to stepping back, starting to run or putting up your

ANDREW HUBERMAN, PICTURED HERE WITH A PHOTOGRAPH OF A GREAT WHITE SHARK. SHARK PHOTOGRAPH BY MICHAEL MULLER (PUBLISHED WITH PERMISSION).

dukes. You need to register right away that something bad is happening, and figure out exactly what it was later.

There's an alternate fast-track route, from the retina to a well-studied brain structure, the amygdala, which speedily carries out many functions, including flagging threats. Signals from the amygdala can trigger secretion of stress hormones from the adrenal glands into the bloodstream, unlocking loads of energy-rich glucose stored in the liver for rapid uptake by the muscles.

The mice that roared

Other important, though not as well-studied, brain centers are involved in visual threat detection and response. Lindsey Salay, a graduate student in Huberman's laboratory, has identified one of those centers, right smack in the middle of the brain. Ironically, the brain center Salay found responds to fear-inducing stimuli by stiffening the spine.

One thing mice are afraid of — innately so, no previous training required — is aerial predators: hawks, owls and so forth. Put a mouse in an open field, and it's a sitting duck.

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Within a second of perceiving an airborne predator, that mouse almost invariably makes a decision to either freeze, which (it hopes) will make it harder to detect, or (if a shelter is available) make an immediate run for it. There aren't a whole lot of other promising options.

To determine how brain activity changes in the presence of a visual threat, Salay employed a laboratory mock-up of a predator's approach: a mouse-scale arena akin to an open field, with a video screen covering most of its ceiling. On that screen could be shown an expanding overhead disk that simulates an approaching bird of prey.

A postdoctoral scholar in Huberman's lab, Melis Yilmaz Balban, PhD, had created this contraption while a student at Harvard and then CalTech. In a study published in 2013, Yilmaz Balban showed that mice sighting a dark overhead expanding disk either run for cover or freeze for an extended period.

Salay compared the brain activity of mice that had been exposed to this "looming predator" for a few minutes with that of mice that hadn't. She located a particular region called the ventral midline thalamus, or vMT (we humans have an analogous structure), that became activated in the presence of the overhead expanding disk but was relatively quiescent in its absence.

Salay found that despite its activation by fear-inducing stimuli, the vMT wasn't just another cog in the brain's run-and-hide machinery. To the contrary: If you directly stimulate mice's vMT sufficiently, she observed, instead of freezing or running for cover they become uncharacteristically inclined to stand their ground. They remain right out there in the open and start rattling their tails.

"You can actually hear their tails thumping on the floor or against the wall of their enclosure," says Salay. This defiant behavior, displayed by macho male mice just before they start fighting or by nursing mouse moms when a strange male intrudes into their space, is observed only rarely in regular mice under simulated aerial attack, and then only after they've ducked into a shelter they can crouch in, safe and sound.

The vMT-stimulated mice also run around more out in the open. That, as well as the tail-rattling, would make the mouse much more visible and tantalizing to a real attacker in real life.

It's as if the mouse is yelling at the approaching hawk, "Yah! C'mon, make my day! You don't scare me, Tweety Bird."

Call it "courage."

Says Salay, "It's like flipping a switch from cowardice to bravado. The vMT is the switch."

And the mice *like* playing Mighty Mouse. Given a choice between two locations, one where they get their vMT stimulated and another where they don't, they preferentially head for the one that generates stimulation.

Humans apparently like it, too. According to studies from the early 1960s, patients preferred stimulation of a brain region analogous to a mouse's vMT over stimulation of any other brain area tested, including ones associated with sexual arousal. Oddly, when asked to describe the sensation they perceived when it was stimulated, they didn't recount titillating tales associated with pleasure. Instead, they reported feeling "frustration and mild anger." Hmmm. And they *liked*

it. This could explain a lot about our attraction to sports, not to mention the chemistry in a person's previous relationships.

In short, the vMT is like Popeye's spinach. Activating it appears to bring on a bird-flipping rush of righteous defiance.

The lion and the gazelle

A GAZELLE RUNNING for its life and the lion chasing it are, in many respects, in similar physical states. Both animals' adrenal glands are pumping furiously, and both animals' livers are shoveling tons of glucose into their bloodstreams. Their hearts are pounding, their breathing is accelerated, their senses are heightened.

So, what's the difference? Well, for one thing, their state of mind. The lion wants to be there; the gazelle really doesn't.

Activating the vMT appears to turn a mouse's mental state in the face of a harrowing situation from gazellelike to lionlike. What if you could do that in humans, too?

"We're hoping to learn how to turn gazelles into lions," says Huberman. Doing that doesn't necessarily require gaining direct physical access to a person's vMT. That's lucky, because you can't just tuck a bunch of electrodes into the middle of people's heads and crank up the juice. So instead, Huberman and his teammates are planning to induce fear under controlled conditions; monitor some of the more easily accessed autonomic states that accompany it; and see if there are reliable, testable ways of reducing it. For this, they've turned to virtual reality.

VR is uniquely capable of capturing visual experiences so that the full sphere of visual input gets reproduced: Put on the goggles, hit the "play" button, and wherever you look, you'll see a 3-D replication of pretty much whatever you would have witnessed in the real-life scenario. Audio input, easily provided, further enhances the experience.

Huberman's group equipped its VR chamber with an observation window so investigators can monitor participants in real time, and with padded walls in case a participant reflexively makes a run for it under the mistaken impression that an open field lies ahead.

After filling out questionnaires concerning their current and general levels of anxiety and fear, participants will be fitted with sensors and filmed as they undergo a series of unsettling VR scenarios, of which the shark encounter is just one. Afterward, they'll be coached in one of a variety of ways that might help them dial down the typically uncomfortable, often decision-hindering, and sometimes debilitating autonomic reactions that, given the corresponding mental state, we categorize as fear. Then they'll be tossed back into the VR chamber for a repeat round of the hair-raising episodes to see if the training worked.

Huberman and his colleagues hope to run hundreds of healthy, normal participants through this just-completed VR chamber in the next year. The idea is to establish baselines for the various parameters being measured.

Eventually Huberman hopes to introduce hundreds or even thousands of participants, including people with post-traumatic stress disorder, generalized anxiety disorders or a variety of phobias, to the chamber.

Many people carry around uncomfortable levels of fearfulness with them even when they're not contending with an oncoming 30-foot-long shark. During their lifetimes, about 5 percent of all Americans will be diagnosed with a severe anxiety disorder, nearly 8 percent will receive a diagnosis of PTSD and more than 10 percent will suffer from a phobia. They can't simply calm themselves by repeating, "It's not real" or "This isn't really a threat."

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Invoking journalistic privilege, I volunteered to be the first person to test the waters, as it were, by being treated to a walk-through of the entire sequence of scare scenarios. So here I stood in the customized chamber, begoggled, headphoned and festooned with multiple electrical leads monitoring my heart rate, breathing and sweat output.

Cameras in the room's upper corners spied on my face and hands, while the goggles fed me virtual-reality footage. (They were also checking my pupil size, a good indicator of a person's arousal level: the wider the pupil opens, the higher the arousal.) Watching through the observation window was Yilmaz Balban, the creator of the "looming predator" paradigm.

VISUALS PIPED IN THROUGH VIRTUAL REALITY GOGGLES PLUS AUDIO AIM TO CREATE TERRIFYING EXPERIENCES FOR HUBERMAN'S STUDY SUBJECTS.

"When I put mice in a box and showed them a defined stimulus — an overhead expanding disk — they exhibited an easily identified and measurable behavioral response: freezing or running for cover," she says. "Now, I wanted to put humans in a box and see what happened and whether that could be measured, too."

So she conducted an online survey asking people what they're afraid of, and received lots of feedback: Plenty of us are afraid of heights, spiders, snakes and vicious dogs. Oh, and sharks.

Scare scenarios and high hopes

In October 2016, Huberman and a few members of his team traveled to Guadalupe, an island off the coast of Baja California where great white sharks abound at that time of year. Accompanying them was famed Hollywood photographer and skilled open-water shark diver Michael Muller. Huberman, Muller and other divers entered a cage that was then submerged 30 meters straight down into a school of great whites. From that submersible, Huberman shot 360-degree "spherical video" (wherever you look, you see whatever was there when the camera was filming the scene). Muller and a few other divers left the cage to get very up-close video of the 14- to 20-foot long, 2-ton creatures.

"Visually speaking, it's about as real as being there," says Huberman. "The only difference is you don't get wet — although some people sweat a lot." I watched this episode unfold all around me during my VR experience.

I was also subjected to scenarios in which I was perched on a branch of a very tall tree hundreds of feet above the sidewalk, or seated next to a vicious, toothy pit bull that "attacked" my arm. Rounding out the picture were computer-generated but nonetheless ultra-realistic bouts of leaping off a plank several stories above the ground, and fending off attacks by a large hairy spider with the rough equivalent of a baseball bat.

In the latter scenario, you're supposed to play a complicated game in which you aim a wand at a wall to make lit-up squares flip to dark and vice versa. But that's just a distraction.

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WEB EXTRA

See our video at http://stan.md/2uN5sev

before he enters his apartment building, and as soon as he enters his apartment, he must wash his hands.

"It's a ritual now," he says. "There has never been a time that I haven't done that, except those two weeks after the ketamine."

When he heard that certain private ketamine clinics are now offering the drug as treatment for OCD, he said he understands why patients take the risks and pay the high prices. As more research has become available, he's begun considering it himself.

"I've been suffering through my OCD for so long, I've gotten to the point where I'd try anything," he says. **SM**

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You soon become aware that there's a gross, hairy tarantula on the wall behind you. At least they give you a bat to smash it with. I chose to do so. But it was rigged. I discovered the bat couldn't kill or even dent the damned spider. It just caused the spider to leap off the wall and fly into my face or onto my clothes. You could say I was moving around a lot during this episode.

Afterward, Yilmaz Balban told me that I was most pumped, autonomically speaking, while I was locked in gladiatorial combat with the spider.

"I wasn't scared, though," I blurted out, not without pride and, perhaps, a hint of emotional amnesia.

"You were aroused."

I guess that's how it feels to have your vMT stimulated.

After spending over an hour under the spell of a pair of VR goggles, ripping them off is somewhat of a shock — a rapid splashdown into what shrugging techies, videogame addicts and others for whom ordinary reality has been demoted call "the default world."

To ease my re-entry, Huberman walked me down the hall into his office, offered me a seat in a body-contoured plastic chair and slapped some headphones on me. For the next 15 minutes, I was guided through a recorded, customized audio de-stressing session consisting largely of controlled-breathing and relaxation exercises. It worked so well that for the last several minutes I didn't know where I was, or care.

It was a preview of what is to come. Huberman wants to put science to work developing tools for systematically reducing pathologic fear and anxiety. After their exposure to the battery of threats, participants will receive training in various methods for doing that.

"Our goal isn't just to learn about fear, but to test ways of engaging in more-adaptive coping — to help people make more logical decisions in the face of fear," Huberman says. "There are a lot of practices already out there that claim to reduce anxiety. We know they have some utility." But rigorous testing of these methods isn't easy, he says, due to the lack of standardization and difficulty in measuring their component inputs or their outcomes with any exactitude.

One of several potential fear-countering techniques the researchers will test is controlled breathing. Choppy, rapid breathing stimulates arousal, whereas deep, slow breathing patterns with emphasized exhalation purportedly induce calm.

"We're not talking about meditation," Huberman says. "This is about how you can control your state by action, not inaction — how to cope when you have to make a split-second decision or when you are stressed and know it but can't seem to snap out of it. We want to come up with protocols that prescribe exact, testable, steps: for instance, inhale for two seconds, hold for two seconds, exhale for four seconds, and don't worry about keeping a mantra in mind — how would we measure that, anyway? Behaviors like breathing, I can measure carefully."

Huberman sees a tremendous potential for testable fear-reduction techniques. "We're talking about testing and developing practices that are teachable, portable and free," he says.

But, he adds, "We're not trying to 'cure' fear. We want to develop coping tools for reducing *irrational* fear.

"Fear can keep you alive. Most people should stay away from sharks." **SM**

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FEATURE

Bionic

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THE NEXT GENERATION

Scientists' ultimate dream is to build a visual prosthesis so small and powerful that it can stimulate specific neurons inside the retina, rather than sundry patches of them. That's the goal of E.J. Chichilnisky, PhD, a Stanford professor of neurosurgery and of ophthalmology.

"Think of the retina as an orchestra," Chichilnisky explains. "When you try to make music, you need the violins to play one score, the oboes to play a different score and so on." Likewise, the retina's 1 million or so ganglion cells are composed of about 20 distinct types. Each plays a slightly different role in transmitting the perception of shape, color, depth, motion and other visual features to the brain.

Chichilnisky joined the Stanford faculty in 2013, after 15 years at the Salk Institute for Biological Studies. Since his days as a Stanford doctoral student in the mid-1990s, he has worked with a variety of physicists and engineers, notably Alan Litke, PhD, of the UC-Santa Cruz Institute for Particle Physics, to develop small but powerful electrode arrays capable of measuring neural activity at the cellular level.

To better understand the patterns of electrical activity in the retina, Chichilnisky and his colleagues use eye tissue taken from primates that have been euthanized for other medical studies. By placing small pieces of retinal tissue atop the microchip arrays, then exposing those samples to various patterns of light, they've been able to record and study the distinctive electrical responses of five different types of retinal ganglion cells, which together account for 75 percent of the visual signal sent to the brain. They've also developed techniques to replicate those electrical patterns, artificially stimulat-