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By Erin Graham

Hugging her stuffed pink bear, 9-year-old Gwendolyn Guay snuggles under a homemade blanket in her hospital bed, watching a Mickey Mouse cartoon. But she's not simply passing the time. Through this seemingly idle activity, she's making a rare contribution to neuroscience.

Streaming out of Gwen's head are scores of fine wires, neatly bound together in a big, gauze-like hat. They're connected to a machine that records electrical pulses picked up from 108 tiny electrodes directly attached to Gwen's brain. Joseph Madsen, MD, her neurosurgeon at Children's Hospital Boston, implanted them a few days ago to help pinpoint the spot in her brain that's misfiring, causing her to have unrelenting epileptic seizures.

Gwen's neurologists will also use the recordings to map the functional areas of her brain, millimeter by millimeter, charting the areas that house her language, movement and memory skills. If the borders between the epileptic and healthy brain tissue are clear, Madsen will be able to surgically remove the defective brain tissue, giving Gwen a good chance at a seizure-free future.

This glimpse into the inner workings of Gwen's brain is invaluable not only to her epilepsy team, but also to a cadre of researchers. Such detailed recordings of the brain's firing patterns, with spatial resolution measured in millimeters, time in milliseconds and voltage in microvolts, are extremely hard to come by, since people don't generally allow their skulls to be opened for the sake of science alone.

For the past decade, several dozen patients in Children's Epilepsy Program, like Gwen, have granted researchers access to this treasure trove of data, and given them the opportunity to conduct their own innovative tests. It's a rare glimpse, since only about 5 percent of epilepsy patients undergo surgery. The data are not only furthering epilepsy research—and helping to make surgery safer and more effective—but also shedding light on how the mind works.

"It's dramatically productive, since there are so many brain functions needing new understanding," says Madsen, who often helps facilitate the experiments. Studies have ranged from the neurological (how do we make memories?) to the nuanced (how do we appreciate music?), and it's these more enigmatic questions that have Madsen most excited. "We want to find out what the brain does at a deep level," he says. "We have this great opportunity to study parts of

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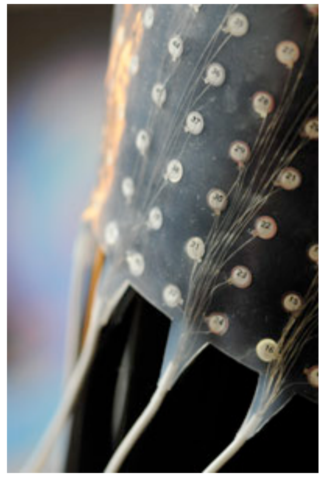
the brain responsible for things like our sense of humor, creativity, how we love someone and why we can have an emotional response to a sunset. These are critical parts of being human and we have an obligation to try to understand them."



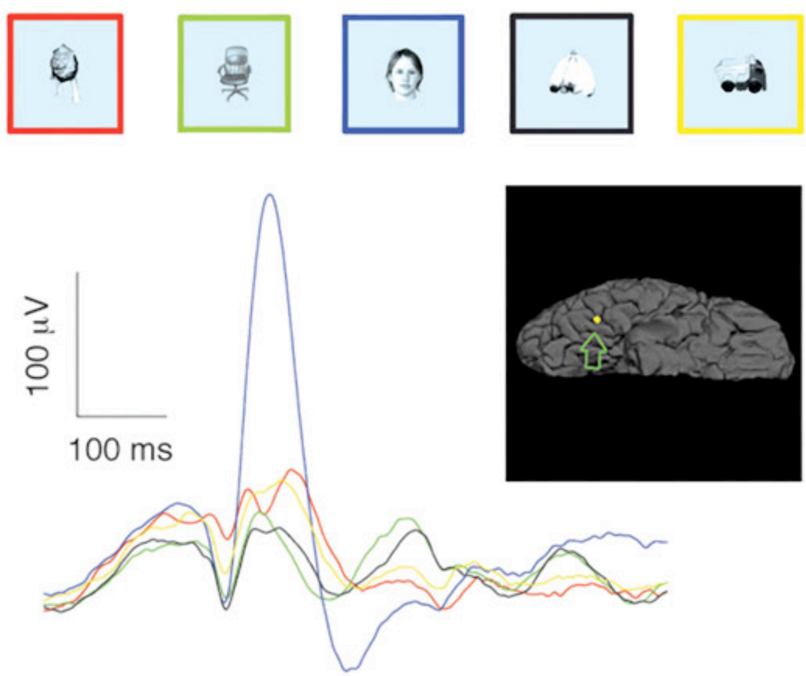
To map Gwen's brain functions, millimeter by millimeter, her surgeons opened her skull and placed thin strips of silicon, studded with 108 electrodes, directly on her brain. The electrodes connect to a computer that records brain firing patterns in exquisite detail. This rare glimpse into the inner workings of the human brain allows researchers to explore everything from how we make memories to how we appreciate music.

A VISIONARY STUDY

Gwen's foray into neuroscience research starts a few days into her week-long, 24-hour-a-day brain recording period, when a team of Children's researchers, working with Gabriel Kreiman, PhD, MSc, of Ophthalmology, pays her a visit. Kreiman has studied the neuronal circuitry of Children's epilepsy patients for years, conducting tests and pairing the results with their brain recordings. He's now looking at how the brain processes visual information, hoping to learn what kinds of circuits the brain uses to recognize objects and form visual memories. "We want to know if certain areas of the brain react when we see a picture of, say, a face," he says. "Are these areas different from those that react to a house or car? And what happens when see several images at once or when we memorize them?"

For several hours, researchers from Kreiman's lab show Gwen pictures on a laptop computer and ask questions to test her memory of them. Sometimes the images are distorted in specific ways to test what happens to Gwen's neurons when she sees something unexpected. The scientists also collect data while Gwen watches Disney cartoons; later, they'll examine how her brain's firing patterns line up with images in the cartoons, frame by frame.

Kreiman will spend months, if not years, deciphering the information. "It's like studying DNA, but instead of trying to break a genetic code, we're trying to decipher a stream of electrical information," he says. Already, he's found that the brain, at an early processing stage, can rapidly recognize objects under a variety of conditions. As the brain's vision algorithms become clearer, Kreiman envisions teaching them to computers so they can act as sets of eyes. "One day computers with video cameras will do visual recognition better than humans," he says. Although it's a long way off, computers could spot terrorists in airports or help drivers avoid collisions. Kreiman even imagines interfacing computers with the brain to give blind people partial sight.



A glimpse at vision
Gabriel Kreiman's research on patients undergoing surgery for epilepsy has found that different kinds of images stimulate responses from different parts of the brain. The graph here shows recordings from a single electrode, color-coded according to the type of object displayed. The yellow dot on the inset brain image indicates a location in the visual cortex that responds selectively to human faces, as shown by the spiking blue line.

PARTNERING TO PREDICT SEIZURES

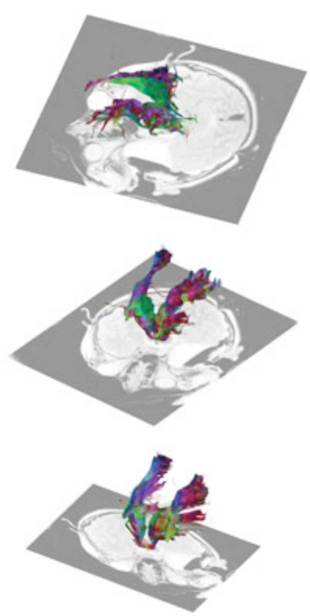
As Gwen's monitoring proceeds, an overhead video camera captures her every expression and head movement. Teaming up with Children's, researchers from the Massachusetts Institute of Technology (MIT) Media Lab have mounted the camera to test an invention called Face Reader, which interprets facial expressions. While Face Reader was designed to help people with autism interpret other people's facial signals, the researchers see another use for it in patients like Gwen. By identifying when she appears to be happy, angry or sad, and then matching these results with the brain recordings, they hope to not only shed light on how facial movements and emotion work together, but also reveal which parts of Gwen's brain are being used for different feelings. "We have these incredible, real-time data that let us quantify what the brain is doing when we express an emotion, or when our mood changes," says Madsen. "This information could be critical for the epilepsy surgery of the future."

Throughout her week of brain monitoring, Gwen wears what looks like a big fuzzy bracelet, part of another MIT collaboration. Small electrodes embedded in this high-tech wristband's fabric log changes in her nervous system by sensing subtle changes in the surface of her skin, like an increase in perspiration or temperature. The researchers will synchronize these data with Gwen's brain recordings and search for patterns, looking for early physical warning signs of a seizure —potentially giving epilepsy patients more ability to predict seizures and greatly improve their quality of life. Doctors also envision a tiny cranial implant that would stop approaching seizures by sending a small electrical impulse into that part of the brain. But to make it work, they need to know where and when to send that signal.

THE BRAIN'S SHIFTING SHAPE

After a week of intensive monitoring, Gwen's surgery is about to begin. To create a final "blueprint" of her brain, her epilepsy team has combined her brain recordings with high-resolution brain imaging scans. But these images never exactly match what surgeons see after they open a patient's skull. When the brain is exposed, its shape can shift by several millimeters, due to pressure changes and a loss of cerebrospinal fluid. The epileptic areas also change position, enough to make some surgical cuts come dangerously close to healthy brain.

Children's Director of Radiology Research, Simon Warfield, PhD, is countering this problem with a technique called diffusion tensor imaging, which creates a 3-D picture of the brain during surgery. The images, taken in just four minutes, show the microscopic fiber tracts and connections between areas of the brain, just as surgeons are determining their navigational course. Children's is one of just two hospitals in the world that have this intraoperative imaging system, known as the MR/OR—and as Madsen operates to remove Gwen's pea-sized piece of epileptic brain tissue, she becomes one of Children's first patients to undergo this live, 3-D brain scan (see images at right).



Tracking tracts
These brain images were taken during Gwen's surgery, while her brain was exposed, using diffusion tensor imaging. The wing-like structures are projections of millions of microscopic tracts of nerve fibers. This new kind of intraoperative

According to Warfield, a better understanding of how the brain changes around epileptic areas may increase the number of patients able to undergo epilepsy surgery. Madsen also sees this technology benefiting patients with brain tumors. "This would especially help if we're worried we're too close to a functional area, like a spinal cord connection, but we don't want to leave any of the tumor behind," he says.

FURTHERING GENETIC STUDIES

Soon after Madsen removes Gwen's epileptic brain tissue, doctors put it into oxygenated fluid and hand it to a team of researchers, giving them a rare chance to study abnormal human brain tissue that still has living cells. "It's a window into what's actually going on in the epileptic brain," says Frances Jensen, MD, Children's director of epilepsy research, who is seeking to understand why seizures happen and develop better drugs to prevent them.

imaging is rarely done—Children's is one of two hospitals in the world that have this technology.

When neuroscientists like Jensen look at regular brain tissue under a microscope, they see what they call the "enchanted loom": intricately woven layers of cells that connect in an organized way and point in a certain direction, in beautifully laid out rows. But damaged tissue doesn't look quite so enchanting. A fundamental question in neuroscience is how epileptic tissue's disorganization leads to a change in the brain's circuitry—or vice versa—and how this leads to a seizure. Jensen believes the answer may lie at the cellular and molecular level. The epileptic brain appears to go through a series of changes at different stages in the disease process, and Jensen aims to find out why.

"If we see certain proteins and genes expressed, we can develop drugs that target only those genes," Jensen says. Current anti-epileptic drugs affect all of the brain's cells, with unwanted effects on mood and cognition; a targeted drug that homes in on epileptic cells alone would be ideal. In addition to studying seizure mechanisms, Jensen can directly test experimental drugs on Gwen's brain tissue, hoping to stop cells from seizing. Typically, she has to test these drugs on animals, whose brains lack the human brain's complex architecture. "To actually test drugs on human tissue is a remarkable opportunity," she says. "What we find out from cases like Gwen's may allow us to treat patients with better medications, so patients may never even need surgery."

SHARING THE WEALTH

For Gwen and her parents, participating in neuroscience research was an easy decision. "For us, it was a no-brainer," jokes Gwen's dad, Stewart. "How else will medicine be advanced unless people are willing to take on academic research challenges? Just think, Gwen's data might be just what it takes for the next advancement."

Madsen has found that nearly every epilepsy patient's family feels the same way; even if they don't benefit personally, they embrace the idea of helping others. "The brain is an ever-changing organ, and there's so much we don't know," says Madsen. "Every day, we're learning things that are important for people with neurological conditions, brain injuries and degenerative diseases. Since we have the opportunity to study these things, it would be wrong to not do so. We get to help kids like Gwen by fixing their seizures, and we get to give her the chance to help thousands of others—including people not even born yet. How amazing is that?"

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