HAVE SQUIDS, WILL TRAVEL

Los Alamos researchers are using the world's most sensitive magnetic-field detector to pinpoint seizure-generating tissue in epileptics' brains and to screen carry-on liquids at airports.

Andrei Matlashov, a member of the SQUID team, with the apparatus used to study magnetic resonance imaging at ultralow magnetic fields. The copper coils that produce the magnetic fields are wound on wooden armatures to avoid the magnetic distortions caused by metal.

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It was 2002, and the Los Alamos SQUID team had a problem. The team had just invented and tested a helmetlike system incorporating the world's most sensitive magnetic-field detectors: superconducting quantum interference devices (SQUIDs). Placed just above the skull, the SQUIDs measured magnetic fields generated by neural electrical currents in the brain and pinpointed the currents' locations to within a quarter millimeter. Such spatial precision would be good enough to guide doctors' attempts to electrically quell or surgically remove "epileptogenic" tissue—the small, localized regions of the brain where epileptic seizures begin—but only if the reference frame in which the positions of this tissue were measured could be made to closely coincide (coregister) with the reference frame of a magnetic resonance image (MRI) of the same brain. An MRI shows the detailed structure a surgeon needs to see.

At the time, however, the two reference frames couldn't be coregistered precisely enough because the images were being produced by two different instruments—the team's helmet and a hospital MRI machine. Each instrument separately produced images with the required spatial precision, but a set of two images, one from each machine, could be coregistered to only 5 millimeters.

When you treat epilepsy surgically, you want all the precision you can get. Brain tissue is highly folded and densely packed with neurons, so even a slight surgical misstep can have disastrous results. Or as Bob Kraus, former SQUID team leader, says, "If someone is cutting into your brain, you want them to know where to cut as precisely as possible."

A Magnetic Disparity

The solution to the coregistration problem might seem obvious: combine the SQUIDs and the MRI machinery into one instrument. The problem is that hospital MRI machines use a powerful magnetic field that will destroy SQUIDs.

SQUIDs are really the only way of measuring the brain's magnetic fields, with a technique called magnetoencephalography, or MEG. These fields have a strength of about 1 picotesla, some 50 million times weaker than Earth's magnetic field. A SQUID can detect a magnetic field as small as half a femototesla, or one 2,000th of a picotesla. The helmet, the team's crowning achievement after 20 years of MEG research, uses 155 SQUIDs arranged on a curved supporting surface that conforms generally to the top of the skull.

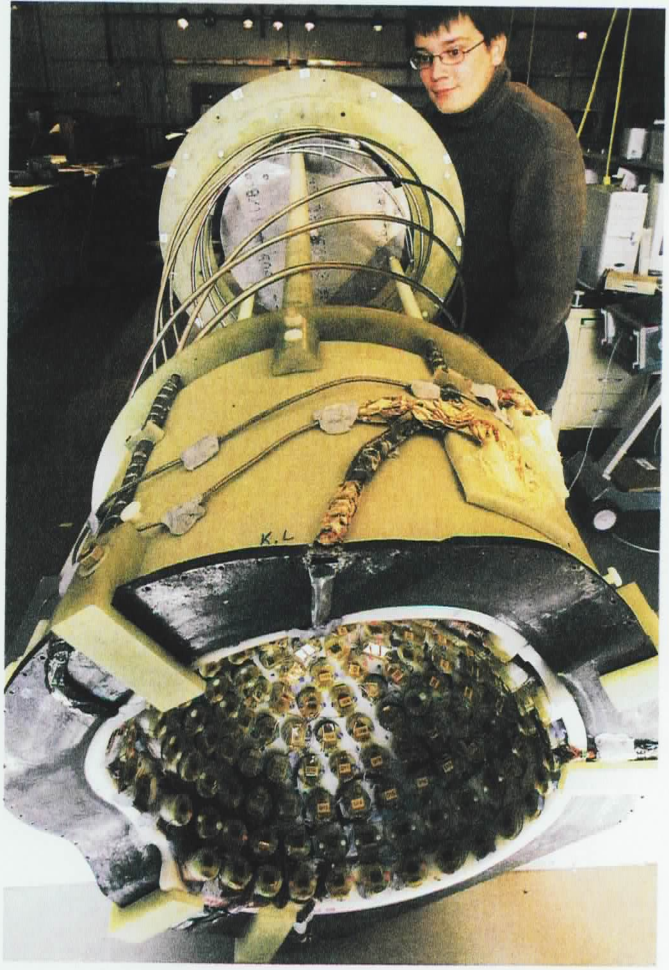
An MRI is created from measurements of nuclear magnetic resonance (NMR) signals, which are magnetic signals emitted by certain nuclei—including hydrogen nuclei (protons)—when their quantum-mechanical "spins" are manipulated in certain ways. Since hydrogen is a major atomic component of water and fat (two of the body's main ingredients), proton NMR signals are commonly used to produce images of organs, muscles, and so forth, that is, to produce MRIs. To produce a hospital MRI, some of the spins are first aligned by the powerful magnetic field of a large superconducting electromagnet, and therein lay the team's dilemma: an instrument combining MRI and MEG imaging would self-destruct the first time it was turned on because the powerful magnet used to produce MRIs would destroy the SQUIDs used to produce MEG images.

Finding Aberrant Brain Tissue

Nonetheless, in and of itself, the MEG helmet is a stunning success. As a method of localizing epileptogenic tissue, MEG is completely noninvasive. In fact, the helmet's SQUIDs do not even touch the skull. And that's a very good thing because, to operate, they must be kept extremely cold—a few degrees above absolute zero. To chill them out, the team immerses them in liquid helium that has been poured into a large thermos supported by a sturdy gantry above a person's head. The thermos is so well insulated that the outer surface—only an inch or so from the subject's skull—is at room temperature.

The helmet's MEG measurements are also extremely precise with respect to time. The SQUIDs have a temporal resolution of about 100 microseconds—short enough to distinguish between electrical signals that occur at almost the same time but arise from patches of epileptogenic tissue in different parts of the brain.

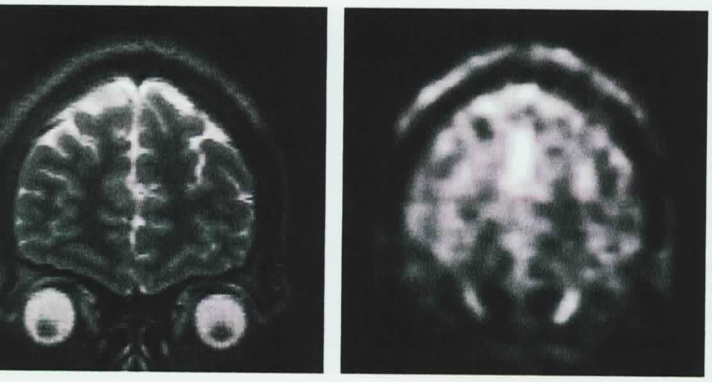
In fact, MEG's temporal resolution is comparable to that of the "gold standard" for localizing epileptogenic activity—electrocorticography (ECoG), which measures the electrical potential of electrodes implanted in or on the brain. However, ECoG has the clear drawback of being about as invasive as it gets.



Jonatan Mattson, a former graduate student on the SQUID team, inspects the helmetlike system the team developed to measure the tiny magnetic fields produced by the brain's neural currents.

The only other technique with comparable temporal resolution is electroencephalography, or EEG, which uses electrodes taped to the scalp and parts of the face to measure changes in electrical potential. EEG is only mildly invasive (the discomfort of tape and conductive gel) but has a more important problem. The signals it detects must pass through various types of tissue and the bone of the skull, all of which have different electrical conductivities that distort the signals. The distortion is worst near openings in the skull, such as eye sockets and ears, and introduces errors in measuring the locations of the epileptogenic tissue. In contrast, magnetic fields measured by the MEG helmet pass through the skull undistorted because there are no magnetic materials within a normal skull.

"However, EEG is cheaper to use than MEG is," Kraus says, "and patients can 'wear' EEG electrodes for a long time to permit near-continuous monitoring of neural activity." In contrast, during a MEG



Images obtained with traditional MRI (left) and ultralow-field (ULF) MRI (right). The ULF MRI image is fuzzier because the signals used to produce it have relatively more noise than those producing traditional MRIs. However, unlike traditional MRI, ULF MRI can be done in the presence of metals, allowing a surgeon to operate and view an MRI of his/her work at the same time. Moreover, ULF MRI can image some types of tissue better than traditional MRI can.

measurement, the patient has to stay put, like a beauty shop patron sitting under a hair dryer.

For those reasons, in spite of the distortion, EEG is currently the diagnostic tool of choice at epilepsy treatment centers, although the most-reliable, most-accurate results for diagnosing epilepsy are actually obtained by combining MEG and EEG, Kraus says.

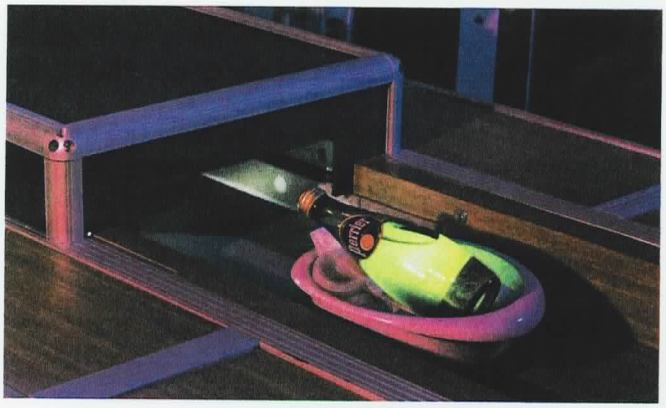
Shutting Out the Noise

However, two new concepts the SQUID team developed and then proved with the helmet could provide significant improvements that make MEG's use more common. Both concepts aim to reduce the interference with MEG measurements caused by magnetic "noise," that is, ambient magnetic fields such as Earth's magnetic field and magnetic fields produced by power lines, electric appliances, and even passing cars. The new concepts so effectively reduce ambient magnetic noise that MEG measurements can be made in a room that has only one layer of magnetic shielding instead of two, as is usually required. A single-layer room is much simpler and therefore less expensive than is a double-layer room.

The first new concept is to use a lead sheet, shaped roughly like a conquistador's helmet, to shield the SQUIDs from ambient magnetic fields. When bathed in liquid helium, the same medium used to cool the SQUIDs, the lead sheet becomes a superconducting "magnetic mirror" that reflects the ambient fields away from the SQUIDs.

The second concept is to use additional SQUIDs outside the shaped lead sheet to measure ambient fields that are not completely reflected by the magnetic mirror. When the data are later processed, the residual magnetic noise is cancelled out by subtracting the signals of these residual fields from the signals measured by the 155 SQUIDs.

Initial tests established that the helmet's novel design put it well ahead of its time and that it was a potential steppingstone to cheaper MEG systems that could be used to help more people who have epilepsy or other brain disorders. But there was still that pesky coregistration problem.



A bottle of Perrier about to pass, on a conveyor belt, into the heart of MagViz, a ULF MRI machine developed for use at airport security portals. MagViz provides MRIs of airline carry-on liquids and identifies the liquids.

Way Less Is More

Then in 2002, the same year the coregistration problem stymied the SQUID team, a potential solution was announced by scientists in California. Berkeley researchers published a paper describing the first use of SQUIDs to perform a new kind of MRI. In this new variant, proton spins are aligned by a relatively weak electromagnet that is turned on for only about a second. Subsequent spin manipulations with even weaker pulsed electromagnets produce NMR signals that are detected by the SQUIDs (see box, next page).

The use of magnetic fields much weaker than that associated with traditional MRI led researchers to christen the new discipline "ultralow-field" (ULF) magnetic resonance imaging, or ULF MRI. This approach clearly provides a way for a single SQUID-based instrument to perform both MRI and MEG imaging and thereby solve the coregistration problem.

Excited by this development, the Los Alamos SQUID team repeated some of the Berkeley group's results and soon went beyond them.

From Brains to Cokes

The team started its ULF MRI odyssey simply, using a single SQUID to measure the NMR signals of whatever happened to be lying around in the laboratory—Coke, V8, and sports drink, for example. "Some of our 'research' was driven by idle curiosity," Kraus admits. Whatever the motivation, the team soon found it was easy to positively identify a liquid from its ULF NMR signal. The team filed these results away and went on to other experiments.

One early experiment measured an NMR signal and a MEG signal from the same brain at the same time—a first step to using a single SQUID-based instrument to image both the brain's structure and its MEG-derived electrical activity. Within a couple of years, the team had also used an array of seven SQUIDs to produce ULF MRI images of a preserved sheep brain, a living postdoctoral researcher's hand, and a living team leader's knees.

Increasing the number of SQUIDs—from one to seven, in this case—is one way to increase the "signal-to-noise" ratios of the NMR signals. A signal with a high signal-to-noise ratio can produce an image with a given quality in a shorter time than can a signal with a lower ratio.

Last year, the team published a paper describing experiments in which they used seven SQUIDs to capture the first ULF MRI images of a living human brain and, at nearly the same time, to record seven channels of MEG data as that brain responded to audio tones. Team members also considered using the SQUIDs

Ultralow-Field MRI

About 63 percent of the atoms in the body are hydrogen, mostly in fat and water. Magnetic resonance imaging (MRI) measures the concentration of those atoms at many points in the body and converts the data into a map, or picture, of the body's tissues.

The hydrogen atoms can be detected because each atom's nucleus—a single proton—has a tiny magnetic field produced by the proton's quantum-mechanical "spin," as shown in Figure A. Normally, the spins point in random directions (Fig. B), so the total magnetic field measured by a detector far from the spins is zero. MRI manipulates the spins so the protons' magnetic fields combine into a field large enough to be measured.

The first step in this process is to align some of the spins in the region of interest with a relatively weak uniform magnetic field B_p (Fig. C). In ultralow-field (ULF) MRI, B_p is produced by an electromagnet that is turned on for a second or two. Figure D is a schematic drawing of the electromagnets that produce B_p (yellow) and another, much weaker magnetic field B_m (gray), as well as three magnetic-field gradients G_x (red), G_y (blue), and G_z (green), which are discussed below. The timing diagrams (Fig. E) show when the electromagnets are turned on and off relative to each other.

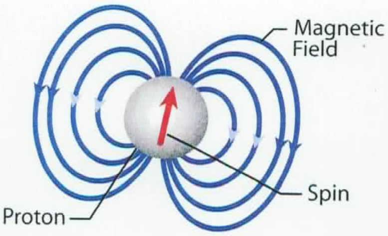
Signals are obtained when B_p is off. The field B_m, which points perpendicular to the aligned spins, is applied to the region for a few seconds. The spins start rotating together ("precessing" in phase) around B_m with a frequency proportional to B_m's strength (Fig. F). The magnetic fields of the precessing spins combine to produce a net magnetic field, B_{NMR}, that is vastly larger than that of a single proton, but still much weaker than B_m. This nuclear magnetic resonance (NMR) signal oscillates at the precession frequency and can be measured by SQUIDs located some distance from the spins.

The strengths of G_x, G_y, and G_z vary linearly with distance in the x, y, and z directions. The total magnetic field then has a slightly different value at each point, so the spins at different points precess at slightly different frequencies. A 3-D map can be produced because each tiny measurement volume in the patient's body produces an NMR signal with a unique frequency that is determined by the volume's position.

As time passes, very slight differences in the frequencies of the spins' rotations, arising from interactions with neighboring spins, cause the spins to rotate out of phase with each other, so B_{NMR} fades away. For B_{NMR} to be measured, the spins' rotations are reversed by reversing B_m. As the spins come back into phase and then fall out of it again, they produce a measurable "echo" signal (bottom of Fig. E). The time it takes an echo signal to rise and fall gives the first of two characteristic times used to distinguish between different types of tissue or different chemicals.

The second characteristic time arises from the fact that after B_p is turned on, the spins take some time to realign. To measure how fast they do, B_p is turned on and off in the usual way, and then an echo signal is measured at a time t_r after B_p is turned off. This procedure is repeated for several different values of t_r. The second characteristic time is obtained from a plot of the peak of B_{NMR} as a function of t_r.

(A)



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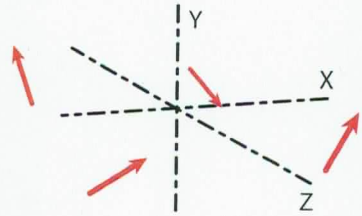

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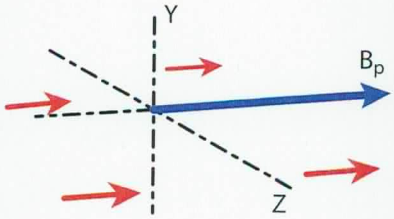

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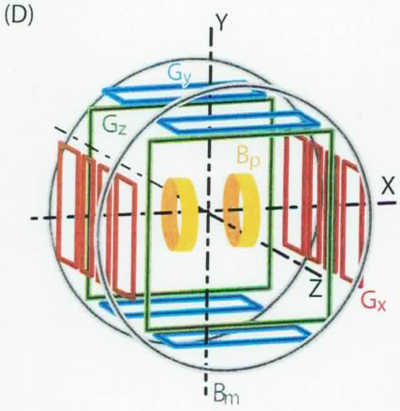

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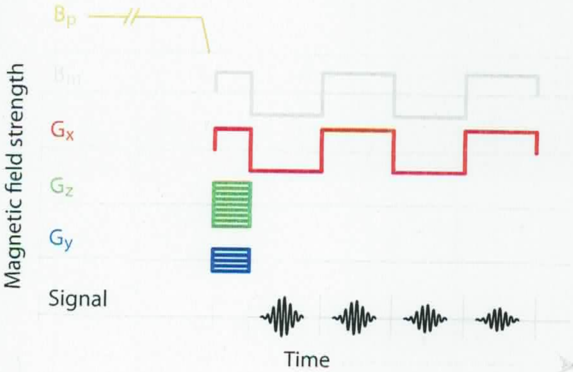

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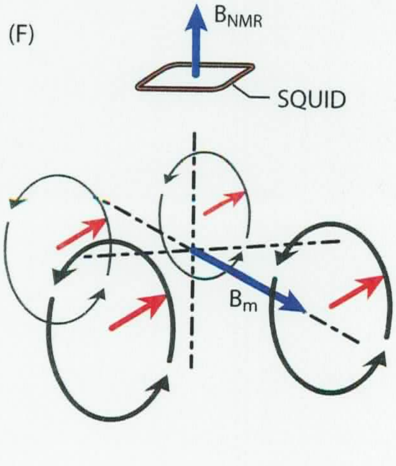

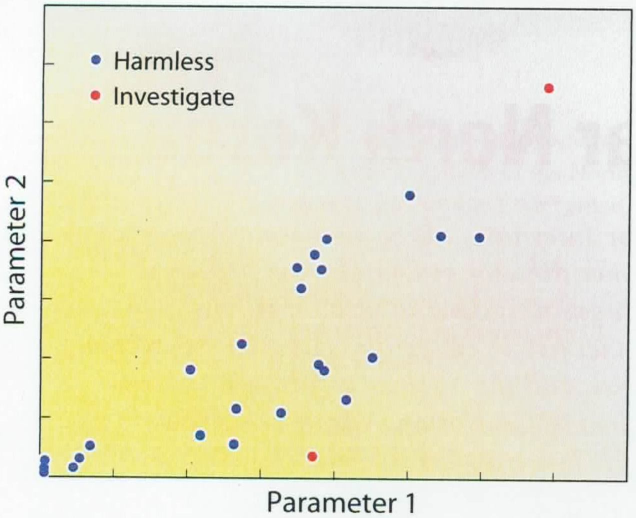

MagViz discriminates between harmless liquids and those requiring further investigation, by security personnel, based on a liquid's position in a space determined by two ULF MRI parameters.

in the MEG helmet to simultaneously image brain structure and MEG sources. They were well on their way to brilliantly solving the coregistration problem—when they were suddenly diverted by world events.

A "Slight" Side Trip

In August 2006 British authorities foiled a terrorist plot to set off liquid explosives onboard an aircraft in flight, and what is known in the air-travel industry as the "3-1-1" rule was born. All carry-on liquids are now limited to 3 ounces each and must be packed together in a single quart-size plastic bag—one per traveler. The delays and inconveniences caused by this rule have been irking millions of air travelers ever since.

One particular air traveler, Michelle Espy, the current head of the SQUID team, would like to see the rule go away so she can take fruit juice on the plane when she travels with her two young children. She's also one of the few people in the world who can probably do something about the rule, thanks to the team's old data on Coke and other liquids. Suddenly what had once been playfulness in the laboratory took on a very serious purpose that drew the attention of the Department of Homeland Security (DHS).

Well aware of the 3-1-1 rule's unpopularity, DHS is actively seeking ways to modify or rescind it. So when a Los Alamos program manager briefed Washington on the team's successes with ULF MRI, the department came calling. Could ULF MRI be used to screen carry-on liquids at airports? Soon DHS was funding a major program at Los Alamos to develop a technology called MagViz.

That program has occupied the team for the last two years, and the results have been spectacular. MagViz provides MRIs of the scanned liquids and, at the same time, identifies them and classifies them as harmless or "threats," even if the liquids are inside metal cans or metal-foil-lined containers. "This would be impossible for traditional MRI," says Espy. In tests last December at Albuquerque's international airport, the Sunport, MagViz took under a minute to scan the liquids in six containers placed in an airport coin tray 4 inches deep.

Because it uses the weak pulsed electromagnets of ULF MRI, MagViz is also safer than a traditional MRI machine would be in a crowded public environment. The superconducting electromagnet used for traditional MRIs is powerful enough to violently suck up nearby steel objects—sometimes with lethal effect, which is why hospitals carefully control what people wear or carry in and around their MRI facilities.

Scanning in the Boondocks, Etc.

MagViz's pulsed electromagnets are also lighter, smaller, and cheaper than the magnet in a hospital MRI machine, which means MagViz's basic design could be used to build portable, inexpensive MRI machines for use in third-world nations and rural areas, as well as at aid stations on the battlefield. Such a machine could even be used by emergency medical technicians to treat a patient and/or perform triage on the way to the hospital, Kraus says.

Team members are excited by the humanitarian potential of portable MRI and by the fact that ULF MRI could jump-start MEG research. But first they must finish MagViz. DHS doesn't want the technology to be commercialized until it can scan an unopened piece of luggage 1 foot deep in less than 1 minute.

The team is working hard to reach that goal and feels it will succeed in another year or so. When that day comes, air travelers around the globe—especially Espy's kids—will be deeply grateful, although most of them will not know that the odious 3-1-1 rule was finally toppled by brain research. ❖

—Brian Fishbine

Former leader of the SQUID team, Bob Kraus is the deputy program director of the Los Alamos Laboratory Directed Research and Development (LDRD) Office. Michelle Espy (not shown) currently heads the SQUID team.