ATHINOULA A. MARTINOS CENTER
FOR BIOMEDICAL IMAGING

20 + 20 VISION

40 Years on the Cutting Edge of Science and Care

The Athinoula A. Martinos Center for Biomedical Imaging

20+20 Vision

40 Years on the Cutting Edge of Science and Care

By Gary Boas

Book design by Ronan Neuman-Hammond

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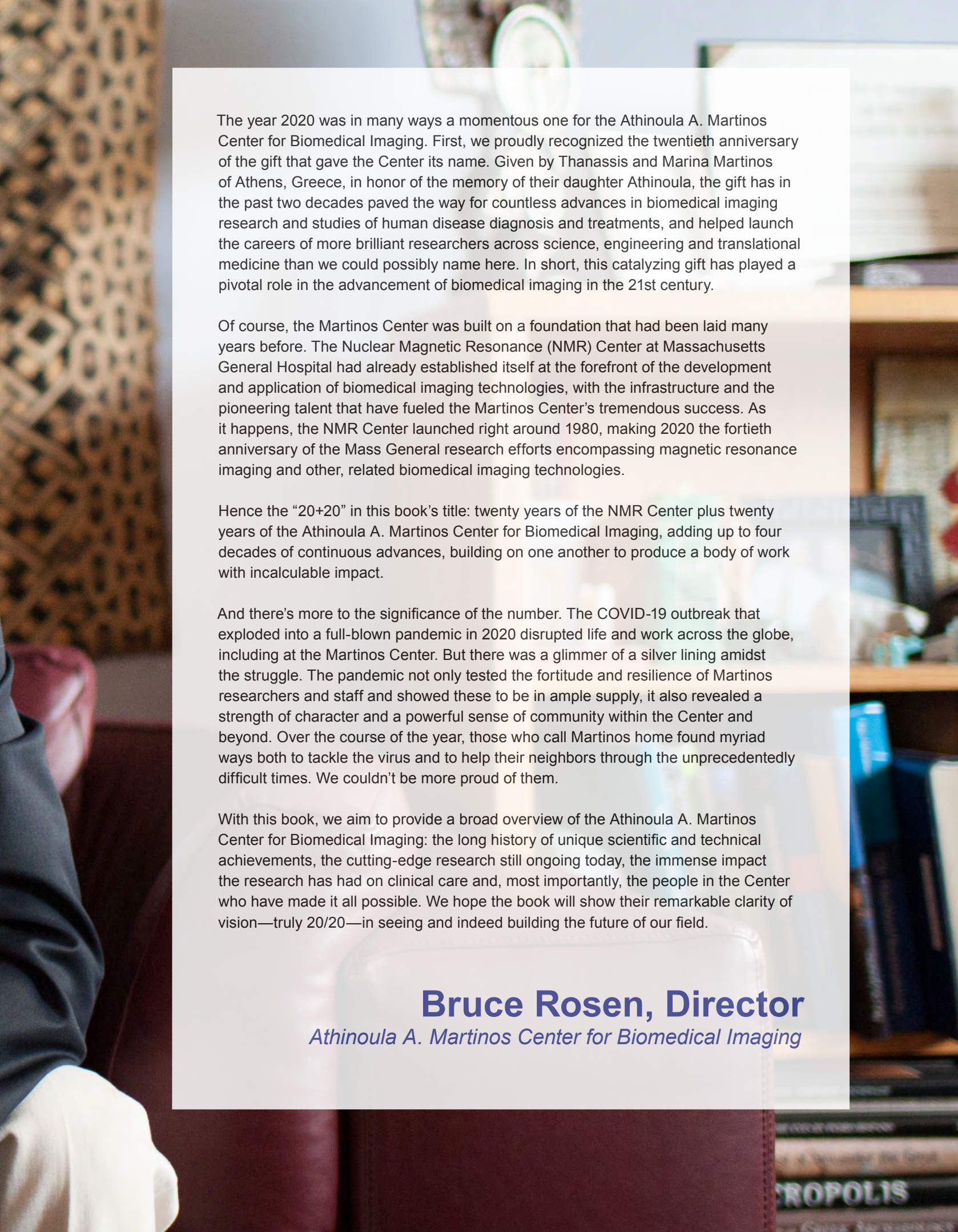


The year 2020 was in many ways a momentous one for the Athinoula A. Martinos Center for Biomedical Imaging. First, we proudly recognized the twentieth anniversary of the gift that gave the Center its name. Given by Thanassis and Marina Martinos of Athens, Greece, in honor of the memory of their daughter Athinoula, the gift has in the past two decades paved the way for countless advances in biomedical imaging research and studies of human disease diagnosis and treatments, and helped launch the careers of more brilliant researchers across science, engineering and translational medicine than we could possibly name here. In short, this catalyzing gift has played a pivotal role in the advancement of biomedical imaging in the 21st century.

Of course, the Martinos Center was built on a foundation that had been laid many years before. The Nuclear Magnetic Resonance (NMR) Center at Massachusetts General Hospital had already established itself at the forefront of the development and application of biomedical imaging technologies, with the infrastructure and the pioneering talent that have fueled the Martinos Center's tremendous success. As it happens, the NMR Center launched right around 1980, making 2020 the fortieth anniversary of the Mass General research efforts encompassing magnetic resonance imaging and other, related biomedical imaging technologies.

Hence the "20+20" in this book's title: twenty years of the NMR Center plus twenty years of the Athinoula A. Martinos Center for Biomedical Imaging, adding up to four decades of continuous advances, building on one another to produce a body of work with incalculable impact.

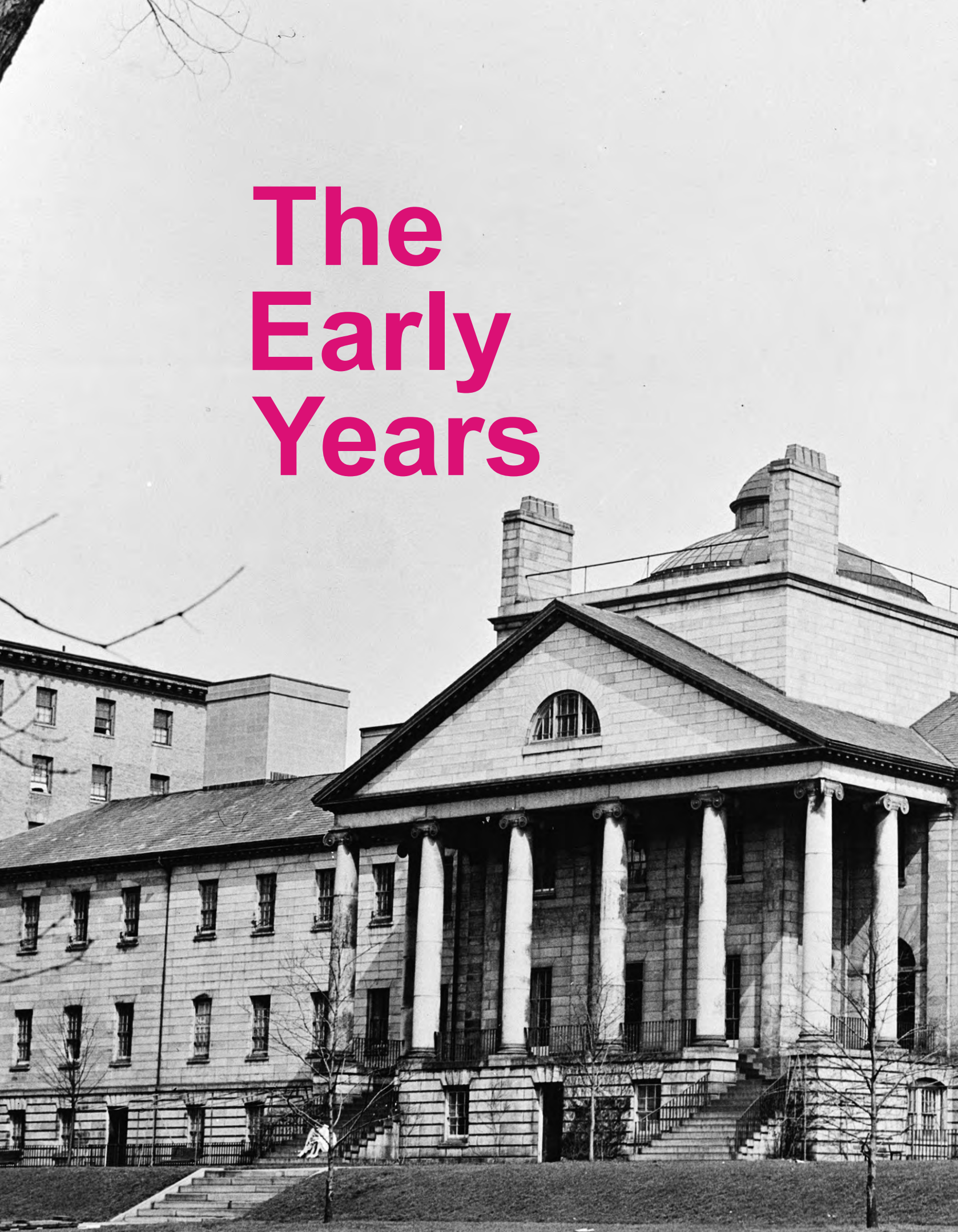
And there's more to the significance of the number. The COVID-19 outbreak that exploded into a full-blown pandemic in 2020 disrupted life and work across the globe, including at the Martinos Center. But there was a glimmer of a silver lining amidst the struggle. The pandemic not only tested the fortitude and resilience of Martinos researchers and staff and showed these to be in ample supply, it also revealed a strength of character and a powerful sense of community within the Center and beyond. Over the course of the year, those who call Martinos home found myriad ways both to tackle the virus and to help their neighbors through the unprecedentedly difficult times. We couldn't be more proud of them.

With this book, we aim to provide a broad overview of the Athinoula A. Martinos Center for Biomedical Imaging: the long history of unique scientific and technical achievements, the cutting-edge research still ongoing today, the immense impact the research has had on clinical care and, most importantly, the people in the Center who have made it all possible. We hope the book will show their remarkable clarity of vision—truly 20/20—in seeing and indeed building the future of our field.

Bruce Rosen, Director

Athinoula A. Martinos Center for Biomedical Imaging

The Early Years



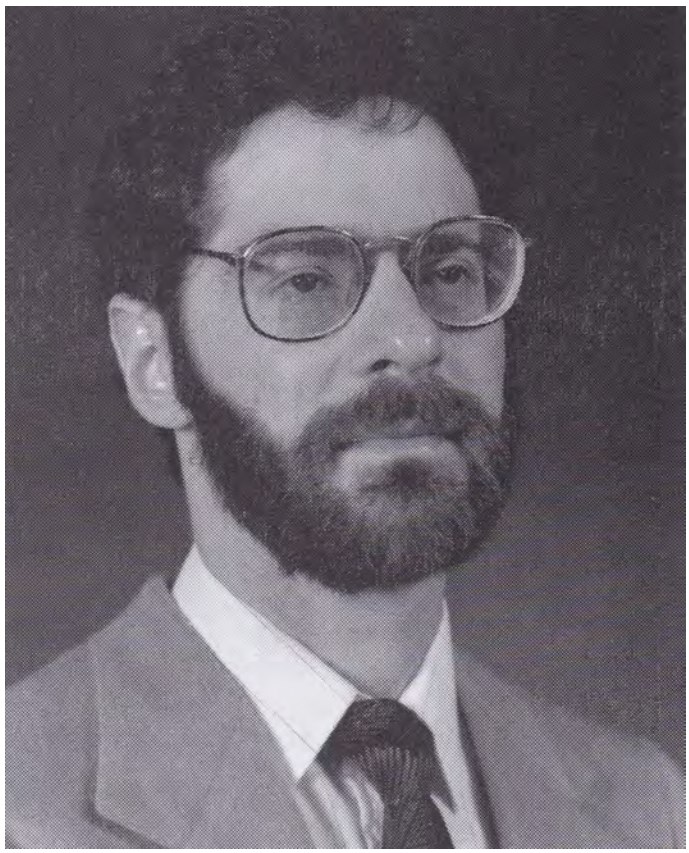
While radiologists at Massachusetts General Hospital had always conducted research—adding to the literature through observational papers about the clinical significance of certain radiological findings, for example—the Radiology department had no formal structure for research until the late 1950s. The research program made important strides in the following decades, with the addition of Gordon Brownell's group working with positron imaging and the acquisition of one of the first computer tomography (CT) scanners. Then, in about 1980, the modern era of Mass General radiology research launched with the advent of magnetic resonance imaging (MRI) and the convening of a group of researchers eager to explore its potential.

The Birth of a Center

Below: Center director Bruce Rosen as a young researcher in Mass General's NMR program.

Opposite: Building 149 rises above the Charlestown Navy Yard in the early 2000s. Photo by Gary Boas.

The following is the story of a research program at Massachusetts General Hospital: a program that entered the world as a small group of physicians and scientists working under the name "the Nuclear Magnetic Resonance (NMR) Center"; grew to encompass teams of investigators designing and building cutting-edge magnetic resonance imaging (MRI) technologies; and today, as the Athinoula A. Martinos Center for Biomedical Imaging, is one of the premier research centers devoted to the development and application of an array of imaging technologies, with hundreds of researchers and staff working together for the advancement of human health.



Let's not get ahead of ourselves, though. Let's start, as they say, at the beginning.

Some 40 years ago, Mass General was developing a new research program in MRI, an emerging technique that could produce images of soft tissue in the body based on the magnetic properties of the nuclei in the tissue—hence the *nuclear magnetic resonance* in the program's name. Because it was noninvasive and did not involve ionizing radiation, MRI offered a promising alternative to other imaging techniques, including computed tomography (CT).

The program launched in about 1980 with Mass General cardiologist Gerald Pohost at the helm. Pohost and a handful of other, similarly adventurous researchers and physicians had banded together to address a host of questions using an experimental 1.4-Tesla small animal MRI scanner and a 0.15-Tesla human head scanner that the hospital had recently acquired. (*Tesla* is the unit of measure applied to the field strength of a magnet.). In a small lab housing the scanner and in nooks and crannies elsewhere in the hospital, they tinkered and talked and generally blazed new trails with the new and largely untested technology.

The Pohost-led group made important strides in those early years, both in working out the possibilities of MRI and in exploring the many ways it could benefit specialties from across the hospital. In doing so, they also established a template for and set

a perfect example of what the NMR program could be. The Center's researchers have never looked back.

Security Clearances and Secret Underground Labs

On a brisk afternoon in Boston in late 1981, Bruce Rosen, a PhD student in the Health Sciences & Technology program at Massachusetts Institute of Technology, walked into a small office on the sixth floor of Mass General's Edwards Building. At the time, Rosen was also wrapping up his requirements for medical school and was hoping to do a radiology clerkship in the hospital's NMR Center, whose base of operations was the office in which he was now standing.

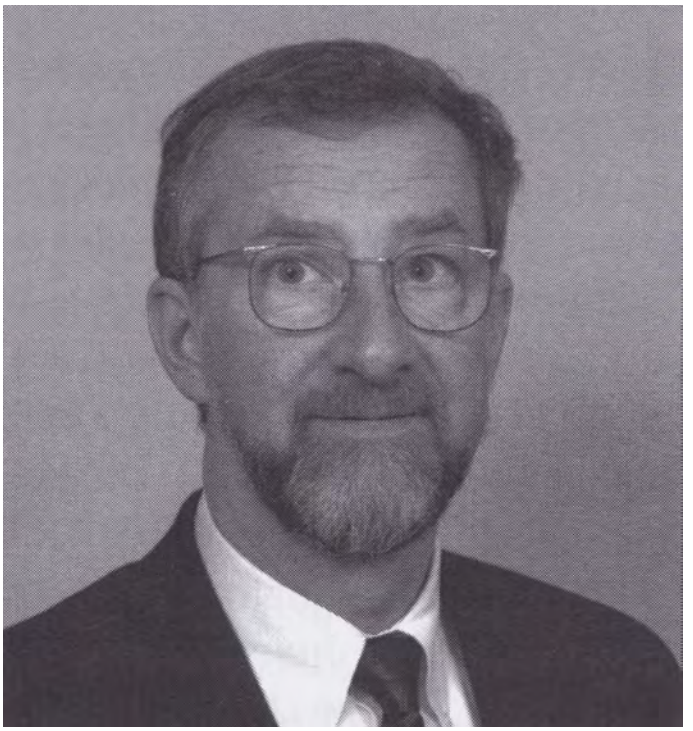
Once inside, he was greeted by Dee Dee Correia, the managing administrator of the Center. Rosen and Correia would go on to work closely together for nearly 35 years, acting as co-conspirators in building a world-class research center until her retirement in 2016, but on this chilly day in 1981, the first time they had met, she was slightly less receptive to his grand designs than she would later come to be.

"She chased me away," Rosen says today with a laugh. "She said, 'Nope, you can't work here. We don't let outsiders in here.' "

"Which was actually true," he adds.

In those early days of MRI, Mass General had an industrial agreement with a company called Technicare, a manufacturer of MRI systems owned by Johnson & Johnson. Technicare felt they were in a competitive position with this new and highly advanced biomedical imaging technology, so security clearances and non-disclosure agreements were required before someone could even set foot in the MRI laboratory.

Rosen can be especially persuasive, though. Despite all the furtiveness over the proprietary technology tucked away in a subbasement on Mass General's main campus, he



Above: Tom Brady, transformational director of the MGH-NMR Center during the 1980s

Opposite background: The back atrium of Building 149 in the Charlestown Navy Yard. Photo by Mike Datko.

Next: The front atrium of Building 149, as seen from the 10th floor. Photo by Mike Datko.

was eventually able to talk his way into the NMR Center.

On the other side of the Center's doors, he found an eclectic and highly accomplished group, with specialists hailing from the four corners of the hospital. In addition to Pohost, the Center's roster included neurologists Phil Kistler and Ferdinando Buonanno (Mass General's Kistler Stroke Research Center would later be named for the former); neuroradiologist Paul New and genitourinary radiologist Jeff Newhouse; Tom Brady, a nuclear medicine specialist with a family medicine background who had come to the hospital to study MRI with Pohost, and who would become director of the Center during the early, transformative years in the 1980s; magnetic resonance physicist Ian Pykett; and others.

The group would continue to grow over the next several years, welcoming into its ranks a handful of young researchers who would go on to play significant roles in the evolution of the Center: Jerry Ackerman, Bruce Jenkins, Greg Sorenson and Van Wedeen.

The multidisciplinary makeup of the early group of researchers was important to the work the NMR Center sought to do. It also set the stage for what the Center would ultimately become: a "full service" facility with researchers representing all stages of the development and application of imaging technologies, from engineers and physicists to neurosurgeons and psychiatrists, working synergistically to tackle all manner of basic science and clinical problems. Looking back on the origins of the Center, Rosen underscores the significance of this point. "The cross-disciplinary flavor of the early group is in our DNA today," he says.

Not surprisingly, given its cross-disciplinary flavor, the Center addressed an array of applications in a wide range of specialties. The researchers' work encompassed studies of stroke, brain tumors and ischemic heart disease, as well as development of contrast agents that would enable them to visualize these conditions with MRI and studies characterizing the hazards of performing MRI in patients who have implants or metal in their body.

They also pursued more technical research in studies with wildly esoteric-sounding descriptions: investigations of chemical shift imaging techniques

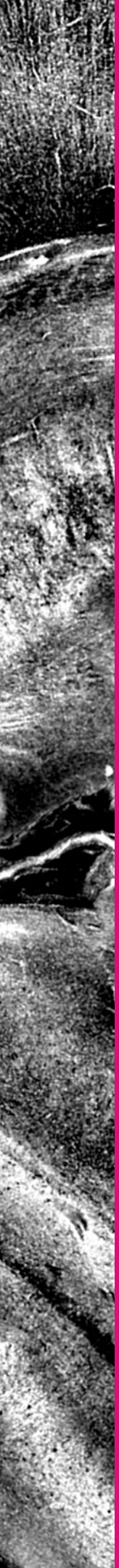
for fat/water imaging, implementation of phase display to differentiate moving from stationary protons, optimization of magnetic resonance pulse sequences for body and surface coil applications, and so on.

Rosen himself gravitated toward the more technical research, working closely with Pykett in exploring the possibilities of chemical shift imaging. This collaboration continued until the latter left Mass General in 1983 to launch a company to develop MRI systems commercially, a move that was slightly distressing for Rosen. “At the time, it was a little traumatic,” Rosen says, “because he was my thesis advisor and he was leaving midway through my PhD.” As we will see, though, Pykett’s leaving the NMR Center would ultimately prove beneficial both for Rosen and for the Center as a whole.

By 1985, the Radiology department was posting annual research budgets of approximately $4.5 million. At the same time, in his annual reports, Radiology chief Juan Taveras was warning hospital administrators that the relative dearth of research space in the department was hindering further progress. Researchers and staff in the burgeoning NMR Center were currently tucked away in hidden corners and shadowy subbasements of the hospital, making the best use possible of whatever resources they could find. But if the Center were to continue to grow, the researchers would need more.

Fortunately, in about 1988, Mass General leased space in the historic Charlestown Navy Yard, a swath of land only a few miles away and across the river, in a structure named simply Building 149. As it happened, the acquisition of this structure slightly preceded the arrival of a new chair of the Radiology department: James Thrall. When recruiting Thrall, Rosen says, the Mass General offered him either 1,000 square feet of research space on the main campus of the hospital or 20,000 square feet in Charlestown. The soon-to-be chair visited Building 149 during his second interview and, later the same day, called Center director Tom Brady to convey his enthusiasm about the space.

Not long after, Brady and Rosen trekked across the river to explore the building themselves. When they arrived, they discovered 18-foot ceilings and windows nearly as tall, which could be removed for easier installation of equipment. They also noted the on-grade construction, which would help in minimizing vibrations, which is crucial for MR imaging. Looking around the vast, empty space, they knew they had found the Center’s new home.



A Brief History of the Charlestown Navy Yard

When the Martinos Center moved to the Charlestown Navy Yard, it joined a long, proud history, dating back nearly two centuries to the beginnings of a nation.

On June 17, 1800, in honor of the 25th anniversary of the Battle of Bunker Hill, the first major battle of the American Revolution, the Massachusetts legislature approved the purchase of a tract of land along the water in Charlestown. Standing in the shadow of Bunker Hill, the land would serve as a shipyard for the nation's young Navy, which had been commissioned only six years before. Purchase of the first 23 acres was completed on August 16, 1800, for the sum of $19,350.

The first ship built in the yard, the 18-gun sloop USS Frolic, was launched on June 22, 1813. The next 55 years saw the construction of another 38 ships and the repair and outfitting of many hundreds more. The new ships included the USS Merrimack, which launched in 1855. Rechristened the CSS Virginia, this vessel later fought in a pivotal battle in the American Civil War, where it engaged the USS Monitor in the first-ever meeting of iron-clad warships.

After the Civil War, the Charlestown Navy Yard underwent several periods of retrenchment and expansion. The latter included the years spanning the Spanish-American War and World War I as well as the years before and during World War II, when the United States created and maintained a two-ocean Navy. By the end of the 1940s, shipbuilding activities slowed to a virtual halt as the Navy focused its attention on the modernization of its existing fleet. The last ship to launch from Charlestown was the Land Ship Tank USS Suffolk County in 1956.

The Charlestown Navy Yard was decommissioned in 1974, after 174 years of operation and service to hundreds of vessels. The last ship to undergo repair in the Navy Yard was also the first: the USS Constitution, a heavy frigate launched in 1797 as one of the first six ships authorized by the Naval Act of 1794. The Constitution entered the public imagination during the War of 1812, where it earned the nickname "Old Ironsides" after British cannonballs appeared to bounce off its wooden hull. The world's oldest commissioned naval vessel still afloat, it remains to this day in the Historic Monument Area of the Charlestown Navy Yard, where its crew of active-duty Navy personnel participates in educational programs and occasional special events.

In 1977, the Charlestown Navy Yard was designated a National Landmark. The City of Boston acquired the land the following year and commenced a major redevelopment effort. By 1989, this effort had grown into the largest preservation and reuse project in the country, with $469 million in private sector investment.

Building 149: the Heart of the Martinos Center

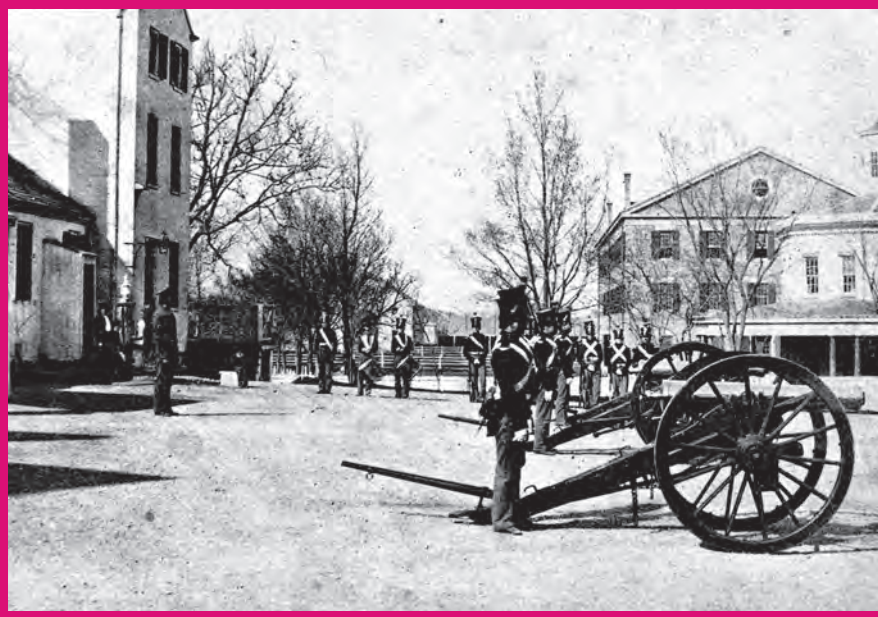
One of the centerpieces of the Navy Yard redevelopment plan was the structure known as Building 149. Completed in 1919, this structure served as a general storehouse for most of its time as a Navy facility. From 1965 until the Yard was decommissioned in 1974, it housed the Computer Applications Support and Development Office, or CASDO, which sought to standardize Management Information Systems for all navy yards through its centralized office design, computer analysis, programming and maintenance efforts.

In the first years after the city acquired the land, developers envisioned Building 149 as a combination of retail space and condominiums and began to renovate the building with this in mind, thus accounting for the marble and brass finishes on the first floor.

By 1983, though, they had come up with a new plan: Building 149 and the adjoining Building 199 would be converted into a combined space called “The Hatchery,” with twelve stories of light industrial/ research facilities, two rooftop telecommunications common-carrier ground-to-satellite stations and 960 parking spaces for Navy Yard tenants, employees and visitors. According to a report submitted to the Boston Redevelopment Authority (BRA) in November 1983, the space would support growth of the electronics, biogenetics and technology fields and other fields then exploding in the Boston area. “The major thrust of ‘The Hatchery,’ ” the developers wrote, “is to provide the needed space to young entrepreneurial companies which are in the forefront of technological evolution.”

There was a hitch, though. The BRA, concerned about the potential for “unacceptable” traffic conditions, wanted to be sure traffic was kept under control as the redevelopment project advanced. A study showed that conventional office space would generate approximately 2.3 times as many vehicle trips per day as biomedical research space, so the BRA proposed a combination of the two in the Navy Yard, with office space generally not exceeding 50% of the overall mix. Presumably based on this new mandate, at least in part, the preferred use of Building 149 shifted to biomedical research.

The rest, of course, is the history you now hold in your hands.



Above top: The Marine barracks in the Charlestown Navy Yard, looking east toward the current location of Building 149, in the late 19th century

Above, bottom: The southwest corner of Building 149, circa 1960s

Functional MRI Origins

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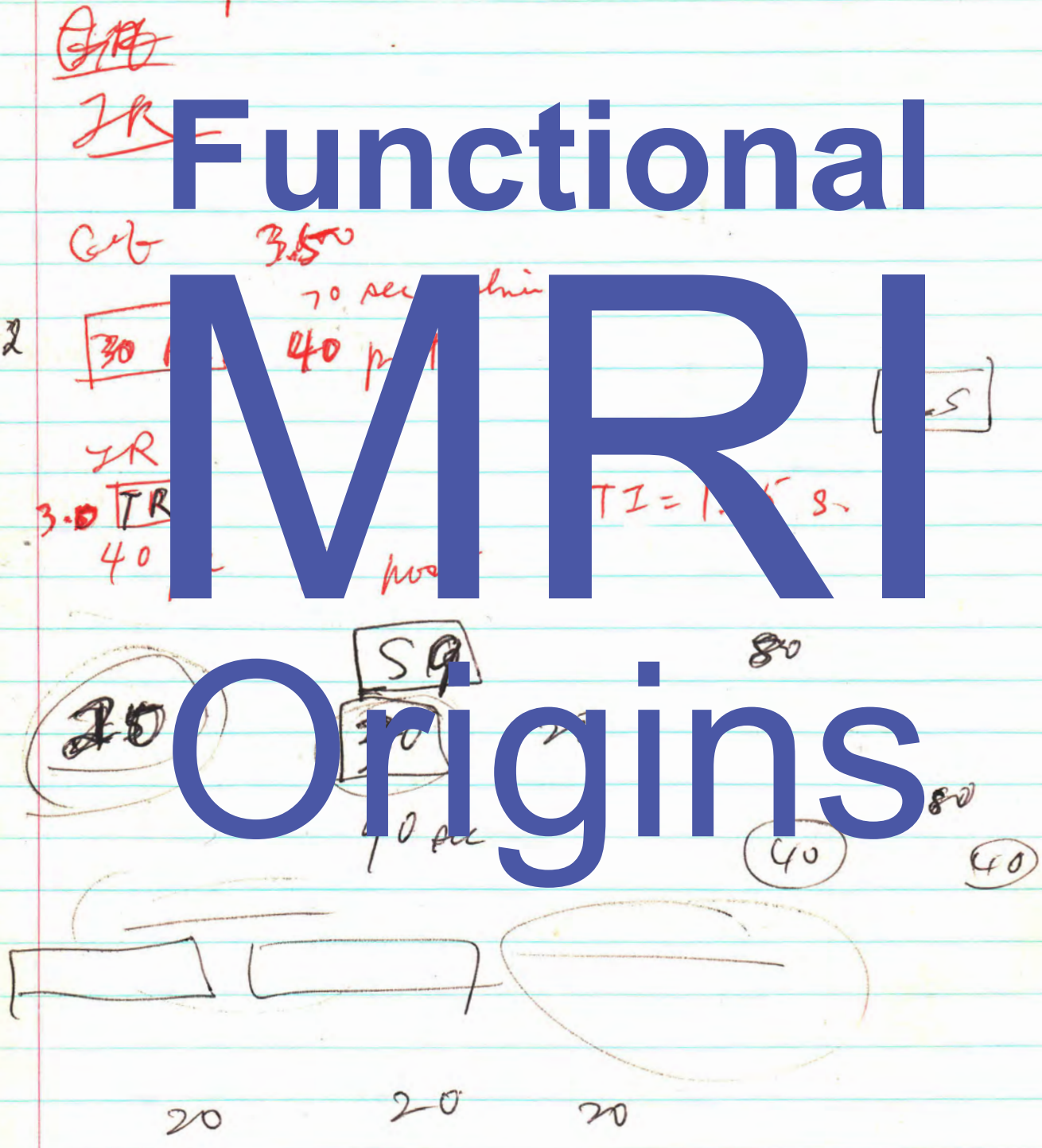

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One of the Center's first major successes after its move to the Navy Yard was the introduction of functional MRI (fMRI) with a pair of papers in 1991 and 1992. While conventional MRI provided structural images of the brain and other soft tissue in the body, fMRI could pinpoint functional changes in the brain associated with different types of neural activity. The studies, by lead authors Jack Belliveau and Kenneth Kwong, respectively, ushered in a new era of functional imaging and inspired application of the technique in a number of different fields.

The Foundations of Functional MRI

When the Martinos Center moved in to Building 149 in the Charlestown Navy Yard, it had a single MRI scanner for human studies: a recently purchased 1.5T system made by GE, which, as a company, was rapidly establishing a foothold in the MRI sphere. (The Center's first FDA-approved clinical system, acquired in 1984, was made by Technicare, a company owned by Johnson & Johnson. When GE bought Technicare a couple of years later, "we kind of switched our corporate allegiance," Center director Bruce Rosen says.)

Though the Center had only the one system at the time, Radiology chief James Thrall pushed for construction of three scanner bays in the Navy Yard, believing the group would soon outgrow a single bay there. While this would require a significant investment, Thrall argued that the facility would ultimately recover the funds by creating a self-liquidating cost center, in which time spent on the scanner would be charged to research grants held by Center investigators and other, outside users—a model still in use today.

The bet would soon pay off. Not long after the move, the Center acquired an MRI scanner with "echoplanar imaging" capabilities made by Advanced NMR Systems—the company started by Ian Pykett, Rosen's former thesis advisor, after he left Mass General. The scanner installed in the Center was the first-ever clinical system with such capabilities. Echoplanar imaging offered greatly reduced acquisition times with MRI, on the order of milliseconds, and thus enabled a host of new applications with the modality.

Not least: Rosen and the Center's Jack Belliveau used it to characterize a phenomenon that Rosen and his postdoctoral fellow Arno Villringer had both observed with MRI after injection of a contrast agent: a rapid initial

drop in the signal measured followed by a slow return to baseline. This work led to the development of the imaging technique now known as *dynamic susceptibility contrast MRI*, which enables measurement of blood flow and other, related parameters.

Thus they set in motion the series of events leading to the introduction of functional MRI. First, Belliveau, a Harvard graduate student working in the Center, demonstrated a practical application of the new technique in the diagnosis of stroke. Belliveau was also intrigued by the possibility of using the technique to measure changes in local blood flow following neural activation. In 1991, he and colleagues published in the journal *Science* the first magnetic resonance images of brain activity related to visual processing, launching a new era in functional brain imaging.

Because it involved injection of a contrast agent, the technique described by Belliveau was limited to only a couple of scans at a time. In 1992, less than six months after publication of the *Science* paper, Kenneth Kwong, a postdoctoral fellow in the Center, described a means of achieving intrinsic contrast—that is, contrast based on innate biological processes—thus addressing the most significant remaining challenge with functional MRI and opening the door to the many thousands of studies reported in the nearly three decades since.

The following is the story of these two studies and the brilliant if occasionally eccentric Martinos researchers who made the studies happen.

Previous: Ken Kwong's lab notes from May 9, 1991

Background: Building 149. Photo by Maria Angela Franceschini

The Life and Science of Jack Belliveau

Mark Cohen, a neuroscientist who in the early 1990s was a young faculty member in the MGH Martinos Center for Biomedical Imaging, paused for a moment before addressing the crowded conference room in downtown Boston. “Somehow,” he said, when he finally spoke, in a soft but deliberate tone, “I feel like I’m a character in Jack’s dream.”

It was a warm summer’s afternoon in 2014 and friends and colleagues had come together to remember Jack Belliveau, the Martinos Center investigator and fMRI pioneer. Belliveau published, in the November 1, 1991, issue of *Science*, the first report of brain activation measured with magnetic resonance imaging, the paper accompanied by the now-iconic cover showing a slice of a brain in a cutaway image of a human head, small areas of it lit up in response to a visual stimulus.

While the symposium was organized around his astounding accomplishments in functional MRI and multimodal imaging, speakers one after the other spoke of the personal traits they knew in Belliveau—the unquenchable thirst for knowledge, the unchecked enthusiasm and the unwavering vision—that made these accomplishments possible.

And they told stories, often very funny and always very warm stories. Stories of how Belliveau revolutionized the field of biomedical imaging, but also of the impact he had on their own lives and careers.

The Roots of a Revolution

The origins of Jack Belliveau’s life’s work date back to the late 1970s, when he was a junior in high school. He started thinking about the brain, about capturing and storing thought, when his father passed away, said Rod Tayler, a childhood schoolmate who flew across the country so he could pay tribute to his old friend. This idea, the possibility of preserving someone’s consciousness even after they have left us, took root and continued to grow, especially when he began to consider his mother’s own mortality. He loved his mother dearly, revered her, really, and would do whatever he could to hold on to her.

This is an essential part of the fMRI tale. As a number of the speakers reminded us, Belliveau’s vision for the technology that would become fMRI was driven by a desire to keep his mother with him, by downloading her consciousness onto a chip. “He really would like to capture a person’s soul in a portrait, a picture that could be recorded and seen,” said Van Wedeen, another young faculty member in the Center at the time of the early fMRI experiments. “It really was his mother.” And as all of them agreed, this extraordinary woman, a church organist and an amateur pilot who made whatever sacrifices were necessary to provide for her son, her only child, was a worthy inspiration for a neuroimaging revolution.

The narrative picks up again in the late 1980s, when Belliveau joined the MGH-NMR Center. Tom Brady, the director of the Center at the time, recalled meeting “this skinny, bright-eyed guy named Jack” who was looking for a new lab in which to pursue his interests in the brain after his initial research in MR spectroscopy. “His last name is French but Jack portrayed himself as an Irishman,” Brady said. “I liked him immediately.” Belliveau quickly integrated into the Center and set to work developing his ideas about the brain.

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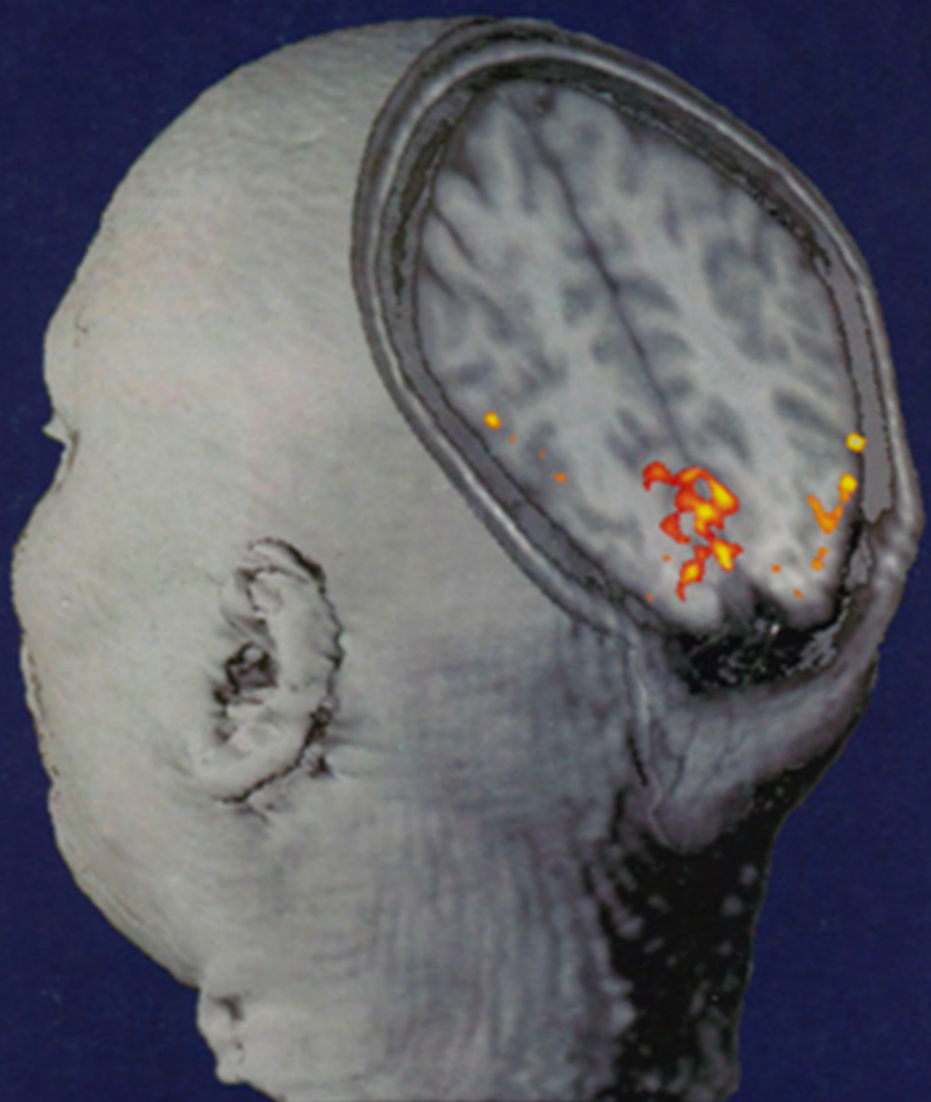
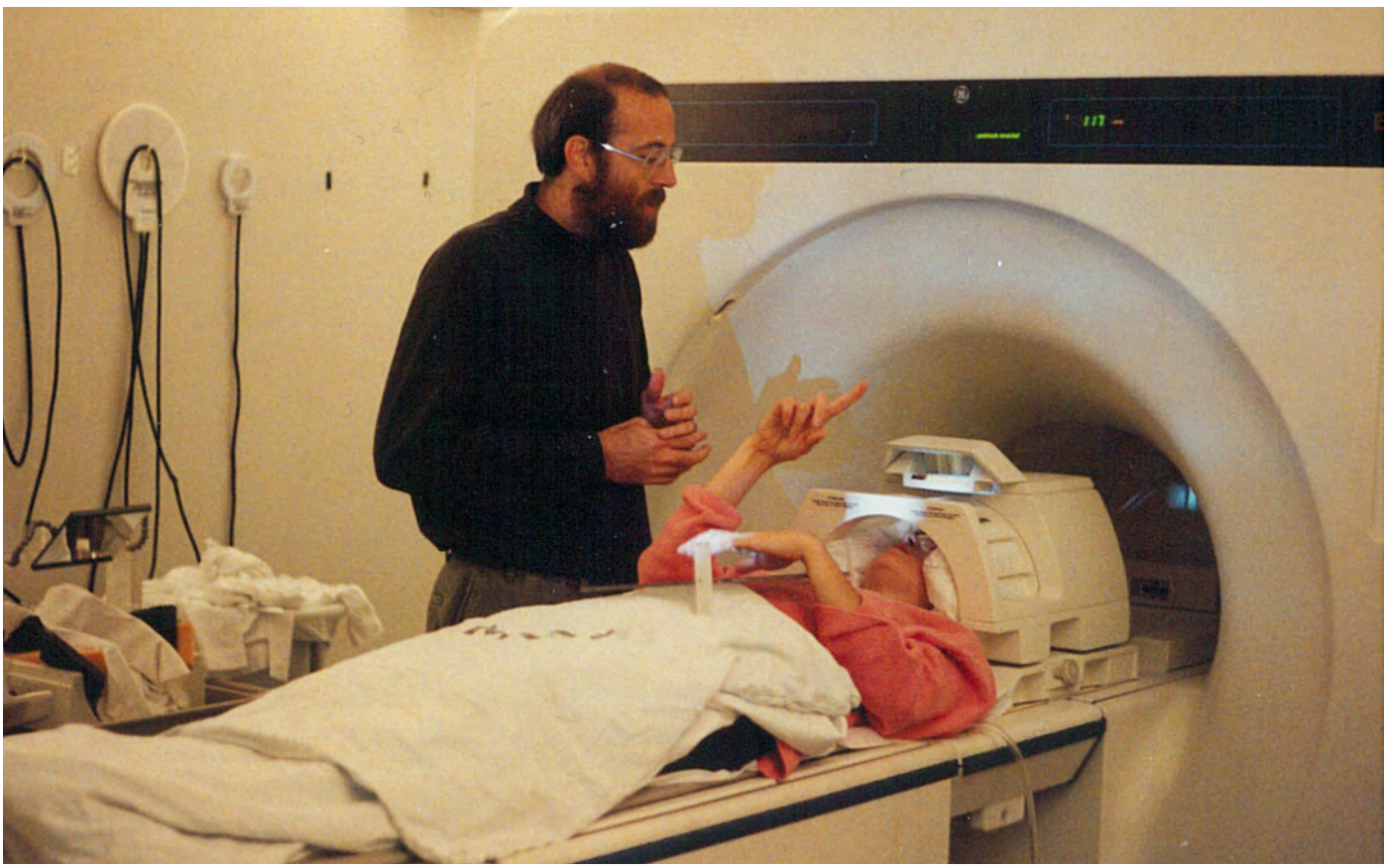


A graduate student, he never had time for the prescribed roles of academic research, nor did he allow them to restrict his boundless enthusiasm or his singular vision. “Jack had no regard whatsoever for the formalism of the academic world,” said James Thrall, then the Chair of the Massachusetts General Hospital Department of Radiology, “but the ultimate regard for the science.” Robert Weisskoff, a Senior Physicist at Advanced NMR Systems at the time phrased it slightly differently; Advanced NMR built the first human-scale echo-planar imaging [EPI] scanner, the key enabling technology that Belliveau would use in his fMRI experiments. “Jack scared the bejesus out of me,” he said with a smile. “He was loud, he was emotional, he was unbelievably energetic … But he was just an amazing motivator.”

An amazing motivator, indeed. Belliveau was convinced MRI could be used to measure brain function—the kind of function that underlies human thought, said Randy Buckner, who joined the Center as a postdoctoral fellow in the mid-1990s and was among the first to perform event-related fMRI experiments. And his clear belief that this was possible, that he could harness the techniques of the day to make the necessary physiological measurements, drove him to push those techniques into areas they had never been before.

Below: Jack Belliveau running an fMRI experiment in 1994. Photo courtesy of Greg Simpson.



To this end, he assembled a crack team of investigators, inspiring them with his own unflagging enthusiasm to follow him down what must have seemed a preposterous path. The researchers worked tirelessly, endlessly attending to an array of small details in pursuit of their goal, but Belliveau never lost sight of the big picture. Roger Tootell recalled one tedious afternoon in an MRI scanner bay with several of the other investigators; Tootell was a neurobiology researcher with Harvard Medical School who later was the first to use fMRI as a tool for fundamental neuroscience studies. “We were trying to get just the tiniest bits of signal out of the scanner,” he said, “and Jack would come breezing in saying, ‘We have to hurry up and finish with these details so we can discover how love works and consciousness,’ and all these kinds of things.”

His seemingly preternatural ability to draw people together and to inspire them to work as a team reflected an important fact about Belliveau: he was a social scientist, said Bruce Jenkins, a young faculty member in the Center during those early years. As in, a scientist who liked to be social. “Jack always had to do experiments with other people,” he said. For him, it was all about interactions with other researchers, where he could talk about the work he was doing and engage in a vigorous exchange of ideas.

Below: Belliveau was also a pioneer of multimodal imaging, with simultaneous fMRI and EEG, for example. He is seen in this 1993 photo demonstrating an EEG cap. Photo courtesy of Greg Simpson.

Above: Belliveau in a scanner bay with John Foxe (left) and Greg Simpson (right) in 1993.

Opposite: An avid golfer, Belliveau took time out from a 1993 meeting in Havana to hit the links. Photos courtesy of Greg Simpson.

Even after publication of the 1991 *Science* paper made him something of a celebrity, Belliveau continued to look beyond the horizon. He knew that "no single technique would be able to capture the symphony of the human brain," Buckner said, so he launched a series of collaborations exploring the potential of what we now know as multimodal imaging. This was long before the Center had a PET scanner or any of the other non-MRI imaging modalities its researchers are developing and applying today, so he jetted around the world meeting and conducting experiments with experts in these other fields, finding ways to delve even deeper into the brain than he already had.

And as he built his own research program, he took on a new role, or at least a formalized version of a role he'd long before adopted: that of mentor. Here, as with everywhere in his life and career, he cut a uniquely colorful figure. Giorgio Bonmassar met Belliveau for an interview for a postdoctoral fellow position in his lab in 1996, in a café in Charlestown, just down the road from the Center. And he gained his first insight into the character of the man who would help shape his professional life when the latter asked, soon after sitting down: "Giorgio, how do you plan to change the world?"

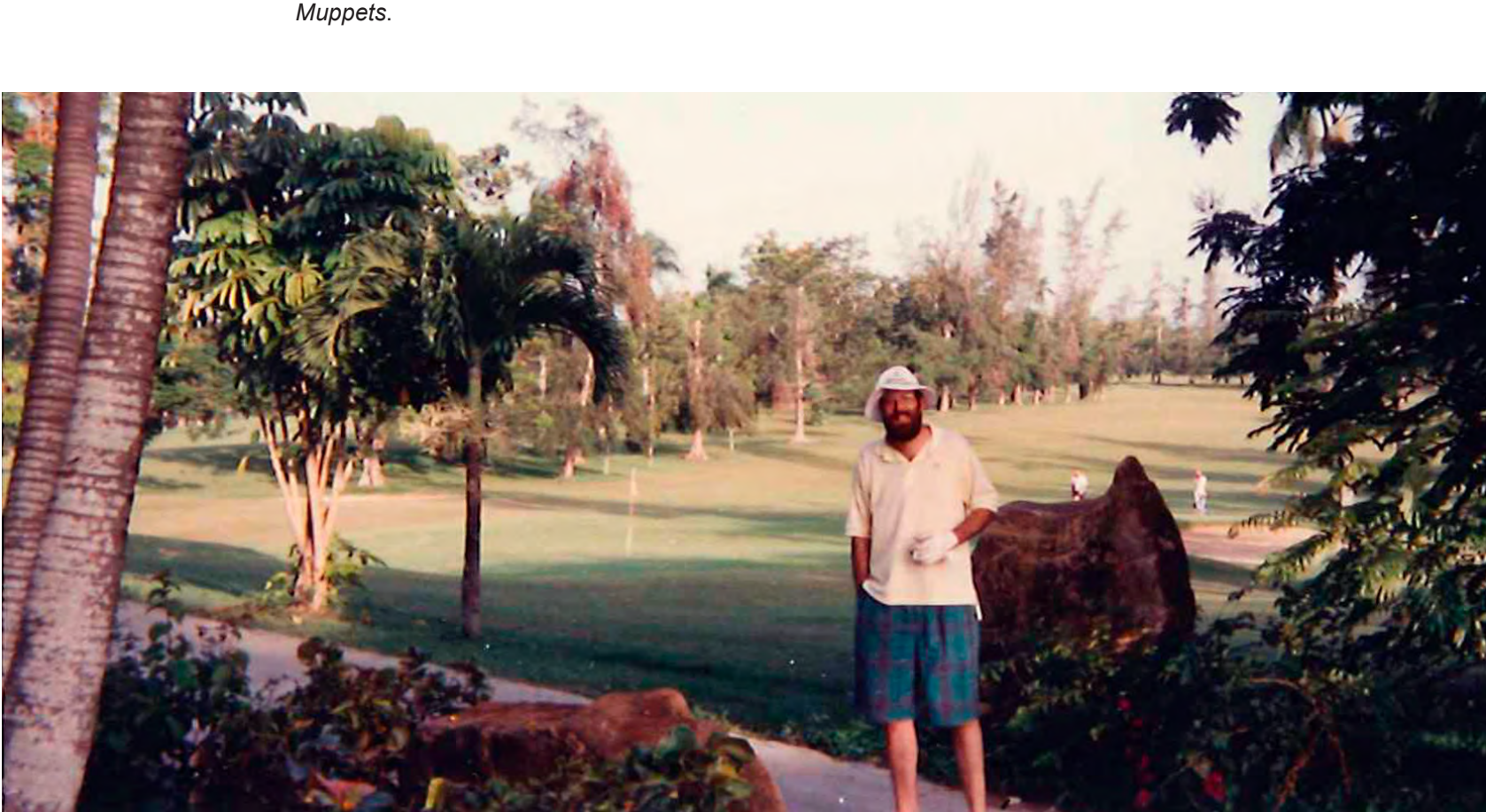
In Life as in Science

For Belliveau, life and science were intimately intertwined. Science wasn't just what he did; it was undeniably and unqualifiedly who he was. This isn't to say, though, that he spent all of his time in the lab. He was very much a sportsman, for example. In addition to skiing and golf—he seems to have introduced a sizable portion of the biomedical imaging community to both—his prowess extended to sailing and scuba diving. Martinos researcher Jyrki Ahveninen told us, for example, that his interview for a postdoctoral fellow position in Belliveau's lab took place 20 feet under the ocean's surface in full scuba gear.

Somehow, amidst all of this, he also found time to be a musician—a drummer. He made a habit of suddenly appearing onstage with bands performing at or near conferences and taking over the drum seat. We heard stories of him leading a smooth jazz combo through a raucous set of Led Zeppelin songs in the south of France, and of him slipping into an orange wig and livening up the closing dinner at a meeting in Sante Fe. Especially during the latter, said Matti Hamalainen, an MEG collaborator and later a Martinos Center faculty member, he resembled nothing so much as fellow drummer Animal, from the TV show *The Muppets*.

It was a remarkable afternoon of stories and remembrances. And after listening to the gathered speakers, one thing was clear to everyone in the room: the history of functional MRI would be markedly different—and decidedly less interesting—without Belliveau as one of its chief protagonists. Bruce Rosen, director of the Martinos Center and the principal investigator of the 1991 *Science* paper, described how Belliveau's larger-than-life persona and his infectious zeal, not to mention his prodigious intellect, naturally made him the center of attention and cast him as a sage character and ultimately a kind of mentor to anyone he encountered. People gravitated toward him, wanted to engage him and hear what he had to say.

Even those who supervised him. Rosen, who recruited Belliveau to the Center and served as his mentor during those early years, recalled that when the latter introduced him to a friend or a colleague the person would invariably ask, "Are you one of Jack's students?" He continued: "Aside from being moderately miffed at the latent height-ism in our society"—Belliveau checked in at 6'3"; Rosen is not quite as tall—"the reality is, that was very much a true statement."



The ‘Unassuming’ Ken Kwong and a Pivotal fMRI Breakthrough

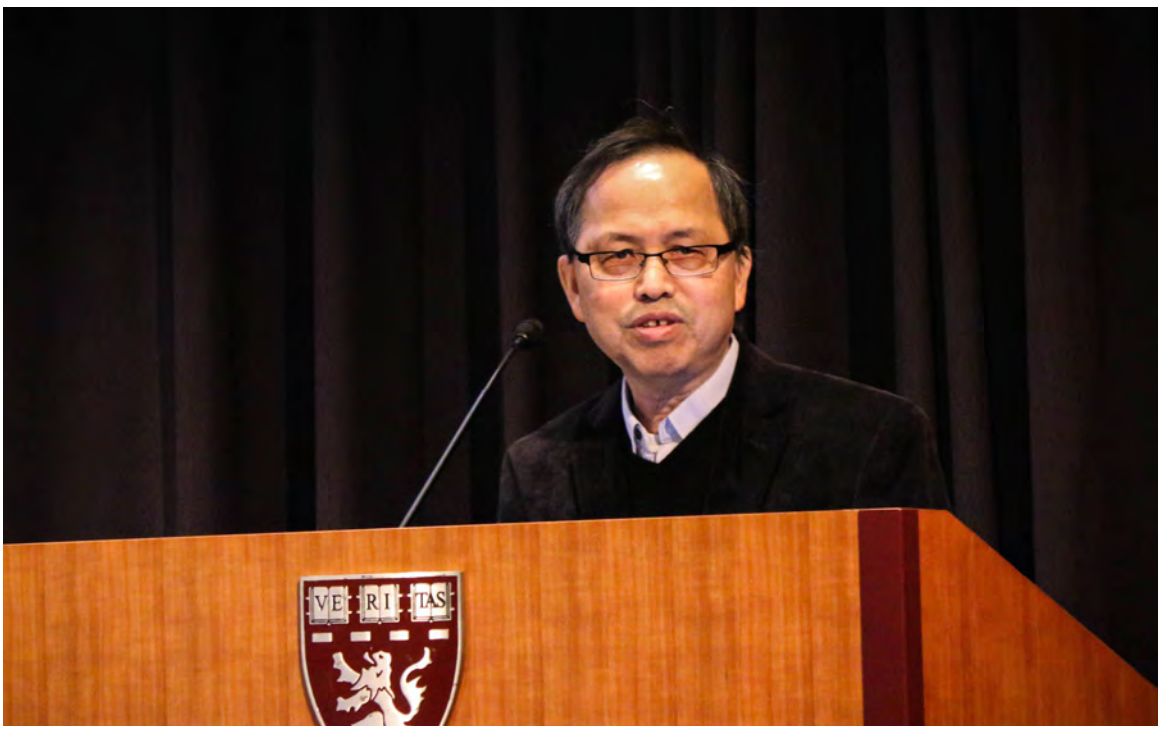
In early 1992 the neuroscience community was flush with excitement. Jack Belliveau had recently published his pioneering work with functional MRI and the possibilities of the approach seemed truly limitless.

Researchers were particularly inspired by the potential for brain mapping that was evident in Belliveau’s work. They could now see, more or less in real time, changes in the brain occurring in response to particular stimuli or tasks. There was just one problem: the need to use an injected contrast agent limited the potential of fMRI in human subjects, as any medically unnecessary injection poses some degree of risk.

As it happened, another Center investigator, a postdoctoral fellow named Kenneth Kwong, had found a way around this problem. In a paper published in June 1992 in *Proceedings of the National Academy of Sciences*, Kwong reported a means to measure intrinsic contrast—that is, contrast occurring naturally in the brain—with fMRI, thus removing the need to use an external agent. In doing so, he positioned the technique for much broader application than would have been possible otherwise, opening the door to the many extraordinary advances we have seen in the nearly 30 years since.

Kwong isn’t one to tout his accomplishments. The book *Quiet*, something of a treatise on the power of introverts, of those who have little need for attention and little if any use for the (over)stimulation of the outside world, describes him as “a brilliant but unassuming scientist” who never asks for recognition for his extraordinary achievements. And indeed, in conversations about

Below: Ken Kwong



the heady early days of functional MRI, he often either downplays the creativity of his insights or deflects attention by pointing to the moments of chance or serendipity that led him to these insights.

Try as he might, though, to understate the significance of his contributions, the results of his work speak loudly enough.

Still, for all the impact his research has had, Kwong didn't actually set out to find the key to performing noninvasive functional MRI. He had come to the Center several years before, to work with MIT graduate student Daisy Chien. In 1990, he was seeking new ways to measure cerebral perfusion—essentially, blood flow in the brain. It was this search that started him down the fMRI path.

The first moment of serendipity he mentions came early in his search, when a brief snippet of conversation with Keith Thulborn, an MGH radiology resident at the time, alerted Kwong to a possible means of measuring perfusion. A very brief snippet, as it happened. "I heard one sentence," Kwong says. "I wasn't even sure he was talking to me."

In a 1982 report, Thulborn had shown in scans of blood samples that MRI could measure changes in the amount of oxygen in the blood. In doing so, he anticipated a phenomenon described by researcher Seiji Ogawa of Bell Laboratories in a 1990 paper, which would come to be known as blood oxygen level dependency, or BOLD.

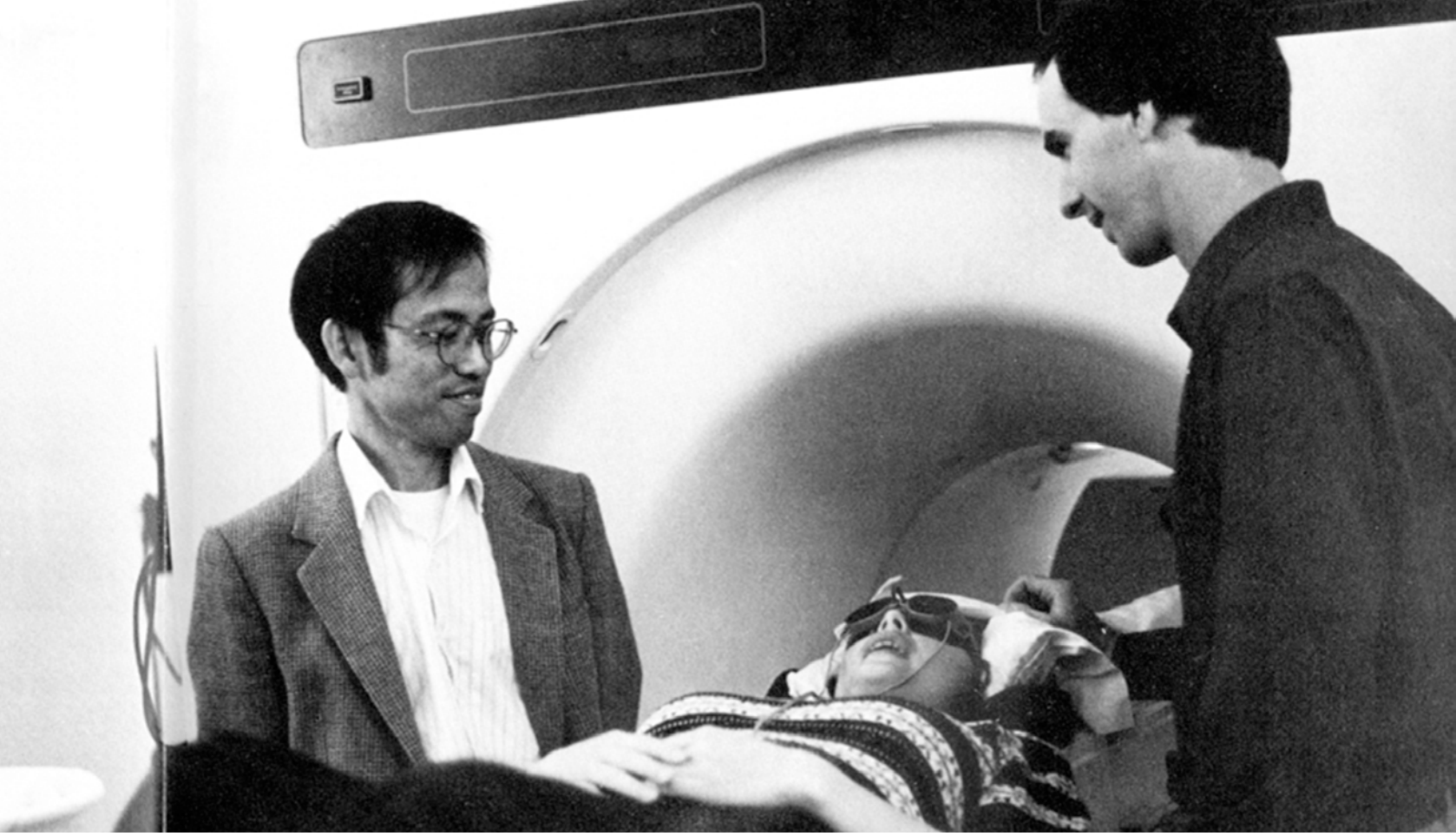
"Had I not caught Keith's sentence I would not have made any link between deoxyhemoglobin and the MR signal," Kwong says today. (*Hemoglobin* is the oxygen-transport protein found in red blood cells. When it is not bound with oxygen, it is called *deoxyhemoglobin*.) "It was not my area of expertise, and at the time I wasn't aware of Ogawa's work." But he had caught it. And now he wanted to know whether measuring deoxyhemoglobin was an option he could put to use.

The first step: designing an experiment. For help with this, he once again turned to something he had overheard in the hallway.

In 1990, even as Kwong was exploring options for measuring perfusion, Jack Belliveau was developing a means to image brain activity with MRI and performing his experiments using visual stimulation to induce changes in activity—the same experiments that would be reported in *Science* in November 1991. Kwong wasn't involved in the functional MRI project but he had heard through the proverbial grapevine what Belliveau was up to. And he saw in it a natural approach to eliciting changes in perfusion.

He talked to Belliveau about his idea to use the visual stimulation paradigm for his own experiments. Belliveau was supportive, offering suggestions about how to go about it and even loaning Kwong a pair of visual stimulation goggles—the now-famous red goggles that researcher Peter Fox had used in the early 1980s and that Belliveau had borrowed and used for his own experiments. (With apologies to Fox, the never-returned goggles are now on display in Mass General's Paul S. Russell Museum of Medical History and Innovation.)

Kwong performed his first experiment with the new approach on the evening of May 9, 1991, in what is now Bay 3 at the MGH Martinos Center for Biomedical Imaging. It's tempting to imagine here a sense of import in the air, a knowing understanding of the significance of what was about to happen. But the fact is, for Kwong, it was a scanning session like any other, especially as he had no expectation of the approach working right out of the gate.



And yet it did. Kwong processed the data acquired during the scan and, “lo and behold, I saw a bright blob coming out of the visual cortex.” More to the point, he noted a clear change in MRI signal due to changes in blood deoxyhemoglobin, which suggested that hemodynamic change during neuronal activation could be observed with MRI. Even with just a single run in a single subject, he knew the experiment had been a success.

So, what next? What do you do when you’re reasonably sure you’ve just made a breakthrough scientific discovery, one that could have far-reaching implications, even beyond what you can imagine, for basic science research and even clinical practice? How do you react? Kwong remembers joking with colleagues in the following days, telling them he had demonstrated cold fusion: a “too good to be true” kind of a result, and a potentially misleading one. Then he rolled up his sleeves and got to work.

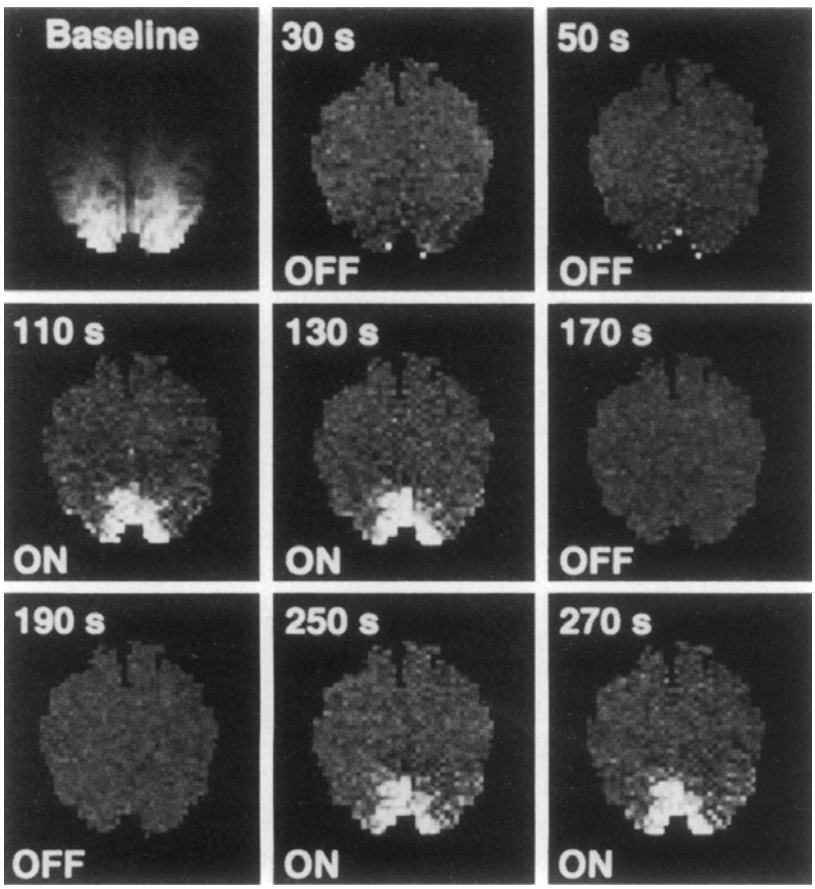
Keeping his enthusiasm in check, he focused on whether the signal differences he had seen were artifacts (that is, anomalies in the image). Indeed, this question occupied him over the next several months as he ran further experiments and analyzed the results, trying to confirm that the changes he observed—both in the original experiments and subsequently—were in fact due to visual activation. Finally, he was confident that they were. Now all that remained was to tell the world what he had found.

Reporting the Findings; Or, the Third Time’s the Charm

Disseminating scientific findings is of course an integral part of the research endeavor. It enables other investigators to absorb the findings, to incorporate them, validate them, challenge them. And it conveys to the world at large what is now possible thanks to the efforts of the study’s authors, as well as of those who came before them. But as researchers everywhere know all too well, getting the word

out isn't always as easy as it might seem. Even if you've just shown that you can measure brain activity entirely noninvasively.

In the wake of his experiments, Kwong planned to submit an abstract describing "work in progress" movies of brain activation to the 10th annual meeting of the Society for Magnetic Resonance in Medicine (SMRM), to be held in San Francisco in August 1991. As was the custom in those pre-online submission days, he hand-delivered the package to FedEx just minutes before the mid-night deadline. Somehow, though, tragically, the package never made it; it was "lost in the mail," ending up wherever it is that missing letters and packages go. This left the announce-ment of Kwong's groundbreaking findings to a mention by Bernice Hoppel during a paper presentation and a short video in a plenary lecture by Tom Brady.



Kwong naturally would have preferred to present his findings in full, but even this brief, tantalizing glimpse of what he had achieved created quite the stir at the meeting. Many in the audience immediately appreciated its potential. Some went back to their labs and initiated similar experiments. Despite the FedEx setback, dissemination of the findings was already underway.

In the meantime, Kwong and colleagues wrote a more comprehensive paper detailing the work. They submitted it to *Nature* in October 1991. A few months later the journal rejected it. Why? Said one of the reviewers: "If the point of this paper is that MRI can be used to map the brain, this point has been made in the *Science* paper [by Belliveau et al.]. If the point of this paper is that MRI can shed new light on the regulation of cerebral hemodynamics and metabolism by neural activity, I am not yet convinced."

Opposite: Ken Kwong (left) and John Baker (right) prepare a volunteer for an fMRI experiment, circa 1991. The subject is wearing the now-famous stimulation goggles, which activate the visual cortex by flashing patterns of light.

Above: Images from Kwong's 1992 Proceedings of the National Academy of Sciences *paper showing activation in the visual cortex in response to stimulation.*

Below: fMRI pioneers and Martinos researchers past and present: Ken Kwong, David Kennedy, Arno Villringer and Bruce Rosen at the fMRI25 symposium in 2016. The daylong symposium celebrated the first quarter-century of the technique.

Opposite: fMRI pioneers Kamil Ugurbil, Peter Bandettini and Ken Kwong, with moderator Marta Bianciardi, during a 'Pioneer Campfire' at the 2019 annual meeting of the International Society for Magnetic Resonance in Medicine (ISMRM). Photo courtesy of Marta Bianciardi.

The authors were disappointed, even a bit frustrated. The reviewer seemed to have missed the major advance that the study offered: dynamic mapping of the brain using only intrinsic contrast. "I was surprised when *Nature* rejected the original paper," Kwong says, in his unassuming way. "I thought that, while one of the reviewers raised some good questions, another didn't understand the significance of the findings."

Still, the researchers soldiered on. They expanded the scope of the report and submitted it to *Proceedings of the National Academy of Sciences* in early 1992. As the old saw goes, the third time's the charm. This paper, "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation," was accepted. The journal published it in June.

With these experiments, Kwong and colleagues demonstrated that imaging of cerebral activation was possible using only naturally occurring contrast, that they could observe changes in the brain following sensory stimulation without having to inject the subject with any kind of external agent. It remained now to explore more fully the potential of the technique, to discover what about the complexities of the brain and the human body as a whole could be learned in applying it. As it turned out, investigators around the world were eager to do just that.

Captivating Tales from the Pioneer Trail

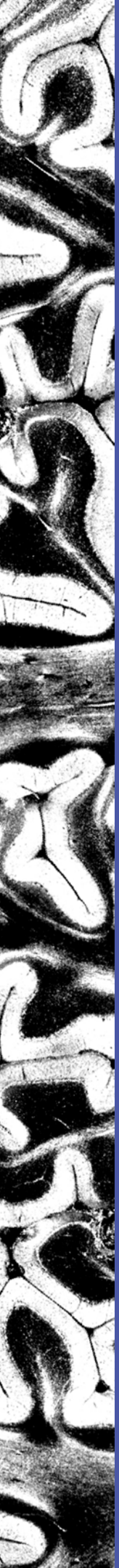
Imagine sitting by a campfire, listening to trail-blazers and other witnesses to key moments in the history of MRI as they casually recount the untold stories behind seminal papers or inventions. Attendees of the International Society for Magnetic Resonance in Medicine (ISMRM) 2019 Annual Meeting had just such an opportunity when they assembled in Montreal. (Minus the campfire itself, of course. Fire codes and all that.)

The Pioneer Campfires—also known as Fireside Chats—offered attendees a chance to meet with the investigators behind any number of breakthroughs over the decades. "The intention was to enable aspiring inventors, scientists and clinicians to personally interact with the people who shaped the field of MR as we know it today, and hopefully be inspired by their stories," says the Martinos Center's Marta Bianciardi, a member of the ISMRM Historical Archives Committee, which put on the series.

In developing the events, Bianciardi proposed to the committee a celebration of pioneers of functional MRI from three separate groups: Ken Kwong from the MGH Martinos Center for Biomedical Imaging, Kamil Ugurbil from the University of Minnesota, and Peter Bandettini from the University of Wisconsin (now at NIH). These researchers published, almost simultaneously in 1992, the first unambiguous dynamic images of brain activity in living humans during stimulation obtained with endogenous blood oxygen level-dependent (BOLD) fMRI.

The chats were a hit with attendees, who particularly enjoyed the informal setting and the opportunity to ask questions of the pioneers. At the fMRI campfire, for example, aspiring inventors, scientists and clinicians got to hear about the technical issues (determining the appropriate coil gradient and EPI sequence, for instance) and the surprises (not least, the fact that the BOLD signal was going up and not down) encountered while running the first fMRI experiments.

Also at the meeting, attendees could see a demonstration of the famous visual stimulation goggles used by Kwong and the MGH group, as well as other fMRI memorabilia, in a kind of pop-up early fMRI museum. The other memorabilia included the computer on which Jack Belliveau wrote his seminal 1991 *Science* paper, original lab notebooks and more.



Behind the Cover

The Story of the Original fMRI Image

The cover image accompanying the 1991 *Science* paper by Jack Belliveau and colleagues reporting the first demonstration of functional MRI is, quite simply, iconic. In that single, evocative picture, we can somehow see the endless possibilities of the emergent imaging technique.

To take a peek behind the cover—to learn a bit more about how the image was conceptualized and ultimately rendered—we checked in with the two authors of the *Science* paper who were primarily responsible for producing it: Mark Cohen and David Kennedy, both of whom worked with Belliveau in the Martinos Center.

Here's what we learned.

Belliveau and his team started thinking about ways to represent the study visually well before they knew *Science* was going to devote the cover to it. They knew the report and results were going to be important, says Cohen, who today is a professor in the UCLA Semel Institute for Neuroscience and Behavior, so they wanted to go the extra mile in highlighting the work.

They began to play around with the images from the paper, and in particular with the image from an oblique cut of the head showing the brain activation in response to the visual stimulus. When they learned from the editors at *Science* that the paper was being considered for the cover, they came up with the idea of presenting the findings in the context of the subject's head, by producing a computer-generated 3D model of the head.

This in itself was a fairly audacious idea. At the time, cover images for *Science* were rarely overtly depictive. Amy Henry, the art director for the journal, generally preferred more textural images: a photo of a field full of rocks, for example, or a high-resolution microscopy image that played on light and dark. She originally would have preferred to do something similar with this issue, Cohen says, but ultimately agreed that the cutaway of the head would be a compelling way to represent the groundbreaking study.

Of course, actually producing the image was another matter. "Back in those days, surface rendering in 3D was not common," says Kennedy, who is now the director of the Division of Neuroinformatics, Department of Psychiatry, at the University of Massachusetts Medical Center. But the researchers had access to an advanced Sun workstation with a high-performance TAAC-1 graphics and image accelerator. The accelerator came with a number of demo videos showing surface and volume rendering, so they knew that what they wanted to do was possible. And in fact they were able to replace the data in one of the demos with their own MRI scans.

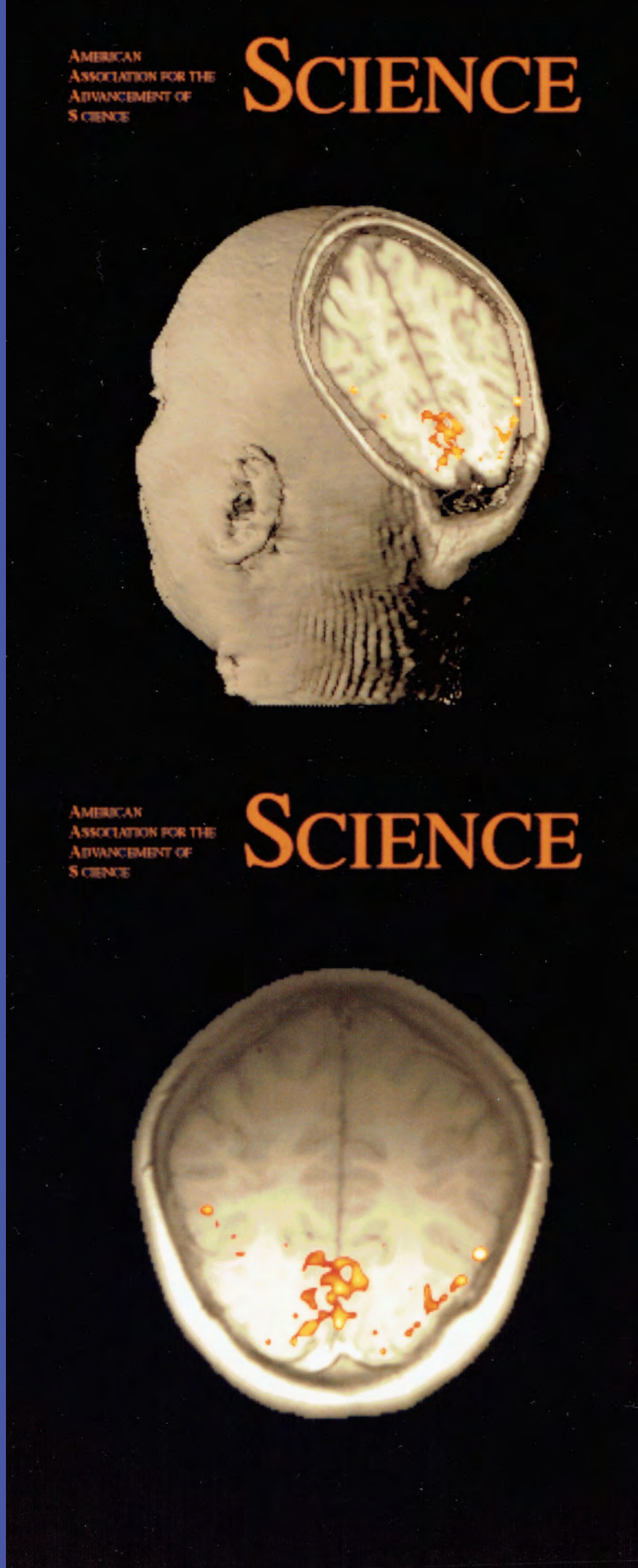
They knew both the angle and the depth at which the oblique scan they were using had been acquired, and were able to cut into the 3D model at the same angle and depth, so the MRI scan in fact appeared in the right part of the head. This much was relatively straightforward. Things got slightly tricky when they had to account for the viewing angle of the head itself. "We wanted enough of the face to be recognizable [as a face], but we also wanted the exposed part of the head in view," Kennedy says. "We probably spent days arguing over the exact angle."

Once the head was turned, the MR scans no longer matched the rendering of the head. The researchers could no longer just overlay

them because the aspect ratio was now off. So they manually adjusted the skew and the magnification of the image, Kennedy adds, “probably in Photoshop or some such thing,” to get the registration just right.

From there, the image was handed back to Cohen, who did a number of adjustments and enhancements—the color toning of the skin, for example—also in Photoshop. But just as they were finalizing it, another consideration arose. It started to look as if the paper were going to appear in the November 1 issue of the journal, so the researchers came up with the idea of making a Halloween cover. “We could go this whole sort of macabre route with it,” Cohen says. The initial thought was to place the image against a black background with the 3D rendering of the head and all of the lettering—the “Science” in the header, etc.—in shades of orange.

In the end, the decision was made not to go with a macabre cover. Because, well, because it was macabre—an aesthetic not usually associated with *Science*. Still, Henry, the art director, agreed to keep the orange lettering. It was, after all, Halloween.

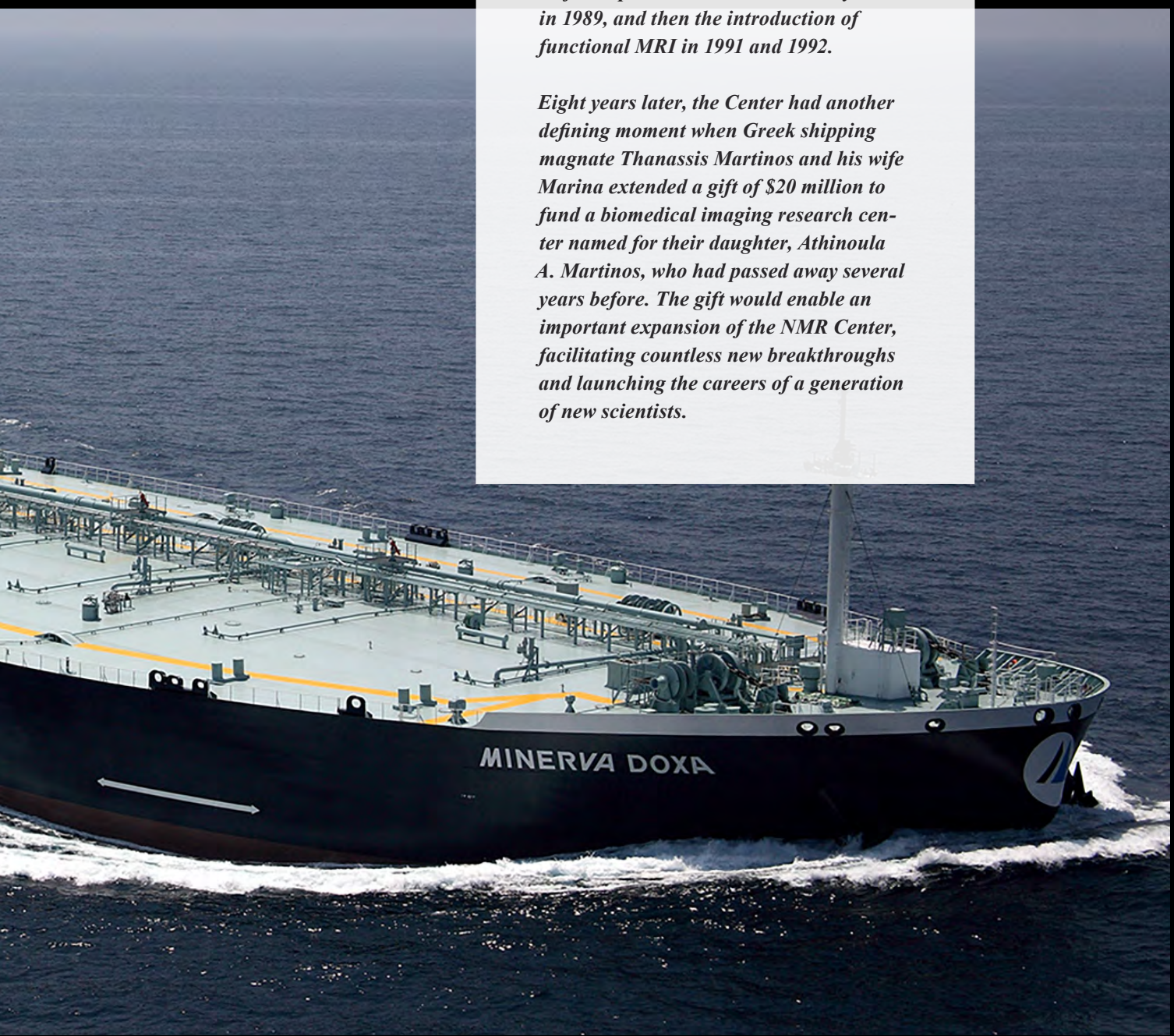


Right: Two proposed alternate, “Halloween” covers for the 1991 Science *paper introducing fMRI. Snapshots of the covers were found only recently amidst a pile of boxes in a closet in the Center. To our knowledge, they are the only extant images of the covers.*

The Martinos Gift

If you were to plot the history of the Martinos Center on a sheet of paper, it would look something like a step function, to borrow a term from the mathematics and physics that underlies much of the Center's work: that is, a function whose graph looks like a stairway, or a series of steps. The first of these, of course, was its formation in about 1980. The next major step was the move to the Navy Yard in 1989, and then the introduction of functional MRI in 1991 and 1992.

Eight years later, the Center had another defining moment when Greek shipping magnate Thanassis Martinos and his wife Marina extended a gift of $20 million to fund a biomedical imaging research center named for their daughter, Athinoula A. Martinos, who had passed away several years before. The gift would enable an important expansion of the NMR Center, facilitating countless new breakthroughs and launching the careers of a generation of new scientists.



In Memory of Athinoula

On a Friday afternoon in 1976, while on vacation on the small but inviting island of Nantucket, Dr. Daniel C. Shannon received an urgent phone call from Thanassis Martinos, the 26-year-old son of a prominent shipping family in Greece. A godchild, the daughter of one of Martinos' ships' captains, was critically ill with heart and lung failure and in a coma and he asked if Shannon might be able to help.

Shannon, the director of Pediatric Intensive Care at Massachusetts General Hospital and a founding faculty member of the MIT-Harvard Health Sciences and Technology (HST) program, said he would do whatever he could. He flew to Athens the next day. By late Sunday, he and the child were back in Boston, where she was admitted to the Pediatric Intensive Care Unit for diagnosis and treatment. Within two weeks, thanks in large part to the excellent care she received at Mass General, she was back home in Greece, where she was able to resume a happy, healthy life.

The story's happy ending is a welcome one. But the child's recovery wasn't the only important outcome of the otherwise terrifying ordeal. Through the shared experience, Thanassis Martinos and his wife Marina forged a deep and lasting friendship with Shannon, a friendship that would only grow stronger over the years and decades to come.

In 1997, Thanassis and Marina's oldest daughter, Athinoula, passed away at the age of 24, after years of struggling with mental health issues. Devastated, the Martinos' turned to Shannon for counsel. Shannon had also lost a daughter and they asked how he had coped with the unimaginable grief.

Their old friend told them he had honored his daughter's memory by establishing a research scholarship fund for young women at the college she had attended. He suggested they consider setting up a scholarship fund in Athinoula's name to support the research, study and training of students in the Health Sciences and Technology program. The Martinos' agreed that this would be a fitting tribute to their daughter and, in partnership with HST, created a fund. The first ten students in the Athinoula A. Martinos Research Scholarship program were announced at the 1997 HST Research Forum at MIT.

After seeing the undeniable impact of the scholarship fund, Thanassis and Marina Martinos decided they wanted to do more. Specifically, they wanted to support more directly research that would advance understandings of neurological disorders and how better to address those disorders. In 1999, they presented a gift of $20 million to the Harvard- MIT Division of Health Sciences and Technology to facilitate development of cutting-edge neuroimaging and other biomedical imaging technologies and fostering multidisciplinary research using those technologies, bridging areas from hardware development to the basic biosciences to clinical investigation.

HST, in turn, invited Massachusetts General Hospital to participate in the founding of the Athinoula A. Martinos Center for Biomedical Imaging, combining the clinical and imaging expertise and extensive imaging facilities of the existing MGH-NMR Center with HST's strengths in engineering and basic neuroscience and the resources represented by the Martinos family gift.

The Martinos Center officially launched in November 2000 under the leadership of NMR Center director Bruce Rosen and with a faculty of approximately forty investigators and more than $23 million in existing biomedical imaging equipment. The Center was housed on the

MGH research campus in the Charlestown Navy Yard, by then the longtime home of the NMR Center, with a satellite facility on the MIT campus providing MIT researchers with access to cutting-edge imaging technologies and thus enabling important, complementary work in normal, healthy populations.

While the members of the Center continued to occupy much of Building 149 in the Navy Yard, the Martinos gift enabled the purchase of Building 75 across the street, which would nearly double the Center's footprint and allow a significant expansion of its research portfolio.

Martha Gray, co-director of HST from 1995 to 2008, who was instrumental in the creation of the Athinoula A. Martinos Center for Biomedical Imaging as well as the Athinoula A. Martinos Imaging Center at the MIT McGovern Institute, reflects on the researchers' many successes in the 20 years since the Center's launch.

"What's amazing to me about the work they have done is, they have a very holistic view of the opportunities afforded by imaging writ large," she says today. "They don't stick with any one kind of imaging. They use whatever tools are available to understand what's happening in disease, and neurological disease in particular, so we can ultimately change the course of disease. They have opened our eyes to the world of possibilities. Without imaging, and the types of imaging they have introduced, we really are blind."

Rosen, in turn, looks back on the days when he and Gray and others were envisioning the shape of a new, integrated MIT-MGH imaging center and ultimately putting their plans into practice, not least with the purchase and overhaul of Building 75 in the Navy Yard.

"It was a heady time, to be sure," he says. "Having the ability to purchase our own building and put our imprimatur on it reflected a measure of independence and arrival, and it gave us the space to break new ground in our research and strike out in new directions."

In this sense, and in many others, the heady time continues to this day.

Snapshots from the 2002 "Brainstorm" meeting in Athens, showcasing work from the newly named Martinos Center.

Opposite, top (from L to R): Nikos Makris, Bruce Jenkins, Ken Kwong, Van Wedeen, Jack Belliveau and Bruce Rosen

Opposite, bottom (from L to R): Carolyn West, Anders Dale, Maria Angela Franceschini, Tamara Knutsen, David Boas and Randy Buckner

Above (from L to R): Anna Devor, David Boas, Maria Angela Franceschini

The Martinos Center's annual retreat, 2004

Martinos Staff

The Martinos Center's countless achievements over the years would not have been possible without the efforts of its indefatigable staff. In the early 2000s, this hardworking group included, from left to right in the photo below: Janice White, Mary Roy, Maureen Kelly, Dee Dee Correia, Monica Langone, Carol Barnstead, Linda Butler, Stacey Ladieu and Mary O'Hara.

Correia served as the Center administrator for more than 35 years, from the time of its inception until her retirement in 2016. We can say entirely without hyperbole that she is the cornerstone upon which the Center was built.

Building 75 Opens Its Doors

In June 2008, with support from the 1999 gift by Thanassis and Marina Martinos, the Athinoula A. Martinos Center for Biomedical Imaging completed a 32,000-square-foot expansion into the newly overhauled Building 75 in the Charlestown Navy Yard, nearly doubling its footprint. While the new space welcomed research programs that had outgrown their old quarters in Building 149, including the RF Coil Lab, which continued to develop advanced radiofrequency coils for ultrahigh-field and other MR scanners, much

of it was specifically designed for and dedicated to the Center's emerging molecular imaging program. The new facilities in Building 75 comprised chemistry and biology wet labs and a host of molecular imaging technologies to propel the exciting research envisioned for the program.

As part of the expansion, the Center also installed a groundbreaking imaging system combining MRI and positron emission tomography (PET): the BrainPET scanner. Developed in collaboration with industry partner Siemens Medical Solutions, the first-of-its-kind scanner integrated a prototype PET imaging system into a Siemens Trio 3T MRI system, thus enabling truly simultaneous imaging of anatomical structures and metabolic and molecular processes in the brain. By offering a comprehensive view of tissue anatomy and physiology, the scanner would prove a vital resource for the molecular imaging effort.

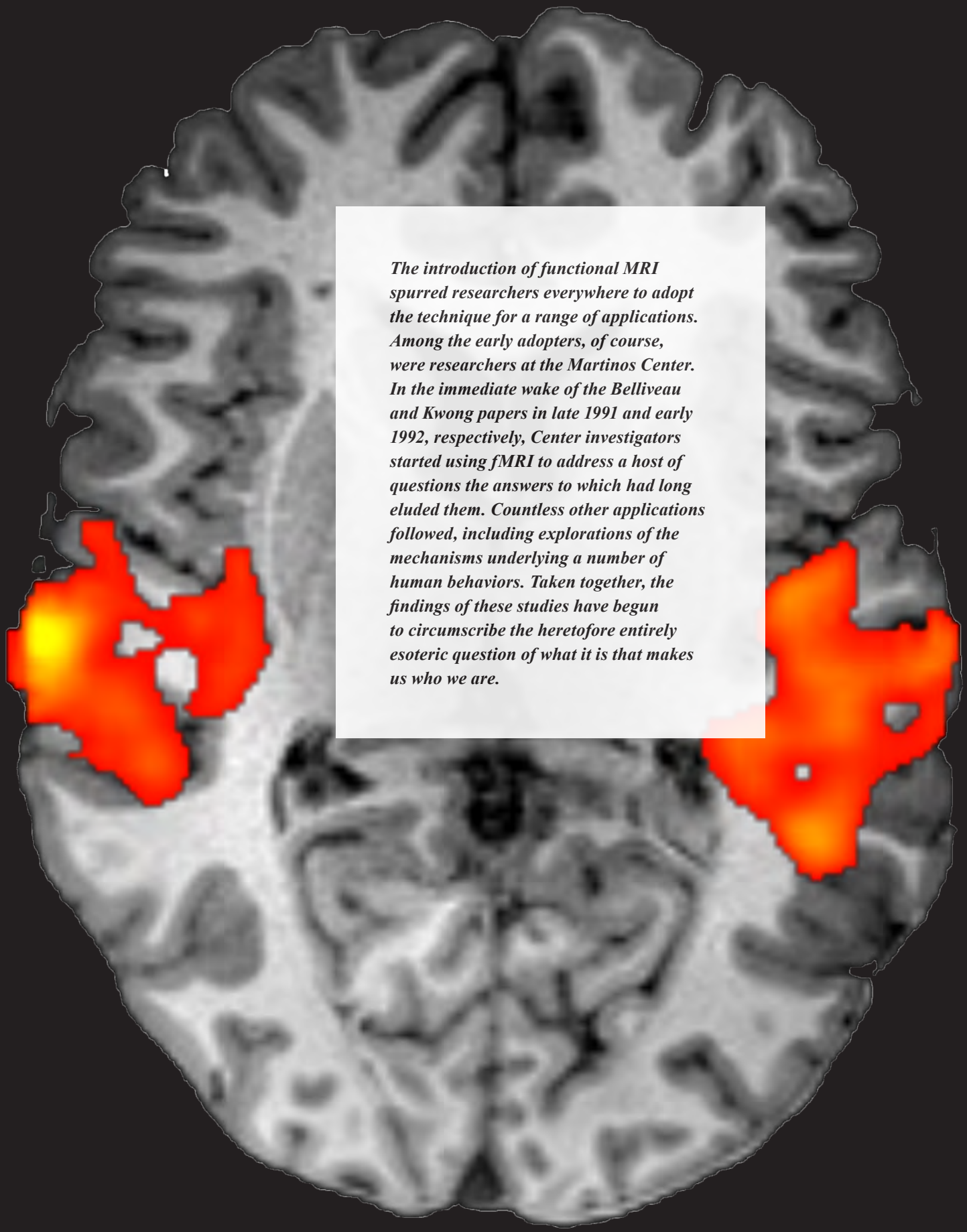
The launch of the new space and enhanced facilities marked a major step forward in the Martinos Center's long history of innovation. The Center was a now a state-of-the-art, 85,000-square-foot laboratory with approximately 60 faculty investigators and over 100 postdoctoral research fellows and graduate students.

The expansion was dedicated in May 2008 at a ceremony attended by Thanassis and Marina Martinos. Center director Bruce Rosen spoke at the ceremony, acknowledging both the tremendous accomplishment of completing the expansion and the many opportunities the facilities opened for the Center. "This expansion completes Thanassis' and Marina's vision for the Martinos Center as a research facility that unites the clinical and imaging expertise of the Massachusetts General Hospital with HST's strengths in engineering and basic neuroscience," he said. Thus, the Center officially began a bold new era of research.

Right: the 2008 dedication of Building 75. Back row (L to R): Phillip Clay, Daniel Shannon, Martha Gray, Greg Sorensen, Bruce Rosen. Front row (L to R): Susan Hockfield, Marina Martinos, Thanassis Martinos. Photo courtesy of Martha Gray.

Functional MRI

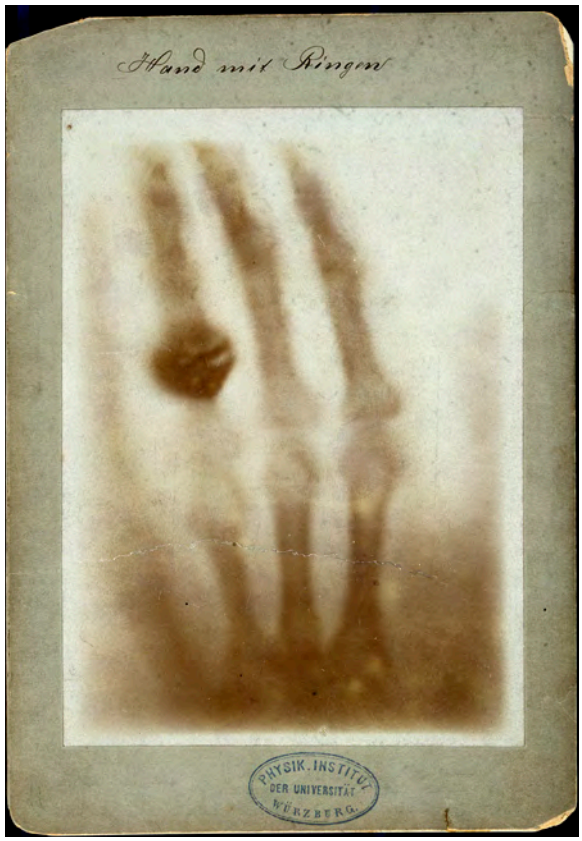
Applications



The introduction of functional MRI spurred researchers everywhere to adopt the technique for a range of applications. Among the early adopters, of course, were researchers at the Martinos Center. In the immediate wake of the Belliveau and Kwong papers in late 1991 and early 1992, respectively, Center investigators started using fMRI to address a host of questions the answers to which had long eluded them. Countless other applications followed, including explorations of the mechanisms underlying a number of human behaviors. Taken together, the findings of these studies have begun to circumscribe the heretofore entirely esoteric question of what it is that makes us who we are.

Is Functional MRI the New X-Ray Vision?

The introduction of the x-ray transformed our understandings of the nature of seeing and knowing. Nearly a century later, functional MRI did it all over again.



In the final days of 1895, a German physicist named Wilhelm Röentgen reported an intriguing discovery: the x-ray, a form of radiation that had enabled him to produce an image of the bones inside his wife's hand. The image was astonishing, offering a view of her anatomy that otherwise would not have been possible until after her demise. Indeed, when she first saw the image, an almost ghoulish rendering of her skeleton stripped of its skin, Anna Bertha Röentgen cried out, "I have seen my death."

When Wilhelm Röentgen sat down with journalist H.J.W. Dam for an interview—the only one he granted in the wake of the discovery—the first question Dam asked was, "Is the invisible visible?" The question referred, of course, to the newfound ability to peer inside the living body, to reveal its heretofore hidden frame, but underneath it lay another question, one with deeper, more profound implications: namely, "Is the unknowable knowable?"

In a very real sense, it was. By opening up our interior selves for inspection, the discovery changed the ways we think about how we see and what we know. No longer were these confined to unobstructed views of people and objects directly in front of our eyes. Now they also encompassed that which was previously inaccessible. Eventually, we even came up with a name for this new type of seeing and knowing: x-ray vision.

Can We Image Human Nature?

Nearly a century after the introduction of x-ray, the debut of fMRI reopened some of the same questions about the nature of seeing and knowing, casting an even keener eye, perhaps, on the matter of what makes us who we are. If x-ray made the invisible visible by revealing our inner anatomies—the structural constituents of our physical forms—fMRI has delved deeper still, probing the areas of the brain responsible for the operations and behaviors that reside at the core of the human condition.

The earliest applications of fMRI already pointed to this broad potential. In 1993, Mass General psychiatrist Hans Breiter and colleagues in the Martinos Center were the first to report use of the technology for assessment of psychopathology, applying it to a study of symptom provocation in patients with obsessive-compulsive disorder. Breiter went on to explore the brain circuitry involved in cocaine addiction, identifying, in a 1997 study, "reward" areas associated with cocaine-induced euphoria. Four years later, he found that the same reward circuitry came into play in gambling, a finding with broad implications.

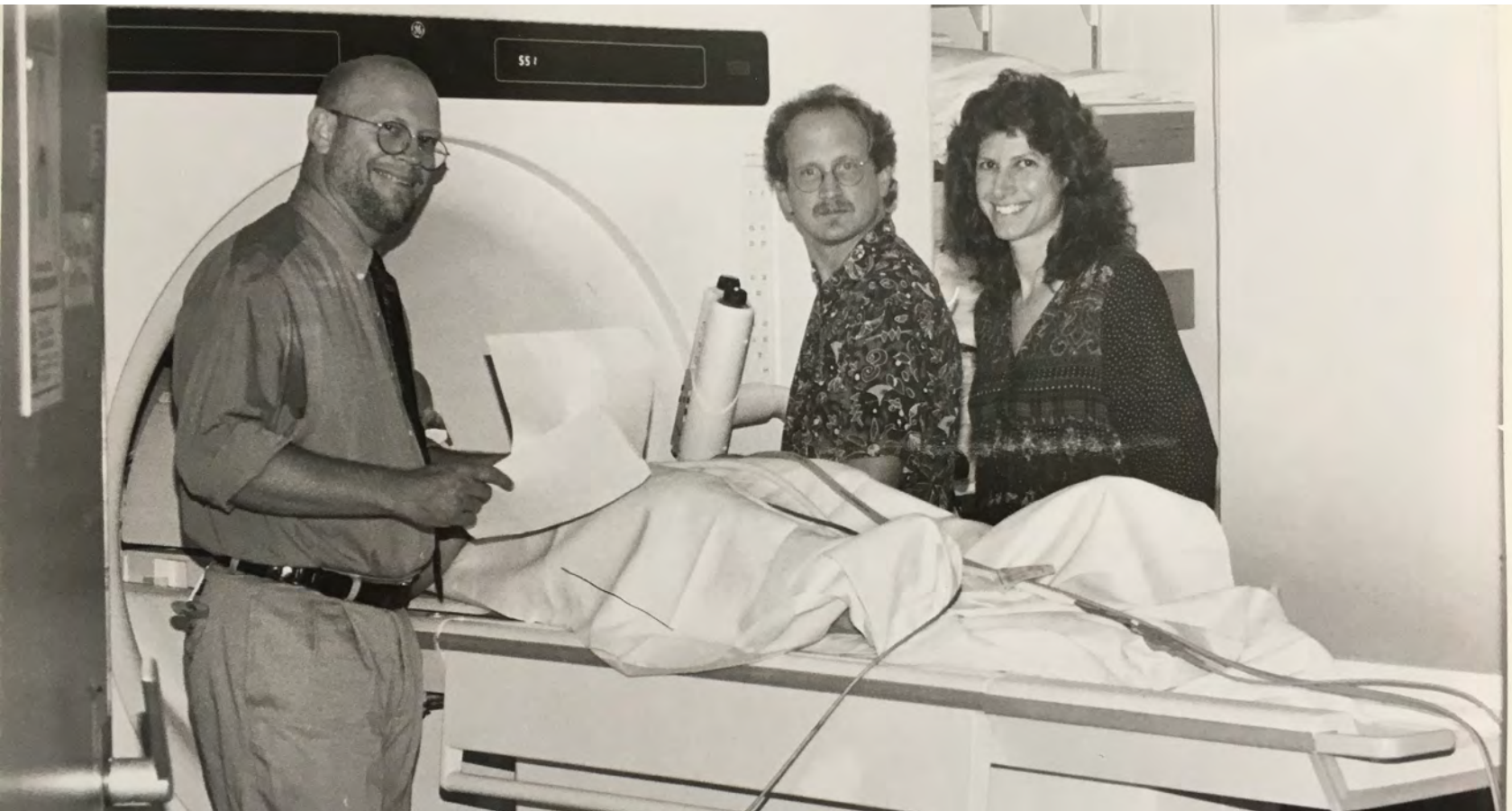
Another of the earliest adopters was neuroscientist Roger Tootell, who used fMRI to gain better understandings of seeing itself. In a series of studies, he and collaborators in the Center called on the new technology to probe the organization of the visual cortex in humans; at the time, nearly everything the research community knew about how the brain organizes around seeing was based on animal models. This work led to an impressive one-two punch in 1995: publications in two of the most prestigious journals in the sciences, *Nature* and *Science*, on consecutive days. On May 11, the researchers published in *Nature* fMRI findings about visual motion after effect. The next day, they reported in *Science* a study in which fMRI revealed the borders of multiple visual areas in the human brain.

In the years since, researchers have continued to circumscribe the mental processes underpinning human behavior. By measuring regional brain activity during cognitive tasks in healthy subjects, they have been able to associate particular cognitive functions with localized areas of the brain, and by extension explore how those areas work together in complicated neural networks to drive such behavior. Thus, fMRI has helped shed light on a number of additional higher-order cognitive functions, including learning and memory, attention, emotions and even social cognition. At the same time, in similar ways, it has yielded insights into a broad range of mental diseases and disorders.

In the following pages, we describe just a few of the many applications of the technology over the past nearly three decades.

Opposite: This x-ray image, the first ever produced, shows the hand and ring of Anna Bertha Röentgen, wife of Wilhelm Roentgen, who discovered the x-ray in 1895.

Below: Psychiatry researchers Hans Breiter (left) and Randy Gollub (right) performing a functional MRI experiment with the Martinos Center's David Kennedy, 1994



The Neuroscience of Personal Space

We all have a need for personal space, the comfort zone we maintain around our bodies, implicitly entreating others not to encroach upon it.

In recent years researchers have been probing the ways in which we regulate this space, looking at how and why our brains tell us when someone is simply too close. These studies have meaningful, real-world implications. Not least, they are showing promise for helping those suffering from mental illness. As well as giving us better understandings of how our brains work generally, they are now also shedding light on the mechanisms of social dysfunction in patients with schizophrenia.

Among the new research tackling these problems is an ongoing study by researchers at the Martinos Center to develop an objective, quantitative means to measure what are known clinically as “negative” symptoms. This is one of the great unmet needs in treating schizophrenia. When people think of the disease they tend to think of “positive” symptoms like hallucinations and delusions, which have over the years come to dominate popular depictions and public perceptions of schizophrenia. But the negative symptoms, symptoms that involve an impairment of motivation and action … these are in fact the most disabling.

Which is why the recent research is so invaluable. “An objective method would go a long way toward helping us find better treatments for these symptoms,” says Daphne Holt, a psychiatrist at Massachusetts General Hospital and an investigator in the Center. “The shocking reality is that, even after decades of intensive testing of potential novel treatments for negative symptoms, at the moment, there are no effective treatments available for them.”

Holt has been exploring a particular, often crippling aspect of these symptoms: social

Daphne Holt and Roger Tootell

withdrawal. People typically understand this to mean not wanting to be around others, but it’s more than just that. Social withdrawal also comprises an inability to read social cues or to understand the perspectives of others. As a result it can prove one of the most devastating components of the disease—especially because it can lead to the person having difficulty holding down a job, for example, or maintaining many relationships, the kinds of things we think of as part of having a normal, fulfilling life.

But what accounts for this? What gears and cogs in the brain are either turning or not turning to cause social withdrawal and its often-debilitating effects? Researchers have a few ideas. Holt has been studying a model of social dysfunction in schizophrenia that proposes a relationship between this and very basic processes in the brain: sensory-motor functioning. One of the more prominent lines of thinking about schizophrenia today, the model suggests that many of the things we view as wrong with the higher cognitive functions are actually consequences of “lower” processes, like sensory-motor ones.

This is where personal space comes in.

In 2014 Holt and colleagues published a study looking at a particular sensory-motor circuit in the brains of healthy subjects using functional MRI. They found that the circuit displayed a specific type of response in the subjects,

and that the response increased as objects appeared to “loom” toward them (as opposed to withdrawing from them). Notably, the experiments also showed that the responses were greatest when social stimuli like human faces were involved, suggesting a role for the circuit in basic social behaviors. Among them: the regulation of personal space.

Realizing the possible significance of this with respect to social dysfunction in schizophrenia, the researchers extended the study to explore the role the circuit plays in patients struggling with the disease. “We began these experiments because it has been well established that the size of personal space is abnormally enlarged in schizophrenia,” Holt says. “Consistent with this, our fMRI study found that both the magnitude of negative symptom burden and the responses of the ‘looming’ circuit to personal space intrusions in schizophrenia patients predicted the degree of personal space enlargement in these patients.”

The relationships they found—between responses to looming stimuli, personal space regulation and negative symptoms—point to the important possibility that disruption of this basic sensory-motor circuit leads to abnormalities in non-verbal social communication, including personal space-related behaviors. If this proves to be the case, Holt and colleagues will have found something of a holy grail in the management of social dysfunction: a neural mechanism that can be specifically targeted by novel treatment approaches.

Enter the Avatars

Recently, Holt has been working with the Center’s Roger Tootell to explore personal space in healthy subjects, yielding insights that can deepen our understandings of personal space and social dysfunction in patients with schizophrenia.

The collaboration has already produced intriguing findings. For example, the researchers measured the preferred personal space between a given human subject and (a) another human subject and (b) an avatar (computer-generated human) in a virtual reality environment and observed that the personal space with an avatar was almost identical to that with human subjects, across multiple types of measurement.

This was a critical finding, Tootell says. “The robust personal space response to an avatar makes it possible to do ‘real science’ on this topic—for example, manipulating only one factor in future studies of personal space. Also, it suggests that the brain calculates personal space, at least in early stages, only very crudely, because it does not distinguish between real versus digital humans.”

Working with avatars has allowed the researchers to dig deep into the brain to learn more about the structures associated with the regulation of personal space. For example, high-spatial-resolution fMRI studies in one of the Center’s 7T scanner showed that an avatar moving towards a subject activates a set of previously unknown “columns”—groups of neurons with similar properties—in inferior parietal cortex. These columns respond best to people who are “too close” or are approaching the personal space boundary.

In the same region, they also found a different set of columns tuned to sensory-based distance—that is, visually near versus far. “Thus, we can see the re-encoding of activity as it changes from visually-based to person-based, in high-resolution columnar maps, in this one common region,” Tootell says.

Eye-Contact Avoidance in Autism

Individuals with autism spectrum disorder often have difficulty looking others in the eyes. This is typically interpreted as a sign of social and personal indifference, but self-reports from people with autism suggests otherwise. Many say that looking others in the eye is uncomfortable or stressful for them; some will even tell you “it burns.”

In 2017, a team of investigators based at the Martinos Center shed light on the brain mechanisms involved in this behavior. They reported their findings in the journal *Scientific Reports*.

“The findings demonstrate that the apparent lack of interpersonal interest in autism is not, contrary to what has been thought, due to a lack of concern,” says Nouchine Hadjikhani, director of neurolimbic research in the Martinos Center and corresponding author of the *Scientific Reports* study. “Rather, they show that this behavior is a way to decrease an unpleasant over-arousal stemming from overactivation in a particular part of the brain.”

The key to the research is the subcortical system in the brain. This system allows orientation toward faces in newborns and later is important for emotion perception. It is also specifically activated by eye contact. Previous work by Hadjikhani and colleagues had revealed that the subcortical system was oversensitive to direct gaze and emotional expression in autism. In the 2017 study, she wanted to take this further. She wanted to see what happens when the gaze is constrained to the eye-region—that is, when the subjects are compelled to look people in the eyes—while viewing images of faces conveying different emotions.

Using functional MRI, she and colleagues measured differences in activation in the components of the subcortical face processing system—superior colliculus, pulvinar nucleus of the thalamus, and amygdala—in people with autism and in control subjects as they viewed faces either freely or with their focus constrained to the eye-region. They found that, while the two groups exhibited similar activation during free viewing, those with autism showed overactivation when they were compelled to concentrate on the eye-region. This was especially true with fearful faces, though effects were also observed with happy, angry and neutral faces.

Below: Nouchine Hadjikhani. Photo by Matti Hämäläinen.

Opposite: Hadjikhani (second from right) and colleagues at the 2004 Martinos retreat

The findings of the study support the hypothesis of an excitatory/inhibitory imbalance in autism (*excitatory* refers to neurotransmitters that stimulate the brain while *inhibitory* refers to those that calm it and provide equilibrium). Such an imbalance, likely the result of diverse genetic and/or perinatal causes, can serve to strengthen excitatory synapses in the subcortical circuitry involved in face perception. This in turn can result in an abnormal reaction to eye contact, an aversive response to direct gaze, and consequently abnormal development of the social brain.

In elucidating the underlying reasons for eye-avoidance, the study also suggest more effective means of engaging individuals with autism. “The findings indicate that forcing children with autism to look into the eyes in behavioral therapy may create a lot of anxiety for them,” Hadjikhani says, “and that one should consider an approach in which a slow habituation to eye-contact may help them overcome this over-reaction. This could allow them to be able to handle eye contact in the long run, thereby avoiding the cascading effects that this eye-avoidance has on the development of the social brain.”

What Is 'Covert Consciousness' and Why Is It So Important?

In a 2017 paper in the journal Brain*, the Center's Brian Edlow, Ona Wu and colleagues reported a study in which they used the imaging techniques functional MRI and EEG to detect "covert consciousness" in the intensive care unit. We checked in with Edlow, associate director of the Center for Neurotechnology and Neurorecovery at Massachusetts General Hospital and an affiliated faculty member in the MGH Martinos Center for Biomedical Imaging, to learn more about the study and its implications for clinical care. Here's what we found.*

Opposite: Using fMRI, the Center's Brian Edlow, Ona Wu and colleagues found evidence of covert consciousness in patients with acute, severe traumatic brain injury Image courtesy of Brian Edlow.

What is covert consciousness?

Covert consciousness is consciousness that cannot be detected by bedside examination. Studies in patients in the chronic stages of recovery from a severe traumatic brain injury (TBI) suggest that approximately 15 percent of those believed to be in a vegetative state or a low-level minimally conscious state based on the bedside exam can actually follow commands during functional MRI or EEG tests.

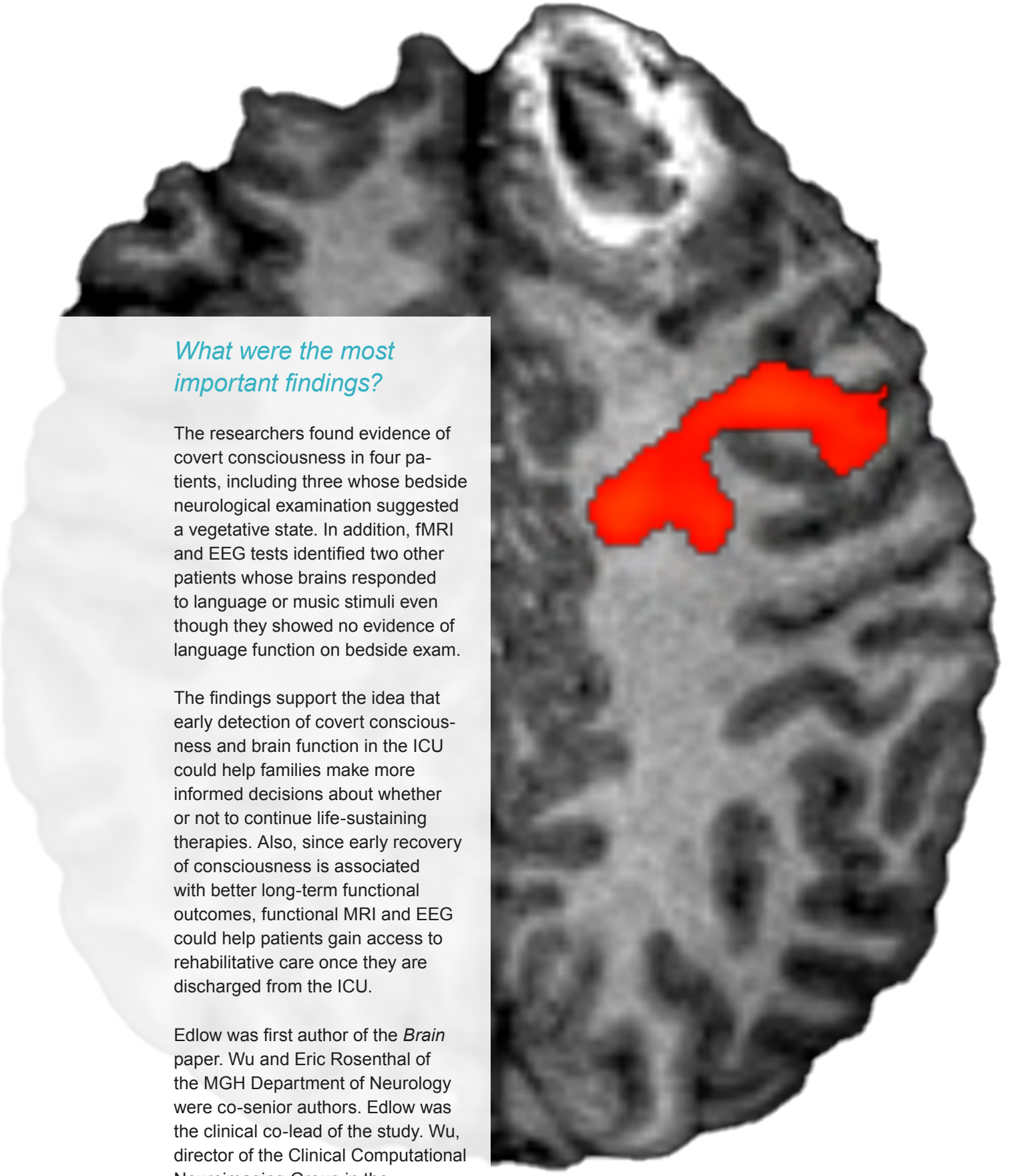
Why do we need a new approach to detecting consciousness?

Today, the bedside neurological exam is the gold standard test for assessing the level of consciousness in a patient with acute severe TBI. Studies have shown, though, that this approach can lead to misclassification of conscious patients as unconscious. There are a number of possible reasons for this—the patient may not be able to express herself by speaking or writing; she may have arm and leg weakness that prevents her from moving in response to a command; she may be receiving medications that sedate her; or the clinician examiner may misinterpret a purposeful movement as a reflexive, non-purposeful one—all of which underscores the need for a means to measure covert consciousness.

What were the goals of the Brain *study?*

The investigators set out to determine whether stimulus-based functional MRI and EEG could reveal covert consciousness in patients in the intensive care unit receiving treatment for acute severe TBI. They also explored whether these advanced techniques could uncover higher levels of brain function, suggesting a potential for recovery of consciousness.

Interestingly, they used music as well as language and motor imagery stimuli in assessing brain function. They included the music stimulus—a classical music clip with no lyrics—because they believed it would provide more information about function in the right side of the brain than the language stimulus. The latter was expected to provide more information about function in the left side of the brain.



What were the most important findings?

The researchers found evidence of covert consciousness in four patients, including three whose bedside neurological examination suggested a vegetative state. In addition, fMRI and EEG tests identified two other patients whose brains responded to language or music stimuli even though they showed no evidence of language function on bedside exam.

The findings support the idea that early detection of covert consciousness and brain function in the ICU could help families make more informed decisions about whether or not to continue life-sustaining therapies. Also, since early recovery of consciousness is associated with better long-term functional outcomes, functional MRI and EEG could help patients gain access to rehabilitative care once they are discharged from the ICU.

Edlow was first author of the *Brain* paper. Wu and Eric Rosenthal of the MGH Department of Neurology were co-senior authors. Edlow was the clinical co-lead of the study. Wu, director of the Clinical Computational Neuroimaging Group in the Center, spearheaded the technical component.

Understanding the Patient-Clinician Relationship

The quality of the patient-clinician relationship is widely held to impact a patient's response to treatment. Exactly how, though, has long remained a mystery. In a study reported in October 2020, Martinos Center researchers began to explore the questions of which parts of the brain and which types of behaviors play a role in the patient-clinician relationship and influence the clinical response.

"We talk about medicine being an art as well as a science, but we know almost nothing about the neurobiology underlying the patient-clinician interaction," says Vitaly Napadow, director of the Center for Integrative Pain NeuroImaging (CIPNI) housed in the Martinos Center and senior author of the paper, published in the journal *Science Advances*. "Understanding the neural underpinnings can play a critically important role in optimizing patient-clinician interactions for clinical benefit."

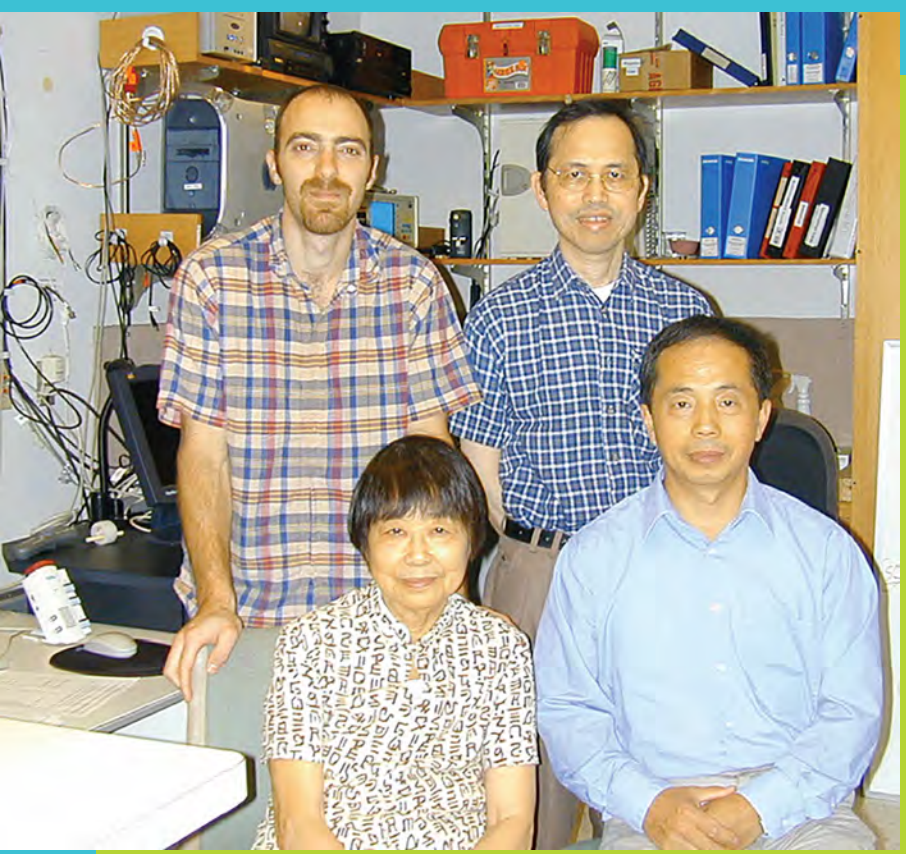
To this end, Napadow and colleagues used the novel imaging platform hyperscanning functional MRI, in which two or more MRI scanners are connected to enable simultaneous tracking of the neural responses in individuals interacting with one another.

For the experiment described in the study, the individuals interacting with one another were an acupuncturist and a chronic pain patient undergoing treatment for pain. The two communicated by way of a video chat as the patient was treated remotely with electroacupuncture and administered a moderate pressure pain. Using hyperscanning and automated video recording analysis, the researchers were able to track the effects of different behaviors on the brain during the patient-clinician interactions.

Why was this important? "Synching up with one another during interpersonal interactions may help optimize brain processing," says Dan-Mikael Ellingsen, the lead author of the study. "And it has been suggested that such physiological concordance may support empathy and social bonding." Ellingsen, a postdoctoral fellow at Martinos Center when he contributed to the study, is now at the Department of Psychology of the University of Oslo.

In fact, the researchers found that clinicians mirrored the facial expressions of patients expecting pain and treatment, and that the same regions of the brain were dynamically synchronized in activity across both patients and clinicians during the interactions. These regions were part of the neural circuitry already known to be associated with social mirroring and the theory of mind, which describes the process of inferring another person's mental state—both of which relate to empathy.

"Thus, the work tells us that mirroring facial expressions can reinforce the patient-clinician bond and boost the impact of treatment," Napadow says, "indicating that the clinical encounter has a demonstrable effect on the brain, emotions and clinical outcomes."



Vitaly Napadow has been an integral part of the acupuncture research effort at the Martinos Center for nearly two decades—since joining the Center in 2001 as a postdoctoral fellow working with Ken Kwong, Jing Liu and Kathleen Hui to understand better the brain's response to acupuncture needling.

He continues this work today as director of the Center for Integrative Pain NeuroImaging (CIPNI), which explores the brain's central role in a range of pain disorders. Recent studies include investigations of how brain plasticity supports acupuncture relief of carpal tunnel syndrome among others.

The photo to the left shows the acupuncture group in the early 2000s: (clockwise from rear left) Napadow, Kwong, Liu and Hui.

The photo above shows members of the CIPNI group in more recent years.

Meet the **Neuronauts**

After publication of the 1991 *Science* paper introducing functional MRI and the worldwide embrace of the new imaging technology, the ever-restless Jack Belliveau continued to break new ground. Armed with the understanding that "no single technique would be able to capture the symphony of the human brain," as Randy Buckner said during the 2014 memorial symposium honoring Belliveau's life and work, he started down the path of what we know now as "multimodal" functional imaging.

At the time, the Martinos Center was still primarily an MRI-based facility, so in order to explore the integration of functional MRI and other imaging modalities—EEG, MEG and PET—he traveled across the US and indeed around the world establishing collaborations with leading experts who were pioneering multimodal imaging with those modalities.

This multi-institutional team came to include Belliveau's group at the Martinos Center; the Dynamic Neuroimaging Laboratory at Einstein College of Medicine in New York with Gregory V. Simpson and colleagues; the Low Temperature Laboratory/BioMag Laboratory at Helsinki University of Technology/Helsinki University Hospital with Risto Ilmoniemi, Hannu Aronen and colleagues; and the Los Alamos National Laboratory/University of New Mexico group with Chris Wood and John George and their colleagues.

The ensuing years were heady times for the team, who were leading the charge in a new era of exploring the human brain directly, sparking advances in understandings of the workings of the brain and the mind for decades to come—and still today. And amidst the constant flurry of activity and the seemingly endless stream of technological breakthroughs, they forged a bond so strong they eventually came up with a slightly tongue-in-cheek name for the small band of intrepid explorers: the Neuronauts.

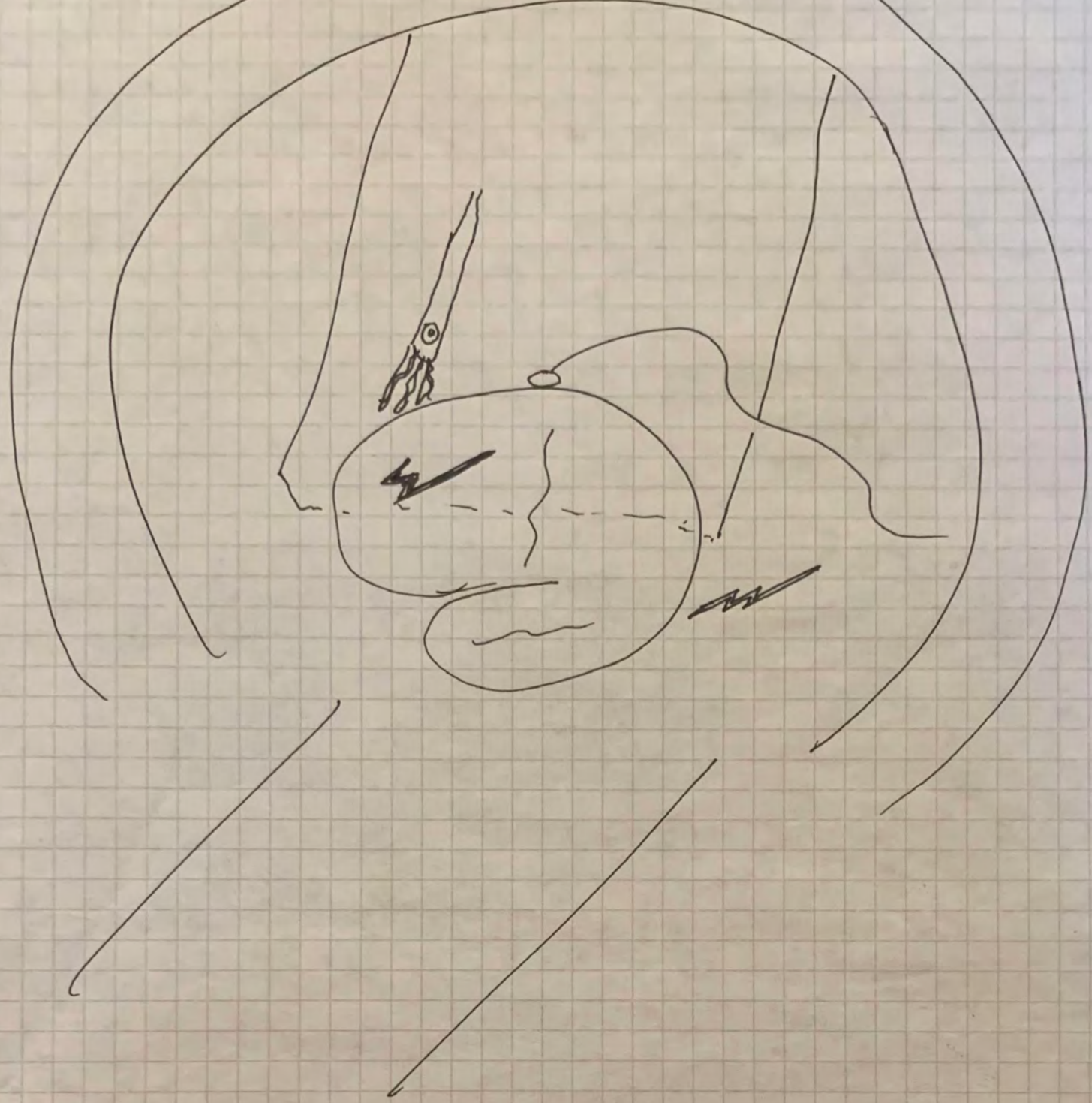
Such is the sense of camaraderie among the members of this group that, decades later, when they learned of the compiling of this book in the summer of 2020, they asked if they could contribute a collective remembrance of those early days of multimodal functional imaging. Following is what they wrote about the Neuronauts and the trailblazing work they did.

The concept of the Neuronauts captured the larger picture of what all four lab groups, and others, were doing together. The name was born of a large number of trips to Helsinki from Greg's and Jack's groups (and many trips to MGH). During these trips we worked for days on end, and enjoyed late evenings together, sharing our dreams and visions. The camaraderie was tremendous—we were so excited to see the results of the first-time integration of our methods. Now we knew what was possible and could imagine what would unfold in the future. The promise of what lay ahead was truly inspirational.

We worked hard together, sharing the frequent frustrations, trying to get things to work, and celebrated the functional imaging results that had never been seen before. We thought big and speculated wildly. The thrill of pushing into new frontiers of science got us thinking about having a name for all of us. Like astronauts exploring space we were making it possible to explore the human brain directly in new ways—Neuronauts!

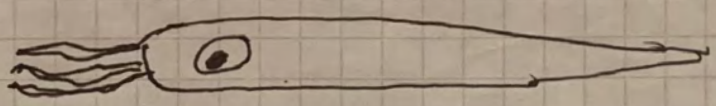
The name came to us one night over dinner and salmiakki in Helsinki when Jack, Greg and his student John Foxe, and Risto and his student Seppo Ahlfors were "brainstorming." We played around with a logo (Greg drew it up on some lab graph paper) to capture the modalities in a whimsical way. The idea of the Neuronauts represents the camaraderie that comes from our years of hard work and success together and the joy of speculating about what it means in the future.

We lost our colleague Jack in 2014. Jack's enthusiasm is still alive in all of us.



NEURONAUTS

SQUIDS



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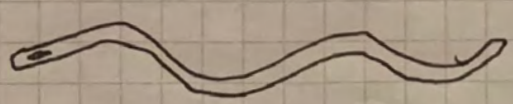
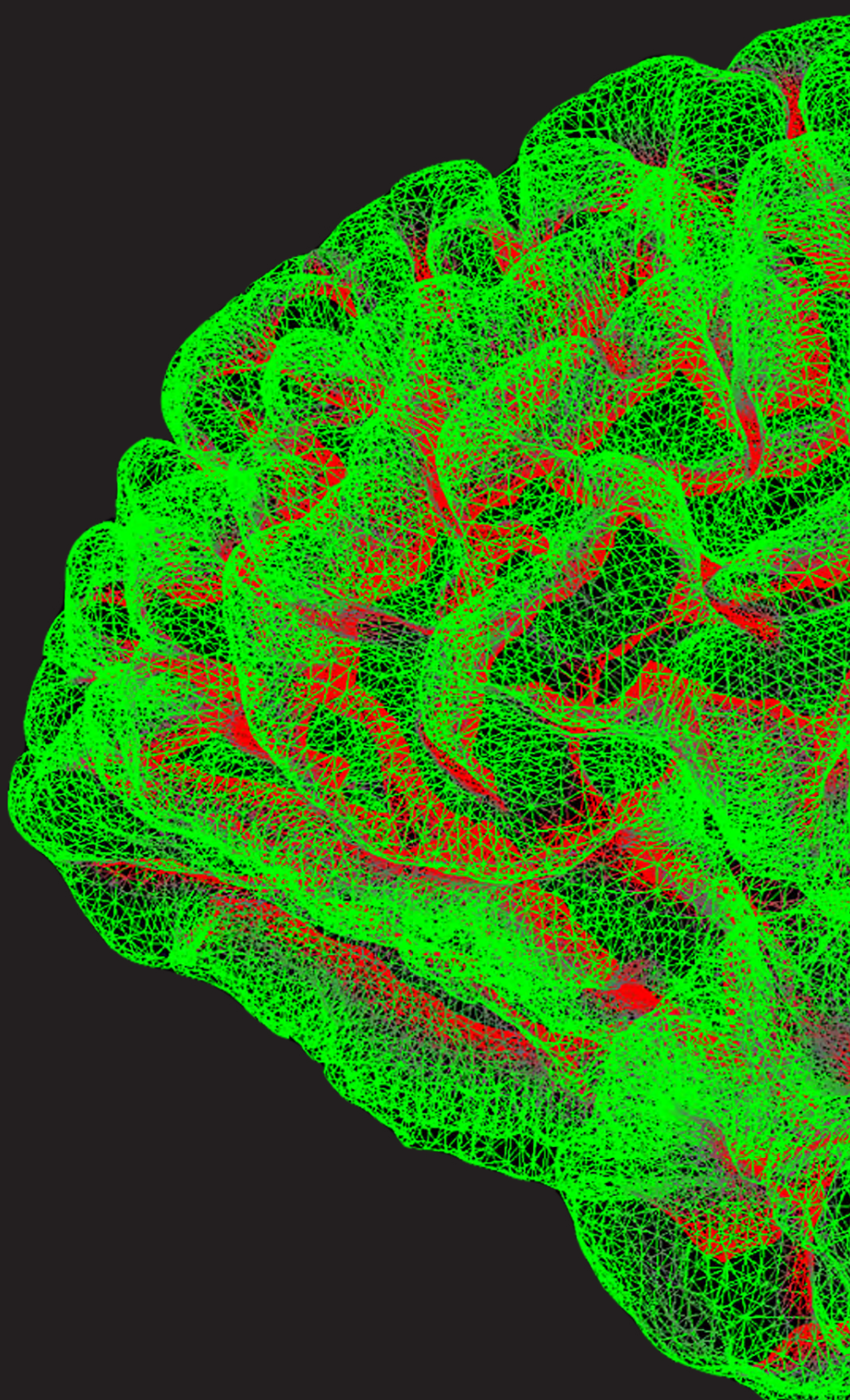
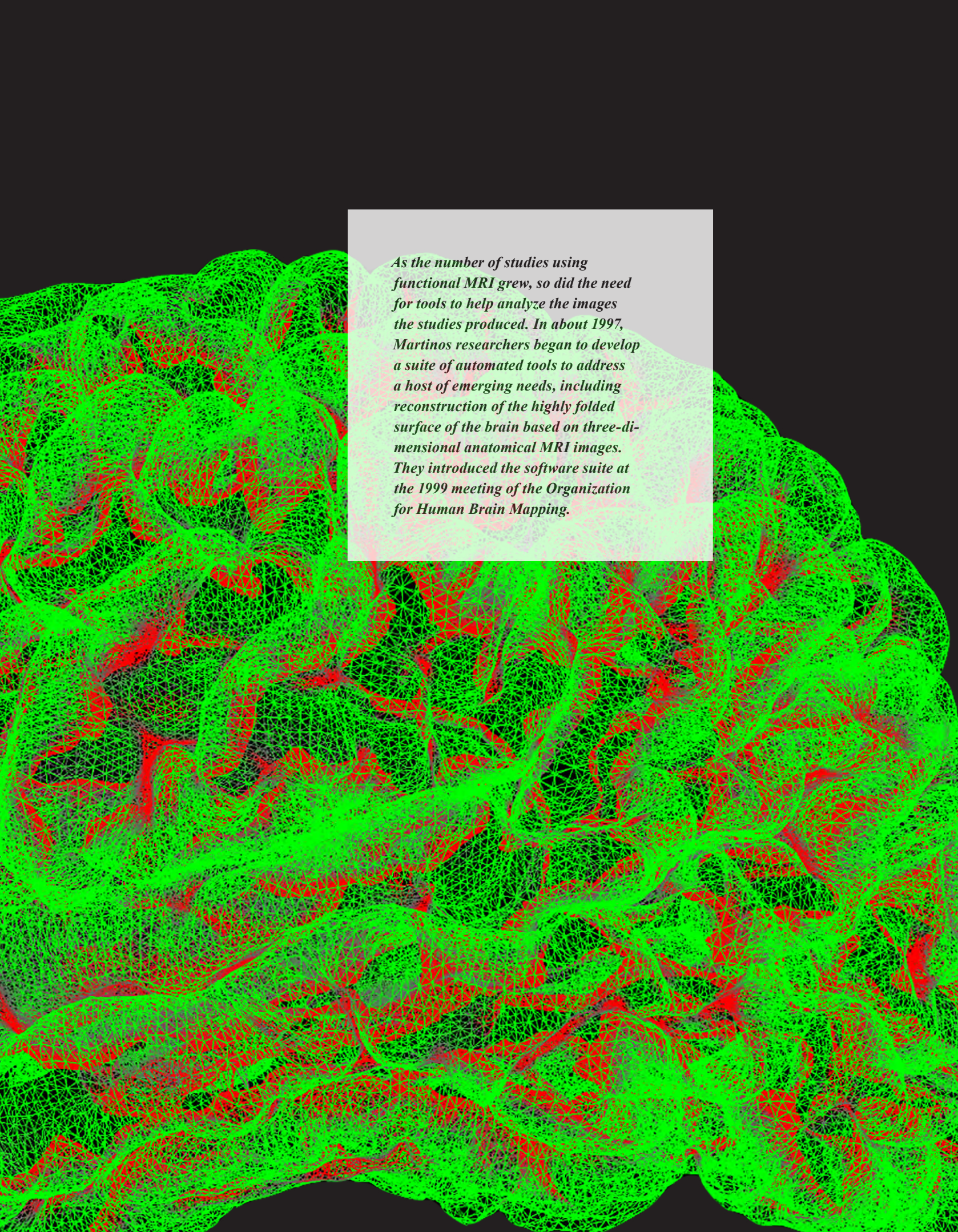


FreeSurfer





As the number of studies using functional MRI grew, so did the need for tools to help analyze the images the studies produced. In about 1997, Martinos researchers began to develop a suite of automated tools to address a host of emerging needs, including reconstruction of the highly folded surface of the brain based on three-dimensional anatomical MRI images. They introduced the software suite at the 1999 meeting of the Organization for Human Brain Mapping.

The First 20 (Plus) Years of FreeSurfer

It's a sunny day in Southern California and the developers of FreeSurfer—a suite of software tools used to analyze data from neuroimaging studies—are preparing for a training session to introduce scientists to the many benefits of the package. To help the scientists find the classroom, they have hung "FreeSurfer Course" signs around the outside of the building, a stone's throw from the beach and the restless waves of the Pacific. They switch on the computers as they await the attendees' arrival.

The door opens and a gentleman drifts in. He's young and tanned and dressed—if dressed is the right word—in flip flops and a tank top. It's not your typical look for a neuroscientist but no matter. All are welcome here. He looks around the room in a quizzical sort of way and, after a moment, asks a single question.

"Is this the free surfer course?"

FreeSurfer—the software package—may not be a household name in the beach bum community but it has become an essential tool for researchers working in the field of neuroimaging. Introduced and continuously developed and refined by Martinos Center investigators, the suite has helped provide ever-deeper insights into the structures of the brain, and thus has played an integral role in advancing our understandings of the brain in both health and disease.

But what does it do exactly? Stated simply, FreeSurfer provides automated analysis of the anatomy of the brain. What does this mean for the typical neuroscientist? Longtime Martinos researcher Doug Greve offers a simple analogy by way of explanation.

"The cortex is a highly folded two-dimensional structure, like a paper bag that has been wadded up into a ball to fit inside a skull," he says. With MRI, data is collected as a series of single images, in effect cutting the wadded-up bag into slices. If something were written on the bag—a topographic map, for example; that is, an image of the world as we perceive it projected onto the cortex—it would be nearly impossible to read from looking at the slices.

This is where the software package comes in. "FreeSurfer essentially stitches these sections together to reconstruct the folded bag, then unfolds it," Greve adds. "The natural language of the cortex is written on the bag, so unfolding it makes it much easier to interpret."

All of this may sound a bit esoteric, really only applying in a rarefied realm of lab coats and science fiction-like technologies. But FreeSurfer also delivers in myriad, real-world ways. Even beyond its many benefits for research applications, where it helps make sense of neuroimaging studies by literally unfolding the mysteries of the brain's anatomy, the software can bolster a wide range of healthcare applications. For example, researchers have used it

to track changes in disease following pharmaceutical interventions, thus facilitating larger, more reliable studies of how to improve those interventions.

A Brief History of Surfing the Brain

The origins of FreeSurfer can be traced to PhD dissertation work by Anders Dale, done in the early 1990s under the supervision of Marty Sereno at the University of California, San Diego. Dale wrote the initial software code while trying to tackle the EEG/MEG inverse problem—essentially the problem of trying to glean information about the brain from electromagnetic signals recorded outside the skull—and in doing so enable reconstruction of the brain's surface with EEG/MEG.

Others had sought ways to model the surface of the brain, to essentially flatten the organ for visualization and analysis purposes; Sereno himself had literally flattened a brain some years before, in the mid-1980s, seeking insight into how to achieve this. The breakthrough in Dale's work came when he and Sereno realized they could infer the outlines of the

Above: Speakers at the 2017 FreeSurfer Symposium react to a one-liner. From left to right: Marty Sereno, David Salat, Arthur Liu (with his head in his hand), Bruce Fischl, Anastasia Yendiki, and Doug Greve. Photo by Caroline Magnain.

Previous: A rendering of the surface of the brain using FreeSurfer

pial surface—that is, the "top" of the gray matter, where adjacent banks of a sulcus are too close to one another to be resolved by MRI—by modeling its "bottom," the boundary between the gray and white matter.

The next stage in the software's history kicked off in 1996. After completing a fellowship at UCSD, Dale joined the Martinos Center for Biomedical Imaging. Here, he continued a collaboration with Roger Tootell's group, applying the code he had written in looking at the visual cortex with the nascent imaging technique functional MRI.

Not long after, Bruce Fischl, a one-time software developer working in industry and a recent PhD graduate in Cognitive and Neural Systems, joined the group as a postdoctoral fellow. Dale and graduate student Arthur Liu were already successfully applying tools they had developed to generate surface models of the brain, but the manual approach they had devised was in some ways limited. "They were the only ones who knew how to use it," Fischl says. "And it took maybe a week per brain."

Fischl set to work and, before long, had replaced all of the manual steps of the process with sophisticated algorithms, leading to significant improvements in how quickly the process could be completed. This was especially important for work in the Center, where there was already a considerable "backlog of brains."

Indeed, the surface reconstruction tool benefited a number of Martinos researchers. Fischl recalls early work by Roger Tootell and Nouchine Hadjikhani mapping the visual processing architecture in the brain, research by Diana Rosas exploring the morphometry of the brain in Huntington's disease, and studies of schizophrenia by Gina Kuperberg.

Dale and Fischl also wanted to be able to share the tool with the wider neuroscience community. Initially, it was labor-intensive enough that it still would have been difficult for others to use. But as the software became more and more automated, it became more and more easy for others to apply it. Finally, Fischl says, "it worked well enough out of the box that we decided to just start giving it away."

The big reveal came in 1999, with a pair of papers in the journal *NeuroImage* and an official launch at that year's Human Brain Mapping meeting in Germany—the latter made possible by the indomitable efforts of the Center's Doug Greve and Thomas Witzel.

The road to this point wasn't always a smooth one, of course. Along the way the investigators encountered the occasional obstacle, the intermittent snag, that would put at risk the continued vitality of the project.

Fischl points to one of these, in particular. In what may have been the greatest existential threat to the software, he says, the researchers couldn't agree on a name for it. Dale suggested "B-Vis," short for "Brain Visualization" but also a nod

Scenes from the 2017 FreeSurfer Symposium. Photos by Caroline Magnain


Surf's Up
SURFER
FREESURFER

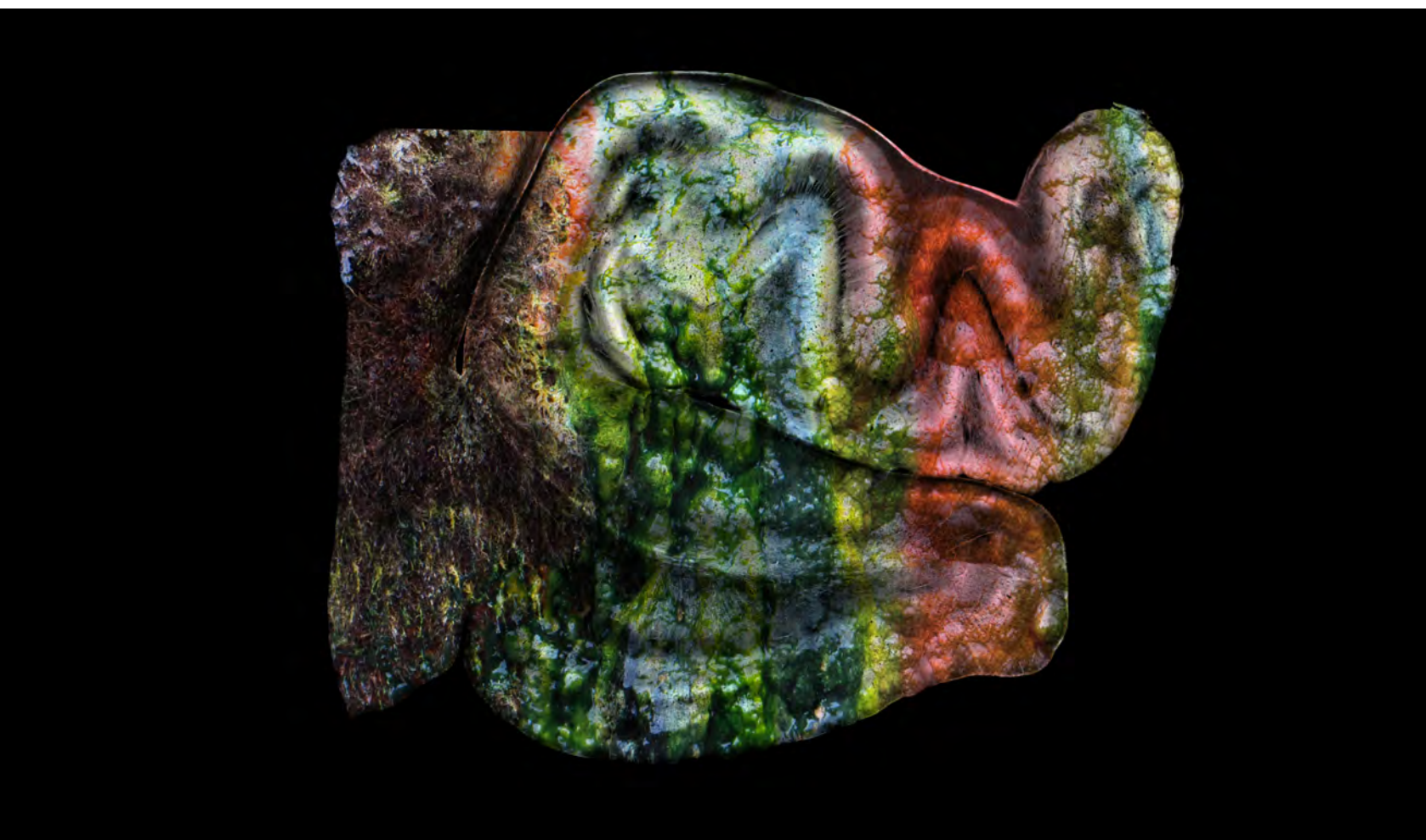
Below: Caroline Magnain, a researcher in the FreeSurfer group, combines her love of photography with her work performing microscopy of the brain, often superimposing one onto the other. This piece, "The Layers of the Hippocampus," was a finalist in the 2019 Mass General Research Institute Image Contest.

to the crude yet often hilarious MTV cartoon *Beavis and Butthead*. This idea was "universally panned," as was collaborator Marty Sereno's characteristically esoteric contribution: "D," a roundabout reference to the little-known "B," a 1980s programming language developed by Bell Labs. Fischl himself, presumably joking, suggested they charge a premium for the software and call it ExorbitantSurfer.

Finally, after considerable debate, they settled on the more pithy—and indeed more accurate—FreeSurfer.

FreeSurfer was an immediate hit with the neuroscience community, and its popularity has exceeded all expectations in the years since. Today, it boasts 48,000 registered licenses, with users around the world applying it to a host of basic science and clinical problems, including investigations of the brain during the aging process, studies of stroke patients and other clinical populations, and development of artificial intelligence and deep learning for biomedical imaging.

At the same time, the FreeSurfer group at the Martinos Center—officially known as the Laboratory for Computational Neuroimaging and led by Fischl—has continued to make its mark. For the past two decades and counting, the group has extended and improved upon the software package in myriad ways and worked tirelessly to serve the ever-expanding FreeSurfer community.



What Tomorrow May Bring

On a brisk day in Boston in November 2017, the Martinos Center hosted a daylong symposium honoring two decades of FreeSurfer. The speakers in the morning looked back on the early days of the technique—a time, said researcher David Salat, maybe slightly wistfully, when Tiger Woods was a fresh young face on the professional golf circuit and Hanson and The Spice Girls ruled the pop music landscape—and on the many successes it has seen in the years since. Fischl, Sereno and Greve stepped up to the podium, as did several other developers and prominent users of the software: Nancy Kanwisher and Arthur Liu as well as Salat, who emphasized the importance of FreeSurfer in his work with structural imaging of the brain during the aging process.

In the afternoon, the speakers turned their gaze to the horizon, to what might be achieved with FreeSurfer in the coming years. Here, they focused on existing applications of the software as well as ones just now emerging. Jon Polimeni spoke about its use for anatomically informed analysis of high-resolution fMRI data while Anastasia Yendiki reviewed the many ways it could improve diffusion imaging and Polina Golland looked toward its ongoing use with data from stroke patients and other clinical populations. Discussing a bold new application, Jayashree Kalpathy-Cramer and Mark Michalski outlined the ways in which the software could bolster artificial intelligence and deep learning in medical imaging.

Full Steam Ahead at 20-Plus Years

Given all of the successes with the software, the FreeSurfer group might feel free to rest on its laurels, to revel in all the ways it has already helped advance healthcare. But of course it never does. In the spring of 2020, the group released the latest version of the suite: FreeSurfer v7.1.0. The software in this version is 20 to 25 percent faster than in previous versions and offers a host of new features. The most prominent of the new features is a tool called Adaptive Multimodal Segmentation (SAMSEG), which can segment whole-head MRI scans into distinct brain regions and perform analyses on each of those regions.

Also, Fischl points to the many ways the software package might benefit from the explosion of artificial intelligence and deep learning in recent years. “Lots of people are showing improvements in the state of the art on small, well-constrained datasets,” he says. “The problem is, how do you translate that into advances in a package like FreeSurfer, which gets applied to tens of thousands of datasets every year, with many different kinds of MRI contrast, resolution, etc.

“Deep learning hasn’t solved this problem yet, but it is something we have made a lot of progress with. And by ‘we’ I mostly mean Eugenio Iglesias, Adrian Dalca, Benjamin Billot and Malte Hoffmann. I’m hoping we can get to the point where we have enough confidence in the algorithms to integrate and distribute them sometime soon.”

Predicting Cognitive Decline in Alzheimer's Disease

The FreeSurfer suite of software tools has helped advance countless studies over the years. Not least: a 2018 paper published in the journal *Neurology* in which a team of investigators led by the Center's David Salat explored the contributions of white matter damage in Alzheimer's disease. Such damage could serve as a biomarker to aid in clinical diagnoses of the disease as well as in predicting changes in cognition over time.

"There is a good deal of evidence linking white matter damage to Alzheimer's," says Emily Lindemer, lead author of the *Neurology* study. Lindemer was a graduate student working in the Martinos Center's Brain Aging and Dementia (BAnD) Lab with senior author Salat when the study was conducted. "White matter signal abnormalities seen on MRI, which reflect white matter damage, have been tied to cognitive decline and dementia. Until this study, though, we still didn't know how prominent a role they played. Nor did we fully understand the relationship between white matter signal abnormalities and the biomarkers amyloid and tau—two proteins in the brain. We set out to study this relationship and the combined impact of the three on cognitive decline."

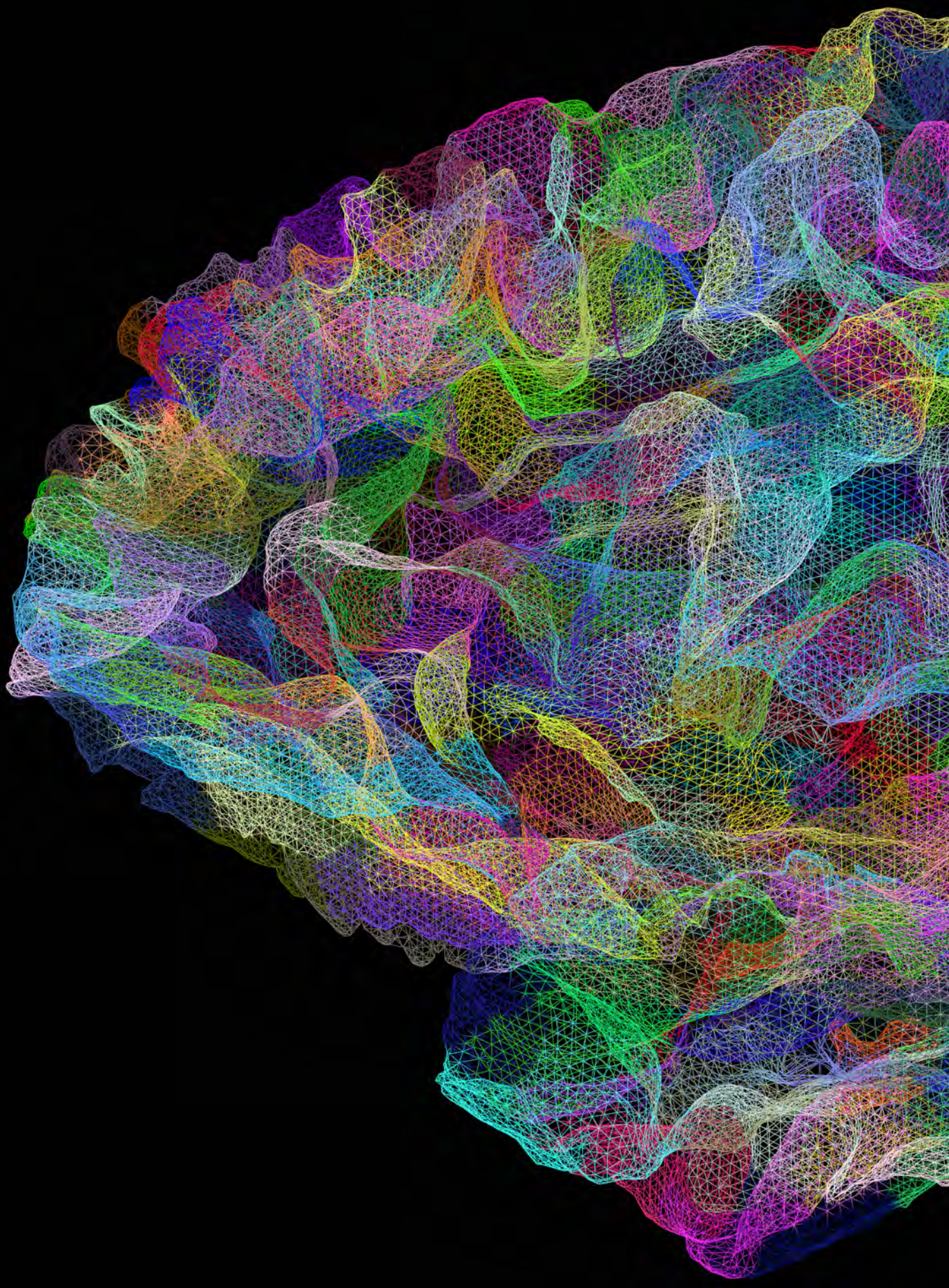
To this end, the researchers examined data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, a University of Southern California-based initiative established to provide researchers with access to imaging findings from the ongoing, large-scale ADNI study. They included data from 236 individuals from the database: 61 with an Alzheimer's diagnosis, 56 cognitively healthy age-matched controls, and 119 with a diagnosis of mild cognitive impairment.

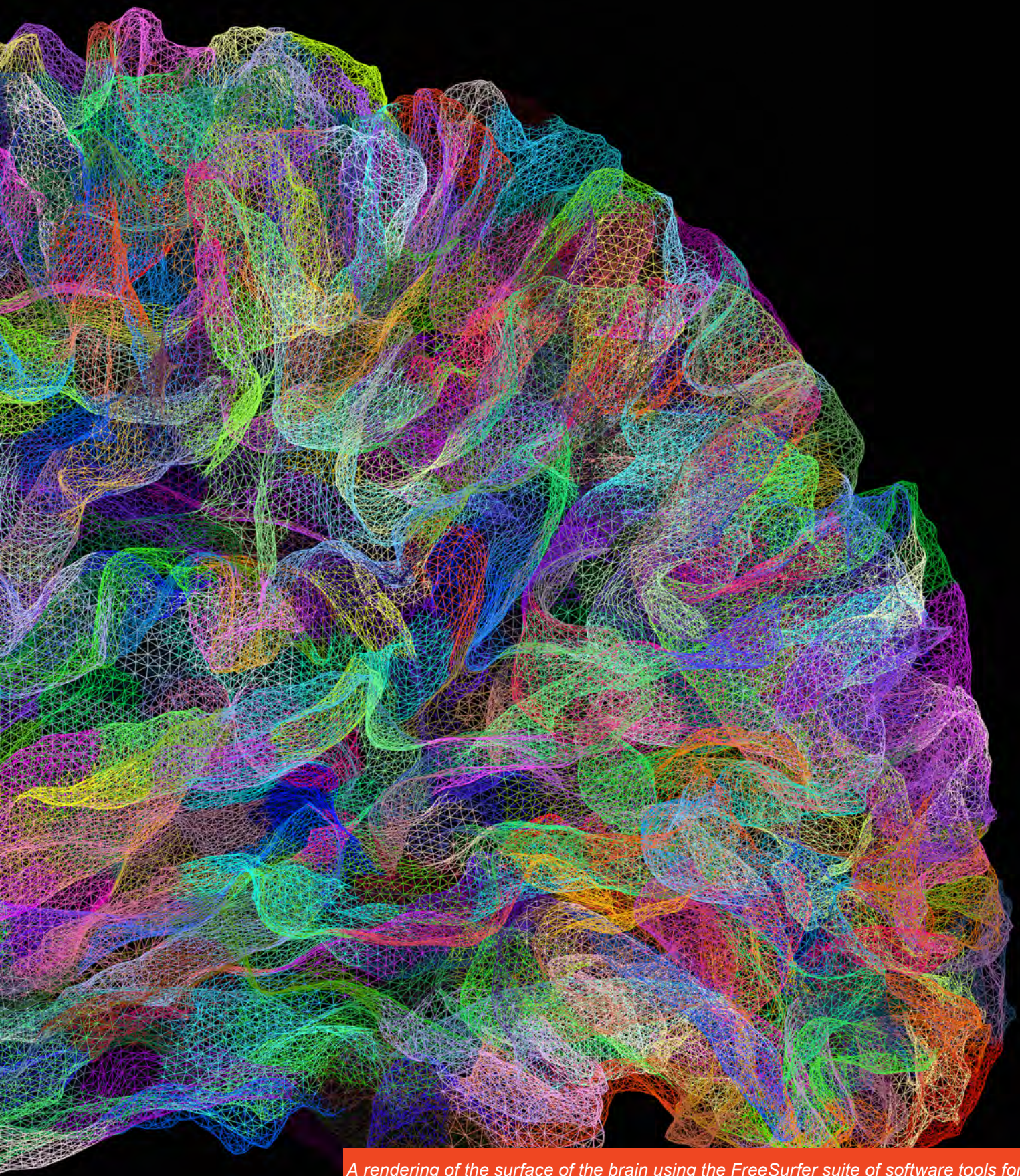
With help from FreeSurfer, the study compared brain imaging measures from two groups of patients with clinical diagnoses of Alzheimer's. The groups differed in the extent to which the biomarkers amyloid and tau were present: one had levels of the biomarkers typical for Alzheimer's disease and the other had lower-than-usual levels. The researchers observed a greater amount of white matter damage in the patients with lower-than-usual biomarker levels and found that the damage was a stronger predictor of a patient's future clinical status. The damage itself was presumed to be the result of deterioration of blood flow to the brain, likely due to vascular disease.

The white matter findings have important implications for clinical care. For example, because they point toward a possible vascular origin in at least some individuals with a clinical diagnosis of Alzheimer's disease, researchers may want to explore the white matter damage presumed to be caused by vascular disease as a potential target for future therapies.

The researchers hope to follow up the findings in future work. "The white matter damage examined here has been described in several prior studies of Alzheimer's disease, yet is not considered a primary feature of the disease," Lindemer says. "It is most often considered a simple independent comorbidity. We are interested in better understanding the etiology of this tissue damage in Alzheimer's disease and specifically how this damage fits in with the classical understanding of the disease."

Above: The Brain Aging and Dementia (BAnD) Lab with principal investigator David Salat, right.





A rendering of the surface of the brain using the FreeSurfer suite of software tools for analysis of data from neuroimaging studies

‘Women in Science’ Group Tackles Sexism, Other Issues

The Martinos Center’s “Women in Science” seminar series brings together investigators, staff and others from throughout the community for a host of important and thought-provoking discussions. The organizers have held several iterations of the series since launching in 2018, while also expanding the resources available to women in the Center and elsewhere.

The roots of these efforts can be traced to early 2017. On the heels of that year’s “Women’s March” in Boston (as well as in Washington, DC, and in many other cities around the world) Allison Stevens, senior lab manager with the Center’s Laboratory for Computational Neuroimaging (LCN), also known as the FreeSurfer group, organized a meeting with several female colleagues to talk about their experiences with sexism in their careers. She did so, she says, as a response to stories she was hearing from women in the Center about the issues they encountered. “I thought if everyone shared those stories with each other, they would see they were not alone. I also hoped speaking with each other could help us come up with solutions for when we would inevitably face the same issues again.”

In hearing about one another’s experiences Stevens and her colleagues in the meeting began to realize just how widespread the problem is in the science community. They decided to do something about it.

“It is important to shine a light on the issues women in science face, for a few reasons,” says Emma Boyd, a research technician in the LCN group who was part of those early discussions and an organizer of the first couple of “Women in Science” series. “First, because awareness of what sexism looks like is lacking. As a consequence, not everyone is aware of their own biases and the harmful behaviors they may be unintentionally supporting. Catching these behaviors may immediately help create a more inclusive work environment. Second, because awareness of how and why science can (and does) exclude women and other minority groups is also lacking.

Allison Stevens (left) and Emma Boyd

“And third, while it is very easy to turn a blind eye to inequalities, we should make every effort to address them. The science community has been having a bit of its own ‘MeToo’ movement and the timing has never been better to have these discussions.”

Coordinated by Boyd—with support from Stevens and others—the initial series took place over nine sessions in April and May 2018. It included lectures, a panel and discussion groups covering a wide variety of topics, as well as a pair of mentor lunches. Among the many topics addressed was the pervasiveness of gender and racial bias in the scientific community. In three sessions (“Implicit and Explicit Race and Gender Bias in STEM,” a follow-up discussion group, and “How to Respond to Sexism in the Moment”), speakers and attendees addressed questions such as ‘Why do we have biases?,’ ‘What does bias look like?’ and ‘How can we be more aware of the implicit biases we hold?’ Exploring these questions—even just defining the underlying terms and concepts (*sexism*, *racism*, *bias*)—can help in identifying sexism in the workplace and determining the most appropriate ways to address it.

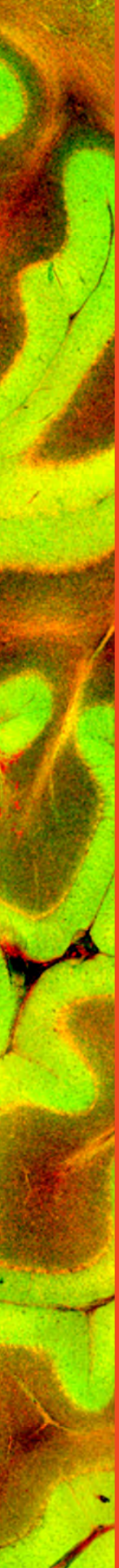
Boyd believed the Martinos Center was well positioned to take on the challenge of addressing sexism in the research arena. “Approximately 40% of the faculty and research fellows in the Center are female, according to the most recent estimate,” she says. “This percentage is significantly higher than the current estimate of the total share of women in the US STEM workforce (approximately 24%). Our community is unique in that we are more gender balanced than average. And on top of that, we have a fantastic community of passionate, bright individuals who have the potential to create social change in the science community.”

Viviana Siless and Emma Boyd

Indeed, they have already begun to do so. Boyd notes that several lab directors in the Center started incorporating discussions of sexism into their lab meetings after the “Women in Science” events helped to frame the issues and how best to address them.

With the inaugural seminar series under their belt, the organizers planned another, eight-week program of events in the fall of 2018. As part of this series, they worked to expand the mentoring workshops, provide more resources on how to respond to sexism, hold negotiation workshops, and bring in new speakers to continue to address the challenges women in science face and the many ways they can take action.

In addition to these efforts, the Women in Science group, led by Viviana Siless, a research fellow in the LCN, from 2019 until the end of 2020, is seeking to make the series more intersectional and accessible for other communities, including LGBTQ communities and communities of color.



The Secret Lives of Martinos Folk

Anastasia Yendiki *on image analysis algorithms and dancing flamenco*

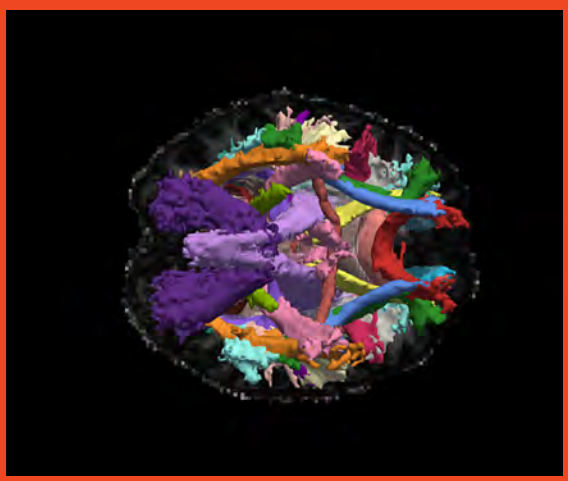
The Martinos Center is spilling over with talent, attracting many of the brightest minds from around the world. But the talent isn't limited to building radiofrequency coils and developing novel pulse sequences for acquisition of MR data.

Anastasia Yendiki is a researcher who focuses on methods for mapping the circuitry of the human brain. At the Martinos Center, she develops robust data analysis methods for diffusion MRI. Her tractography toolbox, TRACULA, is distributed publicly as part of the FreeSurfer software package and used by dozens of labs worldwide to study how brain pathways are affected by disease.

Yendiki is also a flamenco dancer.

She started learning the form in the late 2000s. While attending an MIT journal club one day, she met Lauren O'Donnell, a diffusion MRI researcher at Brigham and Women's Hospital. O'Donnell had recently spent a year in Spain doing advanced study of flamenco and was now teaching a class of her own. Yendiki signed up for the class, absorbing all she could about the dance and putting it into practice. Two years after she started attending, she was asked to join the "Flamenco Boston" performing group.

While there is much to enjoy about Flamenco, she says, she was especially drawn to the synergistic aspect of the form. There is no designated leader or follower but rather a guitarist, singer and dancer exchanging cues and taking turns leading and following. Flamenco uses a set of musical modes, each with its own structure and mood. The performers generally improvise, but always within the constraints defined by these modes. This enables the music and the dance to flow as if one.



She was also won over by the full range of emotions expressed in—and accepted by—flamenco.

"There is a dance for everything, from exuberance to devastation," she says. "It is a space where you can express any of these emotions—in public, no less—and still be strong. You are being strong not by suppressing the emotion, but by experiencing it fully. You are being strong by baring your soul, not by concealing it. There is no deception in flamenco."

Dance and science may seem like unrelated pursuits, appealing to contrasting sides of a performer's personality. Not so, says Yendiki.

"There is an analytical aspect to flamenco that would appeal to an engineer like myself. You have a set of constraints and within those you are trying to come up with something that is creative, elegant and effective."

"In that sense," she says, "it has much in common with designing image analysis algorithms, doesn't it?"

This page: Anastasia Yendiki, neuroscientist and flamenco dancer. Photo by Feda Eid.

Opposite: brain pathways reconstructed automatically with the TRACULA toolbox from an in vivo *diffusion MRI scan*


Optics

Functional MRI was still a young technology in the mid- to late 1990s and had not yet been fully validated, in particular through comparisons with other, related technologies. To this end, the Martinos Center launched an optical imaging program in 1998. Initially, the program focused on the development of functional near-infrared spectroscopy (fNIRS), another young technology capable of imaging blood oxygenation in the brain noninvasively and without use of ionizing radiation. In time, though, it grew beyond its original brief to encompass development of a host of related technologies and application of those technologies to a broad swath of questions in biomedical imaging. Ultimately, this work could contribute to better understandings of how the brain works as well as to improved screening and detection of a variety of pathologies.

Seeing the Light with Optical Imaging Technologies

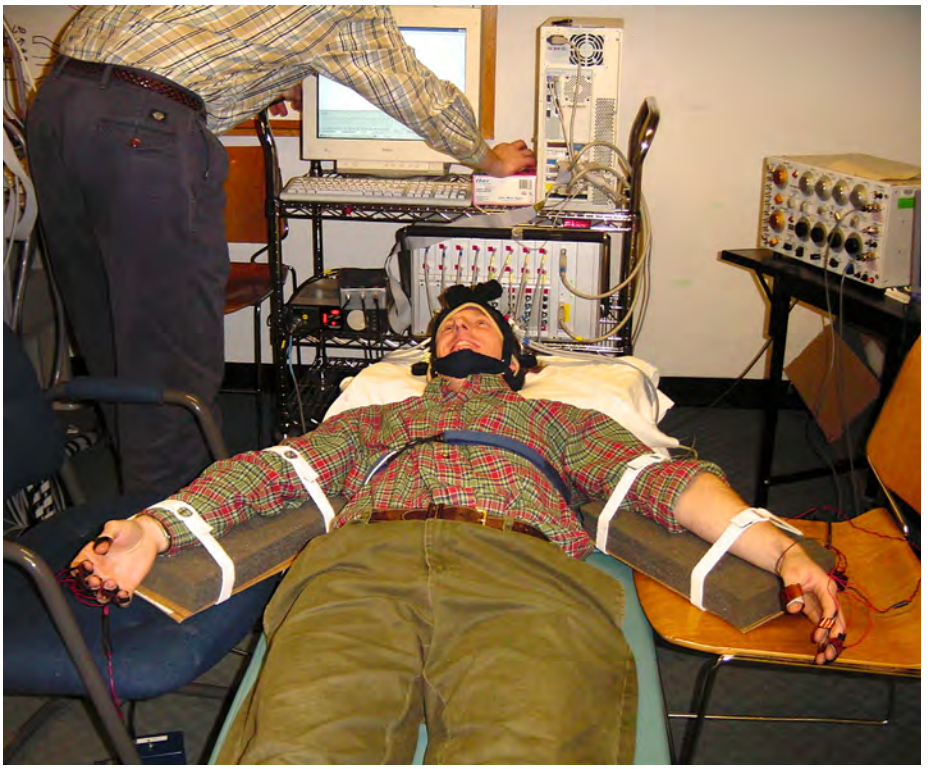
It's late August 2020, the tail end of a long, fraught summer, and David Boas is watching flames dance around the edges of the logs stacked in a fire pit on his patio. Boas, a pioneer in the field of near-infrared spectroscopy and other optical imaging techniques, is musing over a question about what originally brought him to the Martinos Center in the late 1990s. Finally, he looks up from the flames and, in his quiet, deliberate way, starts to tell the story.

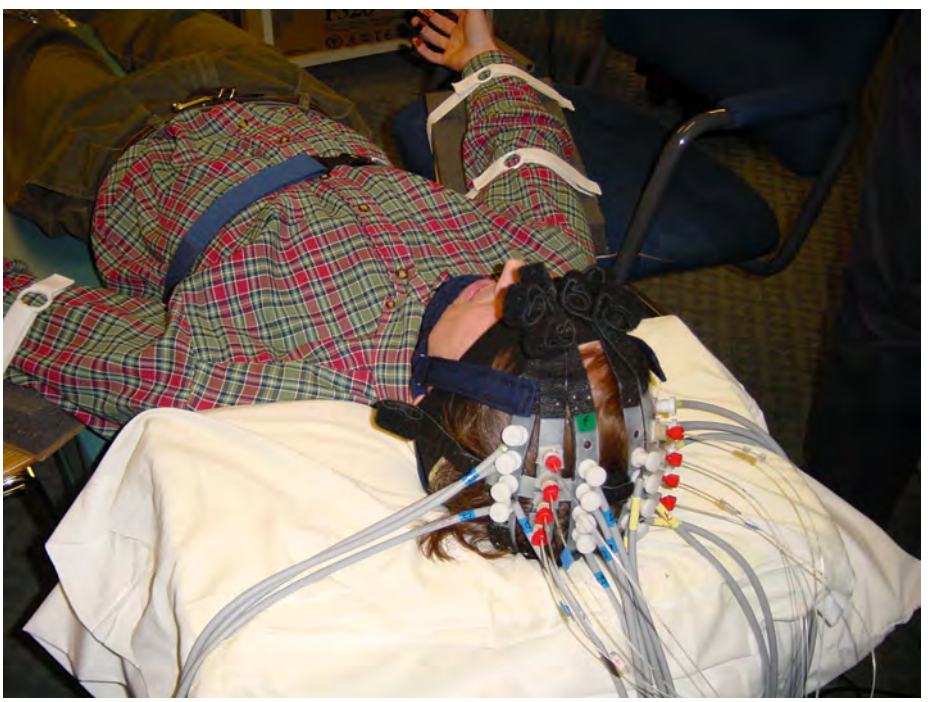
This history of the Optics group at the Martinos Center dates back to 1998, when Boas was a young researcher and faculty member in the Tufts University Department of Biomedical Engineering. During his graduate work in the early 1990s, he had pioneered the technology near-infrared spectroscopy (NIRS), which can noninvasively measure oxygen levels in tissue, and he was now developing the technology further for biomedical applications—including building one of the first-ever functional NIRS devices for monitoring brain activity.

At the same time, some five miles down the road in Charlestown, Martinos Center director Bruce Rosen was looking to validate the still-emerging functional MRI by comparing its results with those from other, related technologies. He learned of Boas' work and, after meeting with him and discussing the possibilities in working with near-infrared spectroscopy, invited him to join the Center's ranks.

Below: The Center's David Boas and Anders Dale on a ferry to the Greek island of Mykonos during a 2002 meeting in Athens.

Opposite: Measuring activity in the brain with an early near-infrared spectroscopy system, 2002





Boas accepted. In the years that followed, the Martinos Center's burgeoning Optics group made one important stride after another with near-infrared spectroscopy. First was further technology development and validation. NIRS works by sending near-infrared light into the brain—tissue is opaque to light in the near-infrared range—and detecting it as it emerges elsewhere on the head. Taking advantage of the light absorption and scattering properties of hemoglobin, the protein in the blood that transports oxygen, it can then determine oxygenation levels in particular regions of the brain.

By 2001, the Optics group had built a fourth-generation NIRS system with 18 lasers and 16 detectors providing whole-head coverage, enabling localization of the NIRS signal throughout the brain. The design worked so well that the researchers still use it today, albeit with more lasers and detectors and additional digital signal processing. "It's still basically the same fundamental design," Boas says, "just faster, with more digital stuff."

Having established the design, the group turned its attention to cross-validation of the technology with fMRI, and then to combining the two modalities to learn more the hemodynamic response to brain activity—the "neurovascular coupling" in which vascular changes reflect the underlying metabolic response to neural activity. In developing improved understandings

of this relationship, the researchers were better able to extract information about brain activity using the portable, noninvasive technology.

The fire continues to crackle. Maria Angela Franceschini, now one of the co-directors of the Optics group, returns to the patio after looking for one of her cats, who has wandered off seeking whatever sorts of adventure cats like to seek. She sits down and picks up the story about the group's early progress with near-infrared spectroscopy.

In 2003, she says, she was applying the technology to a set of functional studies. But analysis of functional NIRS data was still a tedious if not arduous task, involving writing and implementing strings of computer code for every operation. "David and [then-Optics faculty] Joe Culver and Andy Dunn were giving me all of these MATLAB scripts that I had to modify in a million places to analyze my data," she continues. "I said, 'No, I want something I can click on and it works. So for my birthday that year, David developed and gave me HOMER." HOMER, a Simpsons homage and a loosely defined acronym for "Hemodynamic Evoked Response," was a data analysis package with a straightforward graphical user interface (GUI) in place of often-unwieldy scripts. It is, today, the most widely used NIRS package in the world.

New Directions

Over the next several years, Franceschini, also studying brain development in infants, reported a number of studies looking at changes in cerebral blood volume and oxygenation in healthy and diseased infants. In about 2005, she started thinking about incorporating into her work a technique known as diffuse correlation spectroscopy (DCS), which, by adding measures of blood flow, could provide deeper insights into the developing brain. There was a hitch, though: while Boas had already purchased the parts for a DCS system, there was nobody in the lab who could build it.

This is when Stefan Carp joined the Optics group.

Carp, now also a co-director of the group, alongside Franceschini and Sava Sakadžić,

Left: Maria Angela Franceschini

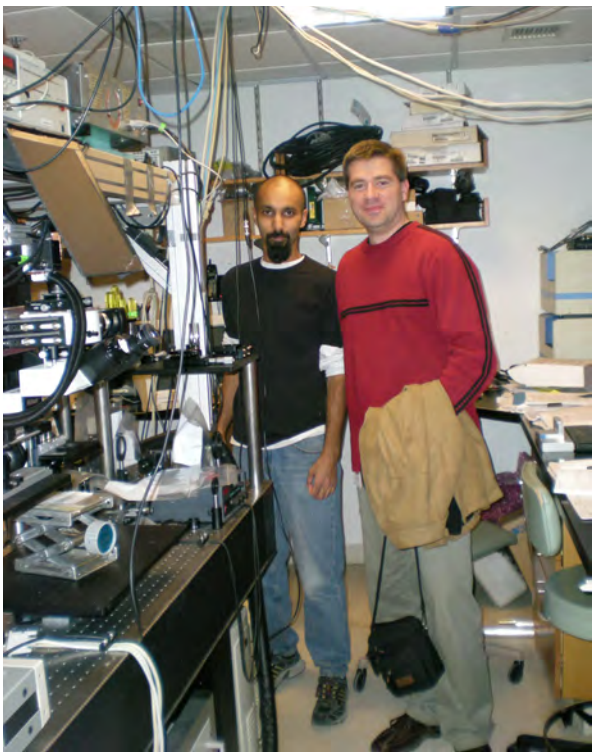
Opposite: Stefan Carp

first came to the Center to work on an optical breast imaging project then underway. The project was briefly held up when he arrived so he asked Boas if there were any other projects he could tackle. "He wanted to do something," Boas recalls, "so I said, 'Here are the parts to build a DCS system, build it.' I thought I would hear from him a few weeks later. He came back the next day and said, 'Now what?' "

In the years since, Carp has also built a research program focused on the development and clinical translation of near-infrared spectroscopy and diffuse correlation spectroscopy to advance both brain health monitoring and breast cancer management. For example, in a 2013 paper, he and colleagues reported a new biomarker—that is, an indicator of disease or the effects of its progression—for breast cancer diagnosis and therapy monitoring based on the breast tissue's response as measured by a novel optical imaging instrument. Following this work, in a 2017 study, they showed they could use the biomarker to characterize the early response of breast tumors to neoadjuvant chemotherapy and predict the eventual treatment outcome. Thus, the optical imaging technology could prove useful in guiding neoadjuvant chemotherapy.

Other major research streams have emerged as well. The early foray into optical breast imaging also spawned an optical molecular imaging effort, now led by Anand Kumar, director of the Optical Molecular Imaging Laboratory at the Martinos Center. In the years since the launch of this effort, Kumar's lab has made significant strides with optical molecular imaging using time-domain fluorescence tomography, specifically by exploiting fluorescence lifetime as a contrast mechanism. The group is currently applying the technology to address challenging questions related to cancer, cardiac disease and neuropathology.

Parallel to all of the above, researchers in the Optics group have used microscopy techniques to uncover aspects of neurovascular coupling that aren't accessible in human studies using NIRS. For example, in 2010, Sava Sakadžić, who is today another co-director of the Optics group, completed an advanced multi-photon microscope that could provide, for the first time, high-resolution maps of both microvascular and tissue oxygenation in animal models. This was possible by pairing the microscope with a special phosphorescent probe that glows briefly when excited with light. The more oxygen surrounding the probe, the briefer the phosphorescence, so the



lifetime of the glow becomes a measure of oxygenation in particular regions of the brain.

In the decade since, the tool has enabled numerous discoveries about the ways in which oxygen is transported to the tissue and diffuses through the tissue. Recently, in a 2020 study reported in *Journal of Cerebral Blood Flow and Metabolism*, Sakadžić and colleagues applied the two-photon microscopy technique to measure microcirculation in the white matter of the brain, an area that is currently poorly understood, largely due to a lack of appropriate imaging methods. The findings of the study provided new insights into the regulation of blood flow in white matter, which could shed light on the mechanisms of white matter deterioration in certain brain conditions.

Opposite, top: Sava Sakadžić and Optics faculty alum Abbas Yaseen in 2008

Opposite, bottom: The Optics @ Martinos group in December 2019

Below: The group's Adriano Peruch ponders an electronics problem. Photo by Shurik Zavriyev.

Maintaining Cerebral Blood Flow During Cardiac Surgery

In April 2020, a team of researchers at the MGH Martinos Center for Biomedical Imaging reported an innovative light-based technique that could help reduce the incidence of neurological injury during aortic arch replacement and other cardiac surgeries.

Hypothermic circulatory arrest (HCA) is widely used to provide a bloodless field of view for aortic arch surgeries by cooling the patient's body to temperatures as low as 68 degrees Fahrenheit and stopping blood circulation. However, because the brain needs oxygen for the lengths of time associated with the procedure—Deep HCA can be maintained for up to 20-30 minutes without the lack of oxygen causing brain injury, but most aortic arch surgeries take longer than this—surgeons use selective cerebral perfusion methods to continue oxygen delivery to the brain while the rest of the body is in HCA.

In current practice, surgeons often use oximetry to monitor and help guide cerebral blood perfusion during surgery. But cerebral oximetry only provides measures of oxygen content in the microvasculature; it cannot tell surgeons how much blood the brain is really getting from the selective cerebral perfusion methods. As a result, by the time the method detects a significant change in oxygenation, injury to the brain may already have occurred. Thus there is need for a device that can measure the brain's blood flow.

To help improve the monitoring of oxygen delivery and consumption during HCA, members of the Optics group at the Martinos Center devised an approach in which they employed a hybrid device including frequency-domain near-infrared spectroscopy (FDNIRS) and diffuse correlation spectroscopy (DCS) to characterize both oxygen consumption rates and blood flow in the brain during the procedure. FDNIRS measures modulated light intensity attenuation and phase shift for more quantitative assessment of blood oxygenation with respect to conventional, "continuous wave" NIRS techniques. DCS takes advantage of intensity fluctuations of laser light (speckles) to quantify cerebral blood flow, noninvasively, at the bedside.

In a presentation at the Optical Society of America's 2020 Biomedical Congress (and in a paper later published in *Journal of Thoracic and Cardiovascular Surgery Techniques*, "The role of diffuse correlation spectroscopy and frequency-domain near infrared spectroscopy in monitoring cerebral hemodynamics during hypothermic circulatory arrests"), the researchers described a study seeking to validate this new approach for monitoring brain blood flow during HCA. The work was performed in collaboration with Dr. Jason Qu, a cardiac anesthesiologist at Massachusetts General Hospital. The results of the study suggest that, because the hybrid device directly measures blood flow—which changes much more quickly than oxygenation—the technology can provide "timely and

accurate" insight into the efficacy of brain protection during the procedure, especially compared to the currently used methods.

Ultimately, says Alexander (Shurik) Zavriyev, a research assistant in the Optics group and first author of the study, the hybrid technology could provide an important new tool for early detection of shortage of oxygen delivery to the brain and potentially provide guidance for selective cerebral blood perfusion during HCA for aortic arch surgeries. "Demonstrating the ability to accurately and simultaneously measure oxygenation and cerebral blood flow during surgery will lead to new approaches to reduce neurological injury and the overall morbidity and mortality associated with anesthesia in general and aortic arch replacement surgeries in particular," he says.

In the short-term, the researchers are seeking to validate the approach further by testing it on a larger group of patients, as well as to fine-tune the hybrid technology—for example, by focusing on the wavelengths of light most advantageous for this application.

Below: The Center's Alexander (Shurik) Zavriyev (right) and Kutlu Kaya, both research assistants in the Optics @ Martinos group, are working with surgeons and anesthesiologists at Massachusetts General Hospital to validate the hybrid optical imaging device. Photo by Allen Alfadhel.

Estimating Tumor Boundaries with Fluorescence Lifetime Imaging

Cancer is the second leading cause of death in the United States, with an estimated 1,762,450 new cases diagnosed and 606,880 deaths in 2019 alone. While important advances have been made in the development of treatments for cancer, including surgery, a number of challenges remain. Not least: surgeons still lack tools that can clearly delineate tumors from normal tissue during tumor resection. In current practice, surgeons estimate tumor boundaries using palpation and visual inspection, but this approach often results in incomplete removal, leading to disease recurrence and repeat surgeries.

Now, the Martinos Center's Rahul Pal and Anand T.N. Kumar and colleagues have developed an optical imaging method that can address this challenge using fluorescence lifetime-based tumor contrast enhancement. They reported the method in late 2019 in *Clinical Cancer Research*.

Establishing tumor boundaries during resection is a major area of interest. In recent years, researchers have been exploring ways to label tumors with fluorescent molecules so they can better highlight the boundaries. One of the approaches they have devised capitalizes on clinically approved antibodies that target specific 'receptors'—called EGFR receptors—that are overexpressed on the cancer cells. Because they are overexpressed, the receptors offer a means to distinguish between tumors and surrounding healthy tissue using fluorescence imaging techniques. But any gains with this approach are mitigated by the fact that EGFR is also expressed in the healthy tissue, creating background fluorescence and thereby reducing the overall contrast between the two.

The Martinos-based team tackled this problem by visualizing the fluorescence lifetimes of the molecules: that is, the average time it takes for the molecules to return to a normal state (typically in the range of nanoseconds) following excitation with pulses of laser light. The conventional optical imaging methods used in previous studies rely on continuous-wave excitation—essentially a beam of light with constant amplitude and frequency—and consequently do not have access to this information.

The advantages of using fluorescence lifetimes for better delineation of tumor boundaries were made evident in the *Clinical Cancer Research* study. Not only did the researchers demonstrate, for the first time, that EGFR-overexpressing tumors exhibit a unique fluorescence lifetime, they also showed

that the fluorescence lifetimes of tumors labeled with EGFR antibodies are considerably longer than those of muscle tissue and liver with nonspecific uptake of the probe. This greater distinction between the two offers a unique opportunity for cancer surgery: namely, says Kumar, director of the Optical Imaging Laboratory at the Martinos Center and senior author of the *Clinical Cancer Research* paper, because it "provides dramatic improvement in the accuracy of tumor detection using existing cancer-targeted dyes that are in clinical trials, while also potentially offering an absolute measure of tumor vs. normal tissue that can help in standardization across multiple image-guided surgery systems."

Having demonstrated the potential of the approach, the researchers are now developing it further for clinical use. To this end, they are pursuing two clinical studies to apply the technology for cancer surgery. In the first, they are exploring its use for comprehensive margin assessment in specimens resected from patients undergoing surgery: an important unmet need, especially as pathology is slow and not always comprehensive in establishing tumor boundaries. If this study proves successful, they will build intraoperative image guidance systems capable of exploiting lifetime contrast of targeted probes in tumors. Once validated for intraoperative imaging, these systems will provide a tool for better estimating tumor boundaries and thus could help in improving outcomes in cancer surgery.

Above: Rahul Pal

Opposite: Anand Kumar

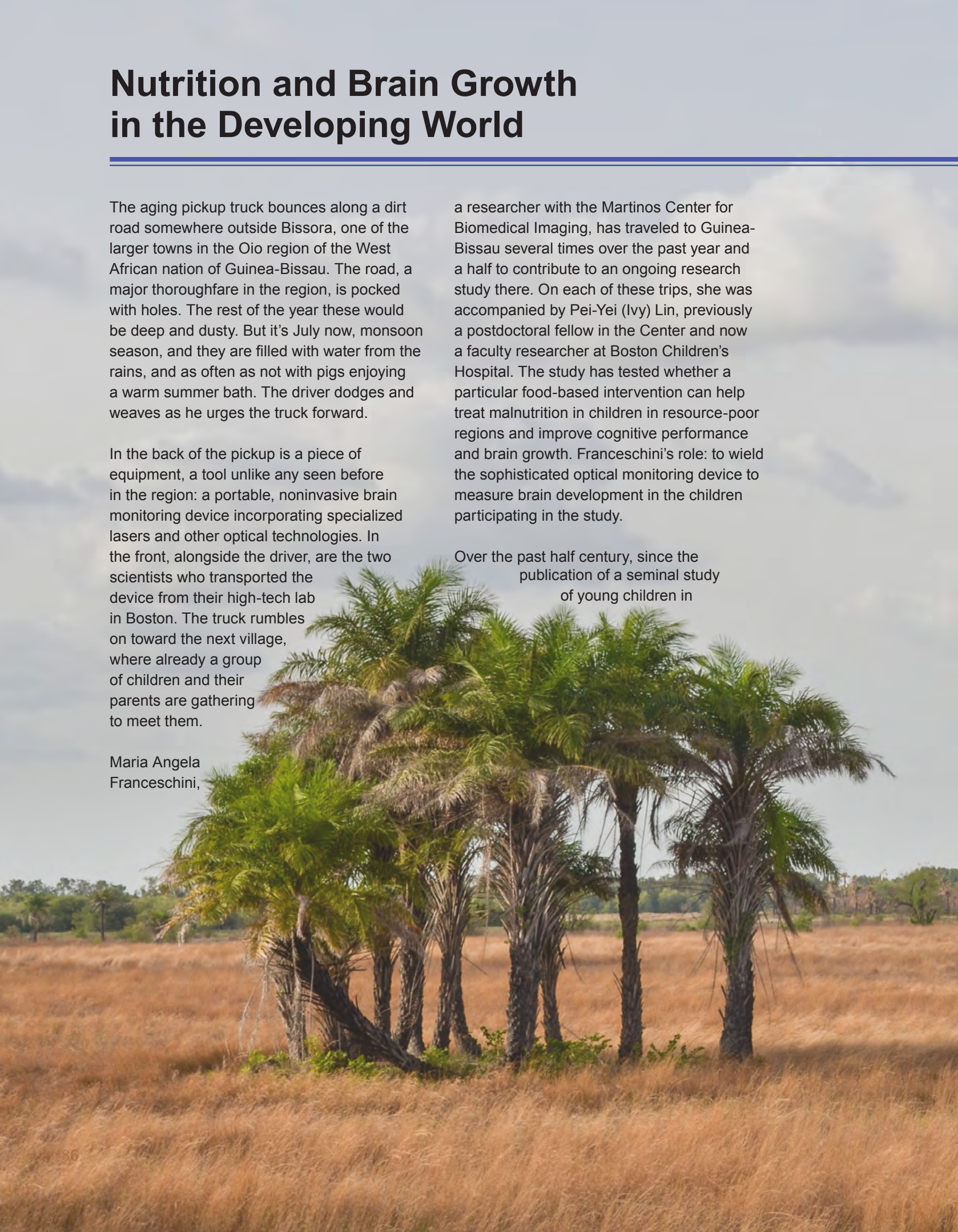
Nutrition and Brain Growth in the Developing World

The aging pickup truck bounces along a dirt road somewhere outside Bissora, one of the larger towns in the Oio region of the West African nation of Guinea-Bissau. The road, a major thoroughfare in the region, is pocked with holes. The rest of the year these would be deep and dusty. But it's July now, monsoon season, and they are filled with water from the rains, and as often as not with pigs enjoying a warm summer bath. The driver dodges and weaves as he urges the truck forward.

In the back of the pickup is a piece of equipment, a tool unlike any seen before in the region: a portable, noninvasive brain monitoring device incorporating specialized lasers and other optical technologies. In the front, alongside the driver, are the two scientists who transported the device from their high-tech lab in Boston. The truck rumbles on toward the next village, where already a group of children and their parents are gathering to meet them.

Maria Angela Franceschini, a researcher with the Martinos Center for Biomedical Imaging, has traveled to Guinea-Bissau several times over the past year and a half to contribute to an ongoing research study there. On each of these trips, she was accompanied by Pei-Yei (Ivy) Lin, previously a postdoctoral fellow in the Center and now a faculty researcher at Boston Children's Hospital. The study has tested whether a particular food-based intervention can help treat malnutrition in children in resource-poor regions and improve cognitive performance and brain growth. Franceschini's role: to wield the sophisticated optical monitoring device to measure brain development in the children participating in the study.

Over the past half century, since the publication of a seminal study of young children in



rural Guatemala, researchers have been developing ever-more refined understandings of the relationship between malnutrition and cognitive outcomes. They have been exploring the significant negative impacts poor diet and other symptoms of poverty can have later in life—in terms of achievement in school and even with respect to mortality—and trying to find ways to prevent these.

A number of studies have directly targeted children's diets, seeking to improve cognitive outcomes by providing the children with nutrition supplements. But these have been shown to have little or no impact unless they are combined with other interventions—medical treatments or social enrichment, for example—leading some to abandon the idea that the supplements alone can help.

Susan B. Roberts thought otherwise. Roberts, a senior scientist and professor of nutrition at the USDA Human Nutrition Research Center on Aging at Tufts University, felt the lack of success in the earlier studies might not have been because food-based interventions generally do not work, but rather because the studies did not use the most optimal nutrition supplements. Current recommendations for those supplements, she noted, do not include particular nutrients that have been shown to be important for cognitive health. With support from local businessman Bill Schawbel and the Boston Foundation, she formulated a new food supplement that incorporated those nutrients and launched the study in Guinea-Bissau to determine its effect on cognitive performance and growth.

The new and improved nutrition supplement wasn't the only novel aspect of the study, though. Most previous investigations relied on tests given to the subjects to determine cognitive performance and how it has changed over time. Roberts wanted a more objective measure of what was happening in the brain, of how the new supplement was actually impacting its development. And for this, she turned to an emerging noninvasive and portable brain monitoring technology.

The Right Tool to Get the Job Done

The scientists set up a makeshift lab in the one-room schoolhouse in the heart of the village. As children and their parents file in, the lab comes alive with spirited chatter. The assembled are decked out in patterned

dresses, bright dashikis, and T-shirts emblazoned with an array of American characters and brands—donated clothes from across an ocean bought in second-hand market stalls in Guinea-Bissau. A young girl appears wearing an irrepressible smile and a Minnie Mouse top.

It feels almost festive. When the scientists arrived in the village, earlier today, many of the children and their parents came out to greet them, laughing and smiling and embracing them. Even now, the area around the schoolhouse is abuzz with conversation. A few of the kids are playing with inflatable balls the scientists brought with them.

Each of the scans takes only a few moments. With the noninvasive technology they are using—near-infrared spectroscopy/diffuse correlation spectroscopy—measurements involve little more than briefly, gently pressing a probe against the head. This system was designed so parents themselves can hold the probe in place, helping to keep the children calm and comfortable during the measurements. Over the course of the next eight days, the scientists will scan 485 children in six different villages.

Introduced a quarter century ago, near-infrared spectroscopy (NIRS) can determine the amount of oxygen in the blood, noninvasively, by transmitting laser light into the body and detecting the light as it emerges. A more recent development, diffuse correlation spectroscopy (DCS) adds measures of blood flow to the optical monitoring toolbox. Together, the two techniques have made it possible to calculate the cerebral metabolic rate of oxygen (CMRO2)—an established marker of brain maturation—relatively easily with a small piece of hardware and a laptop computer.

Franceschini has taken full advantage of this opportunity. Over the past roughly decade and a half, she has worked on the cutting edge of developing and applying combined NIRS-DCS for the study of brain development in newborns and infants. Her work has yielded a number of new insights, and these in turn have pointed to possible interventions in the care of infants. Today, she is also collaborating with clinicians at Massachusetts General Hospital and elsewhere, seeking to establish NIRS-DCS as a tool to guide and optimize individual care.

The technique works for global health applications for the same reasons it works for bedside monitoring in the clinical environment: it is a noninvasive and portable technology, user friendly while also robust. The Guinea-Bissau measurements, performed over the course of the three visits, demonstrated the feasibility of using the technology in remote, resource-poor regions, where portable generators provide the only electricity and the average temperatures hover in the 100-degree range. For all of its advantages elsewhere, MRI wouldn't work here. Nor would most other brain imaging techniques. NIRS-DCS is, simply, the right tool to get the job done.

In addition to validating the technology for this and other, similar global health applications, the pilot study in Guinea-Bissau yielded some important early findings—showing that children who perform poorly on cognitive testing also have lower-than-average measures of cerebral blood flow. Ultimately, the neuroimaging tool could allow the researchers to compare brain maturation before and after the nutrition intervention, to help determine the impact of the intervention on cognitive and neurodevelopmental outcomes.

The study included villages throughout the Oio region of Guinea-Bissau.

The Secret Lives of Martinos Folk

It's Gonna Be a Lot Less Spooky Around Here

If you were in Building 149 of the Martinos Center on any given Halloween in the past decade, you might have come across a possibly startling scene: a nine-foot, anthropomorphic volcano wandering the halls; a moth-man with large, glowing eyes posing for photos; or maybe just a huge globule of gluten kicking back with friends. If you happened to see one of these, or some other, similar tableau, don't be alarmed. Your eyes were not, in fact, deceiving you.

Since joining the Center in 2008, a certain biomedical researcher and Halloween aficionado—let's call him the Masked Scientist—has shared his unabashed love of the holiday with his colleagues here, crafting ever-more elaborate costumes and often debuting them in Building 149 before heading off to Salem, Cambridge or downtown Boston to celebrate with friends. He has called on his extensive engineering background, not to mention his boundless imagination, in designing and constructing the costumes, employing sculpting and 3D-printing skills and incorporating an array of mechanical and electrical elements. The results, as you might imagine, have never been anything less than astounding.

The Masked Scientist declined to meet for an in-person interview for this story, but he agreed to answer a question or three from the safety of his secret lair, a subterranean laboratory done up in the Gothic style. First: Why does he do it? What compels him, year after year, to devote extraordinary amounts of time and energy to the presumably dying art of hand-tooling costumes with lots of tiny, moving pieces. Ultimately, what keeps him going?

"That's simple," came the reply, written on parchment in an ornate, Old English script. "Every time I'm confronted with another seemingly insurmountable project-related challenge, or another astronomical expense for supplies and hardware, or just the prospect of losing weeks of sleep and the stress of leading a double life (scientist by day, Halloween fanatic by night), I just have to remind myself of three simple words to make it all okay … 'Dude, it's Halloween.'"

"Dude, it's Halloween," indeed. To be sure, for many in the Center, the Masked Scientist's big Halloween reveal,

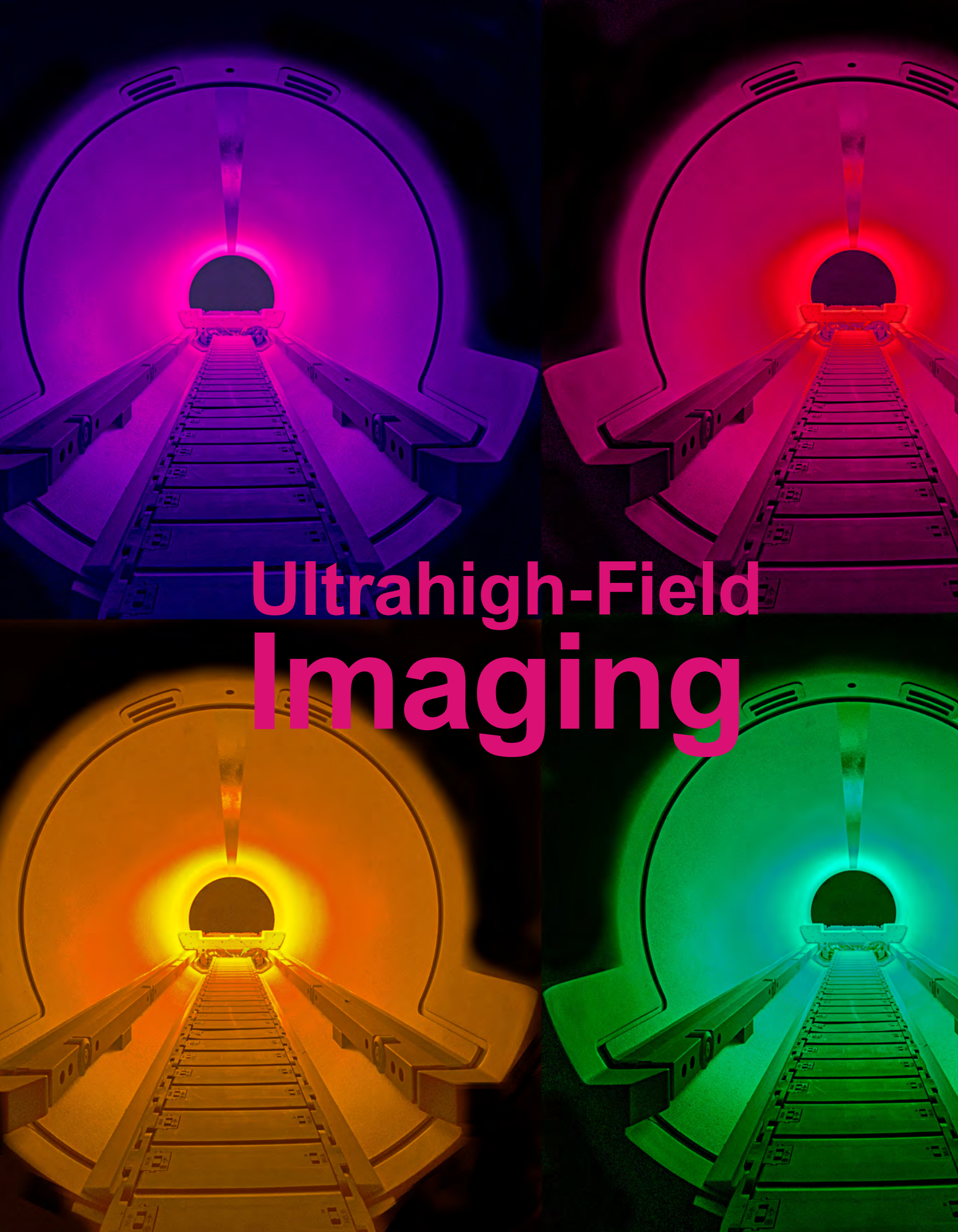
wherein he emerges from his lair in full regalia for the very first time, is the highlight of the holiday. It's a wildly emotional experience, filled with excitement for the unveiling of the Masked Scientist's costume, joy in seeing his creativity and engineering prowess in full bloom, and sheer exhilaration in not knowing until the very last minute whether he's managed to pull it off.

So it was especially difficult to come to terms with the fact that the Masked Scientist left the Center at the end of 2019, moving across town to join the Biomedical Engineering faculty at Northeastern University. Folks at the Center were thrilled for him, of course, and they wished him all the best in his new and surely bracing adventure. But at the same time, they recognized that, in taking another job, he was leaving a huge, likely unfillable, goblin-shaped hole in the Center. Halloween here will never be the same.

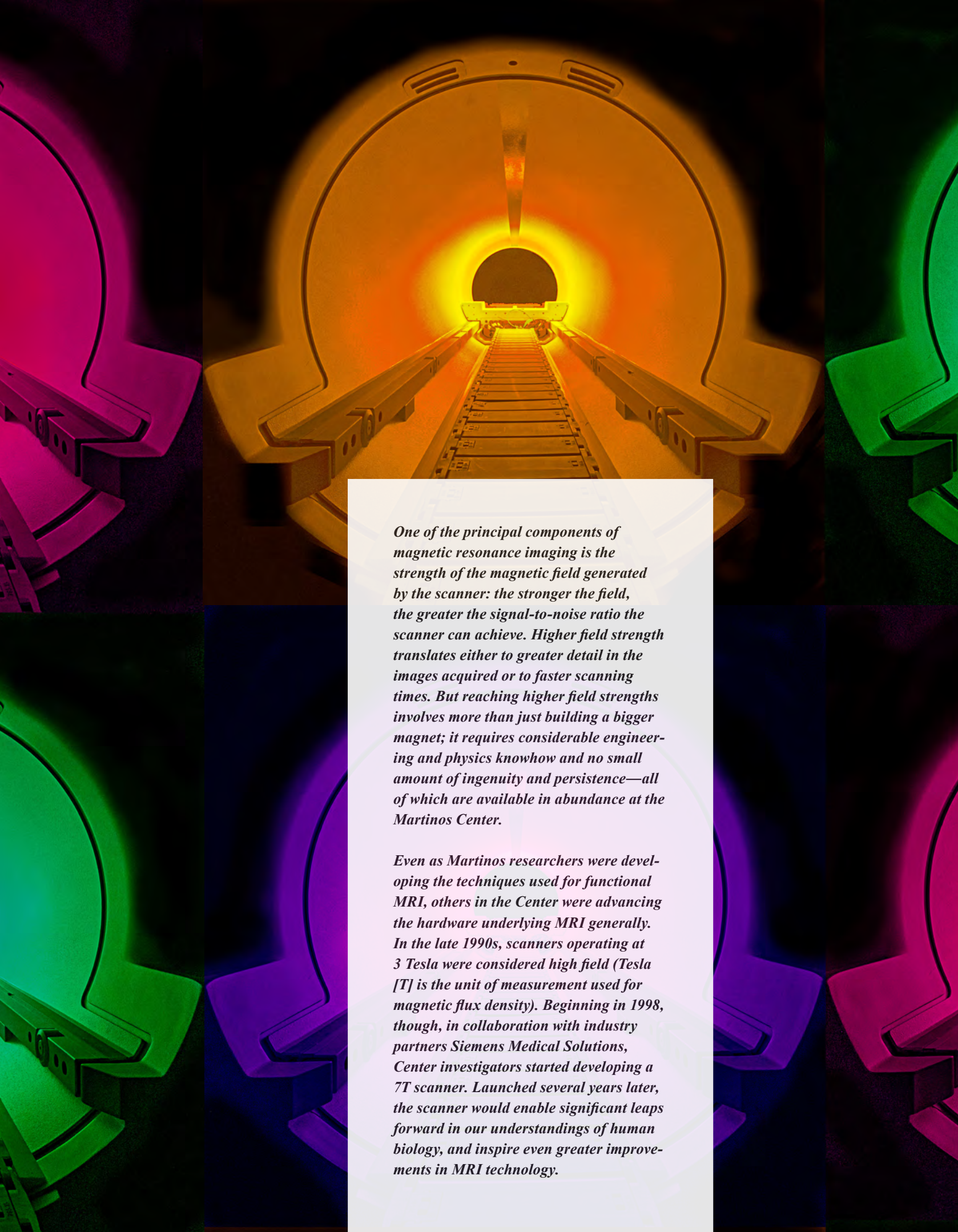
Which leads to the next questions submitted to the man holed up in his lair: Will you miss the Center as much as it will miss you? And if so, what will you miss the most?

"There's no single aspect that I'll miss the most," he wrote, in the same, highly embellished script. "But it really makes my heart sing to see how the Center has grown to fully embrace Halloween and honor its cultural significance and indisputable transcendence. Commemorative gatherings are routinely arranged by both individual labs and for the entire Center. Ornate shrines are constructed in the administrative office and by individual investigators. And countless investigators now honor the occasion by donning the ceremonial attire. These and other efforts make the Martinos Center a shining example from which the entire world can both learn and benefit tremendously!"

In the interest of full disclosure, not everyone is a fan. When asked about the Masked Scientist and the love of Halloween he has inscribed in the Center, Abbas Yaseen, a longtime member of the Martinos community, scoffed. "That dude?" he said, darkly. "WHATEVER!!!" He shook his head and returned to boxing up the contents of his office. Yaseen, as it happened, was also leaving the Center at the end of the year.



Ultrahigh-Field Imaging



One of the principal components of magnetic resonance imaging is the strength of the magnetic field generated by the scanner: the stronger the field, the greater the signal-to-noise ratio the scanner can achieve. Higher field strength translates either to greater detail in the images acquired or to faster scanning times. But reaching higher field strengths involves more than just building a bigger magnet; it requires considerable engineering and physics knowhow and no small amount of ingenuity and persistence—all of which are available in abundance at the Martinos Center.

Even as Martinos researchers were developing the techniques used for functional MRI, others in the Center were advancing the hardware underlying MRI generally. In the late 1990s, scanners operating at 3 Tesla were considered high field (Tesla [T] is the unit of measurement used for magnetic flux density). Beginning in 1998, though, in collaboration with industry partners Siemens Medical Solutions, Center investigators started developing a 7T scanner. Launched several years later, the scanner would enable significant leaps forward in our understandings of human biology, and inspire even greater improvements in MRI technology.

Larry Wald *and the Three Traumas*

If you know Martinos researchers, you know they are often modest and even self-effacing about their accomplishments. It's a part of their charm. In a recent conversation, MRI Core director Larry Wald framed his early days in the Center as a series of traumas. Whatever challenges he might have faced, he undoubtedly handled them with an endless reserve of skill and aplomb. Still, it's fun to imagine those days as he describes them—as one fire after another begging to be put out, or maybe an eternal game of whack-a-mole—so we will indulge him in his humble retelling.

Wald joined the Martinos Center in early 1998, after a stint as an instructor at McLean Hospital in Boston. When he arrived, he was named director of human imaging and tasked with maintaining the Advanced NMR-equipped MRI systems in Building 149, in the same spots where Bays 2 and 3 are today. But his tenure in this position would prove short lived; before long, Wald's role in the Center would change in a somewhat dramatic fashion as the first of his three traumas befell him.

Robert Weisskoff was the head of the MRI Core and chief magnetic resonance physicist at the Martinos Center and the former senior physicist at Advanced NMR Systems who had played an integral role in bringing to the Center the enabling technology for functional MRI. In short, he was an important and stabilizing presence in the Center. But within months of Wald's arrival, he left his position to embark on a new adventure, going to business school and eventually establishing himself in the world of venture capital and private equity. Today, Wald admits that Weisskoff's departure "caused a bit of turbulence." Not because of any interpersonal conflicts or lingering resentment; only because he suddenly found himself in a significantly expanded role—he was now the MRI Core Director.

This, alone, would have been a shock to the system. As it happened, though, the change also came at a critical juncture in the Center's history. Maybe a month after Weisskoff left the Center, its Advanced NMR scanner began a descent into obsolescence. GE stopped providing regular service for the specialized resonant gradient coils used for fMRI, which were originally made and serviced by Advanced NMR. Finding spare parts grew more and more difficult, and the spare parts the researchers did find were often contaminated. The Center's scanners were "slowly sinking under the waves, getting more and more unstable," Wald says. This was the second of his three traumas.

The Center continued for a time with a state-of-the-art GE scanner. It wasn't

long, though, before Bruce Rosen and Greg Sorensen decided to add two more scanners to the Center's arsenal. And if they were adding scanners, they realized, they might also consider switching vendors. GE was perhaps the top vendor at the time; most of the major MRI research centers were GE sites, from Stanford to the Mayo Clinic, from Penn to Duke. But after reevaluating its needs and what the different vendors could offer, the Center decided to switch to Siemens.

This led to the third and final trauma, Wald says. "We had to pull out two more-or-less working GE scanners and put in Siemens scanners that we were completely unfamiliar with," upending any number of ongoing studies in the Center for many months at a time. There was a bright side, though: Wald and the others started working with Siemens' excellent staff, including Andreas Potthast, an engineer working on Siemens' new 3T system (the Center installed the second 3T system the company ever shipped). Potthast and colleagues from Siemens would become integral members of the team and even embraced as part of the Martinos Center family, a relationship that continues to this day.

Adventures on the High Ts

If Wald thought his job would settle into something resembling a normal routine after the turbulence of the first couple of years, well, he would have been mistaken. In 1998, amidst the initial negotiations with Siemens, he attended the annual meeting of the International Society for Magnetic Resonance in Medicine (ISMRM) in Sydney, Australia. After the meeting, he took an extra week to go snorkeling in the Great Barrier Reef. Certainly, no one would argue he didn't deserve a bit of time away from the lab.

Wald might have though he wouldn't miss anything too exciting in that one week. Then again, he had already been around the Center long enough to know never to make such a bet. In any event, when he returned to Charlestown, he found Center director Bruce Rosen, researcher Hans Breiter and others in the throes of writing a white paper seeking funding to build the world's first 7T MRI scanner. The funding came through and, in late 1998, the Martinos team kicked off a project that would occupy Wald for much of the next several years—and usher in *another* new era of magnetic resonance imaging.

Previous: Photo and rendering by Mike Datko

Opposite: Larry Wald

7T at the Martinos Center: An Origin Story

This is the story of the world's first 7T MR scanner—of how the scanner was built with money that may have been seized from drug runners in stealth boats and that was definitely handed over to the Martinos Center by a former CIA operative.

Really, it is.

The story goes like this. One day in about 1998, Center director Bruce Rosen found himself sitting in his office chatting with the head of the Counterdrug Technology Assessment Center (CTAC) in the Office of National Drug Control Policy, the office of the "Drug Czar" in the US federal government. Al Brandenstein was a colorful character, Rosen says—among other things, he had spent time in the seventies working with the CIA in Southeast Asia; doing what, he could not say—and their conversation proved a lively and entirely enjoyable one.

The introduction to Brandenstein came by way of Mass General Psychiatry colleagues and collaborators Steve Hyman and Hans Breiter, who, along with the Psychiatry department's Randy Gollub and a team of Martinos researchers, had performed the first fMRI study of the psychopathology of drug addiction. Hyman had since moved to the National Institutes of Health and through his work there met Brandenstein. Recognizing their common goals, he suggested Brandenstein travel to Boston meet with Breiter and Rosen.

What were those goals? CTAC had previously funded research with positron emission tomography to try to gain better understandings of the neural mechanisms of addiction, in part using money seized in drug raids, seized from the backs of boats or cars or whatever other means of transport. "They used that money, of course, to buy radar and high-speed boats for drug interdiction," Rosen says, "in other words, to try to reduce the supply of drugs. But Brandenstein was rather visionary and also had the notion that he would invest in reducing the demand for drugs."

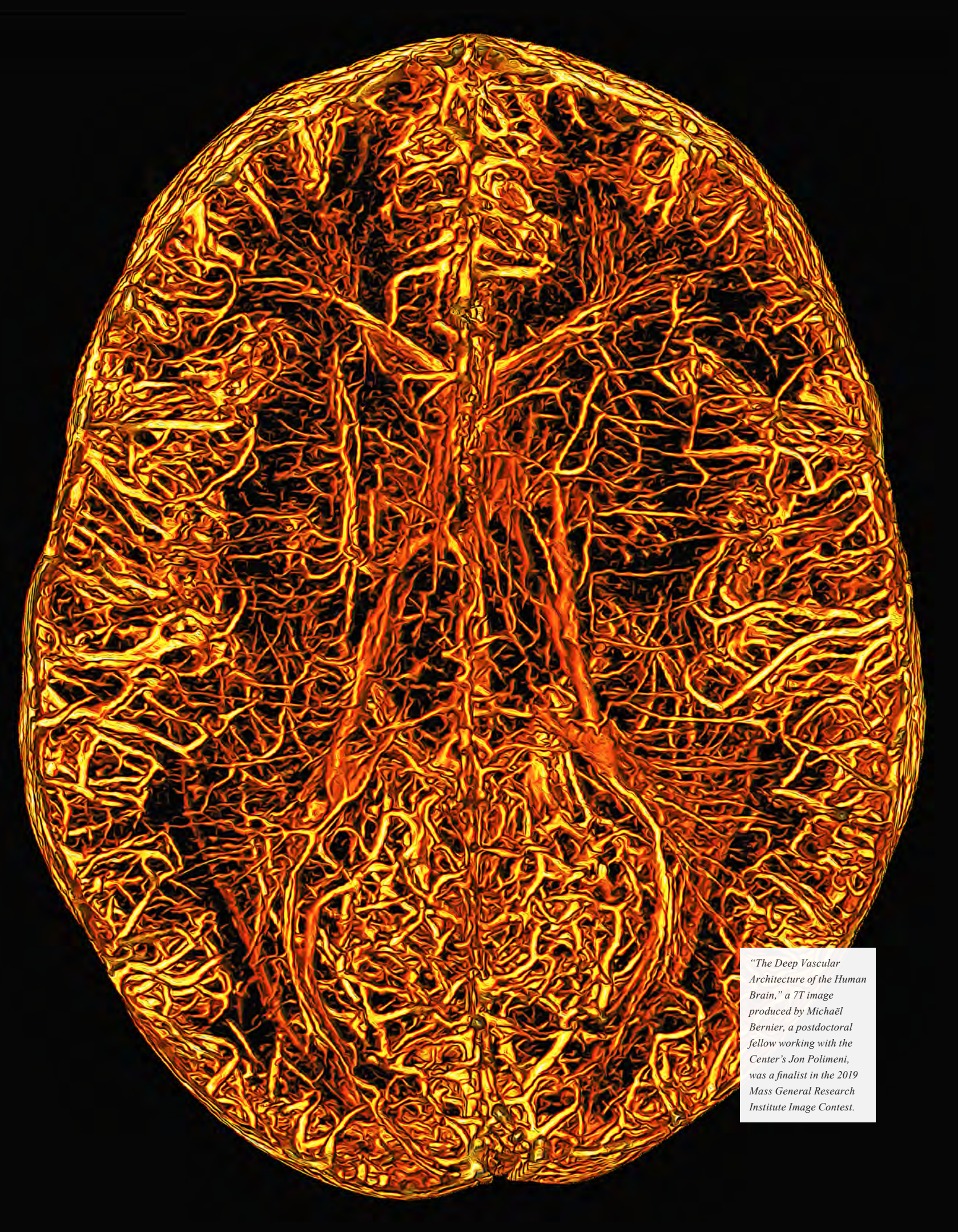
As their conversation began to wind down, Brandenstein looked at Rosen and asked, "How can we help you?" Not expecting a direct offer like this, Rosen quickly scanned a mental list of possibilities. He and colleagues in the Center had been considering a couple of large-scale projects. For example, they had been toying with the idea of installing a magnetoencephalography (MEG) system, another emerging technology at the time, with a price tag of maybe $4 million. "But if someone is asking, what do you want," Rosen says, "you might as well pick the most expensive thing you can think of."

Tommy Vaughan, another Center researcher, had been promoting the idea of building a 6T scanner; at the time, the highest field strength available with MRI was 3T. Rosen knew from previous conversations with Vaughan that developing MR scanners cost roughly a million dollars per Tesla, so his 6T scanner would be about a $6 million venture.

Rosen barely skipped a beat in responding. "We would like to build a 7T scanner."

Hold on. 7T? "Well, I figured, we're not going to get all the money we want," he explains, more than two decades later, "and when they do the 10 percent cut, we'll still have enough for a 6T scanner."

This day was full of surprises, though. Brandenstein asked how much the 7T scanner would cost. Rosen explained it would be about a million dollars per Tesla. The one-time CIA operative considered this for a moment, then looked up and said, "We can do that." With those four words and a short white paper written in the following weeks, the Office of National Drug Policy had committed to supporting a 7T MR scanner at the Martinos Center.

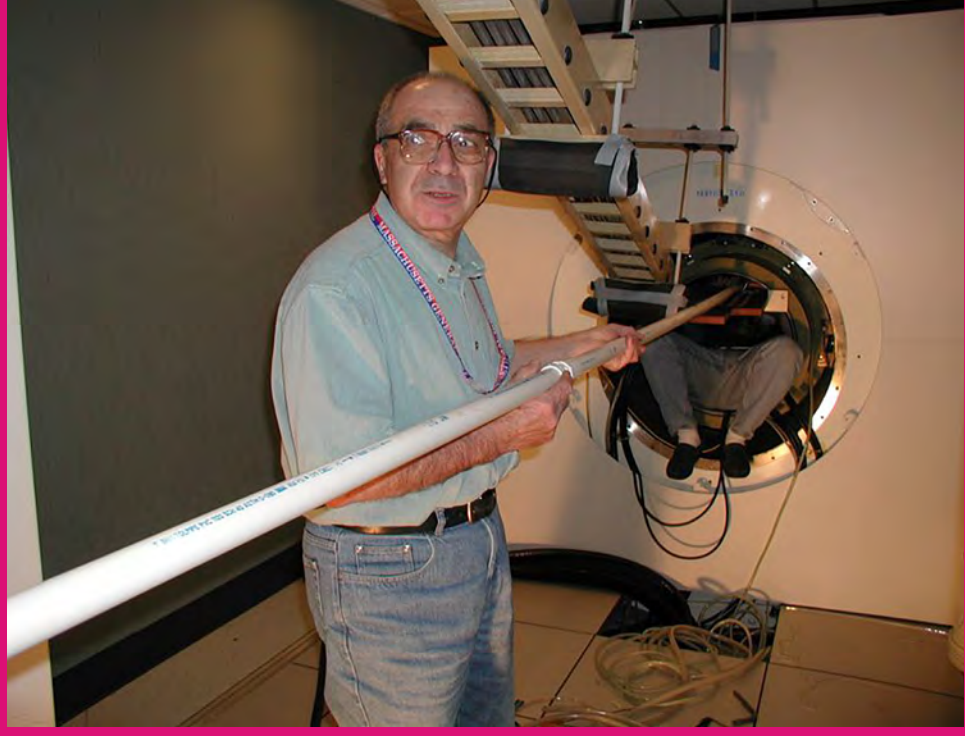


"The Deep Vascular Architecture of the Human Brain," a 7T image produced by Michaël Bernier, a postdoctoral fellow working with the Center's Jon Polimeni, was a finalist in the 2019 Mass General Research Institute Image Contest.

7T MRI Memories

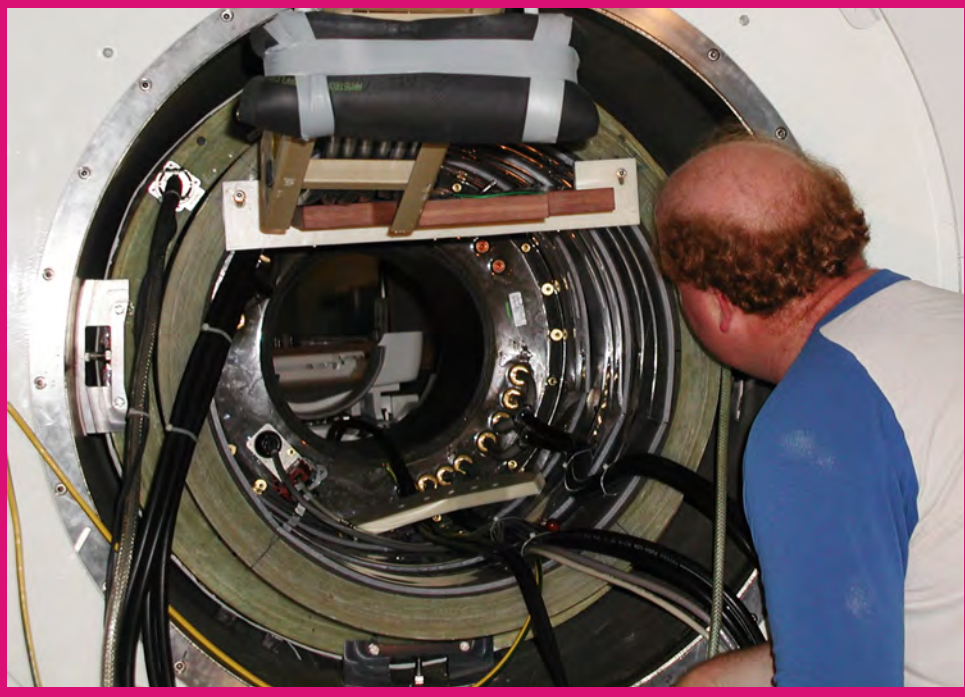
I recall the whiteboard in the 7T console room. I started using this to note down various issues, with the heading “Things that need to be fixed” or words to that effect. It seemed, though, that others on the team considered this to be too negative. So we changed it to “Opportunities for optimization.” Thus it seems we overcame our challenges by—keeping to the 7T team motto [“We keep changing things”]—changing these into opportunities!

— *Christopher Wiggins*



The most exciting part for me was when we had reached the stage in the development of the scanner and the coils where we could run our first volunteer scans—and I could be the first volunteer. I remember how strange it felt [entering such a strong magnetic field], as if you were pushed in on a curved path and once you reached the center you started rotating as if you were in a huge washing machine.

— *Andreas Potthast*



On a Saturday evening one February, Mary Foley called me and said, “Fraaaanz, please come quick, the 7T is underwater.” I hurried over to the Martinos Center and, indeed, water was dripping from the ceiling like crazy. I am an apprenticed electrician and seeing the electrical outlets floating in water scared [the heck out of me]. Anyway, Mary and I resolved it by lifting the outlets to higher levels. A heroic act!

— *Franz Schmitt*

Right: Graham Wiggins (photo courtesy of Christopher Wiggins)

Opposite, top: Simon Sigalovsky (photo courtesy of Franz Schmitt)

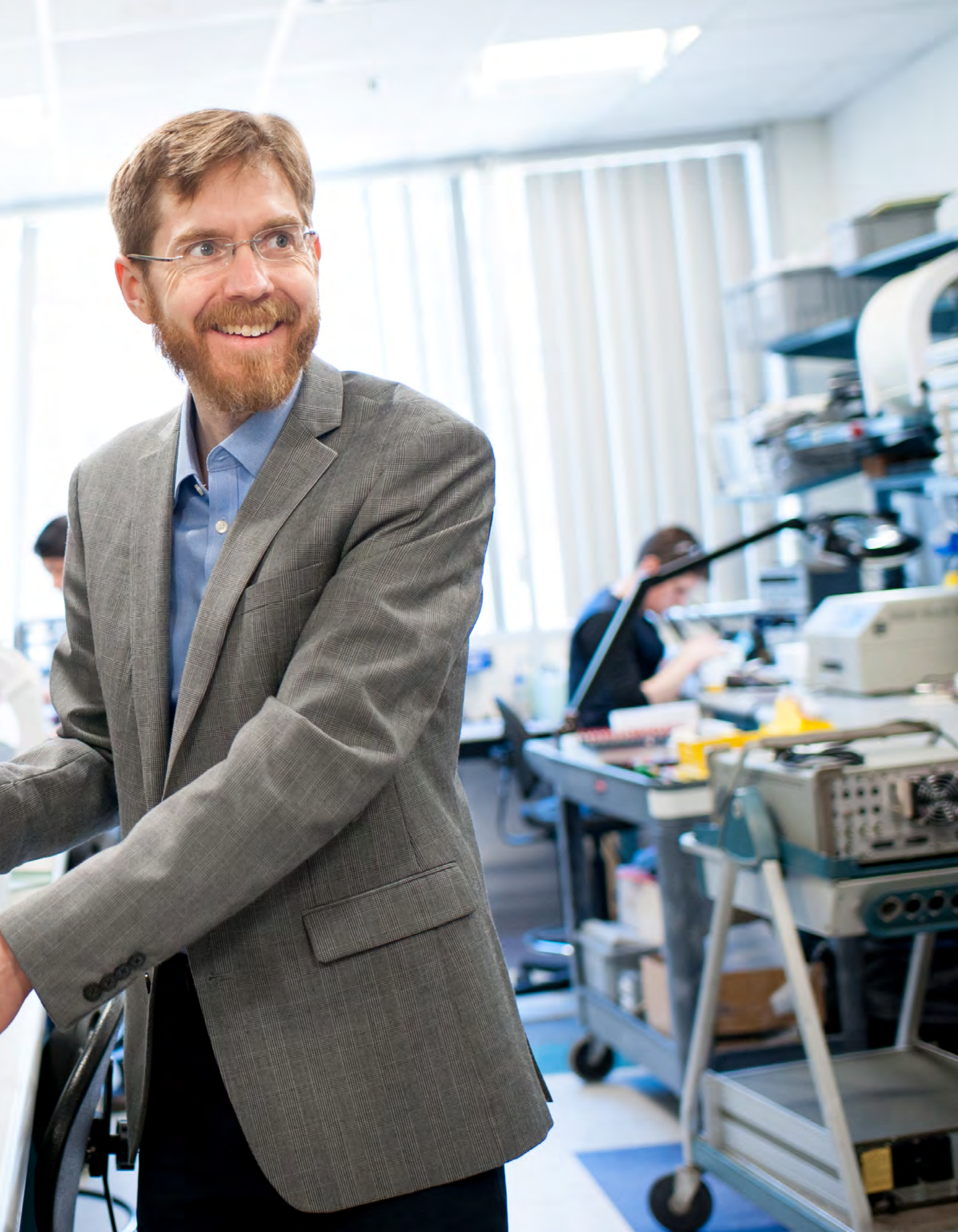
Opposite, middle: Larry Wald (photo courtesy of Franz Schmitt)

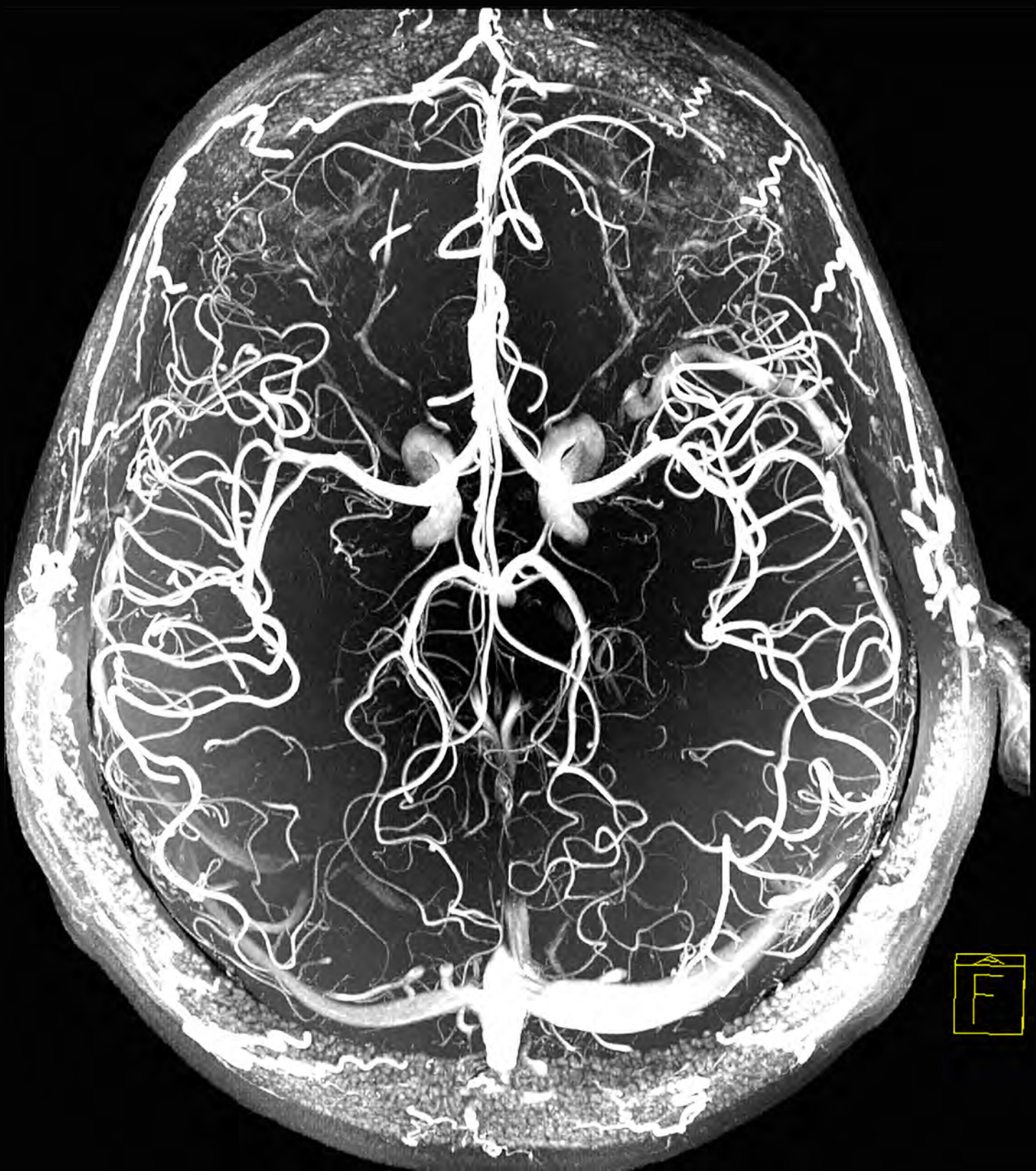
Opposite, bottom: (back row, L to R) Christopher Wiggins, Larry Wald, Simon Sigalovsky, Franz Schmitt, Bernd Stoeckel; (kneeling, L to R) Wilfried Schmidt, Andreas Potthast (photo courtesy of Christopher Wiggins)

With so many memories, it is of course hard to pick a favorite. But perhaps one that I recall often was working with my brother Graham Wiggins. For both Graham and myself, the chance to not just work on the cutting-edge 7T project, but work on it together, was a truly wonderful opportunity. Many of the tales related to his time at MGH have been covered in other settings, but one I think has not been mentioned is the use of the phrase “It’s been a long week.” I think the earliest in the week this was spoken was at 10 AM on a Monday.

- Christopher Wiggins

One of the major thrusts in the Center over the years has been the development of cutting-edge radiofrequency (RF) coil arrays, the components used to detect and sometimes excite the MR signal. For example, faculty member Jason Stockmann develops RF coil arrays with added "B0 shimming" capability, allowing for magnetic field homogeneity to be improved inside the body, reducing image distortions and other artifacts.





Martinos Center faculty member Jon Polimeni produced the stunning image on the opposite page in 2017. The image shows blood vessels of the human brain in a healthy volunteer taken from a non-contrast 3-micron isotropic 3-D Time-of-Flight Magnetic Resonance Angiography maximum intensity projection from a whole-body 7T MRI.

Polimeni is shown below with the Center's Azma Mareyam at the MGH 7T 20th Anniversary Symposium in 2019.

Ultrahigh-field MRI and Multiple Sclerosis

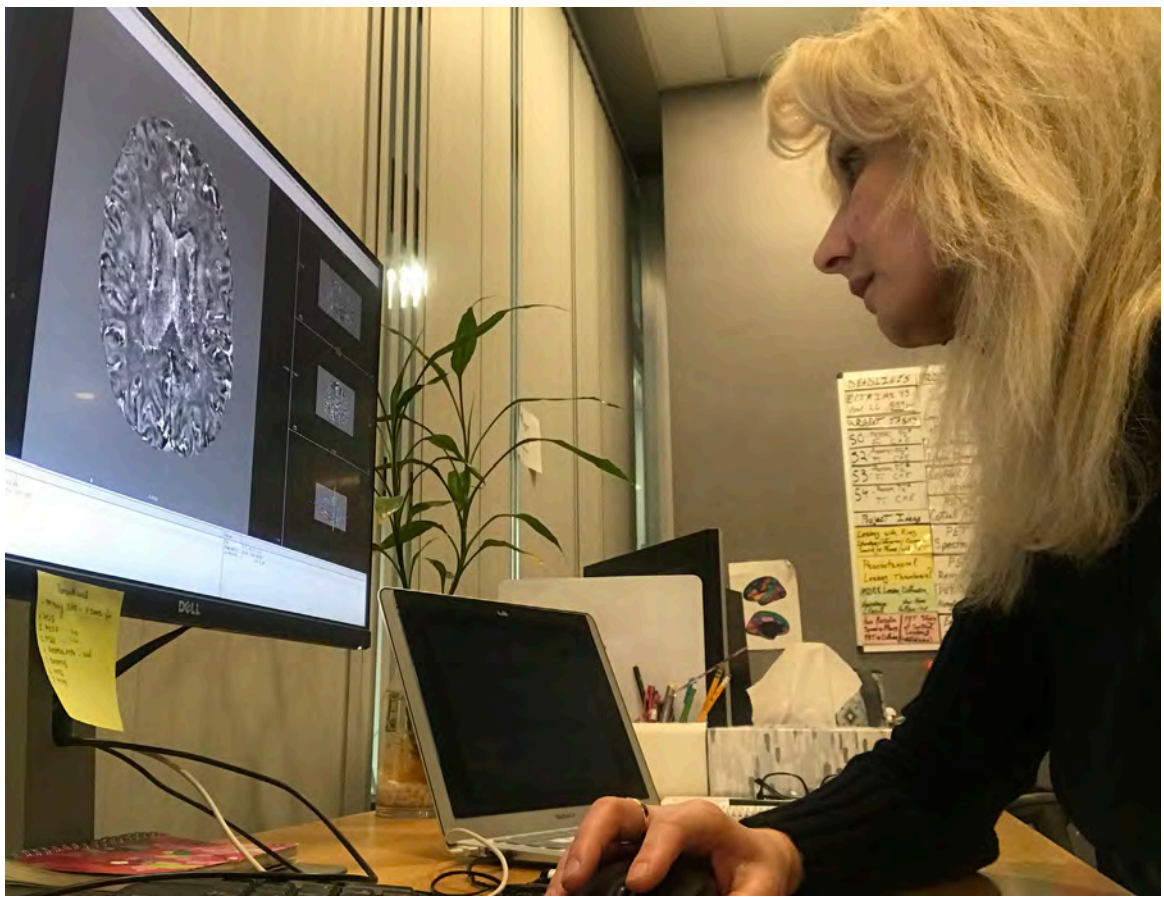
The development of lesions in the brain's cortical gray matter is a strong predictor of neurological disability for people with multiple sclerosis (MS), according to a study reported in 2019 in the journal *Radiology*. The findings suggest a role for ultrahigh-field MRI in monitoring the progression of MS, says Constantina A. Treaba, a researcher working with Caterina Mainero in the Martinos Center's Multiple Sclerosis Imaging Lab and first author of the study.

Multiple Sclerosis, the most common cause of chronic neurological disability in young adults in the West, was once thought to be a disease of the brain's white matter. Recent research has shown, though, that cortical lesions—that is, lesions found in the gray matter of the outer layer of the brain—could develop even earlier than white matter lesions in the course of the disease.

The involvement of cortical lesions raises several questions, Treaba says. Not least: What causes cortical gray matter damage in MS? How quickly do cortical lesions accumulate in MS, especially relative to lesions in the white matter? And what are the contributions of each of these to neurological disability in MS?

Cortical lesions are difficult to see with 3T MRI scanners, commonly

Constantina A. Treaba

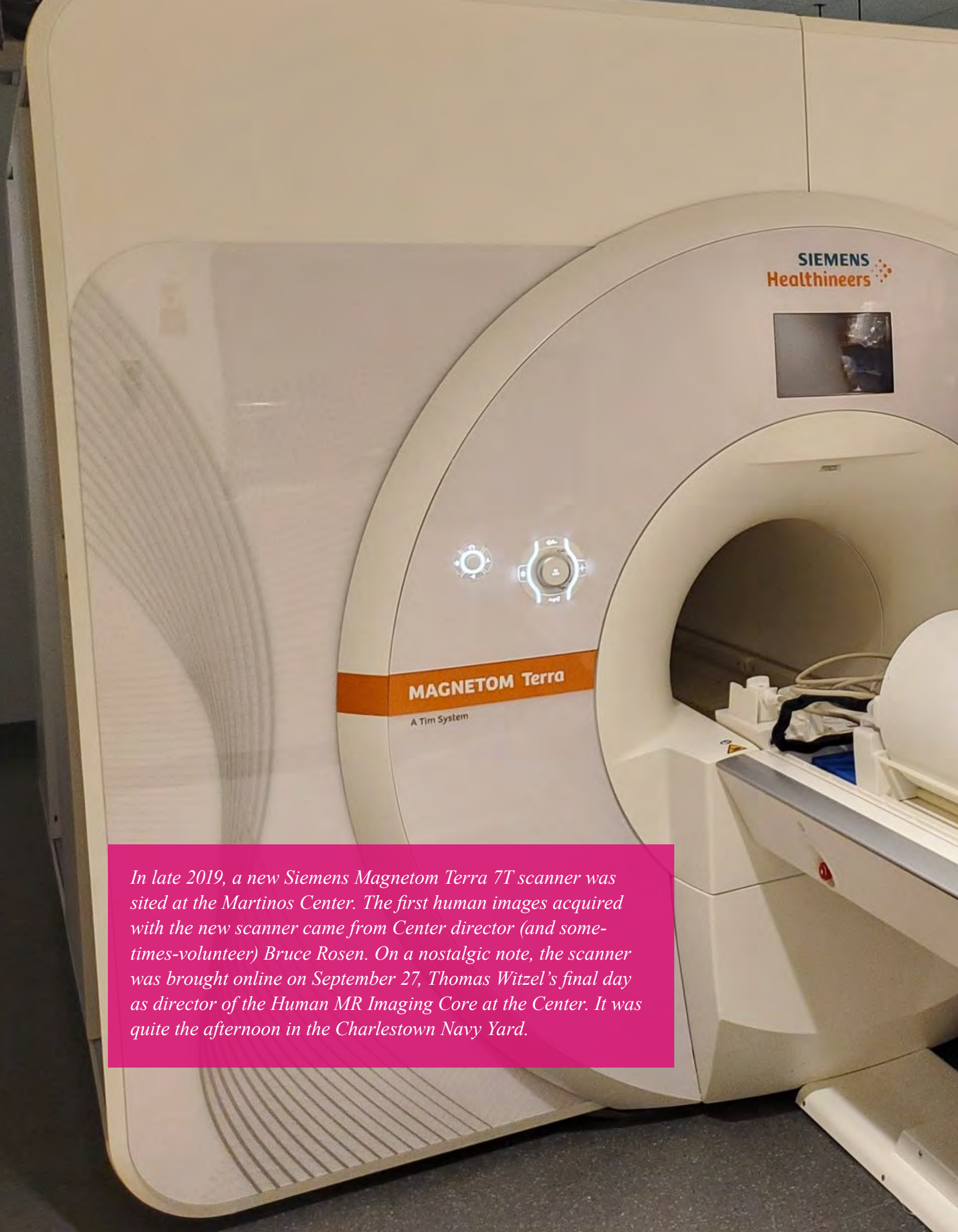


used tools in neuroscience research. So, in order to address these questions, Treaba and colleagues turned to the ultrahigh-field 7T scanner in the Center. With more than twice the magnetic field strength, the 7T offers much greater sensitivity than 3T systems. Using the ultrahigh-field scanner, they followed 20 relapsing-remitting and 13 secondary-progressive MS patients as well as 10 age-matched healthy controls. Relapsing-remitting is a type of MS in which symptoms can either improve or worsen, while secondary progressive is a more advanced disease characterized by more significant disability.

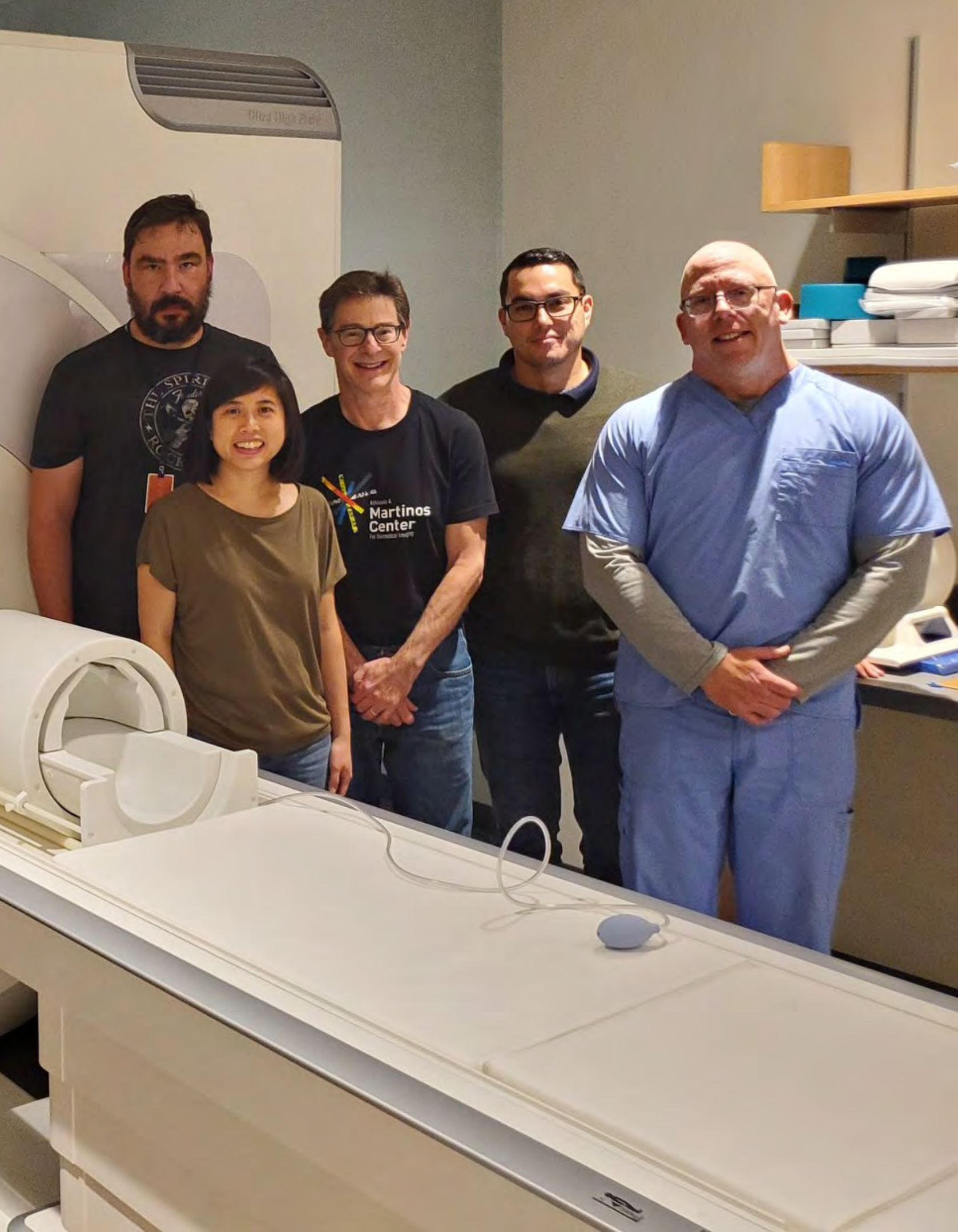
The findings of the study, reported in the *Radiology* paper, were striking. Twenty-five of the MS patients, or 80 percent, developed new cortical lesions. The number of new lesions in the gray matter of the brain was more than twice the number that developed in the white matter. Based on the higher rate of accumulation, Treaba says, cortical lesions were the strongest predictor of disability progression in MS. Notably, in this study, the 7T scanner detected the lesions more frequently than did lower-field scanners in previous studies, underscoring a possible role for ultrahigh-field MRI in following the progression of MS.

“Our results could influence the way we monitor the patients with MS by including cortical lesion assessment as a required step in the evaluation of disease progression and treatment outcomes,” Treaba says.

With respect to the causes of gray matter damage in MS, the study demonstrated that grooves on the brain’s surface called sulci are both the first and the predominant regions involved in cortical lesion development. This finding suggests a possible link between gray matter pathology and a neuroinflammatory process mediated by cerebrospinal fluid, the flow of which may be restricted in the sulci. The researchers hope to explore this possible mechanism further, while also looking into which patient cohorts tend to accumulate more lesions than others.



In late 2019, a new Siemens Magnetom Terra 7T scanner was sited at the Martinos Center. The first human images acquired with the new scanner came from Center director (and sometimes-volunteer) Bruce Rosen. On a nostalgic note, the scanner was brought online on September 27, Thomas Witzel's final day as director of the Human MR Imaging Core at the Center. It was quite the afternoon in the Charlestown Navy Yard.


Martinos
Center

The (Totally True) Legend of **Thomas Witzel** *and the Ultrahigh-Field MRI Quench*

Sometimes we get the hero we need.

In the summer of 2017, the 7T MRI scanner at the MGH Martinos Center suffered a quench: a sudden loss of superconductivity resulting in a complete loss of the scanner's magnetic field. In short, it broke. Without a magnetic field, the instrument was inoperable, unable to produce any kind of MR image.

A quench would be bad under the best of circumstances, but the outlook in this case was especially dire. The 7T, one of the most advanced MR scanners in the world when it was launched in the Center in 2001, had already outlived its design lifetime by six years. Worse still: Magnex Scientific, the UK-based company that built the magnet, had gone out of business some years before the quench, so the scanner was no longer supported by a vendor service contract. In more desperate moments, Center investigators would wonder whether it could ever be repaired.

Enter Thomas Witzel.

The director of the MR Imaging Core, Witzel was responsible for the maintenance and repair of all of the magnetic resonance instrumentation in the Center, including technical oversight of some of the most advanced scanners on the planet. Over the years, he played an integral role in ensuring the smooth day-to-day operation of the Center's many MR systems while spearheading major upgrade projects. A big bear of a man with an offbeat sense of humor, he is known far and wide as a technical maven, a veritable grandmaster in the world of MR hardware. If anyone could get the 7T up and running again, it would most certainly be him.

To help with the project—which was overseen by Center director Bruce Rosen and Larry Wald, director of the NMR Core at the Center—Witzel recruited Dick Marsh, a magnet service engineer with expertise in custom vacuum technology and cryogenics. Together, the two of them dove headlong into the many fixes needed to make the magnet operational again, tackling any problem they encountered with a combination of steely resolve and panache. "Thomas and Dick were a potent problem-solving team," says Jason Stockmann, an assistant professor in the Center who develops MR hardware.

Stockmann regularly contributed to the 7T recovery effort so he had a ringside seat to the seeming miracles the pair performed on a daily basis.

Said miracles are too numerous to list, Stockmann says, but a few examples give a good idea of the kinds of feats Witzel and Marsh regularly achieved. First, the magnet needed to be instrumented with new temperature, pressure, helium-level and boil-off sensors to allow data-logging of these parameters. But the original helium-level sensor was broken and inaccessible for repair, so they installed a new helium fill meter near the top of the cryostat to at least indicate when the magnet was full. Next, the magnet needed to be pre-cooled with liquid nitrogen to 77 Kelvin before switching to liquid helium for the final cool-down to below 4 Kelvin to achieve superconductivity in the niobium-titanium wires. Before switching over to liquid helium, Witzel and Marsh had to be absolutely certain that no ice had formed in the cryostat during this process—nitrogen will freeze below 77 Kelvin. If it did, the consequences in the event of a second quench could be calamitous.

Finally, they had to figure out how to connect to and ramp current into the main field coil and the superconducting "shim" coils. This step called for them to open and close a superconducting switch in the coil while tremendous amounts of current were flowing in the loop: equivalent to some 20 kg of TNT. So it required "not only great expertise," Stockmann says, "but also a fair bit of courage."

They achieved all of this and more using old, incomplete documentation that came with the magnet in 2001.

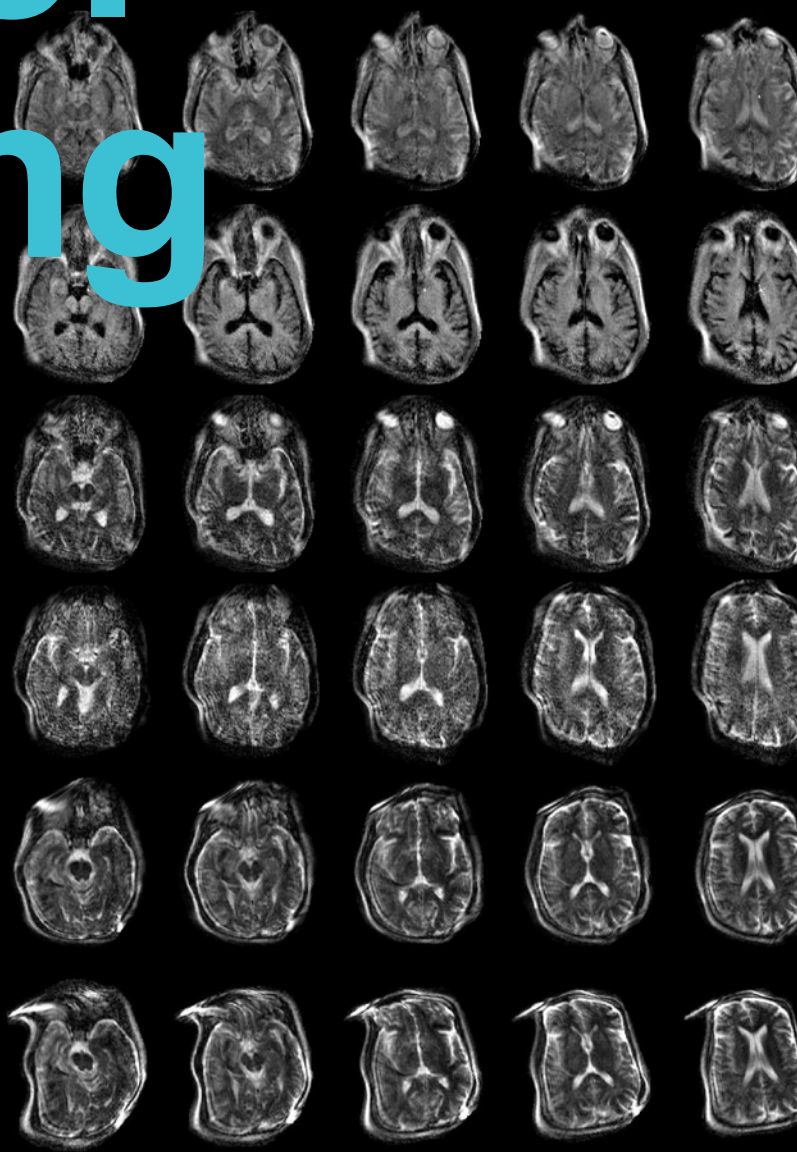
The recovery operation wrapped up in September 2018 and the 7T is now humming along as it was before the quench. Thanks to the sterling efforts of Witzel and Marsh, Center investigators whose research depends on the magnet could get back to the business of wielding it to address a broad range of important biomedical questions.

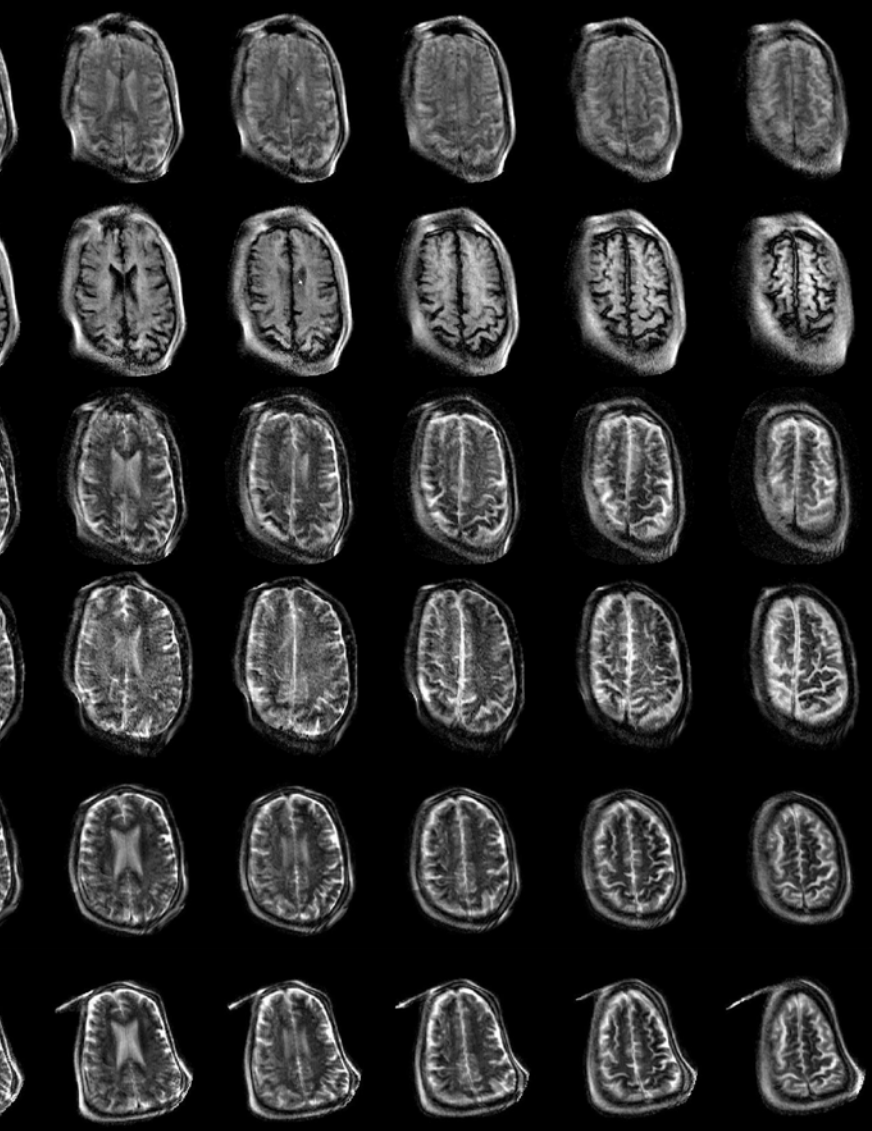
Stockmann marvels at what the pair accomplished.

"Thomas and Dick received some advice from magnet engineers in England," he says, "but mostly they had to piece things together themselves using their wits, what little documentation they had access to, and some MacGyver-style improvisation. Only a few people in the world have the skills, expertise, audacity and tenacity to pull this off."

In recognition of Thomas Witzel's phenomenal work, Jason Stockmann and colleagues presented him the Martinos Center's first-ever "Golden Bore" award. Photo by Matt Rosen.

Low-Field & Novel Imaging





The introduction of ultrahigh-field MRI enabled spatial resolution on scales never seen before, opening the door to a number of applications requiring such exquisite resolution. In many cases, though, lower spatial resolutions are entirely sufficient for the tasks at hand. Here, instead, the applications would benefit from improvements in other areas—improvements in, for example, portability or cost.

Over the past decade or so, Center researchers have sought to address these other needs, in large part by designing and building low-field MRI scanners, or even technologies that move entirely beyond the need for magnetic fields in imaging anatomical structure—novel technologies affectionately described as "no-field" imaging.

The researchers have recently described remarkable achievements in each of these areas. Sometimes, it seems, less is indeed more.

New, Portable Scanner to Bring MRI to the Patient

In late November 2020, a team of researchers at the Martinos Center reported in the journal *Nature Biomedical Engineering* a low-cost, portable MRI scanner they had developed. We checked in with Clarissa Zimmerman Cooley, lead author of the study, to hear more about the scanner. Here is what we learned.

The work addresses the need for greater accessibility with MRI

Undergoing an MRI scan in your doctor's office or in the back of an ambulance might never have seemed possible before. The new technology opens the door to these and other scenarios by sidestepping several of the major requirements of conventional MRI, including the use of a full-body magnet with cryogenic cooling.

"We wanted this to be a truly portable, low-cost device that could be used for new applications and in locations where MRI was previously unavailable," Cooley says. "It was never the goal to compete with the performance of conventional scanners. The device was meant to be a low-cost, point-of-care alternative for detecting brain abnormalities that are visible at a lower field strength and at lower resolution."

Among the team's strengths in the study: good old-fashioned ingenuity

One of the major innovations with this work was the use of a compact array of magnet "cubes" arranged around the head instead of the large superconducting magnet found in conventional MRI scanners. This design significantly reduced the scanner's size and power and cooling needs. But because the magnetic field it generated was nonuniform, the scheme led to distortions in the resulting images. The researchers found a clever way to correct for this, devising an image reconstruction strategy incorporating magnetic field maps showing the spatial distribution of the field patterns measured in the scanner.

Cooley explains: "In traditional scanner designs, the main magnet is highly homogeneous, and a gradient coil system is used to spatially encode the image. In our close-fitting magnet design, it is difficult to create a homogenous field. Instead, we aimed to use the field variation of the inhomogeneous magnet to our advantage—essentially turning a bug into a feature."

The new scanner is the result of reimagining how we do MRI

While much of technology development today is geared toward achieving higher, "better" resolution with MRI, the Martinos researchers set their sights on resolution that is simply "good enough" to obtain the formation you need.

"There are many cases where high-field MRI scanning is not feasible and lower-resolution images are sufficient for answering the clinical question," Cooley says. "You don't necessarily need a 3T scanner to see hydrocephalus, for example. These are the types of applications where our scanner could really make a difference."

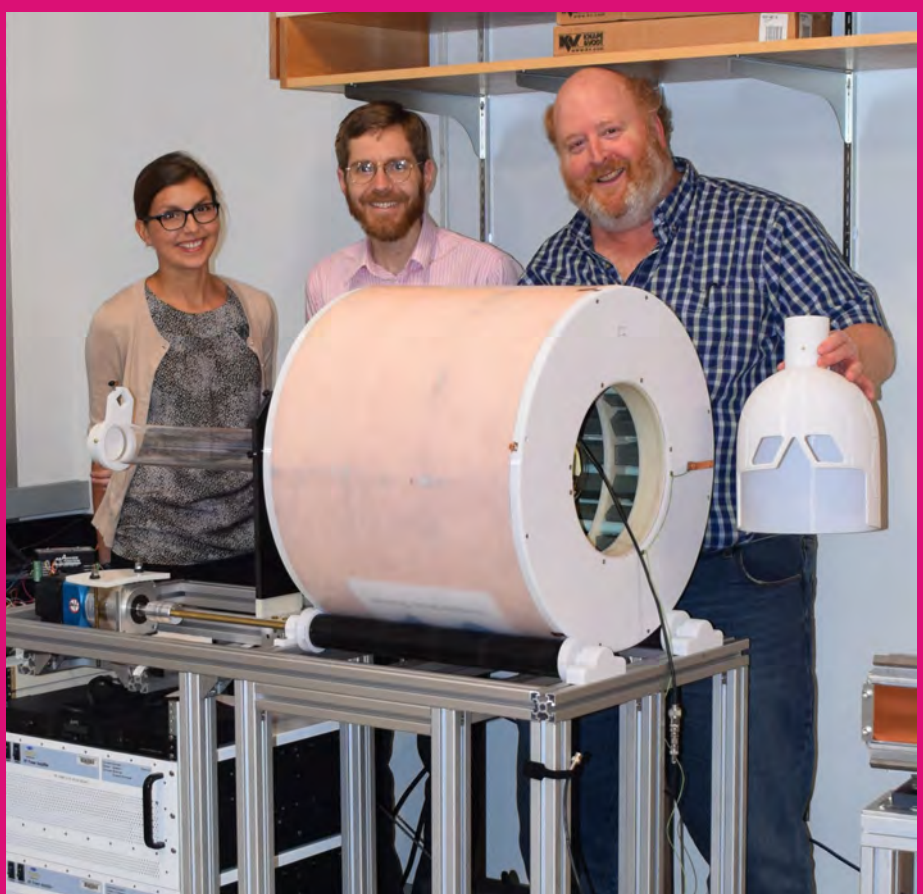
Also, because the scanner is portable and relatively inexpensive, small clinics around the world will have the option of operating their own MRI scanner onsite. Hospitals can benefit as well. For example, in cases where moving a patient presents a risk, researchers can wheel the scanner into the patient's room for scanning.

Ultimately, the technology represents a paradigm shift in MRI, a fundamental reshuffling of how we think about imaging patients. “Portable devices such as ours will allow us, for the first time, to bring the MRI scanner to the patient,” Cooley says. “This will open up a host of new possibilities in diagnostics and monitoring.”

Work continues in readying the scanner for clinical implementation

Having described and demonstrated the technology, the researchers are now developing it further to enable real-world application. For example, electromagnetic interference (EMI) has always been one of the greatest concerns with MRI; it is why conventional scanners are permanently sited in shielded rooms. For true portable imaging, the researchers are integrating EMI detectors into their scanner to mitigate such interference. This will provide greatly improved image quality when the scanner is operated at point-of-care locations where installation of shielded rooms isn’t practical.

EMI mitigation isn’t the only advance the researchers are pursuing. Cooley says: “We are also excited to begin work on a point-of-care MRI scanner specially designed for neonatal patients in the neonatal intensive care unit (NICU). The transport and scanning of sick neonates are logistically difficult and can even be dangerous. The availability of a bedside MRI scanner in the NICU could have tremendous benefits for diagnostics and monitoring of neonatal brain injury.”



Clarissa Zimmerman Cooley, Jason Stockmann and Larry Wald in 2016 with an earlier generation of the portable MRI scanner.

MRI at Bedside

Fundamental research by Matthew Rosen, director of the Low-Field Imaging Laboratory in the Martinos Center, contributed to the early development of a new portable MRI scanner by Hyperfine Research Inc. The potentially game-changing technology was introduced in October 2019 at the American College of Emergency Physicians meeting in Denver.

Over the past several decades, MRI has emerged as a gold standard in biomedical imaging, allowing imaging of structures and even processes in the human body that would have been unimaginable 30 years ago, when the first generation of commercial MRI scanners was introduced. But for all the advances in the years since, the underlying technology—and its inherent limitations—have remained largely the same. MRI scanners today still depend on hulking superconducting magnets to produce the high magnetic fields needed for imaging. As a result, the scanners are confined to highly specialized MRI suites in hospitals or to large, tractor trailer-based units parked on hospitals' lawns.

Rosen started thinking about ways to overcome these limitations in the early 2000s, while a postdoctoral fellow in the Harvard-Smithsonian Center for Astrophysics. He dove headlong into the work when he moved the Martinos Center in 2009. Initially, his efforts in this area were aimed at supporting the Department of Defense and combat casualty care to "break the MRI scanner out of its controlled access environment in the radiology suite and reinvent it in a way that could operate in field-forward environments," he says. This early work inspired efforts in his group to innovate in the area of ultra-low-field MRI, where the magnetic field is essentially "turned down" so the scanner is compatible with both mobile operation and undisclosed shrapnel but still could be sensitive enough to make clinically actionable MRI images in short scan times.

Above: Mass General is now using the portable MRI scanner in the clinic. Shown here with the system are the Center's Matt Rosen and Mass General neurologist Taylor Kimberly. Photo courtesy of Matt Rosen.

Recognizing the potential of portable MRI technology for other point-of-care locations, Rosen co-founded Hyperfine Research with serial entrepreneur Jonathan Rothberg in 2014. Hyperfine subsequently developed its newly introduced bedside MRI scanner, which flips the current paradigm in magnetic resonance imaging by bringing the imaging to the patient. The scanner is not intended to replace high-field MRI, which provides superior resolution and tissue contrast. Rather, the ultra-low-field MRI technology that drives it will make imaging accessible to clinicians and patients in a number of new scenarios.

The unveiling of the bedside MRI scanner in late 2019 followed a successful study of the technology, funded by the American Heart Association, in the Neuro ICU at Yale New Haven Hospital. (Hyperfine is based in Guilford, Conn., not far from New Haven.) Rosen was one of three co-principal investigators of the study, alongside study lead Kevin Sheth from Yale University Department of Neurology and Taylor Kimberly of the MGH Department of Neurology.

Rosen reflects on the synergistic relationships that make possible the sort of innovation seen with the Hyperfine bedside MRI scanner, as well as on the unique environment in the MGH Martinos Center that inspires such fruitful work in developing biomedical imaging technologies.

“This is a truly great example of how basic physics research can create something amazing with the right commercial partner,” he says. “Rothberg and his incredible team at Hyperfine have succeeded in advancing the science and technology as well as taking things to the next level in form factor, cost and performance. Meanwhile, I have been able to lead my academic group into new interesting areas of physics, such as our work with hyperpolarized nanodiamonds and other molecules, quantitative image acquisition strategies for multiparametric contrasts, and more recently all the work we do with machine learning to completely reframe the way raw data is processed into image data.”

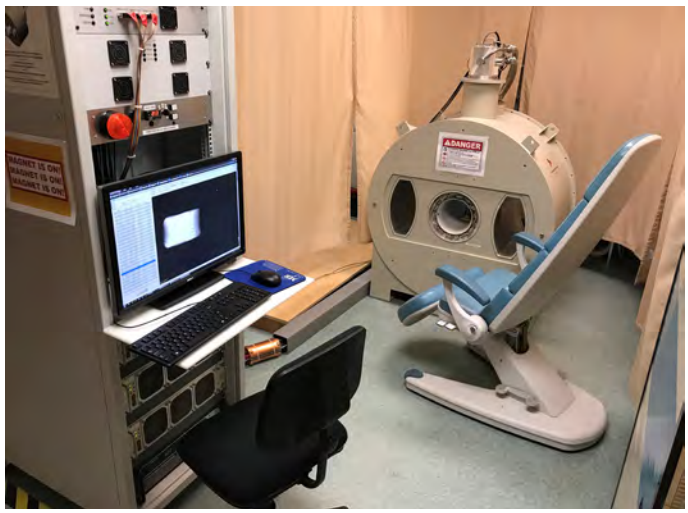
He continues: “Martinos is an incredibly creative place, and very open to the kinds of work that really lead to next-generation successes such as the Hyperfine MRI scanner. It is a wonderful environment and I don’t think this work could have happened without our deep connection to our incredible clinical collaborators.”

Extremity Scanners and ‘Moving’ MRI

MRI scanners rely on superconducting magnets to produce images of the body. However, cooling these magnets to the necessary temperatures involves immersing them in liquid helium baths, a solution both expensive (because, well, it’s helium) and somewhat ungainly.

Now, the Center’s Jerry Ackerman and colleagues are fine-tuning an approach that enables portable MRI by sidestepping this need. Instead of cooling the magnet by submerging it in liquid helium, the new technology, initially developed by the company Superconducting Systems, works by replacing the liquid helium bath with a cryogenic (ultralow temperature) refrigerator.

Conventional scanners already use a similar technology, called cryocooling, but only to meet a relatively small part of the scanners’ cooling needs. “The advance with the Superconducting Systems technology,” Ackerman says, “was coming up with a practical way to provide all of the cooling with a cryocooler.” So rather than relying on a rare and therefore expensive element—helium—cooling of the magnet is powered almost entirely by readily available and comparatively cheap electricity.



As a demonstration of the clinical potential of the technology, Ackerman and colleagues built an “extremity scanner” designed for imaging of patients’ arms and legs. This compact scanner is roughly four feet wide and maybe two feet deep and includes a central bore for the actual imaging and two “dummy” bores added for ergonomic reasons—so the patient can comfortably put both legs in bores rather than inserting only one leg, leaving the other to sit awkwardly outside the scanner.

The extremity scanner is by no means the only potential application of the technology, though. With its compactness, its relatively low purchase cost, its small footprint, and the relatively low expense of cooling the magnet, the Superconducting Systems technology recommends itself for a host of different uses.

Ackerman continues: “The technology doesn’t necessarily allow you to do things you’ve never done before. What it does do is enable you to perform the same tasks you could in a conventional scanner but less expensively and more efficiently. By extension, you may be able to provide imaging services, including high-quality head scans, in places where this previously hasn’t been possible—for example, in resource-limited areas of the developing world.

“Even in places where MRI is already available, the technology provides a less expensive alternative. And because most of your body remains outside the scanner, it’s less intimidating for people with claustrophobia or others who simply don’t like going into a scanner.”

Taking a Stroll With MRI

Not having a large bath of helium suggests another application for the portable MRI technology. In an "interesting, somewhat crazy concept," Ackerman says, he and colleagues are now pursuing development of a moving MRI for applications requiring scanning while the subject is in motion.

He points to vestibular physiology as the primary area of interest in pursuing the technology. Here, scientists study inner ear organs that enable people to sense rotational changes in the head—acting almost like the linear accelerometers behind airbags in cars or rocket guidance systems. Currently, they will put a subject on a moving platform and use infrared sensors, EEG and self-report questionnaires to try to ascertain what is happening in the brain during the movement.

Ackerman understood that functional MRI could provide much of the information the scientists were seeking, if only they could overcome one major obstacle.

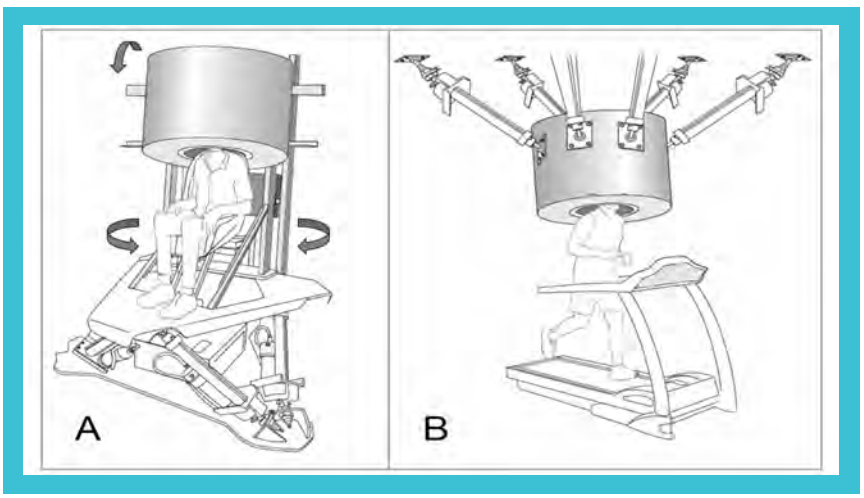
With stationary MRI scanners, any sigificant movements, such as those a subject might make while undergoing physiological testing of the vestibular system, will result in severe motion artifacts in the image—that is, distortions similar to blurring in photography when the subject moves while the camera shutter is open.

To eliminate these effects, Ackerman proposed a new type of moving MRI using the technology behind the extremity scanner to move the magnet along with the head. The liquid helium-free magnet makes this possible. He and colleagues are now in the beginning stages of developing the technology and hope to be able to scale it to humans within a few years.

The proposed system suggests a host of exciting applications. "Once you can use MRI to study a subject moving around, you can imagine learning how the brain moves with respect to the skull," Ackerman says. "My hope is that this will point the way to mapping the mechanical properties of brain tissue in living organisms. This could help with a range of applications, including developing models of traumatic brain injury."

Right: an illustration of the proposed "moving MRI" system

Opposite: The prototype extremity scanner operates at 1.5 Tesla. The next-generation extremity scanner will run at several fields between 0.5 and 1 Tesla.



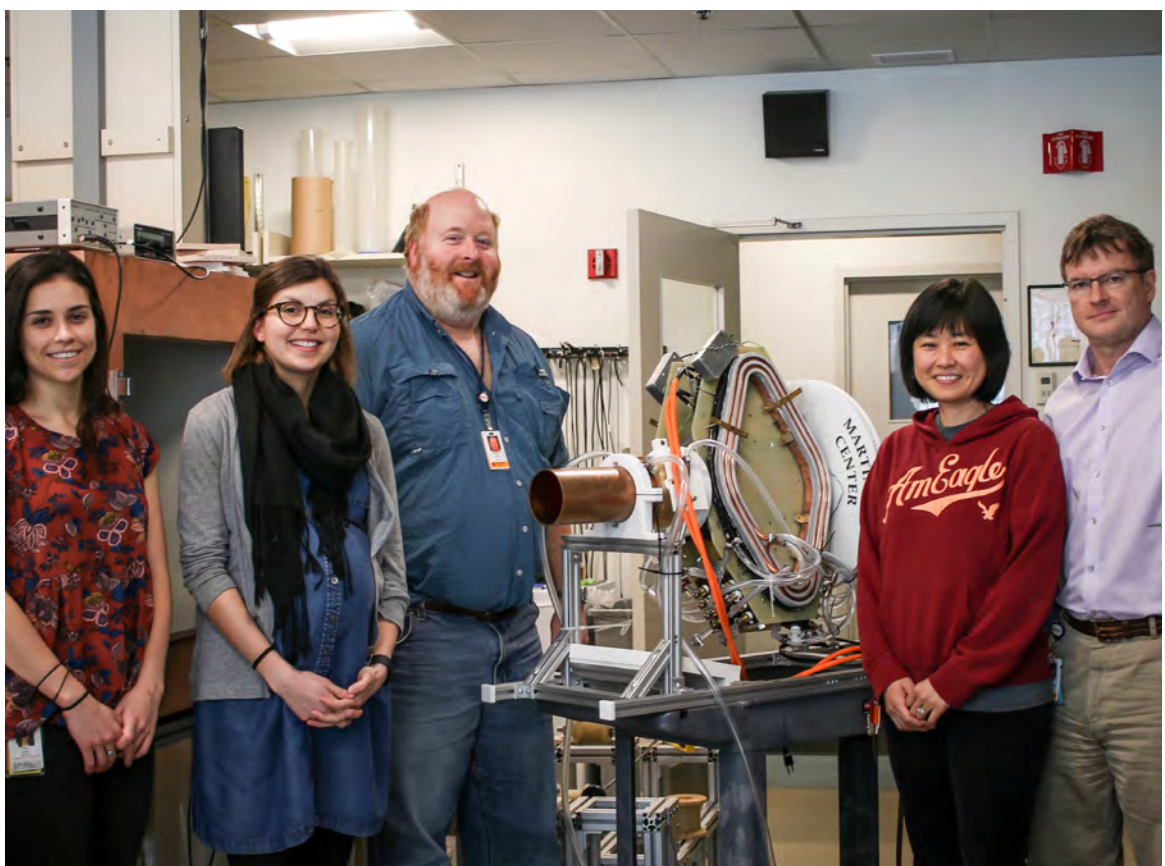
The Road to MPI

Functional MRI has proved a transformative technology, yielding previously unimaginable insights into the workings of the brain. But what if there were another approach, one with dramatically higher sensitivity, that could shed even more light on these mysteries? What might we learn then?

Larry Wald aims to find out.

In late 2017, Wald, the director of the Magnetic Resonance Physics & Instrumentation Group in the Martinos Center, was awarded a grant through the National Institutes of Health's BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies) that will support design and construction of a magnetic particle imaging (MPI) scanner for imaging of the human brain. Once completed and validated, the technology will offer an exciting new means to study activity in the brain. Ultimately, it could replace fMRI as the premier functional neuroimaging tool.

Magnetic particle imaging is not entirely unlike magnetic resonance imaging. Introduced a little more than a decade ago, it uses many of the same principles and shares many of the same technologies as the latter imaging modality. MPI differs in one crucial way, though: it directly detects the magnetization of nanoparticles injected into the body, rather than relying on secondary effects of magnetic resonance relaxation times. Directly imaging the source of contrast like this is what allows for the vastly improved sensitivity.



Members of the MPI group in 2018: Erica Mason, Clarissa Cooley, Larry Wald, Emiri Mandeville and Joe Mandeville. Photo by Caroline Magnain.

Today there are maybe a dozen groups around the world pursuing development of MPI. The researchers in these groups have been focused on a variety of possible applications, including applications in oncology; cell tracking; and cardiovascular, gastrointestinal and lung imaging. Notably, though, with all of the activity surrounding MPI, the researchers have neglected one particular area of interest: that is, the brain.

Wald was struck by this. He watched the groups setting often lofty goals for the technology while studiously avoiding the application directly in front of them. “I thought: ‘Everyone is ignoring the easy stuff,’ ” he says. “If these magnetic particles stay in the blood, and if you then directly detect the particle concentration, you are detecting blood. We have lots of interesting stuff to do with a blood detector in the brain: functional brain imaging!”

Deciding to dig a little deeper, Wald in 2014 applied for and was awarded one of the first BRAIN Initiative grants. With the support of this grant, he and his group set to work assessing the potential of MPI, examining the barriers to its use for neuroimaging in humans and, through simulations, testing the performance of various MPI scanner designs. (An MGH Research Scholar Award, which Wald received the following year, afforded further opportunities to explore the potential of the technology.)

The results of the work were encouraging. Wald and colleagues concluded that a first-generation human-size MPI scanner could offer tenfold higher sensitivity than conventional functional MRI with similar spatial resolution, with the possibility of improvement with further development.

In the wake of the research, they knew that a human-size MPI scanner with the potential to revolutionize neuroimaging was in fact achievable. Now all that remained for them was to make it.

Building a Bigger Mousetrap

The opportunity to construct the scanner came in 2017, when Wald was awarded his second BRAIN Initiative grant. This grant is supporting the construction and validation of an MPI device for use in humans, as outlined during the earlier research. Wald knows there will be challenges to face. “There is currently no human MPI scanner,” he reminds us. “And there is a reason for this: it’s hard.” But he has no doubt that the team he has assembled—which also includes Clarissa Cooley, Ken Kwong, Emiri Mandeville, Joe Mandeville, Erica Mason and Wim Vanduffel—will be able to address the challenges.

What sorts of issues will they need to address? The greatest difficulties may lie in translating the technology for human-size imaging—scaling up the field generation and detection, for example. Wald also anticipates a variety of “industrial type” challenges in designing and building the scanner. Not least: figuring out how to keep a two-ton, water-cooled electromagnet spinning around the subject’s head.

If successful, the new scanner will open up a range of applications for MPI, both in the lab and otherwise.

“We are betting that it will be a valuable tool for neuroscience,” Wald says. “But also, in the clinic, it could monitor for hemorrhage or, with targeted agents, look for tumors. We are hoping to have a solid proof of principle for these at the end of our five-year grant.”

*The (**Nearly**) Lost Art of Scientific Glassblowing*

Scientific glassblowers, like streetcar conductors and silent movie organists, are a vanishing breed.

“There are very few left in the world,” says Matt Rosen, director of the Low-Field Imaging Laboratory at the Martinos Center for Biomedical Imaging. “And even fewer who can manufacture the glass optical pumping cells I use in gas hyperpolarization systems.”

Fortunately, particularly for those who depend on such things, Rosen is working to keep the tradition alive, creating glass equipment for his research and even teaching others the finer points of the practice.

Scientific glassblowing has a long and storied history. Without it we might never have known, for example, Galileo’s thermometer or Edison’s light bulb. But what is it exactly? And how does it differ from, well, regular glassblowing?

Broadly speaking, it is the process of forming molten glass into equipment by blowing short puffs of air into it and shaping it before it cools and hardens. Scientists today use it to make all kinds of apparatus, from beakers and test tubes to very clean ultra-high-vacuum systems.

In many cases glass is the ideal material, Rosen says—not least, in experiments dealing with reactive compounds such as alkali metals.

For more than 20 years Rosen has been using laser optical pumping for hyperpolarization of nuclear spins (in gaseous helium, for example) and this work typically requires an alkali atom as an intermediary.

“These atoms are very reactive,” he says. “In fact, they are explosive in contact with water vapor. So these systems need to be super clean, and made of an alkali-resistant material. Glass is one of the very few materials that have these properties and can handle operation at very high pressure.”

Glassblowing of any sort requires a steady hand and an understanding eye but scientific glassblowing adds another layer of complexity to the kind you might see in crafts fairs or on Home & Garden TV. While the latter generally involves fashioning hanging ornaments, for example, from solid glass rod, the former often relies on hollow glass tubing. And working with hollow tubing, unsurprisingly, can be a great deal more challenging.

Rosen learned the craft when he was a graduate student at the University of Michigan, studying with a master glassblower named Roy Wentz. From Wentz he learned the basics—how to cut, weld, resize and bend tubing, how to make glass-to-metal seals and vacuum pull-offs, and so on—that would help in fabricating the systems he was using in his graduate research.

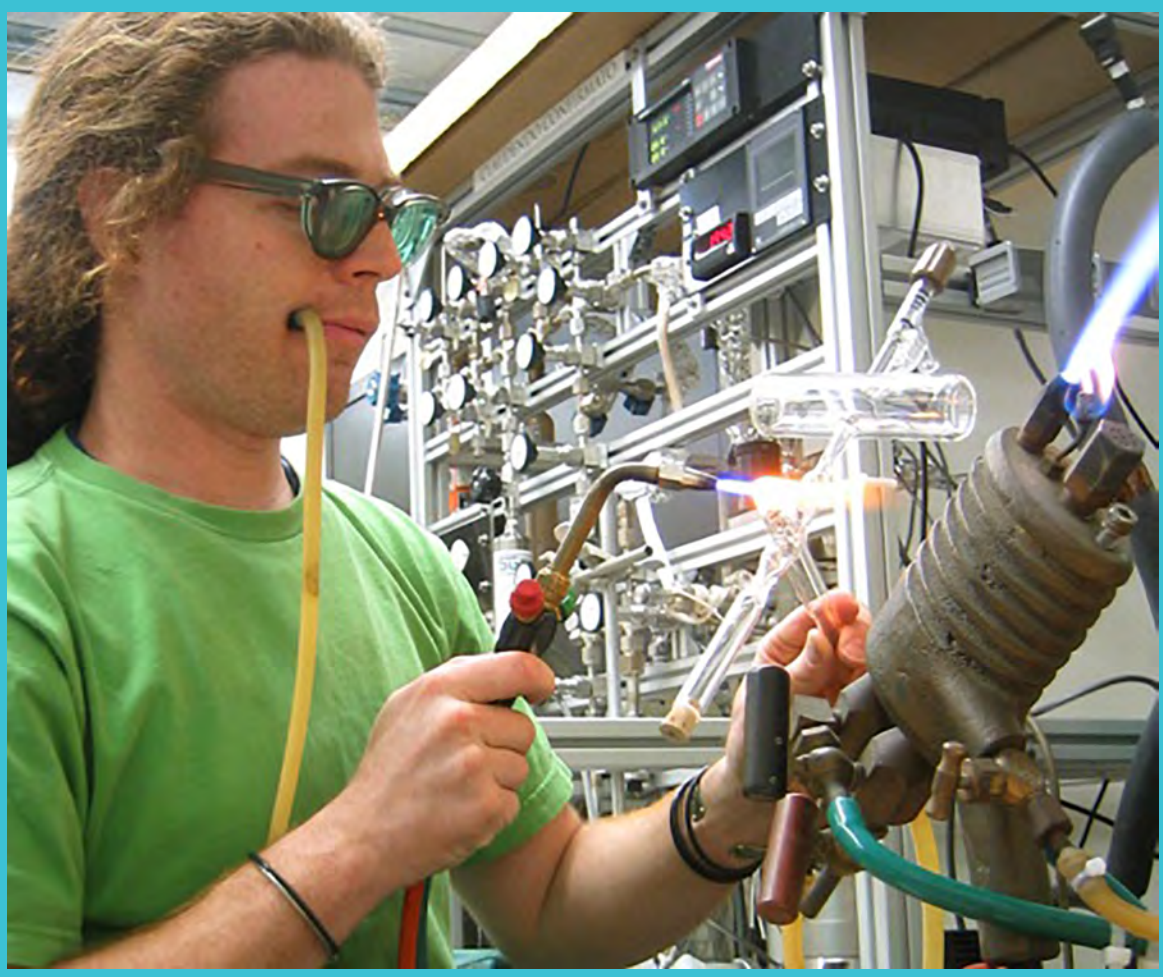
When he arrived at Harvard in 2001, as a postdoctoral fellow in the Harvard-Smithsonian Center for Astrophysics, he found there was no one locally who could help make optical pumping cells and manifolds for his ongoing work. So, armed with his training by the master glassblower, he decided to make them himself.

It wasn't long before students, postdocs and others saw what he was doing and, wanting to learn how they could fashion the glass systems they needed for their own research, started seeking out his help. Before he knew it, he was teaching a scientific glassblowing workshop at Harvard, instructing experimentalists in the atomic physics community about the nearly lost art. As a result, today a new generation of researchers is now carrying the glassblowing torch.

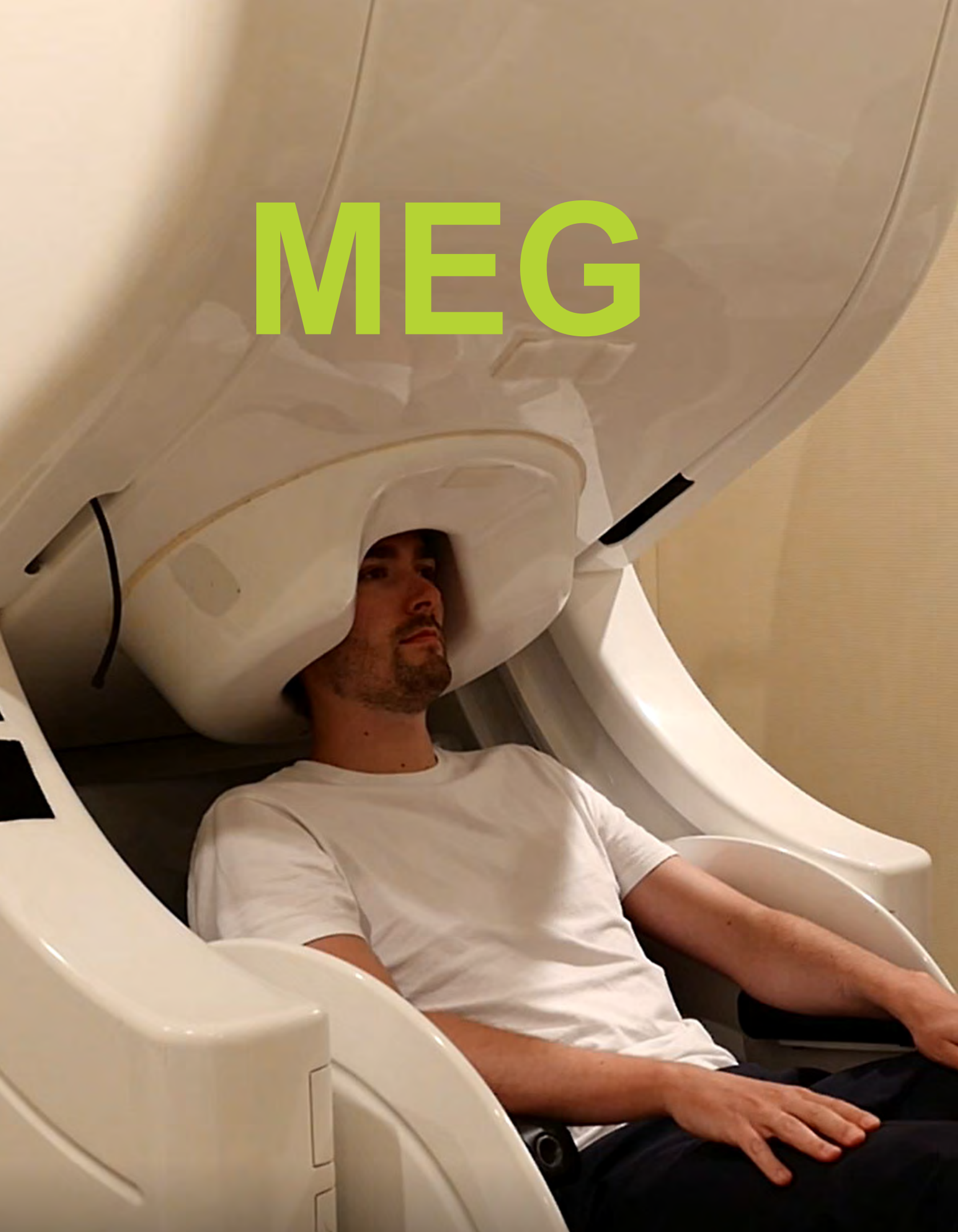
And they are finding it is a very worthwhile endeavor. Scientific glassblowing is challenging and even humbling, Rosen says, but ultimately tremendously satisfying. "It takes endless practice to make things look good. But it is a beautiful skill once you learn it. It is a very creative art form, and also very technically demanding. That is an interesting balance, much like playing a musical instrument."

And like playing an instrument, "mastery takes a lifetime," he says.

Matt Rosen



MEG



For the Martinos Center, the 1990s were largely defined by the ongoing development and refinement of MRI techniques: the application of functional MRI, the introduction of new image analysis tools and the pursuit of higher field strengths. But this was by no means the only area of inquiry in the Center. Especially in the latter part of the decade, Martinos researchers sought to combine functional MRI with other imaging modalities in ways that would provide more robust information than could be acquired with either of the modalities alone. Eventually, the Center would begin to build research programs around the additional technologies. The first of these: magnetoencephalography, or MEG.

The Music of MEG

Previous: photo by Matti Hämäläinen

Below: Matti Hämäläinen (left) plays a duet Opposite: Seppo Ahlfors (rear left) and students during construction of the magnetically shielded room

Every Christmas back home in Finland, the Martinos Center's Matti Hämäläinen gathers with friends for an evening of performing chamber music. He plays both flute and piano on these occasions. In more recent years he has explored the repertoire for "piano four hands" with his former classmate Lauri Malmi, now a professor of computer science at their alma mater, Aalto University (formerly Helsinki University of Technology). Whatever the instrument or configuration of musicians, Hämäläinen appreciates the combination of talent, skill and inter-player cooperation that goes into a successful performance. Not only do you need to play well, you need to play well together. Only then can you make truly beautiful music.

Very much, he says, like doing science at the Martinos Center.

Hämäläinen is director of the David Cohen Magnetoencephalography (MEG) Laboratory at the Martinos Center, working alongside faculty members Steven Stufflebeam, Seppo Ahlfors, David Cohen and Sheraz Khan. Over the past nearly two decades, the researchers have played a crucial role in developing MEG instrumentation, analytical methods and tools, and experimental protocols, and collaborated with others in the Center and elsewhere both in integrating MEG with other imaging modalities and advancing it for a broad range of applications. Together, they have paved the way for MEG to become an important basic research and clinical tool worldwide.

What Exactly Is MEG?

Magnetoencephalography records changes in the very weak magnetic fields surrounding the human head that are caused by electrical activity associated with neuronal currents underlying brain function. The technique offers excellent temporal resolution—on the order of milliseconds—and thus provides a more direct measure of neuronal currents than other imaging modalities, including functional magnetic resonance imaging (fMRI), which derive information about neuronal activity from the much slower neurovascular response.

The technique was introduced more than 50 years ago by MIT researcher David Cohen, who is now a faculty member at the Martinos Center. Cohen developed a way to isolate and record the weak magnetic fields

emanating from the human body by using a magnetically shielded room built around the recording equipment. On New Year's Eve, 1969, using a superconducting quantum interference device (SQUID) developed by researcher James Zimmerman while he was working with the Ford Motor Co., Cohen successfully recorded the biomagnetic signal from Zimmerman's heart. He later applied the technique to the brain, facilitating use of MEG for a range of neuroscience studies.

In the early days of MEG, researchers used either one or several devices called magnetometers to localize electrical activity in the brain. Because these measurements used so few sensors and allowed only small coverage of the brain, researchers had to obtain recordings from multiple locations on the head, making the procedure impractical for routine clinical use. Later, investigators introduced multi-channel MEG systems with enough coverage to localize activity in a registered MRI scan of the brain. In 1992, the first whole-head MEG device, with more than 100 channels, was completed by a team at Helsinki University of Technology—a team that included Matti Hämäläinen. The device was a major breakthrough in the field, opening the door to any number of new types of studies and sparking the imaginations of neuroscience researchers worldwide.

Hämäläinen's accomplishments, both before and after the introduction of the whole-head MEG device, caught the attention of the Martinos Center's Jack Belliveau, who in the mid- to late 1990s was traveling the world seeking out researchers with whom to develop multimodal imaging technologies to delve even deeper into the brain. The pair subsequently launched a fruitful collaboration.

Belliveau was also working with others in the multimodal imaging space: among them, Gregory V. Simpson and his postdoctoral

The MEG group in the early 2000s

fellow Seppo Ahlfors from Albert Einstein College of Medicine, and Risto Ilmoniemi—Ahlfors' PhD advisor—and colleagues from Helsinki University of Technology (Hämäläinen's alma mater) and Helsinki University Hospital.

In about 2000, the Martinos Center decided to launch an MEG program of its own. The first recruits were Ahlfors and neuroscientist and MEG researcher Eric Halgren. Hämäläinen joined in 2001. Cohen was already on board overseeing the construction of a new high-performance magnetically shielded room for the MEG—more than 30 years after he had introduced the modality a couple of miles down the road at MIT.

By 2002, the scanner was up and running and the members of the MEG group were further developing both the hardware and the data analysis tools and collaborating with researchers to apply MEG to a range of different studies. Ahlfors recalls, for example, studies of reading disability in children (Maria Mody and colleagues); studies of the human auditory and multisensory cortex (Belliveau, Jyrki Ahveninen, Iiro Jääskeläinen, Tommi Raij and others); studies of language and memory (Halgren with Ksenija Marinkovic, Anders Dale and others); and studies of obsessive-compulsive disorder (Kristina Ciesielski and colleagues). At the same time, clinical studies of patients with epilepsy were conducted with Steven Stufflebeam and colleagues.

In facilitating such studies over the years, in developing cutting-edge technology and applying it in seemingly countless creative ways, the program has always run like a well-oiled machine, its members working together in perfect tandem.

Or perhaps like a chamber group, playing the music of MEG.

Transcranial Magnetic Stimulation

Work in the Martinos Center has also extended to transcranial magnetic stimulation (TMS), a neuromodulation technique used, for example, to alter neural activity associated with a particular disease and thus potentially change the course of the disease. To date, the most prevalent and perhaps most effective application of the technique has been in the treatment of depression, especially in cases where other therapies have not worked.

The TMS effort in the Center was established in 2006 by researcher Tommi Raij, who was working with Jack Belliveau on several of his many multimodal imaging projects. Raij and colleagues did pioneering work, both in developing the technique itself and in identifying and establishing some of its earliest potential applications.

The cutting-edge research with TMS continued after Raij left the Center in 2014 and researcher Aapo Nummenmaa took the reins of the project. In his work, Nummenmaa has focused in part on improving the precision of the technique. Increased accuracy, Nummenmaa says, will yield greater understandings of the areas of the brain undergoing stimulation and thus could help boost the efficacy of TMS, for both basic science and clinical applications.

On November 30, 2018, the Martinos Center celebrated two landmark events for its MEG program: MEG Core director Matti Hämäläinen's promotion to full professor of radiology at Harvard Medical School and the renaming of the Center's MEG facility in honor of David Cohen, the Martinos faculty member and "father of MEG."

Opposite: David Cohen (left) and Matti Hämäläinen. Photo courtesy of Dimitrios Pantazis.

Above: Photos courtesy of MGH Photo (top) and Maria Mody (bottom)

Photos courtesy of Gary Boas (above, top); Shasha Li (above, bottom); Dimitrios Pantazis (opposite, both top and bottom)


Access Under MR Supervision
David Cohen
MEG Laboratory


MEG Environment:
Access Under MR
1.150
The David Cohen
MEG Laboratory
SEPPO
AHLFORS PhD

Improving Communication Skills in Autism

Recent years have seen improved understandings of the relationship between motor skills and the development of language, particularly in autism spectrum disorder (ASD). Given the core deficit in verbal communication in children and adults on the spectrum, the insights researchers have gained could, in time, aid them in better expressing themselves.

Using MEG, Maria Mody, principal investigator of the Martinos Center's Developmental Language and Reading Research Laboratory, has highlighted one of the ways in which this could happen.

Circumventing Motor Deficits Can Help with Expression

Communication—whether spoken, written or signed—entails the planning and execution of gestures, which of course rely on motor skills. Not surprisingly, if speech gestures are difficult for a person, so too will be language.

"However," says Mody, "what is becoming increasingly evident is that, despite their difficulties with speech, some individuals on the autism spectrum are capable of expressing themselves independently using either a tablet or an AAC ('augmentative and alternative communication') device."

Maria Mody

This makes sense, she says, as manually selecting words and pictures on a device is easier than producing speech. Using a device involves only simple and cognitively less demanding motor gestures: namely, pointing or pressing a button. Speech, in contrast, requires rapid and carefully orchestrated movements of the tongue, lips, larynx and more.

In 2017, Mody and colleagues set out to explore the potential benefits of using tablets or other devices as an alternative to spoken language in minimally verbal adults with autism. Using MEG during a simple motor task (pushing a button), they found significant differences in the supplementary motor area of the cortex between the subjects with autism and age-matched controls: an exciting result, Mody says, as it provided neurophysiological evidence of an underlying deficit in motor control in this population.

Mody believes that nurturing the development of literacy skills in people with autism may, in time, stimulate improvements in their speech capabilities.

“After all,” she says, “speech and print are flip sides of the same coin; reading co-opted spoken language areas in the brain. If we understand the cognitive capacities and sensorimotor capacities of individuals with ASD, we can build an intervention that allows them to use the pathways that are more comfortable for them.”

Motor deficits aren’t the only impairments contributing to the difficulties with verbal interactions. Oftentimes people with autism also have social communication deficits, which can make verbal exchanges especially challenging.

In fact, these social deficits can be the result of motor impairment. In the earliest months of life, motor skills facilitate vocal imitation and the mimicking of facial expressions as infants engage their parents or caregivers. In doing so they open the door to social reciprocity and interpersonal interaction—cornerstones of what we think of as social skills. Motor deficits can lead to disruption of those early activities, with cascading effects with respect to the development of social communication abilities.

And this isn’t the only obstacle individuals on the spectrum can face. In another 2017 study, the Martinos Center’s Nouchine Hadjikhani and colleagues looked at the tendency to avoid eye contact in people with autism and found that this is not simply due to a lack of engagement, as many had previously thought. Instead, the researchers showed, eye contact can cause overactivation in a particular part of the brain, so their avoiding eye contact is a way to mitigate this uncomfortable over-arousal.

All of which underscores the possible benefits of AAC and print communication for people with autism, Mody says.

“Because individuals on the spectrum have social communications deficits, verbal interactions can be particularly challenging. As such, print provides them a means to express themselves, while circumventing the social communication problems. Literary-focused intervention has the potential to open up new opportunities for expression and self-reliance as they seek to navigate society given their social and verbal limitations.”

Diagnosing and Treating Epilepsy, Other Disorders

Originally used only for research purposes, magnetoencephalography has, in more recent decades, been introduced into clinical care. With applications in epilepsy already benefiting from its use, and still others on the horizon, the technique is helping advance diagnosis and treatment for a range of diseases, disorders and injuries.

The Martinos Center for Biomedical Imaging offers a clinical MEG service to aid in many of these applications. Led by Steven Stufflebeam, medical director for the Martinos Center, it is the only such service in the Northeast. Its most common application is presurgical evaluation and surgical planning in epilepsy patients: localizing epileptic discharges, determining the language-dominant hemisphere and mapping the eloquent cortex. Here, MEG is often combined with MR imaging, which provides structural guidance for the analysis of the MEG data.

By localizing epileptic discharges, MEG helps identify the sources of seizures through analyses of spontaneous brain activity. Measurements are typically performed during rest using whole-head MEG combined with electroencephalography (EEG), a closely related method that provides complementary information about electrical activity in the brain.

After a decision is made to remove the tumor or other lesion responsible for the seizures, MEG can map the eloquent cortex to help avoid functional deficits as a result of surgery. A critical use is determining the language-dominant hemisphere of the brain. This measurement is particularly important for patients scheduled for a left anterior temporal lobectomy (ATL), a widely used procedure for medial temporal lobe epilepsy. Such lateralization is vital for preserving quality of life as verbal memory and language can be impacted by ATL.

Beyond determining the language-dominant hemisphere, clinicians use MEG to delineate the language cortex and other areas of the eloquent cortex (for example, motor and visual) to outline the regions they want to avoid during resection. The technique can localize both receptive and productive areas of language with high temporal resolution; the measurements are often combined with fMRI data to improve spatial resolution. Studies have shown that presurgical evaluation of epilepsy patients with MEG leads to improved outcomes in these patients, with greater surgical success and fewer postsurgical deficits.

Emerging Applications: Schizophrenia, Autism and Traumatic Brain Injury

While presurgical evaluation in epilepsy is the primary clinical application of MEG, new applications are emerging. One application is aiding in the diagnosis of schizophrenia. Historically, diagnosis of schizophrenia was based on clinical assessment and evaluation of patients' self-reported experiences, especially as their symptoms become more evident over time. Seeking a more objective measure, clinicians turned to MEG to identify biological markers of the disease such as differences in functional network activity. In recent years, they have explored multimodal imaging, including MEG and fMRI, to provide important classification information that may not be accessible with just one modality.

Applications in autism and traumatic brain injury (TBI) are also on the horizon. While researchers have long known that autism has a neurodevelopmental basis, the actual pathology has remained elusive. Now, using MEG, they have identified electrophysiological biomarkers of the disorder, which can help diagnosis and prognosis as well as contribute to the development of pharmaceuticals for treatment. Similarly, while diagnosis of TBI has been challenging, MEG has shown promise for detecting differences in electrophysiological signals between healthy subjects and TBI patients in both military and civilian settings. at the same time, MEG is widely used for neuroscience studies seeking to understand the sequalae of TBI.

Left: Steven Stufflebeam

MEG Method May Hold the Secret to Baldness

Hair diseases and baldness are often linked to the activity of hair follicles. in 2019, Martinos researchers reported in the journal *Scientific Reports* an MEG-based method that allows them to examine this activity. In doing so, the approach could help advance a range of applications, including testing the effects of different treatments on hair growth.

The method takes advantage of the observation that pressing lightly on an area of the scalp containing healthy hair follicles produces a steady magnetic field that can be measured with MEG. By repeating the measurements in multiple locations on the scalp, the researchers can create in individual subjects maps of follicle-related electrical activity.

In the *Scientific Reports* study, the Martinos team produced such maps for 15 healthy control participants and two participants with a hair loss condition called alopecia. The maps for participants with alopecia showed no electrical activity in locations where pressure was applied. In contrast, the maps for other participants showed electrical activity of varying degrees.

Above: Sheraz Khan

This finding is important because follicles' electrical activity can only be observed magnetically; surface voltages are too difficult to measure.

"What we have here is a quantitative way to see the activity of hair follicles, and as far as we can tell, this is the first time electrical activity has been measured from the follicles themselves," says senior author David Cohen.

Lead author Sheraz Khan adds: "This method provides a quantitative and objective assessment for the health of hair follicles and can be used as a biomarker for the treatment of hair loss."


CP3 43
C5 31
T7 30
P5 53
PO3 87
PO7 86

3 Things You Didn't Know About **David Cohen** *and MEG*

In 2018, the Martinos Center dedicated its advanced magnetoencephalography facility as the David Cohen MEG Laboratory. David Cohen, the inventor of MEG, a leader in the field of biomagnetism for more than 50 years, and a Martinos Center faculty member who was instrumental in building and developing the facility in question, was on hand to help launch the rechristened lab.

In anticipation of the event, we delved into Cohen's long, storied life and career, from his early days devising ways to measure the very weak magnetic fields originating in the human body to some of his equally impressive 21st-century accomplishments. Here are three of the many things we learned.

In another life, Cohen was actually a "really strong magnetic field" kind of guy

In 1957, two years after earning his PhD, Cohen joined the Argonne National Laboratory in Illinois, where he worked as an accelerator physicist specializing in strong magnetic fields. While he enjoyed the work, his thoughts kept drifting to another topic. "I have a fancy job doing high-energy physics and working with big magnets," he says, looking back on those early days. "And for some reason I'm thinking, year in and year out, wouldn't it be fun to measure very weak magnetic fields"—that is, the kind of fields generated by the human body.

In 1963 a group in Syracuse reported the first measurement of the magnetic field of the human heart. In order to minimize the magnetic disturbances associated with everyday urban life, they had performed the experiments in the middle of a field, far away from the hustle and bustle of the city. Cohen had another idea: instead of escaping background noise, block it out by building a magnetically shielded room.

MEG launched on New Year's Eve 1969 with a prominent researcher stripped down to his shorts

What better way to celebrate the holiday, right?

By late 1969, Cohen had built a large, shielded room at the Francis Bitter lab at MIT—a pod-like structure with a stairway descending from an open panel on the side, it looked like something out of a science fiction movie—and was using it to measure the weak magnetic fields emanating from the human body. But the detector he had developed wasn't yielding enough signal. To address this problem, he reached out to researcher James Zimmerman, who had helped introduce the superconducting quantum interference device (SQUID) some five years before. This device could measure extremely weak magnetic fields. It had not yet been shown to work in humans but only because no one had tried.

"Jim arrived near the end of December, complete with SQUID, electronics and nitrogen-shielded glass dewar," Cohen says. "It took a few days to set up his system in the room, and for Jim to tune the SQUID. Finally, we were ready to look at the easiest biomagnetic signal: the signal from the human heart, because it was large and regular. Jim stripped down to his shorts, and it was his heart that we first looked at."

Cohen has been recognized by Guinness World Records. Twice.

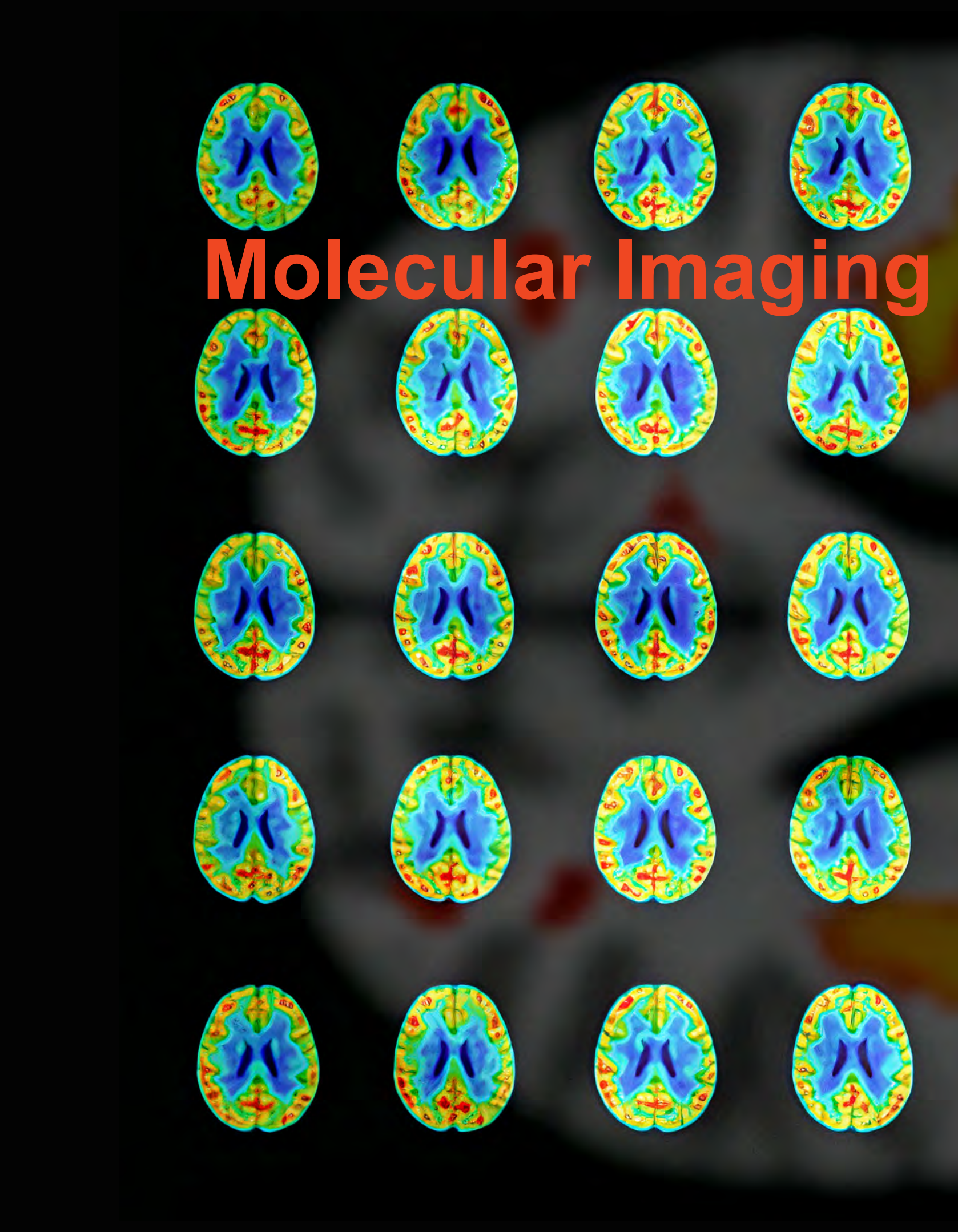
Though he "retired" in 1993, he has remained a highly productive investigator in the years

since: as a visiting scientist at MIT and, since 2001, an associate professor of radiology at the Martinos Center. Today Cohen can look back on a lifetime of accomplishments. Many of these are now inscribed in the dusty, leather-bound tomes of the history of science. But there's one accomplishment that has largely escaped the attention of the academic community.

In May 2013, Cohen and Sheraz Khan, a Center investigator who works closely with Cohen, reported the magnetic field of the wall of the shielded room in the Center's MEG facility: an almost unimaginable 0.5 femtotesla/√Hz. (In recording biomagnetism, researchers want to account for any other sources of magnetism that might impact the measurement.) The paper caught the attention of the reference book and website *Guinness World Records*, which certified the finding as the "weakest magnetic field measured"—a record that still stands today.

This wasn't the first time Cohen had made the pages of *Guinness World Records*. In the 1980s the book recognized him for what was then the weakest magnetic field ever measured: a field of 8 x 10-15 tesla, measured in the shielded room at the Francis Bitter lab at MIT. It was quite the accomplishment, recording such a weak signal. But of course, in 2013, as so many times over the six decades plus of his research career, David Cohen outdid himself.

Left: David Cohen and his magnetically shielded room in 1969


Molecular Imaging

One of the Martinos Center's greatest strengths has always been its embrace of all stops along the translational medicine pathway, from basic science research to implementation of new tools for real-world clinical care. In the early 2000s, its continuing goal of bringing together investigators who bridge the many areas of translational medicine dovetailed with the emergence of the field of molecular imaging, which sought to advance applications related to the diagnosis and treatment of disease, as well as to drug development and monitoring of treatment efficacy, by combining state-of-the-art imaging technologies with molecular biology to visualize and measure the underlying mechanisms of disease.

The molecular imaging program at the Martinos Center was consolidated in 2008 and 2009 with the recruitment of leading experts in the field, the opening of new, dedicated space in Building 75 in the Charlestown Navy Yard and installation of the first simultaneous PET-MRI scanner the US. In the decade-plus since, the program has grown into one of the strongest and most productive molecular imaging efforts anywhere.

Imaging at the Molecular Level

In the fall of 2018, the Martinos Center celebrated ten years of growth that saw its molecular imaging effort emerge as one of the premier molecular imaging programs in the world.

While there had always been a molecular imaging effort of some kind at the Center, it kicked into high gear in 2008 when the Center expanded into Building 75 in the Charlestown Navy Yard—across the street from its original home in Building 149. Following the work of Peter Caravan, whom the Center had hired the year before to help establish a molecular imaging program, the new space offered a large chemistry and biology wet lab footprint, and thus opened the door for researchers to pursue a wide array of molecular imaging studies.

New lab space was just one part of the equation, though. Plans for the new program also included a significant investment in new technologies and other facilities. Ciprian Catana, a pioneer in simultaneous PET-MRI, was recruited at approximately the same time as Caravan. Also in 2008, he oversaw installation of a Siemens BrainPET scanner: the first commercial simultaneous PET-MRI scanner in the US. This was followed, in 2010, by the siting of a Siemens mMR whole-body simultaneous PET-MRI scanner. Jacob Hooker joined the Center a few years after Caravan and Catana and was instrumental in setting up a state-of-the-art PET radiotracer effort, including a cyclotron and radiochemistry production facility enabling the researchers to prepare PET radiotracers for human research studies.

The program continued to grow and today there are some 25 faculty at the Martinos Center who identify with molecular imaging, working with some of the most advanced technology in the field to address a host of biomedical questions.

A Consequential First Decade

Molecular imaging groups in the Center have made significant strides in the years since the program got its start, on a number of fronts. The Caravan Lab, for example, has successfully developed MRI and PET probes for the imaging of fibrosis, and reported a non-gadolinium MRI contrast agent to sidestep the possibility of safety issues with gadolinium-based probes. The Hooker Lab, meanwhile, discovered and introduced a PET tracer called Martinostat that enables, for the first time, imaging of epigenetic changes in the body. The tracer is now widely used by research groups around the world for clinical studies of diseases including cancer, schizophrenia and Alzheimer's disease.

Zdravka Medarova and colleagues have explored use of nanoparticles as a "theranostics" platform for a range of cancer models, demonstrating that delivery of the nanoparticles can shrink primary tumors and prevent metastasis. Also, Chongzhao Ran's group has successfully introduced a number of near-infrared fluorescence (NIRF) imaging probes for *in vivo* detection of amyloid beta in models of Alzheimer's disease. More recently, they have shown they can detect amyloid beta species in the eyes, pointing up the possibility of fast, inexpensive screening of Alzheimer's patients in the future.

Several cutting-edge optical technologies have helped to advance molecular imaging investigations in the Center. Anand Kumar's group has been developing new tools for *in vivo* optical molecular imaging: enabling imaging of a host of disease models using time-domain technology and exploiting fluorescence lifetime contrast to track multiple disease components simultaneously. Further, Sava Sakadžić and Abbas Yaseen have pioneered microscopy-based technologies to explore brain function and energy metabolism at the microscopic scale in living brains of preclinical disease models, while Maria Angela Franceschini, Bin Deng and Stefan Carp have spearheaded the development of novel translatable technologies for measuring blood flow and oxygenation in clinical studies.

The availability of combined PET-MRI in the Center has sparked a number of innovations in molecular imaging. Christin Sander and colleagues have used combined functional imaging to demonstrate neurovascular coupling to receptor occupancy, for instance, and furthermore shown that combined dynamic evaluation of PET and fMRI signals can lead to discovery of new biomarkers—for example, for measurement of receptor internalization. Other studies by Martinos investigators have used novel PET radiotracers to study molecular pathways or targets of clinical disease. Not least of these are studies of pain by Marco Loggia and of alcohol use disorder by Changning Wang.

Just down the hall, Larry Wald and his group are developing magnetic particle imaging (MPI) for neuroimaging applications. MPI is similar to MRI—it uses many of the same principles and shares many of the same technologies—but instead of measuring secondary effects of magnetic resonance relaxation times it directly detects the magnetization of nanoparticles injected into the body, providing vastly improved sensitivity over the latter technique. Perhaps a dozen other groups around the world are developing MPI technologies but Wald was the first to recognize the potential of the technique for applications in the brain.

Background image on previous spread by Jacob Hooker
Opposite: photo by Rosario Marañon

Martinos Center researchers are now building a 7T MR-compatible next-generation PET brain scanner. This scanner will offer dramatically improved temporal and spatial resolution over the current state of the art, which they also had a hand in developing.

In 2008, when human PET-MR imaging was still in its infancy, the Martinos Center sited one of the first MR-compatible PET prototypes—BrainPET—developed by industry partner Siemens Healthineers. By enabling simultaneous PET-MR imaging, the BrainPET opened up applications that would have been difficult if not impossible prior to its introduction. However, because of engineering constraints, it offered lower-than-hoped-for performance, which negatively impacted the image quality achievable with the system. One of the consequences of this difficulty: the scanner does not have time-of-flight capabilities, which has become widely available in PET.

In the decade-plus since the introduction of BrainPET, Center researchers have worked closely with Siemens engineers to address the remaining technical challenges and perform proof-of-principle PET-MR studies demonstrating the potential of the enhanced imaging modality. They started seeking funding to incorporate fixes into the existing system but soon decided to take another approach.

“At some point we said, let’s really go wild and propose to build the best scanner we can build,” says Ciprian Catana, director of the Integrated PET-MR Imaging Laboratory at the Center, “to really push the sensitivity and the temporal resolution in an effort to bring the PET measurements closer to the temporal resolution of the fMRI measurements. Really, this is the motivation underlying our efforts: to achieve high enough temporal resolution to be able to obtain PET measures of dynamic neurochemical processes.”

Defining the State of the Art

In October 2018, the Center celebrated its longstanding molecular imaging program with a symposium highlighting its investigators’ multifaceted research. For Caravan, the symposium drove home how much the molecular imaging effort had grown since he had joined the Center some eleven years before.

“What really stood out was the breadth of work in molecular imaging at Martinos,” he says. The 15 presentations covered optical, PET, MR, magnetic particle and molecular imaging, as well as image-guided therapy, and the range of application areas was similarly diverse. “We heard talks about the use of molecular imaging in immunotherapy and other cancer applications, in Alzheimer’s and other neurodegenerative diseases, in neuropathic pain, in fundamental neuroscience, in cardiovascular disease, in chronic liver disease and in idiopathic pulmonary fibrosis.”

The presentations also emphasized the many innovations in radiochemistry—in molecular probe development, in hardware, and in image analysis and data modeling techniques—to have come out of the Center over the previous decade. “Did you know that four novel PET tracers have been invented and had first-in-human studies performed at the Martinos Center?” Caravan says. “And the innovations in molecular imaging, and their many contributions to the advancement of care, just keep coming.”

Advancing PET Imaging with Quantitative Methods

Senior faculty member Julie Price brings to the Martinos community a wealth of experience with quantitative positron emission tomography (PET). In a recent conversation she described her work and how it can benefit applications both in the lab and in the clinic.

What is quantitative PET?

PET is an *in vivo* imaging modality that detects positron-emitting radiotracers with high detection sensitivity (nanomolar concentrations). When I say quantitative PET, I mean that we study the dynamics of the PET radiotracer *in vivo* to obtain absolute measurement of functional processes: the binding capacity of neuroreceptors, glucose metabolism, blood flow, enzyme activity and more. We use pharmacokinetic modeling methods to do this.

Why is this important?

When you are developing a new radiotracer, for example, you want to make sure that your PET measurements are valid. Specificity and sensitivity studies help to ensure this (e.g., the radiotracer is binding to the receptor/target of interest and a measured change in the PET outcome is in fact reflective of change in the target). Validation studies can be done *in vitro* and in animals but must also be done in humans. PET pharmacokinetic modeling helps us to do this.

Above: Julie Price. Photo by Caroline Magnain.

Opposite: Ciprian Catana

Where has the technique proved especially helpful?

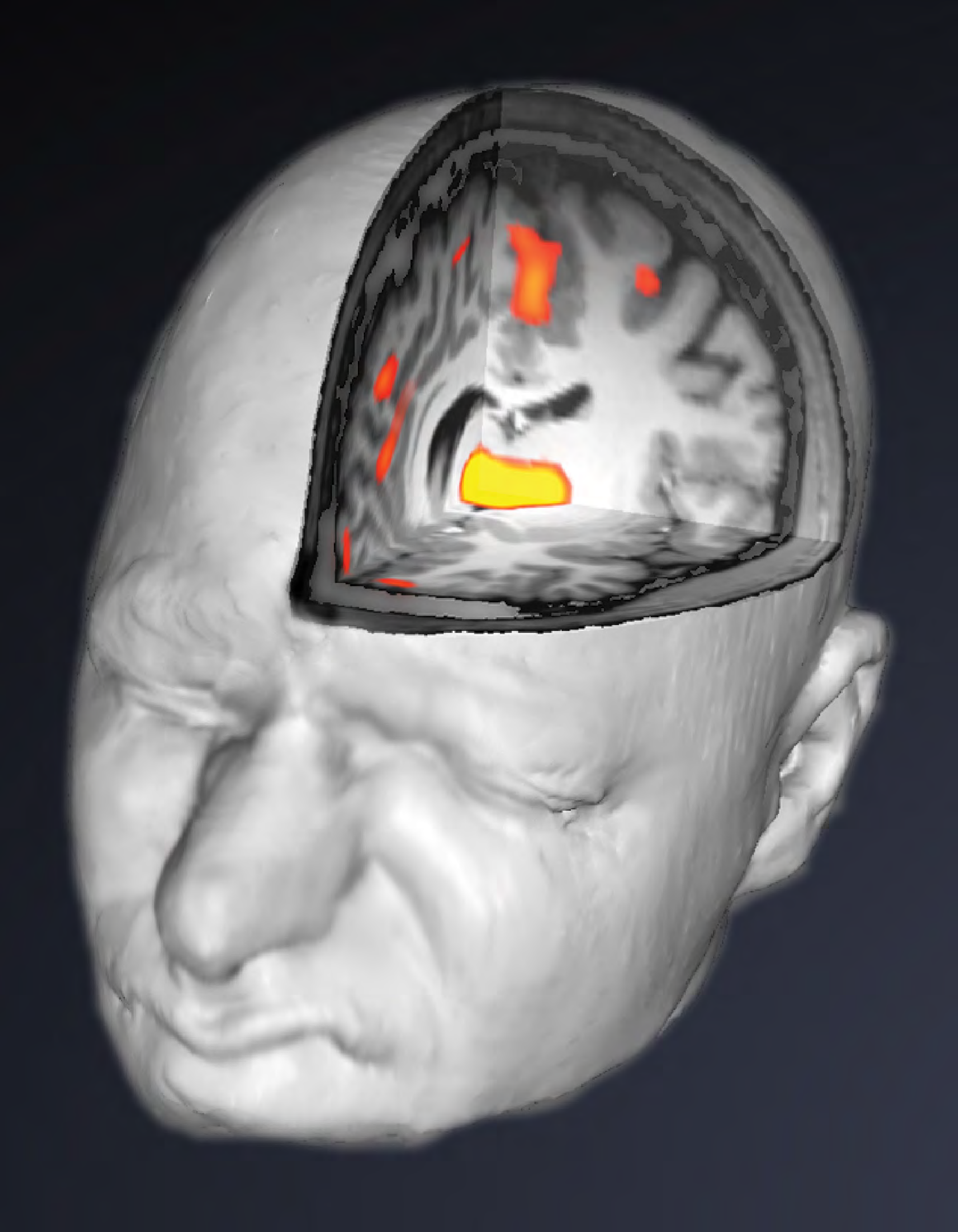
The validation of amyloid-beta plaque tracers included quantitative PET modeling studies that provided a firm basis for routine PET amyloid imaging in Alzheimer's disease (AD). This fueled a new era of AD imaging research and diagnostic criteria for AD were revised to incorporate the use of neuroimaging biomarkers. The whole idea is to detect as early as possible those individuals who might be on the path for AD neurodegeneration and identify those who would most benefit from therapeutic intervention.

Left: Marco Loggia

The Center's Marco Loggia and his group focus on investigations of brain mechanisms underlying the experience of pain in humans, particularly on the study of changes in the brain in patients suffering from chronic pain conditions.

For example, in a 2020 paper in *Brain, Behavior, and Immunity*, they reported widespread inflammation in the brains of veterans diagnosed with Gulf War Illness (GWI). Their findings, obtained with the imaging modalities MRI and PET, could help in identifying and developing therapies for people with GWI as well as other chronic conditions linked to neuroinflammation.

The image to the right is a graphical depiction of "pain in the brain": a structural MRI image of a model (not a patient) affecting an expression of pain with PET data (the colored "blobs") reflecting brain inflammation in patients suffering from chronic pain.



Background: Bo Zhu

Moving Beyond Biopsy for Liver Fibrosis

Chronic liver disease is a growing health concern in the US and around the world, with links to alcoholism, diabetes and even obesity. One of the early manifestations of the disease is fibrosis, an excessive buildup of scar tissue that results from repeated injury to the liver. While its effects can be halted or even reversed if caught early enough, fibrosis can also cause considerable damage, with sometimes devastating outcomes. Untreated, liver fibrosis can progress to cirrhosis, the twelfth leading cause of death in the US; to primary liver cancer; or to liver organ failure.

In 2017, a team of investigators at the Martinos Center described a novel means of detecting and staging liver fibrosis that could yield important advances in how we manage chronic liver disease. They reported the new imaging approach in the journal *Hepatology*.

“We combined two imaging techniques that measure different biophysical properties of liver fibrosis—tissue stiffness and collagen content—to stage the severity of fibrotic progression,” says Bo Zhu, first author of the *Hepatology* paper. “This allows us to take advantage of the strengths of both while also overcoming their respective limitations. The robustness of the combined approach can prove especially important in the clinic, where we rarely know noninvasively the extent to which the disease has progressed, or even regressed in the case of anti-fibrotic treatment.”

At the time of the study, Zhu was a student working in the Caravan Lab in the Center. Today, he is a postdoctoral fellow in Matthew Rosen’s Low-Field Imaging Lab, also in the Center, developing neural network-based image reconstruction techniques.

Currently, biopsy is the gold standard in detecting and staging fibrosis. But this solution is in many ways limited. It suffers sampling error, since it only measures 1/50,000th of the entire liver, which is not necessarily representative of the rest of the organ. And because it is an invasive procedure there is always a risk of complications. Indeed, as many as five percent of biopsy cases result in hospitalization. For these reasons, noninvasive methods that can image the entire liver, repeatedly with little or no chance of complications, would be of tremendous value in the clinic.

Zhu and colleagues looked at two such methods. First was magnetic resonance elastography (MRE). Researchers have focused increasing attention on this technique because of its ability to assess liver fibrosis by imaging the stiffness of the tissue. MRE can reliably stage advanced fibrosis as this is when the tissue stiffens the most. But it is less effective at detection and staging of early fibrosis, when interventions could still stem or even reverse the progression of fibrosis.

This is where the second approach comes in. In more recent years, Peter Caravan’s group in the Center has developed a gadolinium-based MR contrast agent, EP-3533, that can target Type I collagen fibers; Caravan is a senior faculty member in the Center and senior author of the *Hepatology* paper. How can this help in imaging liver fibrosis? Collagen fibers make up much of the excess connective tissue deposited by fibrosis, so imaging the collagen itself means researchers and clinicians can more directly probe the molecular mechanisms of fibrosis. This in turns allows them to detect fibrosis in its earlier stages.

The researchers initially set out simply to compare and contrast the effectiveness of the two methods but soon realized they could take advantage of their complementary

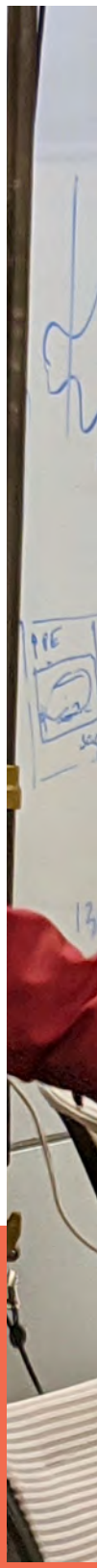
capabilities—collagen imaging was most useful in distinguishing early fibrosis; MRE, in distinguishing advanced fibrosis—to come up with a better means of staging liver disease. “Our findings allowed us to develop a composite fibrosis staging metric, utilizing data from both techniques, obtained in a single imaging exam, which demonstrated superior discrimination across all stages of fibrosis progression,” Zhu says.

Because of its potential for advancing the detection and staging of liver fibrosis—an important clinical need—the researchers next began to explore the possibility of developing the combined approach for use in clinical settings. MRE has already received FDA approval so the primary hurdle to be overcome is approval of the gadolinium-based agent. A company, Collagen Medical, is now pursuing this commercially.

At the same time, the Martinos team is planning further studies with the approach, exploring the ways it can help in other models of liver disease.

“We are now looking in a model of non-alcoholic steatohepatitis, or NASH, which is associated with the epidemics in obesity and diabetes,” Caravan says. “NASH is a cause for great concern these days because it can lead to liver failure, cirrhosis and primary cancer of the liver.”

Above: Peter Caravan



In February 2020, Boston 25 News *interviewed the Center’s Nicole Zurcher about her recent study showing surprisingly low levels of a key protein in the brains of young men with autism spectrum disorder. Photo courtesy of Jacob Hooker.*


Field of View
Readout (RO)
FOV_RO = Base Resolution
Base Resolution = # of samples
along one line in k space
Slice thickness
Scan resolution = FOV_RO
Phase Resolution =
pixels in RO direction
FOV_PE =

Imaging Interactions between Genes and the Environment

When people talk about “nature versus nurture” and how each can shape an individual’s character or behavior, they are really weighing the respective influences of genetics and environment, and ultimately the interactions between the two. Teasing out these interactions has often seemed a difficult if not impossible task. But with the introduction of the breakthrough PET radiotracer [11C] Martinostat, the Center’s Jacob Hooker and colleagues showed that it can be done.

“There’s really been no way to understand the relationship between the genome and the environment at the whole-organ scale, especially as it relates to brain function and changes resulting from the environment,” says Hooker, director of Radiochemistry at the Center and head of the Hooker Research Group. “The idea with Martinostat was to develop an imaging tool that could point us in the direction of that information, or at least answer the question of whether getting there was possible.”

Interactions between the genome and the environment and how they manifest in the occurrence of disease and the development of personality traits, for instance, are known as *epigenetic activity*. Such interactions can take place *in utero* or during early childhood, or later in life as a result of malnutrition, drug abuse or any number of other external factors. Enzymes called histone deacetylases (HDACs) are part of the epigenetic machinery in the body and change the way genetic information is read. Martinostat works by targeting and thus enabling imaging of these enzymes.

Hooker and colleagues introduced the imaging probe with a pair of papers in late 2014. Here, lead authors Changning Wang and Frederick “Al” Schroeder, respectively, described the radiotracer and how it can be used to image HDAC. Next, in a 2016 paper in the journal *Science Translational Medicine*, a team including co-lead authors Hsiao-Ying (Monica) Wey and Tonya Gilbert demonstrated the utility

of Martinostat in healthy human subjects, thus opening the door to further application.

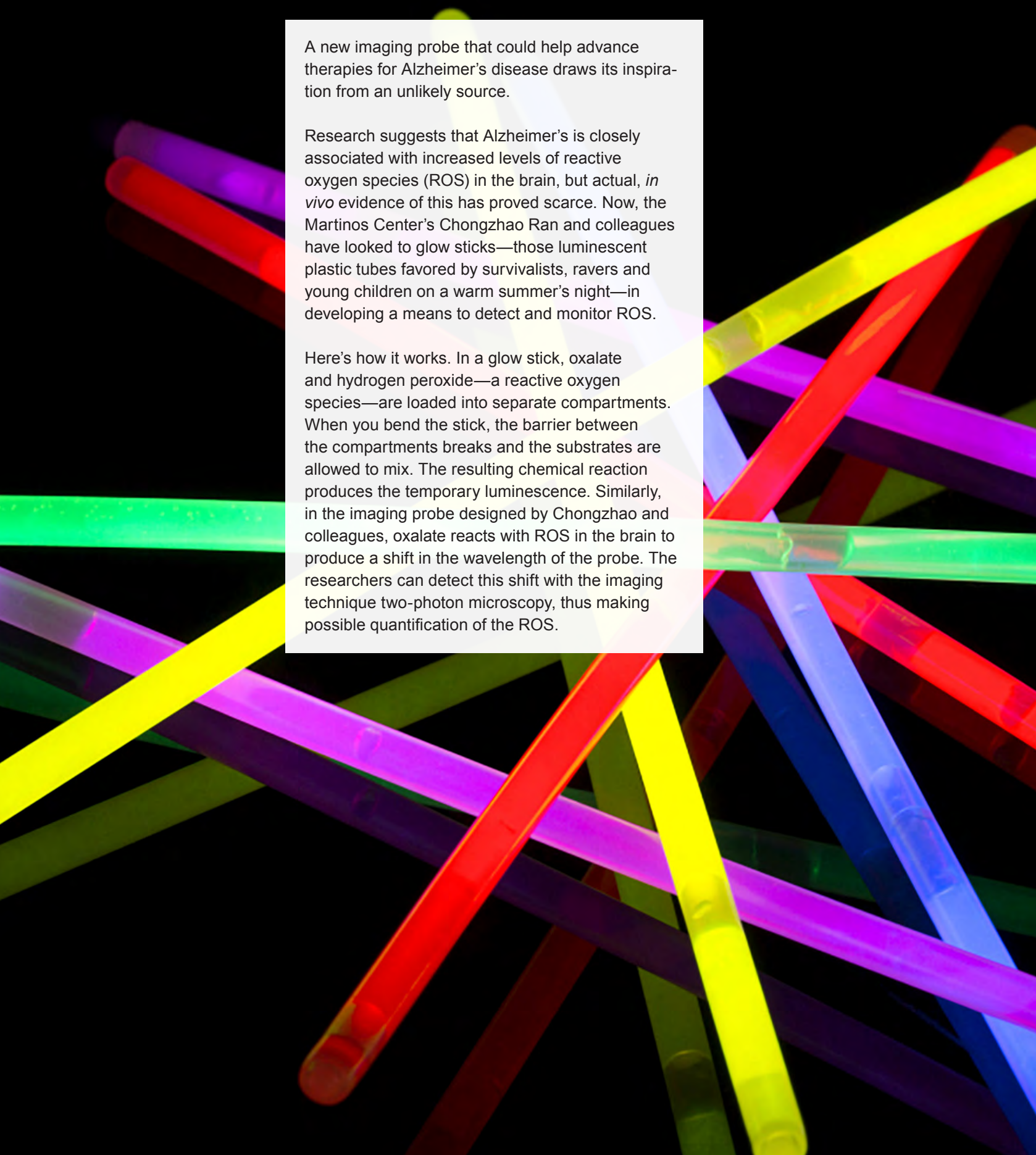
Since publication of the *Science Translational Medicine* paper, the researchers have applied the probe in studies of several neurologic or psychiatric disorders. They have demonstrated HDAC dysregulation in schizophrenia, bipolar disorder and Alzheimer's disease, for example, and are beginning to look at the relationship between the HDAC signal and autism.

At the same time, Hooker and colleagues are helping other institutions get off the ground in adopting the probe themselves. With assistance from the Martinos group, including background information and technical knowhow, researchers at McGill University in Montreal and University of California, San Francisco are now using the probe, while two university medical centers in Asia are either using it or will be soon.

Above: Jacob Hooker

Below: Members of the molecular imaging community at the Martinos Center

The Possible Role of Glow Sticks—Yes, Glow Sticks—in Treating Alzheimer's



A new imaging probe that could help advance therapies for Alzheimer's disease draws its inspiration from an unlikely source.

Research suggests that Alzheimer's is closely associated with increased levels of reactive oxygen species (ROS) in the brain, but actual, *in vivo* evidence of this has proved scarce. Now, the Martinos Center's Chongzhao Ran and colleagues have looked to glow sticks—those luminescent plastic tubes favored by survivalists, ravers and young children on a warm summer's night—in developing a means to detect and monitor ROS.

Here's how it works. In a glow stick, oxalate and hydrogen peroxide—a reactive oxygen species—are loaded into separate compartments. When you bend the stick, the barrier between the compartments breaks and the substrates are allowed to mix. The resulting chemical reaction produces the temporary luminescence. Similarly, in the imaging probe designed by Chongzhao and colleagues, oxalate reacts with ROS in the brain to produce a shift in the wavelength of the probe. The researchers can detect this shift with the imaging technique two-photon microscopy, thus making possible quantification of the ROS.

This opens up a number of opportunities in Alzheimer's research. For example, using the probe could yield reliable information about the changes in ROS concentrations either in the natural progression of the disease or in the wake of treatment. "The data could be very important to determine whether anti-oxidants should be combined with Alzheimer's drugs for treatment in the future," Chongzhao says.

The Martinos-based team reported a study validating the probe in a 2017 paper in *Proceedings of the National Academy of Sciences*. More recently, the researchers have been developing probes with increased sensitivity and longer wavelengths, with the goal of monitoring the changes in ROS concentrations under various treatments with Alzheimer's drugs in preclinical studies.

They have also been looking at the possibility of using the probes directly in humans, taking advantage of ocular imaging and the transparency of the eyes. They have already obtained preliminary data supporting this feasibility.

Right: Chongzhao Ran

The Secret Lives of Martinos Folk

Zeynab Alshelh *fights stereotypes of women in Islam, one karate kick at a time*

Zeynab Alshelh has practiced karate since she was a young child growing up in Australia. For much of the time she has been involved with the sport, she has focused her efforts on the discipline known as shadow fighting, or Kata. Kata comprises a pre-arranged pattern of movements—kicks and punches, sweeps and strikes—that must be carried out with strength and precision, both in the movements themselves and in the transitions between them. Maintaining perfect form is everything. Alshelh says she approaches her Kata practice as if she were creating a work of art—say, writing calligraphy or painting a painting—"that is, as if the smallest movements may have the biggest impact."

Small, bold moves with significant impact is a recurring theme in her life, both in her work and in her karate practice. Her work recently brought her to Boston, where she is a postdoctoral researcher in the Pain and Neuroinflammation Imaging Laboratory at the Martinos Center. Her practice has won her widespread acclaim and no small number of honors and awards, and over the years has also evolved into a form of advocacy against racism and against negative ideologies about women in Islam. A Muslim woman herself, she has encountered a number of these obstacles and responded quietly but decisively: not least, by standing firm in her right to compete in her headscarf. In her insistence on maintaining her Muslim identity while forging a career in the world of karate, she has provided a strong role model for other young women in the sport and helped to dismantle pernicious stereotypes about Islam.

Alshelh began her shadow fighting practice some 15 years ago when her father enrolled her and her brothers in a karate class. She didn't much care for it at first, she says, but she nonetheless wanted to excel at it. Even as a young girl, it seems, commitment and resolve were woven into the fabric of her character. Over the years, especially as she improved, she found she enjoyed karate more and more—to the point where her practice has now become an integral part of her identity.

Competitive sparring, or freestyle fighting, is a relatively recent development for her (she has regularly participated—and placed—in Kata competitions since she was very young). In 2013, she entered the Australian National Championships largely on a whim, trained for a couple of weeks beforehand and, much to her surprise, she says, came in second. "Clearly my years of Kata practice positively influenced my ability to spar," she adds. "This is what is so fantastic about karate: while there are many aspects to it, training in each one assists the other." She went on to place in every state competition she entered and to collect armfuls of additional trophies, a winning streak that culminated with the first-place prize in the 2017 Australian National Championships.

As she climbed in ranking, though, she began to encounter resistance from the World Karate Federation. In 2014, she was selected to represent Australia in the US Open championship tournament. She was thrilled by the opportunity, but her elation quickly turned to disappointment when the federation told her she could not compete with her headscarf, as she always had in Australia. "This began a domino effect and suddenly I found myself denied from other tournaments and getting kicked off the Australian and state team," she says. "I took myself out of the limelight as it became too overwhelming and I trained without competing for a couple of months."

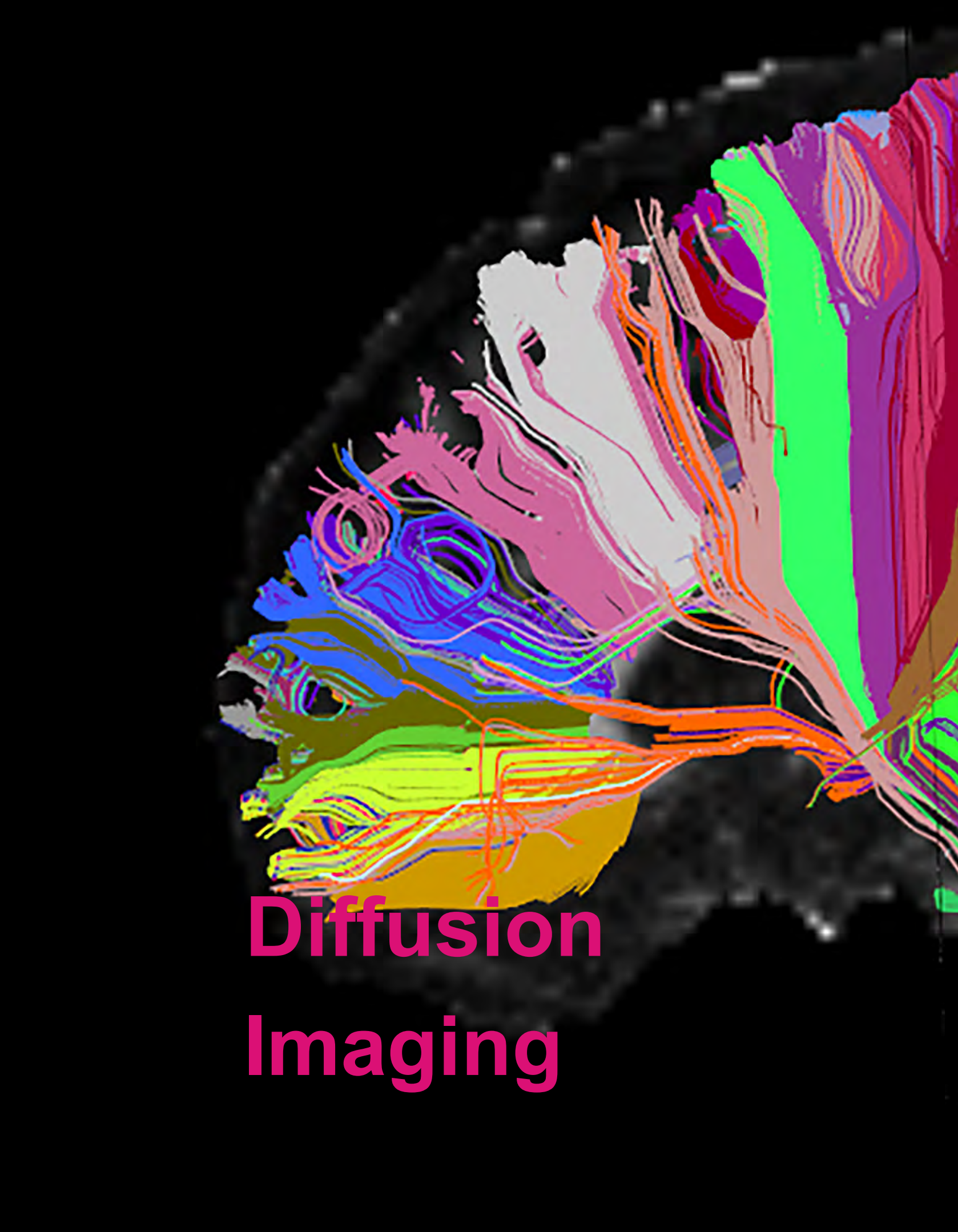
And even as she was reeling from the fallout of the federation's decision, her home karate club in Australia, the one that had welcomed

Above: Zeynab Alshelh

her and nurtured her since she was a child, started to fall apart. Disillusioned and worried about the impact of all of these changes on her emotional well-being, she packed her bags and traveled to Japan—with the hope of regaining confidence both in herself and in the sport.

She couldn't have made a better decision. While abroad, she trained with the Japanese masters and, through them, met leaders of the Japanese Karate Federation. After getting to know her and assessing her skill, the leaders decided she was fit to run her own club, which would be affiliated with the Japanese Karate Federation. She continues: "So, I went back to Australia with newfound confidence and a new project at hand: to take over the club which was falling apart, make it a non-profit organization, and make it mine." The club grew quickly and now has close to 40 students and three support trainers.

From the turmoil of those several years, Alshelh has emerged as an important voice challenging deeply entrenched misconceptions of the Muslim community. By showing that Muslim women can be successful in their sporting and their academic careers, she is providing a strong role model for other young Muslim women, who otherwise see few positive representations of themselves in the media. By asserting her right to compete with her headscarf, she is showing others that Muslim women have the same passions and pursuits as anyone else. And by speaking out publicly—as she has on several occasions—she is helping to steer the conversation about Muslim women in society.



Diffusion Imaging

Functional MRI opened a hugely important window onto the brain by revealing the specific areas of the brain involved in any number of activities or responses to outside stimuli. Seeing, learning, feeling pain. The list goes on. But another piece of the puzzle remained: namely, how did these areas of the brain communicate with one another?

Since the 1990s, Center researchers had been developing a technique called diffusion tensor imaging, an MRI-based method that allowed imaging of the long nerve fibers that facilitate communication between different areas of the brain by tracking water molecules as they travel along them. By the mid-2000s, both scanner technology and reconstruction algorithms had advanced to the point where the researchers could discern tightly packed fibers running in different directions and often crossing over one another—thus launching a new era of what we know now as diffusion imaging.

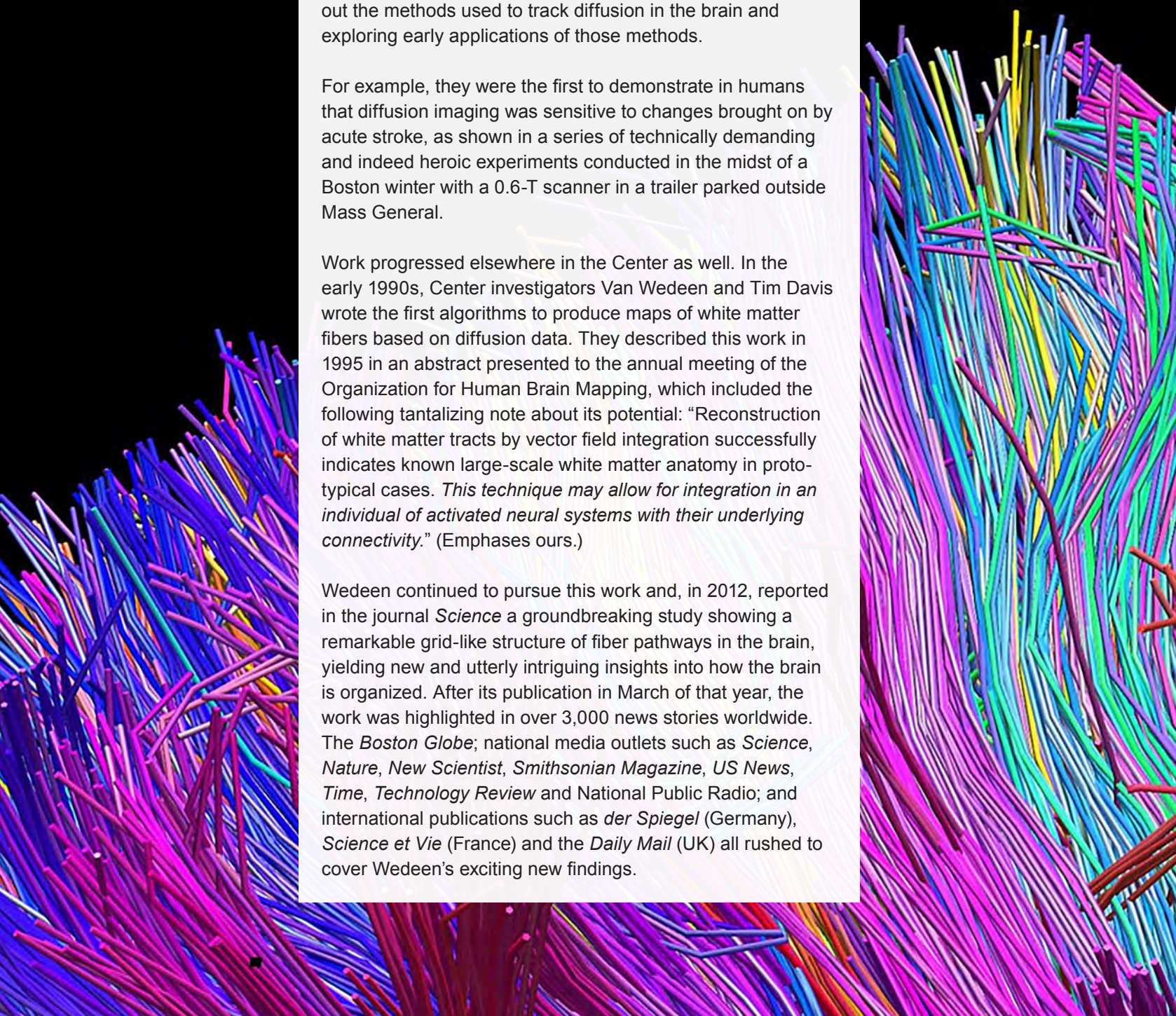
The Roots of Diffusion Imaging

The roots of diffusion imaging with MRI run deep in the Martinos Center. In fact, the first demonstration of diffusion anisotropy in the human brain— anisotropy would later be one of the core principles underlying the development of the approach —was reported by Martinos graduate student Daisy Chien in 1988, in a conference paper presented to the Society for Magnetic Resonance in Medicine. A series of papers by Chien and colleagues followed (her colleagues included the Center's Ken Kwong, who would soon introduce a means to measure brain activity entirely noninvasively), both fleshing out the methods used to track diffusion in the brain and exploring early applications of those methods.

For example, they were the first to demonstrate in humans that diffusion imaging was sensitive to changes brought on by acute stroke, as shown in a series of technically demanding and indeed heroic experiments conducted in the midst of a Boston winter with a 0.6-T scanner in a trailer parked outside Mass General.

Work progressed elsewhere in the Center as well. In the early 1990s, Center investigators Van Wedeen and Tim Davis wrote the first algorithms to produce maps of white matter fibers based on diffusion data. They described this work in 1995 in an abstract presented to the annual meeting of the Organization for Human Brain Mapping, which included the following tantalizing note about its potential: "Reconstruction of white matter tracts by vector field integration successfully indicates known large-scale white matter anatomy in prototypical cases. *This technique may allow for integration in an individual of activated neural systems with their underlying connectivity.*" (Emphases ours.)

Wedeen continued to pursue this work and, in 2012, reported in the journal *Science* a groundbreaking study showing a remarkable grid-like structure of fiber pathways in the brain, yielding new and utterly intriguing insights into how the brain is organized. After its publication in March of that year, the work was highlighted in over 3,000 news stories worldwide. The *Boston Globe*; national media outlets such as *Science*, *Nature*, *New Scientist*, *Smithsonian Magazine*, *US News*, *Time*, *Technology Review* and National Public Radio; and international publications such as *der Spiegel* (Germany), *Science et Vie* (France) and the *Daily Mail* (UK) all rushed to cover Wedeen's exciting new findings.



Based on the trailblazing work Wedeen and colleagues had done over the years, the National Institutes of Health chose the Martinos Center to help build a next-generation device to enable the same kind of imaging in humans. In September 2010, the NIH awarded grants totaling $40 million for what would be known as the Human Connectome Project. The recipients of the grants were two consortia with the common goal of mapping structural connections within the human brain, one of which was led by the Martinos Center in collaboration with the Laboratory of Neuro Imaging at the University of California, Los Angeles (now at the University of Southern California).

The MGH/UCLA consortium would focus on developing the MRI technology that would enable imaging of neural pathways: the structural connections by which different areas of the brain communicate. They would achieve this with a new 3T “Connectom” MRI scanner. Designed and built collaboratively by Larry Wald and Van Wedeen and their respective teams at the Martinos Center and engineers at Siemens Healthcare, this scanner would offer unprecedented sensitivity and resolution of the human brain’s white matter connectivity: that is, its “Connectome.”

Installation of the Connectom scanner at the Martinos Center (the dropped “e” in the name was intentional) was completed in September 2011. With the powerful new tool in place, the MGH-UCLA team made steady and important progress in developing, optimizing and testing the new hardware, pulse sequences and reconstruction methods designed expressly for the unique gradient system of the scanner. The Martinos Center’s efforts focused on characterizing and optimizing its performance for human brain imaging, eventually opening the door to studies with healthy human volunteers.

Previous spread: Image by Vivian Siless

Background image courtesy of the Human Connectome Project

Studying Anxiety and Depression with Diffusion MRI

Anxiety disorders and depression are widespread among adolescents in the US, affecting as many as one in four 13- to 18-year-olds. Determining the best course of treatment can be difficult, though, as we still don't fully understand the biology underlying them.

Now, using cutting-edge brain imaging technology, a study under way at the Martinos Center for Biomedical Imaging could offer new insights into this biology, and in doing so help improve the ways we approach anxiety and depression. Ultimately, the work could also yield a quantitative means of diagnosing the disorders.

Examining Mental Disorders as Part of the Human Connectome

The study, the Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA) study, emerged from the Human Connectome Project (HCP), a large-scale, multi-institutional collaboration including the Martinos Center. The HCP has demonstrated since its launch in 2010 an extraordinary ability to map the neural pathways in the healthy human brain. Using a range of MRI-based technologies, many of them developed in the Martinos Center, it has already helped answer a range of seemingly intractable basic science questions.

Begun in late 2015, the BANDA study is now also applying these technologies to a population of adolescents with anxiety disorders and depression. In fact, it is among the first projects funded by the National Institutes of Health to look at a disease population using data collection protocols developed by the HCP.

The study is thus an important step forward, says Anastasia Yendiki, principal investigator of the Martinos Center site of the study. It opens up new areas of inquiry for the HCP while also aiding a population very much in need of the insights it can provide.

"Our understanding of the biological mechanisms of mental illness is still limited," she says. "This makes it very challenging to predict which treatment will work for which patient. We hope that, by mapping the brain signatures of depression and anxiety disorders at an age that is critical for brain development, we can discover reliable biomarkers that will allow doctors to perform accurate diagnoses and prescribe appropriate treatments for patients."

The study has been recruiting patients from three different sites across Boston, including the Child Cognitive Behavioral Therapy program at MGH as well as sites at Boston University and McLean Hospital. It has also been recruiting patients from among those presenting to the general child outpatient psychiatry

department at MGH. All of the scanning for the study is done at the Martinos Center using the state-of-the-art MRI instrumentation housed there.

Yendiki has played a dual role in both the development and the application of the methods used in the study—a role for which she has been lauded in the mainstream press, especially as she and colleagues have pressed forward with the data collection stage of the study. In 2017, the magazine *Fast Company* named her one of the 100 most creative people in business, citing her work in mapping "the back roads of our brains." The same year, *InStyle* magazine included her on a list of "badass women" defying preconceptions of gender and generally making the world a better place.

Diffusion MRI and the Highways and Byways of the Brain

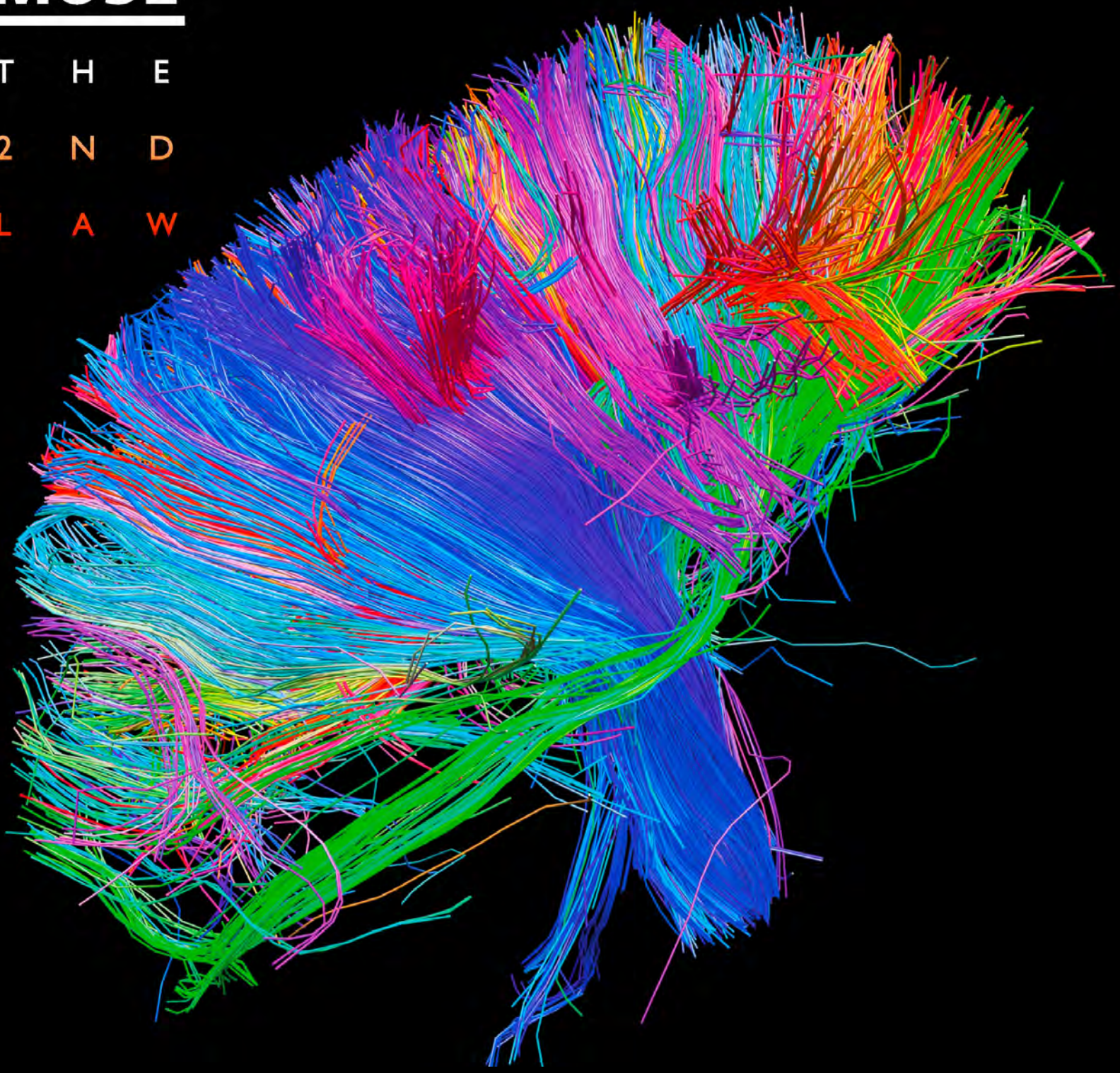
The researchers are exploring the brain mechanisms of anxiety disorders and depression by studying the wiring between different areas of the brain, and in particular by scrutinizing the white-matter fiber bundles that connect those areas using a technology known as diffusion MRI.

Introduced in the late 2000s, diffusion MRI has already yielded important insights into major pathways in the human brain: the superhighways of neural connectivity. Now, as the technology improves, researchers are seeing smaller pathways, one- or two-lane roads merging with the highways and then pulling away again, twisting and turning toward some other part of the brain.

Right: Anastasia Yendiki

MUSE

THE 2ND LAW



Being able to image these smaller roads is especially important, Yendiki says, because the changes in connectivity associated with anxiety and depression are not likely to disrupt an entire highway. Rather, they are more likely to be subtle disruptions of specific offshoots. For this reason, the investigators have been exploring ways to further refine the reconstruction of white-matter fiber bundles using diffusion MRI.

In a 2018 paper in the journal *NeuroImage*, the researchers reported an algorithm they developed to parse the hundreds of thousands of brain connections obtained from a high-resolution diffusion MRI scan, and group them into anatomically meaningful bundles. Typically, such algorithms will bundle connections based on their proximity to each other. This can be problematic, though, as fibers near one another do not necessarily belong to the same pathway. In the 2018 paper, Yendiki and colleagues—including first author Viviana Siless as well as researchers Ken Chang and Bruce Fischl—presented an algorithm that bundles connections based on the surrounding anatomical structures that they pass through or pass near to. In doing so, the algorithm "behaves more like an anatomist," Yendiki says. Indeed, in a validation study using healthy subject data from the Human Connectome Project, the landmark-based approach showed a 20 percent improvement in the overlap with manually defined pathways.

Any number of other applications could also benefit from use of the algorithm, including studies looking at large data sets with substantial anatomical variability, such as healthy subjects and disease populations like Alzheimer's or epilepsy patients, or healthy subjects across a wide range of ages.

Opposite: The rock band Muse used an image produced by the Human Connectome Project on the cover of their 2012 album The 2nd Law.

Buckle Up: With New Techniques, MRI is Faster than Ever Before

With its exquisite soft-tissue contrast and unique ability to probe brain function, MRI has revolutionized our understanding of the brain in both health and disease. But because of its speed—it acquires scans at a relatively slow clip—it doesn't always meet the needs of today's cutting-edge applications.

Kawin Setsompop found a way to change this.

Setsompop, a longtime investigator in the Martinos Center, developed a pair of techniques for MRI that effectively speed up scans, thus yielding dramatically higher imaging resolution. By optimizing the interplay between imaging hardware, MR physics and neuroscience, the techniques enable study of the living, functioning brain at much finer scales than was previously possible. Setsompop says his goal was to increase the sensitivity and efficiency of MRI by an order of magnitude or more.

The advances he has described could have a major impact on healthcare. Implementing them will improve detection of subtle changes in both structure and function in the brain, and this in turn will benefit a range of applications: from basic science applications such as those encompassed by the Human Connectome Project to diagnosis, prognosis and treatment of central nervous system (CNS) disorders including multiple sclerosis and epilepsy.

Setsompop's work in this area dates back to his graduate school days at MIT, when he set out to tackle a problem associated with ultrahigh-field MRI. A relatively new advance at the time, ultrahigh-field MRI suffered from an inherent limitation: the higher field strengths used with the technology led to inhomogeneity in the magnetic field, and this produced artifacts in the image. Hoping to address this—and thus to improve the overall efficacy of the approach—Setsompop and colleagues, including Elfar Adalsteinsson, his PhD advisor at MIT, started developing strategies that could mitigate these effects.

He continued his efforts after joining the Martinos Center as a postdoctoral fellow working with Larry Wald. In 2011, he and colleagues in the Center introduced the first of his strategies to speed up MRI scans: blipped-CAIPI Simultaneous MultiSlice (SMS) imaging. This technique

allows investigators to acquire up to ten planes, or “slices,” of brain images at a time—instead of just one—enabling much faster snapshots of brain physiology.

Three years later, Setsompop and his team at the Center introduced Wave-CAIPI SMS, which provides an order of magnitude improvement in data acquisition efficiency for a variety of clinically important MRI scans. This technique enables clinicians to speed up current MRI clinical exams—ultimately leading to reductions in healthcare costs—or to obtain much more detailed scans in the same time it would take to complete a conventional clinical exam, either at 7T or the more conventional 3T.

Right: Kawin Setsompop

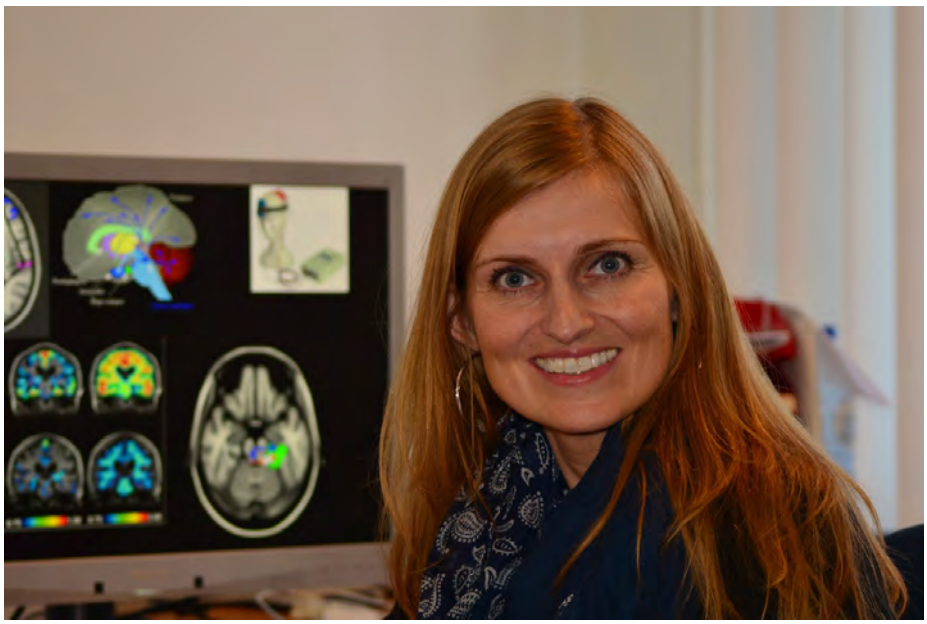
Structural Connectivity and Alzheimer's Disease

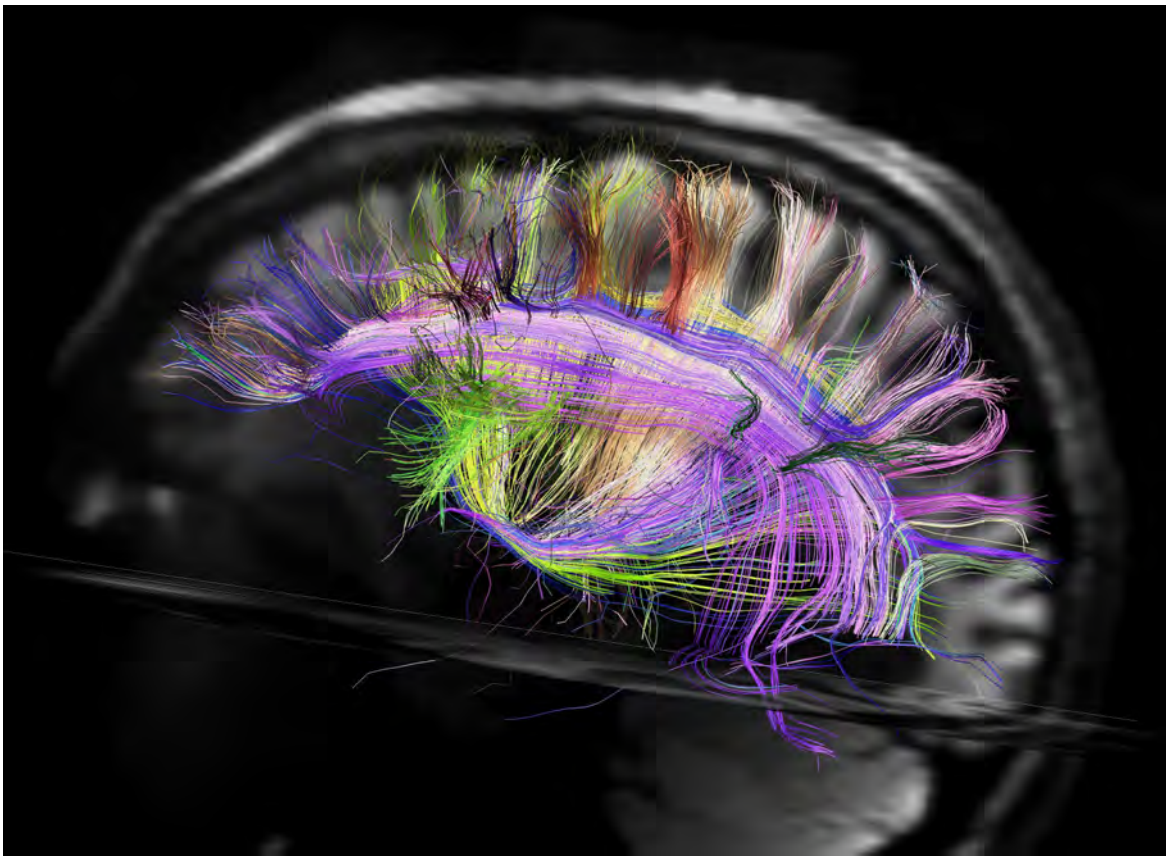
In Alzheimer's, the proteins amyloid-beta and tau begin to accumulate in the brain many years before any clinical signs of the disease are evident. Propagation of these proteins throughout the brain has been linked to cognitive decline in Alzheimer's, but exactly how they spread has long been a mystery.

In a study reported in the journal *Nature Neuroscience* in February 2018, the Martinos Center's Heidi Jacobs and colleagues shed new light on the question. The researchers looked at 256 older individuals enrolled in the Harvard Aging Brain Study and found evidence that tau propagates through structural connections in the brain. Importantly, this spread seems to be driven by amyloid pathology. The findings thus confirmed the interrelated contributions of amyloid, tau and specific structural connections to memory decline in preclinical Alzheimer's.

Animal models of Alzheimer's have suggested the importance of connectivity in the spread of the proteins. Jacobs and colleagues were able to establish this *in vivo* in humans using the recently developed positron emission tomography (PET) tracer flortaucipir (FTP) in conjunction with established diffusion tensor imaging (DTI) methods and amyloid PET imaging.The study has wide-ranging implications for Alzheimer's and other disorders. "These findings are important for current disease models," says Jacobs, first author of the *Nature Neuroscience* paper, "to better understand the mechanisms underlying the interaction between amyloid and tau pathology and how these pathologies drive neurodegeneration and cognitive decline. Furthermore, these findings are important for designs of future clinical trials, suggesting that drugs targeting amyloid pathology should aim to intervene early in the disease process, before tau pathology has spread outside the medial temporal lobe. This means that trials should also consider monitoring tau pathology."

Right: Heidi Jacobs





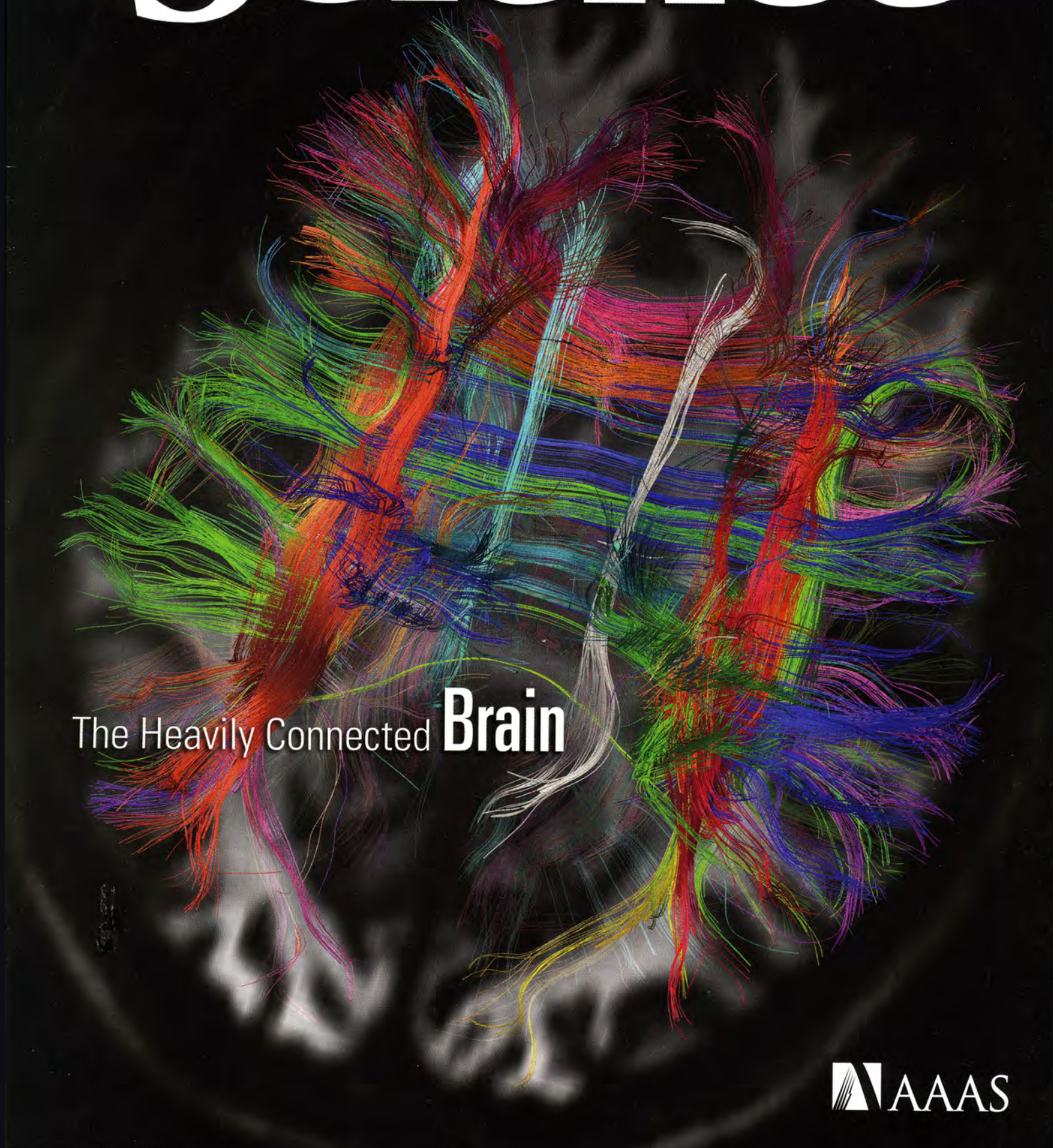
Above: An early, now-iconic diffusion image by Van Wedeen.

Next spread, left page: A diffusion MRI study by Martinos Center researchers was highlighted on the cover of the Nov. 1, 2013, issue of Science. *(Image by Van Wedeen, Aapo Nummenmaa, Ruopeng Wang and Larry Wald.)*

Next spread, right page: For the cover story for the Feburary 2014 issue of National Graphic, *science writer Carl Zimmer visited Van Wedeen's lab at the Martinos Center and later described the many advances Wedeen and colleagues were making with diffusion imaging. (Brain image on the cover by Van Wedeen and Larry Wald.)*

1 November 2013 | $10

Science



The Heavily Connected Brain

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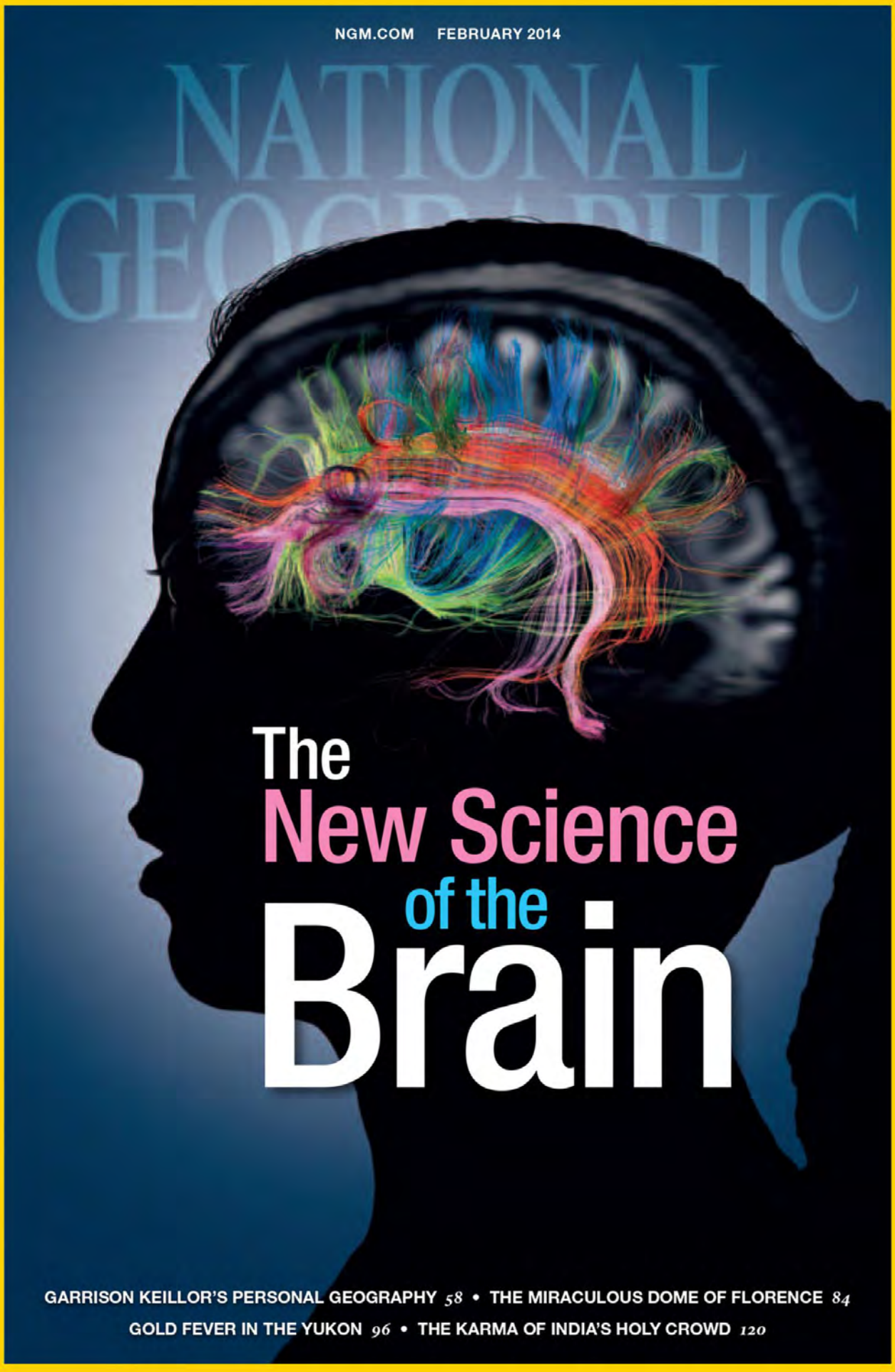


The New Science of the Brain

Artificial Intelligence

Recent years have seen considerable growth in the application of artificial intelligence in healthcare, especially in radiology, where it can aid in detection and diagnosis of disease using sophisticated image analysis algorithms. And Martinos Center researchers have been helping lead the charge, developing cutting-edge AI tools for a wide range of applications.

Artificial Intelligence Improves Treatment Monitoring in Patients with Glioma

This year, some 78,000 primary brain and other central nervous system (CNS) cancers will be diagnosed in the US alone. Researchers are actively developing new therapies for glioma, the most common type of primary brain tumor, but challenges remain in assessing whether patients are responding to treatment with the therapies.

To address these challenges, a team of Martinos Center researchers and colleagues have devised a deep learning algorithm that automatically measures tumor volume based on MR images, providing more rapid and more consistent treatment monitoring for patients. The researchers are now working to integrate the algorithm into the neuroradiology and neuro-oncology clinical workflows at Mass General.

"We are excited to develop new algorithms that can increase the reliability of challenging clinical workflows," says Ken Chang, a graduate student in the Martinos Center and first author of a paper published in the journal *Neuro-Oncology* in 2019 describing the algorithm. "Without accurate methods of treatment response assessment, it is difficult to know if a therapy for a given patient is effective or whether an alternative therapy should be considered. We believe the utilization of machine learning-based tools can help physicians provide the best care possible to patients."

Limitations in Current Gold Standard Measurements of Treatment Response

In current practice, assessing a glioma patient's response to treatment is based on manual measurements of tumor burden guided by Response Assessment in Neuro-Oncology (RANO) criteria. Using these criteria, clinicians can identify the response as "complete response," "partial response," "stable disease" or "progression," based on specific imaging and clinical features. The RANO-based method offers a beneficial approach to treatment monitoring but is time-intensive and can vary depending on who performs the measurement. Also, to facilitate ease of use for the clinicians doing the reading, the approach relies on bi-directional diameter measures. Such measures, however, are

Previous spread: background image by Bo Zhu

Left (from L to R): the QTIM lab's Elizabeth Gerstner, Jayashree Kalpathy-Cramer and Ken Chang

unlikely to provide an accurate representation of the size of the tumor since gliomas are often irregular in shape. Volumetric measures would be more valuable for treatment monitoring purposes, but such measures would be impracticable for manual assessments of tumor burden because of the time and effort required.

The Martinos Center researchers therefore developed an algorithm for automatic measurement of tumor volumes as well as bi-directional measurement—an approach they call AutoRANO. This work grew out of recent advances in the field of deep learning, a type of artificial intelligence capable of performing complex tasks by using layers to learn progressively higher-level features from an image. The researchers built the algorithm using DeepNeuro, an open-source deep learning software package for neuroimaging developed by the Quantitative Translational Imaging in Medicine (QTIM) laboratory at the Martinos Center. In doing so, they worked closely with physicians from both Mass General and Brigham and Women's Hospital to fully optimize it for clinical use.

In the *Neuro-Oncology* study, the team validated the algorithm's performance by comparing the automated measurements in two patient cohorts with manual measurements by experts. They first demonstrated the algorithm's superiority in learning and performing brain extraction, a challenging preprocessing step often giving rise to difficulties downstream. Its strength in this area enabled robust tumor segmentation based on both FLAIR hyperintensity and contrast enhancement. The tool also performed well in automatically calculating RANO measurements from the contrast enhancement segmentations, showing high agreement with the manually generated tumor volumes. With these results and other findings, the study underscored the possible clinical utility of the algorithm in patients with glioma. The research team is now actively working with information technology engineers to add the algorithm into clinical workflows at Mass General for neuroradiology and neuro-oncology. The goal is a tool with a user-friendly interface that seamlessly incorporates into the radiology picture archiving and communication system (PACS).

Clinical Workflows to Benefit

Once integrated into workflows, the algorithm has the potential to offer a host of benefits for physicians and patients. In addition to providing more reliable quantitative metrics to aid with clinical decision-making in treatment monitoring, it could also foster development of new treatments for patients with glioma within clinical trials. It could also work well with other automated tools currently under development in the QTIM laboratory, including an algorithm that can predict particular mutations in patients with glioma using MRI data. These mutations are associated with longer survival and could help guide treatment decisions.

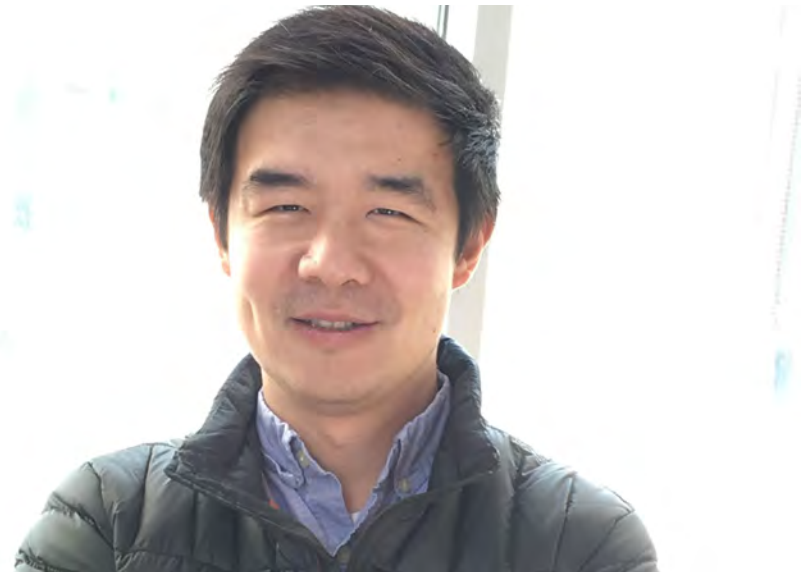
All of which is good news for the field, and for the healthcare arena generally. "Deep learning will transform all aspects of radiology," Chang says, "from image acquisition, to reconstruction, to diagnosis and clinical decision-making. Algorithms will automate many difficult tasks that are prone to human error, with clinicians and scientists in the driver's seat. The integration of machine and human intelligence will improve the technical components of diagnosis and treatment. At the same time, integration will allow the physicians more flexibility to focus on the human aspects of care."

Learning to See: AI Technique Dramatically Improves the Quality of Medical Imaging

A radiologist's ability to make accurate diagnoses from high-quality diagnostic imaging studies directly impacts patient outcome. However, acquiring sufficient data to generate the best quality imaging comes at a cost—increased radiation dose for computed tomography (CT) and positron emission tomography (PET) or uncomfortably long scan times for magnetic resonance imaging (MRI). In 2018, a team of researchers based at the Martinos Center addressed this challenge with a new technique based on artificial intelligence and machine learning, enabling clinicians to acquire higher quality images without having to collect additional data. They described the technique—dubbed AUTOMAP (automated transform by manifold approximation)—in a paper published in the journal *Nature*.

"An essential part of the clinical imaging pipeline is image reconstruction, which transforms the raw data coming off the scanner into images for radiologists to evaluate," says Bo Zhu, a researcher in the Center and first author of the *Nature* paper. "The conventional approach to image reconstruction uses a chain of handcrafted signal processing modules that require expert manual parameter tuning and often are unable to handle imperfections of the raw data, such as noise. We introduce a new paradigm in which the correct image reconstruction algorithm is automatically determined by deep learning artificial intelligence.

"With AUTOMAP, we've taught imaging systems to 'see' the way humans learn to see after birth, not through directly programming the brain but by promoting neural connections to adapt organically through repeated training on real-world examples. This approach allows our imaging systems to automatically find the best computational strategies to produce clear, accurate images in a wide variety of imaging scenarios."



The technique represents an important leap forward for biomedical imaging. In developing it, the researchers took advantage of the many strides made in recent years both in the neural network models used for artificial intelligence and in the graphical processing units (GPUs) that drive the operations, since image reconstruction—particularly in the context of AUTOMAP—requires an immense amount of computation, especially during the training of the algorithms. Another important factor was the availability of large datasets ("big data"), which are needed to train large neural network models such as AUTOMAP. Because it capitalizes on these and other advances, Zhu says, the technique would not have been possible five years before the *Nature* study and maybe not even one year before.

AUTOMAP offers a number of potential benefits for clinical care, even beyond producing high-quality images in less time with MRI or with lower doses with x-ray, CT and PET.

Because of its processing speed, the technique could help in making real-time decisions about imaging protocols while the patient is in

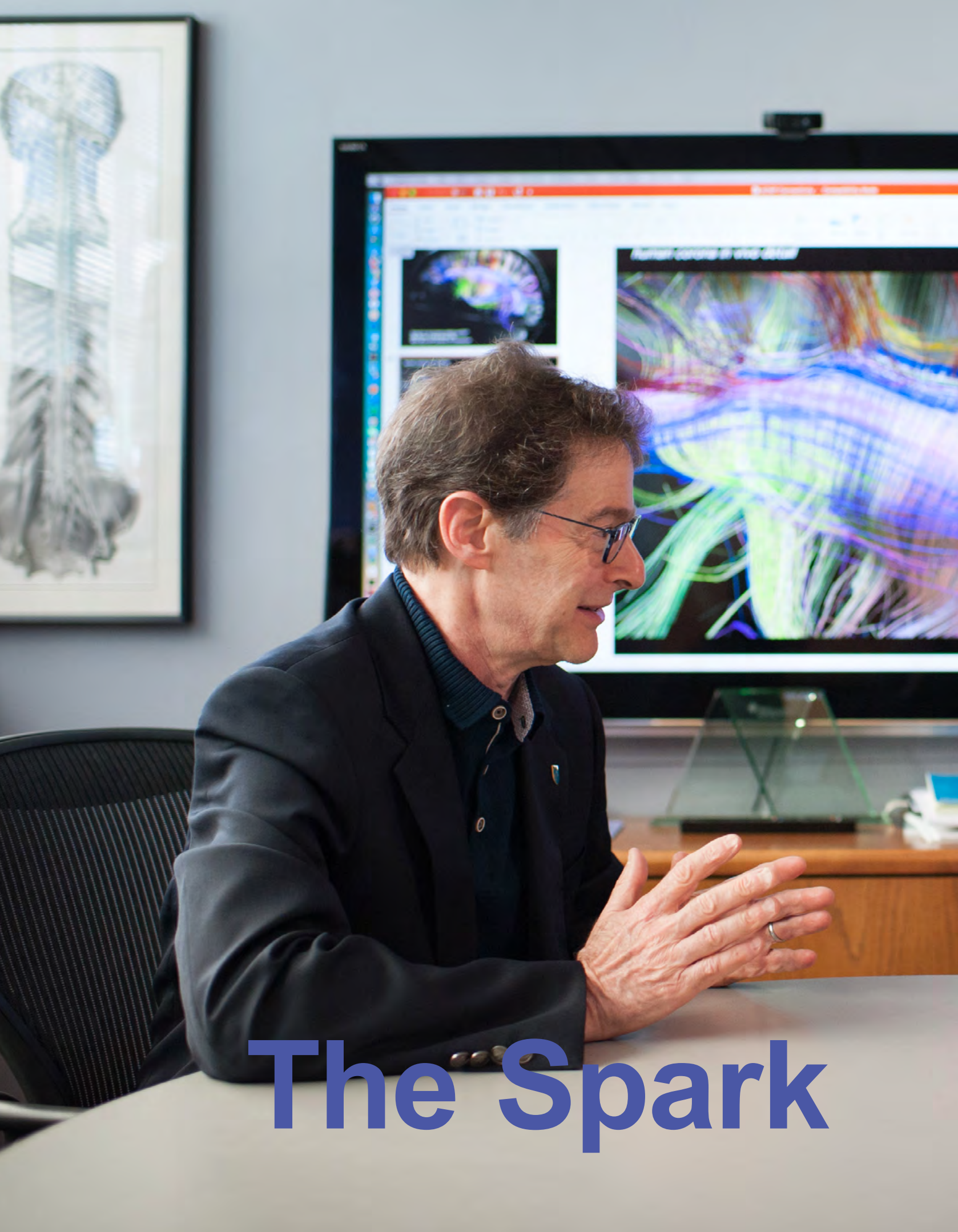
the scanner. “Since AUTOMAP is implemented as a feedforward neural network, the speed of image reconstruction is almost instantaneous – just tens of milliseconds,” says senior author Matt Rosen, director of the Low-Field MRI and Hyperpolarized Media Laboratory and co-director of the Center for Machine Learning at the Martinos Center. “Some types of scans currently require time-consuming computational processing to reconstruct the images. In those cases, immediate feedback is not available during initial imaging, and a repeat study may be required to better identify a suspected abnormality. AUTOMAP would provide instant image reconstruction to inform the decision-making process during scanning and could prevent the need for additional visits.”

Notably, the technique could also aid in advancing other artificial intelligence and machine learning applications. Much of the current excitement surrounding machine learning in clinical imaging is focused on computer-aided diagnostics. Because these systems rely on high-quality images for accurate diagnostic evaluations, AUTOMAP could play a role in advancing them for future clinical use.

Rosen is ebullient in discussing the potential of the technique. “Our AI approach is showing remarkable improvements in accuracy and noise reduction and thus can advance a wide range of applications,” he says. “We’re incredibly excited to have the opportunity to roll this out into the clinical space where AUTOMAP can work together with inexpensive GPU-accelerated computers to improve clinical imaging and outcomes.”

Opposite: Bo Zhu

Left: Matt Rosen



The Spark

In 2017, the Martinos Center introduced a new logo as part of a rebranding effort. Known affectionately as "the Spark," the logo represents everything that is special about the Center and its people: the diversity, the energy, the creativity, and so much more. In the years since, it has come to embody, in a profound way, who we are, both as an academic research institution and as a community and indeed a family.

The State of the Center Today

In 2013, the Martinos Center welcomed its first-ever executive director, Bill Shaw, who had previously served with Partners Healthcare as associate director of research, ventures and licensing. Over the next seven years, Shaw would oversee considerable growth and expansion in the Center, not least on the operations side of the equation.

Today, the Center's infrastructure is as robust as it's ever been, and the sense of identity and community among its faculty and staff could not be stronger.

In 2020, the Martinos Center is home to nearly 150 faculty members and several hundred more postdoctoral fellows, students and staff. With more than 200 grants submitted every year, Center investigators are working with over $60 million in funding. In the past year alone, they have reported the findings from their research in more than 500 peer-reviewed papers.

The Martinos footprint also continues to grow—to over 75,000 square feet today. The additional space in part accommodates a host of new, cutting-edge imaging systems. Not least of these: a Siemens Magnetom Terra 7T MRI scanner, a next-generation MEG device with optically pumped magnetometers and a prototype magnetic particle imaging (MPI) scanner currently under construction.

The Center has seen increasing collaboration in recent years, with academic labs, medical device and pharmaceutical companies and other organizations both in the US and abroad. At the same time, it has sought to foster a greater sense of camaraderie within its own walls. In addition to the new logo and brand system, which contribute to a shared identity among Martinos researchers and staff (see opposite page), the Center has organized a growing number of events to reinforce a sense of community: among them, the popular "Art in mARTinos" gallery event, several "Martinos Day" open houses, faculty retreats and more.

But of all the ways one might measure success, the Center is most proud of the people it continues to attract and retain. As we have seen throughout this book, Martinos researchers and staff are among the most talented, most productive and most fascinating people you will find anywhere.

Below: Executive Director Bill Shaw

Opposite (clockwise from upper left): Rob Barry; Maria Angela Franceschini and friend; Melissa Haskell, Clarissa Cooley and Christin Sander; David Boas.

The Spark Seen ’Round the World

The Martinos Center introduced its new logo in the spring of 2017. We call it, simply, the “Spark.” Comprised of images acquired with cutting-edge technologies from throughout the Center, the logo is a bold expression of our culture, philosophy and vision.

What does the Spark say about the Center? Martinos investigators are scientists, catalysts and futurists, radical in thought and collaborative in approach. Together, they act as agents of change. The new logo represents both the spark of creativity behind this change and the diverse views and collective energy that ultimately make it possible.

The researchers proudly wore this expression of who they are and what they do as they traveled the world in the wake of its introduction—from Honolulu, Hawaii, to the West African nation of Guinea-Bissau, and on again to the banks of the Volga River in Russia.

The Administrative Staff Today

Above: The coolest administrative staff anywhere—we'll fight you if you say otherwise—on its 2019 annual outing. Back row, from left to right: Nelson Gicana, Jill Smith, Matt Vest, Alex White Hogue, Mary Roy, Donna Crowe. Middle row, from left to right: Monica Langone, Krystal Whitfield, Karen Dervin. Front row, from left to right: Stacey Ladieu, Jinan Bouraslan, Allison Stevens.

Opposite, top: Everyone's favorite financial analyst and senior grants manager—Peter Hickey and Mary Roy—with Radiology chief James Brink. Hickey and Roy were both entirely deservedly nominated for "Imaging Service Excellence" awards in 2018.

Opposite, bottom: From the "We Already Knew This" file: Partners Healthcare recognized Donna Crowe's excellence in April 2019, presenting her with a "Partners in Excellence" award for her always outstanding work as office manager for the Martinos Center for Biomedical Imaging.


2018 Partners in Excellence
INDIVIDUAL AWARD
PRESENTED TO
Donna Crowe

The Secret Lives of Martinos Folk

Carol Barnstead *& the Center's cast of colorful characters*

Gary here, stepping out of the third person for a moment to tell the story of a conversation I had a while back, a conversation that neatly summed up one of my favorite things about working in the Martinos Center. It feels appropriate to include the story here, near the end of this book and near the end of our narrative about what makes the Center so unique and so special.

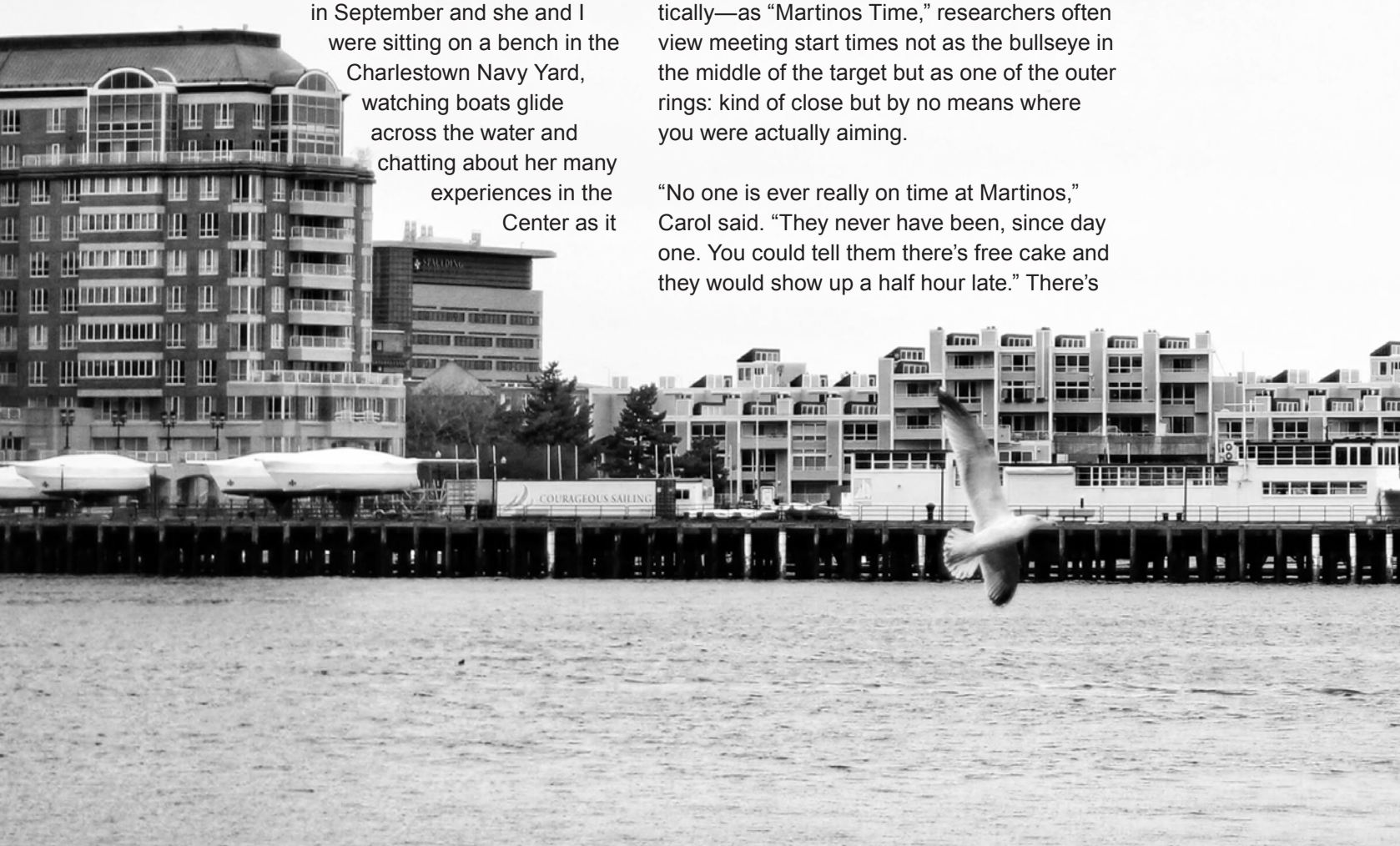
I have this theory that you need to be a character to work at the Martinos Center—you have to be a bit of an oddball, albeit in a fun, quirky kind of way. I'm not sure whether this is a prerequisite enforced during one of the hiring steps or is simply the result of some kind of self-selection process. Whatever the case, I know it in my bones to be true: people who have no imagination or appreciation of others' eccentricities just won't cut it here.

In late 2019, I ran my theory by Carol Barnstead. Carol had retired from the Center a few months before, after some 31 years of helping keep it afloat by overseeing the assignment of visas and managing other HR concerns. It was a warm, early fall day in September and she and I were sitting on a bench in the Charlestown Navy Yard, watching boats glide across the water and chatting about her many experiences in the Center as it grew from a handful of researchers in a shadowy subbasement of MGH to the major facility it is today. I figured if anyone could confirm the theory, it would be her.

She laughed when I explained my idea—though, notably, she didn't try to refute it. "Well, if you're not a character when you arrive," she said, "you will be shortly after."

We sat for a while, teasing out the theory, turning it over and inspecting it from various angles. Our conversation was wide-ranging, blithely skipping from one topic to the next. We talked, for example, about the propensity toward tardiness in the Center. In what is known colloquially—and probably euphemistically—as "Martinos Time," researchers often view meeting start times not as the bullseye in the middle of the target but as one of the outer rings: kind of close but by no means where you were actually aiming.

"No one is ever really on time at Martinos," Carol said. "They never have been, since day one. You could tell them there's free cake and they would show up a half hour late." There's



too much else going on, and it's too easy to get caught up in whatever is happening in the Center *right now*, minutes before you're slated to be somewhere else in the building.

But it isn't their occasional disregard for the artificial constraints of time and schedules that makes Martinos folk special. Rather, it's the impulses underlying their chronic lateness: an openness to possibilities and a willingness—a sense of obligation, even—to pursue any idea that arises wherever (and for however long) it may take them, whether it emerges in the lab, in a heady conversation in the hallway or simply in the fever dream of one's own thoughts. In the end, Carol and I decided, the tardiness itself isn't the point. It's the reasons for the tardiness that make the Martinos Center the hotbed of science that it is.

As we were discussing the finer points of chronic lateness, people from the Center started strolling by our perch along the water: colleagues from the administrative staff, a couple of postdoctoral fellows, someone from the research staff. Several stopped and chatted with Carol, asking how she was enjoying her well-deserved retirement; others smiled and said hello as they passed. Once we were alone again, Carol remarked upon how open and friendly Martinos folk are, and how genuinely interested in others they seem to be. In thinking back on our conversation, the word *open* cropped up repeatedly as we were talking about the Center and its denizens. Members of the Martinos community exhibit a refreshing openness, not only to new ideas but to new people and

Background: a view from Pier 6 in the Charlestown Navy Yard

Next spread, left page: Carol Barnstead

Next spread, left page: Bruce Jenkins

new perspectives. And this openness reflects an inquisitiveness about the world at large—an inquisitiveness that, in the end, underlies all of the excellent work they do in the Center.

Oftentimes, researchers' and staff members' broadmindedness carries over into their extracurricular activities. This is one of my favorite traits of Martinos folk: so many of them maintain a diverse array of interests, evidencing both a passion for and an excellence in a range of pursuits. They are at the top of their game not only as scientists, but also as bagpipers and karate champions, flamenco dancers and roller derby competitors. In some cases, you can draw a straight line between their vocation (science) and their avocation. The Center's Anastasia Yendiki once told me, for example, that she enjoys flamenco in part because it shares with her work developing data analysis software an important analytical component; in both, she said, "you have a set of constraints and within those you are trying to come up with something that is creative, elegant and effective." The relationship between vocation and avocation may be less clearly defined in other cases, but it is no less durable or real. In any outside endeavor they pursue, Martinos folk are driven by the same energy and enthusiasm that animate their work within the Center.

Which brings me back to why Carol and I were chatting in the first place. When she retired, a colleague in the Center suggested I interview her to tap into the vast institutional memory she holds in her head. But in my initial discussions with her I was reminded of what a character she is in her own right—anyone who has interacted with her over the years will surely agree—and how she embodies many of the traits that make the Martinos Center such a fascinating place. She is undoubtedly open to new people and new perspectives; in the course of her work overseeing the assignment of visas, she has developed lifelong friendships with folks from all four corners of the globe. And she exhibits the same boundless curiosity as so many others in the Center.

Did you know, for example, that Carol is a Ricardian, a student of the murky history of England's Richard III? Her journey into this rarefied realm began with the Beatles, who inspired in her a love of all things British, and has included an invitation to England to witness the reinternment of Richard's remains. In this and in many other ways, she has demonstrated the sort of inquisitiveness about the world that has always been a hallmark of the Martinos community.

So Carol was both in good company and good company herself for the nearly three decades she was with the Center. And she is quick to tell you how truly lucky she feels. As she and I sat there, on a bench overlooking the harbor on a warm, early fall day in September, she reminisced about the company she kept for all those years. "The people at the Martinos Center are very special," she said. "I wouldn't have worked there as long as I did if I didn't like the work environment, and the work environment was the people."

The Center's **Bruce Jenkins***: Born to Be Wild*

Bruce Jenkins is a pioneer in the field of pharmacological MRI. He has published widely on the relationship between pharmacological agents and functional connectivity in the brain, for example, and was one of the first to work out the principles of dopamine-mediated neurovascular coupling.

He is also a riotously funny guy.

Play a round of golf with him sometime. It's less a morning of lining up shots and reading the breeze and more a sidesplitting roaming bout of riffing on an extraordinarily broad range of topics.

So it's no surprise to learn he did a bit of standup back in the nineties. He started with open mics at the *Catch a Rising Star* comedy club in Harvard Square and eventually made enough of a name for himself that he was receiving regular, assigned slots at the club, working alongside the likes of Louis C.K. and David Cross.

Hearing him tell stories of the early days of the Martinos Center—he joined the group in about 1987—you can imagine where he got at least some of his material.

Just as importantly, you get the sense that Martinos researchers have always fallen on the quirky side. That their offbeat nature has been baked into the culture of the Center from the very beginning.

To wit: he tells of a night many years ago when a group of Center researchers found themselves at a chic Karaoke bar in San Francisco. After an aperitif or two, Center director Tom Brady decided that he, Jenkins and Jack Belliveau should climb on stage and sing the counterculture anthem "Born to Be Wild."

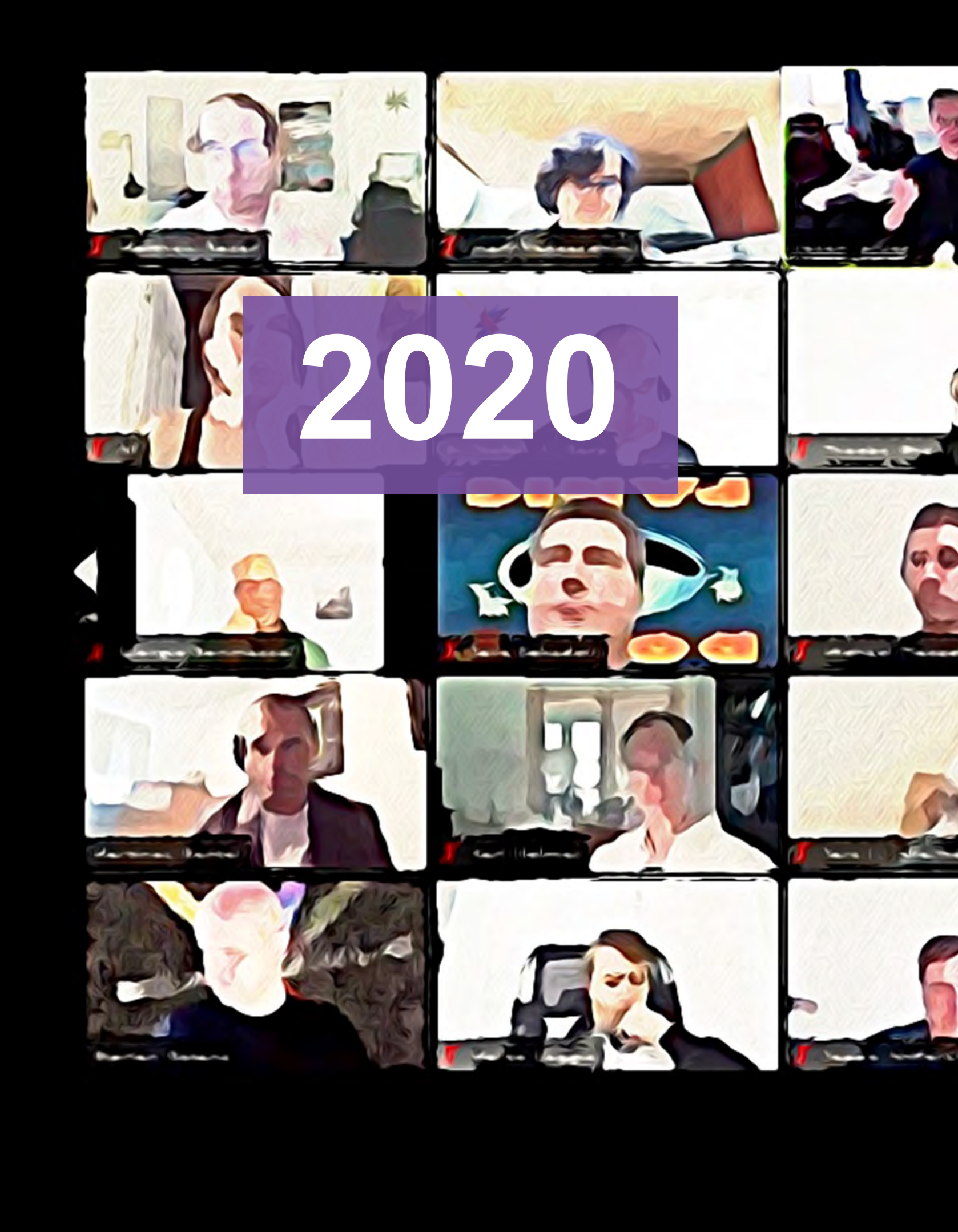
There was just one problem: "Jack was a drummer, not a singer," Jenkins says, diplomatically. "Tom Brady," he adds, maybe slightly less diplomatically, "was tone deaf."

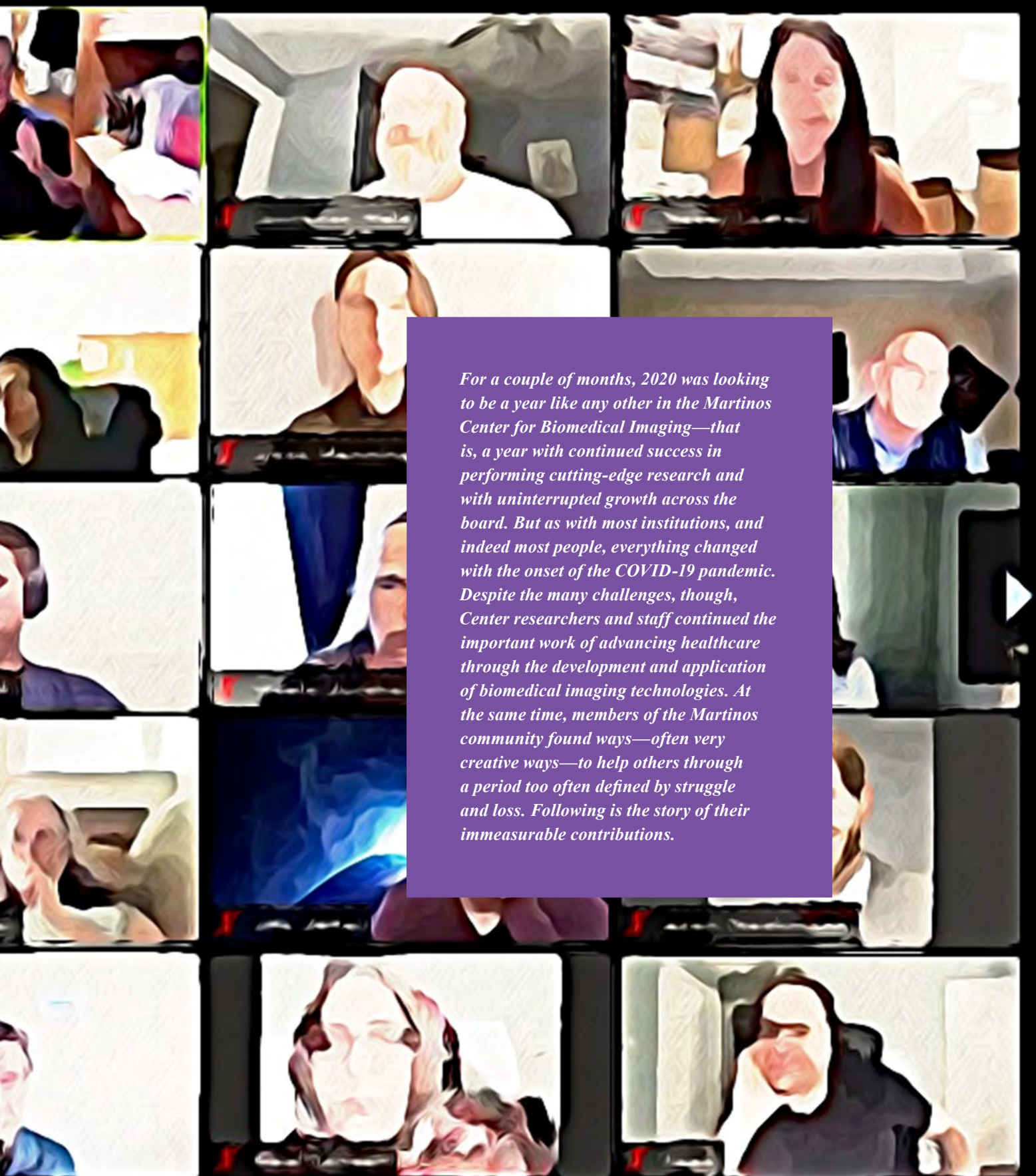
Moving on to a different topic, he reveals the fun-loving origins of the Center's now-state-of-the-art IT infrastructure.

Sometime in the mid-nineties, Anders Dale and a group of others decided that everyone in the Center should have a UNIX workstation, enabling networking for a range of scientific and—not incidentally—less-scientific applications.

We got all these Silicon Graphics machines," Jenkins says, "and at about 6pm we would all get together to play [iconic single- and multiplayer computer game] *Doom*, with the sounds of explosions reverberating throughout the building."

So, to summarize: Work hard, play hard. Belt out your favorite tunes like there's no one listening. And don't worry too much about the lie of the ball. Words to live by. Indeed, if you think about it, this might just be a Martinos Center creed.


2020



For a couple of months, 2020 was looking to be a year like any other in the Martinos Center for Biomedical Imaging—that is, a year with continued success in performing cutting-edge research and with uninterrupted growth across the board. But as with most institutions, and indeed most people, everything changed with the onset of the COVID-19 pandemic. Despite the many challenges, though, Center researchers and staff continued the important work of advancing healthcare through the development and application of biomedical imaging technologies. At the same time, members of the Martinos community found ways—often very creative ways—to help others through a period too often defined by struggle and loss. Following is the story of their immeasurable contributions.

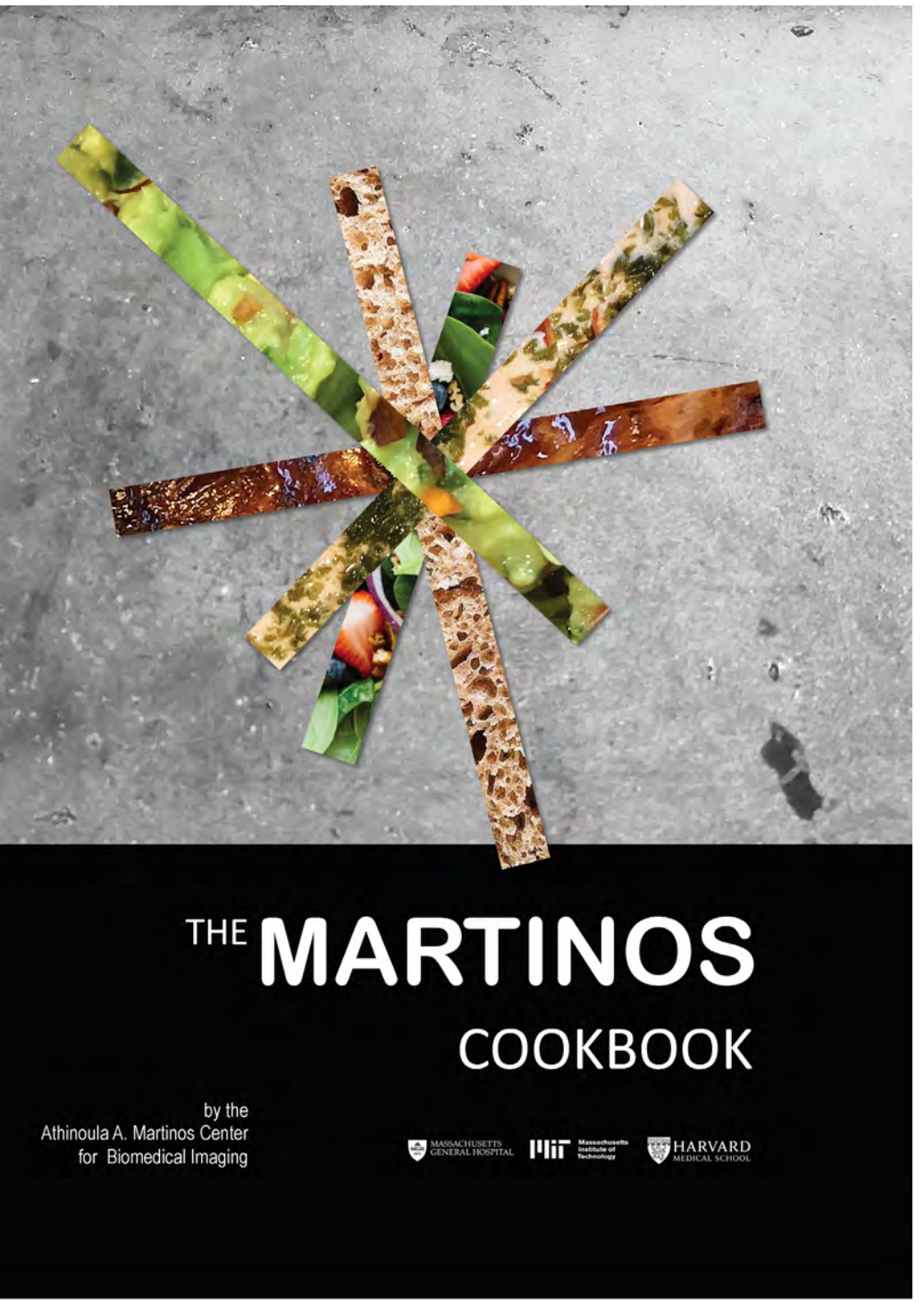
The Martinos Center Responds

The usual hustle and bustle of the Martinos Center for Biomedical Imaging came to a dramatic halt in March 2020 when the COVID-19 outbreak was declared a pandemic. But members of the Martinos community were anything but idle during the weeks and months that followed. Even as the pandemic continued to grow, many Center researchers and staff stepped into new roles to help with the COVID-19 response.

Beginning in April, Mass General redeployed staff from across the hospital to meet the needs of the surge in COVID-19 cases. Many in the Martinos Center answered the call: among them, Paula S. Lara Mejia, a clinical research coordinator with the Michael VanElzakker group, who assisted clinicians in COVID-19 ICUs by listening for alerts from portable ventilators not connected to the hospital's central alarm system.

The researchers and staff members were glad to be able to contribute. "As someone applying to medical school, it has been very interesting to be in this environment during the pandemic," Lara Mejia told us at the time. "I'm very honored to be able to play a small role on the front lines and grateful for this experience."

Even as some in the Center were redeploying to ICUs, others were finding ways to help outside the hospital. A few of the many examples:



With imaging studies on hold, nurse practitioner Amy Kendall asked for a temporary reassignment to the Ragon Institute at MGH, MIT and Harvard to help with a biospecimen repository study with COVID-19 patients.

Benjamin Bearce, a software developer in the Quantitative Translational Imaging in Medicine (QTIM) lab, created, with support from the Center's Sam Schoerning, a website to connect overtaxed direct care providers with volunteers from the Mass General community who could help with grocery shopping, pet care and many other needs at home.

Don Straney, a staff electrical engineer with the Center, teamed up with a pair of grassroots efforts, making face shield visors and designing circuit boards for COVID-19 projects.

Just as importantly, Martinos folk banded together to support one another, especially during the early days of the pandemic. For instance, in July, the Center published a cookbook collecting more than 70 recipes from members of the Martinos community, representing cuisines from around the world and covering every meal from throughout the day.

The cookbook served as a fundraiser—the Center offered it as a free downloadable PDF and asked for

Previous spread:

Left page: Paula S. Lara Mejia (top) and Amy Kendall (bottom)

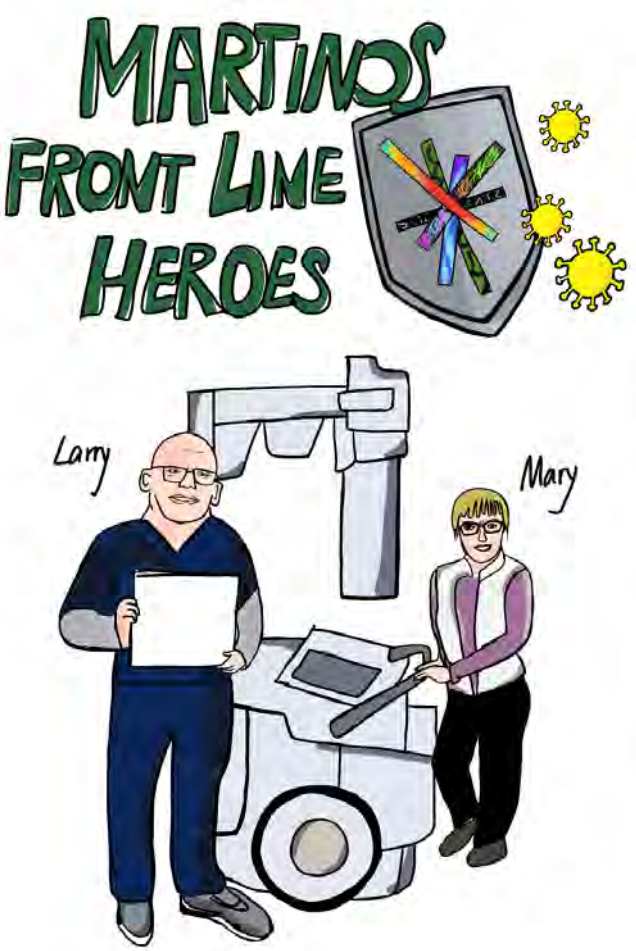
Right page: the cover of the Martinos cookbook, designed by the Center's Laura Gee, who also compiled the cookbook.

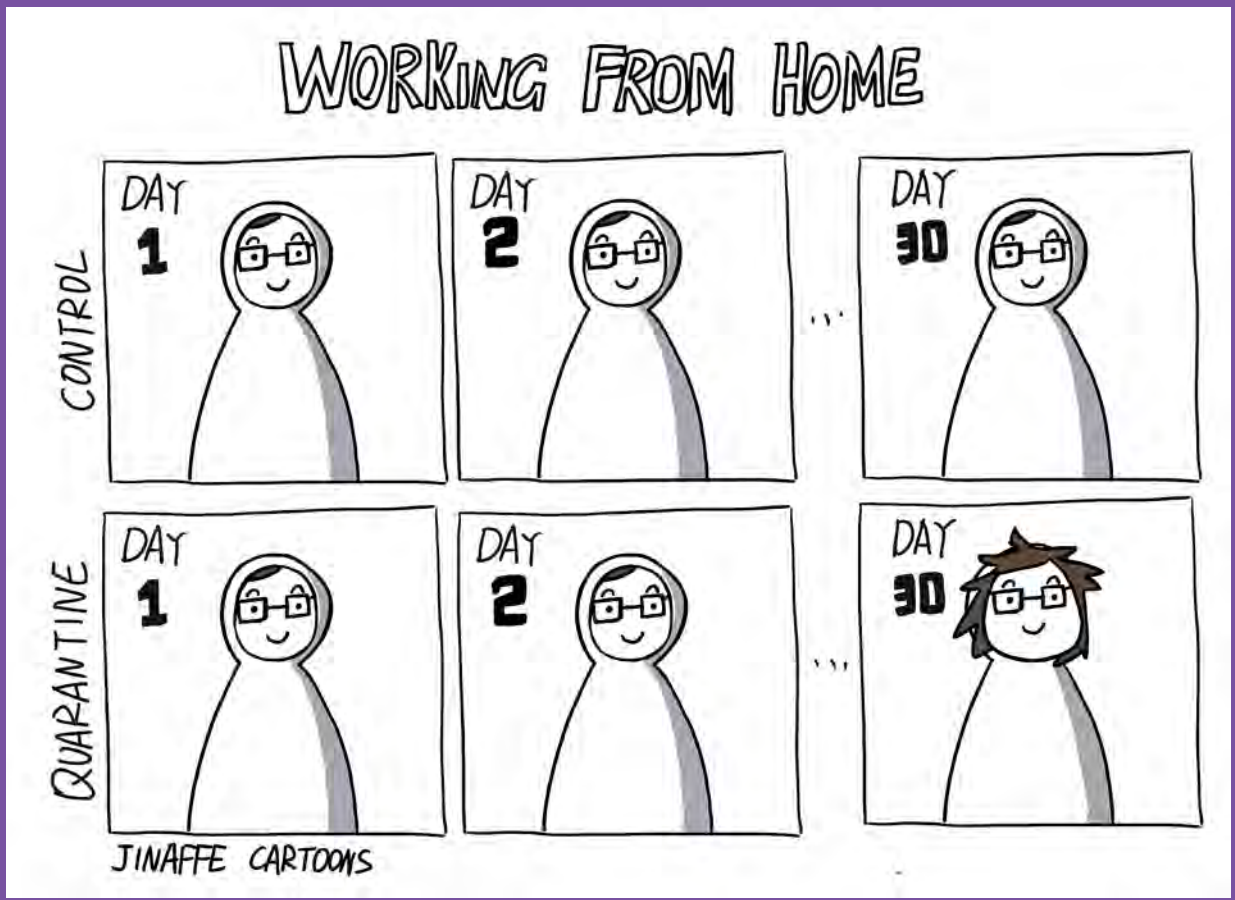
This spread: A pair of cartoons by Jingyuan Chen

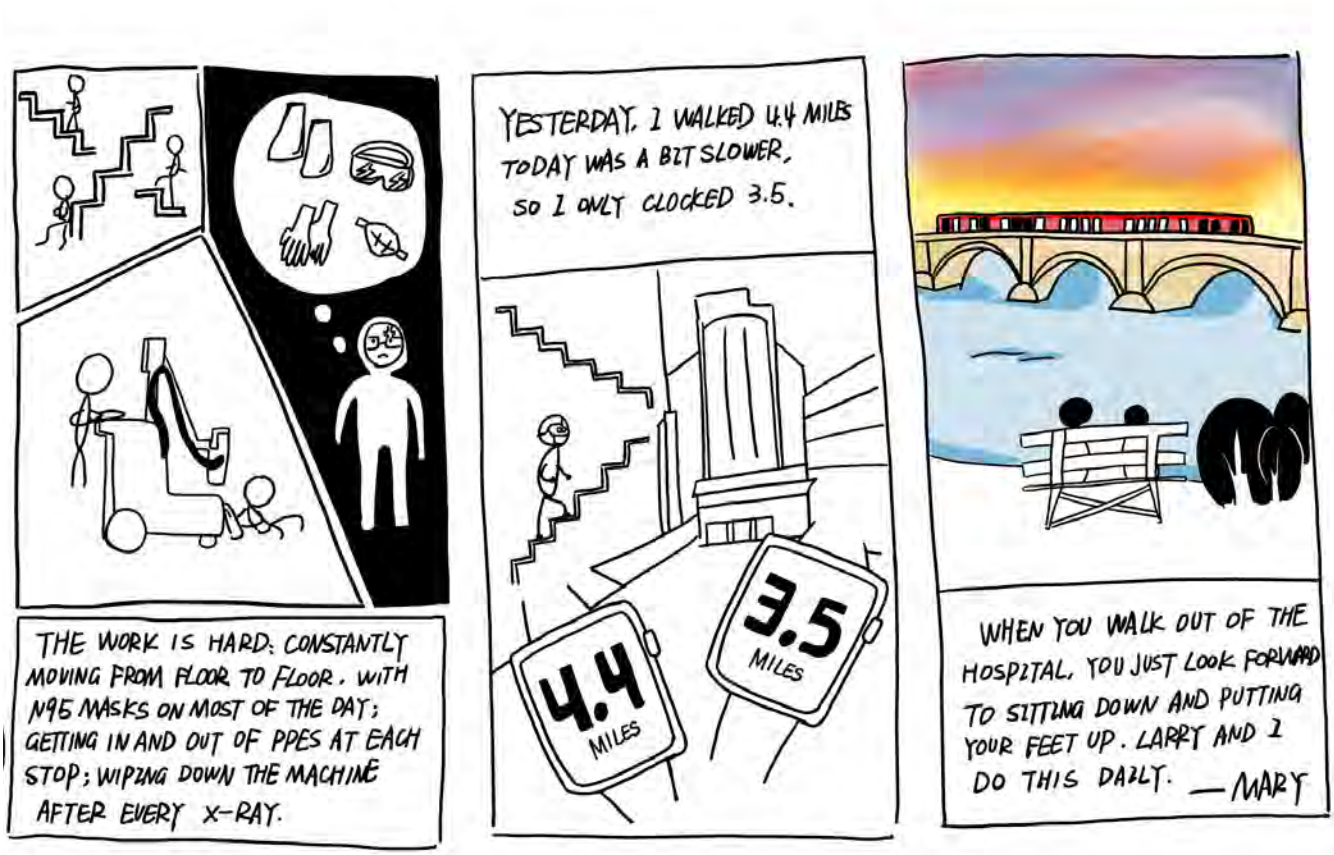
donations of any amount to the MGH COVID-19 Response Effort—but it also provided a kind of salve for members of the community experiencing the isolating effects of the pandemic.

Marco Loggia, the Martinos researcher who set the cookbook in motion with a video sharing one of his own recipes, later explained: "During these challenging times, filled with uncertainty, anxieties and social isolation, sharing homemade recipes felt like a wonderful way to feel more connected; a little like inviting each other to our own homes. Talking about each other's recipes became the start of many conversations and was an excuse to catch up, making up for all those water cooler chats that are currently not possible."

Efforts to support both the Martinos and the broader communities even extended to drawing cartoons. Beginning in April, the Center's Jingyuan Chen created a series of cartoons offering gently amusing takes on life during lockdown. She also gave us a poignant story of two Martinos staff members—senior MR technicians Mary O'Hara and Larry White—who redeployed early in the pandemic to run portable x-ray scans of patients with suspected COVID-19.




WORKING FROM HOME
CONTROL
DAY 1
DAY 2
DAY 30
QUARANTINE
DAY 1
DAY 2
DAY 30
JINAFFE CARTOONS

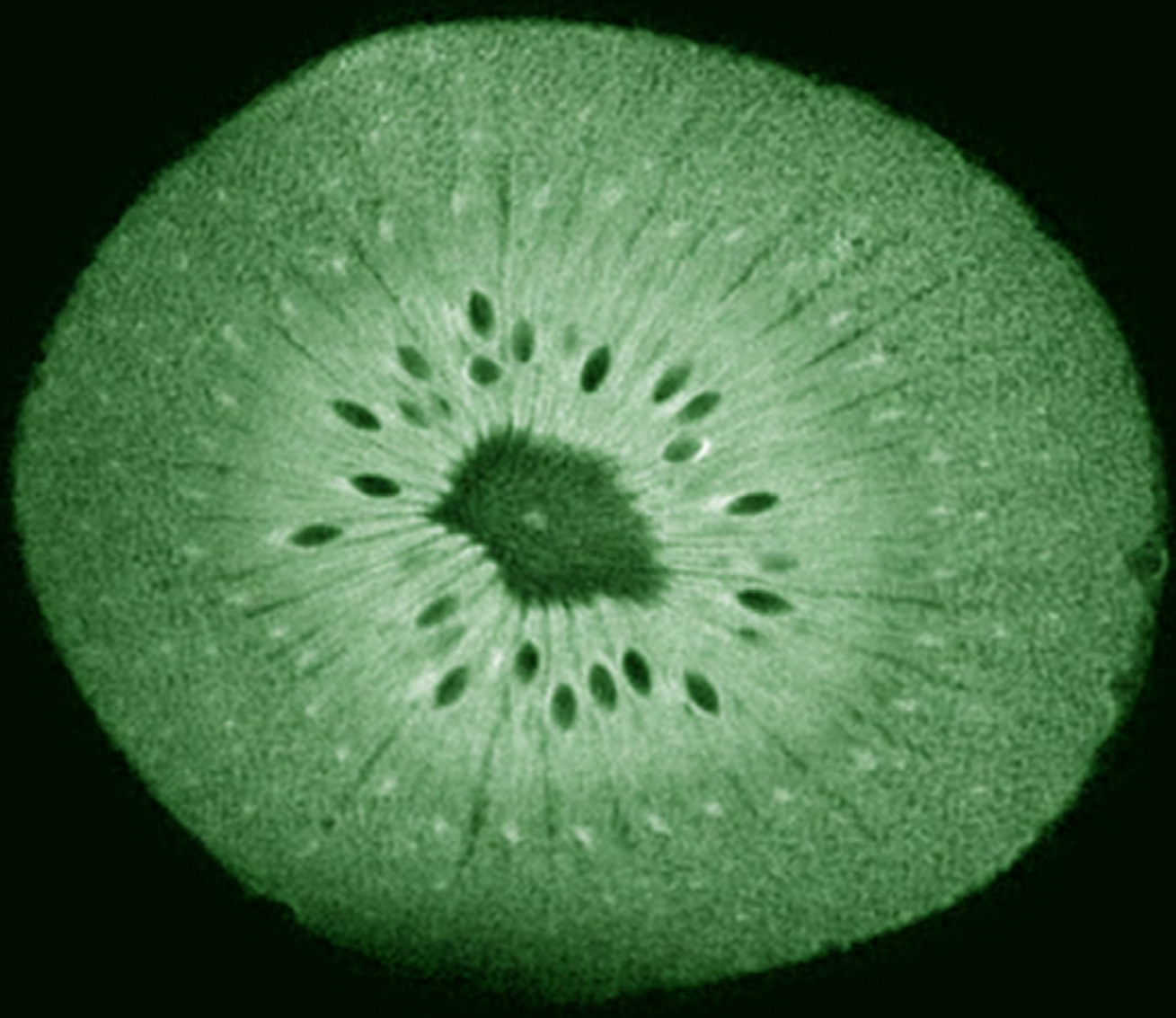

THE WORK IS HARD: CONSTANTLY MOVING FROM FLOOR TO FLOOR. WITH N95 MASKS ON MOST OF THE DAY; GETTING IN AND OUT OF PPES AT EACH STOP; WIPING DOWN THE MACHINE AFTER EVERY X-RAY.
YESTERDAY, I WALKED 4.4 MILES TODAY WAS A BIT SLOWER, SO I ONLY CLOCKED 3.5.
4.4 MILES
3.5 MILES
WHEN YOU WALK OUT OF THE HOSPITAL, YOU JUST LOOK FORWARD TO SITTING DOWN AND PUTTING YOUR FEET UP. LARRY AND I DO THIS DAILY. — MARY

2020 Image Contest

In August, the Mass General Research Institute opened submissions for its third annual image contest. With contributions from across Massachusetts General Hospital and its affillate institutions, the image contest gives researchers an opportunity to share images of their work and the stories behind their science and offers the general public an inside look at Mass General. Following are just a few of the many excellent submissions from Martinos researchers and staff, accompanied by the researchers' own descriptions of the images.

Kiwi
By Jerry Ackerman

This image was created as part of a research program to develop a compact MRI scanner for extremities (arms and legs). We wanted to test its performance before we have permission to scan humans. A kiwi is about the same diameter as a human wrist and serves as a convenient test subject. This image shows a high level of detail … and it really looks like a sliced kiwi! (We did not, of course, actually slice the kiwi.)



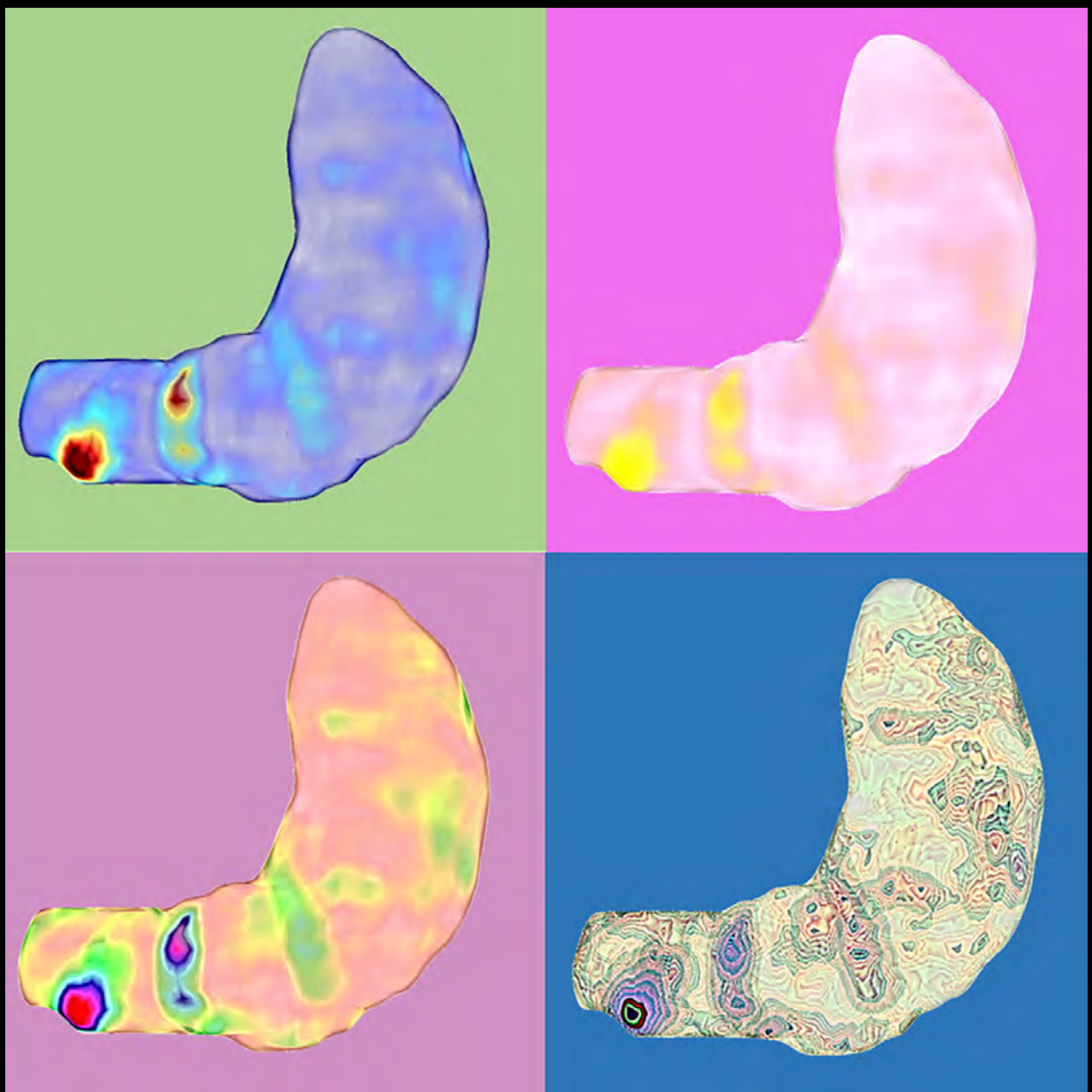
Serpentine Migration
By Don Straney

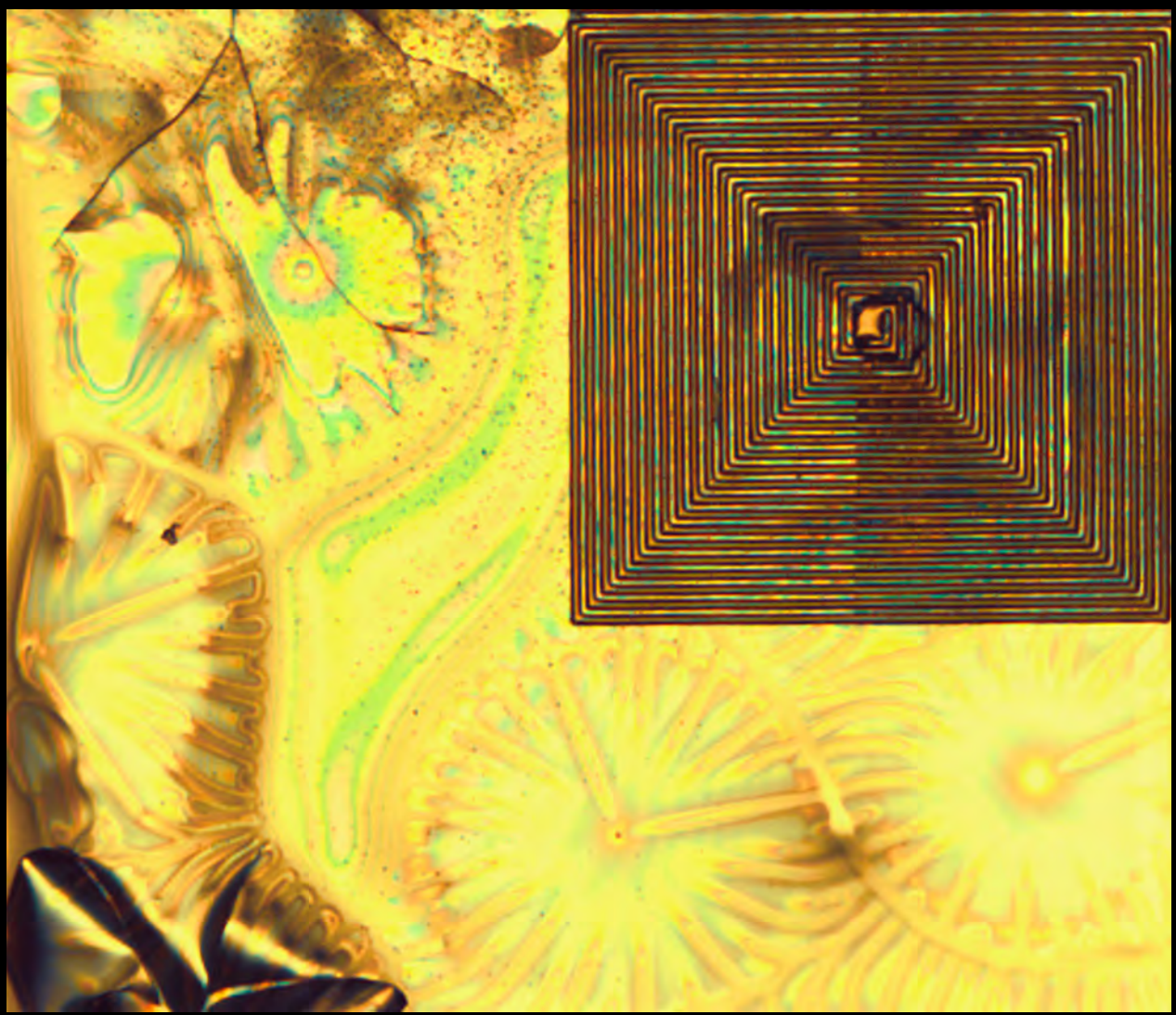
As a staff engineer, most of my time is spent developing and building electronics for the research groups here at the Martinos Center for Biomedical Imaging, but I'm also responsible for the automated magnet-health monitoring hardware on this 20-year-old 7T MRI system, which has hosted some unique research as a rare high-field human system but has not been covered by a service contract for a long time due to its age—we have to be on our toes to keep this magnet intact.

This is Your Stomach on Pineapple Pudding
By Roberta Sclocco

Gastric peristalsis can only be observed in its entirety by looking at the whole stomach volume continuously over time. This is not possible with current imaging techniques, which are limited by requiring breath hold to avoid motion in the images. We aim to make it as comfortable as possible for gastroenterology patients to have gastric evaluations. Our MRI technique works with free breathing, so gastric peristalsis can be observed without discomfort or time constraints. We are trying to understand what kind of information can be extracted from our images, and we hope to provide a useful tool for use in clinical settings.

When you eat, the top portion of your stomach expands to make space for the food. In order to move the food down and out of the stomach, the stomach wall is squeezed by contractions traveling from top to bottom (peristalsis), and generating the striped-like pattern. To observe such pattern, we asked participants to eat some pineapple pudding, since pineapple will make their stomachs look bright in the images without using other contrast agents such as gadolinium.



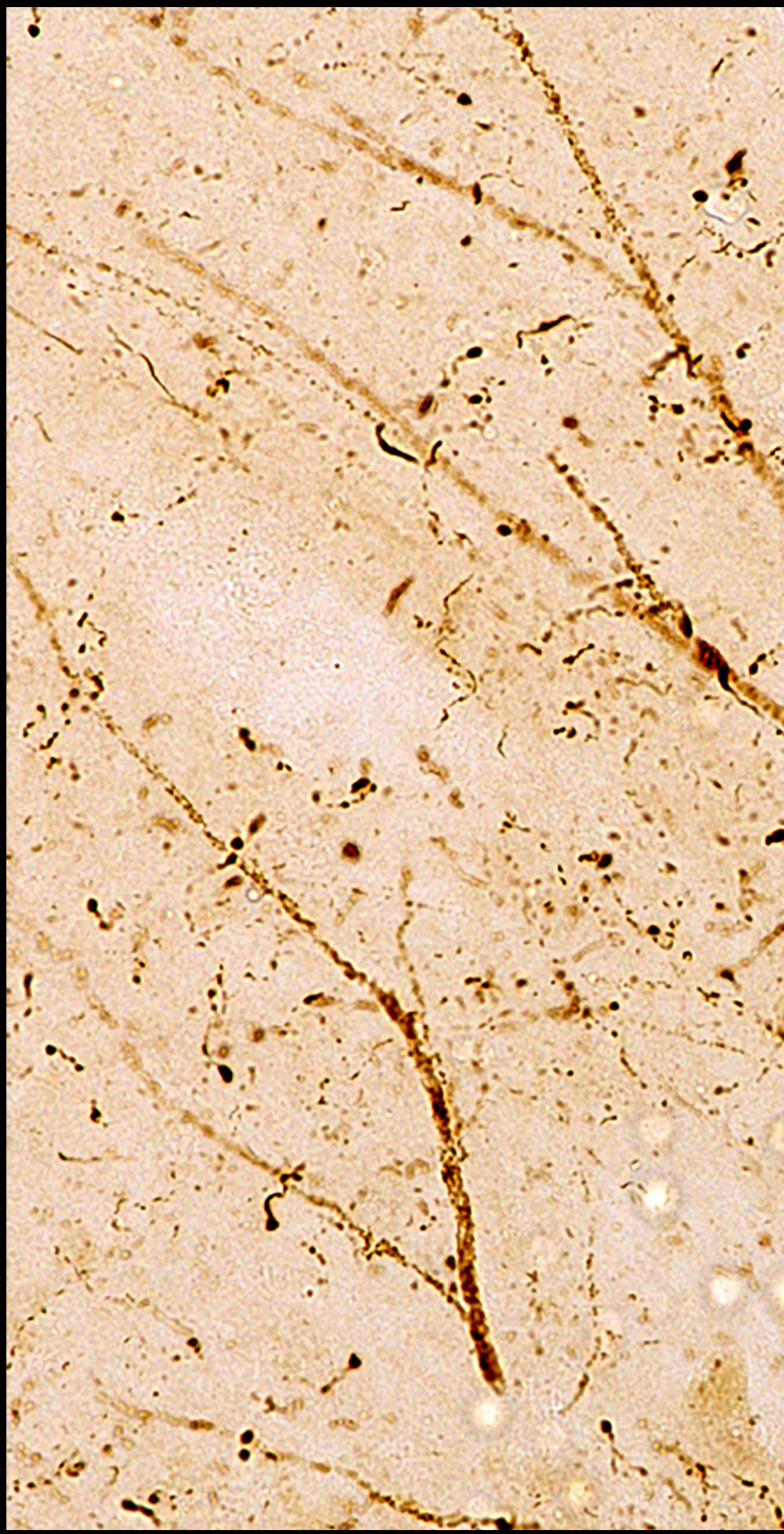


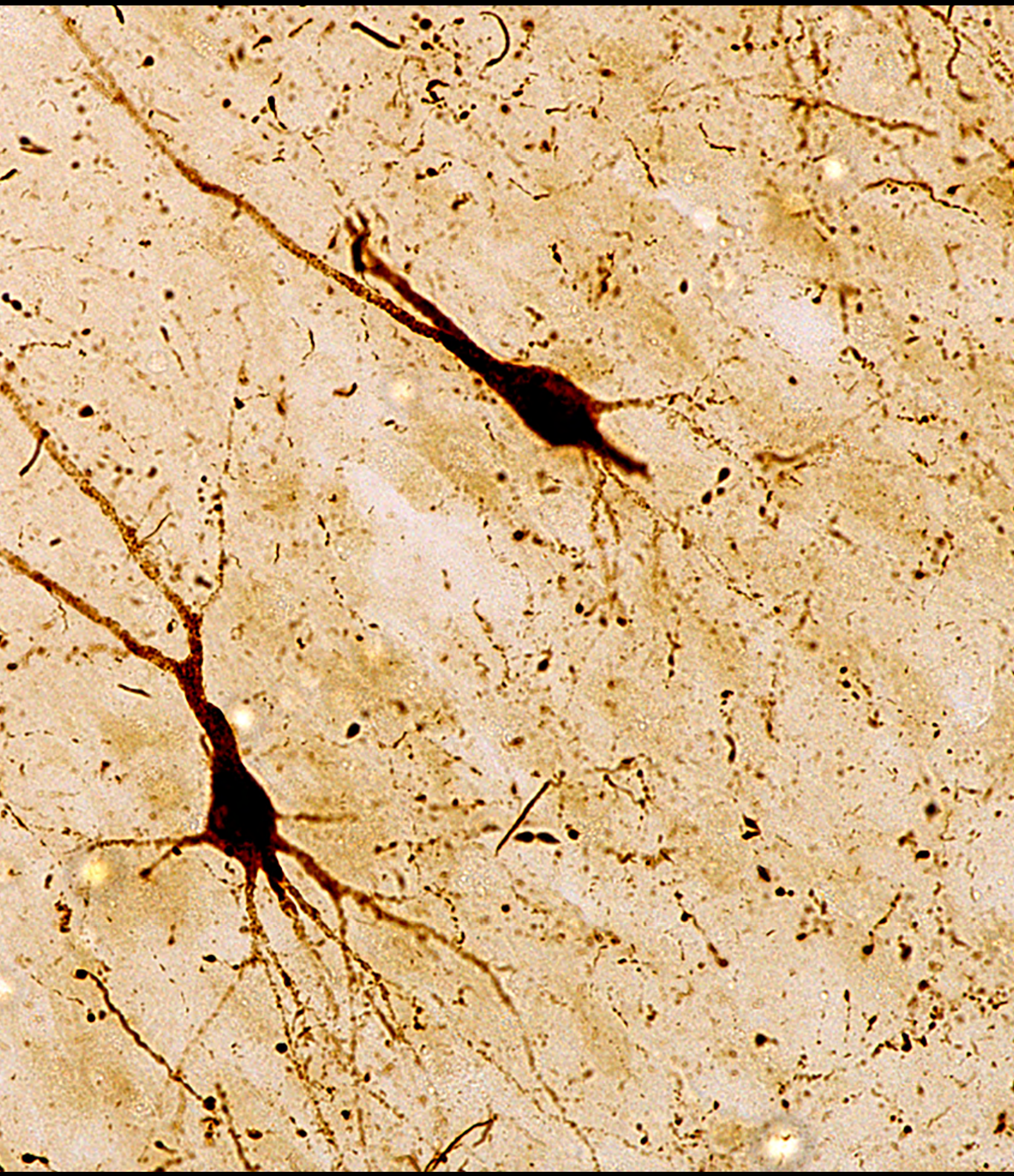
TIME for Intelligent Design
By Sean Downs

Photolithography is a powerful tool that allows for the design of nano-scale systems. At the Center for Nanoscale Systems (CNS), at Harvard, we design nano-coils for neuromodulation of the cervical vagus nerve. This is an image of an attempted coil design for neuromodulation of the cervical vagus nerve. We were checking the coil design to make sure each layer was aligned properly and we inadvertently created a picture of an owl and a clock from wet plastic and light.

It Takes Two to Tangle
By Josue Llamas Rodriguez

This is an image of two ghost tangles consumed by hyperphosphorylated tau, better known as neurofibrillary tangles, the main biomarker for Alzheimer's Disease. Neurofibrillary tangles are strongly correlated with cognitive dementia, and we can see with great detail the morphology of these neurons. I was performing immunohistochemistry, and while a lot of the tau we see is more "flame shaped" with random shapes, it caught my eye to see such a perfectly delineated neuron; it really exemplifies the dendrites and the nearby neighbors which often share the same fate. By exploring early markers of Alzheimer's pathology which precede cognitive symptoms, we have a better chance of coming up with potential therapeutic methods before it's too far along in the disease.





AI Measures COVID-19 Lung Disease Severity on Chest X-Rays

Early in 2020, a team of researchers at Massachusetts General Hospital was developing an artificial intelligence (AI) algorithm that could measure disease severity and detect change from medical images, which could help inform clinical decision-making. By March, they had described two potential applications of the algorithm. Monitoring disease progression in retinopathy of prematurity on retinal photographs showed a great deal of promise, as did evaluating disease severity in knee osteoarthritis on x-rays.

The researchers started thinking about other possible uses; because the algorithm architecture is flexible, it could be generalized to other clinical applications. But then the COVID-19 outbreak emerged as a global pandemic, scrambling the work of researchers and clinicians.

Matthew D. Li is a resident physician in the Department of Radiology at Mass General and a member of the Quantitative Translational Imaging in Medicine (QTIM) Lab at the Martinos Center for Biomedical Imaging, the group that developed the algorithm. When the hospital experienced a surge of patients with COVID-19, he volunteered to redeploy to a COVID-19 inpatient service to help with the effort to treat them. “While I was there,” he says, “I noticed there is a lot of information in a chest x-ray that isn’t really extracted or communicated in the report,” information that could convey to clinicians the severity of the findings. To help clinicians take advantage of this information, he and colleagues in the QTIM group set out to create an AI tool that could extract it from chest x-rays. They reported the tool in late July in the journal *Radiology: Artificial Intelligence*.

Objective Measures of Severity and Change

Clinicians often use imaging to evaluate both the severity and progression of disease, in many cases by assigning severity to one of several categories based on the imaging findings and seeing whether and how the classification changes on follow-up. This approach has limitations, though. Because manual readings are inherently subjective, there is inevitably variability in clinicians’ interpretations of the severity.

In their work done before the pandemic, the members of the QTIM group addressed this challenge by developing an automated algorithm for disease severity evaluation and change detection on a continuous spectrum. Based on the Siamese neural network, a type of deep learning architecture originally deployed in the 1990s for verification of credit card signatures, this algorithm takes two medical images as inputs and outputs a quantitative measure of difference in disease severity between the two images.

Having decided to apply it to imaging of COVID-19, the researchers set about training the algorithm—that is, feeding it imaging data so it could learn to extract patterns from other, similar data. For pretraining, they used a publicly available chest x-ray data set, CheXpert, from Stanford Hospital in Palo Alto, with 224,316 chest x-rays. For subsequent training, they used 314 admission chest x-rays from patients hospitalized at Mass General for COVID-19 during the period of April 1 to April 10, 2020. Further testing was done with additional COVID-19 data sets.

Now that it has been trained, when fed a new chest x-ray, the algorithm can extract a quantified measure of COVID-19 lung disease severity called the pulmonary x-ray severity (PXS) score. Comparisons with ground-truth interpretations by multiple Mass General radiologists showed correlations between PXS scores and tedious manually annotated scores for severity.

Informing Clinical Decision-Making

In the wake of the *Radiology: Artificial Intelligence*s study, Jayashree

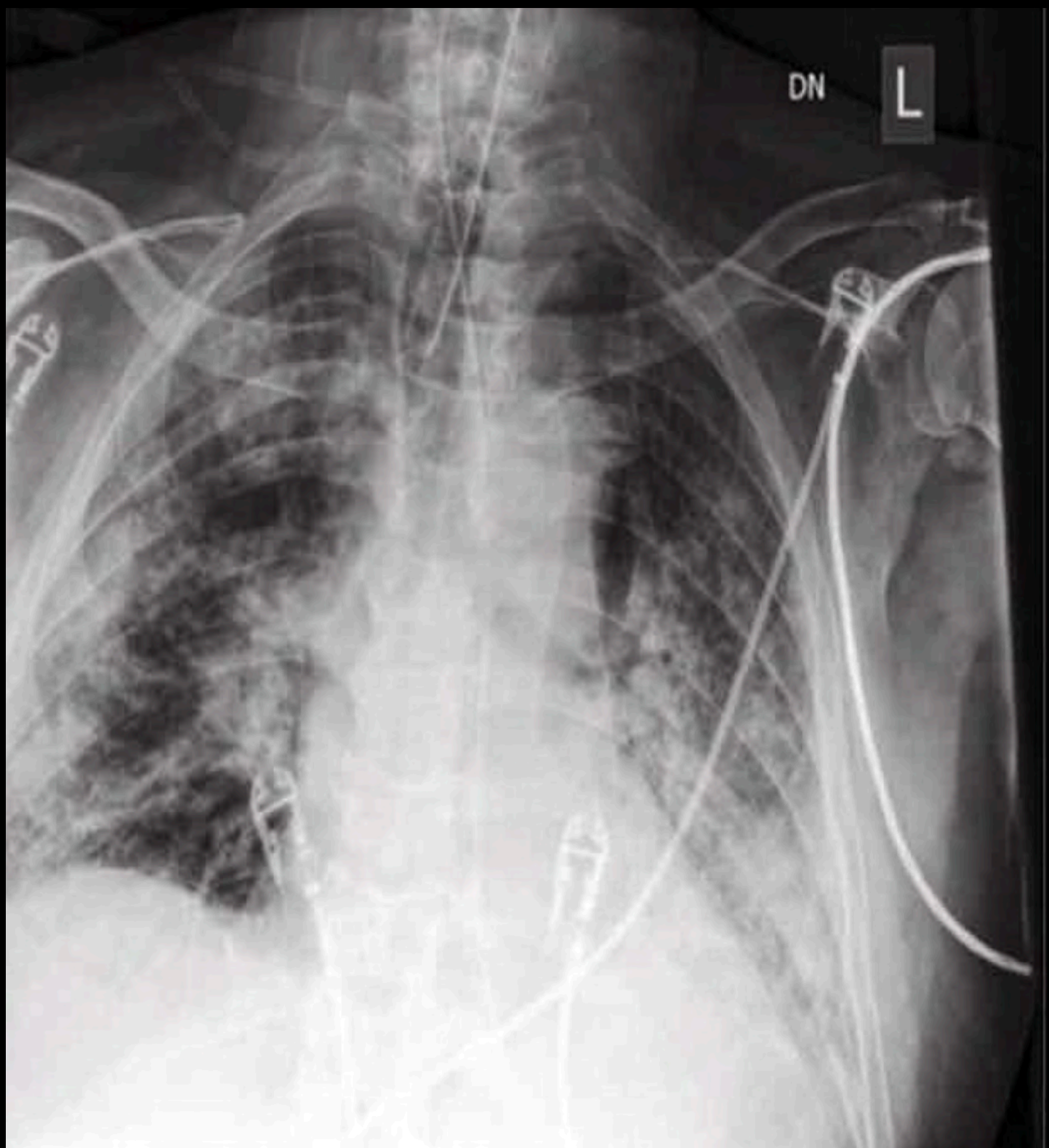
Kalpathy-Cramer, senior author of the study and director of the QTIM Lab, described several possible use cases for the algorithm. First, she said, was enabling standardized radiologist reporting and thus addressing the challenge of inter-rater and intra-rater variability. When a frontline clinician reads the radiologist's report, a descriptor is only useful if it is reproducible (severe means severe, mild means mild, etc.). The PXS score may help improve this reproducibility. The algorithm could also be helpful in clinical decision-making, as the PXS score can help predict subsequent intubation (needing a ventilator) or death. For example, by setting a PXS score threshold, frontline clinicians could use it to help assess the risk of patient decompensation, along with other clinical data like lab values and vital signs. To this end, the researchers were working to validate the algorithm in several additional cohorts so it could better generalize to broader patient populations.

Another possible application in patients with COVID-19 is monitoring the progression of the disease, providing a quantifiable answer to the question of whether or not a patient is getting better. Here, the authors of the study were working with Bruce Fischl and Adrian Dalca, both of the Laboratory for Computational Neuroimaging, also at the Martinos Center, to incorporate novel registration techniques to improve change detection with the algorithm.

Opposite: Jayashree Kalpathy-Cramer

Left: Matthew D. Li

Following: a pair of images demonstrating use of the algorithm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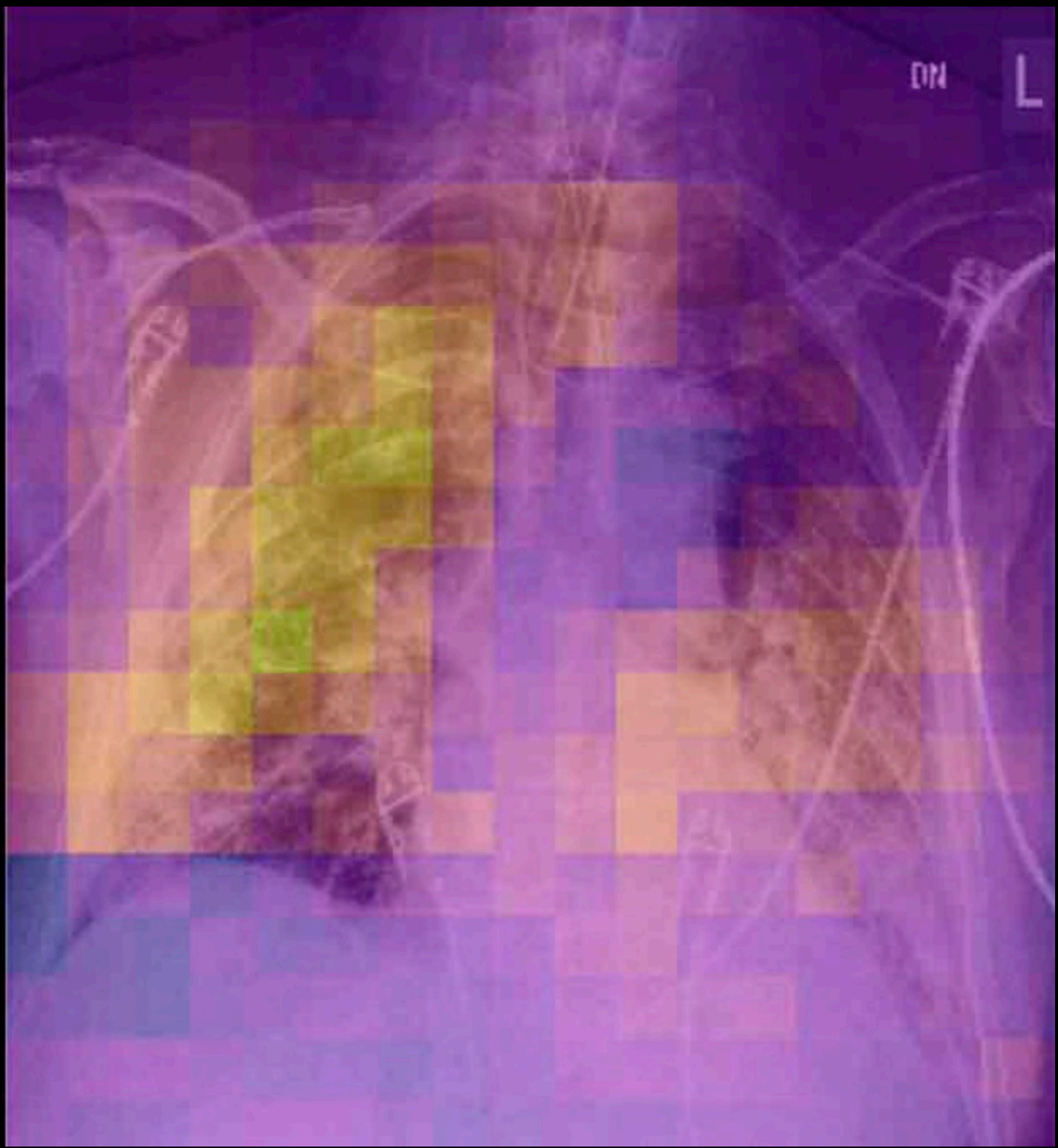
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Will Social Distancing Have a Lasting Impact on ‘Personal Space’?

Martinos Center faculty members are studying the possible long-term effects of social distancing during the COVID-19 pandemic.

Daphne Holt and Roger Tootell have long explored the neuroscience of personal space, seeking deeper understandings of the “comfort zone” we maintain around our bodies, consciously or not, and how the brain works to regulate this space.

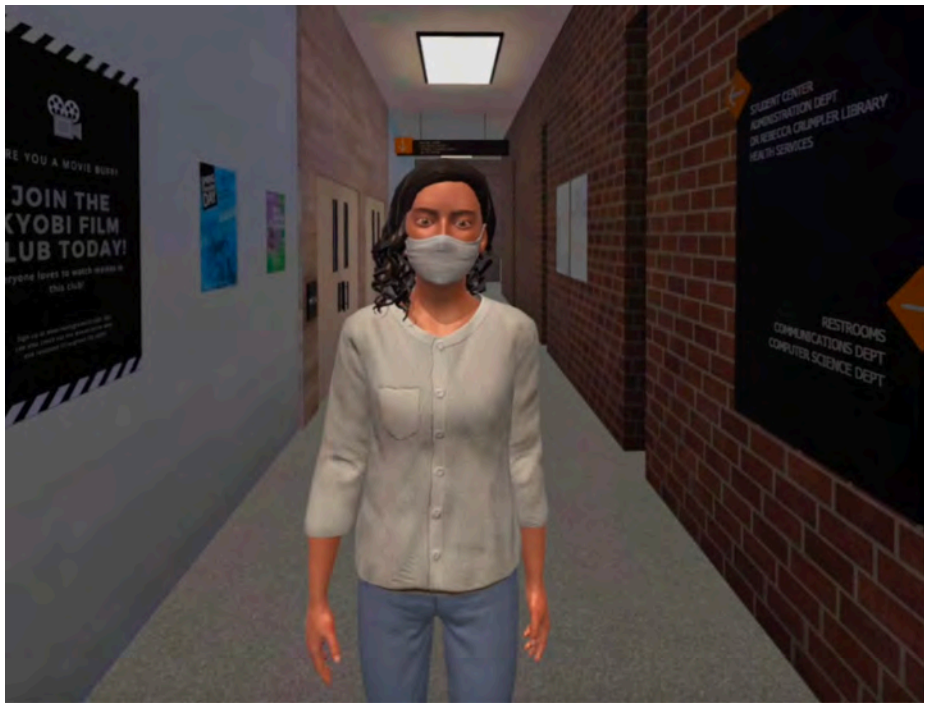
Two years ago, Holt and Tootell began using a new paradigm to help advance this work: a virtual reality model that provided a more reliable means to track individuals’ sense of personal space. After enrolling 19 subjects and measuring their responses to approaching avatars (virtual “persons”) in the virtual reality environment, they were optimistic about the new paradigm and what it might tell them about the neural underpinnings of personal space.

And then the COVID-19 pandemic hit.

The pandemic not only shut down all experiments at the Martinos Center for a number of months, it also presented a confounding factor when the studies resumed later in the summer. Namely: because it created dramatically different circumstances for subjects, the researchers could no longer conduct the experiments under the same conditions as before, and therefore would have to discontinue the original study.

However, Holt and Tootell saw an opportunity in the disruption to their work that the pandemic had caused: they could bring back subjects from the original round of experiments and, by comparing the measurements obtained before and after the onset of the pandemic, explore the potential impact of COVID—not least, the social distancing protocols put in place to help fight the virus—on individuals’ sense of personal space.

Ultimately, twelve of the subjects returned for additional experiments. The researchers analyzed the data from these new measurements,



Left: A screen-capture from a virtual reality-based intervention the researchers have developed. The intervention can serve as a type of exposure therapy, with approaching avatars, for patients with social functioning challenges associated with increased personal space requirements.

and were intrigued by what they found. First, they noticed that personal space had expanded in the subjects, both in real life and in virtual reality. This observation pointed to a real, intrinsic change in their personal space requirement during the pandemic.

At the same time, they had asked the subjects questions about how worried they were about contracting the COVID-19 virus, hoping to understand the relationship between personal space and their level of concern about being infected. When looking at the data, they indeed saw a correlation between the two, suggesting a possible broader struggle for those who are more concerned about the virus.

“These findings support an idea that goes back to Freud’s original insights,” Holt says. “Our conscious worries and beliefs about our lives can influence our day-to-day behavior in ways that we’re not aware of. In this case, the influence of the pandemic on our minds could affect our ability to interact comfortably with other people for quite some time.”

And it’s not only interpersonal interactions that could be impacted. Other aspects of our daily lives might also prove challenging. “Although we are generally not aware of it,” Tootell says, “many buildings are designed based on a ‘normal’ personal space. This was about two feet before the pandemic. If the average personal space requirement has now become larger, then certain architectural features—small rooms and elevators—may feel too crowded, at least until personal space requirements relax again.”

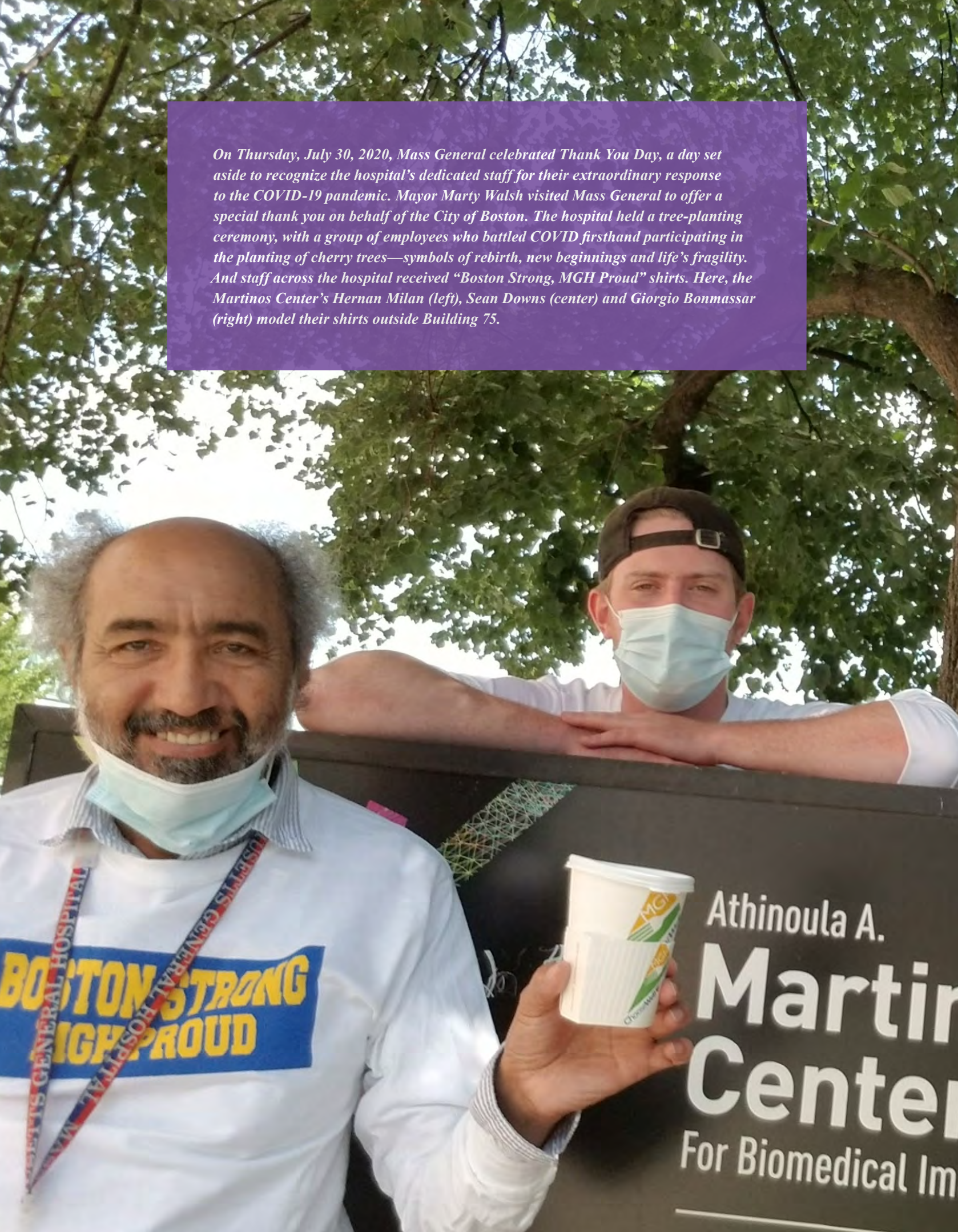
If they relax again. Holt and Tootell emphasize that we don’t yet know whether the increase in personal space size will reverse itself after the pandemic eventually subsides or proves an enduring change. This question is an important one, not only because the answer will tell us something about the plasticity of brain mechanisms associated with personal space but also because personal space size often serves as a marker of social functioning.

For example, correlations have been found between personal space size and social withdrawal and other negative symptoms in schizophrenia, mediated by a specific sensory-motor circuit in the brain. If the recently observed increases in personal space endure even post-COVID, many people may experience persistent difficulties in social functioning—difficulties that might need to be addressed clinically.

In fact, this team of scientists and clinicians, including Nicole DeTore and Sarah Zapetis, is currently developing a virtual reality-based intervention to help modify personal space in cases where social functioning is compromised: a type of exposure therapy in which patients are acclimated to the simulated physical closeness of other people in a safe, virtual way. The intervention could be beneficial for patients with social dysfunctions stemming from pandemic-related distancing as well as those who experience negative symptoms of schizophrenia or other diseases.

Ultimately, the ability to perform high-resolution imaging of the brain circuitry involved in regulating personal space could play an additional role in treating these patients.

“In the future we may be able to improve the function of this part of the brain directly, using virtual reality interventions like the one we’ve developed,” Holt says. “This would allow us to refine the treatment and its dosing based on the responses of a person’s brain. This could end up being very useful in treating something as difficult to measure as someone’s ability to feel comfortable with others.”



On Thursday, July 30, 2020, Mass General celebrated Thank You Day, a day set aside to recognize the hospital's dedicated staff for their extraordinary response to the COVID-19 pandemic. Mayor Marty Walsh visited Mass General to offer a special thank you on behalf of the City of Boston. The hospital held a tree-planting ceremony, with a group of employees who battled COVID firsthand participating in the planting of cherry trees—symbols of rebirth, new beginnings and life's fragility. And staff across the hospital received "Boston Strong, MGH Proud" shirts. Here, the Martinos Center's Hernan Milan (left), Sean Downs (center) and Giorgio Bonmassar (right) model their shirts outside Building 75.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Detecting Consciousness in Unresponsive Patients with COVID-19

In August 2017, the Martinos Center's Brian Edlow and colleagues reported a study in which they demonstrated use of functional MRI to detect "covert consciousness" in otherwise unresponsive patients in the ICU with severe traumatic brain injury. By recording responses to language or music stimuli in the patients' brains, even when they found no evidence of language function on bedside examination, the researchers showed the technology could help patients' families make critical decisions about continuing care.

Three years later, amidst the surge of COVID-19 cases in Boston and across the Northeast, Edlow and others in the Center and elsewhere reported using fMRI to detect signs of consciousness in a patient recovering from the disease. The findings, published in the journal *Annals of Neurology*, suggested that unresponsive patients with COVID-19 could have a better chance of recovery than researchers had previously believed.

The paper describes a 47-year-old patient who contracted the virus and subsequently developed progressive respiratory failure. Like many with severe COVID-19, the patient remained unresponsive after surviving critical illness, fluctuating between coma and a minimally conscious state for several weeks.

Standard imaging tests revealed considerable structural damage to the patient's brain, auguring a poor prognosis. However, imaging with a technique known as resting-state fMRI told a different story.

Resting-state fMRI assesses the strength of the connections between brain networks by measuring spontaneous oscillations of activity in the brain. When Edlow and colleagues scanned the patient using the technique, they were surprised to find robust functional connectivity in the default mode network (DMN), a brain network thought to be involved in human consciousness. Studies have shown that stronger DMN connectivity in patients with disorders of consciousness predicts better neurologic recovery.

The connectivity observed in the patient with COVID-19 was comparable in strength to the connectivity seen in healthy individuals, suggesting the prognosis might not be as bleak as standard imaging tests implied. In fact, twenty days after the scan, on hospital day 61, the patient began following verbal commands, both blinking his eyes and opening his mouth on command. On day 66, the patient followed four out of four vocalization commands. By this time, he also consistently demonstrated gaze tracking with his eyes in response to visual and auditory stimuli.

The findings of the study underscore the need to know as much as possible about the status of the brain in disorders of consciousness. "Because there are so many

unanswered questions about the potential for recovery in unresponsive patients who have survived severe COVID-19, any available data that could inform prognosis are critical," says Edlow, director of the Laboratory for NeuroImaging of Coma and Consciousness at Mass General, an affiliated faculty member in the Martinos Center, and senior author of the *Annals of Neurology* paper. "Our unexpected observations do not prove that functional MRI predicts outcomes in these patients, but they suggest that clinicians should consider the possibility that unresponsive survivors of severe COVID-19 may have intact brain networks. We should thus exercise caution before presuming a poor neurologic outcome based on our conventional tests."

Left: Bruce Rosen

Opposite: Brian Edlow

The application of functional MRI to critically ill patients with COVID-19, as described in the paper, represents the culmination of decades of work by countless researchers in the Martinos Center and elsewhere—researchers seeking to develop a technology capable of revealing the secrets of the brain, including the mysteries of consciousness itself, and ultimately translate it to clinical care.

Bruce Rosen, director of the Martinos Center, co-author of the *Annals of Neurology* paper and one of the architects of functional MRI, reflects on how far the method has come since the early 1990s, when a handful of young researchers in the Center—at least one of them dreaming of capturing and downloading consciousness onto a chip—launched a series of bold, mad scientist-level experiments seeking nothing less than a means to measure activity in the brain.

"We never would have guessed the myriad ways in which fMRI would contribute both to our understandings of the brain and to the advancement of human health," he says today. "But when you gather together groups of people like we've had here over the years and connect them with the types of resources made possible by the Martinos gift, really anything is possible."

The Center's "Martinos Day," May 29, 2019


Martinos Center