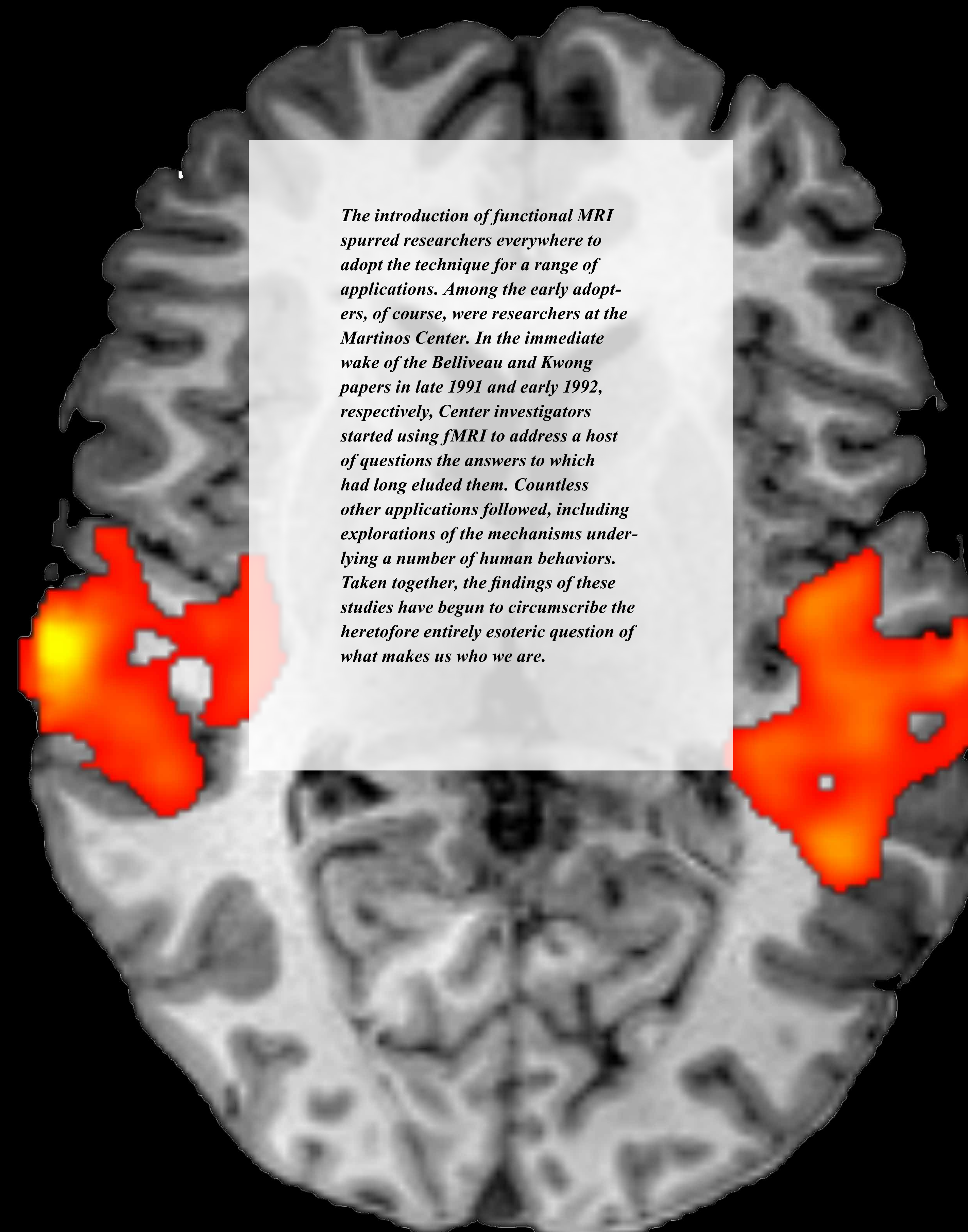
Functional MRI Applications



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 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 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.

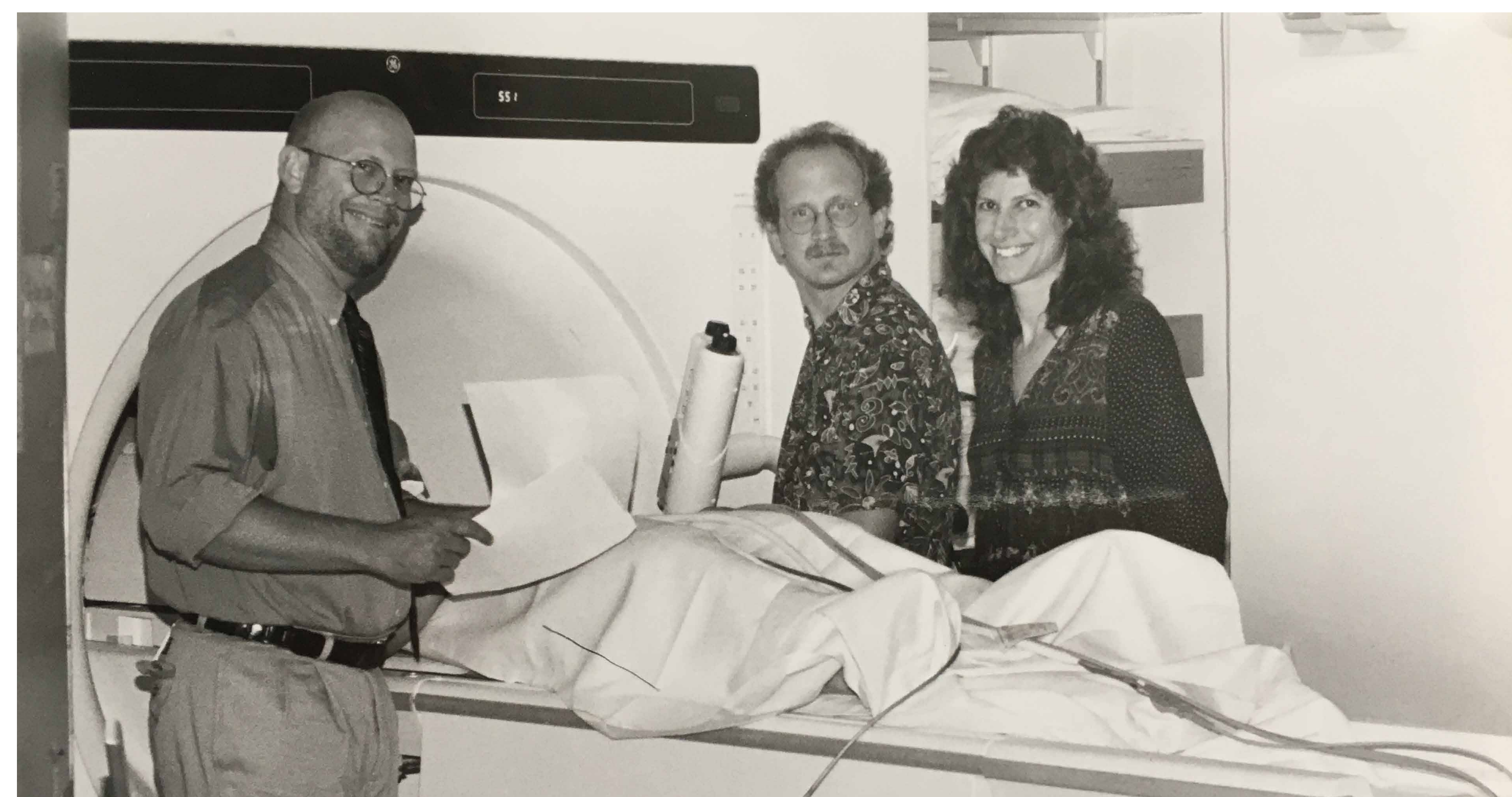
Above: This X-ray image, the first ever produced, shows the hand and ring of Anna Bertha Roentgen, wife of Wilhelm Roentgen, who discovered the X-ray in 1895.

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

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.



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.

Above: Daphne Holt and Roger Tootell

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 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 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 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' in 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 electronic 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.

The original functional MRI methods measured changes in in the brain in response to the subject performing motor tasks, for example, or to visual stimuli such as flashing patterns of light. The brain is always active, though, even in the absence of external stimulation. This intrinsic activity produces spontaneous fluctuations in the signal that fMRI measures, which can reveal information about the functional organization of the brain.

Since the 1990s, researchers have been using fMRI to probe this organization, which they have dubbed resting-state functional connectivity, in both health and disease. In health, the researchers have identified a number of strongly interconnected neural networks that are active when a subject is at rest. With respect to disease, they have recorded altered connectivity in, for example, neurological or mental disorders. Thus, by imaging these networks and how they may change over time, resting-state functional MRI can help advance a wide range of applications.

In 2014, the Martinos Center hosted the fourth biennial conference on Resting State and Brain Connectivity in Cambridge. Shown here is Center director Bruce Rosen speaking during the conference.

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," said Nouchine Hadjikhani, an associate professor of radiology at Harvard Medical School, director of neurolimbic research in the Martinos Center and corresponding author of the new 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/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 suggests 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 said, "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."

The co-authors of the Scientific Reports study were Nicole R. Zürcher, Amandine Lassalle and Noreen Ward of the MGH Martinos Center; Jakob Åsberg Johnels, Eva Billstedt and Christopher Gillberg of Gothenburg University, Gothenburg, Sweden; Quentin Guillon of the Lyon Neuroscience Research Center, Lyon, France; Loyse Hippolyte of the University of Lausanne, Lausanne, France; and Eric Lemonnier of CRA, of Limoges, France.

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 traumatic brain injury. They also explored whether these advanced techniques could uncover higher levels of brain function, suggesting a potential for recovery of consciousness, and whether the early brain responses they observed were associated with better long-term functional outcomes.

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 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

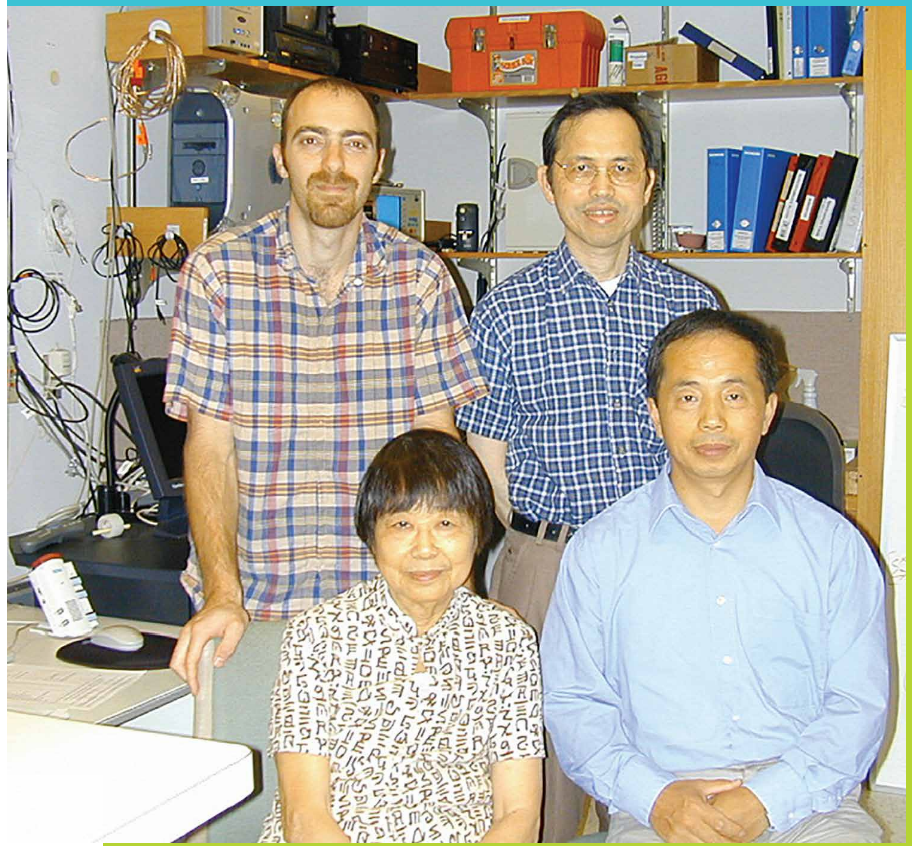
First author Dan-Mikael Ellingsen and research assistant Kylie Isenburg preparing an fMRI hyperscan subject

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."

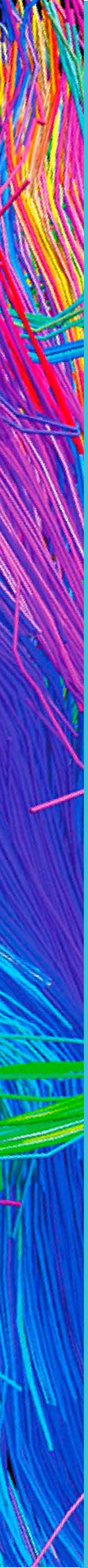


Vitaly Napadow has been an integral part of the acupuncture effort at the Martinos Center for nearly two decades—since joining the Center in 2001 as a postdoctoral fellow working with Ken Kwong, Jing Liu and Kathleen Hui to understand better the brain's response to acupuncture needling.

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 acupuncture and carpal tunnel syndrome among others.

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

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



Meet the **Neuronauts**

After the 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 ensuring 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 human brain and 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 the 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.