

On Introducing Noninvasive fMRI: A Conversation With Ken Kwong

[November 29, 2016](#) Gary Boas

In the early months of 1992 the neuroscience community was flush with excitement. Jack Belliveau, a graduate student with the MGH-NMR Center (now the MGH Martinos Center for Biomedical Imaging), had recently published in *Science* 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.

Fortunately, another Center investigator, a postdoctoral fellow named Kenneth Kwong, found a way past this. In June of 1992, in a paper published 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. By thus removing the necessity for an external agent, he opened up the technique for much broader use than would have been possible otherwise, making possible many of the extraordinary advances we've seen in the years since.

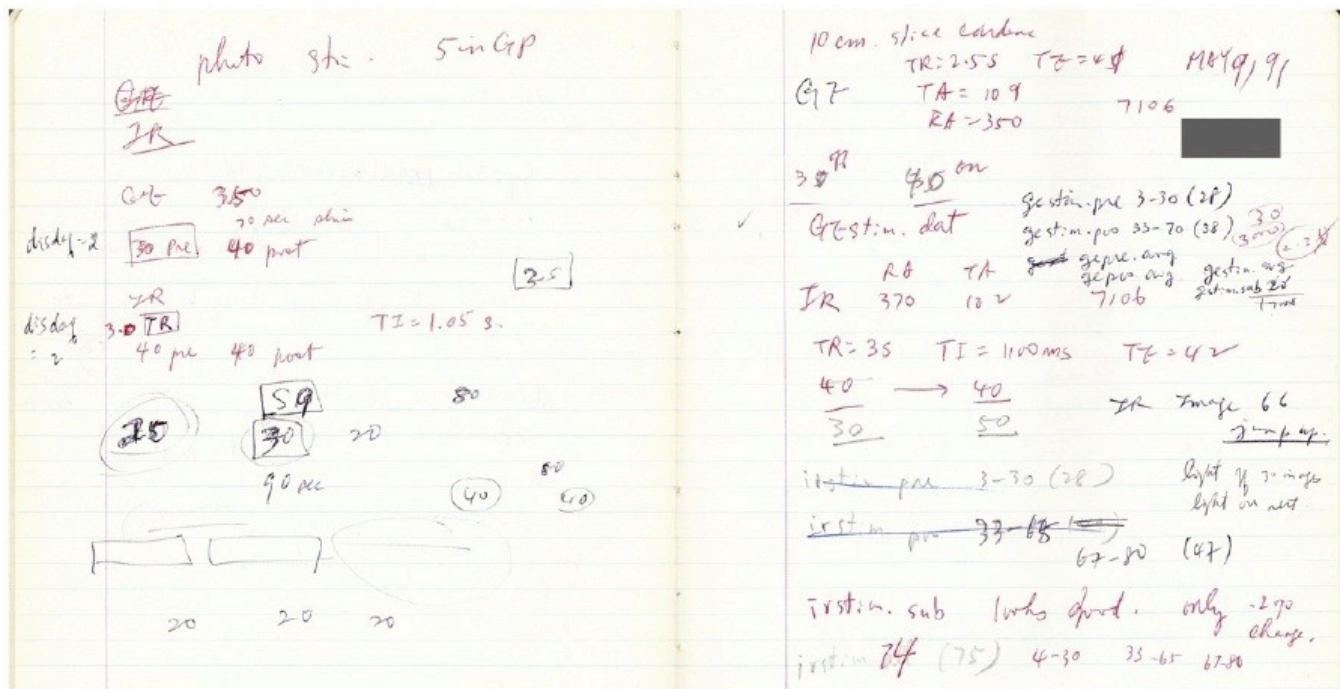
Kwong isn't one to tout his accomplishments. The book *Quiet*, something of a treatise on the power of introverts, of those who have little need for attention and little if any use for the (over)stimulation of the outside world, describes him as "a brilliant but unassuming scientist." And indeed, in a recent conversation about those early days of fMRI, he often downplayed the creativity of his insights during the run-up to the experiments and the experiments themselves, or deflected attention by pointing to the moments of chance or serendipity that led him to those insights.

In any event, the results of his work speak loudly enough.

Still, one can't help but wonder: What led to these successes? Where did he get the ideas that helped to bring about a revolution in functional neuroimaging? And importantly, how did he actually make them work?

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, in about 1988, to work with MIT graduate student Daisy Chen—an early advisee of Martinos Center Director Bruce Rosen—in developing and applying diffusion MRI methods as part of Chen's Ph.D. thesis. In 1990, when he started down the fMRI path, he was seeking new ways to measure cerebral perfusion—essentially, blood flow in the brain. One possible means could be found in the MRI technique that would come to be known as arterial spin labeling. This had provoked quite a bit of excitement among academic research types when it was first described earlier in the year. But he wanted to test other approaches as well, to try to determine which of them would work best.

He found particular inspiration in a 1982 report by Keith Thulborn and colleagues. Here was the first moment of serendipity in the story. A brief snippet of conversation with Thulborn—who in 1990 was a radiology resident at MGH—alerted him to the possibility that changes in the oxygenation of the blood could cause a measureable change in MRI signal. A very brief snippet, as it happened. "I heard one sentence," Kwong said. "I wasn't even sure he was talking to me." This suggested to Kwong another possible means to measure perfusion. Thulborn had shown in blood samples that changes in deoxyhemoglobin could impact the MR parameter T2*, anticipating what Seiji Ogawa of Bell Laboratories would describe in a 1990 paper, a phenomenon that would come to be known as blood oxygen level dependency (BOLD).



Kwong's lab notes from his initial fMRI measurements

More than 25 years later, he muses over the bit of happenstance that led him to this realization. “Had I not caught Keith’s sentence I would not have made any link between deoxyhemoglobin and the MR signal,” he said. “It was not my area of expertise, and at the time I wasn’t aware of Ogawa’s work.” Still, now that he was aware of Thulburn’s result, he wanted to see whether deoxyhemoglobin was an option that he could put to use.

The first step: designing an experiment. From experience, he knew that one of the most robust ways to test measures of perfusion was to induce changes in cerebral blood flow. He was already doing this with a CO₂ protocol in animal models, testing whether diffusion MRI could be used to measure changes in perfusion (he notes that he wasn’t successful). But because delivering CO₂ to human subjects would require a more elaborate experimental setup, he decided to use another, alternative approach. For this, he once again turned to something he’d overheard in the hallway.

Throughout 1990, even as Kwong was studying up on arterial spin labeling, often in exchanges with researcher David Chesler, and the relationship between deoxyhemoglobin and T₂^{*}, the Center’s Jack Belliveau was developing a means to image brain activity with MRI and performing his seminal experiments using a visual stimulation paradigm—the experiments that would be reported in *Science* in November 1991. Kwong

wasn’t involved in this project but he’d heard through the proverbial grapevine what Belliveau was up to. And he saw in it a natural approach to inducing changes in flow.

He talked to Belliveau about his idea to use the same visual stimulation paradigm. Belliveau was very supportive, offering suggestions about how to go about it and even loaning Kwong a pair of visual stimulation goggles—the same, famous red goggles that researcher Peter Fox had used in his seminal stimulation rate experiments in the early 1980s and that Belliveau had borrowed and used for his own experiments. Next, Kwong, who otherwise worked largely by himself, started gathering colleagues, some of them from Belliveau’s team, to help run the experiments.

The first of these experiments took place on the evening of May 9, 1992, in what is now Bay 3 at the MGH Martinos Center. 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 it was the first time he was trying this new approach and he had no expectation of it working right out of the gate. He doesn’t recall if David Kennedy was at the console with him, but he remembers learning from him earlier in the day the anatomical location of the visual cortex of the brain.

Brigitte Poncelet wasn't at the console, but she had provided him with her time course subtraction routine also that day.

The subject this particular evening was a friend of Kwong's—an MIT student and an always-game participant in the mad scientist-like experiments under way in the Center.

Since he had no idea whether either of the MRI sequences would even work, he applied Poncelet's subtraction paradigm immediately after the end of the imaging session. "Lo and behold," he said, "in both methods 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 in the T2* images as well as blood flow-related changes in the T1-weighted data. This 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 significant 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 about having just 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. 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'd found.

Getting the word out; 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 your 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 and of those that 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 midnight 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 announcement of Kwong's groundbreaking findings to a mention by Bernice Hoppel during a paper presentation and a short video in a plenary lecture by Brady.

Kwong naturally would have preferred to present his findings in full, but even this brief, tantalizing glimpse of what he'd 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 under way.

In the meantime, Kwong and colleagues wrote a more comprehensive paper detailing the work. They submitted it to *Nature* in October of 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."

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 endogenous contrast. "I was surprised when *Nature* rejected the original paper," Kwong said, 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.