

## Chapter 2

# The Birth of Functional MRI at the Medical College of Wisconsin

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In 1991, I was a second-year graduate student looking for a Ph.D. thesis project. I was looking to work on something related to extracting functional and/or physiological information from MRI, and I was exploring flow, chemical shift imaging, and Le Bihan's "intravoxel incoherent motion" (IVIM) hypothesis in which the  $b$ -value is set to about 50 with the idea that it will sensitize the image to small localized activation-induced changes in perfusion through randomly oriented capillaries. I had two co-advisors. The first was Dr. Jim Hyde at the Biophysics Research Institute at the Medical College of Wisconsin (MCW) in a suburb of Milwaukee called Wauwatosa, and the second was Dr. Carl Crawford from the Applied Science Laboratory at General Electric Medical Systems, 15 miles to the west, in Waukesha. This was part of an effort to grow collaborations between the two groups, and I believe it worked incredibly well—although the program was discontinued after I passed through it. Having offices at GE and at MCW was extremely useful to my project, especially in the early stages. Initially, Norbert Pelc was my GE-based co-advisor, but he left for Stanford about a month after I started. Thankfully, Carl picked me up to keep the collaboration going.

As I was starting graduate school, I quickly realized that my fellow graduate student, Eric Wong, well into his project which involved the design of gradient coils and perfusion pulse sequences, had overlapping interests with me, and he was more fun to talk and work with than anyone I knew, so I started working with him more. He taught me most of what I know about MR physics and data processing, and he was perhaps the key to the success of functional MRI (fMRI) at MCW as well as my own early success with fMRI.

In 1991, 2 weeks before the meeting of what is now called the International Society of Magnetic Resonance in Medicine (ISMRM), then called the Society of Magnetic Resonance in Medicine (SMRM), held in the beginning of August in

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**Fig. 2.1** *Top left to bottom right:* the sequence of making the gradient coil for performing EPI and first fMRI experiment. Eric, his wife Denise, and I made this in 36 h over the weekend before SMR. After designing the coil layout on his NeXT computer, Eric printed out the sheets, which we traced on to the PVC (i.e., sewer) pipe. These patterns were then gouged out with a Dremel tool (we went through several), and the wires were literally hammered in. Then, the next layer of epoxy was applied, and the process was repeated. *SMR Society of Magnetic Resonance*

San Francisco, Eric wanted to apply his novel pulse sequence for measuring perfusion (Wong and Hyde 1991) to humans. It required echo-planar imaging (EPI), and therefore when using the standard 1.5T clinical GE gradient amplifiers (100 A) at the time, required the use of a low inductance local gradient coil to allow rapid gradient switching. Since he had so far only constructed a small wrist/rodent local gradient coil for EPI, he did not have human results. Within 2 days, Eric had the human head local gradient coil design worked out. He could work relatively rapidly on design since he had been optimizing gradient element placement methods for this thesis work. With the completion of this design, he, his wife Denise, and I were in the machine shop applying layers of epoxy and wire to poly(vinyl chloride) (PVC) sewer pipe. Two days of continuous work later, we had a working gradient coil. Eric then fashioned, within a few more days, a radio frequency (RF) coil that was fixed inside the gradient coil. From design to construction completion (gradient and RF coil), the process took less than a week. A few pictures from that process are shown in Figs. 2.1 and 2.2. After Eric successfully scanned an apple with a conventional multi-shot sequence, Denise put her head in with beautiful results. We then tried

**Fig. 2.2** Our first local head gradient coil for performing EPI. It was a three-axis gradient coil, designed by Eric Wong. Inner diameter was 26.5 cm. On the standard GE gradients at the time (100 A), the gradient strength was about 2 G/cm for all three axes with a rise time of 50  $\mu$ s from zero to full scale



EPI, and it worked flawlessly. Here, the gradient coil had balanced torque and was simply strapped to the table for use—which, in retrospect, might be considered a risky thing to do since there is an extremely small but nonzero probability that it could torque while on the table. While there were risks involved, we were extremely careful as we wheeled the gradient coil and accompanying apparatus multiple times through the long tunnels of the hospital between our offices and the hospital 1.5T usually very late at night—and spending about 30 min for setup and takedown. Data were saved on 20-MB reel-to-reel tape. It was not until about 1996 that data were transferred over the network from the scanner. Until then, we perfected the use of our “sneakernet.” I recall working hours on a lone VT100 terminal in the chilled equipment room as data were saved and pulse sequences compiled.

It turned out that the final results using Eric’s perfusion measuring pulse sequence were not successful since the sequence was also extremely sensitive to motion. Nevertheless, we were primed for the flurry of activity that was to come after the meeting.

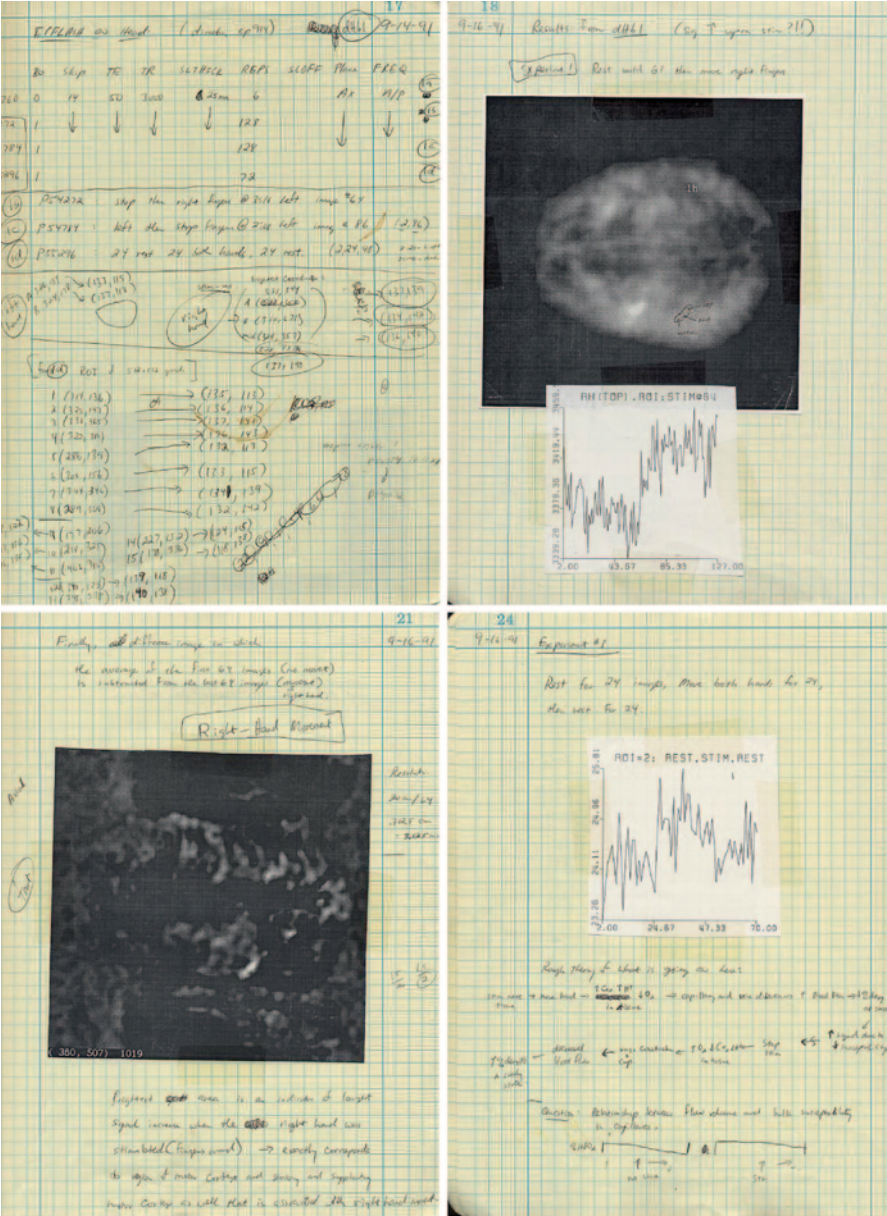
At the SMRM meeting, on August 12, 1991, Eric and I were in the auditorium during Dr. Tom Brady’s plenary lecture on “Future Prospects for MR Imaging” (Brady 1991). Dr. Brady was the director of the Massachusetts General Hospital-Nuclear Magnetic Resonance (MGH-NMR) Center at the time. At some point in his lecture, he said something paraphrased to, “...and this is brand new...we are able to use MRI to see function *without* any contrast agent! Here’s a movie provided to me by Ken Kwong at our center....” He showed the movie of a series of sequential grainy, low-resolution axial EPI subtraction images of a plane that included visual cortex—depicted at the bottom of the image. When a flashing checkerboard was shown to the subject, the visual cortex “lit up.” Our jaws fully dropped. Tom went on, “and we don’t really know yet what the mechanism is behind this....” My primary reaction to this was “I have a thesis project!” I then recall standing afterwards in a circle of excited scientists outside the door of the plenary. Bob Turner was there, mentioning something about susceptibility contrast.

When we came back from SMRM, we immediately went to work. I called up Robert Weisskoff, a lead scientist at the MGH-NMR Center who was part of their project, to ask a few questions about details. He mentioned that they used gradient-echo EPI with a TE (Echo Time) of about 50 ms to maximize susceptibility contrast since the leading hypothesis was that there was a change in blood susceptibility with brain activation. He mentioned that if we had a temporal signal-to-noise ratio (SNR) of about 100 (which MGH had), we would certainly be able to see something. There was one piece of information that I forgot to ask about: Tom Brady, at his plenary, did not seem to make it clear which way the signal went. All he said was that the movie was a series of subtraction images. At the time, I did not catch *what was subtracted from what*. In other words, I did not know whether he was showing the signal to go up or down with activation. To me, it made sense to think that the signal would go down with activation as cerebral oxygen metabolism went up. Whether it went up or down, I just was intent on repeating these results.

Within a week of the meeting, gradient-echo EPI was running and, rather than performing visual stimulation—for which we were not set up—we opted to perform a motor task. I pulled out a text book showing the organization of the homunculus. Since we could only collect one slice at the time and were not fully certain of where the function was supposed to be on the cortex, we chose extremely thick slices—up to 2.5 cm. The in-plane resolution was between 3.12 and 3.75 mm (20–24 cm field of view (FOV) and  $64 \times 64$  matrix). TR was 2–3 s. We only collected up to 128 sequential slices. I was the guinea pig for our first experiment. Our first couple of experiments did not quite work because of RF coil issues causing extremely low SNR, but on September 14, 1991, we tried again after a few RD coil tweaks. After 2 days of data reconstruction and processing, we had results that looked convincing. Figure 2.3 shows a few pages from my notebook of these early results. As mentioned, there was some confusion, at least to me, which way the signal should go. While I kept looking for signal decreases, the signal always appeared to increase in the contralateral motor cortex with finger tapping. Finally, going back to the literature, specifically a paper by Fox and Raichle (1986) describing a positron emission tomography (PET)-based measure of activation-induced decreases in oxygen extraction fraction, we were convinced that the signal should go up and had evidence that it should from the literature. Reading over Ogawa's early work (Ogawa et al. 1990a, b), it was also clear that endogenous blood oxygenation level-dependent (BOLD) susceptibility contrast was the likely mechanism of functional MR contrast. We were ready to start writing up the paper.

I performed a few more experiments using a prototype head-only  $z$ -axis gradient coil at GE medical systems. Because it was a  $z$ -gradient, we were only able to perform EPI in the coronal plane, which turned out to be a very convincing demonstration of motor strip activation. Later experiments were performed in October through January that included left, right, both, complex (a specific sequence of taps), imagined simple finger tapping, imagined complex, reading, and listening to spoken words. We also then performed experiments to probe the dynamics of the signal change as well as to prove that it was, in fact related to a change in  $T2^*$ . To prove that it was a  $T2^*$  effect, we repeated the experiment at different echo times (this was before we had multi-echo





**Fig. 2.3** A few pages from the notebook of Peter Bandettini on September 14 and September 16, 1991. These were the first successful results of fMRI at MCW. Initially, there was surprise that the signal increased with activation

EPI capability). We also performed spin-echo versus gradient-echo imaging to show that this was a bulk susceptibility effect rather than a “pure” T2 effect.

Processing for these first data sets involved no statistics but, rather, a rudimentary form of correlation analysis. We calculated the vector product with a simple box car function—an idea that Eric suggested during a conversation while scanning. Later, Andre Jesmanowicz refined the formalism considerably, resulting in our correlation analysis paper (Bandettini et al. 1993).

During the weeks following these successful results, I recall entering Jim Hyde’s office, showing him my results, and suggesting that this would be a great thesis project as it is a novel use of MRI with some extremely interesting aspects to study, including MR physics, physiology, and neuroscience. His initial reaction was along the lines of “You have a thought...you don’t have a thought. It seems soft and a bit fuzzy. I’m not sure if this would be the best project. Talk to Dr. Tikofsky. He’ll wisen you up.” This was sage advice of course. Dr. Tikofsky was a professor at MCW who performed single-photon emission computed tomography (SPECT). On seeing our initial results, he almost fell off his chair and immediately confirmed the importance of this finding to Dr. Hyde. Jim embraced this advice, allowed me to continue on, and began his own highly successful and 20 years running development of a relatively large contingent of scientists at MCW Center towards fMRI development and application. In this sense, Dr. Tikofsky was a key element to the project. He helped jump-start the enthusiasm. Key players who entered into this effort in late 1992 were Shi-Jiang Li, Ted DeYoe, Jeff Binder, Elliot Stein, Steve Rao, Tom Prieto, Tom Hammeke, Zerrin Yetkin, Victor Haughton, and many others. In biophysics, Jim mobilized the considerable skills and creativity of many talented scientists at MCW with the inception of a highly successful program project grant.

On the other hand, Carl Crawford told me that this project was too far from his expertise and perhaps too “hot” to be a thesis project. He worried about a Ph.D. student competing against the likes of Bob Turner, and perhaps wisely so. This was good advice which I knew that there was no way I would follow. We amicably parted ways and luckily, within a few weeks, Dr. Scott Hinks, a relatively new member of GE’s Applied Science Laboratory team, agreed to be my co-advisor. He found the science of endogenous susceptibility contrast extremely interesting, and importantly, very rich for a thesis project. It was critical to have an advisor from GE for my project. Not only was Scott very patient, careful, and insightful but also access to GE’s facilities—usually well after working hours—was important for much of our development of EPI and fMRI processing. We designed our full-pass filters for our EPI sequence using GE’s filter tool, and it somehow made its way into product—likely never used by anyone else. Almost no one at GE had any idea of what this too casually dressed kid sauntering in after hours and on weekends was doing.

One more key element in the biophysics team was Andre Jesmanowicz. With a dynamic force and boundless enthusiasm, he jumped into this effort shortly after we had produced our first results, and his impact was immediate. He significantly refined correlation analysis methods and improved the processing platform before Bob Cox came along with the analysis of functional neuroimages (AFNI) at MCW. He also wrestled our ornery Bruker 3T scanner into a high level of reliability and

performance for fMRI and MRI. Everyone at MCW agrees though that Eric Wong was likely the most important person in all of this. He wrote the pulse sequences from scratch, designed, built, and interfaced the gradient and RF coils, and he developed the EPI recon—all while finishing up his own thesis work.

Rather than submit the results to a very high-profile journal, I decided that I simply wanted them to be published as quickly as possible in the most reputable yet rapid turnaround journal available. I submitted the manuscript as a Communication to Magnetic Resonance in Medicine on February 5, 1992. It was accepted on March 31, 1992 and finally published in June of 1992 (Bandettini et al. 1992), about a week before the seminal Proceedings of the National Academy of Sciences (PNAS) papers of Kwong et al. (1992) and Ogawa et al. (1992). While our paper was the first published by about a week, I prefer to strongly emphasize that our group was a distant third with regard to when the first successful fMRI experiments were carried out. Without the pioneering work of Kwong and Ogawa, we would not have been able to have the rapid success that we did.

In the time between when the paper was submitted and when it came out, realizing that it was important to report these results as soon as possible, I decided to give my first presentation on our fMRI results at the SMRI meeting in April of 1992. This meeting was held 6 months out of phase of SMR, had a more clinical focus, and was not typically attended by our group. A few years later, the meetings were combined into ISMRM. My abstract was accepted as an oral presentation. As a second-year graduate student, this was a huge event for me. Perhaps more nervous than I have ever been in my life, with no one from MCW in the audience, I was somehow able to deliver a pretty good talk, having practiced it well over 50 times in the days leading up. The main points of this presentation included the following: a demonstration of selective right and left motor cortex with left- and right-hand tapping, respectively, a demonstration of TE dependence, and a comparison of spin-echo versus gradient-echo effects. These latter two results helped show that the mechanism was bulk susceptibility contrast with a compartment size on the order of 10  $\mu\text{m}$  (red blood cells to mid-sized veins). Also in the session were Dr. Ken Kwong giving his first results and Dr. Michael Stehling talking about his results at 1 T. After the session was over, I recall being very honored, as an impressionable young graduate student, that Keith Thulborn, a pioneer in blood susceptibility contrast, came up to congratulate me on a good talk. Another anecdote was that Ken Kwong later told me that it was my demonstration of alternating left then right motor cortex activity that finally convinced him that fMRI was real! A very generous statement but Ken likely knew it was real well before I even imagined it was possible.

After the presentation in April of 1992 and after the first publications came out in June of 1992, we continued work on understanding fMRI contrast mechanisms and on finding better ways to extract more subtle and quantitative information from the fMRI time series. I defended my thesis on Halloween, October 31, 1994, and have been working along the same research avenues since those heady times two decades ago.

MCW is still thriving with regard to fMRI. In 1995, Bharat Biswal, another graduate student of Dr. Hyde's, introduced the revolutionary finding of functionally

relevant resting-state signal correlations, which has given birth to an entirely new and explosively growing field of MRI-based functional connectivity mapping. Almost all of the scientists who were active at the beginning at MCW are highly established and successful and still performing research in fMRI. Even now, fMRI itself shows no sign at all of slowing down in any way. New innovations, applications, and findings continue to increase. The more carefully and precisely we look at the signal, the more we see. With a certain amount of ground-work preparation, the right people having come together, and a healthy amount of serendipity, MCW developed fMRI extremely early in the game and has contributed substantially to the field in basic methodology development and in both clinical and neuroscience applications.

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