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Lawrence Berliner *Editors*

fMRI: From Nuclear Spins to Brain Functions

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Preface

In the past two decades, a plethora of magnetic resonance (MR) techniques have rapidly evolved to become indispensable in studies of the human brain in health and disease by providing otherwise unavailable measurement capabilities. This avalanche of methodological developments was, to a large extent, initiated with the introduction of functional magnetic resonance imaging (fMRI), using endogenous deoxygenated hemoglobin contrast in 1992. fMRI provides the ability to indirectly map neuronal activity noninvasively in animal and human brains. Early results depicting images of increased neuronal activity in the human brain came from work conducted at the University of Minnesota, Massachusetts General Hospital and University of Wisconsin, Milwaukee. Subsequent to its introduction, fMRI evolved at a rapid pace, propelled by initiatives undertaken in many research centers and laboratories to understand the basic mechanisms underlying the MR-detected functional mapping signals, improve instrumentation, image acquisition, and image reconstruction methods, enhance detection sensitivity and accuracy, develop evermore complex analysis approaches to exploit the data maximally, and design increasingly sophisticated experiments to probe the unique capabilities of the human brain. In this book, we have asked some of the leaders in each of these areas that define the contemporary state of fMRI, including the individuals whose early work introduced fMRI, to review, explain, and discuss the state of their respective areas and peer into the future. The book also contains selected applications of the methodology that probe the brain at several different spatial scales dictated by its complex architecture and organization.

After the first section recalling the history of the invention of fMRI (Chaps. 1–3), the physiological and anatomical underpinnings of fMRI are reviewed (Chaps. 4–6). As fMRI is not a direct measure of neuronal activity, these chapters provide the background knowledge on the underlying brain processes (namely neurovascular coupling and electrophysiology) and anatomical correlates of fMRI activity. In the next section (Chaps. 7–14), the fMRI acquisition and modeling methods are introduced. Besides the standard gradient- and spin-echo fMRI acquisitions, there are many fMRI methods measuring alternative contrasts, such as cerebral blood flow and volume, modeling schemes to quantify tissue parameters, such as cerebral metabolic rate of oxygen, and deducing brain connectivity. The last chapter of this section on

resting-state fMRI provides the bridge to fMRI applications (Chaps. 15–22). The success of fMRI was largely due to the possibility to noninvasively study cognitive systems, which was previously a domain of cognitive psychology, by delivering the neuronal correlates of visual and auditory perception, of sensation and motor execution and of high-cognitive processes such as decision-making. In addition, fMRI has entered the fields of clinical and animal research. Note that it is not possible within a volume of an fMRI book to cover all fields of fMRI applications. The interested reader is referred to specialized books on these topics. The last section of this book (Chaps. 23–30) reviews emerging fMRI approaches and applications, such as genetics and fMRI, multimodal imaging, multivariate decoding, high-field fMRI, spectroscopy, and smart contrast agents, beyond the mainstream of current research and ends with a speculative outlook on the future of fMRI.

This book is a witness to the large progress made in the past two decades in probing brain activity at various spatial scales and specificity. For example, neuronal clusters with similar and highly specialized and elementary response properties have been traditionally investigated in animal models using numerous different invasive approaches (e.g., electrophysiology, optical imaging, etc.); however, continued developments of the noninvasive functional and morphological imaging capabilities with MR make this work increasingly possible directly in humans. At the second, larger spatial scale, the focus is on identifying interacting ensembles of such functionally distinct computational clusters and the neural circuits that connect them to account for mental activities and behavior. The methodological developments in fMRI in its approximately two decades of lifetime have provided critical and often pioneering contributions to research at this scale.

Putting this volume together owes its origins not only to the prominent and unparalleled space occupied by fMRI in studying the human brain but also to a get together of the three editors in Germany. One of the editors (L. Berliner) at the time was on a sabbatical in Berlin. Uğurbil, after having given a lecture on fMRI at a workshop in Berlin was happily trapped there due to the volcanic eruptions in Iceland that led to the cancellation of all flights over northern Europe. Uludağ, who is a true Berliner (of Istanbul origin), was visiting his family. The plan for the book was hatched at a breakfast meeting at a coffee shop in Berlin Mitte.

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Part I
History of fMRI

Chapter 1
From BOLD Contrast to Imaging Human Brain Function

Kâmil Uğurbil and Seiji Ogawa

The authors of this chapter are together responsible for one of the efforts that introduced functional brain imaging with magnetic resonance (fMRI) in experiments that were carried out in the Center for Magnetic Resonance Research (CMRR), University of Minnesota.

This effort came about because of the early experiments started by one of us (S. Ogawa) in the rodent brain with a small-animal magnetic resonance (MR) instrument; the goal was to achieve very high image contrast and to find some signal component that could reflect the physiological condition of the brain. Gradient-echo approach was employed with as thin a slice as possible and the best achievable magnetic field homogeneity. Such high-resolution gradient-echo images ($60 \times 60 \times 500\ \mu m^3$) of the rodent brain showed many intracortical dark lines running approximately perpendicular to the cortical surface; the presence of such structures in an MR image had not been discussed by anyone previously. During one MR experiment with an anesthetized mouse, most of the dark lines disappeared when the breathing air was switched to pure O_2 in order to rescue the mouse, as it appeared to start choking. This intriguing observation led to another experiment in which a mouse was euthanized with carbon monoxide (CO) in order to leave CO–hemoglobin in the blood when the mouse died. CO–hemoglobin is diamagnetic as opposed to deoxyhemoglobin which is strongly paramagnetic. As suspected, there were no dark lines in images of the brain of the CO-asphyxiated animal. The cause of the dark lines observed under anesthetized but physiological conditions was thus identified as the local susceptibility-induced field variation around blood vessels,

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mostly intracortical veins, which contained paramagnetic deoxyhemoglobin in red blood cells. This contrast seen in gradient-echo images disappeared in spin-echo images due to the refocusing of susceptibility-induced phase shifts. The intra-vessel blood signal in spin-echo images was barely visible because of the small partial volume in a voxel and a very short T_2 at very high B_0 (7 and 8.4 T; Ogawa et al. 1990b). Gradient-echo images had a sensitivity enhancement of the contrast because the susceptibility-induced magnetic field inhomogeneities extended significantly beyond the vessel wall into the surrounding tissue, thus amplifying the effect in the high magnetic field. Ogawa had described the echo time dependence of these contrast signals in a talk at the Society for Magnetic Resonance in Medicine (SMRM) meeting in San Francisco in 1988; the contents of this presentation was largely ignored.

This image contrast was named "BOLD" (blood oxygenation level-dependent) contrast by Ogawa since it was dependent on the content of deoxyhemoglobin in the blood (Ogawa et al. 1990a). The main factors involved in the BOLD effect were all very familiar to Ogawa from his earlier research topics. Various factors that potentially influenced BOLD contrast—namely, cerebral blood flow (CBF) changes, increased anesthesia monitored by EEG signals, and glucose levels lowered by insulin—were checked (Ogawa et al. 1990a). There were still a few points that needed to be clarified in order to characterize the BOLD effect. They were the sensitivity of the MR signal to blood oxygenation (Ogawa et al. 1993a) and the relation of blood oxygenation and blood volume to R2* (Ogawa et al. 1993b). The latter was tested by simulations assuming a near anaerobic process (Fox and Raichle 1986) for oxygen demand. Bob Turner called at some point when these experiments were being carried out, informing Ogawa of his partial ischemic experiment on cat brains, where he was observing the same deoxyhemoglobin-induced susceptibility effect that was published earlier in 1990 by Ogawa et al. The BOLD effect results were shown to Dr. Raichle during his visit to Bell Laboratories in January of 1991, and potential human applications of the technique to obtain functional maps analogous to the ones Dr. Raichle was generating using the positron emission tomography (PET) method was discussed.

PET studies showing CBF increases upon activation of the brain had already been reported at the time BOLD contrast was described. The connection between that body of work and BOLD contrast did not go unnoticed. Although the BOLD work was based on manipulation of oxygenation levels in the blood in the rat model through pharmaceutical and/or metabolic interventions, the potential use of the BOLD contrast to possibly achieve functional imaging in the brain, in a way analogous to the PET approach, was discussed (Ogawa et al. 1990a; submitted to the Proceedings of the National Academy of Sciences (PNAS) of the USA in August and published in December 1990). In the "Discussion" section of this 1990 PNAS manuscript, it was stated:

> PET imaging relies on a family of tracer method for measuring different physiological quantities including blood volume, blood flow, and regional oxygen extraction (13). BOLD contrast adds to a similar, emerging set of functional MRI methodologies that are likely to be complementary to PET imaging in the study of regional brain activity.

This possibility coincided well with a programmatic development that the other one of us (Uğurbil) was pursuing at the University of Minnesota at about the same time in the late 1980s; this programmatic effort culminated in the establishment of a high magnetic field instrument in the 1990s for MR imaging and spectroscopy studies in the human body (Uğurbil 2012, 2014; Uğurbil et al. 1993). The magnetic field targeted was 4 T, at a time when the commercially available, "high-field" MR scanners operated at 1.5 T. The provenance of this 4-T system can be traced to a pioneering effort undertaken at Bell Laboratories to extend MR spectroscopy to the study of biological problems in intact biological systems; this effort was being carried out in the Biophysics Department of Bell Labs led by Robert Shulman, and we (Ogawa and Uğurbil) were both part of this effort (e.g., see review Shulman et al. 1979). Figure 1.1 shows two of us together with Robert Shulman many years later at Yale University where Shulman moved to as faculty member after leaving Bell Laboratories; the occasion was a meeting held to celebrate the 20th anniversary of the introduction of fMRI.

The successes in going from bacterial suspensions in Bell Labs to intact animal models in the Uğurbil laboratory (e.g., Robitaille et al. 1989; Uğurbil et al. 1989) at the University of Minnesota motivated the 4-T project. However, it was envisioned from the beginning that the 4 T would reach for much more than just MR spectroscopy; rather, the interest was in obtaining unique biological information using MR techniques, whatever that technique may be. Thus, with the elucidation of the BOLD contrast, which relies on magnetic susceptibility-induced magnetic field

Fig. 1.1 Uğurbil and Ogawa with Robert Shulman (*middle*) at Yale University in 2012, at a symposium organized to celebrate the 20th anniversary of the introduction of fMRI

differences and increases with increasing magnetic fields, it was natural to pursue imaging of brain activity in humans using this contrast mechanism with the 4-T system. The potential of a revolutionary impact that such an accomplishment would have in neurosciences did not escape us. Consequently, exploring functional imaging became the highest priority project in the 4-T program. Even before this magnet arrived in Minnesota and even before the PNAS paper by Ogawa et al. (1990a) appeared in press, we started talking about pursuing functional imaging in the human brain together using the 4-T system destined for Minneapolis. Evidence of this discussion can in fact be found in the 1990 PNAS paper (Ogawa et al. 1990a), where it is stated that

> The results shown here indicate that BOLD contrast can be used to noninvasively monitor in real time the blood oxygenation levels of brain areas in response to central nervous system drugs that affect basal metabolism or blood flow. Although BOLD-image contrast is enhanced at high magnetic fields, the effect is observed at 4.7 T, a field strength that is close to the highest field strength (4 T) presently available for human subjects.

It took several years after the decision was reached to acquire the large-bore (125-cm diameter) 4-T magnet from Siemens to achieve a functional system in Minneapolis. The electronics for this system was developed in the manufacturing plant of Spectroscopy Imaging Systems (SISCO), a joint venture at the time between Siemens and Varian, Fremont, California, using a second, smaller-bore 4-T magnet that was also built by Siemens (this magnet later ended up in the Brookhaven National Laboratories). When ready, the electronics were shipped from California while the 125-cm-bore 4-T magnet was shipped from Erlangen (Germany) to Minneapolis, to be integrated on site in the CMRR. This 4-T magnet was not really designed for shipping (it did not have shipping restrains, for example). The transport strategy had to be carefully thought out. A brand new, specially equipped Mercedes truck was employed. The entire truck was shipped to the USA by sea and the magnet did not leave this truck on its journey from Erlangen, Germany to Minneapolis. The 4-T magnet arrived in Minneapolis in 1990. However, the magnet was damaged in transport and had to be repaired. When the system finally became operational in CMRR, the very first experiment we started on this system was fMRI. Had the 4-T instrument been delivered earlier or had it functioned right away, we would have certainly achieved fMRI earlier. This historically important magnet is now a "garden art work" in the courtyard of CMRR in Minneapolis (Fig. 1.2).

As we waited for the 4-T instrument, we did not want to talk about the plans to pursue functional imaging or the excitement we felt about this prospect. We also did not consider pursuing fMRI at 1.5 T because we were focused on the BOLD contrast, which, as previously stated, is a susceptibility effect. As such, we did not think BOLD contrast would be sufficiently strong at low fields like 1.5 T. In principle, we were right, although incomplete in our understanding of potential sources for functional imaging signals. Particularly, the early fMRI experiments, performed as single slice studies using fast repetition times and large flip angles, were prone to inflow effects, mostly associated with large vessels with fast flows. These and other predominantly large vessel effects can generate strong stimulus-evoked imaging signals even at 1.5 T, albeit inadequate ones if high spatial fidelity to sites of neuronal activity is desired.

Fig. 1.2 K. Uğurbil with the 125-cm-bore 4-T magnet in the courtyard of the CMRR at the University of Minnesota where the fMRI effort described in this chapter was carried out

We asked Ravi Menon, who had joined the Uğurbil group as a postdoctoral fellow, to take on the functional imaging effort. Ravi, Jutta Ellermann (who was also an Uğurbil research fellow at the time), and two of us performed the experiments together, often taking turns as subjects. Both of us proved at the end to be the worst subjects with respect to seeing any stimulus-induced signal changes in the brain. Jutta had the best response; images that appeared in our first paper reporting fMRI (Ogawa et al. 1992) are from her brain. David Tank from Bell Laboratories joined us at times for these experiments, and he participated in the data collection, advised us on neuroscience aspects of the studies, and wrote software for data analysis and visualization. Seong-Gi Kim also joined the Uğurbil group as a postdoctoral fellow later in the effort and started working with us on the early fMRI experiments. Much had to be done since the 4-T system was an immature platform. We had to build human-sized radiofrequency (RF) coils at this high frequency for the first time (the task of Hellmut Merkle, now at NIH); we had to implement pulse sequences virtually from scratch to collect the data (done by Ravi and later by Seong-Gi Kim and Xiaoping Hu) and develop protocols to transfer these data to other computers for analysis; we had to deal with problems of a new instrument, such as imprecise synchronization of gradients with data acquisition that led to extensive ghosting and regulatory hurdles for performing studies at 4 T for the first time. Echo planar imaging (EPI), that has now become the most commonly employed imaging approach for fMRI, was not available generally on any system, let alone a high-field 4-T system.

We started collecting data for BOLD functional imaging on humans sometime early in 1991. We had to pause several times due to instrumentation problems and/

or changes. We used gradient-recalled-echo imaging (i.e., fast low angle shot, FLASH). Obviously, in these early experiments, we worried about whether the results were real, if they were motion artifacts, or instrumental glitches, etc.

By the time we went to the SMRM annual meeting that was held in San Francisco in August 1991, we had functional images. We knew sometime before this meeting that the Massachusetts General Hospital (MGH) was working on similar experiments. Lin Jelinsky, the head of Seiji's department in Bell Laboratories at the time, told us that she had been visiting MGH, heard about their efforts and was told not to tell Seiji about their work. She felt obligated to tell them of our attempts to develop fMRI in Minneapolis. The abstract book of the 1991 SMRM annual meeting did not contain any abstracts from any group reporting attempts at fMRI; clearly, at the time of the abstract deadline, no one was able to submit or thought of submitting a BOLD fMRI abstract to this annual meeting. But Tom Brady from MGH gave a plenary talk in this conference and, in this lecture, showed functional images of visual stimulation obtained with BOLD contrast. At this meeting, we could have shown BOLD fMRI images as well and, in fact, had some images with us. Clearly, however, having an image or two is different than publishing in a rigorous journal the irrefutable introduction of a new, previously unknown, and unique method. Consequently, we did not feel we were at a stage where we could rush to publish these unique results; it appears that our MGH colleagues may have felt similarly. Thus, it took another ~6 months before the papers from these two groups were submitted for publication within 5 days of each other. When we look at some of the original data from our laboratories now, we are amazed how good they were. Likely, we were all being too cautious. But then, this was an extraordinary development that required extraordinary evidence. In fact, despite the rapidly increasing number of early fMRI papers from different groups, skepticism about the approach persisted for some time, ascribing the results to motion artifacts, a possibility we worried about in the early studies and addressed using hemifield visual stimulation that specifically activates the hemisphere contralateral to the stimulated visual field.

We submitted our paper to Nature first. It was rejected after a few weeks without being sent to scientific review, with the usual rejection letter saying that it was not of "general interest." After the rejection, we recouped and sent it to PNAS, USA, where it was received in March 1992 and appeared in press in July 1992 (Ogawa et al. 1992).

Approximately, a week before the publication of our paper and the paper from MGH, a short communication demonstrating fMRI in the human motor cortex appeared in press (Bandettini et al. 1992). This is also one of the first papers demonstrating fMRI; the authors of this paper were apparently inspired by Tom Brady's talk at the August 1991 SMRM annual meeting and started working on the project subsequent to that meeting (Bandettini 2012; Bandettini et al. 1992; also see chapter by Bandettini in this book).

Clearly, in the two decades since its discovery, BOLD fMRI has led to a revolution in the ability to visualize human brain activity, going from the early experiments demonstrating relatively coarse images of activity in the visual cortex to mapping cortical columns, constructing mental experiences of an individual, and

defining functional connections among different brain regions (these are all topics that are covered by chapters in this book). The huge impact fMRI has already had in the study of human brain function continues to increase rapidly due to improved instrumentation (in particular the introduction of ultrahigh (7 T and above) magnetic fields), new data acquisition methods that enable whole brain, high-resolution images in approximately a second and innovative data analysis methods. All of this has been possible by the fortuitous combination of the fact that we are endowed with a complex paramagnetic molecule sequestered in our blood vessels, and that neuronal activity has spatially specific metabolic and physiologic consequences.

References

Bandettini PA (2012) Functional MRI: a confluence of fortunate circumstances. Neuroimage 61:A3–A11.

Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS (1992) Time course EPI of human brain function during task activation. Magn Reson Med 25:390–397

Fox PT, Raichle ME (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci U S A 83:1140–1144

Ogawa S, Lee T-M, Kay AR, Tank DW (1990a) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87:9868–9872

Ogawa S, Lee T-M, Nayak AS, Glynn P (1990b) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson Med 14:68–78

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Uğurbil K (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 89:5951–5955

Ogawa S, Lee TM, Barrere B (1993a) Sensitivity of magnetic resonance image signals of a rat brain to changes in the cerebral venous blood oxygenation. Magn Reson Med 29:205–210

Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Uğurbil K (1993b) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. Biophys J 64:803–812

Robitaille PM, Lew B, Merkle H, Sublett E, Lindstrom P, From AH, Garwood M, Bache RJ, Uğurbil K (1989) Transmural metabolite distribution in regional myocardial ischemia as studied with 31P NMR. Magn Reson Med 10:108–118

Shulman RG, Brown TR, Uğurbil K, Ogawa S, Cohen SM, den Hollander JA (1979) Cellular applications of 31P and 13C nuclear magnetic resonance. Science 205:160–166

Uğurbil K (2012) The road to functional imaging and ultrahigh fields. Neuroimage 62:726–735

Uğurbil K (2014) Magnetic resonance imaging at ultrahigh fields. IEEE Trans Biomed Eng 61:1364–1379

Uğurbil K, Garwood M, Merkle M, Path G, Robitaille PM, Hendrich K, Zhang J, Tristani M, Yoshiyama M, From AHL, Bache RJ (1989) Metabolic consequences of coronary stenosis. Transmurally heterogeneous myocardial ischemia studied by spatially localized 31P NMR spectroscopy. NMR Biomed 2:317–329

Uğurbil K, Garwood M, Ellermann J, Hendrich K, Hinke R, Hu X, Kim SG, Menon R, Merkle H, Ogawa S, Salmi R (1993) Imaging at high magnetic fields: initial experiences at 4 T. Magn Reson Q 9:259–277

Chapter 2
The Birth of Functional MRI at the Medical College of Wisconsin

Peter A. Bandettini

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 μs 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 64×64 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

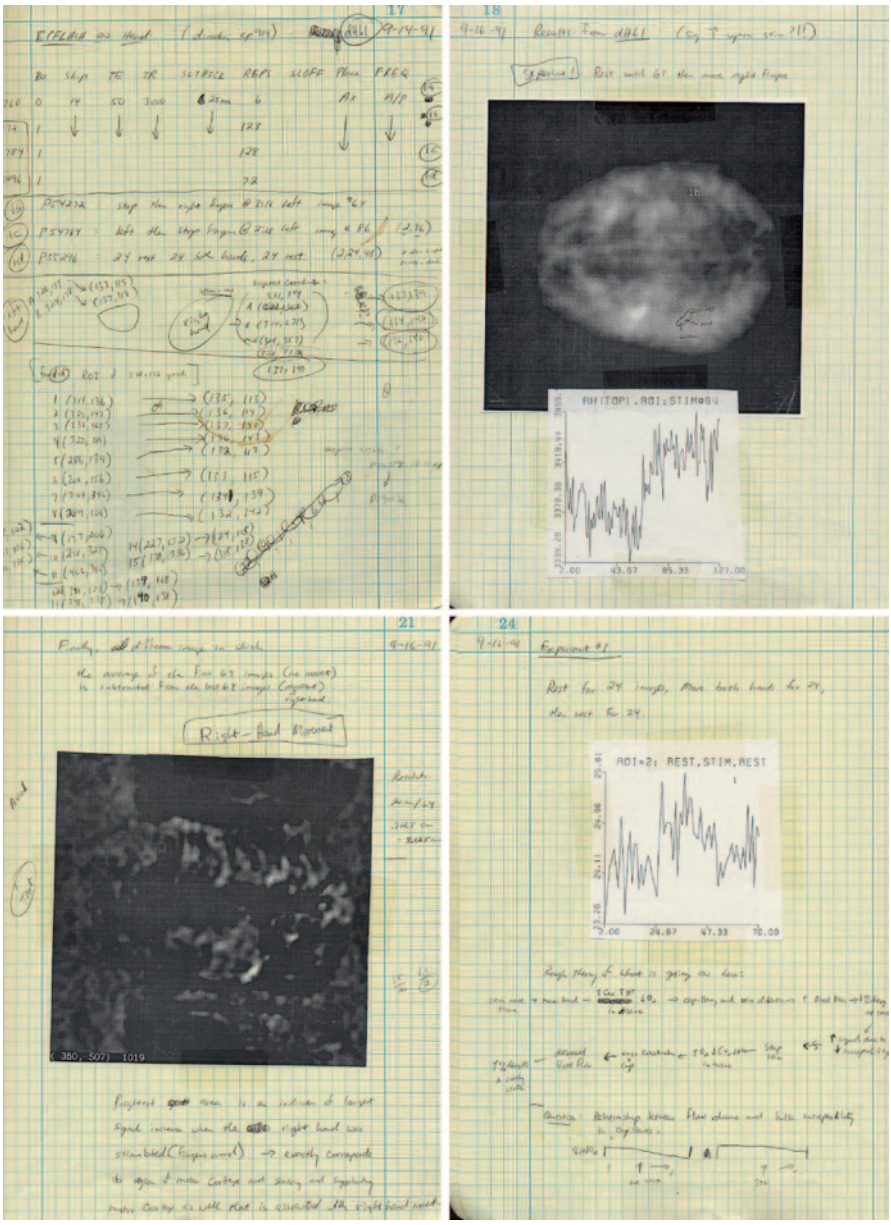

Fig. 2.3 A few pages from the notebook of Peter Bandettini on September 14 and September 16, 1991. These were the first successful results of fMRI at MCW. Initially, there was surprise that the signal increased with activation