Chapter 1
From BOLD Contrast to Imaging Human Brain Function

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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.

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